



National Toxicology Program

U.S. Department of Health and Human Services

APPENDICES FOR
NTP MONOGRAPH ON DEVELOPMENTAL EFFECTS AND
PREGNANCY OUTCOMES ASSOCIATED WITH CANCER
CHEMOTHERAPY USE DURING PREGNANCY

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1.0 APPENDIX A – HUMAN CARCINOGENICITY CLASSIFICATION AND FDA PREGNANCY CATEGORIES

Appendix A Table 1: Classification of chemotherapeutic agents in the NTP monograph with regard to human carcinogenicity and the FDA pregnancy categories

Chemotherapeutic agent	IARC Classification*	NTP Report on Carcinogens**	FDA Pregnancy Category***
5-Fluorouracil	3	NA	D
6-Mercaptopurine	3	NA	D
6-Thioguanine	NA	NA	D
Actinomycin D	3	NA	D
All- <i>trans</i> retinoic acid	NA	NA	D
Amasacrine	2B	NA	NA
Behenoyl cytosine arabinoside	NA	NA	NA
Bleomycin	2B	NA	D
Busulfan	1	NA	D
Capecitabine	NA	NA	D
Carboplatin	NA	NA	D
Carmustine	2A	NA	D
Chlorambucil	1	Known	D
Cisplatin	2A	Reasonably anticipated	D
Cyclophosphamide	1	Known	D
Cytarabine	NA	NA	D
Dacarbazine	2B	Reasonably anticipated	C
Dasatinib	NA	NA	D
Daunorubicin	2B	NA	D
Docetaxel	NA	NA	D
Doxorubicin	2A	Reasonably anticipated	D
Epirubicin	NA	NA	D
Erlotinib	NA	NA	D
Etoposide	1	NA	D
Fludarabine	NA	NA	D
Gemcitabine	NA	NA	D
Gemtuzumab ozogamicin	NA	NA	D
Hydroxyurea	3	NA	D
Idarubicin	NA	NA	D
Ifosfamide	3	NA	D
Imatinib	NA	NA	D
Interferon alpha	NA	NA	C

Appendix A Table 1: Classification of chemotherapeutic agents (continued)

Chemotherapeutic agent	IARC Classification*	NTP Report on Carcinogens**	FDA Pregnancy Category***
Irinotecan	NA	NA	D
Lapatinib	NA	NA	D
Lomustine	2A	NA	D
Melphalan	1	Known	D
Methyl-GAG	NA	NA	NA
Methotrexate	3	NA	X
Mitoxantrone	2B	NA	D
Nilotinib	NA	NA	D
Nimustine	NA	NA	NA
Nitrogen mustard	2A	Reasonably anticipated	D
Oxaliplatin	NA	NA	D
Paclitaxel	NA	NA	D
Procarbazine	2A	Reasonably anticipated	D
Rituximab	NA	NA	C
Streptozotocin	2B	NA	D
Tamoxifen	1	Known	D
Teniposide	2A	NA	D
Trastuzumab	NA	NA	D
Triethylenemelamine	3	NA	NA
Trofosfamide	NA	NA	NA
Vinblastine	3	NA	D
Vincristine	3	NA	D
Vindesine	NA	NA	NA
Vinorelbine	NA	NA	D

*International Agency for Research on Cancer (IARC) classifications (<http://monographs.iarc.fr/ENG/Classification/index.php>) updated November 6, 2012. Groups: 1 – Carcinogenic to humans; 2A – Probably carcinogenic to humans; 2B – Possibly carcinogenic to humans; 3 - Not classifiable as to its carcinogenicity to humans; and 4 – Probably not carcinogenic to humans.

**Based on NTP. 2011. Report on Carcinogens, 12th Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. 499 pp.

Categories: Known to be a human carcinogen OR Reasonably anticipated to be a human carcinogen.

***See full descriptions of FDA pregnancy categories A, B, C, D, and X at www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.57.

Abbreviations: NA = not available.

2.0 APPENDIX B – LITERATURE SEARCH STRATEGY

Initial literature searches

Initial literature searches were conducted on April 9, 2010 and June 7, 2010. The initial search of all databases was conducted with a focus on 4 key concepts: chemotherapy, pregnancy, pregnancy outcomes, and human studies. For PubMed, the initial search was conducted in a series of steps. First, only MeSH terms were combined across the 4 key concepts to capture the more relevant studies. Then, textwords were searched within the 'in process' and 'supplied by publisher' content to retrieve items not yet indexed with MeSH. A final search was done combining the textwords to capture all possible records on the subject. When available, MeSH terms were used for searching in PubMed in addition to textwords. For the 4 key concepts of the search, the following terms were used: (MeSh [mh]; subheading [sb] under MeSH; title and abstract search [tiab]; and subset [sb] – searches for new records to PubMed that are in the 'in process' or 'publisher' subsets)

1. Chemotherapy

- a. MeSH – a variety of possible MeSH terms and combinations of terms were used: Antineoplastic agents (both as Mesh and pharmacological action), antineoplastic protocols, "chemotherapy, adjuvant," neoplasms/drug therapy; (neoplasms[mh] AND pregnancy[mh] AND "combined modality therapy"[mh])
- b. Textwords - chemotherap* OR antineoplastic OR "anti tumor" OR "anti tumour" OR "4 aminofolic acid" OR "4 epidoxorubicin" OR "5 fluorouracil" OR "6 mercaptopurine" OR "6 thioguanine" OR Abraxane OR adrucil OR "all-trans retinoic acid" OR ATRA OR altretamine OR adriamycin OR "actinomycin D" OR aminopterin OR Anastrozole OR "ARA-C" OR arimidex OR aromasin OR "behenoyl cytosine arabinoside" OR bevacizumab OR BHAC OR bleomycin OR bortezomib OR busulfan OR busulfex OR carboplatin OR capecitabine OR carmustine OR Cerubidine OR chlorambucil OR cisplatin OR cisplatinum OR cyclophosphamide OR cytarabine OR cytosar OR "cytosine arabinoside" OR Cytoxan OR dacarbazine OR dasatinib OR daunorubicin OR daunoxome OR deltasone OR docetaxel OR doxorubicin OR efudex OR eldisine OR Ellence OR Eloxatin OR emcyt OR encitabine OR epirubicin OR erlotinib OR etopophos OR etoposide OR estramustine OR exemestane OR fareston OR femara OR fludara OR fludarabine OR folex OR fulvestrant OR Faslodex OR gefitinib OR gemcitabine OR gemtuzumab OR gemzar OR gleevec OR glivec OR herceptin OR hexamethylmelamine OR hydroxycarbamide OR hydroxyurea OR idarubicin OR IFEX OR ifosfamide OR imatinib OR "interferon alpha" OR iressa OR irinotecan OR ixabepilone OR ixempra OR lapatinib OR letrozole OR lomustine OR matulane OR mechlorethamine OR melphalan OR methotrexate OR "mitomycin c" OR mitoxantrone OR mustargen OR "mustine Hcl" OR mutamycin OR myleran OR mylotarg OR navelbine OR nilotinib OR "nitrogen mustard HCl" OR nolvadex OR novantrone OR oncovin OR oxaliplatin OR ozogamicin OR paclitaxel OR paraplatin OR pemetrexed OR pentostatin OR platinol OR prednisone OR procarbazine OR rituxan OR rituximab OR sorafenib OR sprycel OR streptozocin OR sunitinib OR sunrabin OR sutent OR tamoxifen OR tarceva OR tasigna OR taxol OR taxotere OR temodar OR temozolomide OR teniposide OR thioplex OR thiotepa OR toposar OR topotecan OR toremifene OR trastuzumab OR tretinoin OR tykerb OR velban OR velcade OR vepesid OR vesanoid OR vinblastine OR vincasar OR vincrex OR vincristine OR vindesine OR vinorelbine OR VM26 OR VP16 OR Vumon OR Xeloda OR zanosar

2. Pregnancy

- a. MeSH – pregnancy, maternal-fetal exchange, maternal-fetal relations

Exemestane[tiab] OR aromasin[tiab] OR 5-fluorouracil[tiab] OR Adrucil[tiab] OR Efudex[tiab] OR Gemzar[tiab] OR gemcitabine[tiab] OR Herceptin[tiab] OR Trastuzumab[tiab] OR Rituximab[tiab] OR Rituxan[tiab] OR Gemtuzumab[tiab] OR ozogamicin[tiab] OR Mylotarg[tiab] OR Hydroxyurea[tiab] OR hydroxycarbamide[tiab] OR Hydrea[tiab] OR Droxia[tiab] OR Gleevec[tiab] OR Imatinib[tiab] OR Glivec[tiab] OR Ixemptra[tiab] OR ixabepilone[tiab] OR Lapatinib[tiab] OR Tykerb[tiab] OR Nilotinib[tiab] OR Tasigna[tiab] OR Dasatinib[tiab] OR Sprycel[tiab] OR Fludarabine[tiab] OR Fludara[tiab] OR Letrozole[tiab] OR Femara[tiab] OR Methotrexate[tiab] OR Amethopterin[tiab] OR L- mexate[tiab] OR folex[tiab] OR Mitomycin[tiab] OR mutamycin[tiab] OR Mitoxantrone[tiab] OR novantrone[tiab] OR Navelbine[tiab] OR vinorelbine[tiab] OR Prednisone[tiab] OR Deltasone[tiab] OR Tamoxifen[tiab] OR Nolvadex[tiab] OR Taxotere[tiab] OR docetaxel[tiab] OR Thiotepa thioplex[tiab] OR Vincristine[tiab] OR Oncovin[tiab] OR vincex[tiab] OR Vincasar[tiab] OR PES[tiab] OR Xeloda[tiab] OR capecitabine[tiab] OR Bleomycin[tiab] OR Cytosine arabinoside[tiab] OR ARA-C[tiab] OR cytosar[tiab] OR cytarabine[tiab] OR Behenoyl[tiab] OR cytosine arabinoside[tiab] OR Enocitabine[tiab] OR BHAC[tiab] OR Sunrabin[tiab] OR Dacarbazine[tiab] OR 6-Mercaptopurine[tiab] OR Streptozotocin[tiab] OR Zanosar[tiab] OR Procarbazine[tiab] OR matulane[tiab] OR Busulfan Busulfex[tiab] OR Myleran[tiab] OR Carmustine[tiab] OR BiCNU[tiab] OR Interferon alpha[tiab] OR Intron A[tiab] OR 6-thioguanine[tiab] OR All-trans retinoic acid[tiab] OR ATRA[tiab] OR Vesanoid[tiab] OR Tretinoin[tiab] OR Vinblastine[tiab] OR Vindesine[tiab] OR Eldisine[tiab] OR Mustargen[tiab] OR Mechlorethamine) AND (Pregnancy[tiab] OR pregnant[tiab] OR gestation*[tiab] OR "in utero"[tiab] OR fetal[tiab] OR fetus[tiab] OR foetus[tiab] OR embryo[tiab] OR embryonic[tiab] OR neonat*[tiab] OR prenatal[tiab] OR perinatal[tiab] OR postnatal[tiab]) AND (women[tiab] OR woman[tiab] OR mother[tiab] OR patient[tiab]) AND ("in process"[sb] OR publisher[sb])

3.0 APPENDIX C – SUMMARY TABLES FOR CANCER CHEMOTHERAPEUTIC AGENTS WITH MORE THAN 10 CASES

Appendix C contains data tables for chemotherapeutic agents for which there were more than 10 reported cases (patients) treated with chemotherapy for cancer during pregnancy.

Appendix C Table 1. 5-Fluorouracil – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
5-Fluorouracil (Dose/schedule NS)	Case series	1 of 13 (Pt 6)	Cervix	3 rd	Cisplatin	NS	34	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	(Abellar <i>et al.</i> 2009)
5-Fluorouracil (600 mg/m ² every 3 wks, 5 cycles)	Case report	1	Breast	1 st , 2 nd	Epirubicin, Cyclophosphamide, Tamoxifen (2 nd , 3 rd) Radiation analgesic (2)	C-section	35	Signs of premature delivery [spontaneous preterm labor]. Female infant: 2,070 g [N], Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was healthy with normal hematological and biochemistry parameters.	At 12 months, she showed no disorder, congenital abnormality, or disease.	(Andreadis <i>et al.</i> 2004)
5-Fluorouracil (900 mg on days 1 and 8, 6 cycles)	Case report	1	Breast	2 nd First@wk 17	Cyclophosphamide, Doxorubicin	Vaginal	NS	Male infant: weight NS, Apgar scores 8 and 9. Newborn was phenotypically normal with a full head of hair.	At 1.5 years, he was well developed.	(Barnicle 1992)
5-Fluorouracil (1,200 mg weekly)	Case series	1 of 3 (Pt 2)	Breast	1 st , 2 nd , 3 rd First@wk 7.5 Last@wk 28.5	Methotrexate, Radiation therapy (2 nd)	NS	29	Male infant: 820 g (SGA), Apgar scores NS. Newborn was small for gestational age.	At 8.5 years, hypertelorism, frontal hair whorl, an upsweep of the frontal hairline, microcephaly, low-set ears, micrognathia, and right palmar simean crease. He stutters, has verbal expressive difficulties, and has an intelligence quotient of 70.	(Bawle <i>et al.</i> 1998)
5-Fluorouracil (1,000 mg/m ² every 3 to 4 wks, 1 to 6 cycles)	Case series	24 of 24	Breast	2 nd and/or 3 rd	Doxorubicin, Cyclophosphamide	NS	38 (mean), 33-40 (group range)	Three patients delivered pre-term because of severe preeclampsia (1 pt) or idiopathic preterm labor (2 pt). Individual pregnancy outcomes were not provided. Apgar scores were ≥ 9 in all cases. One newborn had a low birth weight for gestational age (<10 th percentile; SGA), 23 had normal birth weight for age.	At 6 months to 8 years (group range), all were alive.	(Berry <i>et al.</i> 1999)

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Newborns had no malformations. One newborn was diagnosed with hyaline membrane disease, and 2 newborns had tachypnea (resolved by 48 hours). One newborn was born 2 days after chemotherapy and experienced transient leucopenia. Two newborns had substantial hair loss.		
5-Fluorouracil (Dose/schedule NS)	Case series	3 of 5 (Pt 1, 2, 3)	Breast	2 nd , 3 rd	Epirubicin, Cyclophosphamide	C-section	36	Infant, sex NS: 2,920 g, Apgar scores 7 or greater at 1 and 5 minutes. Newborn was healthy with no congenital malformations or intrauterine growth retardation.	No	(Bodner-Adler <i>et al.</i> 2007)
				2 nd , 3 rd	Epirubicin, Cyclophosphamide	Vaginal	38	Infant, sex NS: 2,940 g, Apgar scores 7 or greater at 1 and 5 minutes. Newborn was healthy with no congenital malformations or intrauterine growth retardation.		
				2 nd , 3 rd	Epirubicin, Cyclophosphamide	C-section	36	Infant, sex NS: 2,530 g, Apgar scores 7 or greater at 1 and 5 minutes. Newborn was healthy with no congenital malformations or intrauterine growth retardation.		
5-Fluorouracil (Dose/schedule NS)	Survey, registry	18 of 104 infants from Table 2	Breast	2 nd , 3 rd	Doxorubicin, Cyclophosphamide, Paclitaxel, Epirubicin	NS	35.9 (group mean)	Infant sex NS: 2,667 g (group mean), Apgar scores NS. None of the infants had malformations. Other effects (number of infants): transient tachypnea (1), jaundice (1), intrauterine growth retardation, and hyperbilirubinemia (1).	At 0.3 to 11.3 years, all children were normal phenotype. At 42 months (group mean, n=17), no long-term complications; group mean weight was 48 th percentile.	(Cardonick <i>et al.</i> 2010)

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
		4 of 12 from Table 6	Colorectal	2 nd , 3 rd	None	NS	NS	Infant sex NS: Birth weight and Apgar scores NS. One infant had hemi-hypertrophy of the lower extremity. Three infants were normal without malformations.	At age 48 months (group mean, n=3 infants), child with hemihypertrophy receiving occupation and physical therapy for motor delays. [Remaining children were normal.]	
5-Fluorouracil (600 mg/m ² on days 1 and 4, 3 cycles)	Case report	1	Breast	3 rd First@wk 28 Last@wk 34	Doxorubicin, Cyclophosphamide	Vaginal, induced	36	Mild fetal growth restriction and progressive reduction in amniotic fluid. Female infant: 2,350 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was in good condition with normal blood count.	At 24 months, healthy with weight and height in the 50 th percentile and normal psychoneurological development.	(Cordoba <i>et al.</i> 2010)
5-Fluorouracil (Pt 1 - 500 mg/m ² for 5 days, 2 cycles; Pt 2 - 500 mg/m ² for 5 days, 2 cycles, 750 mg/m ² for 5 days, 1 cycle; Pt 3 - 750 mg/m ² for 5 days, 3 cycles)	Case series	3 of 3	Breast	2 nd First@wk 24	Vinorelbine, Epi-doxorubicin, Cyclophosphamide	C-section	34	Female infant: 2,320 g, Apgar scores 8, 3, and 10 at 1, 3, and 5 minutes. Newborn was normal with no dysmorphic features. Anemia at day 21, resolved.	At 35 months, growth and development were normal.	(Cuvier <i>et al.</i> 1997)
				3 rd First@wk 29	Vinorelbine	Vaginal	37	Male infant: 3,230 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with no dysmorphic features.	At 34 months, growth and development were normal.	
				3 rd First@wk 28	Vinorelbine	Vaginal	41	Male infant: 3,300 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal with no dysmorphic features.	At 23 months, growth and development were normal.	
5-Fluorouracil (300-500 mg/m ² per day for 7 days, 5 cycles)	Case report	1	Breast	2 nd , 3 rd	Doxorubicin, Cyclophosphamide	C-section	38	Male infant: 5 lb 14 oz [2,665 g], Apgar scores NS. Newborn developed jaundice, but was otherwise healthy with normal blood count and chemistry.	At 4 months, 50 th percentile for weight with normal blood count and chemistry. At 15 and 24 months, excellent health and normal development.	(Dreicer and Love 1991)

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
5-Fluorouracil (Dose/schedule NS)	Case series, retrospective	7 of 15 [see note in pregnancy outcome column]	Breast	2 nd and/or 3 rd	Cyclophosphamide Doxorubicin	NS	35 (Group average) (Range 32-40)	Individual pregnancy outcomes were not provided. Seven live births with no congenital malformations. No stillbirths, miscarriages, or perinatal deaths in any pregnancies treated during the 2 nd and 3 rd trimesters. [15 pts received chemotherapy during pregnancy; 4 pts were not included because of a lack of data on chemotherapy treatment]	No	(Garcia-Manero <i>et al.</i> 2009)
5-Fluorouracil (400 mg/m ² bolus, 2,400 mg/m ² 46-hour infusion)	Case report	1	Rectal	2 nd , 3 rd First@wk 20 Last@wk 30	Oxaliplatin	Vaginal, induced	33.6	Female infant: 5 lb 6 oz [2,438 g] , Apgar scores 8 and 8 at 1 and 5 minutes. Newborn was normal.	At 3.5 years, she had no deficits, was in the 60 th percentile for height and the 45 th percentile for weight.	(Gensheimer <i>et al.</i> 2009)
5-Fluorouracil (mean, 535 mg/m ²)	Survey, retrospective	16 of 20 (Pts 1, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 20)	Breast	1 st First@wk 4	Epirubicin, Cyclophosphamide	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Giacalone <i>et al.</i> 1999)++
				2 nd First@wk 24	Vinorelbine	C-section	34	Infant sex and weight NS: Apgar scores 8 and 10. Newborn was anemic but had no malformations and normal body weight for gestational age.	At 80 months, alive and well.	
				2 nd First@wk 24	Vinorelbine	Vaginal	40	Infant sex and weight NS: Apgar scores 9 and 10. Newborn was normal with no malformations and normal body weight for gestational age.	At 40 months, alive and well.	
				2 nd , 3 rd First@wk 24	Doxorubicin, Cyclophosphamide	Vaginal	35	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 60 months, alive and well.	

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd First@wk 25	Mitoxantrone, Cyclophosphamide	C-section	33	Infant sex and weight NS, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn experienced respiratory distress and had normal body weight for gestational age.	At 12 months, alive and well.	
				2 nd , 3 rd First@wk 27	Doxorubicin	C-section	35	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 120 months, alive and well.	
				2 nd , 3 rd First@wk 27	Mitoxantrone, Cyclophosphamide	C-section	33	Infant sex NS: 1,460 g. Apgar scores 8 and 10 at 1 and 5 minutes. Newborn had intrauterine growth retardation (SGA).	At 32 months, alive and well.	
				3 rd First@wk 28	Epirubicin, Cyclophosphamide	C-section	31	Infant sex and weight NS, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn died on day 8, but had normal body weight for gestational age; no etiology was diagnosed. No malformations observed.	--	
				2 nd , 3 rd First@wk 29	Epirubicin, Cyclophosphamide	C-section	35	Infant sex and weight NS, Apgar scores 6 and 10 at 1 and 5 minutes. Newborn had leukopenia and had normal body weight for gestational age.	At 18 months, alive and well.	
				3 rd First@wk 30	Vinorelbine	Vaginal	38	Infant sex and weight NS: Apgar scores 10 and 10. Newborn was normal with no malformations and had normal body weight for gestational age.	At 75 months, alive and well.	
				3 rd First@wk 31	Epirubicin, Cyclophosphamide	C-section	34	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal.	At 10 months, alive and well.	

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd First@wk 31	Doxorubicin, Cyclophosphamide	C-section	34	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 120 months, alive and well.	
				3 rd First@wk 31	Epirubicin, Cyclophosphamide	C-section	33	Infant sex and weight NS, Apgar scores 6 and 10 at 1 and 5 minutes. Newborn experienced respiratory distress and had normal body weight for gestational age.	At 6 months, alive and well.	
				3 rd First@wk 31	Epirubicin, Cyclophosphamide	C-section	34	Infant sex and weight NS, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 16 months, alive and well.	
				3 rd First@wk 32	Vinorelbine	C-section	35	Infant sex and weight NS: Apgar scores 10 and 10. Newborn was normal with no malformations and had normal body weight for gestational age.	At 12 months, alive and well.	
				3 rd First@wk 35	Epirubicin, Cyclophosphamide	Vaginal	37	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 50 months, alive and well.	
5-Fluorouracil (Dose/schedule NS, 5 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 6 Last@wk 24	Cyclophosphamide, Methotrexate	Vaginal	30	Spontaneous preterm labor. Male infant: 1,000 g [SGA], Apgar scores NS. Newborn was 3 rd percentile for body weight, length and head circumference. Newborn appeared normal, apart from respiratory distress and an inguinal hernia.	At 22 months, normal growth and development, and karyotype.	(Giannakopoulos <i>et al.</i> 2000)

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
5-Fluorouracil (600 mg/m ² , 4 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 23	Epirubicin, Cyclophosphamide	C-section	35	Premature rupture of membranes. Female infant: 3,420 g, Apgar score 8. No congenital malformations were noted in the newborn. Mild, transient tachypnea required oxygen support. All blood exams were in normal range.	No	(Ginopoulos <i>et al.</i> 2004)
5-Fluorouracil (2 doses of 500 mg/m ² on days 1 and 4, 1 to 6 cycles (group mean = 4 cycles), 3 to 4 wks apart)	Case series	40 of 57 [Data on pregnancy outcomes available for only 40 pregnancies]	Breast	NS First@wk 11-34 (range) 23 (median) Last@wk 35	Doxorubicin, Cyclophosphamide	60% vaginal, 40% C-section	37 (group mean) (29-42 range; n=52)	Individual pregnancy outcomes not provided. Infant sex and Apgar scores NS: group mean birth weight = 2,890 g (range = 1,289 to 3,977g; n=47). No stillbirths, miscarriages, or perinatal deaths (n=55). Pregnancy outcomes provided for 40 infants (number of infants): normal (44), Down syndrome (1), club foot (1), bilateral ureteral reflux (1). Other health effects (number of infants): breathing difficulties (11), and neutropenia, thrombocytopenia, and subarachnoid hemorrhage (1)	Follow-up on children (ages 2-157 months; n=39). All children except the one with Down syndrome were thought to have normal development by their parents. One other school-age child had attention-deficit/hyperactivity disorder.	(Hahn <i>et al.</i> 2006)
5-Fluorouracil (Dose/schedule NS)	Cohort, retrospective	7 of 72	Breast	2 nd or 3 rd	Doxorubicin, Cyclophosphamide, Paclitaxel, Cisplatin	NS	NS	Individual pregnancy outcomes were not provided. No congenital malformations were diagnosed in the newborns.	No	(Ibrahim <i>et al.</i> 2000)†
5-Fluorouracil (Dose/schedule NS; Pt 10, 3 cycles)	Survey, retrospective	1 of 49 from Table 4 (Pt 10)	Breast	2 nd , 3 rd or 3 rd	Cyclophosphamide, Methotrexate	NS	37	Infant sex, weight and Apgar scores NS. Newborn born alive and without malformation.	No	(Ives <i>et al.</i> 2005)

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
5-Fluorouracil (Dose/schedule NS, 2-6 cycles)	Case series	6 of 18	Breast	NS First@wk 12-33 22 (mean)	Doxorubicin, Cyclophosphamide	NS	NS	Infant sex, weight and Apgar scores NS. Newborns were alive and healthy; no malformations were observed.	At follow-up, normal growth patterns without physical or neurological deficits (n=5 children, oldest child is 42 months).	(Jameel and Jamil 2007)
5-Fluorouracil (400 mg/m ² bolus followed by 2,400 mg/m ² 46-hour infusion, biweekly, 10 cycles)	Case report	1	Colon	1 st , 2 nd , 3 rd First @ wk 13	Oxaliplatin	C-section	33	Premature rupture of membranes. Twins, male and female infants: 2,200 g each, Apgar scores 10 at 1 minute for both. Both were healthy with no malformations.	At 2 years, both were developing normally.	(Jeppesen and Osterlind 2011)
5-Fluorouracil (500 mg/day for 5 days, every 6 wks, 2 cycles)	Case series	2 of 2	Breast	1 st First@wk 2 Last@wk 9	Melphalan	--	--	Induced abortion at gestation wk 10.	--	(Jochimsen <i>et al.</i> 1981)
			Breast	1 st First@wk 1 Last@wk 7	Melphalan	--	--	Spontaneous abortion at gestation wk 10.	--	
5-Fluorouracil 400 mg/m ² bolus followed by 2,400 mg/m ² infusion over 46 hours every 2 wks, 4 cycles	Case report	1	Colorectal	2 nd , 3 rd	Oxaliplatin	C-section	31.5	Female infant: 1,175 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn spent 33 days in the neonatal unit, 1 day on a ventilator. She was hypothyroid.	At 11.75 months of age (adjusted for prematurity), there were no abnormal physical findings apart from a flaky red spot on the top of her head. She was beginning to walk, had normal blood parameters, a normal Denver Developmental Screening Test, and was being treated for gastro-esophageal reflux and hypothyroidism.	(Kanate <i>et al.</i> 2009)
5-Fluorouracil (500 mg/m ² on days 1 and 4 every 21 to 28 days)	Case series	4 of 4	Breast	3 rd First@wk 33	Cyclophosphamide, Doxorubicin	NS	36	Infant sex, weight and Apgar scores NS.	At 65 months, healthy with normal development.	(Kuerer <i>et al.</i> 2002)
				2 nd , 3 rd First@wk 26	Cyclophosphamide, Doxorubicin	NS	40	Infant sex, weight and Apgar scores NS.	At 44 months, healthy with normal development.	

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd First@wk 26	Cyclophosphamide, Doxorubicin	NS	35	Preeclampsia. Infant sex, weight and Apgar scores NS.	At 33 months, healthy with normal development.	
				3 rd First@wk 31	Cyclophosphamide, Doxorubicin	NS	36	Infant sex, weight and Apgar scores NS.	At 33 months, healthy with normal development.	
5-Fluorouracil (Dose/schedule NS, 5 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 2 Last@wk 19	Cyclophosphamide, Epirubicin (1 st), Methotrexate (2nd), Radiation therapy (1 st)	--	--	Induced abortion at gestation wk 19. Male fetus: 280 g (50 th percentile for gestational age). Fetal examination revealed micrognathia, skin syndactyly of the 1 st and the 2 nd fingers of both hands, shortened 2 nd and 3 rd fingers and clinodactyly of the 5 th finger; both feet had a broad forefoot with a short 1 st toe and osseous syndactyly of the 4 th and the 5 th metatarsal bones.	--	(Leyder <i>et al.</i> 2010)
5-Fluorouracil (Dose/schedule NS)	Case report	1	Breast	3 rd First@wk 32 Last@wk 35	Doxorubicin, Cyclophosphamide	C-section	37.5	Female infant: weight and Apgar scores NS. The newborn was healthy.	No	(Logue 2009)
5-Fluorouracil (Pt 1 - 500 mg/m ² , 1 cycle; Pt 2 - 600 mg/m ² , 4 cycles; Pt 3 - 750 mg/m ² , 3 cycles; Pt 4 - 750 mg/m ² , 3 cycles)	Case series	4 of 4	Breast	3 rd First@wk 27	Doxorubicin	C-section	34	Female infant: 2,600g, Apgar score 10 at 1 minute. Newborn had no congenital abnormality or intrauterine growth restriction.	At 17 years, no evidence of impaired intelligence quotient; physical and sexual development was normal.	(Mathelin <i>et al.</i> 2005)
				2 nd , 3 rd First@wk 21 Last@wk 31	Doxorubicin	Vaginal	34	Female infant: 2,820 g, Apgar score 10 at 1 minute. Newborn had no congenital abnormality or intrauterine growth restriction.	At 11 years, no evidence of impaired intelligence quotient; physical and sexual development was normal.	
				2 nd , 3 rd First@wk 21 Last@wk 27	Epirubicin	C-section	34	Female infant: 2,790 g, Apgar score 10 at 1 minute. Newborn had no congenital abnormality or intrauterine growth restriction.	At 3.5 years, no evidence of impaired intelligence quotient, and physical development was normal.	

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd First@wk 25 Last@wk 32	Epirubicin	Vaginal	35	Female infant: 3,690 g, Apgar scores 10 at 1 minute. Newborn had no congenital abnormality or intrauterine growth restriction.	No	
5-Fluorouracil (600 mg/m ² , 2 cycles)	Case report	1	Breast	3 rd	Cyclophosphamide, Epirubicin	C-section	35	Eclamptic seizures at wk 35. Infant sex NS: 1,650 g [SGA], Apgar scores NS. Newborn had no malformations.	No	(Muller <i>et al.</i> 1996)
5-Fluorouracil (500 mg/m ² on day 1 of 21-day cycles, 4 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 13 Last@wk 25	Doxorubicin, Cyclophosphamide, Docetaxel (2 nd , 3 rd)	Vaginal	39	Male infant: 6.8 lbs [3,084 g], Apgar scores normal. Newborn was healthy and had normal blood counts.	No	(Nieto <i>et al.</i> 2006)
5-Fluorouracil (Dose/schedule NS)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 16	Doxorubicin, Cyclophosphamide	Vaginal	38	Male infant: 2,400 g [SGA], Apgar scores 5 and 8 at 1 and 5 minutes. Newborn showed flat nasal bridge, bulbous nasal tip, high-arched palate, syndactyly and radial deviation of the first and second fingers, single transverse palmar creases, cleft between second on third fingers, hypoplasia of the fifth fingers, and a dystrophic nail of the fourth left finger. The brain showed bilateral ventriculomegaly and colpocephaly. There was a bicuspid aortic valve.	At 15 months, he could sit without help and walk unaided. At 3 years, visual evoked potential was normal; growth and neuromotor development were delayed.	(Paskulin <i>et al.</i> 2005)
5-Fluorouracil (Dose/schedule NS)	Cohort, retrospective	2 of 14 from Tables 3 and 4 (Pts 7, 12)	Breast	1 st , 2 nd First@wk 2 Last@wk 26	Doxorubicin, Cyclophosphamide	NS	34	Infant sex NS: 2,170 g, Apgar scores NS. Newborn had no complications or major malformation.	No	(Peres <i>et al.</i> 2001)
				1 st First@wk 5 Last@wk 8	Cyclophosphamide, Methotrexate	--	--	Fetal death [Stillbirth] at gestation wk 25, no malformations.	--	

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
5-Fluorouracil (600 mg/m ² on days 1 and 8, every 4 wks)	Survey, retrospective	1 of 28	Breast	1 st	Methotrexate, Cyclophosphamide	--	--	Spontaneous abortion after 1 st cycle of chemotherapy. [No fetal data reported.]	--	(Ring <i>et al.</i> 2005)
		11 of 28		2 nd and/or 3 rd First@wk 15 – 33 (group range)	Methotrexate, Cyclophosphamide	NS	37 (median); 30-40 (group range)	Intrauterine growth restriction due to placental insufficiency (n=1 pregnancy). Individual pregnancy outcomes were not provided. There were no congenital malformations, and none of the infants had a birth weight lower than the 10 th percentile for gestational age. Another child had a hemangioma on his abdomen deemed not causally related to chemotherapy. Two infants had respiratory distress.	No	
5-Fluorouracil (Dose NS, days 1 and 8 every 4 wks; Pt 1 - cycles NS and Pt 2 - 2 cycles)	Case series	2 of 4 (Pts 1, 3)	Breast	3 rd	Methotrexate, Cyclophosphamide	Vaginal	38	Infant sex, weight, and Apgar scores NS. Newborn was healthy.	At 3 years, in good health.	(Schotte <i>et al.</i> 2000)
			Breast	3 rd First@wk 28	Doxorubicin, Cyclophosphamide	Vaginal, induced	37.5	Infant sex NS: 2,200 g [SGA] . Apgar scores NS. Newborn was normal.	No	
5-Fluorouracil (800 mg 3 wks apart, 2 cycles)	Case report	1	Breast	3 rd First@wk 31 Last@wk 34	Epirubicin, Cyclophosphamide, Radiation therapy	Vaginal	36	Spontaneous preterm labor. Female infant: 1,889 g [SGA] , Apgar score 9 at 5 minutes. Newborn had no congenital anomalies.	At 6 wks, she was doing well.	(Sharma <i>et al.</i> 2009)
5-Fluorouracil (500 mg approx every 3 days, 15 cycles)	Case report	1	Breast	2 nd , 3 rd	None	C-section	NS	Infant sex and Apgar scores NS: 6 lbs 11 oz [3,033 g] . Newborn had no abnormalities until 1.5 hours when it became cyanotic with jerking extremities. After 24 hours of oxygen treatment (34%) there was apparent total recovery.	"The infant has remained well up to the present time" [age NS] .	(Stadler and Knowles 1971)

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
5-Fluorouracil (600 mg 5 days a wk for a month)	Case report	1	Bowel	1 st , 2 nd First@wk 11-12	Radiation diagnostic (1 st)	--	--	Diminished overall volume of amniotic fluid. Induced abortion at gestation wk 16: fetus showed bilateral radial aplasia and absent thumbs, 2 fingers on the left hand and 1 finger on the right hand were absent, a single umbilical artery, hypoplastic aorta, pulmonary hypoplasia, hypoplastic thymus, esophageal aplasia, aplasia of the duodenum, biliary hypoplasia, absent appendix, imperforate anus, common bladder and rectum, renal dysplasia, and aplastic ureters. Authors could not clearly attribute these abnormalities to 5-fluorouracil.	--	(Stephens <i>et al.</i> 1980)
5-Fluorouracil (Dose NS, every 2 wks for 5 months, 10 cycles)	Case report	1	Colon	2 nd , 3 rd First@wk 18 Last@wk 36	Irinotecan	Vaginal	37 + 5 days	Female infant: 5 lb 14 oz [2,665 g], Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was born without complications.	At 4 months, development was normal with no teratogenic effects.	(Taylor <i>et al.</i> 2009)
5-Fluorouracil (Dose/schedule NS)	Case series	1 of 2 (Pt 2)	Breast	1 st , 2 nd , 3 rd First@wk 13	Doxorubicin, Cyclophosphamide, Methotrexate (3 rd)	C-section	35	Elevation of blood pressure to 150/100. Female infant: 2,260 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn showed normal T-cell activity and no evidence of an abnormality.	At 24 months, growth and development were normal.	(Turchi and Villasis 1988)

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
5-Fluorouracil (Dose/schedule NS)	Survey, retrospective	3 of 27 (Pts 1, 2, 26)	Breast	3 rd First@wk 32	Doxorubicin, Cyclophosphamide	C-section	36	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
			Breast	3 rd First@wk 32	Epirubicin, Cyclophosphamide	C-section	40	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.		
			Pancreas	3 rd First@wk 31	Cisplatin	Vaginal	33	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.		
5-Fluorouracil (Pt 1 - 500 mg/m ² , 6 cycles; Pt 2 - 500 mg/m ² , 3 cycles)	Survey, retrospective	2 of 62 [62 pts received chemotherapy while pregnant; the number of pts who received 5-fluorouracil while pregnant was not provided.]	NS	2 nd , 3 rd First@wk 20 Last@wk 35	Epirubicin, Cyclophosphamide	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had bilateral small protuberance on phalanx 5.	No	(Van Calsteren <i>et al.</i> 2010)
			NS	2 nd , 3 rd First@wk 22 Last@wk 28	Doxorubicin, Cyclophosphamide, Radiation therapy (1 st , 2 nd)			Infant sex, weight, and Apgar scores NS. Newborn had doubled cartilage ring in both ears.		
5-Fluorouracil (Dose/schedule NS)	Cohort, retrospective	4 of 21 (Pts 1, 3, 18, 19)	Breast	1 st	Cyclophosphamide, Methotrexate	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Zemlicks <i>et al.</i> 1992b)
				1 st	Cyclophosphamide, Methotrexate, Vincristine, Tamoxifen	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	
				3 rd	Doxorubicin, Cyclophosphamide, Tamoxifen	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	

Appendix C Table 1. 5-Fluorouracil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Cyclophosphamide, Methotrexate	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well, but with intrauterine growth restriction (SGA).	No	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the 5-fluorouracil timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†This paper was not included in the tally of pregnancy outcomes (highlighted in light grey). Ibrahim *et al.* (2000) was not included because it was not possible to determine the individual treatment regimens of the 7 patients receiving chemotherapy during pregnancy.

††Giacalone *et al.* (1999) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; IUGR=Intrauterine growth retardation; SGA = small for gestational age.

Appendix C Table 2. 6-Mercaptopurine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Mercaptopurine (Dose/schedule NS)	Case series, retrospective	5 of 7 from Table 1 (Pts 1, 3, 5, 6, 7)	Leukemia, ALL	1 st [see note in reference column]	Vincristine, Doxorubicin, Methotrexate, Cyclophosphamide	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 19 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
			Leukemia, AML	1 st	Doxorubicin, Cytarabine, Methotrexate	Vaginal	36	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, ALL	2 nd	Doxorubicin, Vincristine, Cyclophosphamide, Methotrexate	Vaginal	38	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st	Doxorubicin, Cyclophosphamide, Methotrexate	Vaginal	37	Male infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, AML	2 nd	Doxorubicin, Cytarabine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		3 of 4 from Table IV (Pts 2, 3, 4)	Leukemia, CGL	1 st	Busulfan	Vaginal	39	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 12 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, CGL	1 st	Busulfan	Vaginal	37	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, CGL	2 nd	None	C-section	34	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
6-Mercaptopurine (Dose/schedule NS, total dose 4,300 mg)	Case series	1 of 16 (Pt 7)	Non-Hodgkin lymphoma	1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Methotrexate	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn showed no apparent congenital abnormalities.	Authors state that at ages ranging from 3 to 11, all 16 children showed normal growth and development	(Avilés <i>et al.</i> 1990) [†]
6-Mercaptopurine (Dose/schedule NS)	Case series, retrospective	12 of 20 pregnancies [11 of 18 pts] (Table 1: Cases 1, 2, 3, 6, 7, 8, 10, 12, 13, 15, 16, 20; Cases 10 and 16 are 2 pregnancies of the same pt)	Leukemia, ALL	2 nd , 3 rd	None	[Vaginal]	[38]	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 22 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	(Avilés and Niz 1988) [Six of these pregnancies (1, 2, 3, 6, 7, and 8) were first reported in Pizzuto <i>et al.</i> (1980). We counted them only once using Aviles <i>et al.</i> (1988).]
			Leukemia, ALL	1 st , 3 rd	Cyclophosphamide, Methotrexate	[Vaginal]	[38]	Male infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 13 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Methotrexate, Cyclophosphamide, Cytarabine	[Vaginal]	[40]	Female infant: 2,300 g [SGA] , Apgar scores NS. Newborn had no congenital malformations.	At 12 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	1 st , 2 nd , 3 rd	Cytarabine, Methotrexate, Vincristine, Cyclophosphamide	[C-section]	[34]	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had pancytopenia and no congenital malformations. Died of septicemia at 21 days; blood counts were normal at death.	--	
			Leukemia, ALL	2 nd , 3 rd	Cytarabine, Vincristine, Methotrexate	[Vaginal]	[38]	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn had no congenital malformations. Died of gastroenteritis at 90 days.	--	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, Methotrexate	[C-section]	[33]	Female infant: 1,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Doxorubicin, Vincristine, Methotrexate	NS	NS	Female infant: 2,900 g, Apgar scores NS. Newborn had no congenital malformations. [Case 10, pregnancy 1]	At 7 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	1 st , 2 nd , 3 rd	Cytarabine, Doxorubicin, Vincristine, Methotrexate	NS	NS	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	2 nd , 3 rd	Doxorubicin, Vincristine, Methotrexate, Cyclophosphamide	NS	NS	Female infant: 2,700 g, Apgar scores NS. Newborn had pancytopenia and no congenital malformations. At 4 wks, blood counts and bone marrow samples were normal.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, Methotrexate	NS	NS	Male infant: 2,600 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	1 st , 2 nd	Vincristine, Doxorubicin, Methotrexate	NS	NS	Male infant: 2,850 g, Apgar scores NS. Newborn had no congenital malformations. [Case 10, pregnancy 2]	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, Methotrexate, Etoposide	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
6-Mercaptopurine (75 mg daily)	Case series	1 of 5 (Pt 1)	Leukemia, ALL	2 nd , 3 rd First@wk 17	Doxorubicin (2 nd), Vincristine (2 nd), Asparaginase (2 nd), Methotrexate, Cyclophosphamide	Vaginal	[~39]	Female infant: 3,200 g, Apgar scores NS. Newborn was normal.	At 40 months, had normal development and growth.	(Awidi <i>et al.</i> 1983)
6-Mercaptopurine (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd or 2 nd , 3 rd	Behenoyl-ara-C, Daunorubicin, Cytarabine, Mitoxantrone	C-section	34	Female infant: 2,960 g, Apgar scores NS. Newborn was healthy.	At 16 months, no abnormalities.	(Azuno <i>et al.</i> 1995)
6-Mercaptopurine (Dose NS, weekly)	Case series	2 of 2	Leukemia, ALL	1 st First@wk 3 Last@wk 4	Methotrexate, Vincristine	--	--	Spontaneous abortion [at ~6 wks of gestation. No fetal data reported.]	--	(Bergstrom and Altman 1998)
			Leukemia, ALL	1 st , 2 nd	Methotrexate, Vincristine	Vaginal, induced	32	Preeclampsia at 32 wks. Female infant: 4 lb 15 oz [2,240 g] , Apgar scores NS. Newborn was premature; she had no abnormalities.	Subsequent exams [age NS] showed no abnormalities.	
6-Mercaptopurine	Case series, retrospective	1 of 18 (Pt 5)	Leukemia, ALL	3 rd	Vincristine, Methotrexate	NS	No births were premature [Term]	Female infant: 6 lb, 3 oz [2,807 g] , Apgar scores NS. Birth weight was normal [for gestational age] .	At 8 years, normal.	(Blatt <i>et al.</i> 1980)
6-Mercaptopurine (Dose/schedule NS)	Case series, retrospective	1 of 5 (out of 322 total; see note in pregnancy outcomes)	Leukemia, AML	NS [1st, 2nd]	None	--	--	Spontaneous abortion [at ~19 wks of gestation] . Mother died 3 days later. [Note: Of the 5 pregnant patients in this study, this pregnancy was the only one in which chemotherapy was	--	(Boggs <i>et al.</i> 1962)

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								administered during the pregnancy. The remaining 317 patients were all ages and both sexes.]		
6-Mercaptopurine (Dose/schedule NS)	Survey, registry	1 of 3 from Table 5	Leukemia, ALL	2 nd , 3 rd	Cytarabine, Cyclophosphamide, Daunorubicin, Methotrexate, Vincristine, Asparaginase	NS	35.5 (group mean)	Infant sex NS; 2,341 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 9 years, normal phenotype. At 41 to 109 months (group range, n=2), no long-term complications; group mean weight was 65 th percentile.	(Cardonick <i>et al.</i> 2010)
6-Mercaptopurine (75 mg daily, then 100 mg daily)	Case report	1	Leukemia, AML	2 nd , 3 rd [First@wk16]	Methotrexate (2 nd), Vincristine (2 nd)	C-section	37	Preeclampsia [at gestation wk 36]. Male infant: 6 lbs [2,722 g], Apgar score 7. Newborn was normal.	At 2 years, there were no deleterious effects of the chemotherapy.	(Coopland <i>et al.</i> 1969)
6-Mercaptopurine (100 mg daily)	Case report	1	Leukemia, ALL	1 st	Doxorubicin (2 nd), Vincristine (1 st , 2 nd , 3 rd), Methotrexate (1 st , 3 rd), Cytarabine (3 rd)	C-section	36	Male infant: 2,400 g, Apgar scores NS. Newborn was polycythemic and jaundiced but otherwise normal.	At 6 months, growth and development were normal.	(Dara <i>et al.</i> 1981)
6-Mercaptopurine (100 to 150 mg daily)	Case report	1 (1 pt with 2 pregnancies)	Leukemia, CGL	1 st , 2 nd , 3 rd	Radiation therapy (1 st)	Vaginal	36	Spontaneous preterm labor. Infant sex, weight, and Apgar scores NS. Newborn was premature but otherwise unremarkable.	At approximately 2 years, alive and well.	(Diamond <i>et al.</i> 1960)
				1 st , 3 rd	Busulfan (1 st , 2 nd , 3 rd); Radiation therapy (1 st)	C-section	NS [~8 months]	Female infant: 1,077 g (SGA), Apgar scores NS. Newborn had extreme intrauterine arrest, bilateral microphthalmia, bilateral corneal opacities, and cleft palate. External genitalia were poorly developed except for a prominent clitoris.	At 2 months, infant had grunting respiration and cough. At 10 wks, the infant was found dead. Necropsy revealed disseminated cytomegaly and hypoplasia of thyroid and ovaries, among other abnormalities.	

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Mercaptopurine (100 mg daily)	Case series	1 of 3 (Pt 1)	Leukemia, AML	3 rd	Vincristine, Methotrexate	Vaginal	34	Premature rupture of membranes. Female infant: 2,350 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had a cushingoid appearance.	At 8 wks, weight and height were normal for gestational age.	(Doney <i>et al.</i> 1979)
6-Mercaptopurine (Dose/schedule NS)	Case series	3 of 5 (Pts 2, 3, 4)	Leukemia, AML	1 st First@wk 1 [Last@~wk6]	Methotrexate, Doxorubicin (1 st), Vincristine (1 st , 3 rd), Daunorubicin (3 rd), Cytarabine (3 rd)	Vaginal	38	Female infant: 2,800 g, Apgar scores 8 and 10 at 1 and 5 minutes.	At 7 years, development was normal.	(Feliu <i>et al.</i> 1988)
			Leukemia, AMML	1 st First@wk 1 [Last@~month 2]	Methotrexate, Cytarabine (2 nd)	Vaginal	38	Male infant: 2,750 g, Apgar scores 6 and 8 at 1 and 5 minutes.	At 7 years, development was normal.	
			Leukemia, ALL	1 st , 2 nd	Daunorubicin, Vincristine, Cytarabine	--	--	Mother and fetus died at 23 wks of gestation. Fetal morphology was normal.	--	
6-Mercaptopurine (Pt 1 - 50 mg daily; Pt 4 - 150 mg, reduced to 75 mg daily; Pt 6 - 325 mg, reduced to 50 mg daily; Pt 7 - 250 mg, reduced to 100 mg daily)	Case series	4 of 8 (Pts 1, 4, 6, 7)	Leukemia, acute stem cell	1 st , 2 nd , 3 rd	None	Vaginal	At term	Female infant: 6 lb 8 oz [2,948 g], Apgar scores NS. Newborn was normal and healthy.	To date, she was completely healthy [age NS].	(Frenkel and Meyers 1960)
			Leukemia, AGL	2 nd , 3 rd	None	Vaginal	NS [9 months]	Female infant: weight and Apgar scores NS. Newborn was well.	At 2 years, she remained well.	
			Leukemia, AGL	2 nd , 3 rd	Methotrexate (3 rd)	Vaginal	NS [near term]	Female infant: 5 lb 4 oz [2,381 g], Apgar scores NS. Newborn was normal, clinically and hematologically.	At 17 months, normal and doing well.	

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	3 rd	None	Vaginal	NS [~7 months]	Spontaneous preterm labor. Female infant: 3 lbs 8 oz [1,586 g], Apgar scores NS. Newborn was premature but hematologically and otherwise normal.	At 6 months, she was well.	
6-Mercaptopurine (70 mg/m ² for 10 days)	Case report	1	Leukemia, AML	2 nd , 3 rd	Mitoxantrone, Behenoyl-ara-C	C-section	35 + 4 days	Preterm labor at beginning of 3 rd trimester was treated and resolved. Premature rupture of membranes at 35 wks + 4 days of gestation. Male infant: 1,882 g [SGA], Apgar scores NS. Newborn had low birth weight and was thrombocytopenic and leukocytopenic but had no anomalies or chromosomal abnormalities.	No	(Gondo <i>et al.</i> 1990)
6-Mercaptopurine (Dose/schedule NS)	Case series	4 of 17 (Pts 12, 15, 16, 17)	Leukemia, AML	2 nd First@wk 19	Daunorubicin, Cytarabine	NS	36	Female infant: weight and Apgar scores NS. Newborn had no malformations.	No	(Greenlund <i>et al.</i> 2001)
				2 nd First@wk 20	Vincristine	NS	36	Male infant: 2,130 g [SGA], Apgar scores NS. Newborn had no malformations.	No	
				2 nd First@wk 20	None	--	--	Fetal death [stillbirth; No fetal data were reported.]	--	
				3 rd First@wk 29	Methyl-GAG	NS	36	Female infant: 2,530 g, Apgar score 6. Newborn had no malformations.	No	
6-Mercaptopurine (Dose/schedule NS)	Case report	1	Leukemia, ALL	3 rd First@wk 30 Last@wk 34	Cyclophosphamide (2 nd , 3 rd), Daunorubicin (2 nd), Vincristine (2 nd , 3 rd), Asparaginase (2 nd , 3 rd), Cytarabine, Methotrexate (intrathecal)	Vaginal	36	Transient oligohydramnios. [Spontaneous preterm labor.] Male infant: 2,150 g [SGA], Apgar scores 2 and 8 at 1 and 5 minutes. Newborn was normal, with normal hematology and neurology.	No	(Hansen <i>et al.</i> 2001)

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								There was mild meconium aspiration syndrome and jaundice, which were successfully treated.		
6-Mercaptopurine (Dose/schedule NS)	Case report	1	Leukemia, ALL	1 st [First@ ~month 2]	Nitrogen mustard (1 st)	--	--	Spontaneous abortion [within 1 month after 6-mercaptopurine treatment was initiated]. Fetus was grossly normal, no histological evaluation performed.	--	(Hoover and Schumacher 1966)
6-Mercaptopurine (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Doxorubicin, Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, Vincristine, Aclarubicin, Cytarabine, Cycloctidine, ATRA, Mitoxantrone, Idarubicin, Asparaginase	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994)†
6-Mercaptopurine (Dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Doxorubicin (2 nd), Vincristine, Asparaginase (2 nd) Methotrexate, Cyclophosphamide	C-section	NS [at term]	Female infant: 3,800 g, Apgar scores NS. Newborn was clinically normal, with slight leucopenia (resolved after 2 wks).	At follow-up [age NS], child was progressing well with normal blood counts and no neurological disturbance or congenital abnormality.	(Khurshid and Saleem 1978)
6-Mercaptopurine (50 mg daily)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Vincristine, Cyclophosphamide (3 rd), Cytarabine (3 rd), Methotrexate (intrathecal, 3 rd)	Vaginal	38	Male infant: 6 lb 8.5 oz [2,963 g], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was normal.	At 7 months, he continued to thrive and had a normal karyotype.	(Krueger <i>et al.</i> 1976)
6-Mercaptopurine (Dose/schedule NS)	Case series	3 of 12 (Pts 1, 5, 8)	Leukemia, CML	NS	Radiation therapy	Vaginal	35	Spontaneous preterm labor. Infant sex and Apgar scores NS: 4 lbs 9 oz [2,070 g]. Newborn was premature.	Authors state that at ages ranging from 3 months to 10 years, no congenital abnormalities or blood dyscrasia.	(Lee <i>et al.</i> 1962)

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, CML	NS	Radiation therapy, Busulfan	Vaginal	34	Spontaneous preterm labor. Infant sex and Apgar scores NS: 4.5 lbs [2,041 g] . Newborn was premature.		
			Leukemia, ALL	NS	None	Vaginal	38	Infant sex, weight, and Apgar scores NS. Newborn was normal.		
6-Mercaptopurine (50 mg every other day)	Case series, retrospective	1 of 29 [only 1 pt treated with cancer during pregnancy; remainder of pts were exposed to chemotherapy in childhood]	Leukemia, acute	1 st , 2 nd , 3 rd	NS	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had an asymptomatic cardiac murmur of unknown type.	No	(Li and Jaffe 1974)
6-Mercaptopurine (Pt 1 - 2.5 mg/kg bw daily; Pt 2 - 3.5 mg/kg bw daily)	Case series	2 of 2	Leukemia, AML	2 nd , 3 rd First@wk 14	Radiation therapy (2 nd)	Vaginal	NS [~28]	Spontaneous preterm labor. Female infant: 1,340 g, Apgar scores NS. Newborn was premature but normal.	At 2 years, normal in every respect.	(Loyd 1961)
			Leukemia, AML	3 rd	None	Vaginal	NS	Infant sex and Apgar scores NS: 6 lb 10 oz [3,004 g] . Newborn was normal.	No	
6-Mercaptopurine (50 mg twice daily)	Case report	1	Leukemia, AML	1 st , 2 nd , 3 rd	None	Vaginal	32	[Spontaneous preterm labor.] Male infant: 1,810 g, Apgar scores NS. Newborn was premature and anemic but had no physical malformations.	At 9 months, he weighed 7,240 g, had mild normochromic normocytic anemia, and the spleen was just palpable.	(McConnell and Bhoola 1973)
6-Mercaptopurine (2.5 mg/kg bw/day)	Case report	1	Leukemia, ALL	1 st	None	Vaginal	NS [~ 7 months]	Spontaneous preterm labor. Infant sex and Apgar scores NS: 3 lb 3 oz [1,446 g] . Newborn seemed healthy, but died at 48 hours. Autopsy revealed no congenital	--	(Merskey and Rigal 1956)

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								deformity or hematological abnormality; well-defined hyaline membrane and poor aeration of alveoli.		
6-Mercaptopurine (70 mg daily)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25 Last@wk 31	Behenoyl-ara-C, Daunorubicin	C-section	33 + 6 days	Intrauterine growth restriction. Premature separation of placenta. Female infant: 1,410 g [SGA], Apgar scores 1 and 8 at 1 and 5 minutes. Newborn was severely premature with no visible congenital anomaly.	At 5 months, she was well with no neurologic or hematologic abnormalities.	(Morishita <i>et al.</i> 1994)
6-Mercaptopurine (Dose/schedule NS)	Survey, retrospective	1 of 4 from Table 3 (Pt 15)	Leukemia, ALL	1 st , 2 nd , 3 rd First@wk 3	Cyclophosphamide	NS	NS	Placenta abruption (placental detachment) Stillbirth. Polydactyly.	--	(Mulvihill <i>et al.</i> 1987)
6-Mercaptopurine (Dose/schedule NS)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd , 3 rd	None	Vaginal	1 month before term [NS]	[Spontaneous preterm labor.] Male infant: weight and Apgar scores NS. Newborn was normal in all respects.	At 1.5 years, he remained normal.	(Neu 1962)
6-Mercaptopurine (Pt 1 - 200 mg daily; Pt 3 - 100 mg daily; Pt 4 - 150 mg daily)	Case series	3 of 5 (Pts 1, 3, 4)	Leukemia, AML	2 nd First@wk 22	None	--	--	Mother died suddenly in gestation wk 23. Fetus was normal by external examination.	--	(Nicholson 1968)
			Leukemia, ALL	1 st , 2 nd First@wk 11	None	--	--	Mother died at gestation wk 19. [No fetal data reported.]	--	
			Leukemia, ALL	3 rd First@wk 32	None	Vaginal	33	Spontaneous preterm labor. Female infant: 2,185 g, Apgar scores NS. Newborn survived.	No	
6-Mercaptopurine (60 mg/m ² daily)	Case report	1	Leukemia, ALL	2 nd First@wk 23.5 Last@wk 27.5	Vincristine (1 st , 2 nd), Methotrexate (intrathecal, 1 st) Cyclophosphamide, Asparaginase, Daunomycin [Daunorubicin], Radiation therapy	Vaginal	34	Premature rupture of membranes. Female infant: 2,380 g, Apgar score 8 at 5 minutes. Newborn was well developed but was hydropic with marked abdominal distention, slight	At 1 year, development was normal.	(Okun <i>et al.</i> 1979)

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								cardiomegaly, and severe bone marrow suppression. She was treated with blood transfusions and with digitalis and diuretics for congestive heart failure.		
6-Mercaptopurine (150 mg daily)	Case report	1	Leukemia, AML	2 nd [First@ ~wk21]	None	Vaginal	NS [~22]	Spontaneous preterm labor 3 days following treatment. Male infant: 1 lb 5 oz [595 g], Apgar scores NS. Newborn died after 3 hours.	--	(O'Leary and Bepko 1963)
6-Mercaptopurine (50 mg daily)	Case report	1	Leukemia, acute	NS	None	Vaginal	NS	Stillbirth. Examination of the blood did not reveal leukemia.	--	(Parekh <i>et al.</i> 1959)
6-Mercaptopurine (Schedule NS; total doses: Pt 1 – 5,950 mg Pt 2 – 15,800 mg Pt 3 – 18,300 mg Pt 6 – 250 mg Pt 7 – 4,000 mg Pt 8 – 1,000 mg)	Case series	6 of 9 (Pts 1, 2, 3, 6, 7, 8 from Table 2)	Leukemia, ALL	2 nd , 3 rd	None	Vaginal	38	Female infant: 2,800 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 15 years, alive and healthy.	(Pizzuto <i>et al.</i> 1980)† [This case series is included in Aviles 1988 (1988)]
				1 st , 3 rd	Methotrexate, Cyclophosphamide	Vaginal	38	Male infant: 3,000 g, Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 7 years, alive and healthy.	
				1 st , 2 nd , 3 rd	Vincristine, Methotrexate, Cyclophosphamide, Cytarabine	Vaginal	40	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 6 years, alive and healthy.	
				1 st , 2 nd , 3 rd	Cytarabine, Methotrexate, Vincristine, Cyclophosphamide	C-section	34	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had no apparent congenital malformations but was pancytopenic. At 21 days, died from septicemia.	--	

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd	Cytarabine, Vincristine, Methotrexate	Vaginal	38	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations. At 90 days, died from gastroenteritis.	--	
				1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, Methotrexate	C-section	33	Female infant: 1,900 g, Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 16 months, alive and healthy.	
6-Mercaptopurine (150 mg daily in 1 st cycle, 100 g daily decreased to 25 g in 2 nd cycle)	Case report	1	Leukemia, AMML	1 st , 3 rd	None	Vaginal	34	Spontaneous premature rupture of membranes. Male infant: 2,100 g, Apgar scores NS. Newborn was in good condition without apparent anomalies.	At 3 months, growth was normal.	(Ravenna and Stein 1963)
6-Mercaptopurine (Dose NS, daily)	Survey, retrospective	1 of 7 (Pt 1)	Leukemia, ALL	2 nd , 3 rd	Vincristine	C-section	37	Male infant: 2,960 g, Apgar score 9 at 5 minutes. Newborn was healthy.	At 4 years, he was healthy and in the 98 th percentile for height and weight.	(Reynoso <i>et al.</i> 1987)
6-Mercaptopurine (150-200 mg daily)	Case report	1	Leukemia, AML	3 rd	None	Vaginal	38	Female infant: 2,778 g, Apgar scores NS. Newborn was in good condition.	No	(Rigby <i>et al.</i> 1964)
6-Mercaptopurine (Pt 2 - 150 mg daily, decreased to 100 mg daily; Pt 3 - 175 mg daily for 3 days; Pt 4 - 25-150 mg daily)	Case series	3 of 4 (Pts 2, 3, 4)	Leukemia, AGL	1 st , 2 nd	Aminopterin, Demecolcin (2 nd)	Vaginal	NS [~ 6 months]	Spontaneous preterm labor. Male infant: 730 g, Apgar scores NS. Newborn was premature, had no malformations, and died at 12 hours of respiratory difficulty.	--	(Rothberg <i>et al.</i> 1959)
				2 nd	None	--	--	Mother died [at ~5 months; infant delivered via C-section, postmortem]. Male infant: 995 g, Apgar scores NS. Newborn was premature, had respiratory difficulties, and died at 2 hours.	--	

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st , 2 nd , 3 rd	None	Vaginal	At term	Male infant: 6 lbs 9.5 oz [2,991 g], Apgar scores NS. Newborn had no abnormalities.	At 6 wks, he was healthy and blood counts were normal.	
6-Mercaptopurine (Pt 1 - dose/schedule NS, total 2,100 mg; Pt 3 - 50 mg daily, total 7,000 mg)	Case series	2 of 6 (Pts 1 and 3)	Leukemia, AML	3 rd	Daunorubicin (2 nd , 3 rd), Cytarabine (2 nd , 3 rd)	Vaginal, induced	32	Labor was induced because mother was seriously ill. Female infant: 2,041 g, Apgar score 9 at 1 minute. Newborn was normal.	At 5 years, no congenital or developmental abnormalities.	(Roy <i>et al.</i> 1989)
				2 nd , 3 rd	None	Vaginal	Near term [NS]	Male infant: weight and Apgar scores NS. Newborn was normal.	No	
6-Mercaptopurine (60 mg/m ² daily)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Daunorubicin (2 nd), Vincristine (2 nd), Asparaginase (2 nd) Cyclophosphamide, Cytarabine, Methotrexate (IT), Radiation therapy	Vaginal	40	Female infant: weight and Apgar scores NS. Newborn was healthy, had a full head of hair, and no abnormalities. Cytogenetic analysis of lymphocytes showed a normal karyotype but some chromosome breakage and a ring chromosome.	No	(Schleuning and Clemm 1987)
6-Mercaptopurine (100 mg daily)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 26 Last@wk 33	None	Vaginal	39	Female infant: 7 lb 14 oz [3,572g], Apgar scores NS. Newborn was alive; blood count and differential were normal.	No	(Schumacher 1957)
6-Mercaptopurine (150 mg daily)	Case report	1	Leukemia, lymphocytic (probably sub-acute)	1 st , 2 nd , 3 rd	None	Vaginal	Full term [38]	Male infant: 7 lb 6.5 oz [3,359 g], Apgar scores NS. Newborn was normal.	At 6 months, remained in good health.	(Sinykin and Kaplan 1962)
6-Mercaptopurine (50-200 mg daily)	Case series	1 of 4 (Pt 19)	Leukemia, AGL	1 st , 2 nd	Aminopterin, Demecolcine	Vaginal	NS [~4 months]	Spontaneous abortion: Fetus, sex NS, weighted 1 lb 9 oz [706 g], had no malformations, and died at 19 hours.	--	(Smith <i>et al.</i> 1958)
6-Mercaptopurine (50 mg/day)	Case report	1	Leukemia, AML	1 st , 2 nd , 3 rd	Colcemid (2 nd , 3 rd), Methyl-GAG (2 nd , 3 rd)	Vaginal	7 th month	Male infant: 1,730 g, Apgar scores NS. Newborn showed no evidence of developmental abnormalities.	No	(Stevenson <i>et al.</i> 1966)

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Mercaptopurine (200 mg daily)	Case report	1	Leukemia, ALL	3 rd First@wk 36	None	Vaginal	At term	Infant sex and Apgar scores NS, 7 lb 4 oz [3,289 g]. Newborn was normal.	No	(Stewart 1964)
6-Mercaptopurine (350 mg for 5 days every 2 wks)	Case series	1 of 2 (Pt 1)	Leukemia, ALL	2 nd , 3 rd	Vincristine, Daunorubicin (2 nd), Asparaginase (2 nd), Methotrexate	C-section	37	Twin infants, male and female: 2,500 g (male) and 2,400 g (female), Apgar scores NS. Both newborns were normal at physical examination with normal T-cell populations. At 24 hours, both newborns had diarrhea and were lethargic, and the female was also hypotonic; full recovery was completed by 2 wks.	At 54 months, both children are normal with no evidence of immunologic suppression.	(Turchi and Villasis 1988)
6-Mercaptopurine (100 mg 5 days per wk and 50 mg 2 days per wk)	Case report	1	Leukemia, APL	1 st , 2 nd	ATRA (1 st)	Vaginal, induced	34	Male infant: 2,490 g, Apgar scores 6 and 10 at 1 and 5 minutes. Newborn was healthy and without anomalies, but there was [respiratory] distress and mild jaundice associated with prematurity.	At 9 months, growth and development were normal.	(Valappil <i>et al.</i> 2007)
6-Mercaptopurine (50 mg/m ² daily for 40 days)	Survey, retrospective	1 of 62 [62 pts received chemotherapy while pregnant; the number of pts who received 6-mercaptopurine while pregnant was not provided]	NS	2 nd , 3 rd First@wk 24 Last@wk 32	Vincristine, Daunomycin, Cyclophosphamide, Asparaginase, Methotrexate	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had a hemangioma.	No	(Van Calsteren <i>et al.</i> 2010)
6-Mercaptopurine (Dose/schedule NS)	Case report	1	Leukemia, acute	1 st , 2 nd , 3 rd	None	Vaginal	NS	Female infant: 2,760 g, Apgar scores NS. Newborn was healthy.	She continued normally and in good health [age NS, at least 8 years].	(Wegelius 1975)

Appendix C Table 3. 6-Mercaptopurine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Mercaptopurine (Dose/schedule NS)	Cohort, retrospective	1 of 21 (Pt 11)	Non-Hodgkin lymphoma	1 st	None	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
6-Mercaptopurine (1,100 mg total/schedule NS)	Survey, retrospective	1 of 48 (Table 2: Pt 3)	Leukemia, CML	1 st First@wk6 Last@wk10	Busulfan	--	--	Induced abortion at gestation wk 16. [No fetal data reported.]	--	(Zuazu <i>et al.</i> 1991)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the 6-mercaptopurine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). In order to avoid counting the same cases more than once, we did not include the following studies: (Pizzuto *et al.* 1980, Avilés *et al.* 1990). The cases in Aviles *et al.* (1990) were not included in the text analysis because they were reported in a subsequent retrospective case series (Avilés *et al.* 1991). The case series reported in Pizzuto *et al.* (1980) was not included because these patients were included in Aviles *et al.* (1988). Kawamura *et al.* (1994) was not included in the text analysis because of a lack of individual data on timing of exposure, co-treatments, and pregnancy outcomes.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AGL = acute granulocytic leukemia; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; AMML = acute myelomonocytic leukemia; APL = acute promyelocytic leukemia; CML = chronic myelogenous leukemia; CGL = chronic granulocytic leukemia; ATRA = all-*trans* retinoic acid; behenoyl-ara-C = behenoyl cytosine arabinoside; IT = intrathecal; SGA = small for gestational age.

Appendix C Table 4. 6-Thioguanine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Thioguanine (5 X 80 mg, schedule NS)	Case report	1	Leukemia, AML	1 st First@wk 5 Last@wk 5	Cytarabine (1 st), Daunorubicin (1 st)	C-section	“At the expected date” [NS]	Polyhydramnios. Female infant: 2,800 g, Apgar scores 2, 7, and 6 at 1, 5, and 10 minutes. Newborn was treated for severe respiratory distress associated with choanal stenosis and pneumothorax. She had mild hypotelorism; severe brachycephaly; hypoplasia of the anterior cranial base, supra-orbital structures, and naso- and oropharynx; premature closure of both coronal sutures and the metopic suture; bilateral 4-finger hands with hypoplastic thumbs; bilateral absent radii; small ostium secundum-type atrial septal defect.	At 13 months, she was underweight, had mild generalized hypotonia, and slightly retarded motor milestones; fine motor development and social development were normal. Her head appeared mesocephalic.	(Artlich <i>et al.</i> 1994)
6-Thioguanine (70 mg/m ² daily, days 12-17; 2 cycles, 4 wks apart)	Case report	1	Leukemia, AML	3 rd First@wk33 Last@wk 37	Cytarabine	Vaginal	38	Male infant: 2,948 g, Apgar scores NS. Newborn was normal with normal chromosomal analysis. After 48 hours he developed jaundice (resolved by day 8).	At 5 months, developing normally.	(Au-Yong <i>et al.</i> 1972)
6-Thioguanine (80 mg every 12 hours for 5 days, 3 cycles)	Case series	1 of 5 (Pt 5)	Leukemia, acute (erythroleukemia)	2 nd , 3 rd First@~wk 26	Doxorubicin, Cytarabine	Vaginal	[~36]	Female infant: 2,980 g, Apgar scores NS. Newborn was normal.	At 1 month, normal.	(Awidi <i>et al.</i> 1983)
6-Thioguanine (100 mg/m ² twice a day, days 1-9)	Case report	1	Leukemia, APL	2 nd First@wk 21	Cytarabine, Doxorubicin, Vincristine	C-section	30	Preeclampsia at days 5 and 15 of chemotherapy was treated and resolved. Male infant: 1,320 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was normal with normal blood work. At 20 minutes, he experienced tachypnea and progressive respiratory failure requiring intermittent ventilation. By 3.5	At 70 days, infant discharged from the hospital in excellent condition with normal hematological values and karyotype.	(Bartsch <i>et al.</i> 1988)

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								hours, he had developed severe respiratory distress syndrome requiring intubation (resolved by 6 days after treated with surfactant).		
6-Thioguanine (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd	Cytarabine, Daunorubicin	Vaginal, induced	34	Female infant: 2,470 g, Apgar scores 6 and 7 at 1 and 5 minutes. Newborn was normal.	At 12 months, well.	(Catanzarite and Ferguson 1984)
6-Thioguanine (100 mg/m ² twice a day, days 1-7)	Case report	1	Leukemia, APL	2 nd First@wk 22	Cytarabine (2 nd , 3 rd), Doxorubicin	C-section	28	Intrauterine growth restriction at 28 wks of gestation and no response to nonstress test at 28 wks of gestation. Male infant: 1,140 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal; placenta had multiple infarcts but no leukemia infiltration.	At 14 months, normal chromosomal analysis. At 20 months normal physical and psychological assessment.	(D'Emilio <i>et al.</i> 1989)
6-Thioguanine (160 mg twice a day for 5 days; 3 cycles, 5 days apart)	Case report	1	Leukemia, AMML	3 rd	Cytarabine	C-section	39	Male infant: 3,200g, Apgar scores 6 and 9 at 1 and 5 minutes. Newborn showed no signs of bone marrow depression and chromosome analysis was normal. There was no congenital abnormality and no evidence of leukemia in the infant or the placenta.	At 15 months, excellent health and normal development.	(de Souza <i>et al.</i> 1982)
6-Thioguanine (Pt 2 - 90 mg/m ² twice a day for 7 days; Pt 3 - 2 cycles: 90 mg/m ² twice a day for 7 days (first cycle), 118 mg/m ² twice a day for 7 days (second cycle 1 wk later))	Case series	2 of 3 (Pts 2 and 3)	Leukemia, AML	2 nd	Hydroxyurea, Daunorubicin, Cytarabine, Vincristine	--	--	Induced abortion at gestation wk 21. Male fetus: 308 g. Fetus had no external defects or gross abnormalities in organogenesis, and had normal organ weights, except for an enlarged spleen.	--	(Doney <i>et al.</i> 1979)
				3 rd	Hydroxyurea, Daunorubicin, Cytarabine, Vincristine	Vaginal	31	Spontaneous preterm labor at 4 wks after admission. Male infant: 2,130 g, Apgar scores 7 and 8 at 1 and 5 minutes. During the first 2 days the	At 4 months, experiencing mild infections. At 4.5 and 13.5 months, Denver Developmental Screening tests were normal. At 13.5 months, complete blood	

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								premature newborn was anemic, hyponatremic, hyperkalemic, hypocalcemic, and hypoglycemic – resolved within 7 months.	count and general physical examination were unremarkable, but growth parameters were depressed (< 3 rd percentile).	
6-Thioguanine (14 x 160 mg, 2 cycles)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd First@wk 18/19	Cytarabine (2 nd , 3 rd), Daunorubicin (2 nd , 3 rd), Methotrexate (2 nd , 3 rd)	Vaginal	39	Female infant: weight and Apgar scores NS. Newborn was healthy.	No	(Ebert <i>et al.</i> 1997)
6-Thioguanine (Dose/schedule NS)	Case series	1 of 5 (Pt 5)	Leukemia, AML	2 nd First@wk 20	Daunorubicin, Cytarabine	Vaginal	32	Infant sex NS: 1,500 g, Apgar scores 6 and 7 at 1 and 5 minutes. Newborn was morphologically normal.	No	(Feliu <i>et al.</i> 1988)
6-Thioguanine (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd	ATRA, Daunorubicin, Cytarabine (2 nd , 3 rd), Mitoxantrone (2 nd , 3 rd)	Vaginal, induced	35	Female infant: 2,490 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was healthy and had no physical abnormalities.	At 4 months, development has been without complications.	(Giagounidis <i>et al.</i> 2000)
6-Thioguanine (160 mg/day for 5 days, 2 cycles)	Case report	1	Leukemia, AML	3 rd	Daunorubicin (2 nd , 3 rd), Cytarabine(2 nd , 3 rd)	Vaginal	37	Male infant: 2,880 g, Apgar scores NS. Newborn was healthy and normal.	At 16 months, normal growth and development.	(Gokal <i>et al.</i> 1976)
6-Thioguanine (Dose/schedule NS)	Case series	2 of 17 from Table II (Pts 9 and 11)	Leukemia, AML	2 nd , 3 rd First@wk 26	Daunorubicin, Cytarabine	NS	38	Male infant: 3,240 g, Apgar score 8. Newborn had no malformations.	No	(Greenlund <i>et al.</i> 2001)
				2 nd , 3 rd First@wk 24	Doxorubicin, Cytarabine, Vincristine	NS	31.5	Female infant: 1,135 g [SGA], Apgar scores NS. Newborn had no malformations.		
6-Thioguanine (Dose/schedule NS)	Case series, retrospective	1 of 14 from Table 1 (Pt 7)	Leukemia, AML, ALL	3 rd First@wk 34	Vincristine, Cytarabine	NS	NS	Infant sex, weight and Apgar scores NS. Newborn was normal, but had low hemoglobin.	At 26 months, constant cold, weight < 10 th percentile. Growth was 10 th percentile. Immune function test and complete blood count (CBC) were normal.	(Gulati <i>et al.</i> 1986)
6-Thioguanine (Dose/schedule NS)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25	Cytarabine, Daunorubicin (3 rd)	Vaginal	37	Female infant: 2,990 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal, both physically and cytogenetically.	No	(Hamer <i>et al.</i> 1979)

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Thioguanine (120 mg/day for 5 days; 2 cycles, 5 days apart)	Case report	1	Leukemia, AML	1 st First@wk 10	Cytarabine (1 st , 2 nd), Vincristine (2 nd), Rubidomycin [Daunorubicin](2 nd)	--	--	Induced abortion at gestation wk 20. Female fetus: macroscopically and microscopically normal with normal karyotype and no evidence of blood dyscrasia.	--	(Lilleyman <i>et al.</i> 1977)
6-Thioguanine (100 mg/m ² daily for 5 days; 4 cycles, 4 wks apart)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 22 Last@wk 34	Daunorubicin (2 nd), Cytarabine	Vaginal	40	Male infant: 2,860 g [SGA], Apgar scores NS. Newborn was physically normal, no visual or hearing defects were detected; blood, bone marrow, cytogenetic analysis, and electrocardiography were all normal.	At 7 months, normal in every aspect.	(Lowenthal <i>et al.</i> 1978)
6-Thioguanine (100 mg twice a day for 1 wk, 3 cycles)	Case report	1	Leukemia, AML	3 rd First@wk 28 Last@wk 33	Cytarabine	Vaginal	39	Female infant: 2,835 g, Apgar scores NS. Newborn was normal and healthy; chromosome studies were normal.	At 30 months, normal physical and mental development.	(Manoharan and Leyden 1979)
6-Thioguanine (2.5 mg/kg daily)	Case report	1 (1 pt with 2 pregnancies)	Leukemia, AML	2 nd First@wk 20	Cytarabine	--	--	Induced abortion at gestation wk 24. Male fetus: 2 lb 3 oz [992 g]. No congenital abnormalities were noted at autopsy. Tissue culture showed 2 normal male spreads, 2 spreads with trisomy C, and 1 cell with trisomy C and 1 very abnormal chromosome.	--	(Maurer <i>et al.</i> 1971)
				[1 st]	Cytarabine	--	--	Induced abortion. Tissue culture showed no abnormal chromosomes.		
6-Thioguanine (2.5 mg/kg orally every other day)	Case series	2 of 20 (only 2 pts treated during pregnancy)	Leukemia, AML	NS [at least 1 st]	Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	(Moreno <i>et al.</i> 1977)
			Leukemia, AML	NS [at least 1 st]	Cytarabine	Vaginal	Term	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	At 2 years, normal and well.	

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Thioguanine (100 mg twice a day for 7 days; 4 cycles, 3 wks apart)	Case series	2 of 2	Leukemia, AML	3 rd First@wk 27	Daunorubicin, Cytarabine	Vaginal	40	Male infant: 5,000 g, Apgar scores NS. Blood count and karyotype were normal.	At 6 months, remains well.	(O'Donnell <i>et al.</i> 1979)
			Leukemia, ALL	2 nd , 3 rd First@wk 15	Daunorubicin, Cytarabine	--	--	Severe preeclamptic toxemia at gestation wk 29. Intrauterine death [stillbirth] at gestation wk 30. No congenital abnormalities were noted.	--	
6-Thioguanine (45 mg/m ² daily for 7 days followed by a 7-day rest period, 4 cycles)	Case report	1	Leukemia, AGL	2 nd , 3 rd First@wk 25	Cytarabine, Vincristine	NS	39	Infant sex NS: 2,250 g [SGA], Apgar scores NS. No abnormalities were detected.	At 8 months, developing normally.	(Pawlinger <i>et al.</i> 1971)
6-Thioguanine 1 st pregnancy: 160 mg twice a day for 8 days; 2 nd pregnancy: NS)	Case report	1 (1 woman with 2 pregnancies)	Leukemia, AMML	2 nd First@wk 22	Cytarabine	--	--	Intrauterine death [stillbirth] at gestation wk 26. No fetal abnormalities were noted.	--	(Plows 1982)
				2 nd , 3 rd	Cytarabine	C-section	39	Female infant: 3,133 g, Apgar scores 6 and 8. Newborn was normal.	No	
6-Thioguanine (160 mg/day for 14 days; 3 wks later she began treatment with 120 mg/day for 5 days each wk)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 26	Cytarabine	Vaginal	39	Male infant: 3,540 g, Apgar scores of 9 and 9 at 1 and 5 minutes. Newborn showed no abnormalities.	At 4 months, normal karyotype. At 12 months, developing normally and in excellent health.	(Raich and Curet 1975)
6-Thioguanine (100 mg/m ² twice a day, days 1, 2, 10, and 11 (induction) and days 1, 2, and 3 (maintenance); case 2 received 3 induction cycles)	Case series	2 of 2	Leukemia, AML	2 nd , 3 rd First@wk 25	Cytarabine, Daunomycin [Daunorubicin], Mitoxantrone,	C-section	34	Male infant: 2,220 g, Apgar scores 3, 6, and 8 at 1, 5, and 10 minutes. Newborn required intubation for 7 minutes. His phenotype was rigorously normal; bone X-ray, central nervous system echography, and blood tests were all normal.	Follow-up was uneventful [age NS].	(Requena <i>et al.</i> 1995)
				2 nd , 3 rd First@wk 20	Cytarabine, Daunomycin [Daunorubicin], Mitoxantrone, Etoposide	C-section	34	Female infant: 2,100 g, Apgar scores 6, 7, and 9 at 1, 5, and 10 minutes. Newborn showed no phenotypic abnormalities; radiologic controls, sonograms, and blood tests were normal.	Follow-up has been satisfactory [age NS].	

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Thioguanine (Dose/schedule NS)	Survey, retrospective	3 of 7 (Pts 2, 3, and 7)	Leukemia, CGL	3 rd	Cytarabine, Daunorubicin	Vaginal	34	[Spontaneous preterm labor.] Male infant: 2,290 g, Apgar score 9 at 5 minutes. Newborn had mild thrombocytopenia, resolved within 11 days.	At 18 months, normal growth and development.	(Reynoso <i>et al.</i> 1987)
			Leukemia, AML	2 nd [First@wk 25, table states 3rd]	Cytarabine, Daunorubicin	Vaginal	29	[Spontaneous preterm labor.] Male infant: 1,000 g, Apgar score NS. Newborn showed no malformations at birth, but congenital adherence of the iris to the posterior cornea of the left eye was diagnosed at age 2.		
			Leukemia, AML	2 nd , 3 rd	Cytarabine, Daunorubicin, Cyclophosphamide, Vincristine	Vaginal, induced	39	Male infant: 3,420 g, Apgar score 10 at 5 minutes. Newborn was healthy.		
6-Thioguanine (120 mg twice a day, days 1-5; 2 or 3 cycles, 3 wks apart)	Case series	2 of 6 (Pts 4 and 5)	Leukemia, AML	2 nd First@wk 22	Daunorubicin, Cytarabine	C-section	33 (text) 34 (table)	Serial ultrasound showed poor fetal growth. Male infant: weight and Apgar scores NS. Newborn had Down syndrome.	No	(Roy <i>et al.</i> 1989)
				3 rd	Daunorubicin, Cytarabine	Vaginal, induced	34	Female infant: 1,930 g, Apgar scores NS. Newborn was normal.		
6-Thioguanine (60 mg twice a day for 5 days, monthly)	Case report	1 (1 pt with 2 pregnancies)	Leukemia, acute	1 st , 2 nd , 3 rd	Cytarabine	C-section	38	Male infant: 2,212 g [SGA] , Apgar scores 9 and 9 at 1 and 5 minutes. Physical findings were normal except for distal limb defects. The medial 2 digits of both feet were absent, with intact tarsals; the remaining lateral 3 toes and metatarsals appeared normal; the distal phalanges of both thumbs were absent, and the remnant of the right thumb was very hypoplastic.	At 2 months, normal karyotype. At 16 months, normal development and excellent health.	(Schafer 1981)

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st	Cytarabine	C-section	Term	Female infant: 2,912 g, Apgar scores 9 and 9 at 1 and 5 minutes. Physical findings were entirely normal.	At 2 months, normal karyotype. At 4 months, normal development.	
6-Thioguanine (80 mg/m ² twice a day for 5 days; 5 cycles, 15 days apart)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 27	Cytarabine	Vaginal	35	[Spontaneous preterm labor] Female infant: 1,430 g [SGA] , Apgar scores 8 and 9. Newborn had a mildly decreased platelet count and increased bilirubin on day 4 – resolved by 2 wks; she had a normal karyotype.	At 1 year, normal weight and development; no evidence of any drug-related abnormality.	(Taylor and Blom 1980)
6-Thioguanine (160 mg twice a day for 7 days; 2 cycles, 3 wks apart)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd First@wk24	Doxorubicin, Daunorubicin, Cytarabine	Vaginal	32	Spontaneous preterm labor. Female infant: 2,000 g, Apgar scores NS. Newborn had a premature appearance, but was normal with no obvious clinical abnormalities.	At 13 months, feeding and weight gain are satisfactory, developmental milestones have been normal.	(Tobias and Bloom 1980)
6-Thioguanine (60 mg/m ² daily for 21 days)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 27	Daunorubicin (2 nd), Vincristine (2 nd), Cyclophosphamide, Cytarabine, Methotrexate (intrathecal), Amsacrine (3 rd)	Vaginal	33	Spontaneous rupture of membranes. Male infant: 1,928 g [Table 2 states 1,925 g] , Apgar scores 9 and 10 at 1 and 5 minutes. Newborn's physical examination was unremarkable with normal cerebral ultrasound, hearing, and echocardiography. He exhibited transient myelosuppression that was treated and resolved by day 20, including leukopenia at birth, neutropenia at day 2, anemia and thrombocytopenia at day 3. Treated for a urinary tract infection on day 7.	At 24 months, normal growth and development.	(Udink ten Cate <i>et al.</i> 2009)

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Thioguanine (100 mg/m ² twice a day for 7 days)	Case report	1	Leukemia, AML	2 nd	Doxorubicin (2 nd , 3 rd), Cytarabine (2 nd , 3 rd), Vincristine (3 rd)	C-section	29	Fetal suffering per ultrasonography and cardiotocography at wk 29. Female infant: 1,000 g, Apgar score 6 at 1 minute. Newborn was macroscopically normal, but had hyaline membrane disease and moderate meningeal hemorrhage.	At 3.5 years, doing well, normal weight and hematological parameters.	(Veneri <i>et al.</i> 1996)
6-Thioguanine (Dose/schedule NS)	Case series	3 of 4 (Pts 1, 2, and 4)	Leukemia, AML	2 nd First@wk 17 Last@wk 22	Daunorubicin, Cytarabine	NS	30	Premature rupture of membranes, possibly the result of a medical evaluation of the placenta. Female infant: 1,180 g. Apgar scores and condition of newborn NS. Placenta had myeloblastic infiltration.	At 5 years, normal development and excellent health.	(Volkenandt <i>et al.</i> 1987)
				2 nd First@wk 23	Daunorubicin, Cytarabine	C-section	42	Male infant: 3,840 g, Apgar scores NS. Newborn was healthy, but had 6 toes on his right foot (there is a family history of polydactyly).	At 22 months, normal development and excellent health.	
				2 nd First@wk 15	Daunorubicin, Cytarabine	NS	20	Intrauterine fetal death [spontaneous abortion at gestation wk 20] at 5 wks after initiation of chemotherapy. Fetus (sex NS): 40 g. Autopsy revealed no abnormalities and no leukemic infiltration.	--	
6-Thioguanine (Dose NS, 9 days)	Cohort, retrospective	2 of 21 (Table 1, Pts 12, 16)	Leukemia, CML	1 st	Daunorubicin, Hydroxyurea, Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
			Leukemia, AML	2 nd First@wk 24	Doxorubicin, Cytarabine	--	--	Stillbirth at gestation wk 26: Fetus had bruising and petechiae over multiple areas, otherwise normal.	--	

Appendix C Table 5. 6-Thioguanine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
6-Thioguanine (Dose/schedule data limited - Table 2: Pt 2 – 1 cycle Pt 36 – 2 cycles Pt 26 – 3 cycles Pt 24 – 2 cycles Pt 25 – 1 cycle)	Survey, retrospective	5 of 48 (5 of 56 total pregnancies; Table 2: Pts 2, 36, 26, 24, and 25)	Leukemia, AML	1 st First@wk 11 Last@wk 11	Daunorubicin, Cytarabine, Vincristine	--	--	Spontaneous abortion at 20 days post-chemotherapy. [No fetal data reported.]	--	(Zuazu <i>et al.</i> 1991)
			Leukemia, AML	2 nd First@wk 20 Last@wk 27	Daunorubicin, Cytarabine, Vincristine	C-section	37	Infant: 2,100 g [SGA] , sex and Apgar scores NS. Newborn was premature.	At 3 years, normal.	
			Leukemia, AML	2 nd First@month 5 Last@month 6	Daunorubicin, Cytarabine, Vincristine	Vaginal	NS	Infant: sex, weight, and Apgar scores NS. Newborn had normal outcome.	At 3 years, normal.	
			Leukemia, AML	3 rd First@wk 28	Daunorubicin, Cytarabine, Vincristine	Vaginal	36	Infant: 2,400 g, sex and Apgar scores NS. Newborn was normal with normal karyotype.	At 4 years, normal follow-up.	
			Leukemia, AML	3 rd First@wk 29	Daunorubicin, Cytarabine, Vincristine	--	--	Fetal death [stillbirth] during treatment. C-section postmortem: fetus without macroscopical anomalies.	--	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the 6-thioguanine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AGL = acute granulocytic leukemia; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; AMML = acute myelomonocytic leukemia; APL = Acute promyelocytic leukemia; CGL = chronic granulocytic leukemia; ATRA = all-*trans* retinoic acid; SGA = small for gestational age.

Appendix C Table 6. Actinomycin D – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Actinomycin D (Dose NS; given on day 1 of an 8-day regimen; 4 cycles)	Case report	1	Choriocarcinoma, uterus	NS [2 nd] First@> wk 20	Etoposide, Methotrexate, Cyclophosphamide, Vincristine	Vaginal	32	Spontaneous preterm delivery [spontaneous preterm labor]. Female infant: 1,383 g, Apgar scores 8 and 9. Newborn was developmentally normal.	At 42 months, normal development.	(Brudie <i>et al.</i> 2011)
Actinomycin D (Dose/schedule NS)	Survey, registry	1 of 12 from Table 6	Rhabdomyosarcoma	2 nd , 3 rd	Vincristine, Cyclophosphamide	C-section	33	Infant sex NS: 2,948 g, Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 5.3 years, normal phenotype.	(Cardonick <i>et al.</i> 2010)
Actinomycin D (Dose/schedule NS)	Case report	1	Kidney, Wilms tumor	2 nd	Vincristine	C-section	28	Female infant: 1,130 g, Apgar scores NS. Newborn had no abnormalities but suffered respiratory stress syndrome and was in the neonatology unit for 2 months.	At 10 months, healthy.	(Corapcioglu <i>et al.</i> 2004)
Actinomycin D (Dose/schedule NS)	Case report	1	Rhabdomyosarcoma	2 nd First@wk 23	Vincristine, Ifosfamide	C-section	29	Anhydramnios and fetal growth restriction at 4 wks after chemotherapy administration. Female infant: 720 g [SGA], Apgar scores 3, 7, and 7 at 1, 5, and 10 minutes. Newborn exhibited anuria and didn't pass urine for 7 days, at which time she died. Postnatal cerebral ultrasound detected bilateral intraventricular hemorrhage and left occipital meningeal hematoma. Autopsy found extensive cerebral lesions associated with prematurity but revealed no renal lesions or chromosome abnormality. Placenta revealed large areas of ischemic necrosis without chorioamnionitis.	No	(Fernandez <i>et al.</i> 1989)
Actinomycin D (0.5 mg/d, 4 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 20 Last@wk 32	Vincristine, Cyclophosphamide	Vaginal	39 + 6 days	Male infant: 4,310 g, Apgar scores 8 and 9 at 1 and 5 minutes.	No	(Frederiksen <i>et al.</i> 1991)
Actinomycin D (0.5 mg for 5 days, 1 cycle)	Case report	1	Choriocarcinoma, vagina	2 nd	Methotrexate, Chlorambucil	Vaginal	NS	Twin infants (sex NS): 1,770 and 1,880 g; Apgar scores NS. Both newborns and placenta appeared normal.	At approximately 2 years, no adverse effects of chemotherapy at follow-up.	(Freedman <i>et al.</i> 1962)

Appendix C Table 7. Actinomycin D (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Actinomycin D (0.45 mg on days 1, 2, and 3 for 1 cycle, then 0.5 mg on days 1, 2, and 3 for a second cycle)	Case report	1	Sarcoma, Ewing	3 rd First@wk 29 Last@wk 32	Doxorubicin, Cyclophosphamide, Vincristine, Radiation therapy	Vaginal, induced	36	Female infant: 5 lb 3 oz [2,353 g], Apgar scores 9 and 9. Newborn appeared normal.	At 3 months, growing adequately with no known abnormalities.	(Gilliland and Weinstein 1983)
Actinomycin D (Dose/schedule NS)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd [First@> wk 25]	Cyclophosphamide, Bleomycin, Vincristine, Doxorubicin	C-section	34	Female infant: 1,750 g, Apgar scores 7 and 9. Infant required intravenous calcium and was treated for mild respiratory distress syndrome for 2 days. No major problems after 3 days.	Child progressing normally [age NS, > 4 years later].	(Haerr and Pratt 1985)
Actinomycin D (0.4 mg on days 3 to 7 of a 7-day cycle, 3 cycles)	Case report	1	Choriocarcinoma, ovary	3 rd First@wk 30	Methotrexate Vinblastine	Vaginal, induced	37	Male infant: 5 lb 13 oz [2,637 g]. Apgar score 10. Newborn appeared normal but developed transitory focal seizures, urinary tract infection, and was found to have unilateral talipes equinovarus (clubfoot).	At 5 months, results of physical examination were normal.	(Hutchison <i>et al.</i> 1968)
Actinomycin D (0.5 mg 5 days of 4-wk cycle, 6 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 16	Vincristine, Cyclophosphamide	Vaginal	37	Spontaneous preterm labor. Male infant: 2,850 g, Apgar scores NS. Newborn was normal.	No	(Kim and Park 1989)
Actinomycin D (0.015 mg/m ² maximum dose 500 microg/day for 5 days, every 3 rd wk, 3 cycles)	Case report	1	Rhabdomyosarcoma	2 nd , 3 rd	Vincristine, Cyclophosphamide	Vaginal	36.5	Spontaneous preterm labor. Female infant: 2,443 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was healthy and normal on physical examination.	No	(Martin <i>et al.</i> 1997)
Actinomycin D (45 µg/kg every 3 wks, 3 cycles)	Case report	1	Kidney, Wilms tumor	2 nd , 3 rd First@wk 22	Vincristine	C-section	33	Male infant: 2,400 g, Apgar scores 8 and 9 at 5 and 10 minutes. Newborn was healthy and adequately developed for gestational age.	At 4 years, normal development.	(Maurer <i>et al.</i> 2009)
Actinomycin D (1 mg/m ² weekly, 3 cycles)	Case report	1	Rhabdomyosarcoma	2 nd	Doxorubicin, Cyclophosphamide	C-section	29 + 3 days	Female infant: 2,800 g, Apgar score 9. Newborn's physical exam was normal, as were blood tests.	No	(Meazza <i>et al.</i> 2008)
Actinomycin D (Dose NS, 3 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 23 Last@wk 36	Vincristine, Cyclophosphamide	Vaginal	37	Female infant: 3,285 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was grossly normal.	No	(Montz <i>et al.</i> 1989)

Appendix C Table 7. Actinomycin D (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Actinomycin D (Dose NS, 2 cycles)	Case report	1	Ovary	2 nd , 3 rd Last@wk 31	Vincristine, Cyclophosphamide	Vaginal	33	Spontaneous preterm labor. Female infant: 4 lb 4 oz [1,904 g], Apgar score 9. Newborn was healthy.	At 8 months, normal development.	(Weed <i>et al.</i> 1979)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the actinomycin D timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Fernandez *et al.* (1989) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 8. All-Trans Retinoic Acid (ATRA) – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
ATRA (45 mg/m ² daily)	Case report	1	Leukemia, APL	2 nd , 3 rd	Idarubicin, Cytarabine (3 rd)	C-section	34	Female infant: 1,950 g, Apgar scores NS. Newborn was healthy with no abnormalities following physical examination and laboratory tests.	No	(Breccia <i>et al.</i> 2002)
ATRA (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd	Idarubicin	C-section	28	<p>Ultrasound measured fetal ascites, oligohydramnios, and high umbilical artery resistance indicating placental insufficiency and intrauterine growth retardation. Premature rupture of membranes.</p> <p>Female infant: 1,475 g, Apgar scores 2, 4, and 6 at 1, 5, and 10 minutes. Newborn was in poor condition with pulmonary hypoplasia, bilateral pneumothoraxes, and patent ductus arteriosus (which closed after indomethacin was given).</p>	At 6 months, the baby continued on nasal oxygen and diuretics with significant respiratory effort and poor overall growth.	(Carradice <i>et al.</i> 2002)
ATRA (Dose/schedule NS)	Survey, retrospective	3 of 37 from Table 1 (Pts 2, 4, 8; see note in reference column)	Leukemia, AML	1 st (Diagnosis @wk 7)	Daunorubicin, Cytarabine	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005) [Pt 14 was diagnosed in the 3rd trimester and treated with ATRA, but was not included in the text analysis because it was not possible to determine if she received chemotherapy during pregnancy.]
				1 st (Diagnosis @wk 9)	Daunorubicin, Cytarabine	--	--	Induced abortion. [No fetal data reported.]		
				1 st (Diagnosis @wk 5)	Daunorubicin, Cytarabine	--	--	Induced abortion. [No fetal data reported.]		

Appendix C Table 9. All-Trans Retinoic Acid (ATRA) (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
ATRA (45 mg/m ² daily)	Case series	1 of 3 (Pt 3) [only 1 pt treated with chemotherapy during pregnancy]	Leukemia, APL	3 rd	None	Vaginal	34	Spontaneous preterm labor. Female infant: 1,980 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 4 years, growth was normal, and there were no complications.	(Consoli <i>et al.</i> 2004)
ATRA (Dose/schedule NS)	Case series	1 of 32 (Pt 15)	Leukemia, AML	2 nd First@wk 21 Last@wk 25	Idarubicin	C-section	34	Infant, sex NS: 1,950 g, Apgar scores 8 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
ATRA (Pt 1 - 45 mg/m ² , Pt 2 - 45 mg/m ² daily for 30 days, then dose was “tapered”)	Case series	2 of 2	Leukemia, APL	2 nd , 3 rd First @wk 24	Cytarabine, Daunorubicin	Vaginal	32	Female infant: 2,300 g, Apgar scores NS. Newborn was normal.	At 10 months, she was healthy.	(Delgado-Lamas and Garces-Ruiz 2000)
				2 nd , 3 rd First@wk20	Cytarabine, Daunorubicin	Vaginal	36	Female infant: 2,200 g, Apgar scores NS. Newborn had no apparent malformations but had respiratory distress that required support for 15 days.	At 5 months, growth and development were normal.	
ATRA (Dose/schedule NS)	Case series	1 of 18 (Pt 4)	Leukemia, AML	2 nd , 3 rd	Daunorubicin, Cytarabine	Vaginal	NS [~28]	Spontaneous preterm labor. Male infant: 1,050 g, Apgar scores NS. Newborn was premature with normal body weight for gestational age and hematological values. He suffered respiratory distress and died after 1 day.	--	(Dilek <i>et al.</i> 2006)
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	2 nd , 3 rd	None	C-section	34	Female infant: 2,610 g, Apgar scores NS. Newborn was healthy and had no physical abnormalities.	At 9 months, there were no complications with growth and development.	(Fadilah <i>et al.</i> 2001)
ATRA (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd	Idarubicin	C-section	31 + 2 days	Male infant: 1,742 g, Apgar scores 5 and 7 at 1 and 5 minutes. Newborn had respiratory distress, and jaundice that required treatment.	At 2 months, his general health and neurologic condition were good.	(Ganzitti <i>et al.</i> 2010)
ATRA (45 mg/m ² daily)	Case report	1	Leukemia, APL	2 nd	6-Thioiguanine, Cytarabine (2 nd , 3 rd), Daunorubicin, Mitoxantrone (2 nd , 3 rd)	Vaginal, induced	35	Female infant: 2,490 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was healthy with no physical abnormalities.	At 4 months, there were no developmental complications.	(Giagounidis <i>et al.</i> 2000)

Appendix C Table 9. All-Trans Retinoic Acid (ATRA) (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
ATRA (45 mg/m ² , schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd First@wk 26 Last@wk 30	None	C-section	30	Female infant: weight and Apgar scores NS. Newborn developed cardiac arrhythmia and had a cardiac arrest but was resuscitated and made satisfactory progress.	No	(Harrison <i>et al.</i> 1994)
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	2 nd , 3 rd	None	Vaginal	33	Spontaneous preterm labor. Female infant: 2,765 g, Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was normal. Newborn had mild hyperbilirubinemia and small bilateral subependymal hemorrhages.	No	(Incerpi <i>et al.</i> 1997)
ATRA (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Doxorubicin, Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Aclarubicin, Cytarabine, Cycloctidine, Vincristine, Mitoxantrone, Idarubicin, Asparaginase	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994) [†]
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	3 rd	None	C-section	37	Fetal arrhythmia. Male infant: 2,450 g, Apgar scores 6 at birth and 10 at 5 minutes.	At 4 years, normal development with no physical abnormalities detected.	(Leong <i>et al.</i> 2000)
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	2 nd	None	C-section	40	Female infant: weight and Apgar scores NS. Newborn was healthy.	No	(Lin <i>et al.</i> 1996)
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	3 rd	None	Vaginal	38	Male infant: 4,000 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 9 months, there were no complications in development.	(Lipovsky <i>et al.</i> 1996)
ATRA (45 mg/m ² , schedule NS)	Case report	1	Leukemia, APL	1 st , 2 nd , 3 rd	None	Vaginal	32	Female infant: 1,863 g, Apgar scores NS. Newborn was healthy and neurologically normal.	No	(Morton <i>et al.</i> 1995) [†] Abstract only

Appendix C Table 9. All-Trans Retinoic Acid (ATRA) (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
ATRA (70 mg/day)	Case report	1	Leukemia, APL	3 rd First@wk 30	None	C-section	32 (day 12 of treatment)	Fetal distress syndrome on day 9 of treatment. Female infant: 2,080 g, Apgar scores 1 and 9 at 1 and 5 minutes. Normal newborn.	At 7 months, normal development and no malformations.	(Nakamura <i>et al.</i> 1995)
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	3 rd First@wk 29	None	Vaginal	29	Prior to chemotherapy, fetus was diagnosed with Potter syndrome (oligohydramnios and bilateral renal agenesis). Spontaneous preterm labor. Infant: age, weight, and Apgar scores NS. Newborn died 30 minutes after birth. Authors concluded that treatment induced labor.	--	(Sham 1996)
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	1 st , 2 nd , 3 rd First@~wk 3	None	C-section	32	Male infant: 1,820 g, Apgar scores NS. Newborn's physical examination was unremarkable. Respiratory distress and jaundice were resolved at 11 and 7 days, respectively.	At 15 months, growth and development were normal.	(Simone <i>et al.</i> 1995)
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	2 nd , 3 rd First@wk 14 Last@ wk 32	Idarubicin	C-section	36.7	Early signs of preeclampsia at 36.7 wks of gestation. Female infant: 2,270 g, Apgar scores 6 and 9 at 1 and 5 minutes. Newborn was not malformed and was treated for transient mild respiratory distress. Infant had moderate dilation of right atrium and right ventricle, 2 small secundum atrial defects and a small patent ductus arteriosus.	At 1.5 months, there was adequate somatic growth and no clinical signs of congestive heart failure. The dilation of the right atrium and right ventricle resolved, the ductus arteriosus had closed, and the secundum atrial septal defects persisted, although they were hemodynamically insignificant.	(Siu <i>et al.</i> 2002)
ATRA (45 mg/m ² /day, dosage later reduced by 50%)	Case report	1	Leukemia, APL	2 nd , 3 rd First@wk 23	None	Vaginal	32	Spontaneous preterm labor. Twin infants, sex NS: 1,975 g (Twin A) and 1,850 g (Twin B), Apgar scores were "normal."	At 8 months, no signs of neurological or visual impairment, and the children were thriving.	(Stentoft <i>et al.</i> 1994)

Appendix C Table 9. All-Trans Retinoic Acid (ATRA) (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Newborns were normal. Twin B required continuous positive airway pressure for a few days.		
ATRA (45 mg/m ² /day)	Case series	3 of 3	Leukemia, APL	3 rd	None	C-section	32	Male infant: 2,318 g, Apgar scores NS. Newborn had respiratory distress syndrome.	At 12 months, normal growth and development.	(Takitani <i>et al.</i> 2005) [Pt 2 was first reported in Terada <i>et al.</i> (1997), but is included in the text analysis using the Takitani <i>et al.</i> (2005) reference.]
				3 rd	None	C-section	33	[Fetal growth retardation, arrhythmia, abnormal systolic motion of mitral value.] Male infant: 1,904 g, Apgar scores NS. Newborn had respiratory distress syndrome and premature atrial contraction.	At 3 months, normal growth and development.	
				3 rd	None	C-section	33	Male infant: 1,634 g, Apgar scores NS. Newborn had respiratory distress syndrome and a patent ductus arteriosus.	At 36 months, normal growth and development and no intellectual disability.	
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	3 rd First@wk 30	None	C-section	33 + 6 days	Fetal growth retarded at 33 wks + 4 days of gestation; arrhythmia, abnormal systolic anterior motion of the mitral valve. Male infant: 1,904 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn showed blocked atrial premature contractions and arrhythmia, which disappeared by the following day.	No	(Terada <i>et al.</i> 1997) [†] [This case report was included as Pt 2 in Takitani <i>et al.</i> (2005), thus it was not counted separately in the text analysis.]
ATRA (40.5 mg/m ² /day)	Case report	1	Leukemia, APL	1 st First@wk 11-12	6-Mercaptopurine (1 st , 2 nd)	Vaginal, induced	34	Slight enlargement of cistern magna, but normal-looking brain structure at gestation wk 23. Male infant: 2,490 g, Apgar scores 6 and 10 at 1 and 5 minutes. Newborn was healthy and without anomalies apart from [respiratory] distress and mild jaundice.	At 9 months, growth and development were normal.	(Valappil <i>et al.</i> 2007)

Appendix C Table 9. All-Trans Retinoic Acid (ATRA) (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
ATRA (45 mg/m ² /day)	Case report	1	Leukemia, APL	3 rd First@wk 28	None	C-section	32	Male infant: 2,380 g, Apgar scores NS. Newborn had no abnormalities, and was treated for respiratory distress.	At 5 months, growth and development were normal.	(Watanabe <i>et al.</i> 1995)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the all-*trans* retinoic acid timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

† Papers not included in the text analysis (highlighted in light grey). Kawamura *et al.* (1994) was not included because it did not include individual treatment, timing of exposure, and pregnancy outcomes. We did not include data from published abstracts in the text summary for the agent (Morton *et al.* 1995). The case report by Terada *et al.* (1997) was not included in the text summary because this case was also included in the case series reported by Takitani *et al.* (2005). However, we did include the pregnancy complications and fetal details of this case from Terada *et al.* (1997).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; ATRA = all-*trans* retinoic acid.

Appendix C Table 10. Bleomycin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Bleomycin (10 mg/m ² on days 1 and 14, 2 to 4 cycles)	Case series	3 of 6 (Pts 1, 5, 6)	Hodgkin lymphoma	2 nd First@wk 21	Doxorubicin, Vinblastine, Dacarbazine	C-section	29	Female infant: 2,400 g, Apgar scores NS. Newborn was healthy.	At 10 years, healthy.	(Anselmo <i>et al.</i> 1999)
				2 nd First@wk 16	Doxorubicin, Vinblastine	C-section	NS [~36]	Preeclampsia. Female infant: 2,180 g, Apgar scores NS. Newborn was healthy.	At 7 months, healthy.	
				2 nd	Doxorubicin, Vinblastine	C-section	33	Female infant: 3,130 g, Apgar scores NS. Newborn was healthy.	No	
Bleomycin (Dose NS, 1 to 6 cycles)	Case series, retrospective	10 of 14 in Table II (Pts 2, 3, 4, 6, 7, 8, 11, 12, 13, 14)	Hodgkin lymphoma	2 nd [see note in reference column]	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	38	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				1 st	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	37	Male infant: 3,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Doxorubicin, Vinblastine, Dacarbazine	C-section	34	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st	Doxorubicin, Vinblastine, Dacarbazine, Nitrogen Mustard, Vincristine, Procarbazine	Vaginal	38	Female infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Doxorubicin, Vinblastine, Dacarbazine, Nitrogen Mustard, Vincristine, Procarbazine	Vaginal	37	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	38	Female infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	40	Male infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Vinblastine, Dacarbazine	C-section	40	Female infant: 3,450 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Nitrogen Mustard, Vincristine, Procarbazine, Doxorubicin, Vinblastine, Dacarbazine	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		12 of 18 in Table III (Pts 2, 4, 5, 6, 7, 8, 10, 14, 15, 16, 17, 18)	Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin, Vincristine	C-section	39	Male infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st	Cyclophosphamide, Doxorubicin, Vincristine	C-section	40	Male infant: 3,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Cyclophosphamide, Doxorubicin, Vincristine	Vaginal	37	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Doxorubicin, Vincristine, Cytarabine	Vaginal	37	Male infant: 2,900 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Doxorubicin, Vincristine	Vaginal	38	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Epi-doxirubicin, Vincristine, Cytarabine, Etoposide, Methotrexate	Vaginal	37	Male infant: 2,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Doxorubicin, Vincristine	Vaginal	38	Female infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Doxorubicin, Vincristine, Cytarabine, Etoposide, Methotrexate	Vaginal	40	Female infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd	Cyclophosphamide, Doxorubicin, Vincristine	C-section	38	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Cyclophosphamide, Epidoxorubicin, Vincristine	Vaginal	39	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Epidoxorubicin, Vincristine, Cytarabine, Etoposide, Methotrexate	Vaginal	40	Male infant: 2,800 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Epidoxorubicin, Vincristine, Cytarabine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Bleomycin (Total dose: 120 mg – Pt 2, 5, 11, 14, 16; 180 mg – Pt 3; 210 mg – Pt 4; 110 mg – Pt 6; 260 mg – Pt 7; schedule NS)	Case series	9 of 16 (Pts 2, 3, 4, 5, 6, 7, 11, 14, and 16)	Non-Hodgkin lymphoma	1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin	NS	35-39 (group range)	Individual pregnancy outcomes are not provided. Birth weights were 2,200 g to 3,900 g (group range). All babies were born alive, and none of the newborns showed apparent congenital malformations.	At ages ranging from 3 to 11 years, normal growth and development.	(Avilés <i>et al.</i> 1990) [†]
				2 nd , 3 rd	Methotrexate, Cyclophosphamide, Vincristine, Doxorubicin					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin					

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Methotrexate, Cyclophosphamide, Vincristine, Doxorubicin, Etoposide					
				1 st , 2 nd	Cyclophosphamide, Vincristine, Doxorubicin					
				1 st , 2 nd , 3 rd	Methotrexate, Cyclophosphamide, Vincristine, Doxorubicin, 6-Mercaptopurine					
				1 st , 2 nd	Cyclophosphamide, Vincristine, Doxorubicin					
				1 st , 2 nd , 3 rd	Etoposide, Methotrexate, Cyclophosphamide, Vincristine, Cytarabine					
				1 st , 2 nd	Cyclophosphamide, Vincristine, Doxorubicin					
Bleomycin (Dose/schedule NS)	Case series, retrospective	16 of 26 from Table 2	Hodgkin lymphoma	NS	Doxorubicin, Dacarbazine, Vinblastine, Epirubicin	NS	NS	Birth weight, group range: 2,800-4,300 g. Individual pregnancy outcomes, birth weights, and Apgar scores were not provided.	In this long-term follow-up, ranging from 5 to 26 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001)†
		29 of 29 from Table 3	Non-Hodgkin lymphoma	NS	Cyclophosphamide, Doxorubicin, Vincristine	NS	NS	Birth weight, group range: 2,350-4,050 g.		
Bleomycin (20 mg/m ² daily for 5 days; 4 cycles, 3 wks apart)	Case report	1	Ovary	2 nd	Etoposide, Cisplatin	C-section	36	Intrauterine growth restriction. At 36 wks, severe preeclampsia.	At 21 months, normal growth and development and no evidence of minor or major malformations.	(Benjapibal <i>et al.</i> 2010)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Male infant: 1,560 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no gross malformations		
Bleomycin (Dose/schedule NS)	Survey, registry	20 of 31 pts from Table 3 [21 of 32 infants]	Hodgkin lymphoma	2 nd or 2 nd , 3 rd	Doxorubicin, Vinblastine, Dacarbazine	NS	35.9 (group mean)	Infant sex NS: 2,587 g (group mean), Apgar scores NS. Nineteen newborns were normal with normal body weight for gestational age, including 1 set of twins. Malformations observed in 2 infants: 1 had plagiocephaly, and 1 had syndactyly of the 4 th and 5 th fingers. 3 newborns were hypoglycemic.	At 0.5 to 10 years (n=20), all children were normal phenotype. At 4 to 112 months (group range, n=15), 1 child in the group had chronic broncolitis, 1 had recurrent otitis media, and 1 had asthma; group mean weight was 67 th percentile.	(Cardonick <i>et al.</i> 2010)
		3 of 9 from Table 4	Ovary	2 nd , 3 rd	Etoposide, Cisplatin	NS	38.1 (group mean)	Infant sex NS: 2,639 g (group mean), Apgar scores NS. Two newborns were normal with normal body weight for gestational age and 1 newborn had a genetic hearing loss (both parents were carriers), intrauterine growth retardation (SGA), and a spontaneous mutation for neurofibromatosis.	At 63.3 months (group mean, n=7), 1 child had motor/language delay; group mean weight was 35 th percentile.	
Bleomycin (15 units/m ² on days 2, 8, and 15; 1 cycle)	Case report	1	Ovary	2 nd First@wk 19	Cisplatin, Vinblastine	Vaginal	Term	Male infant: 3,232 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn appeared healthy.	[At ~4.5 years,], normal development with a normal male karyotype.	(Christman <i>et al.</i> 1990)
Bleomycin (Dose/schedule NS)	Case series	4 of 32 (Pts 8, 9, 18, 19)	Hodgkin lymphoma	3 rd First@wk 30 Last@wk 36	Doxorubicin, Vinblastine	C-section	36	Infant sex NS: 2,650 g, Apgar scores 8 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
				2 nd , 3 rd First@wk 15 Last@wk 35	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	36	Infant sex NS: 2,169 g, Apgar scores 6 and 9. Newborn was healthy.		
				2 nd First@wk 24 Last@wk 27	Doxorubicin, Vinblastine, Dacarbazine	C-section	37	Infant sex NS: 2,850 g, Apgar scores 8 and 8. Newborn was healthy.		

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd First@wk 24 Last@wk 26	Doxorubicin, Vinblastine, Dacarbazine,	C-section	37	Infant sex NS: 2,450 g, Apgar scores 9 and 9. Newborn was healthy.		
		2 of 32 (Pts 20 and 30)	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 24 Last@wk 37	Doxorubicin, Cyclophosphamide, Etoposide, Cytarabine, Vincristine	C-section	35	Infant sex NS: 1,980 g; Apgar scores 8 and 9. Newborn was healthy.		
				3 rd First@wk 34 Last@wk 37	Epirubicin, Cyclophosphamide, Etoposide, Cytarabine, Vincristine	Vaginal	36	Infant sex NS: 3,020 g; Apgar scores 9 and 9. Newborn was healthy.		
Bleomycin (Dose/schedule NS)	Case series	2 of 21 (Pts 7 and 10; Pt 7 had 2 pregnancies)	Hodgkin lymphoma	1 st	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	NS	Male infant: 2,500 g, Apgar scores NS. Newborn had growth retardation (SGA), but was healthy with no hematological abnormalities. [Pt 7, 1st pregnancy]	At 65 months, alive.	(Dilek <i>et al.</i> 2006)
				2 nd , 3 rd	Doxorubicin, Vinblastine, Dacarbazine	--	--	Fetal death [stillbirth in the 8th month. No fetal data reported; Pt 7, 2nd pregnancy]	--	
				1 st	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	NS	Female infant: 2,500 g, Apgar score NS. Newborn had growth retardation (SGA) and a floating thumb malformation on the left hand (partial agenesis of a metacarpal bone and hypoplasia of 2 phalanges).	At 43 months, alive.	
Bleomycin (15 mg, 1 dose)	Case report	1	Hodgkin lymphoma	2 nd First@wk 17	Doxorubicin, Vinblastine, Dacarbazine	--	--	Induced abortion after first dose of chemotherapy. [No fetal data reported.]	--	(D'Incalci <i>et al.</i> 1983)
Bleomycin (30 U weekly)	Case report	1	Ovary	2 nd First@wk 25 + 5 days	Etoposide, Cisplatin	C-section	28 + 1 day	Mild to moderate bilateral ventriculomegaly at 26 wks of gestation + 5 days.	No	(Elit <i>et al.</i> 1999)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Female infant: 1,085 g, Apgar scores 7 and 8. Newborn had mild to moderate respiratory distress syndrome and apnea of prematurity. Newborn had profound ventriculomegaly and cerebral atrophy.		
Bleomycin (Dose NS, days 1 and 2, 3 cycles)	Case report	1	Hodgkin lymphoma	2 nd First@wk 25	Doxorubicin, Vinblastine, Dacarbazine	C-section	38	Serial ultrasounds detected small for gestational age fetus. Male infant: 1,650 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 10 months, remained well.	(Fadilah <i>et al.</i> 2006)
Bleomycin (10 mg/m ² , 8 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	1 st , 2 nd First@wk 13 Last@wk 34	Cyclophosphamide, Vincristine	Vaginal	Full term	Male infant: 2,500 g, Apgar scores NS. Newborn showed no signs of abnormalities at birth.	At 1 year, developing normally. Chromosome banding studies detected no abnormalities.	(Falkson <i>et al.</i> 1980)
Bleomycin (20 IU/m ² , 5 days/wk, 3 cycles)	Case report	1	Ovary	3rd	Etoposide, Cisplatin	C-section	36	Oligohydramnios and estimated fetal weight < 5 th percentile observed 2 wks after last dose [age NS]. Male infant: 2,500 g [SGA], Apgar score 9-10 at 15 minutes. Newborn had mild glandular hypospadias at birth and an otherwise normal appearance.	At 1 month, ultrasound of the brain and kidney were normal, as were hearing studies and eudiometry. At 8 months, normal physical and neurological development.	(Ghaemmaghami <i>et al.</i> 2009)
Bleomycin (30 U once, 5 cycles, 3 wks apart)	Case series	1 of 3 (Case 2)	Ovary	2 nd First@wk 18	Etoposide, Cisplatin	C-section	35	Premature rupture of membranes. Infant sex NS: 2,400 g, Apgar scores 7 and 9 at 1 and 5 minutes.	At 1 year, developing normally.	(Ghaemmaghami and Hasanzadeh 2006)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Bleomycin (dose/schedule NS)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd [First@> wk 25]	Actinomycin D, Cyclophosphamide, Vincristine, Doxorubicin	C-section	34	Female infant: 1,750 g, Apgar scores 7 and 9. Infant required intravenous calcium and was treated for mild respiratory distress syndrome for 2 days. No major problems after 3 days.	Child progressing normally [age NS, > 4 years later].	(Haerr and Pratt 1985)
Bleomycin (15 mg once weekly, 5 cycles (Pt 1) or 2 cycles (Pt 2), 4 wks apart)	Case series	2 of 2	Ovary	2 nd First@wk 22	Etoposide, Cisplatin	Vaginal	40	Small for gestational age fetus. Male infant: 2,610 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn showed no gross malformations.	At 1 month, brain and kidneys were normal by ultrasound. At 6 years, normal physical and neurological development.	(Han <i>et al.</i> 2005)
				3 rd First@wk 30	Etoposide, Cisplatin	Vaginal, induced	38	Male infant: 2,970 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn showed no gross malformations at birth.	At 7.5 months, he had an intussusception; at 26 months, normal physical and neurological development.	
Bleomycin (15 mg on days 1, 2, and 3; 3 cycles, 4 wks apart)	Case report	1	Ovary	2 nd First@wk 21 Last@wk 29	Etoposide, Cisplatin	Vaginal, induced	39	Mild preeclampsia. Female infant: 2,769 g, Apgar scores 4 and 7 at 1 and 5 minutes. Newborn was anemic; no fetal anomalies were identified.	Normal development as assessed by the Child Development Assessment Team [age NS].	(Horbelt <i>et al.</i> 1994)
Bleomycin (10 mg/m ² , schedule NS, 3.5 cycles)	Case report	1	Hodgkin lymphoma	2 nd First@wk 21	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	41	Female infant: weight was within normal limits. Apgar score 9. Newborn was healthy.	At follow-up [age NS], no physiological or developmental abnormalities.	(Iriyama <i>et al.</i> 2011)
Bleomycin (Dose/schedule NS, 7-8 cycles)	Case series	2 of 18	Hodgkin lymphoma	NS First@wk 12-33 22 (mean)	Doxorubicin, Vinblastine, Dacarbazine	NS	NS	Infants' sex, weight and Apgar scores NS. Newborns were alive and healthy; no malformations were observed.	At follow-up, normal growth patterns without physical or neurological deficits (n=5 children, oldest child is 42 months).	(Jameel and Jamil 2007)
Bleomycin (15 mg for 5 days, 2 cycles, 3 wks apart)	Case report	1	Ovary	3 rd First@wk 29	Etoposide, Cisplatin	C-section	39	Female infant: 3,100 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn showed no gross malformations.	At 1 month, brain and kidneys were normal by ultrasound. At 1.5 years, normal physical and neurological development.	(Karimi Zarchi <i>et al.</i> 2008)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Bleomycin (Dose/schedule NS, 3 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 27	Doxorubicin, Vinblastine, Dacarbazine	C-section	39	Male infant: 2,350 g [SGA], Apgar scores NS. Newborn was HIV negative and clinically well (mother was HIV positive).	At 9 months, clinically well.	(Klepfish <i>et al.</i> 2000)
Bleomycin (Dose/schedule NS, 4 cycles)	Case series	3 of 27 (only 3 pts received chemotherapy during pregnancy)	Ovary	2 nd and/or 3 rd First @ wk 22.8-30.6	Etoposide, Cisplatin	NS	Full term	Individual pregnancy outcomes NS. Newborns were healthy with no congenital malformations.	No	(Kwon <i>et al.</i> 2010)
Bleomycin (10 mg/m ² on day 10, 3 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 22 Last@wk 28	Cyclophosphamide, Vincristine, Doxorubicin, Teniposide	C-section	31	Preeclampsia and fetal growth retardation. Male infant: 1,380 g, Apgar scores 7, 9 and 10 at 1, 5 and 10 minutes. Newborn had no congenital abnormalities, but had hyperbilirubinemia (treated and resolved in 3 days). Placenta had extensive infarction.	At 18 months, normal growth.	(Lambert <i>et al.</i> 1991)
Bleomycin (4 doses over 10 days at 30, 15, 5, and 5 mg)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd First@wk 36 Last@wk 37	Cyclophosphamide (2 nd , 3 rd), Vincristine (2 nd , 3 rd), Doxorubicin (2 nd , 3 rd), Teniposide (2 nd , 3 rd), Methotrexate (intrathecal)	Vaginal	37	Female infant: 3,750 g, Apgar score 9. Newborn had a normal heart and a normal blood count and no abnormality.	No	(Lowenthal <i>et al.</i> 1982)
Bleomycin (Dose/schedule NS, 1 cycle)	Case series	1 of 2 (Pt 2)	Ovary	2 nd First@wk 20	Etoposide, Cisplatin	C-section	31	Infant sex, weight and Apgar scores NS. Newborn required intensive care for hyaline membrane disease [respiratory distress syndrome].	No	(Malhotra and Sood 2000)
Bleomycin (10 mg on days 1 through 5, 2 cycles, 3 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 27	Vinblastine, Cisplatin	C-section	32	Male infant: 1,900 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn experienced a mild episode of transient tachypnea but was otherwise normal.	At follow-up, normal development [age NS].	(Malone <i>et al.</i> 1986)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Bleomycin (30 mg on day 1, 2 cycles, 4 wks apart)	Case report	1	Cervix	2 nd First@wk 17 Last@wk 20	Cisplatin	C-section	38	Male infant: 2,850 g, Apgar scores 8 and 10 at 1 and 5 minutes.	At 3 years, normal physical and neurological development.	(Marana <i>et al.</i> 2001)
Bleomycin (8 mg, 5 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd Last@wk 35	Cyclophosphamide, Vincristine, Etoposide, Doxorubicin, Methotrexate	Vaginal	35.5	Spontaneous preterm labor after last chemotherapy dose. Male infant: birth weight was 75 th percentile for gestational age, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no physical abnormalities.	At 11 months, alive and well.	(Moore and Taslimi 1991)
Bleomycin (15 mg on days 1, 8, and 15; 3 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 20 Last@wk 28	Cisplatin, Vinblastine	C-section	31	Intrauterine growth restriction at 28 wks of gestation. Marked reduction in amniotic fluid at 31 wks of gestation. Maternal hypertension. Female infant: 1,070 g [SGA], Apgar scores NS. Newborn was apparently normal.	At 65 months, no sign of metabolic or hematologic abnormality.	(Motegi <i>et al.</i> 2007)
Bleomycin (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 18	Methotrexate, Doxorubicin, Cyclophosphamide, Vincristine	C-section	28	Spontaneous preterm labor at 10 th wk of chemotherapy. Male infants (twins): weights and Apgar scores NS. Newborns were without apparent malformation or hematological suppression.	At 12 months, apparently healthy.	(Nantel <i>et al.</i> 1990)
Bleomycin (10 mg/m ² on day 7, 2 cycles)	Case report	1	Hodgkin lymphoma	2 nd	Nitrogen Mustard, Vincristine, Procarbazine, Doxorubicin, Vinblastine	NS	Term	Female infant: weight and Apgar scores NS. Newborn had favorable outcome. Infant administered AZT for 6 wks because mother was HIV positive.	At 2 years, child had normal height and weight, and was HIV positive.	(Okechukwu and Ross 1998)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Bleomycin (4 mg/m ² on days 1 and 8, 5 cycles, 4 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 21	Cyclophosphamide, Vincristine	Vaginal	Term	Mild uterine contractions with 3 rd cycle of chemotherapy, subsided. Female infant: 7 lb 4.5 oz [3,303 g], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn showed no sign of abnormalities.	At 1 year, developing normally with no evidence of malformations.	(Ortega 1977)
Bleomycin (Dose/schedule NS)	Cohort, retrospective	1 of 14 from tables 3 and 4 (Pt 14)	Hodgkin lymphoma	1 st First@wk 3 Last@wk 7	Nitrogen Mustard, Vincristine, Procarbazine, Doxorubicin, Vinblastine, Dacarbazine	--	--	Induced abortion at gestation wk 18: No malformations; toxic degenerative changes in liver and kidneys, placenta with villus degeneration and vascular toxic degeneration	--	(Peres <i>et al.</i> 2001)
Bleomycin (30 mg daily for 3 days, 1 cycle)	Case report	1	Adenocarcinoma (primary not located)	2 nd First@wk 26	Etoposide, Cisplatin	Vaginal	27	Spontaneous preterm labor. Female infant: 1,190 g, Apgar scores 3 and 8 at 1 and 5 minutes. Infant developed severe respiratory distress and pneumothorax, (on room air by day 10). Infant developed a profound leucopenia with neutropenia by day 3 (resolved by day 13). Blood transfusions for anemia associated with immaturity were required twice. Platelet count fell, but the infant never became frankly thrombocytopenic. No demonstrable neurological abnormality, and cerebral ultrasound remained normal throughout the neonatal period. At the age of 10 days, infant was noted to be losing her scalp hair, and there was an associated rapid loss of lanugo.	At 1 year, neurodevelopmental progress was normal, but there was moderate sensorineural hearing loss.	(Raffles <i>et al.</i> 1989)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Bleomycin (15 units, schedule NS)	Case report	1	Sarcoma, Kaposi	3 rd	Doxorubicin, Vinblastine	Vaginal	33-34	Female infant: 1,150 g, Apgar scores 6, 7, and 9 at 1, 5, and 10 minutes. Newborn was <10 th percentile for weight, length, and head circumference, blood count and gases were normal, and mild hyperbilirubinemia required phototherapy.	At 4 months, apparently well and thriving.	(Rawlinson <i>et al.</i> 1984)
Bleomycin (9 mg/m ² every other wk, 6 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Etoposide, Doxorubicin, Cyclophosphamide, Vincristine	NS	37	Male infant: 3,200 g, Apgar scores NS. Newborn was healthy.	At 21 months, well with no evidence of iatrogenic complications.	(Rodriguez and Haggag 1995)
Bleomycin (Dose/schedule NS, 3 cycles (Pt 15) or 2 cycles (Pt 16))	Survey, retrospective	2 of 27 from Table 1 (Pts 15, 16)	Hodgkin lymphoma	2 nd , 3 rd First@wk 24	Doxorubicin, Vinblastine, Dacarbazine	C-section	36	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 27	Doxorubicin, Vinblastine, Dacarbazine	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.	No	
Bleomycin (10 U/m ² , schedule NS, 2 or 3 cycles)	Survey, retrospective	2 of 62 [62 pts received chemotherapy while pregnant; the total number of pts who received bleomycin while pregnant was not provided]	NS	2 nd , 3 rd First @wk 25	Nitrogen Mustard, Vincristine, Procarbazine, Doxorubicin, Vinblastine	NS	NS	Infant sex, birth weights, and Apgar scores NS. Newborn had pectus excavatum.	No	(Van Calsteren <i>et al.</i> 2010)

Appendix C Table 11. Bleomycin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			NS	2 nd , 3 rd First@wk 26	Nitrogen Mustard, Vincristine, Procarbazine, Doxorubicin, Vinblastine, Radiation therapy (2 nd)	NS	NS	Infant sex, birth weights, and Apgar scores NS. Newborn had bilateral partial syndactyly of digits 2 and 3.		

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the bleomycin timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). In order to avoid counting the same cases more than once, we did not include the following studies: (Avilés *et al.* 1990, Avilés and Neri 2001). The cases in Avilés *et al.* (1990) were not included in the text analysis because they were reported in a subsequent retrospective case series (Avilés *et al.* 1991). The cases from retrospective case series Avilés *et al.* (2001) were not included because it included both new cases and long-term follow-up on previously reported case series (Avilés and Niz 1988, Avilés *et al.* 1991) without individual pregnancy outcomes.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age; U = units.

Appendix C Table 12. Busulfan – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Busulfan (2 mg daily)	Case report	1	Leukemia, CML	1 st	None	--	6	Induced abortion in gestation wk 6. Histological examination of the embryo revealed myeloschisis (cleft spinal cord).	--	(Abramovici <i>et al.</i> 1978)
Busulfan (Dose/schedule NS)	Case series, retrospective	3 of 4 (Table IV, Pts 1, 2, 3)	Leukemia, CGL	1 st [see note in reference column]	None	Vaginal	39	Male infant: 2,800 g, Apgar scores NS. Newborn had no congenital abnormalities.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This report gives the trimester that chemotherapy was initiated but not the duration of treatment.]
				1 st	6-Mercaptopurine	Vaginal	39	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital abnormalities.	At 12 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	6-Mercaptopurine	Vaginal	37	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital abnormalities.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Busulfan (8 mg daily, decreasing through pregnancy)	Case report	1	Leukemia, AGL	2 nd , 3 rd First@wk 20 Last@wk 37	None	Vaginal	39	Female infant: 2,101 g [SGA], Apgar scores NS. Newborn measurements were 2 standard deviations below mean for gestational age but otherwise normal by physical examination. Pyelograms revealed a hydronephrotic left kidney, dilated left ureter, and no right ureter or kidney.	At 4 months, the left kidney had spontaneously decreased in size. At 19 months, height and weight remained 2 standard deviations below the mean for age. Infant tested normal in Denver Developmental Screening tests at 4 and 19 months.	(Boros and Reynolds 1977)
Busulfan (2 mg daily)	Case report	1	Leukemia, CML	1 st Last@wk 8	None	Vaginal	NS	Female infant: 3,900 g, Apgar scores NS. Newborn was normal in all respects.	At 3 months, thrived and developed normally.	(Dennis and Stein 1965)

Appendix C Table 13. Busulfan (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Busulfan (4-6 mg daily)	Case report	1	Leukemia, CGL	1 st , 2 nd , 3 rd	6-Mercaptopurine (1 st , 3 rd), Radiation therapy (1 st)	C-section	NS [~ 8 months]	Female infant: 1,077 g (SGA), Apgar scores NS. Newborn had extreme intrauterine arrest, bilateral microphthalmia, bilateral corneal opacities, and cleft palate. External genitalia were poorly developed except for a prominent clitoris.	At 2 months, infant had grunting respiration and cough. At 10 wks, the infant was found dead. Necropsy revealed disseminated cytomegaly and hypoplasia of thyroid and ovaries, among other abnormalities.	Diamond <i>et al.</i> 1960)
Busulfan (2 or 4 mg daily)	Case report	1	Leukemia, CGL	1 st , 2 nd , 3 rd	None	C-section	NS [8 or 9 months]	Male infant: 2,183 g, Apgar scores NS. Newborn displayed no developmental abnormalities.	At 4 months, development was normal.	(Dugdale and Fort 1967)
Busulfan (2 or 4 mg daily)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	37	Male infant: 2,000 g [SGA], Apgar scores NS. Newborn was normal but required surgical treatment of pyloric stenosis at 2 months.	At 3 years, development was normal.	(Earll and May 1965)
Busulfan (2 mg twice daily, reduced to 1 mg twice daily, then 0.5 mg daily, then increased)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	NS [~38]	Female infant: 1,985 g [SGA], Apgar scores NS. Newborn was small but otherwise normal-appearing.	At 5 wks, was apparently developing in the usual manner.	(Izumi 1956)
Busulfan (2 mg/day)	Case series	1 of 2 (Pt 2)	Leukemia, CML	2 nd , 3 rd	None	Vaginal	Term	Male infant: 2,740 g. Apgar scores NS. Newborn was normal.	No	(Johnson 1972)
Busulfan (Dose/schedule NS)	Case series	4 of 12 (Pts 2, 5, 9, 10; Pt 10 had 2 pregnancies)	Leukemia, CML	1 st	Radiation therapy	--	--	Spontaneous abortion at 1 month of gestation. [No fetal data reported.]	--	(Lee <i>et al.</i> 1962)
					6-Mercaptopurine, Radiation therapy	Vaginal	34	Spontaneous preterm labor. Infant sex NS, 4.5 lbs [2,041 g], Apgar scores NS. Newborn was premature.	Authors state that at ages ranging from 3 months to 10 years, no congenital abnormalities or blood dyscrasia.	
					Radiation therapy	Vaginal	40	Infant sex, weight, and Apgar scores NS. Newborn was normal.		

Appendix C Table 13. Busulfan (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
					Radiation therapy	Vaginal	39	Infant sex, weight, and Apgar scores NS. Newborn was normal. [Pt 10, pregnancy 1].		
					Radiation therapy	Vaginal	38	Infant sex, weight, and Apgar scores NS. Newborn was normal. [Pt 10, pregnancy 2].		
Busulfan (1 mg twice weekly)	Case series	1 of 2 (Pt 2)	Leukemia, CML	1 st , 2 nd	None	Vaginal	NS	Male infant: 7 lb 11 oz [3,486 g] , Apgar scores NS. Newborn was normal in all respects.	At 11 months, he remained normal.	(Neu 1962)
Busulfan (4 mg daily)	Case series	1 of 5 (Pt 5)	Leukemia, CML	3 rd First@wk 30	None	Vaginal	33	Spontaneous preterm labor. Male infant: 1,620 g [SGA] , Apgar scores NS. Newborn condition NS.	At 37 months, he was alive and well.	(Nicholson 1968)
Busulfan (6 mg daily, reduced to 4 mg daily)	Case report	1	Leukemia, CGL	NS	None	Vaginal	NS	Female infant: 1,956 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was grossly normal.	At 24 months, she was well.	(Nolan <i>et al.</i> 1971)
Busulfan (4 mg daily for 7 months; total 688 mg)	Case report	1	Leukemia, CML	1 st , 2 nd First@wk 1 Last@wk 16	None	C-section	Full term	Male infant: 2,020 g, Apgar scores 7. Newborn was normal.	No	(Norhaya <i>et al.</i> 1994)
Busulfan (Dose/schedule NS)	Case report	1	Leukemia, CML	3 rd	None	Vaginal	36	Spontaneous preterm labor. Male infant: 1,950 g [SGA] , Apgar scores were 6/7; [assumed to be 6 at 5 minutes and 7 at 10 minutes] . Newborn was alive.	At postnatal visit, he was thriving [age NS] .	(Ozumba and Obi 1992)
Busulfan (Dose/schedule NS)	Cohort, retrospective	1 of 14 from Tables 3 and 4 (Pt 3)	Leukemia, CML	2 nd , 3 rd First@wk 26 Last@wk 36	None	NS	36	Infant sex and Apgar scores NS, 2,600 g. Newborn had no complications.	At 11 years, development was normal.	(Peres <i>et al.</i> 2001)
Busulfan (2-6 mg daily)	Case report	1	Leukemia, CML	1 st	None	Vaginal	NS [37]	Male infant: 2,300 g [SGA] , Apgar scores NS. Newborn was normal by physical examination.	At 30 days, he died of an acute staphylococcus infection.	(Ruiz Reyes and Tamayo Perez 1961)
Busulfan (4-6 mg daily)	Case report	1	Leukemia, CML	1 st , 3 rd	None	Vaginal	40	Male infant: 2,440 g [SGA] , Apgar scores NS. Newborn's physical examination was negative.	At 1 year, he was perfectly well.	(Sherman and Locke 1958)

Appendix C Table 13. Busulfan (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Busulfan (2 mg every other day)	Case series	1 of 2 (Pt 2)	Leukemia, CGL	1 st , 2 nd	None	Vaginal	Full term	Infant sex, weight, and Apgar scores NS. Newborn was normal.	No	(Smalley and Wall 1966)
Busulfan (2-8 mg daily)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd First@wk 1 Last@wk 30	None	Vaginal	NS [~39]	Male infant: 3,370 g. Apgar scores NS. Newborn was apparently normal.	His present clinical state is normal [age NS].	(Uhl <i>et al.</i> 1969)
Busulfan (Average 4 mg daily)	Case report	1	Leukemia, CGL	1 st , 2 nd , 3 rd	None	Vaginal	NS [~9 months]	Male infant: 2,400 g, Apgar scores NS. Newborn had premature appearance but showed no congenital defects. Blood values were within normal range.	At 3.5 years, no serious defects.	(White 1962)
Busulfan (Pt 1: up to 12 mg daily; Pt 2: 4 mg daily)	Case series	1 of 2	Leukemia, CML	1 st , 3 rd	None	Vaginal	NS [~9 months]	Female infant: 3,200 g, Apgar scores NS. Newborn was normal.	No	(Williams 1966)
Busulfan (Dose/schedule NS)	Cohort, retrospective	1 of 21 (Pt 13)	Leukemia, CML	1 st	None	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	(Zemlickis <i>et al.</i> 1992b)
Busulfan (Table 1: Pt 1 - 4mg/day; Table 2: Pt 3 - 98 mg total in 4 wks; Pt 1 - 168 mg total in 4 months)	Survey, retrospective	3 of 48 Table 1: Pt 12 Table 2: Pts 3, 1)	Leukemia, CML	1 st	None	NS	36	Spontaneous preterm labor.	At 5 years, normal.	(Zuazu <i>et al.</i> 1991)
			Leukemia, CML	1 st First@wk 6 Last@wk 10	6-Mercaptopurine	--	--	Induced abortion at gestation wk 16. [No fetal data reported.]	--	
			Leukemia, CML	2 nd , 3 rd First@4 th month Last@8 th month	None	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal.	At 5 years, normal growth.	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the busulfan timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus of infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AGL = acute granulocytic leukemia; CML = chronic myelogenous leukemia; CGL = chronic granulocytic leukemia; SGA = small for gestational age.

Appendix C Table 14. Carboplatin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Carboplatin (AUC = 5, weekly, every 3 wks, 5 cycles)	Case report	1	Lung	2 nd , 3 rd	Paclitaxel	C-section	30	Spontaneous preterm labor. Male infant: weight and Apgar scores NS. Newborn was healthy with no evidence of metastasis.	At 5 months, his development was normal.	(Azim <i>et al.</i> 2009b)
Carboplatin (Dose/schedule NS, 3 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 25 Last@wk 31	None	Vaginal	33	Infant sex and Apgar scores NS. 2,280 g. Newborn was healthy.	No	(Barut <i>et al.</i> 2011)
Carboplatin (Dose/schedule NS)	Survey, registry	3 of 7 from Table 4	Ovary	2 nd , 3 rd	None (1 pt) or Paclitaxel (2 pts)	NS	38.1 (group mean)	Infant sex NS: 2,639 g (group mean), Apgar scores NS. None of the infants had malformations. Newborns were normal with normal body weights for gestational age.	At 0.5 to 3 years, all were normal phenotype. At 63.3 months (group mean, n=7), group mean weight was 35 th percentile. One child had motor/language delay at 1 year of age.	(Cardonick <i>et al.</i> 2010)
		1 of 12 from Table 6	Central nervous system (CNS)	2 nd	None	--	--	Spontaneous abortion at gestation wk 19. Fetus had gastroschisis.	--	
Carboplatin (AUC = 5, 1 cycle)	Case series	1 of 3 (Pt 2)	Cervix	3 rd First@wk 29 + 2 days	Paclitaxel	C-section	33 + 3 days	Male infant: 2,190 g, Apgar scores NS. Newborn showed no signs of toxicity.	At 48 months, normal development.	(Chun <i>et al.</i> 2010)
Carboplatin (529 mg (AUC = 3) biweekly, 5 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 24 + 5 days	Paclitaxel	C-section	36 + 2 days	Female infant: 2,062 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn showed no serious effects of chemotherapy.	At 40 months, she remained healthy with no serious problems.	(Doi <i>et al.</i> 2009)
Carboplatin (AUC = 6, every 3 wks)	Case report	1	Breast	2 nd , 3 rd First@wk 14 + 6 days Last@wk 30	Docetaxel, Trastuzumab (2 nd)	C-section	33 + 2 days	Anhydramnios and intrauterine growth restriction at 20 wks + 4 days of gestation. Male infant: weight less than 3 rd percentile (SGA), Apgar scores NS. Newborn showed inconspicuous development and normal renal function and urinalysis.	No	(Gottschalk <i>et al.</i> 2011)

Appendix C Table 15. Carboplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Carboplatin (AUC = 5, day 1, 1 cycle)	Case report	1	Lung	2 nd First@wk 25	Gemcitabine	C-section	28 + 4 days	Female infant: 1,040 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was anemic, required surfactant treatment and a conventional ventilator for 29 days, and developed sepsis on day 36, from which she recovered well.	At 8 months, she was weaned from oxygen therapy and was on high-calorie formula milk. Her neurodevelopment was age appropriate.	(Gurumurthy <i>et al.</i> 2009)
Carboplatin (300 mg/m ²)	Case report	1	Ovary	3 rd First@wk 30	Cisplatin (2 nd) Cyclophosphamide (2 nd , 3 rd)	C-section	36	Gestational diabetes and preeclampsia at 30 and 34 wks of gestation. Male infant: 3,600 g, Apgar scores 9 and 9. Newborn was grossly normal in appearance.	At 12 months, normal growth, neurologic findings, and renal function.	(Henderson <i>et al.</i> 1993)
Carboplatin (AUC = 5 every 3 wks, 3 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 25 Last@wk 32	Paclitaxel	C-section	35	Male infant: 2,450 g, Apgar scores 9, 10, and 10. Newborn was healthy. He showed minor respiratory distress and mild anemia, but no neurologic, psychomotor, or developmental abnormalities.	At 20 months he showed no abnormalities.	(Hubalek <i>et al.</i> 2007)
Carboplatin (400 mg/m ² every 4 wks, 3 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 22 Last@wk 28	None	C-section	37	Male infant: 3,245 g, Apgar scores 9 and 9. Newborn appeared normal with no myelosuppression and normal renal function.	Infant continued to develop normally [time of follow-up NS] .	(Koc <i>et al.</i> 1994)
Carboplatin (AUC = 5, 6 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 16-17 Last@wk 32	Paclitaxel	C-section	35.5	Infant, sex NS: 2,500 g, Apgar scores 9, 9, and 9 at 1, 5, and 10 minutes. Newborn had normal physical examination and laboratory tests.	At 15 months, there was no evidence of neurologic, renal, growth, or hematologic sequelae.	(Mendez <i>et al.</i> 2003)
Carboplatin (AUC = 5, 4 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 22 Last@wk 35	Paclitaxel	C-section	35	Male infant: 2,600 g, Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was healthy.	At 6 months, he showed no evidence of neurologic, renal, growth, or hematologic sequelae.	(Modares Gilani <i>et al.</i> 2007)
Carboplatin (350 mg/m ² , 2 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 27 Last@wk 30	None	C-section	34	Female infant: 1,900 g, Apgar scores 9 and 10. Newborn was healthy.	At 18 months, development was normal.	(Picone <i>et al.</i> 2004)

Appendix C Table 15. Carboplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Carboplatin (AUC = 6 , 4 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 21 Last@wk 33	None	C-section	33	Male infant: 2,222 g, Apgar scores 9 and 10 at 1 and 5 minutes.	At 12 months, he was normal.	(Tabata <i>et al.</i> 2008)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the carboplatin timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix C Table 16. Cisplatin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (Dose/schedule NS)	Case series	5 of 13 (Pts 5, 6, 7, 8, 9)	Cervix	2 nd	None	NS	27	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	(Abellar <i>et al.</i> 2009)
			Cervix	3 rd	5-Fluorouracil	NS	34	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	
			Ovary	2 nd , 3 rd	None	NS	39	Newborn sex, weight, and Apgar scores NS. Newborn had experienced intrauterine growth restriction (SGA).	No	
			Ovary	2 nd , 3 rd	None	NS	39	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	
			Adenoid cystic carcinoma	2 nd	Cyclophosphamide, Doxorubicin	NS	25	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	
Cisplatin (100 mg/m ² , 4 cycles, 4 wks apart)	Case report	1	Neuroblastoma	2 nd , 3 rd	Etoposide	C-section	35	Intrauterine growth restriction observed at 35 wks of gestation. Male infant: 1,835 g [SGA], Apgar scores 6 and 8 at 1 and 5 minutes. Newborn showed no evidence of neutropenia or other post-chemotherapy sequelae. A brainstem auditory-evoked response was normal.	At 20 days, normal.	(Arango <i>et al.</i> 1994)
Cisplatin (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, diffuse lymphoblastic	3 rd	Doxorubicin, Vincristine, Cyclophosphamide, Asparaginase, Cytarabine	C-section	NS	Male infant: 2,600 g. Apgar scores NS. Newborn was apparently healthy.	At 2 years, no growth retardation, mental retardation, or malformations were noted.	(Ataergin <i>et al.</i> 2007)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (50 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Cervix	2 nd , 3 rd First@wk 23 Last@wk 32	Vincristine	C-section	32 + 6 days	Male infant: 1,920 g, Apgar scores 9, 10 and 10 at 1, 5 and 10 minutes. Newborn developed respiratory distress syndrome at 32 hours and required mechanical ventilation until day 5.	At 4 wks, in good condition; at [~77 months] , developing normally.	(Bader <i>et al.</i> 2007a)
Cisplatin (100 mg/m ² , 2 cycles)	Case report	1	Ovary	3 rd	Cyclophosphamide	Vaginal	35	Polyhydramnios at 33 wks of gestation. Premature rupture of membranes at 35 wks of gestation. Male infant: 2,600 g, Apgar scores 5 and 7 at 1 and 5 minutes. Polyhydramnios was observed. Newborn had respiratory difficulty for 12 hours, but was otherwise normal.	At 18 months, progressing normally without neurodevelopmental abnormalities.	(Bayhan <i>et al.</i> 1999)
Cisplatin (50 mg/m ² , 2 cycles)	Case report	1	Cervix	2 nd First@wk 24	None	C-section	28	Preeclampsia at 28 wks. Infant sex, weight, and Apgar scores NS. Newborn was healthy.	No	(Benhaim <i>et al.</i> 2008)
Cisplatin (20 mg/m ² on days 1-5, 4 cycles, 3 wks apart)	Case report	1	Ovary	2 nd First@wk 15	Bleomycin, Etoposide	C-section	36	Ultrasound revealed small for gestational age, but normal, fetus. Male infant: 1,560 g [SGA] , Apgar scores 9 and 10 at 1 and 5 minutes. Newborn did not have any evidence of malformations.	At 21 months, no evidence of major or minor malformations; normal growth and development.	(Benjapibal <i>et al.</i> 2010)
Cisplatin (100 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Cervix	2 nd First@wk 25 Last@wk 31	None	C-section	35 + 3 days	Male infant: 2,380 g, Apgar scores 7, 9, and 10 at 1, 5, and 10 minutes. Newborn was treated for hypoglycemia and received oxygen for 48 hours.	At 15 months, well clinically.	(Boyd <i>et al.</i> 2009)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (20 mg/m ² on days 1-5, 3-4 wks apart)	Case series	1 of 3 (Pt 3)	Ovary	2 nd , 3 rd First@wk 26	Etoposide	Vaginal, induced	38	Oligohydramnios and probable intrauterine growth retardation at 38 wks of gestation. Female infant: 2,320 g [SGA], Apgar scores NS. Newborn was healthy. Placenta had foci of villous edema.	At 9 months, developing normally.	(Buller <i>et al.</i> 1992)
Cisplatin (75 mg/m ² for first 4 cycles, and 63 mg/m ² for last 2 cycles; cycles were 10 days apart)	Case report	1	Cervix	2 nd First@wk 17 Last@wk 27 [table] or 28 [text]	None	C-section	32	Male infant: 1,715 g [SGA], Apgar scores NS. Newborn had no abnormalities and had slightly elevated serum creatinine that normalized within a few days.	At 6 months, thriving well with normal psychomotor development.	(Caluwaerts <i>et al.</i> 2006)
Cisplatin (Dose/schedule NS)	Survey, registry	1 of 31 from Table 3	Non-Hodgkin lymphoma	3 rd	Cytarabine, Etoposide	NS	34.0 (group mean)	Infant sex NS: 2,576 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 2 months, normal phenotype. At 34 to 82 months (group range, n=6), 1 child in the group had a speech delay; group mean weight was 46 th percentile.	(Cardonick <i>et al.</i> 2010)
		4 of 7 from Table 4 [assumed that only 1 pt had twins]	Ovary	2 nd , 3 rd	Bleomycin, Etoposide (3 pts) or Paclitaxel (1 pt)	NS	38.1 (group mean)	Infant sex NS: 2,639 g (group mean), Apgar scores NS. Four newborns (including 1 set of twins) were normal with normal body weight for gestational age. 1 infant had genetic hearing loss (both parents were carriers), a spontaneous mutation for neurofibromatosis, and intrauterine growth retardation (SGA).	At age 11, 1 child (with a normal twin) had Asperger syndrome, attention-deficit disorder, and delays in school. At 63.3 months (group mean, n=7), 1 child had motor/language delay; group mean weight was 35 th percentile.	
		2 of 12 from Table 6	Cervix	2 nd , 3 rd	None (1 pt) or Vincristine (1 pt)	NS	32 (group mean)	Infant sex NS: 2,173 g (group mean), Apgar scores NS. Both newborns were normal.	At 12 to 87 months (group range, n=4), no long-term complications; group mean weight was 59 th percentile.	
		1 of 12 from Table 6	Lung	2 nd , 3 rd	Vincristine, Vinorelbine, Radiation therapy	NS	36	Infant sex NS: 2,495 g, Apgar scores NS. Newborn was normal; placenta had areas of infarction.	At 2 months, there were no complications.	

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (2 cycles over 6 wks, doses NS)	Case report	1	Tongue, squamous cell carcinoma	2 nd First@~wk 26 Last@wk 32	Paclitaxel	C-section	32	Male infant: weight and Apgar scores NS. Admitted to NICU with jaundice and anemia.	At 1 year, anemic, diagnosed as hereditary spherocytosis. At 13 months, feeding and active, but was low birth weight and height for gestational age.	(Cheung <i>et al.</i> 2009)
Cisplatin (100 mg/m ² on day 1, 1 cycle)	Case report	1	Ovary	2 nd First@wk 19	Vinblastine, Bleomycin	Vaginal	Term	Male infant: 3,232 g, Apgar scores 8 and 9 ant 1 and 5 minutes. Newborn appeared healthy.	[At ~4.5 years,] normal development with a normal karyotype.	(Christman <i>et al.</i> 1990)
Cisplatin (Pt 1 - 75 mg/m ² , 3 cycles. Pt 3 - 75 mg/m ² , 2 cycles)	Case series	2 of 3 (Pts 1 and 3)	Cervix	2 nd , 3 rd First@wk 26 Last@wk 32	Paclitaxel	C-section	35 + 5 days	Female infant: 2,570 g, Apgar scores NS. Newborn showed no signs of toxicity.	At 3 months, well and healthy.	(Chun <i>et al.</i> 2010)
				3 rd First@wk 31 Last@wk 34	Paclitaxel	C-section	36 + 5 days	Male infant: 2,600 g, Apgar scores NS. Newborn had no abnormalities.	At 5 years, normal development.	
Cisplatin (25 mg/m ² on days 1-3, 2 cycles, 4 wks apart)	Case report	1	Melanoma	2 nd First@wk 23 Last@wk 26.5	Tamoxifen, Carmustine, Dacarbazine	C-section	30	Female infant: 1,520 g, Apgar scores NS. Pathology revealed a malignant melanoma in the placenta.	At 17 months (corrected to 15 months for early delivery), normal muscle tone and reflexes, and, overall, age-appropriate evaluations.	(DiPaola <i>et al.</i> 1997)
Cisplatin (20 mg/m ² for 5 days, 1 cycle)	Case report	1	Ovary	2 nd First@wk 25 + 5 days	Etoposide, Bleomycin	C-section	28 + 1 day	Mild to moderate bilateral ventriculomegaly at 26 wks of gestation + 5 days. Female infant: 1,085 g, Apgar scores 7 and 8. Newborn had mild to moderate respiratory distress syndrome and apnea of prematurity. Newborn also had profound ventriculomegaly and cerebral atrophy.	No	(Elit <i>et al.</i> 1999)
Cisplatin (75 mg/m ² , 6 cycles, 3 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 17 Last@wk 34	None	C-section	36	Male infant: 3,000 g, Apgar scores 9 and 9 at 1 and 5 minutes.	At 42 months, no evidence of neurologic, renal, growth, or hematologic sequelae.	(Ferrandina <i>et al.</i> 2005)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (Pt 1 - 50 mg/m ² , every 2 wks; Pts 2 to 9 - 75 mg/m ² once every 3 wks; 4 cycles (median), ranging from 2 to 6 cycles)	Case series	9 of 9	Cervix	2 nd and/or 3 rd First@after 16 wks (median)	Vincristine	C-section	35 (median; range 30-36)	Infant (sex NS): 1,330 g, Apgar scores NS. Newborn had no congenital malformations.	No	(Fruscio <i>et al.</i> 2012)
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	None	C-section	35 (median; range 30-36)	Infant (sex NS): 2,890 g, Apgar scores NS. Newborn had no congenital malformations.	No	
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	Paclitaxel	C-section	35 (median; range 30-36)	Infant (sex NS): 2,030 g, Apgar scores NS. Newborn had no congenital malformations and required mechanical ventilation immediately after birth (resolved).	No	
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	Paclitaxel	C-section	35 (median; range 30-36)	Infant (sex NS): 1,900 g, Apgar scores NS. Newborn had no congenital malformations, and had an intraventricular hemorrhage. Newborn was discharged as healthy after 40 days.	No	
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	None	C-section	35 (median; range 30-36)	Infant (sex NS): 2,450 g, Apgar scores NS. Newborn had no congenital malformations.	No	
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	None	C-section	35 (median; range 30-36)	Infant (sex NS): 2,990 g, Apgar scores NS. Newborn had no congenital malformations.	No	
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	None	C-section	35 (median; range 30-36)	Infant (sex NS): 2,890 g, Apgar scores NS. Newborn had no congenital malformations.	No	
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	None	C-section	35 (median; range 30-36)	Infant (sex NS): 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	No	
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	None	C-section	35 (median; range 30-36)	Infant (sex NS): 2,200 g, Apgar scores NS. Newborn had no congenital malformations.	No	

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (Pt 5 - 450 mg/m ² , 6 cycles; Pt 6 - 50 mg/m ² , 1 cycle; Pt 8 - 200 mg/m ² , 4 cycles; Pt 9 - 175 mg/m ² , 5 cycles; Pt 11 - 180 mg/m ² , 3 cycles; Pt 12 - 135 mg/m ² total over 3 cycles)	Case series	6 of 15 (Pts 5, 6, 8, 9, 11, 12)	Ovary	2 nd First@wk 18	None	C-section	35.6	Infant sex NS: 2,690 g. Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was well with no malformations, but had anemia.	Well and healthy at follow-up. [Follow-up examinations were conducted at ages ranging from 2 to 198 months. Individual ages NS.]	(Gambino <i>et al.</i> 2011)
			Cervix	2 nd First@wk 21	None	Vaginal	22	Premature rupture of membranes. Spontaneous abortion. [No fetal data reported.]	--	
			Cervix	2 nd First@wk 23	Vincristine	C-section	32.1	Infant sex NS: 1,690 g, Apgar scores 5 and 8 at 1 and 5 minutes. Newborn was well with no malformations, but had anemia.	Well and healthy at follow-up. [Follow-up examinations were conducted at ages ranging from 2 to 198 months.]	
			Ovary	2 nd First@wk 19	None	C-section	34	Infant sex NS: 1,970 g, Apgar scores 7 and 10 at 1 and 5 minutes. Newborn was well with no malformations.	Well and healthy at follow-up. [Follow-up examinations were conducted at ages ranging from 2 to 198 months.]	
			Cervix	2 nd , 3 rd First@wk 27	None	C-section	36	Infant sex NS: 2,590 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was well with no malformations.	Well and healthy at follow-up. [Follow-up examinations were conducted at ages ranging from 2 to 198 months. Individual ages NS.]	
			Urethral	3 rd First@wk 30	None	C-section	33.2	Infant sex NS: 2,370 g, Apgar scores 8 and 8 at 1 and 5 minutes. Newborn was well with no malformations.	Well and healthy at follow-up. [Follow-up examinations were conducted at ages ranging from 2 to 198 months.]	

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (75 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Lung	2 nd First@wk 21 Last@wk 27	Paclitaxel	C-section	30	At gestation wk 30, brain metastasis lead to tonic-clonic seizures in mother. Male infant: 1,720 g, Apgar scores of 3 and 4 at 1 and 5 minutes. Newborn developed acute respiratory distress syndrome requiring mechanical ventilation for 24 hours. Newborn had no congenital abnormalities.	At 15 months, well with normal development and growth.	(Garcia-Gonzalez <i>et al.</i> 2008)
Cisplatin (75 mg/m ² on day 1, 3 cycles, 3 wks apart)	Case report	1	Lung	3 rd	Vinorelvine [Vinorelbine]	C-section	39	Infant sex NS: 2,910 g, Apgar score 9. Newborn was healthy.	No	(Garrido <i>et al.</i> 2008)
Cisplatin (40 mg/m ² , 4 cycles, 1 wk apart)	Case series	1 of 21	Cervix	NS	Brachytherapy	NS	NS	Individual pregnancy outcomes NS. No abnormalities or malformations were reported for 11 newborns. One newborn died of fetal cardiac arrest.	No	(Germann <i>et al.</i> 2005)†
Cisplatin (20 mg/m ² daily for 5 days, 3 cycles, 1 wk apart)	Case report	1	Ovary	3 rd	Etoposide, Bleomycin	C-section	36	Oligohydramnios and estimated fetal weight < 5 th percentile observed 2 wks after last dose [age NS]. Male infant: 2,000g [SGA], Apgar score 9-10 at 15 minutes. Newborn had mild glandular hypospadias, but otherwise had a normal appearance.	At 1 month, ultrasound of the brain and kidney were normal, as were hearing studies and eudiometry. At 8 months, normal physical and neurological development.	(Ghaemmaghami <i>et al.</i> 2009)
Cisplatin (20 mg/m ² , for 5 days, 5 cycles, 3 wks apart)	Case series	1 of 3 (Pt 2)	Ovary	2 nd , 3 rd First@wk 18	Etoposide, Bleomycin	C-section	35	Premature rupture of membranes. Infant sex NS: 2,400 g, Apgar scores 7 and 9 at 1 and 5 minutes.	At 1 year, developing normally.	(Ghaemmaghami and Hasanzadeh 2006)
Cisplatin (75 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Cervix	2 nd , 3 rd First@wk 22 Last@wk 28	None	C-section	32	Male infant: 2,120 g, Apgar scores NS. Newborn showed no sign of metabolic or hematologic abnormality.	At 12 months, normal development.	(Giacalone <i>et al.</i> 1996)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (25 mg/m ² on days 1-3, 2 cycles, 4 wks apart)	Case report	1	Melanoma	2 nd	Interferon (1 st) Dacarbazine, Radiation therapy (2 nd , 3 rd , [calendar dates and wks of gestation are inconsistent])	C-section	28 + 3 days	Intrauterine growth retardation (fetal growth at 3 rd percentile) at 28 wks of gestation. Male infant: 735 g [SGA], Apgar scores 6, 8, and 8. Newborn was healthy without signs of metastatic melanoma.	Uneventful, age-appropriate development [age NS].	(Gottschalk <i>et al.</i> 2009)
Cisplatin (70 mg/m ² for 5 days, 5 cycles (Pt 1) or 2 cycles (Pt 2); cycles were 4 wks apart)	Case series	2 of 2	Ovary	2 nd , 3 rd First@wk 22	Etoposide, Bleomycin	Vaginal	40	Small for gestational age fetus. Male infant: 2,610 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn showed no gross malformations.	At 1 month, brain and kidneys were normal by ultrasound. At 6 years, normal physical and neurological development.	(Han <i>et al.</i> 2005)
			Ovary	3 rd First@wk 30	Etoposide, Bleomycin	Vaginal, induced	38	Male infant: 2,970 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn showed no gross malformations at birth.	At 7.5 months, intussusception; at 26 months, normal physical and neurological development.	
Cisplatin (100 mg/m ² , 2 cycles)	Case report	1	Ovary	2 nd First@wk 20	Cyclophosphamide (2 nd , 3 rd), Carboplatin (3 rd)	C-section	36	Gestational diabetes and preeclampsia at 30 and 34 wks of gestation. Male infant: 3,600 g, Apgar scores 9 and 9. Newborn was grossly normal in appearance.	At 12 months, normal growth, neurologic findings, and renal function.	(Henderson <i>et al.</i> 1993)
Cisplatin (100 mg/m ² , 3 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 21 Last@wk 29	Etoposide, Bleomycin	Vaginal, induced	39	Mild preeclampsia. Female infant: 2,769 g, Apgar scores 4 and 7 at 1 and 5 minutes. Newborn was anemic; no fetal anomalies were identified.	Normal development as assessed by the Child Development Assessment Team [age NS].	(Horbelt <i>et al.</i> 1994)
Cisplatin (50 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Ovary	2 nd	Cyclophosphamide	C-section	30	Spontaneous preterm labor with premature rupture of membranes at 29 wks of gestation. Breech presentation.	Normal growth and neurological and mental development [age NS].	(Huang <i>et al.</i> 2004)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Female infant: 1,816 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn was active.		
Cisplatin (Dose/schedule NS)	Cohort, retrospective	7 of 72	Breast	2 nd or 3 rd	Doxorubicin, Cyclophosphamide, 5-Fluorouracil, Paclitaxel	NS	NS	Individual pregnancy outcomes were not provided. No congenital malformations were diagnosed in the newborns.	No	(Ibrahim <i>et al.</i> 2000)†
Cisplatin (50 mg/kg, 1 dose)	Case report	1	Cervix	1 st First@wk 10	None	--	--	Induced abortion [at approximately 13 wks of gestation]. Male fetus, all fetal organs were examined histologically. The testis showed the presence of a giant cell (possible megakaryocyte), all other tissues appeared normal.	--	(Jacobs <i>et al.</i> 1980)
Cisplatin (100 mg/m ² , 1 dose)	Case report	1	Lung	2 nd , 3 rd First@wk 26	Vinorelbine	C-section	26 + 4 days	Patient had rapidly progressive respiratory symptoms. Infant sex and weight NS, Apgar scores 7 and 8 at 1 and 5 minutes. Newborn was healthy. At 10 days, transient decrease in white blood cell and platelet counts (recovered by 3 wks).	No	(Janne <i>et al.</i> 2001)
Cisplatin (40 mg/m ² , 7 cycles, 1 wk apart)	Case report	1	Cervix	2 nd , 3 rd First@wk 24 Last@wk 30	None	C-section	33	Spontaneous preterm labor at 31 wks of gestation, treated and subsided. Female infant: 2,450 g, Apgar score NS. Newborn had a mild elevation of serum creatinine (resolved by day 8).	At 14 months, normal neuropsychomotor development.	(Karam <i>et al.</i> 2007)
Cisplatin (20 mg/m ² for 5 days, 2 cycles, 3 wks apart)	Case report	1	Ovary	3 rd First@wk 29	Etoposide, Bleomycin	C-section	39	Female infant: 3,100 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn showed no gross malformations.	At 1 month, brain and kidneys normal by ultrasound; at 1.5 years, normal physical and neurological development.	(Karimi Zarchi <i>et al.</i> 2008)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (35 mg/m ² on days 1 and 8, 6 cycles, 3 wks apart)	Case report	1	Lung	1 st , 2 nd First@wk 9	Gemcitabine (2 nd), Docetaxel	C-section	33	Female infant: 1,490 g [SGA], Apgar scores 8, 9, and 10 at 1, 5, and 10 minutes. Newborn showed no evidence of hearing, thyroid, adrenal, hepatorenal, and hematologic dysfunction, or gross congenital malformations.	[At 2 months,] developing normally.	(Kim <i>et al.</i> 2008)
Cisplatin (100 mg/m ² once a month, 2 cycles)	Case report	1	Adenoid cystic carcinoma, submandibular gland	1 st First@wk 5 Last@wk 10	Doxorubicin, Cyclophosphamide	C-section	25	Spontaneous preterm labor Male infant: 912 g, Apgar scores 1 and 6 at 1 and 5 minutes. Newborn had blepharophimosis, microcephaly, and hydrocephalus.	No	(Kim <i>et al.</i> 1996)
Cisplatin (100 mg/m ² , 6 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd	Cyclophosphamide	Vaginal	36.5	Premature rupture of membranes and labor at 36.5 wks of gestation. Male infant: 3,060 g, Apgar scores 7 and 8. Shortly after delivery, newborn developed tachycardia and respiratory distress requiring intubation (resolved within 24 hours).	At 28 months, normal physical and mental development.	(King <i>et al.</i> 1991)
Cisplatin (80 mg/m ² on day 1, 4 cycles, 3 wks apart)	Case report	1	Lung	3 rd First@wk 27	Etoposide	C-section	34	Male infant: weight NS, Apgar scores 9 and 9. Newborn was normal.	No	(Kluetz and Edelman 2008)
Cisplatin (Dose/schedule NS, 4 cycles)	Case series	3 of 27 (only 3 pts received chemotherapy during pregnancy)	Ovary	2 nd and/or 3 rd First@wk 22.8-30.6 (group range)	Etoposide, Bleomycin	NS	Full term	Individual pregnancy outcomes NS. Newborns were healthy with no congenital malformations.	No	(Kwon <i>et al.</i> 2010)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (25 mg/m ² on days 1-3, 4 cycles)	Case report	1	Melanoma	1 st , 2 nd	Carmustine, Dacarbazine, Tamoxifen	C-section	34	Male infant: 2,750 g, Apgar scores 10 and 10 at 1 and 5 minutes. No dysmorphism detected in the newborn.	At 1 year, social, hearing, and gross and fine motor assessments were normal; however, he was diagnosed with microphthalmia and severe hypermetropia.	(Li <i>et al.</i> 2007)
Cisplatin (50 mg/m ² , 2 cycles 2 wks apart)	Case series	2 of 2	Cervix	3 rd First@wk 28 Last@wk 30	Paclitaxel	C-section	34	Spontaneous preterm labor at 29 wks of gestation + 3 days was treated, subsided. Male infant: 2,200 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no malformations and no evidence of metabolic or hematologic abnormality.	At 21 months, normal development.	(Li <i>et al.</i> 2011)
				3 rd First@wk 30 Last@wk 32	Paclitaxel	C-section	34	Male infant: 2,200 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn had no malformations.	At 13 months, in good general condition.	
Cisplatin (Dose/schedule NS, 5 cycles)	Case series	2 of 15 (Pts 9, 15)	Ovary	2 nd	Etoposide	NS	NS	Infant sex NS: 3,190 g, Apgar scores NS. Newborn was healthy with no malformations.	No	(Machado <i>et al.</i> 2007)
				2 nd	Etoposide	NS	NS	Infant sex NS: 2,200 g, Apgar scores NS. Newborn was healthy with no malformations.	No	
Cisplatin (50 mg/m ² , 7 cycles, 3 wks apart)	Case report	1	Ovary	2 nd , 3 rd	Cyclophosphamide	Vaginal, induced	37-38	Male infant: 3,275 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn had no abnormalities.	At 18 months, progressing normally without neurodevelopmental abnormalities.	(Malfetano and Goldkrand 1990)
Cisplatin (Dose/schedule NS)	Case series	1 of 2 (Pt 2)	Ovary	2 nd First@wk 20	Etoposide, Bleomycin	C-section	31	Infant sex, weight, and Apgar scores NS. Newborn required intensive care for hyaline membrane disease [respiratory distress].	No	(Malhotra and Sood 2000)
Cisplatin (75 mg/m ² on day 1, 2 cycles, 3 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 27	Vinblastine, Bleomycin	C-section	32	Male infant: 1,900 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn experienced a mild episode of transient tachypnea but was otherwise normal.	Normal at follow-up [age NS].	(Malone <i>et al.</i> 1986)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (50 mg/m ² on days 2 and 3, 2 cycles, 4 wks apart)	Case report	1	Cervix	2 nd First@wk 17 Last@wk 20	Bleomycin	C-section	38	Male infant: 2,850 g, Apgar scores 8/10 at 1 and 5 minutes.	At 3 years, normal physical and neurological development.	(Marana <i>et al.</i> 2001)
Cisplatin (20 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Cervix	2 nd , 3 rd	None	C-section	32	Male and female infants (twins): 2,020 g (male) and 1,790 g (female), Apgar scores for both twins were 9/10. Both newborns showed normal development. One neonate required respiratory support.	No	(Marnitz <i>et al.</i> 2009) [†] [This case was not included in the text analysis because it was Pt 1 in Marnitz <i>et al.</i> (2010)].
Cisplatin (20 mg/m ² on days 1-3 every 3 wks; Table 1: Pt 3 – 2 cycles [text says Pt 2], all other Pts – 3 cycles)	Case series	7 of 7	Cervix	2 nd , 3 rd	None	C-section	32 + 2 days	Birth weight: 1,600-2,960 (group range). Individual pregnancy outcomes NS. For 8 newborns (Pt 1 had twins with normal body weight for gestational age), all were healthy and without renal, hepatic, auditory, neurologic, or hematopoietic impairment.	At a mean follow-up of 7 months, all had normal development.	(Marnitz <i>et al.</i> 2010) [More details on Pt 1 in Marnitz <i>et al.</i> (2009)]
				2 nd , 3 rd	None	C-section	32 + 1 day			
				2 nd , 3 rd	None	C-section	35 + 1 day			
				2 nd , 3 rd	None	C-section	32 + 6 days			
				2 nd , 3 rd	None	C-section	33 + 4 days			
				2 nd , 3 rd	None	C-section	32			
Cisplatin (75 mg/m ² on day 1, 3 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 20 Last@wk 28	Bleomycin, Vinblastine	C-section	31	Intrauterine growth restriction and marked reduction in amniotic fluid at 28 and 31 wks of gestation, respectively. Maternal hypertension. Female infant: 1,070 g [SGA], Apgar scores NS. Newborn was apparently normal.	At 65 months, pediatric follow-up did not detect any sign of metabolic or hematologic abnormality.	(Motegi <i>et al.</i> 2007)
Cisplatin (100 mg, 4 cycles)	Case report	1	Ovary	2 nd First@wk 18	Cyclophosphamide, Doxorubicin	C-section	33	Male infant: 1,896 g, Apgar scores 9/10. No anomalies or deformities were noted in the newborn.	Growth of the child has been normal [age NS].	(Ohara and Teramoto 2000)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (100 mg/m ² for 3 cycles, 75 mg/m ² for last cycle; cycles were 3 wks apart)	Case report	1	Ovary	3 rd Last@wk 28	None	C-section	31	Male infant: 1,740 g, Apgar scores 6 and 9 at 1 and 5 minutes. Newborn was in good condition.	At 10 months, alive and well with no evidence of hearing impairment or developmental delay.	(Otton <i>et al.</i> 2001)
Cisplatin (75 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Cervix	2 nd , 3 rd	Paclitaxel (2 nd , 1 st cycle only)	C-section	35	Female infant: 2,400 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was in good condition with no sign of metabolic or hematologic abnormality. Auditory brainstem evoked potentials were normal.	At 10 months, in good general condition.	(Palaia <i>et al.</i> 2007)
Cisplatin (Dose/schedule NS)	Cohort, retrospective	2 of 14 from Tables 3 and 4 (Pts 1, 11)	Hodgkin lymphoma	2 nd First@wk 26	Etoposide, Cytarabine	NS	36	Infant sex NS: 2,540 g, Apgar scores NS. Newborn had jaundice and non-hemolytic anemia.	No	(Peres <i>et al.</i> 2001)
			Non-Hodgkin lymphoma	2 nd First@wk 22	Etoposide			Fetal death [stillbirth] at gestation wk 26. No malformations.		
Cisplatin (Dose/schedule NS, 3 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 23 Last@wk 31	Etoposide	C-section	39	Male infant: 3,130 g, Apgar scores 10, 10, and 10. Newborn had a normal aspect [no malformations], and clinical examinations were normal.	No	(Poujade <i>et al.</i> 2008)++
Cisplatin (75 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Cervix	2 nd First@wk 18	None	C-section	32	Male infant: 1,920 g, Apgar scores 8.8 at 1 and 5 minutes. Newborn developed respiratory distress syndrome after 15 minutes and required intubation; switched to mechanical ventilation on day 2 until day 6. Newborn also had anemia requiring transfusion on day 2, and parenteral feeding until day 3.	At 2 years, no evidence of abnormalities in neuropsychomotor development.	(Rabaiotti <i>et al.</i> 2010)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (55 mg daily for 3 days)	Case report	1	Adenocarcinoma (primary not located)	2 nd First@wk 26	Bleomycin, Etoposide	Vaginal	27	Spontaneous preterm labor. Female infant: 1,190 g, Apgar scores 3 and 8 at 1 and 5 minutes. Infant developed severe respiratory distress and pneumothorax (room air by day 10). Infant developed a profound leucopenia with neutropenia by day 3 (resolved by day 13). Blood transfusions for anemia associated with immaturity were required twice. The platelet count fell, but the infant never became frankly thrombocytopenic. There was no demonstrable neurological abnormality, and cerebral ultrasound remained normal throughout the neonatal period. At the age of 10 days the infant was noted to be losing her scalp hair, and there was an associated rapid loss of lanugo.	At 1 year, neurodevelopmental progress is normal, but there is a moderate sensorineural hearing loss.	(Raffles <i>et al.</i> 1989)
Cisplatin (70 mg/m ² , 5 cycles, 4 wks apart)	Case report	1	Ovary	1 st , 2 nd First@wk 14 Last@wk 29	Paclitaxel	C-section	34	Persistent pregnancy-induced hypertension at 32 wks of gestation. Male infant: 1,750 g [SGA], Apgar scores NS. Newborn cried after birth and did well postnatally.	At 18 months, normal growth and development.	(Raghunath and Shashi 2006)
Cisplatin (100 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Ovary	2 nd , 3 rd Last@wk 32	None	C-section	34 + 4 days	Female infant: 1,980 g, Apgar scores 7, 8, and 9. Newborn required positive airway pressure for 3 days. Newborn also had anemia requiring transfusion.	At 1 and 2 years, normal physical and psychological evaluation.	(Robova <i>et al.</i> 2007)
Cisplatin (75 mg/m ² , 4 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 21	Docetaxel	C-section	34	Anhydramnios and left-sided ventriculomegaly diagnosed prior to chemotherapy; ventriculomegaly increased during chemotherapy treatment.	--	(Rouzi <i>et al.</i> 2009)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Female infant: 2,245 g, Apgar scores 3 and 6 at 1 and 10 minutes. Newborn died 5 days after delivery because of congenital malformations diagnosed prior to chemotherapy.		
Cisplatin (30 mg/m ² for wks 25, 27, and 29; 40 mg/m ² for wks 26, 28, and 30)	Case report	1	Cervix	2 nd , 3 rd First@wk 25 Last@wk 30	Vincristine	C-section	31	Male infant: 1,660 g, Apgar scores 7/8. Newborn had an uncomplicated neonatal course.	Child remains healthy [at age of approximately 4 years].	(Seamon <i>et al.</i> 2009)
Cisplatin (75 mg/m ² , every 3 wks for 2 cycles)	Case report	1	Ovary	3 rd	Paclitaxel	C-section	34	Female infant: 1,900 g, Apgar scores 8 at 5 minutes. Newborn was healthy with normal laboratory tests.	At 73 months of age, normal growth and development.	(Serkes <i>et al.</i> 2011)
Cisplatin (75 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Ovary	3 rd First@~wk 29 Last@~wk 35	Paclitaxel	C-section	37	Female infant: 2,800 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal with no evidence of hearing, thyroid, adrenal, hematological, or congenital abnormalities.	At 30 months, normal growth and development.	(Sood <i>et al.</i> 2001)
Cisplatin (50 mg/m ² , 6 cycles (Pt 1) or 4 cycles (Pt 2))	Case series	2 of 2	Cervix	2 nd , 3 rd First@wk 21 Last@wk 30	Vincristine (2 nd)	C-section	34	Female infant: 2,160 g, Apgar scores NS. Newborn was viable and had an uneventful neonatal period.	No	(Tewari <i>et al.</i> 1998)
			Cervix	2 nd , 3 rd First@wk 21 Last@wk 29	Vincristine	C-section	32	Male infant: 1,700 g, Apgar scores NS. Newborn was viable.	At 2 years, very healthy.	
Cisplatin (750 mg/m ² , 3 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 24 Last@wk 32	Cyclophosphamide	Vaginal, induced	34	Male infant: 2,280 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no complications.	At 12 months, growing and developing normally.	(Tomlinson <i>et al.</i> 1997)

Appendix C Table 17. Cisplatin – (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cisplatin (25 mg/m ² /day on days 1 and 4 of a 21-day cycle, 3 cycles)	Case report	1	Ovary	3 rd	Etoposide	C-section	38	Intrauterine growth retardation. Male infant: 2,180 g [SGA], Apgar scores were 8 at 1 minute and 9 at 5 minutes. Newborn had no gross fetal anomalies, but did have hypoglycemia and hyperbilirubinemia.	[At age ~14 months,] normal growth.	(Tseng and ChangChien 2004)
Cisplatin (Dose/schedule NS, 1 cycle)	Survey, retrospective	1 of 17 (Pt 26)	Pancreas	3 rd First@wk 31	5-Fluorouracil	Vaginal	33	Infant sex, weight, and Apgar scores NS. Newborn had no malformations, but was premature with low birth weight.	No	(Ustaalioglu <i>et al.</i> 2010)
Cisplatin (Dose/schedule NS)	Cohort, retrospective	1 of 21 (Pt 21)	Ovary	3 rd	Cyclophosphamide, Doxorubicin	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with and normal body weight per gestational age.	No	(Zemlickis <i>et al.</i> 1992b)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the cisplatin timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Paper not included in text analysis (highlighted in light grey). Ibrahim *et al.* (2000) was not included because it was not possible to determine the individual treatment regimens of the 7 patients receiving chemotherapy during pregnancy. A retrospective case series reported by Germann *et al.* (2005) was not included because the individual pregnancy outcomes of patients treated with chemotherapy were not specified. A case report by Marnitz *et al.* (2009) was not included in the text summary analysis because this twin pregnancy was included in a subsequent case series (Marnitz *et al.* 2010).

††Poujade *et al.* (2008) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 18. Cyclophosphamide – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Dose/schedule NS)	Case series	5 of 13 (Pts 2, 3, 4, 9, 10)	Breast	2 nd	Doxorubicin	NS	36	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	(Abellar <i>et al.</i> 2009)
			Breast	2 nd	Doxorubicin	NS	39	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.		
			Breast	2 nd	Doxorubicin	NS	33	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.		
			Adenoid cystic carcinoma	2 nd	Doxorubicin, Cisplatin	NS	25	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.		
			Non-Hodgkin lymphoma, diffuse large B-cell	2 nd , 3 rd	Vincristine, Doxorubicin	NS	32	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.		
Cyclophosphamide (750 mg/m ² on days 1 and 8)	Case report	1	Leukemia, ALL	2 nd	Idarubicin, Vincristine	C-section	28	Male infant: 1,024 g, Apgar scores of 6, 8, and 8 at 1, 5, and 10 minutes. Newborn had no growth restriction or gross malformations. He had respiratory distress, necrotizing enterocolitis, and ventricular hemorrhage. Acute cardiac failure, attributed to idarubicin, occurred during the first 3 days after birth; infant was treated, and cardiac function returned to normal after 3 days.	At 18 months, neurological status was normal, but he showed a slight delay in language acquisition.	(Achtari and Hohlfield 2000)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (1,000 mg/m ² on day 1, 1 cycle)	Case report	1	Leukemia, ALL	3 rd	Vincristine, Daunorubicin, Asparaginase	C-section	33	Preterm premature rupture of the membranes, fetal distress. Male infant: 1,750 g, Apgar scores 4 and 6 at 1 and 5 minutes. Newborn was morphologically normal, but was pale, lethargic, tone-decreased, and had respiratory distress requiring intubation (resolved by day 7).	At 6 months, normal growth and development.	(Ali <i>et al.</i> 2009a)
Cyclophosphamide (600 mg/m ² , 5 cycles, 3 wks apart)	Case report	1	Breast	1 st	5-Fluorouracil, Epirubicin, Tamoxifen (2 nd , 3 rd), Radiation, analgesic (2 nd)	C-section	35	Signs of premature delivery [spontaneous preterm labor]. Female infant: 2,070 g; Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was phenotypically normal and had normal hematological and biochemical values.	At 12 months, functioning normally with no disorder, congenital abnormality or disease observed.	(Andreadis <i>et al.</i> 2004)
Cyclophosphamide (40 mg/kg, schedule NS)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd	Methotrexate	--	--	Induced abortion in the 4 th month of gestation. Fetus weighed 1,070 g and was without gross abnormality.	--	(Armitage <i>et al.</i> 1977)
Cyclophosphamide (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, diffuse lymphoblastic	3 rd First@wk 31	Doxorubicin, Vincristine, Asparaginase, Cisplatin, Cytarabine	C-section	NS	Male infant: 2,600 g. Apgar scores NS. Newborn was apparently healthy.	At 2 years, no growth retardation, mental retardation, or malformations were noted.	(Ataergin <i>et al.</i> 2007)
Cyclophosphamide (1,000 mg/m ² on day 2, 2 cycles, 3 wks apart)	Case report	1	Ovary	3 rd	Doxorubicin, Vincristine	C-section	37	Female infant: 2,500 g, Apgar scores NS. Newborn was healthy with no abnormality. There were multiple tumor deposits in the placenta.	No	(Ateser <i>et al.</i> 2007)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Dose/schedule NS)	Case series, retrospective	3 of 7 from Table I (Pts 1, 5, and 6)	Leukemia, ALL	1 st [see note in reference column]	Vincristine, Doxorubicin, 6-Mercaptopurine, Methotrexate	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 19 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				2 nd	Vincristine, Doxorubicin, 6-Mercaptopurine, Methotrexate	Vaginal	38	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Doxorubicin, 6-Mercaptopurine, Methotrexate	Vaginal	37	Male infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		18 of 18 from Table III	Non-Hodgkin lymphoma	2 nd	Vincristine, Doxorubicin	Vaginal	38	Female infant: 3,400 g, Apgar scores NS. Newborn had no congenital malformations.	At 18 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Doxorubicin, Bleomycin	C-section	39	Male infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Doxorubicin, Etoposide, Methotrexate	Vaginal	40	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 15 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Doxorubicin, Bleomycin	C-section	40	Male infant: 3,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Vincristine, Doxorubicin, Bleomycin	Vaginal	37	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Doxorubicin, Bleomycin, Cytarabine	Vaginal	37	Male infant: 2,900 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Doxorubicin, Bleomycin	Vaginal	38	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Epirubicin, Bleomycin, Cytarabine, Etoposide, Methotrexate	Vaginal	37	Male infant: 2,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Doxorubicin	Vaginal	38	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Doxorubicin, Bleomycin	Vaginal	38	Female infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Doxorubicin	Vaginal	37	Female infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Vincristine, Doxorubicin, Methotrexate, Cytarabine	Vaginal	39	Female infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Doxorubicin, Etoposide, Methotrexate	Vaginal	37	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Doxorubicin, Bleomycin, Methotrexate, Cytarabine, Etoposide	Vaginal	40	Female infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Doxorubicin, Bleomycin	C-section	38	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Epirubicin, Vincristine, Bleomycin	Vaginal	39	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Epirubicin, Vincristine, Bleomycin, Methotrexate, Etoposide, Cytarabine	Vaginal	40	Male infant: 2,800 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Epirubicin, Vincristine, Bleomycin, Cytarabine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Total doses: Pt 1 – 4,000 mg Pt 2 – 8,600 mg Pt 3 – 6,100 mg Pt 4 – 6,500 mg Pt 5 – 3,600 mg Pt 6 – 5,800 mg Pt 7 – 8,900 mg Pt 8 – 2,400 mg Pt 9 – 6,400 mg Pt 10 – 6,100 mg Pt 11 – 7,500 mg; schedule NS)	Case series	16 of 16	Non-Hodgkin lymphoma	2 nd , 3 rd	Vincristine, Doxorubicin, Methotrexate	NS	NS	Individual pregnancy outcomes are not provided. Birth weights were 2,200 g to 3,900 g (group range). All babies were born alive, and none of the newborns showed apparent congenital malformations.	At ages ranging from 3 to 11 years, normal growth and development.	(Avilés <i>et al.</i> 1990) [†]
				1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, Bleomycin					
				2 nd , 3 rd	Vincristine, Doxorubicin, Bleomycin, Methotrexate					
				1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, Bleomycin					
				3 rd	Vincristine, Doxorubicin, Bleomycin, Methotrexate, Etoposide					
				1 st , 2 nd	Vincristine, Doxorubicin, Bleomycin					
				1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, Bleomycin, Methotrexate, 6-Mercaptopurine					

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Vincristine, Doxorubicin, Methotrexate, Etoposide					
				1 st , 2 nd , 3 rd	Vincristine, Doxorubicin					
				2 nd , 3 rd	Vincristine, Doxorubicin, Methotrexate, Cytarabine					
				1 st , 2 nd	Vincristine, Doxorubicin, Bleomycin					
				2 nd , 3 rd	Vincristine, Doxorubicin, Methotrexate, Cytarabine, Etoposide					
				3 rd	Vincristine, Doxorubicin, Methotrexate, Etoposide					
				1 st , 2 nd , 3 rd	Vincristine, Bleomycin, Methotrexate, Cytarabine, Etoposide					
				3 rd	Vincristine, Doxorubicin					
				1 st , 2 nd	Vincristine, Doxorubicin, Bleomycin					
Cyclophosphamide (Dose/schedule NS)	Case series, retrospective	10 of 29 from Table 1	Leukemia, ALL	NS	Vincristine, Doxorubicin	NS	NS	Birth weight, group range: 2,500-3,675 g. Individual pregnancy outcomes, birth weights, and Apgar scores were not provided.	In this long-term follow-up, ranging from 5 to 26 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001)†

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
		29 of 29 from Table 3	Lymphoma	NS	Vincristine, Doxorubicin, Bleomycin	NS	NS	Birth weight, group range: 2,350-4,050 g. Individual pregnancy outcomes, birth weights, and Apgar scores were not provided.		
Cyclophosphamide (Dose/schedule NS)	Case series, retrospective	4 of 18 from Table 1 (Pt 2, 3, 6, and 13)	Leukemia, ALL	1 st , 3 rd	6-Mercaptopurine, Methotrexate	[Vaginal]	[38]	Male infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 13 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	(Avilés and Niz 1988) [Details on Pts 2, 3, and 6 were first reported in Pizzuto <i>et al.</i> (1980); these cases are counted only once using Avilés <i>et al.</i> (1988).]
				1 st , 2 nd , 3 rd	Vincristine, Methotrexate, 6-Mercaptopurine, Cytarabine	[Vaginal]	[40]	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn had no congenital malformations. Alive at 12 years.	At 12 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				1 st , 2 nd , 3 rd	Vincristine, Methotrexate, 6-Mercaptopurine, Cytarabine	[C-section]	[34]	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had pancytopenia and no congenital malformations. Died of septicemia at 21 days; blood counts were normal at death.	--	
				2 nd , 3 rd	Vincristine, Methotrexate, 6-Mercaptopurine, Doxorubicin	NS	NS	Female infant: 2,700 g, Apgar scores NS. Newborn had pancytopenia and no congenital malformations. At 4 wks, blood counts and bone marrow samples were normal.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (300 weekly, cycles NS)	Case series	1 of 5 (Pt 1)	Leukemia, ALL	2 nd , 3 rd First@wk 17	Doxorubicin (2 nd), Vincristine (2 nd), Asparaginase (2 nd), Methotrexate, 6-Mercaptopurine	Vaginal	~39	Female infant: 3,200 g, Apgar scores NS. Newborn was normal.	At 40 months, normal development and growth.	(Awidi <i>et al.</i> 1983)
Cyclophosphamide (600 mg for 5 days, 1 cycle)	Case report	1	Non-Hodgkin lymphoma	1 st First@wk 12	Radiation (2 nd)	Vaginal	39	Male infant: 2,850 g, Apgar score 10 at birth. Newborn had no gross abnormalities.	At 5 months, doing well.	(Ba-Thike and Oo 1990)
Cyclophosphamide (150 mg daily for 14 days of 28-day cycle, 6 cycles)	Case report	1	Breast	2 nd First@wk 17	Doxorubicin, 5-Fluorouracil	Vaginal	NS	Male infant: weight NS, Apgar scores 8 and 9. Newborn was phenotypically normal with a full head of hair.	At 1.5 years, he was well developed.	(Barnicle 1992)
Cyclophosphamide (1,000 mg/m ² , 2 cycles)	Case report	1	Ovary	3 rd	Cisplatin	Vaginal	35	Polyhydramnios at 33 wks of gestation. Premature rupture of membranes at 35 wks of gestation. Male infant: 2,600 g, Apgar scores 5 and 7 at 1 and 5 minutes. Newborn experienced respiratory difficulty during the first 12 hours, but was otherwise normal.	At 18 months, progressing normally without any neurodevelopmental abnormalities.	(Bayhan <i>et al.</i> 1999)
Cyclophosphamide (1,000 mg, 1 cycle)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd [First@ month 7]	Vincristine, Methotrexate (intrathecal)	Vaginal	7 th month	Spontaneous preterm labor 1 wk after starting chemotherapy. Female infant: weight and Apgar scores NS. Newborn was premature, but healthy.	At 3 years, general growth was satisfactory. Hematological parameters, bone marrow, immunoglobulin levels, lymphocyte function, and karyotype were within normal levels.	(Berrebi <i>et al.</i> 1983)
Cyclophosphamide (500 mg/m ² , 1-6 cycles, 3 or 4 wks apart)	Case series	24 of 24	Breast	2 nd and/or 3 rd	Doxorubicin, 5-Fluorouracil	NS	38 (mean), 33-40 (group range)	Three pts delivered preterm because of severe preeclampsia (1 pt) or idiopathic preterm labor (2 pt). Individual pregnancy outcomes were not provided. Apgar scores were ≥ 9 in all cases. One newborn had a low birth weight	At 6 months to 8 years (group range), all were alive.	(Berry <i>et al.</i> 1999)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								for gestational age (< 10 th percentile; SGA), 23 had normal birth weight for age. Newborns had no malformations. One newborn was diagnosed with hyaline membrane disease, and 2 newborns had tachypnea (resolved by 48 hours). One newborn was born 2 days after chemotherapy and experienced transient leucopenia. Two newborns had substantial hair loss.		
Cyclophosphamide (Dose/schedule NS)	Case series, retrospective	1 of 18 (Pt 1)	Sarcoma, undifferentiated	1 st First@month 3	Doxorubicin, Vincristine, AMSA	NS	No births were premature [Term]	Male infant: 6 lb 5 oz [2,863 g], Apgar scores NS. Newborn was normal and birth weight was normal [for gestational age].	At 2.5 years, normal.	(Blatt <i>et al.</i> 1980)
Cyclophosphamide (Dose/schedule NS, 3 cycles (Pt 1), 6 cycles (Pt 2), or 4 cycles (Pt 3))	Case series	3 of 5 (Pts 1, 2, and 3)	Breast	2 nd , 3 rd	5-Fluorouracil, Epirubicin	C-section	36	Infant sex NS: 2,920 g, Apgar scores were in the normal range. Newborn was normal, no congenital malformations or intrauterine growth retardation.	No	(Bodner-Adler <i>et al.</i> 2007)
				2 nd , 3 rd	5-Fluorouracil, Epirubicin	Vaginal	38	Infant sex NS: 2,940 g, Apgar scores were in the normal range. Newborn was normal, no congenital malformations or intrauterine growth retardation.		
				2 nd , 3 rd	5-Fluorouracil, Epirubicin	C-section	36	Infant sex NS: 2,530 g, Apgar scores were in the normal range. Newborn was normal, no congenital malformations or intrauterine growth retardation.		
Cyclophosphamide (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Doxorubicin, Vincristine	Vaginal, induced	34	Infant sex NS: 3,043 g, Apgar scores 9, 9, and 9. The newborn was not compromised.	No	(Brown <i>et al.</i> 2001)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Dose NS; given on days 8 of an 8-day regimen, 4 cycles)	Case report	1	Choriocarcinoma, uterus	NS [2 nd] [First@ >20 wks]	Actinomycin D, Methotrexate, Vincristine, Etoposide	Vaginal	32	Spontaneous preterm delivery [spontaneous preterm labor]. Female infant: 1,383g, Apgar scores 8 and 9. Newborn was developmentally normal.	At 42 months, normal development.	(Brudie <i>et al.</i> 2011)
Cyclophosphamide (Dose/schedule NS)	Survey, registry	(101 of 104 infants from Table 2)	Breast	2 nd or 2 nd , 3 rd	Doxorubicin, 5-Fluorouracil, Doxetaxel, Paclitaxel, Epirubicin	NS	35.9 (group mean)	Infant sex NS: 2,667 g (group mean), Apgar scores NS. Ninety-seven newborns were normal phenotype. Four newborns had malformations (number affected): small main pulmonary artery fistula (1), pyloric stenosis (1), talipes (clubfoot) and left eye hemangioma (1), and suspected holoprosencephaly (1). 93 newborns had normal body weight for gestational age. Neonatal complications (number affected): intrauterine growth retardation (8), thrombocytopenia, died at 13 months because of a severe autoimmune disorder (1), neutropenia (1), sepsis and anemia (1), hyperbilirubinemia or jaundice (6), hypocapnia with hypotonia (1), transient tachypnea, apnea and/or respiratory distress syndrome (6), gastroesophageal reflux, or difficulty in feeding (3), and meconium [aspiration] (1).	At 42 months (group mean, n=91 from Table 7), long-term complications were (number affected): periventricular leukomalacia and developmental delay requiring OT and PT (infant had hypocapnia at birth) (1), gastroesophageal reflux (1), mild speech delay (2), mild hearing loss and recurrent otitis media (1), recurrent otitis media (3), reactive airway disease (2), selective IgA deficiency not requiring treatment (1). Group mean weight was 48 th percentile.	(Cardonick <i>et al.</i> 2010)
		8 of 31 pts (8 of 32 infants) from Table 3	Non-Hodgkin lymphoma	2 nd , 3 rd	Doxorubicin, Vincristine	NS	34.0 (group mean)	Infant sex NS: 2,576 g (group mean), Apgar scores NS. One fetus died at 30 wks; autopsy was normal. Seven newborns were without malformations and had normal body weight per gestational age. Neonatal	At 0.2 to 5.3 years (n=20 from Table 3), all children were normal phenotype. At 34 to 82 months (group range, n=6): 1 child in the group had a speech delay; group mean weight was 46 th	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								complications (number affected): jaundice (2), anemia (1), and transient tachypnea (1).	percentile.	
		1 of 3 from Table 5	Leukemia, ALL	2 nd , 3 rd	Cytarabine, Daunorubicin, 6-Mercaptopurine, Methotrexate, Vincristine, Asparaginase	NS	35.5 (group mean)	Infant sex NS: 2,341 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 9 years, normal phenotype. At 41 to 109 months (group range, n=2), no long-term complications; group mean weight was 65 th percentile.	
		1 of 12 from Table 6	Rhabdomyosarcoma	2 nd , 3 rd	Vincristine, Actinomycin D	C-section	33	Infant sex NS: 2,948 g, Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 5.3 years, normal phenotype.	
Cyclophosphamide	Survey, retrospective – utilizing data from the rituximab global drug safety database	3 of 20 from Table 2	Non-Hodgkin lymphoma, B-cell	3 rd	Rituximab, Doxorubicin, Vincristine	NS	35	Male infant: weight and Apgar scores NS. Newborn was premature.	No	(Chakravarty <i>et al.</i> 2011) [This entry excludes 2 case reports (Decker <i>et al.</i> 2006, Friedrichs <i>et al.</i> 2006) that are included separately in this table.]
			Non-Hodgkin lymphoma	2 nd First@wk 18	Rituximab, Doxorubicin, Vincristine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal.		
			Non-Hodgkin lymphoma	2 nd First@wk 21	Rituximab, Doxorubicin, Vincristine	NS	33	Preeclampsia. Female infant: weight and Apgar scores NS. Newborn was normal.		

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Dose/schedule NS)	Survey, retrospective	3 of 37 from Table 1 (Pts 13, 30, 35)	Leukemia, ALL	1 st (Diagnosis @wk 9)(Pt 13)	Daunorubicin, Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005) [Did not include Pt 9 because it was not clear whether the pt received chemotherapy while pregnant.]
			Leukemia, ALL	1 st (Diagnosis @wk 10) (Pt 30)	Daunorubicin, Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, ALL	1 st (Diagnosis @wk 9)(Pt 35)	Daunorubicin, Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	
Cyclophosphamide (Dose NS, 5 days, 1 cycle)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd First@wk 28	Rituximab, Vincristine	C-section	~29	Female infant: 1,263 g, Apgar scores 9 and 9 at 1 and 5 minutes. Newborn had respiratory distress and omphalitis, but no myelosuppression. Discharged at 46 days in adequate condition.	No	(Cordeiro <i>et al.</i> 2009)
Cyclophosphamide (600 mg/m ² on day 1, 3 cycles, 3 or 4 wks apart)	Case report	1	Breast	3 rd First@wk 28 Last@wk 34	5-Fluorouracil, Doxorubicin	Vaginal, induced	36	Mild fetal growth restriction and progressive reduction in amniotic fluid. Female infant: 2,350 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was in good condition with a normal blood count.	At 24 months, healthy with weight and height in 50 th percentile and normal psychoneurological development.	(Cordoba <i>et al.</i> 2010)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (1,200 mg/m ² at 14-day intervals, 6 cycles)	Case series	1 of 3 (Pt 1)	Breast	2 nd First@wk 25	5-Fluorouracil, Epirubicin, Vinorelbine	C-section	34	Female infant: 2,320 g, Apgar scores 8, 3, and 10 at 1, 3, and 5 minutes. Newborn was normal with no dysmorphic features. Anemia at day 21, resolved.	At 35 months, growth and development were normal.	(Cuvier <i>et al.</i> 1997)
Cyclophosphamide (650 mg/m ² on days 1 and 8, through remainder of pregnancy)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 18	Vincristine, Procarbazine	NS	37	Female infant: 2,000 g [SGA], Apgar scores NS. Newborn had no abnormalities, and chromosomal analysis was normal.	At 1 year, no abnormalities.	(Daly <i>et al.</i> 1980)
Cyclophosphamide (Dose/schedule NS)	Case series	3 of 32 from Table I (Pts 4, 20 and 30)	Breast	2 nd First@wk 14 Last@wk 22	Doxorubicin	Vaginal	38	Infant sex NS: 3,150 g, Apgar scores 9 and 10. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
			Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 24 Last@wk 37	Doxorubicin, Etoposide, Cytarabine, Bleomycin, Vincristine	C-section	35	Infant sex NS: 1,980 g, Apgar scores 8 and 9. Newborn was healthy.	No	
			Non-Hodgkin lymphoma	3 rd First@wk 34 Last@wk 37	Epirubicin, Etoposide, Cytarabine, Bleomycin, Vincristine	Vaginal	36	Infant sex NS: 3,020 g, Apgar scores 9 and 9. Newborn was healthy.	No	
Cyclophosphamide (750 mg/m ² , 6 cycles, 2 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd	Rituximab, Doxorubicin, Vincristine	Vaginal	33	Spontaneous preterm labor and delivery. Female infant: weight within 50 th -90 th percentile, Apgar scores 8, 10, and 10. Newborn was healthy, but B-cells were severely diminished at birth (recovery began at 6 wks, complete by 12 wks).	At 8 and 16 wks, normal immunological response to vaccinations. At 16 months, no physiological or developmental abnormalities.	(Decker <i>et al.</i> 2006)
Cyclophosphamide (Dose/schedule NS, 4 cycles)	Case report	1	Breast	2 nd	Doxorubicin	NS	NS	Male infant: weight and Apgar scores NS. Newborn was healthy.	No	(Diamond <i>et al.</i> 2009)
Cyclophosphamide (Dose/schedule NS, 6 cycles (Pt 11))	Case series	2 of 18 (Pts 11 and 13)	Hodgkin lymphoma	1 st	Vincristine, Doxorubicin	NS	NS	Female infant: 3,000 g Apgar scores NS. Newborn was normal.	At 12 months, alive.	(Dilek <i>et al.</i> 2006)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	2 nd , 3 rd	Vincristine, Doxorubicin	NS	NS	Male infant: 2,500 g Apgar scores NS. Newborn was of low birth weight, but without hematological abnormality.	At 35 months, alive.	
Cyclophosphamide (400 mg/m ² on days 1-5)	Case report	1	Hodgkin lymphoma	3 rd First@wk 29	Vincristine	C-section	35	Female infant: 2,300 g Apgar scores NS. Newborn was well.	No	(D'Incalci <i>et al.</i> 1982)
Cyclophosphamide (150 mg/m ² on days 3-12, 5 cycles, 4 wks apart)	Case report	1	Breast	2 nd , 3 rd	5-Fluorouracil, Doxorubicin	C-section	38	Male infant: 5 lb 14 oz [2,665 g], Apgar scores NS. Newborn developed jaundice, but was otherwise healthy with normal blood count and chemistry.	At 4 months, 50 th percentile for weight with normal blood count and chemistry. At 15 and 24 months, excellent health and normal development.	(Dreicer and Love 1991)
Cyclophosphamide (10 mg/kg for 7 days, 1 course)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd [First@wk26]	None	Vaginal	NS [33]	False labor on 4 th day of treatment, strong uterine contractions [preterm labor] 3 days after last dose of cyclophosphamide (treated with bed rest, then subsided). Male infant: 2,160 g, Apgar scores NS. Newborn was normal.	No	(Durodola 1979)
Cyclophosphamide (Dose/schedule NS, 4 cycles)	Case report	1	Neuroendocrine carcinoma, vagina	2 nd First@wk 17 Last@wk 27	Doxorubicin, Vincristine	C-section	29	Male infant: 1,100 g, Apgar scores 5 and 6 at 1 and 5 minutes. Newborn was viable and, because of prematurity, received intensive care for 55 days, at which time he was discharged without complications.	At 6 years, highly functional with no neurodevelopmental delays.	(ElNaggar <i>et al.</i> 2012)
Cyclophosphamide (1,000 mg/m ² , 8 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	1 st , 2 nd , 3 rd First@wk 13 Last@wk 34	Vincristine, Bleomycin	Vaginal	Full term	Male infant: 2,500 g, Apgar scores NS. Newborn showed no signs of abnormalities.	At 1 year, developing normally. Chromosomal banding studies found no abnormalities.	(Falkson <i>et al.</i> 1980)
Cyclophosphamide (275 mg/day for 5 days every 3 wks)	Case report	1	Ovary	2 nd , 3 rd First@wk 20 Last@wk 32	Vincristine, Actinomycin D	Vaginal	39 + 6 days	Male infant: 4,310 g, Apgar scores 8 and 9 at 1 and 5 minutes.	No	(Frederiksen <i>et al.</i> 1991)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Dose/schedule NS, 6 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 20	Rituximab, Doxorubicin, Vincristine	C-section	41	Female infant: weight and Apgar scores NS. Newborn was healthy but with complete absence of B-cells. A fast B-cell recovery was seen in the wks following birth.	At 26 months, normal growth and development.	(Friedrichs <i>et al.</i> 2006)
Cyclophosphamide (700 mg/m ²)	Case report	1	Non-Hodgkin lymphoma	1 st	Doxorubicin, Vincristine	Vaginal	NS	Male infant: 3,400 g, Apgar score 10 at 10 minutes. Newborn had a normal appearance.	At 2 months, condition is satisfactory.	(Garcia <i>et al.</i> 1981)
Cyclophosphamide (Dose/schedule NS, 2 cycles)	Case series	1 of 2 (Pt 2)	Non-Hodgkin lymphoma, large B-cell	3 rd First@wk 28 Last@wk 32	Doxorubicin Vincristine	Vaginal	33	Male infant: 1,645 g, Apgar scores 8 and 9 at 1 and 5 minutes. Developed necrotizing enterocolitis that was successfully treated and leukopenia that resolved in 2 days.	No	(Garcia <i>et al.</i> 1999)
Cyclophosphamide (Dose/schedule NS)	Case series, retrospective	7 of 15 [see note in pregnancy outcome column]	Breast	2 nd and/or 3 rd	5-Fluorouracil, Doxorubicin	NS	35 (group average) (Range 32-40)	Individual pregnancy outcomes were not provided. Seven live births with no congenital malformations. No stillbirths, miscarriages, or perinatal deaths in any pregnancies treated during the 2 nd and 3 rd . [15 pts received chemotherapy during pregnancy; 4 pts were not included because of a lack of data on chemotherapy treatment]	No	(Garcia-Manero <i>et al.</i> 2009)
Cyclophosphamide (Dose/schedule NS, 3 cycles)	Case report	1	Non-Hodgkin lymphoma	3 rd	Doxorubicin, Vincristine	Vaginal	Full term	Female infant: Birth weight and Apgar scores NS. Newborn showed no congenital anomalies.	At 4 wks, infant weighed 2,800 g; chromosomal analysis revealed no breaks or translocations. At 26 months, doing well.	(Garg and Kochupillai 1985)
Cyclophosphamide (300-1,200 mg/m ² , 1-4 cycles, 15-28 days apart)	Survey, retrospective	13 of 20 from Table 3 (Pts 1, 3, 6, 7, 10, 11, 12, 14, 15, 16, 17, 19, and 20)	Breast	1 st First@wk 4	5-Fluorouracil, Epirubicin	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Giacalone <i>et al.</i> 1999)++

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd First@wk 23	Epirubicin	--	--	Stillbirth at 26 wks. [No fetal data reported.]	--	
				2 nd , 3 rd First@wk 24	5-Fluorouracil, Doxorubicin	Vaginal	35	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 60 months, alive and well.	
				2 nd , 3 rd First@wk 25	5-Fluorouracil, Mitoxantrone	C-section	33	Infant sex and weight NS, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn experienced respiratory distress and had normal body weight for gestational age.	At 12 months, alive and well.	
				3 rd First@wk 27	5-Fluorouracil, Mitoxantrone	C-section	33	Infant sex and weight NS, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn had intrauterine growth retardation (SGA).	At 32 months, alive and well.	
				3 rd First@wk 28	5-Fluorouracil, Epirubicin	C-section	31	Infant sex and weight NS, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn died on day 8, no etiology was diagnosed. No malformations observed and had normal body weight for gestational age.	--	
				3 rd First@wk 29	5-Fluorouracil, Epirubicin	C-section	35	Infant sex and weight NS, Apgar scores 6 and 10 at 1 and 5 minutes. Newborn had leukopenia and normal body weight for gestational age.	At 18 months, alive and well.	
				3 rd First@wk 31	5-Fluorouracil, Epirubicin	C-section	34	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 10 months, alive and well.	
				3 rd First@wk 31	5-Fluorouracil, Doxorubicin	C-section	34	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 120 months, alive and well.	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd First@wk 31	5-Fluorouracil, Epirubicin	C-section	33	Infant sex and weight NS, Apgar scores 6 and 10 at 1 and 5 minutes. Newborn experienced respiratory distress and had normal body weight for gestational age.	At 6 months, alive and well.	
				3 rd First@wk 31	5-Fluorouracil, Epirubicin	C-section	34	Infant sex and weight NS, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 16 months, alive and well.	
				3 rd First@wk 32	Epirubicin	C-section	37	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 6 months, alive and well.	
				3 rd First@wk 35	5-Fluorouracil, Epirubicin	Vaginal	37	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal and had normal body weight for gestational age.	At 50 months, alive and well.	
Cyclophosphamide (Dose/schedule NS, 5 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 6 Last@wk 24	5-Fluorouracil, Methotrexate	Vaginal	30	Spontaneous preterm labor. Male infant: 1,000 g [SGA], Apgar scores NS. Newborn was 3 rd percentile for body weight, length, and head circumference. Newborn appeared normal, but experienced respiratory distress requiring support for 2 days. An inguinal hernia was diagnosed and repaired.	At 22 months, normal growth, development, and karyotype.	(Giannakopoulou <i>et al.</i> 2000)
Cyclophosphamide (1,000 mg on day 1, 2 cycles)	Case report	1	Sarcoma, Ewing	3 rd First@wk 29 Last@wk 32	Doxorubicin, Actinomycin D, Vincristine, Radiation therapy	Vaginal, induced	36	Female infant: 5 lb 3 oz [2,353 g], Apgar scores 9 and 9. Newborn appeared normal.	At 3 months, growing adequately with no known abnormalities.	(Gilliland and Weinstein 1983)
Cyclophosphamide (600 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Breast	2 nd , 3 rd First@wk 23	5-Fluorouracil, Epirubicin	C-section	35	Premature rupture of membranes.	No	(Ginopoulos <i>et al.</i> 2004)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Female infant: 3,420 g, Apgar score 8. Newborn had no congenital malformations. Mild, transient tachypnea required oxygen support. All blood exams were in normal range.		
Cyclophosphamide (600 mg/m ² , 4 cycles)	Case report	1	Breast	1 st , 2 nd	Doxorubicin, Paclitaxel (2 nd , 3 rd)	C-section	37	Preeclampsia. Male infant: 5.4 lb [2,449 g], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal, with normal blood counts.	At 12 months, normal physical growth and development.	(Gonzalez-Angulo <i>et al.</i> 2004)
Cyclophosphamide (100 mg/day during entire pregnancy with an additional dose of 1,810 mg over 6 days midway through the first trimester)	Case report	1	Hodgkin lymphoma	1 st , 2 nd , 3 rd	None	Vaginal	NS	Male infant: 4 lb 4 oz [1,928 g], Apgar scores NS. Newborn had a groove extending to the uvula on each side of the midline of the hard palate, a flattened nasal ridge, a small skin tag on the anterior mid-abdomen, a slightly hypoplastic middle phalanx of the fifth finger, and bilateral inguinal hernia sacs. The feet were wider at the heels and tapered towards the toes. There were 4 toes on each foot; the first and fourth toes were larger than the middle 2, with some degree of overlap.	At 1 year, developing normally with a normal karyotype.	(Greenberg and Tanaka 1964)
Cyclophosphamide (Dose/schedule NS)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd [First@> wk 25]	Actinomycin D, Bleomycin, Vincristine, Doxorubicin	C-section	34	Female infant: 1,750 g, Apgar scores 7 and 9. Infant required intravenous calcium and was treated for mild respiratory distress syndrome for 2 days. No major problems after 3 days.	Child progressing normally [age NS, > 4 years later].	(Haerr and Pratt 1985)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (500 mg/m ² on day 1, 1-6 cycles (group mean = 4 cycles), 3-4 wks apart)	Case series	40 of 57 [Data on pregnancy outcomes available for only 40 pregnancies]	Breast	NS First@wk 11-34 (group range; group median = wk 23) Last@wk 35	Doxorubicin, 5-Fluorouracil	60% were Vaginal; 40% were C-section	37 (group mean); 29-42 (group range; n=52)	Individual pregnancy outcomes were not provided. Infant sex and Appgars scores NS: group mean weight = 2,890 g (range: 1,389-3,977 g; n=47). No stillbirths, miscarriages, or perinatal deaths occurred with exposure during 2 nd and 3 rd trimester (n=55). Pregnancy outcomes provided for 40 infants (number affected): Down syndrome (1), clubfoot (1), and bilateral ureteral reflux (1). 11 infants had breathing difficulties (11), and 1 infant had neutropenia, thrombocytopenia, and a subarachnoid hemorrhage.	Follow-up on children (ages 2-157 months; n=39). All children except the one with Down's syndrome were thought to have normal development by their parents. One other school-age child had attention-deficit/hyperactivity disorder.	(Hahn <i>et al.</i> 2006)
Cyclophosphamide (Dose NS, day 1, 3 cycles, 4 wks apart)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 26 Last@wk 34	Daunorubicin (2 nd), Vincristine, Asparaginase, 6-Mercaptopurine (3 rd), Cytarabine (3 rd), Methotrexate (intrathecal, 3 rd)	Vaginal	36	Transient oligohydramnios. [Spontaneous preterm labor.] Male infant: 2,150 g [SGA], Apgar scores 2 and 8 at 1 and 5 minutes. Newborn required oxygen therapy because of meconium aspiration (resolved by day 4) and developed transient hyperbilirubinemia. Physical and neurological examinations and blood counts were normal. Placenta had mild chorionitis with multiple small infarcts.	No	(Hansen <i>et al.</i> 2001)
Cyclophosphamide (1,500 mg, followed by 2,500 mg, 2 wks apart)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd	None	Vaginal, induced	NS	Male infant: 3,180 g, Apgar score 9. Newborn was normal and had normal hematologic values.	At 1 year, healthy with normal growth.	(Hardin 1972)
Cyclophosphamide (600 mg/m ² (first 2 cycles) and 1,000 mg/m ² (last cycle))	Case report	1	Ovary	2 nd , 3 rd First@wk 20	Cisplatin (2 nd), Carboplatin (3 rd)	C-section	36	Gestational diabetes and preeclampsia at 30 and 34 wks of gestation.	At 12 months, normal growth, neurologic findings, and renal function.	(Henderson <i>et al.</i> 1993)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Male infant: 3,600 g, Apgar scores 9 and 9. Newborn was grossly normal in appearance.		
Cyclophosphamide (500 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Ovary	2 nd	Cisplatin	C-section	30	Spontaneous preterm labor with premature rupture of membranes at 29 wks of gestation. Breech presentation. Female infant: 1,816 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn was active.	At follow-up [age NS], normal growth pattern, including neurologic and mental development.	(Huang <i>et al.</i> 2004)
Cyclophosphamide (Dose/schedule NS)	Cohort, retrospective	7 of 72	Breast	2 nd or 3 rd	5-Fluorouracil, Doxorubicin, Paclitaxel, Cisplatin	Vaginal	NS	Individual pregnancy outcomes were not provided. No newborn had a congenital malformation.	No	(Ibrahim <i>et al.</i> 2000)†
Cyclophosphamide (Dose/schedule NS, 6 cycles)	Case report	1	Breast	1 st , 2 nd	Docetaxel, Doxorubicin	C-section	32	Male infant: birth weight and Apgar scores were within normal limits. Newborn had no anomalies.	No	(Ibrahim <i>et al.</i> 2006)† (Abstract only)
Cyclophosphamide (600 mg/m ² on day 1, 4 cycles, 3 wks apart)	Case report	1	Breast	2 nd First@wk 24	Doxorubicin	Vaginal	36.5	Female infant: 2,530 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal.	At 40 months, normal growth and development.	(Inbar and Ron 1996)
Cyclophosphamide (Dose/schedule NS; Pt 2, 4 cycles; Pt 10, 3 cycles)	Survey, retrospective	2 of 49 from Table 4 (Pts 2 and 10)	Breast	2 nd , 3 rd or 3 rd	Doxorubicin	NS	37	Infant sex, weight, and Apgar scores NS. Newborn born alive and without malformation.	No	(Ives <i>et al.</i> 2005)
				2 nd , 3 rd and/or 3 rd	Methotrexate, 5-Fluorouracil	NS	37	Infant sex, weight, and Apgar scores NS. Newborn born alive and without malformation.	No	
Cyclophosphamide (Dose/schedule NS, 1-6 cycles)	Case series	1 of 18	Sarcoma, soft tissue	NS First@wk 12-33 22 (mean)	Vincristine, Doxorubicin, Dacarbazine	--	--	Spontaneous abortion at gestation wk 22. [No fetal data reported.]	--	(Jameel and Jamil 2007)
		6 of 18	Breast		5-Fluorouracil, Doxorubicin	NS	NS	Infants' sex, weight and Apgar scores NS. Newborns were alive and healthy; no malformations were observed.	At follow-up, normal growth patterns without physical or neurological deficits (n=5 children, oldest child is 42 months).	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Doxorubicin, Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Aclarubicin, Vincristine, Cycloctidine, Mitoxantrone, Idarubicin, ATRA, Asparaginase	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994)†
Cyclophosphamide (600 mg/m ² , 6 cycles, 3 wks apart)	Case report	1	Breast	2 nd , 3 rd First@wk 14	Doxorubicin	Vaginal	31	Male infant: 1,474 g, Apgar scores 8 and 8 at 1 and 5 minutes. Newborn had no physical abnormality but had apnea, tachypnea, respiratory distress requiring intubation (resolved by day 2 after surfactant therapy), hyperbilirubinemia, and hypoglycemia (both resolved after 5 days).	At 1 year, in good health with normal growth and development.	(Kerr 2005)
Cyclophosphamide (Dose/schedule NS, 2 cycles over 4 wks and then monthly)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Doxorubicin (2 nd), Vincristine, Asparaginase (2 nd), Methotrexate, 6-Mercaptopurine	C-section	NS [at term]	Female infant: 3,800 g, Apgar scores NS, Newborn was clinically normal, with slight leucopenia (resolved after 2 wks).	At follow-up [age NS], child was progressing well with normal blood counts and no neurological disturbance or congenital abnormality.	(Khurshid and Saleem 1978)
Cyclophosphamide (200 mg/day for 5 days, 6 cycles, 1 month apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 16	Vincristine, Actinomycin D	Vaginal	37	Spontaneous preterm labor. Male infant: 2,850 g, Apgar scores NS. Newborn was normal.	No	(Kim and Park 1989)
Cyclophosphamide (500 mg/m ² once a month, 2 cycles)	Case report	1	Adenoid cystic carcinoma, submandibular gland	1 st First@wk 5 Last@wk 10	Doxorubicin, Cyclophosphamide	C-section	25	Spontaneous preterm labor Male infant: 912 g, Apgar scores 1 and 6 at 1 and 5 minutes. Newborn had blepharophimosis, microcephaly, and hydrocephalus.	No	(Kim <i>et al.</i> 1996)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (600 mg/m ² for 2 cycles, 100 mg/m ² for 3 cycles)	Case report	1	Ovary	2 nd	Cisplatin	NS	36.5	Premature rupture of membranes and labor at 36.5 wks of gestation. Male infant: 3,060 g, Apgar scores 7 and 8. Newborn had respiratory distress requiring intubation (resolved within 24 hours).	At 28 months, normal physical and mental development.	(King <i>et al.</i> 1991)
Cyclophosphamide (Dose/schedule NS, 2 cycles)	Case report	1	Leukemia, ALL	3 rd	Cytarabine, Methotrexate (intrathecal), Vincristine (2 nd , 3 rd), 6-Mercaptopurine (2 nd , 3 rd)	Vaginal	38	Male infant: 6 lb 8.5 oz [2,963 g], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was normal with normal blood counts.	At 7 months, thriving with no chromosomal anomalies.	(Krueger <i>et al.</i> 1976)
Cyclophosphamide (500 mg/m ² on day 1, cycles were 3 or 4 wks apart)	Case series	4 of 4	Breast	3 rd First@wk 33	Doxorubicin, 5-Fluorouracil	NS	36	Infant sex, weight, and Apgar scores NS.	At 65 months, healthy with normal development.	(Kuerer <i>et al.</i> 2002)
				2 nd , 3 rd First@wk 26	Doxorubicin, 5-Fluorouracil	NS	40	Infant sex, weight, and Apgar scores NS.	At 44 months, healthy with normal development.	
				2 nd , 3 rd First@wk 26	Doxorubicin, 5-Fluorouracil	NS	35	Preeclampsia. Infant sex, weight, and Apgar scores NS.	At 33 months, healthy with normal development.	
				3 rd First@wk 31	Doxorubicin, 5-Fluorouracil	NS	36	Infant sex, weight, and Apgar scores NS.	At 33 months, healthy with normal development.	
Cyclophosphamide (50-100 mg/day over a 25-day period)	Case report	1	Hodgkin lymphoma	2 nd First@wk 23 Last@wk 27	Vinblastine (2 nd , 3 rd)	C-section	~37	Male infant: 3,060 g, Apgar score 9. Newborn had no apparent anomalies.	At 17 months, normal growth and development with no abnormal chromosomes.	(Lacher and Geller 1966)
Cyclophosphamide (800 mg/m ² (day 1) and 200 mg/m ² (days 2-5), 2 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 26 Last@wk 29	Vincristine, Doxorubicin, Cytarabine, Etoposide, Ifosfamide	C-section	32	Male infant: 1,731 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no anomalies, but was cyanotic and experienced respiratory distress.	At 1 year, mild developmental delays, but otherwise healthy.	(Lam 2006)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (750 mg/m ² on day 1, 3 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 22 Last@wk 28	Doxorubicin, Vincristine, Teniposide, Bleomycin	C-section	31	Preeclampsia and fetal growth retardation at gestation wk 28. Fetal distress at gestation wk 31. Male infant: 1,380 g, Apgar scores 7, 9, and 10 at 1, 5, and 10 minutes. Newborn had no abnormalities, but experienced hyperbilirubinemia (treated and resolved in 3 days). Placenta had extensive infarction.	At 18 months, normal growth with no sign of damage that could be related to chemotherapy during pregnancy.	(Lambert <i>et al.</i> 1991)
Cyclophosphamide (50 mg/day for first 20 wks, 50 mg every other day for remainder of pregnancy)	Case report	1	Multiple myeloma	1 st , 2 nd , 3 rd	None	C-section	Full term	Male infant: 2,523 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no apparent congenital anomalies and a normal karyogram. Newborn had an abnormal serum protein electrophoretic pattern and elevated gamma globulin levels.	At 28 months, in good health with normal serum protein electrophoretic results.	(Lergier <i>et al.</i> 1974)
Cyclophosphamide (Dose/schedule NS, 5 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 2 Last@wk 19	5-Fluorouracil, Epirubicin (1 st), Methotrexate (2 nd), Radiation therapy (1 st)	--	--	Induced abortion at gestation wk 19. Male fetus: 280 g (50 th percentile for gestational age). Fetal autopsy revealed micrognathia, skin syndactyly of the 1 st and the 2 nd fingers of both hands, shortened 2 nd and 3 rd fingers and clinodactyly of the 5 th finger; both feet had a broad forefoot with a short 1 st toe and osseous syndactyly of the 4 th and the 5 th metatarsal bones.	--	(Leyder <i>et al.</i> 2010)
Cyclophosphamide (Dose/schedule NS, 2 cycles)	Case report	1	Breast	3 rd First@wk 32 Last@wk 35	5-Fluorouracil, Doxorubicin	C-section	37.5	Female infant: Birth weight and Apgar scores NS. Newborn was alive and healthy.	No	(Logue 2009)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (400 (first 2 cycles) or 750 (remaining cycles) mg/m ² on day 1, 6 cycles, 2.5-3 wks apart)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 22 Last@wk 37	Doxorubicin, Vincristine, Teniposide, Bleomycin (3 rd), Methotrexate (intrathecal, 3 rd)	Vaginal	37	Female infant: 3,750 g, Apgar score 9. Newborn was fully developed with normal heart and blood counts; no abnormality was detected.	No	(Lowenthal <i>et al.</i> 1982)
Cyclophosphamide (600 mg/ m ² every 2 wks for 4 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 22 Last@wk 28	Doxorubicin, Paclitaxel (3 rd)	C-section	38	Transient uterine contractions after 2 nd cycle of chemotherapy. Twin infants, sexes NS: Baby A – 2,354 g [SGA], Apgar scores 7 and 8 at 1 and 5 minutes; Baby B – 2,426 g [SGA], Apgar scores 8 and 9 at 1 and 5 minutes. Both newborns were healthy.	At 16 months, twins were in good health.	(Lycette <i>et al.</i> 2006)
Cyclophosphamide (Dose/schedule NS, 6 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 13 + 4 days	Doxorubicin, Vincristine, Rituximab, Cytarabine (IT)	Vaginal	39	Female infant: 2,270 g [SGA], Apgar scores 6 and 9. Newborn was viable with low birth weight.	At 10 months, healthy.	(Magloire <i>et al.</i> 2006)
Cyclophosphamide (600 mg/m ²)	Case report	1	Breast	2 nd First@wk 13	Doxorubicin	C-section	4 wks prior to due date [NS]	Female infant: 5 lb 11 oz [2,548 g], Apgar scores NS. Newborn was healthy.	No	(Mahon <i>et al.</i> 2001)
Cyclophosphamide (750 mg/m ² , 7 cycles, 3 wks apart)	Case report	1	Ovary	2 nd , 3 rd	Cisplatin	Vaginal, induced	37-38	Male infant: 3,275 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn had no abnormalities.	At 18 months, progressing normally without neurodevelopmental abnormalities.	(Malfetano and Goldkrand 1990)
Cyclophosphamide (2.2 g/m ² every 3 wks, 3 cycles)	Case report	1	Rhabdomyosarcoma	2 nd , 3 rd	Vincristine, Actinomycin D	Vaginal	36.5	Spontaneous preterm labor. Female infant: 2,443 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was healthy and normal on physical examination.	No	(Martin <i>et al.</i> 1997)
Cyclophosphamide (Dose/schedule NS, 4 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 9 + 3 days Last@wk 17	Docetaxel	C-section	36 + 2	Placenta insufficiency, IUGR, oligohydramnios, pre-eclampsia, HELLP syndrome. Pathological fetal heart rate, reverse flow in the umbilical		(Massey Skatulla <i>et al.</i> 2012)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								artery, fetal centralization, and negative A wave in the venous duct. Male infant: 1,680 g (< 5 th percentile), Apgar scores 3, 7, and 9 at 1, 5, and 10 minutes. Newborn had no malformations but required cardiopulmonary resuscitation, was hypoglycemic for 5 days, had a single focal convulsion, and was treated for thrombocytopenia. Brain ultrasound showed no abnormality, and there was no evidence of periventricular leukomalacia.		
Cyclophosphamide (1,200 mg/day for 5 days, then 3 wks later, 1,200 mg once)	Case report	1	Non-Hodgkin lymphoma	NS [2 nd , 3 rd First @27 wk]	Mitoxantrone, Vincristine	C-section	31	Low biophysical profile score and abnormal cardiotocogram. Male infant: 1,700 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn was viable with no evidence of hematological suppression. Respiratory distress syndrome due to prematurity was successfully treated.	At 14 months, fit and well.	(Mavrommatis <i>et al.</i> 1998)
Cyclophosphamide (Dose/schedule NS for 1 st 2 cycles, 1,200 mg/m ² daily on days 43-45; 3rd cycle)	Case report	1	Sarcoma, Ewing	3 rd	Methotrexate, Doxorubicin, Vincristine	C-section	~7 months	Spontaneous preterm rupture of membranes and labor. Male infant: 2,200 g, Apgar scores NS. Newborn was healthy with normal blood counts.	At 10 wks, normal growth and development.	(Meador <i>et al.</i> 1987)
Cyclophosphamide (500 mg/m ² weekly, 3 cycles)	Case report	1	Rhabdomyosarcoma	2 nd	Actinomycin D, Doxorubicin	C-section	29 + 3	Female infant: 2,800 g, Apgar score 9. Newborn's physical exam was normal, as were blood tests.	No	(Meazza <i>et al.</i> 2008)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (600 mg/m ² , 5 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 17	Doxorubicin, Vincristine (2 nd)	Vaginal, induced	37	Female infant: 6 lb 13 oz [3,090 g], Apgar scores NS. Newborn was normal in appearance.	At 1 year, normal development.	(Metz <i>et al.</i> 1989)
Cyclophosphamide (500 mg/m ² on day 1, 4 cycles, 3 wks apart)	Case report	1	Breast	2 nd , 3 rd	Doxorubicin	C-section	35	Idiopathic preterm labor at gestation wk 30 (treated and resolved). Oligohydramnios at gestation wk 35. Female infant: 2,490 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was in good condition with no myocardial dysfunction.	Echocardiograms were conducted every 3 months after birth for 2 years; there was no evidence of myocardial damage.	(Meyer-Wittkopf <i>et al.</i> 2001)
Cyclophosphamide (Dose/schedule NS)	Case report	1	Ovary	2 nd , 3 rd First@wk 23 Last@wk 36	Vincristine, Actinomycin D	Vaginal	37	Female infant: 3,285 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was grossly normal.	No	(Montz <i>et al.</i> 1989)
Cyclophosphamide (1,000 mg, 5 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd Last@wk 35	Doxorubicin, Vincristine, Bleomycin, Methotrexate, Etoposide	Vaginal	35.5	Spontaneous preterm labor after last chemotherapy dose. Male infant: Birth weight was in the 75 th percentile for gestational age, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no apparent physical abnormalities.	At 11 months, alive and well.	(Moore and Taslimi 1991)
Cyclophosphamide (600 mg/m ² , 5 cycles (Pt A and B) or 4 cycles (Pt C), 3 wks apart)	Case series	3 of 5 (Pts A, B, and C)	Breast	2 nd , 3 rd	Doxorubicin	C-section	36	Infant sex, weight, and Apgar scores NS. All newborns were healthy; no abnormalities were observed.	No	(Morris <i>et al.</i> 2009)
				2 nd , 3 rd	Doxorubicin	C-section	35			
				2 nd , 3 rd	Doxorubicin	C-section	35			
Cyclophosphamide (600 mg/m ² , 2 cycles)	Case report	1	Breast	3 rd	5-Fluorouracil, Epirubicin	C-section	35	Eclamptic seizures at wk 35 Infant sex NS: 1,650 g [SGA], Apgar scores NS. Newborn had no malformations.	No	(Muller <i>et al.</i> 1996)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (Dose/schedule NS)	Survey, retrospective	2 of 27 [27 pts received chemotherapy while pregnant; the total number of pts who received cyclophosphamide while pregnant was not provided]	Leukemia, ALL	1 st First@wk 8	6-Mercaptopurine	--	--	Placenta abruption (placental detachment) Stillbirth. Polydactyly.	--	(Mulvihill <i>et al.</i> 1987)
			Leukemia, AML	2 nd , 3 rd First@wk 13	Radiation therapy (1 st , 2 nd), Daunorubicin (2 nd), Cytarabine (2 nd), Vincristine	NS	NS	Infant sex, weight, and Apgar scores NS. Normal at delivery.	No	
Cyclophosphamide (Total dose of 2,100 mg administered over 4 months)	Case report	1	Breast	1 st , 2 nd	Doxorubicin, Radiation therapy (Cobalt 60) (1 st)	NS	~39	Slowed fetal growth at gestation wk 27. Female infant: 2,980 g, Apgar score 9. Newborn had an imperforate anus and rectovaginal fistula; chromosomal analysis was normal.	At follow-up [age NS], small but otherwise doing well.	(Murray <i>et al.</i> 1984)
Cyclophosphamide (600 mg/m ² 3-weekly, 3 cycles)	Case series	1 of 2 (Pt 2)	Breast	2 nd , 3 rd	Doxorubicin	Vaginal, Induced	32 or 33	Male infant: 1,800 g, Apgar scores NS. Newborn was healthy.	No	(Murray and Werner 1997)
Cyclophosphamide (Dose NS, weekly for 10 wks)	Case report	1	Non-Hodgkin lymphoma	2 nd First@wk 18	Methotrexate, Doxorubicin, Vincristine, Bleomycin	C-section	28	Spontaneous preterm labor at 10 th wk of chemotherapy. Male infants (twins): Birth weight and Apgar scores NS. Both newborns were without apparent malformation or hematologic suppression.	At 12 months, healthy.	(Nantel <i>et al.</i> 1990)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (500 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Breast	1 st , 2 nd First@wk 13 Last@wk 25	5-Fluorouracil, Doxorubicin, Docetaxel (2 nd , 3 rd)	Vaginal	39	Male infant: 6.8 lb [3,084 g] , Apgar scores were normal. Newborn was healthy and had normal blood counts.	No	(Nieto <i>et al.</i> 2006)
Cyclophosphamide (150 mg on days 1-4, 4 cycles)	Case report	1	Ovary	2 nd First@wk 18	Cisplatin, Doxorubicin	C-section	33	Male infant: 1,896 g, Apgar scores 9 and 10. Newborn had no noticeable anomalies or deformities.	At follow-up [age NS] , normal growth with no functional dysfunctions.	(Ohara and Teramoto 2000)
Cyclophosphamide (100 mg/m ² daily for 2 wks)	Case report	1	Leukemia, ALL	2 nd First@wk 16.5 Last@wk 18.5	Vincristine (1 st , 2 nd), Methotrexate (intrathecal, 1 st), Asparaginase, Daunomycin [Daunorubicin] , 6-Mercaptopurine, Radiation therapy	C-section	34	Premature rupture of membranes. Female infant: 2,380 g, Apgar score 8 at 5 minutes. Newborn was normally developed, but hydroptic and had an enlarged liver and spleen. She had a petechial rash on her abdomen and extremities and slight cardiomegaly. She experienced transient severe myelosuppression requiring transfusions (resolved after ~3 wks). She was treated with digitalis and diuretics for congestive heart failure.	At 1 year, normal developmental status.	(Okun <i>et al.</i> 1979)
Cyclophosphamide (125-200 mg/m ² daily for 14 days, 5 cycles, 4 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@~wk 21	Vincristine, Bleomycin	Vaginal	Term	Mild uterine contractions during 3 rd course of chemotherapy, subsided. Female infant: 3,300 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was normal.	At 1 year, normal development with no evidence of malformations.	(Ortega 1977)
Cyclophosphamide (Dose/schedule NS)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last @wk 16	5-Fluorouracil, Doxorubicin	Vaginal	38	Male infant: 2,400 g [SGA] , Apgar scores 5 and 8 at 1 and 5 minutes. Newborn had microcephaly, bilateral ventriculomegaly and colpocephaly, a bicuspid aortic valve, a flat nasal bridge with bulbous nasal tip, a high-arched	At 15 months, he could sit without help and walk unaided. At 3 years, visual evoked potential was normal; growth and neuromotor development were delayed.	(Paskulin <i>et al.</i> 2005)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								palate, and multiple hand deformities; the karyotype and clinical pathology were normal.		
Cyclophosphamide (Dose/schedule NS)	Cohort, retrospective	2 of 14 from Tables 3 and 4 (Pts 7, 12)	Breast	1 st , 2 nd First@wk 2 Last@wk 26	5-Fluorouracil, Doxorubicin	NS	34	Infant sex NS: 2,170 g, Apgar scores NS. Newborn had no neonatal complications or major malformation.	No	(Peres <i>et al.</i> 2001)
			Breast	1 st First@wk 5 Last@wk 8	5-Fluorouracil, Methotrexate	--	--	Fetal death [Stillbirth] at gestation wk 25. No malformations.	--	
Cyclophosphamide (600 mg/m ² every 3 wks, 3 cycles)	Case series	1 of 2 (Case 2)	Breast	2 nd , 3 rd First@wk 26	Doxorubicin	Vaginal, induced	36	Male infant: 3,100 g; Apgar scores NS. Newborn was healthy with normal blood counts.	At 18 months, no medical problems; all teeth were sound.	(Peretz and Peretz 2003)
Cyclophosphamide (800 mg/m ² on day 1 and 200 mg/m ² on days 2-5, 2 cycles, 6 wks apart)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 16	Vincristine, Doxorubicin, Ifosfamide, Etoposide, Cytarabine, Rituximab	--	--	Decreased amniotic fluid at gestation wk 18 and early intrauterine growth restriction at gestation wk 22; similar effects at 23.5 wks of gestation. At 68 days of treatment, vaginal bleeding, spontaneous preterm labor, and no fetal heart tones. Stillbirth at gestation wk 26. [No fetal data reported.]	--	(Peterson <i>et al.</i> 2010)
Cyclophosphamide (Schedule NS, total doses: Pt 2 – 3,150 mg, Pt 3 – 25,000 mg, Pt 6 – 5,000 mg)	Case series	3 of 9 (Pts 2, 3, 6)	Leukemia, ALL	1 st , 3 rd	6-Mercaptopurine, Methotrexate	Vaginal	38	Male infant: 3,000 g, Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 7 years, alive and healthy.	(Pizzuto <i>et al.</i> 1980)† [This case series was included in Aviles <i>et al.</i> 1988 (1988), thus we did not include this case series in the text analysis of the table.]

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st , 2 nd , 3 rd	Vincristine, Methotrexate, 6-Mercaptopurine, Cytarabine	Vaginal	40	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 6 years, alive and healthy.	
				1 st , 2 nd , 3 rd	Cytarabine, 6-Mercaptopurine, Methotrexate, Vincristine	C-section	34	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had no apparent malformations but was pancytopenic. At 21 days, died from septicemia.	--	
Cyclophosphamide (600 mg/m ² , 4 cycles, 2 wks apart)	Case series	1 of 2 (Case 1)	Breast	2 nd First@wk 14	Doxorubicin, Docetaxel (2 nd , 3 rd)	Vaginal	34	Hydrocephalus noted at gestation wk 17 (dilated lateral and 3 rd ventricle). Infant sex NS: Birth weight and Apgar scores NS. Newborn had mild hydrocephalus, which regressed spontaneously over several months.	At 28 months, normal development.	(Potluri <i>et al.</i> 2006)
Cyclophosphamide (750 mg/m ² on day 1, 5 cycles)	Case report	1	Non-Hodgkin lymphoma, SPTCL	2 nd , 3 rd First@wk 20	Doxorubicin, Vincristine	Vaginal, induced	36	Female infant: 3,245 g, Apgar scores 9, 9, and 9. Newborn was healthy and showed neither growth retardation, nor physical or neurological deficits.	No	(Reimer <i>et al.</i> 2003)
Cyclophosphamide (750 mg/m ² on day 1 of 3-wk cycles, 4 cycles)	Case report	1	Non-Hodgkin lymphoma, diffuse large B-cell	2 nd	Vincristine, Doxorubicin, Rituximab	C-section	33	Infant, sex NS: 2,500 g, Apgar scores 10, 10, and 10. Newborn was healthy.	At 35 months, completely normal growth.	(Rey <i>et al.</i> 2009)
Cyclophosphamide (Dose/schedule NS)	Survey, retrospective	3 of 6 (Cases 4, 6, and 7)	Leukemia, AML	2 nd , 3 rd	Daunorubicin, Cytarabine, Vincristine	Vaginal	34	Spontaneous preterm labor. Male infant: 2,510 g, Apgar score of 9 at 1 minute. Newborn was healthy with normal peripheral blood counts and no congenital malformations.	At 7 years, healthy with weight and height in the 100 th percentile.	(Reynoso <i>et al.</i> 1987) [More detailed follow-up on Case 6 was reported in Zemlickis <i>et al.</i> (1993).]

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	1 st , 2 nd , 3 rd	None	Vaginal, induced	37	Female and male infants (twins): 1,490 g (female) [SGA] and 1,300 g (male) [SGA], Apgar scores 9 at 5 minutes (female), or 2 and 9 at 1 and 5 minutes (male). Both newborns had normal blood counts and chromosome studies; the newborn female appeared healthy. The male newborn had Madelung's deformity of the right arm (paraxial hemimelia, absent thumb, and hyperflexion of the wrist – also called clubhand), an esophageal atresia, an anomalous inferior vena cava, undescended testes, and duplication of the collecting systems of both kidneys.	At 17 years, the female has had normal growth, with normal intellectual and sexual development. At age 11, the male had learning problems, a low IQ, and a cold thyroid nodule. At 14 years, he had a ruptured retroperitoneal neuroblastoma arising from his adrenal gland. At 16 years, he was diagnosed with papillary thyroid carcinoma. At 17 years, he is alive with no evidence of metastatic disease.	
			Leukemia, AML	2 nd , 3 rd	Daunorubicin, Cytarabine, Vincristine, 6-Thioguanine	Vaginal, induced	39	Male infant: 3,420 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was healthy with normal peripheral blood counts and no congenital malformations.	At 11.5 years, healthy with normal growth and intellectual development.	
Cyclophosphamide (100-150 mg daily for 14 days, every 4 wks for 1-6 cycles or 600 mg/m ² on day 1 every 3 wks)	Survey, retrospective	1 of 28	Breast	1 st	Methotrexate, 5-Fluorouracil	--	--	Spontaneous abortion after 1 st cycle of chemotherapy. [No fetal data reported.]	--	(Ring <i>et al.</i> 2005)
		11 of 28	Breast	2 nd and/or 3 rd First@wk 15-33 (group range)	Methotrexate, 5-Fluorouracil	NS	37 (median); 30-40 (group range)	Intrauterine growth restriction due to placental insufficiency (n=1 pregnancy). Spontaneous preterm labor and delivery (n=1 pregnancy).	No	
		11 of 28			Doxorubicin	NS				
5 of 28	Epirubicin	NS		Individual pregnancy outcomes were not provided. None of the infants had congenital malformations. None of the infants had a birth weight lower than the 10 th percentile for gestational age (n=17 infants).						

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								One child had a hemangioma on his abdomen deemed not causally related to chemotherapy. Two infants had respiratory distress.		
Cyclophosphamide (375 mg/m ² , 6 cycles, 2 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Doxorubicin, Vincristine, Etoposide, Bleomycin	NS	37	Male infant: 3,200 g, Apgar scores NS. Newborn was healthy.	At 21 months, well with no evidence of iatrogenic complications.	(Rodriguez and Haggag 1995)
Cyclophosphamide (Dose/schedule NS)	Case report	1	Adult T-cell leukemia/lymphoma	2 nd First@wk 26	Hydroxyurea, Doxorubicin, Vincristine	C-section	~28	Male infant: birth weight and Apgar scores NS. Newborn was healthy.	No	(Safdar <i>et al.</i> 2002)
Cyclophosphamide (650 mg/m ² , 3 cycles, 2 wks apart)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Cytarabine, 6-Mercaptopurine, Methotrexate (IT), Vincristine (2 nd), Asparaginase (2 nd), Daunorubicin (2 nd), Radiation therapy	Vaginal	40	Female infant: weight and Apgar scores NS. Newborn was healthy, had a full head of hair, and no abnormalities. Cytogenetic analysis of lymphocytes showed a normal karyotype but some chromosome breakage and a ring chromosome.	No	(Schleuning and Clemm 1987)
Cyclophosphamide (Dose NS, days 1 and 8 every 4 wks, Pt 1 – cycles NS, Pt 2 – 2 cycles)	Case series	2 of 4 (Pts 1, 4)	Breast	3 rd	5-Fluorouracil, Methotrexate	Vaginal	38	Infant sex, weight, and Apgar scores NS. Newborn was healthy.	At 3 years, in good health.	(Schotte <i>et al.</i> 2000)
			Breast	3 rd First@wk 28	5-Fluorouracil, Doxorubicin	Vaginal, induced	37.5	Infant sex NS: 2,200 g [SGA]. Apgar scores NS. Newborn was normal.	No	
Cyclophosphamide (Maintenance courses with monthly doses of 100 mg/m ² , number of cycles NS.)	Case report	1	Sarcoma, granulocytic (breast)	NS	Daunorubicin, Vincristine, Cytarabine	Vaginal	NS	Female infant: 7 lb 2 oz [3,232 g], Apgar scores NS. Newborn was completely normal.	No	(Sears and Reid 1976)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (800 mg, 2 cycles, 3 wks apart)	Case report	1	Breast	3 rd First@wk 31 Last@wk 34	5-Fluorouracil, Epirubicin, Radiation therapy	Vaginal	36	Spontaneous preterm labor. Female infant: 1,889 g [SGA], Apgar score 9 at 5 minutes. Newborn had no congenital anomalies.	At 6 wks, doing well.	(Sharma <i>et al.</i> 2009)
Cyclophosphamide (Dose NS, every 2 wks, 4 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 24	Doxorubicin, Paclitaxel (3 rd)	C-section	36	Oligohydramnios noted in 3 rd trimester following the 4 th treatment with paclitaxel. Infant sex and Apgar scores NS: 5 lb 4 oz [2,381 g]. Newborn was healthy; echocardiogram and blood count were normal.	No	(Shieh and Mehta 2011)
Cyclophosphamide (Dose NS, 3 weekly cycles)	Case report	1	Leukemia, ALL	3 rd First@wk 32	Vincristine, Daunorubicin, Cytarabine, Asparaginase	Vaginal, induced	~35	Female infant: 6.8 lb [3,084 g], Apgar scores NS. Newborn was normal.	At 16 months, healthy with a normal blood count.	(Sigler <i>et al.</i> 1988)
Cyclophosphamide (Dose/schedule NS, 3 cycles)	Case report	1	Breast	3 rd	Doxorubicin	Vaginal	37	Male infant: 3,130 g, Apgar scores NS. Newborn was healthy.	At 12 months, healthy with normal development.	(Skrablin <i>et al.</i> 2007)
Cyclophosphamide (600 mg/m ² every 21 days, 3 cycles)	Case report	1	Cervix (small cell carcinoma)	2 nd , 3 rd First@wk 23	Doxorubicin	C-section	35	Male infant: 6 lb [2,721 g, normal for age], Apgar scores NS. Newborn was healthy.	No	(Smyth <i>et al.</i> 2010)
Cyclophosphamide (Dose/schedule NS, 3 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	3 rd	Doxorubicin, Vincristine	Vaginal, induced	36	Female infant: 2,400 g, Apgar scores NS. Newborn was healthy and without congenital anomalies.	No	(Soliman <i>et al.</i> 2007)
Cyclophosphamide (1,000 mg on day 1, 3 cycles)	Case report	1	Non-Hodgkin lymphoma	3 rd	Doxorubicin, Vincristine	Vaginal	Full term	Infant sex NS: 2,860 g, Apgar score 9 at 1 minute. Newborn appeared normal, but the placenta was small (350 g).	At 3 years, normal development with no physical or mental abnormalities.	(Toki <i>et al.</i> 1990)
Cyclophosphamide (560 mg/day for 3 days, followed 2 wks later by 100 mg/day gradually increasing to 150 mg/day over 10 wks)	Case report	1	Hodgkin lymphoma	1 st , 2 nd	Radiation therapy (1 st)	--	--	Induced abortion at ~6 months. Male fetus: 470 g. Fetus had a complete absence of phalanges in both feet and there was a single left coronary artery. The placenta was small (171 g) and showed hydropic degeneration of the villi.	--	(Toledo <i>et al.</i> 1971)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cyclophosphamide (75 mg/m ² , 3 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 24 Last@wk 32	Cisplatin	Vaginal, induced	34	Male infant: 2,280 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no complications.	At 12 months, normal growth and development.	(Tomlinson <i>et al.</i> 1997)
Cyclophosphamide (Dose/schedule NS; cycles were 3 wks apart starting ~wk 11 through duration of pregnancy)	Case series	1 of 2 (Pt 2)	Breast	1 st , 2 nd , 3 rd First@wk 13	Doxorubicin, 5-Fluorouracil, Methotrexate (3 rd)	C-section	35	Elevation of blood pressure to 150/100. Female infant: 2,260 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn had normal T-cell activity and no evidence of abnormality.	At 24 months, normal growth and development.	(Turchi and Villasis 1988)
Cyclophosphamide (1,000 mg/m ² on day 8 (1 st cycle) or days 1 and 15 (2 nd cycle), 2 cycles, 4 wks apart)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 23	Daunorubicin (2 nd), Vincristine (2 nd), Cytarabine (2 nd , 3 rd), 6-Thioguanine (2 nd , 3 rd), Methotrexate (intrathecal; 2 nd , 3 rd), Amsacrine (3 rd)	Vaginal	33	Spontaneous rupture of membranes. Male infant: 1,928 g [Table 2 states 1925 g], Apgar scores 9 and 10 at 1 and 5 minutes. Physical examination of the newborn was unremarkable, but he developed transient myelosuppression requiring transfusions: at birth he had leukopenia, by day 2 he had developed neutropenia, and by day 3 he had developed anemia and thrombocytopenia; all were resolved by day 20. He also developed a urinary tract infection on day 7.	At 24 months, normal growth and development.	(Udink ten Cate <i>et al.</i> 2009)
Cyclophosphamide (Dose/schedule NS, 1-4 cycles)	Survey, retrospective	4 of 27 from Table 1 (Pts 1, 2, 3, 5)	Breast	3 rd First@wk 32	5-Fluorouracil, Doxorubicin	C-section	36	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
				3 rd First@wk 32	5-Fluorouracil, Epirubicin	C-section	40	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.		
				3 rd First@wk 34	Doxorubicin	C-section	39	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.		

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd First@wk 24	Doxorubicin	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.		
		4 of 27 from Table 1 (Pts 17, 18, 19, 20)	Non-Hodgkin lymphoma	3 rd First@wk 29	Doxorubicin, Vincristine	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.		
				3 rd First@wk 29	Rituximab, Doxorubicin, Vincristine	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.		
				3 rd First@wk 32	Doxorubicin, Vincristine	Vaginal	40	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.		
				3 rd First@wk 27	Rituximab, Doxorubicin, Vincristine	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn had no congenital malformations.		
		1 of 27 from Table 1 (Pt 24)	Sarcoma, soft tissue	3 rd First@wk 32	Doxorubicin, Vincristine, Dacarbazine	C-section	33	Infant sex, weight, and Apgar scores NS. Newborn was premature and had low birth weight, but no congenital malformations		
Cyclophosphamide (Pt 1 - 600 mg/m ² (wk 26, 29, 32); Pt 2 - 100 mg/m ² on day 8 (wk 24, 28, 32); Pt 3 - 500 mg/m ² (wk 20, 23, 26, 32, 35); Pt 4 - 500 mg/m ² (wk 22, 25, 28))	Survey, retrospective	4 of 62 [62 pts received chemotherapy while pregnant; the total number of pts who received cyclophosphamide while pregnant was not provided]	NS	2 nd , 3 rd First@wk 26 Last@wk 32	Doxorubicin	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had hip subluxation.	No	(Van Calsteren <i>et al.</i> 2010)

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd First@wk 24 Last@wk 32	Methotrexate, Vincristine, Daunomycin [Daunorubicin] , Asparaginase, 6- Mercaptopurine,	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had a hemangioma.	No	
				2 nd , 3 rd First@wk 20 Last@wk 35	5-Fluorouracil, Epirubicin	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had a bilateral small protuberance on phalanx 5.	No	
				2 nd , 3 rd First@wk 22 Last@wk 28	5-Fluorouracil, Doxorubicin, Radiation therapy (1 st , 2 nd)	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had doubled cartilage ring in both ears.	No	
Cyclophosphamide (Dose/schedule NS)	Case report	1	Sarcoma	3 rd First@wk 28	Doxorubicin, Vincristine	Vaginal	32.5	Spontaneous preterm rupture of membranes and labor. Female infant: 2 lb 14 oz [1,304 g; SGA], Apgar scores 9 and 9. Newborn was viable with no respiratory distress or difficulty feeding.	At 2.5 years, normal neurological and physical development.	(Webb 1980)
Cyclophosphamide (Dose NS, 2 cycles)	Case report	1	Ovary	2 nd , 3 rd Last@wk 31	Vincristine, Actinomycin D	Vaginal	33	Spontaneous preterm labor. Female infant: 4 lb 4 oz [1,904 g], Apgar score 9. Newborn was healthy.	At 8 months, normal development.	(Weed <i>et al.</i> 1979)
Cyclophosphamide (450 mg daily for 5 days, 2 cycles)	Cohort, retrospective	3 of 21 from Table 1 (Pts 1, 3, 18, 19)	Breast	1 st	Methotrexate, 5-Fluorouracil	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
				1 st	Methotrexate, 5-Fluorouracil, Vincristine, Tamoxifen	NS	NS	Infant sex NS: Birth weight and Apgar scores NS. Newborn was alive and well with no malformations and normal body weight for gestational age.	No	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Doxorubicin, Cyclophosphamide, Tamoxifen	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	
				3 rd	Methotrexate, 5-Fluorouracil	NS	NS	Infant sex NS: Birth weight and Apgar scores NS. Newborn had intrauterine growth retardation (SGA), but was alive and well with no complications or malformations.	No	
		1 of 21 from Table 1 (Pt 14)	Non-Hodgkin lymphoma	2 nd	Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	
		1 of 21 from Table 1 (Pt 21)	Ovary	3 rd	Doxorubicin, Cisplatin	NS	NS	Infant sex NS: Birth weight and Apgar scores NS. Newborn was alive and well with no complications or malformations, and normal body weight for gestational age.	No	
Cyclophosphamide (200 mg/day)	Case report	1	Leukemia, ALL	1 st , 2 nd , 3 rd Last@wk 33	None	Vaginal	37	Female and male infants (twins): 1,250 g (female) [SGA] and 1,190 g (male) [SGA] , Apgar scores NS. Both newborns experienced severe respiratory depression. The female newborn appeared healthy. The male newborn had Madelung's deformity of the right arm (hyperflexion of the wrist, marked ulnar deviation, radial hemimelia, abnormal thumb), esophageal atresia, an abnormal inferior vena cava, an abnormal renal collecting system (cross-renal atopia), and the testes were not palpable.	At 9 years, the female had surgery to correct strabismus; at 22 years, the female has had normal growth and sexual development. At 2 through 4 years, the male had severe anemia; at 4 years, chromosome studies were normal; at 11 years, he had learning problems, a low IQ (81), and a hard thyroid nodule that affected swallowing – diagnosed as papillary thyroid carcinoma. At 13 years, right testis cryptorchidism was corrected and a	(Zemlickis <i>et al.</i> 1993)† [This case report is follow-up on Case 6 in Reynoso <i>et al.</i> (1987), thus this case report was not tallied in the in the text analysis.]

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
									rudimentary left testis was removed. At 14 years, he had a ruptured retroperitoneal neuroblastoma arising from his adrenal gland. At 16 years, he was diagnosed with metastatic papillary thyroid carcinoma and has suffered 2 recurrences [age 22 years].	
Cyclophosphamide (Table 1: Pt 13 – 3 cycles Pt 30 – 1 cycle Pt 31 – 1 cycles Table 2: Pt 43 – 3 cycles Pt 6 – 1 cycle Pt 41 – 3 cycles Pt 34 – 1 cycle)	Survey, retrospective	7 of 48 (Table 1: Pts 13, 30, and 31; Table 2: Pts 43, 6, 41, and 34)	Hodgkin lymphoma	1 st	Vincristine	NS	Term	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	At 10 years, normal.	(Zuazu <i>et al.</i> 1991)
			Non-Hodgkin lymphoma	1 st	Vincristine	--	--	Spontaneous abortion at gestation wk 6. [No fetal data reported.]	--	
			Non-Hodgkin lymphoma	1 st	Doxorubicin, Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	
			Hodgkin lymphoma	1 st First@wk 11	Vinblastine, Procarbazine	C-Section	38	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	No	
			Non-Hodgkin lymphoma	1 st First@wk 12	Vincristine, Procarbazine, Triethylene-melamine	--	--	Induced abortion at gestation wk 14. [No fetal data reported; Pt 6, 1 st pregnancy.]	--	
			Non-Hodgkin lymphoma	2 nd First@wk 22	Doxorubicin, Vincristine	C-section	37	Infant: sex, weight, and Apgar scores NS. Normal baby.	No	

Appendix C Table 19. Cyclophosphamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Hodgkin lymphoma	3 rd First and Last@wk 30	Vinblastine, Procarbazine	C-section	NS	Infant: sex, weight, and Apgar scores NS. Newborn with anemia that resolved.	At 3 years, normal at follow-up.	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the cyclophosphamide timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

† Papers not included in text analysis (highlighted in light grey). In order to avoid counting the same cases more than once, we did not include the following studies: (Pizzuto *et al.* 1980, Avilés *et al.* 1990, Zemlickis *et al.* 1993, Avilés and Neri 2001). The cases in Aviles *et al.* (1990) were not included in the text analysis because they were reported in a subsequent retrospective case series (Avilés *et al.* 1991). The 3 patients (2, 3, and 6) from Pizzuto *et al.* (1980) were not included because this case series was reported in Aviles *et al.* (1988); however, we did use the age at delivery and additional fetal information from Pizzuto *et al.* (1980) not reported in Aviles *et al.* (1988). The retrospective case series Aviles and Neri (2001) was not included because it included both new cases and long-term follow-up on previously reported case series (Avilés and Niz 1988, Avilés *et al.* 1991) without individual pregnancy outcomes. The case report on twins exposed *in utero* by Zemlickis *et al.* (1993) was a detailed follow-up on Case 6 of the case series by Reynoso *et al.* (1987); thus, we did not include Case 6 of Reynoso *et al.* (1987) in our text analysis. Two studies were not included in the text analysis because of a lack of individual data on timing of exposure, co-treatments, and pregnancy outcomes (Kawamura *et al.* 1994, Ibrahim *et al.* 2000). Finally, we did not include abstracts in the text analysis (Ibrahim *et al.* 2006).

††Giacalone *et al.* (1999) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; SPCTL = subcutaneous panniculitis-like T-cell lymphoma; AMSA = amsacrine; behenoyl-ara-C = behenoyl cytosine arabinoside; IT = intrathecal; IUGR = intrauterine growth retardation; HELLP = hemolysis, elevated liver enzymes, and low platelet count syndrome; SGA = small for gestational age.

Appendix C Table 20. Cytarabine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (96 mg/day for 1 month)	Case report	1	Leukemia, APL	2 nd , 3 rd	Daunorubicin (1 st)	Vaginal	39	Male infant: 3,050 g, Apgar scores NS. Newborn was normal, including blood count and chromosomal analysis.	At 4 months, normal physical exam and neurological behavior.	(Alegre <i>et al.</i> 1982)
Cytarabine (100 mg/m ² , schedule NS)	Case series	2 of 8 (2 of 10 pregnancies; Pts 4, 5)	Leukemia, AML	2 nd First@wk 26	Daunorubicin	--	--	Spontaneous abortion on 7 th day of chemotherapy [stillbirth at ~gestation wk 27; No fetal data reported.]	--	(Ali <i>et al.</i> 2003)
				2 nd First@wk 24	Daunorubicin	--	--	Intrauterine death [stillbirth] during chemotherapy. Placental and fetal morphology normal.	--	
Cytarabine (7 X 80 mg around time of conception, 4 X 80 mg at 35-37 days postconception; schedule NS)	Case report	1	Leukemia, AML	1 st First@wk 1 Last@wk 5	6-Thioguanine (1 st), Daunorubicin	C-section	"At the expected date" [NS]	Polyhydramnios. Female infant: 2,800 g, Apgar scores 2, 7, and 6 at 1, 5, and 10 minutes. Newborn was treated for respiratory distress associated with choanal stenosis and pneumothorax. She also presented with mild hypotelorism, severe brachycephaly, hypoplasia of the anterior cranial base, supra-orbital structures, and naso- and oropharynx, premature closure of both coronal sutures and the metopic suture, bilateral 4-fingered hands with hypoplastic thumbs, bilateral absent radii, and a small ostium secundum-type atrial septal defect.	At 13 months, she was underweight, had mild generalized hypotonia, and slightly retarded motor milestones. Fine motor development and social development were normal. Her head appeared mesocephalic.	(Artlich <i>et al.</i> 1994)
Cytarabine (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, diffuse lymphoblastic	3 rd	Doxorubicin, Vincristine, Cyclophosphamide, Asparaginase, Cisplatin	C-section	NS	Male infant: 2,600 g. Apgar scores NS. Newborn was apparently healthy.	At 2 years, no growth retardation, mental retardation, or malformations were noted.	(Ataergin <i>et al.</i> 2007)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (80 mg/m ² daily for 5 days, 2 cycles)	Case report	1	Leukemia, AML	3 rd First@wk 33 Last@wk 37	6-Thioguanine	Vaginal	38	Male infant: 2,948 g, Apgar scores NS. Newborn was normal with normal chromosomal analysis. After 48 hours, he developed jaundice (resolved by day 8).	At 5 months, normal development.	(Au-Yong <i>et al.</i> 1972)
Cytarabine (Dose/schedule NS)	Case series, retrospective	9 of 43 (3 in Table I: Pts 3, 4, 7; 6 in Table III: Pts 6, 8, 12, 14, 17, 18)	Leukemia, AML	1 st [see note in reference column]	Doxorubicin, 6-Mercaptopurine, Methotrexate	Vaginal	36	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, normal growth and development.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
			Leukemia, AML	3 rd	Doxorubicin	C-section	39	Female infant: 2,800 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 15 years, normal growth and development.	
			Leukemia, AML	2 nd	Doxorubicin, 6-Mercaptopurine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, normal growth and development.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin, Vincristine, Bleomycin	Vaginal	37	Female infant: 2,900 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, normal growth and development.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Epirubicin, Vincristine, Etoposide, Bleomycin, Methotrexate	Vaginal	37	Male infant: 2,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, normal growth and development.	
			Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Doxorubicin, Vincristine, Methotrexate	Vaginal	39	Female infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, normal growth and development.	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Doxorubicin, Vincristine, Methotrexate, Etoposide, Bleomycin	Vaginal	40	Female infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, normal growth and development.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Epirubicin, Vincristine, Bleomycin, Etoposide, Methotrexate	Vaginal	40	Male infant: 2,800 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 3 years, normal growth and development.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Epirubicin, Vincristine, Bleomycin	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, normal growth and development.	
Cytarabine (Pt 10 – 500 mg, Pt 12 – 600 mg, Pt 14 – 700 mg; schedules NS)	Case series	3 of 16 (Pts 10, 12, 14)	Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate	NS	NS	Individual pregnancy outcomes are not provided. Birth weights were 2,200-3,900 g (group range). All babies were born alive and none of the newborns showed apparent congenital malformations.	At ages ranging from 3 to 11 years, normal growth and development.	(Avilés <i>et al.</i> 1990) [†]
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Etoposide					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Bleomycin, Methotrexate, Etoposide					
Cytarabine (Dose/schedule NS)	Case series, retrospective	4 of 29	Leukemia, acute	NS	Daunorubicin	NS	NS	Individual data and outcomes NS. Birth weight: 3,085 g (median); 2,500-3,675 g (range).	In a follow-up study of 84 children, ages ranging from 6 to 29 years, learning and educational performance	(Avilés and Neri 2001) [Remaining 7 cases may
		3 of 29	Leukemia, acute	NS	Mitoxantrone	NS	NS			

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
		4 of 29	Leukemia, acute	NS	Idarubicin	NS	NS		were normal. No congenital, neurological, or psychological abnormalities were observed.	have been reported in other publications by this author, thus are not included here.]
Cytarabine (Dose/schedule NS)	Case series, retrospective	9 of 20 (Pts 3, 6, 7, 9, 11, 12, 17, 18, 19)	Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Methotrexate, Cyclophosphamide, 6-Mercaptopurine	[Vaginal]	[40]	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 12 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	(Avilés and Niz 1988) [Four of these pregnancies (3, 6, 7, and 9) were first reported in Pizzuto <i>et al.</i> (1980). We counted them only once using Aviles <i>et al.</i> (1988).]
			Leukemia, ALL	1 st , 2 nd , 3 rd	6-Mercaptopurine, Methotrexate, Vincristine, Cyclophosphamide	[C-section]	[34]	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had pancytopenia and no congenital malformations. Died from septicemia at 21 days; blood counts were normal at time of death.	--	
			Leukemia, ALL	2 nd , 3 rd	Vincristine, Methotrexate, 6-Mercaptopurine	[Vaginal]	[38]	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn had no congenital malformations. Died from gastroenteritis at 90 days.	--	
			Leukemia, AML	3 rd	Vincristine	NS [C-section]	N [33]S	Female infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	2 nd , 3 rd	Doxorubicin	NS	NS	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	1 st , 2 nd , 3 rd	Doxorubicin, Vincristine, Methotrexate, Cyclophosphamide	NS	NS	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	1 st , 2 nd , 3 rd	Doxorubicin, Vincristine	NS	NS	Female infant: 3,250 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	1 st , 2 nd	Doxorubicin	NS	NS	Male infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations. [Pt B, pregnancy 2]	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	2 nd , 3 rd	Doxorubicin	NS	NS	Female infant: 2,600 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
Cytarabine (Pt 1 – 160 mg IV every 24 hours for 4 days; Pt 5 – 100 mg every 12 hours for 5 days; Pt 4 – 1 cycle; Pt 5 – 3 cycles)	Case series	2 of 5 (Pts 4, 5)	Leukemia, AML	2 nd First@~wk 16	Vincristine, Doxorubicin	--	--	Spontaneous abortion at gestation wk 17. [No fetal data reported.]	--	(Awidi <i>et al.</i> 1983)
			Leukemia, acute (erythroleukemia)	2 nd , 3 rd First@~wk 26	Doxorubicin, 6-Thioguanine	Vaginal	[~36]	Female infant: 2,980 g, Apgar scores NS. Newborn was normal.	At 1 month, normal.	
Cytarabine (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd or 2 nd , 3 rd	Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Mitoxantrone	C-section	34	Female infant: 2,960 g, Apgar scores NS. Newborn was healthy.	At 16 months, no abnormalities.	(Azuno <i>et al.</i> 1995)
Cytarabine (100 mg/m ² every 12 hours for 9 days)	Case report	1	Leukemia, APL	2 nd First@wk 21	6-Thioguanine, Vincristine, Doxorubicin	C-section	30	Preeclampsia at days 5 and 15 of chemotherapy, treated and resolved. Male infant: 1,320 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was normal with normal blood work. At 20 minutes, he experienced tachypnea and progressive respiratory	At 70 days, infant discharged from the hospital in excellent condition with normal hematological values and karyotype.	(Bartsch <i>et al.</i> 1988)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								failure requiring intermittent ventilation. By 3.5 hours, he had developed severe respiratory distress syndrome requiring intubation (resolved by 6 days after treated with surfactant).		
Cytarabine (2 x 1 g/m ² on days 1-3 of a 28-day cycle, then 1 g/m ² on days 2-6 for 1 cycle)	Case report	1	Leukemia, AML	2 nd First@wk 22 Last@wk 26	Mitoxantrone, Idarubicin, Fludarabine (3 rd), Gemtuzumab-ozogamicin (3 rd)	C-section	33	Fetus developed cardiomyopathy, transient cerebral ventriculomegaly, mild fetal anemia, and intrauterine growth restriction after initiation of chemotherapy. Male infant: 1,695 g, Apgar scores 8 and 9 at 5 and 10 minutes. Newborn was anemic and required ventilation but adapted fast and showed no abnormalities and no clinical signs of dysmorphia.	At 6 months, no residual signs of cardiomyopathy or hydrocephalus.	(Baumgartner <i>et al.</i> 2009)
Cytarabine (100 mg/m ² /day, days 1-7, 2 cycles)	Case report	1	Leukemia, AML	2 nd	Daunorubicin	C-section	28 + 1 day	Male infant: 1,130 g, Apgar scores 5-6-7. Newborn showed no malformations, and heart function was normal. Blood transfusions and granulocyte colony stimulating factor were administered for anemia. The child recovered fully and was considered healthy.	No	(Biener <i>et al.</i> 2009)
Cytarabine (Dose/schedule NS)	Case series, retrospective	1 of 18 (Pt 3)	Leukemia, AML	2 nd	None	NS	No premature birth [Term]	Male Infant: 10 lb [4,536 g] , Apgar scores NS. Newborn was normal with normal birth weight [for gestational age] .	At 7 years, growth and development were normal; no major abnormalities.	(Blatt <i>et al.</i> 1980)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (Intrathecal, dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Vincristine, Daunorubicin, Asparaginase, Methotrexate (intrathecal)	C-section	30	Female infant: 1,266 g, Apgar scores 5 and 8 at 1 and 5 minutes. Newborn's physical examination, hematologic parameters, sepsis assessment, and cancer screening were normal.	No	(Bottsford-Miller <i>et al.</i> 2010)
Cytarabine (1,000 mg/m ² /day for 4 days)	Case report	1	Leukemia, APL	3 rd	Idarubicin (2 nd , 3 rd), ATRA (2 nd , 3 rd)	C-section	34	Female infant: 1,950 g, Apgar scores NS. Newborn showed no apparent abnormalities by physical examination or routine laboratory tests.	No	(Breccia <i>et al.</i> 2002)
Cytarabine (160 mg/day for 7 days, 2 cycles)	Case report	1	Leukemia, AML	2 nd First@wk 24	Daunorubicin	C-section	29	Female infant: 1,350 g, Apgar scores 2 and 9 at 1 and 5 minutes. Newborn had seizures, respiratory distress, and bilateral pneumothorax that subsequently stabilized, and she was discharged in good condition.	At 14 months, physically and psychologically normal.	(Cantini and Yanes 1984)
Cytarabine (Dose/schedule NS)	Survey, registry	1 of 31 from Table 3	Non-Hodgkin lymphoma	3 rd	Cisplatin, Etoposide	NS	34.0 (group mean)	Infant sex NS: 2,576 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 2 months, normal phenotype. At 34 to 82 months (group range, n=6), 1 child in the group had a speech delay; group mean weight was 46 th percentile.	(Cardonick <i>et al.</i> 2010)
		1 of 3 from Table 5	Leukemia, CML	1 st	None	NS	42	Infant sex NS: 3,544 g, Apgar scores NS. Newborn was normal with normal birth weight for gestational age.	At 7 years, normal phenotype. At 17.5 months (group mean, n=3), no long-term complications; group mean weight was 73 rd percentile.	
		1 of 3 from Table 5	Leukemia, ALL	2 nd , 3 rd	Cyclophosphamide, Daunorubicin, 6-Mercaptopurine, Methotrexate (intrathecal), Vincristine, Asparaginase	NS	35.5 (Group mean)	Infant sex NS: 2,341 g (group mean), Apgar scores NS. Newborn was normal with normal birth weight for gestational age.	At 9 years, normal phenotype. At 41 to 109 months (group range, n=2), no long-term complications; group mean weight was 65 th percentile.	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd	Daunorubicin, 6-Thioguanine	Vaginal, induced	34	Female infant: 2,470 g, Apgar scores 6 and 7 at 1 and 5 minutes. Newborn was normal.	At 12 months, well.	(Catanzarite and Ferguson 1984)
Cytarabine (Dose/schedule NS)	Survey, retrospective	15 of 37 from Table 1 (Pts 2, 3, 4, 5, 8, 10, 12, 21, 22, 25, 27, 28, 31, 36, 37) [see note in reference column]	Leukemia, AML	1 st (Diagnosis @wk 7) (Pt 2)	ATRA, Daunorubicin	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005) [In addition, Pts 1, 6, 7, 11, 15, 18, 19, 23, 24, 26, 32, and 33 were diagnosed in the 3 rd trimester and treated with cytarabine, but were not included because it was not possible to determine if they received chemotherapy during pregnancy.]
			Leukemia, AML	2 nd (Diagnosis @wk 15)(Pt 3)	Idarubicin	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	1 st (Diagnosis @wk 9) (Pt 4)	ATRA, Daunorubicin	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	1 st (Diagnosis @wk 6) (Pt 5)	Idarubicin	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	1 st (Diagnosis @wk 5) (Pt 8)	ATRA, Daunorubicin	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 23) (Pt 10)	Daunoxome [Daunorubicin]	C-section	Premature	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	Evolution has been normal with regard to growth and development in those who have been followed [Age NS].	
			Leukemia, AML	2 nd (Diagnosis @wk 16) (Pt 12)	Daunorubicin, Etoposide	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	1 st (Diagnosis @wk 9)(Pt 21)	Daunorubicin	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 18) (Pt 22)	Daunorubicin	Vaginal	Term	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	Evolution has been normal with regard to growth and development in those who have been followed [Age NS].	
			Leukemia, AML	1 st (Diagnosis @wk 13) (Pt 25)	Daunorubicin, Mitoxantrone	--	--	Spontaneous abortion (fetus had died) [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 17) (Pt 27)	Idarubicin	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 16) (Pt 28)	Daunorubicin, Mitoxantrone	--	--	Induced abortion. [No fetal data reported.]	--	
Leukemia, AML	2 nd (Diagnosis @wk 19) (Pt 31)	Daunorubicin	--	--	Induced abortion. [No fetal data reported.]	--				

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	1 st (Diagnosis @wk 10) (Pt 36)	Daunorubicin	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 22) (Pt 37)	Daunorubicin	Vaginal	Term	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	Evolution has been normal with regard to growth and development in those who have been followed [Age NS] .	
Cytarabine (100 mg/m ² daily for 10 days; 1,000 mg/m ² every 12 hours for 6 days)	Case report	1	Leukemia, AML	2 nd , 3 rd	Idarubicin (2 nd)	C-section	33 + 4 days	Intrauterine growth retardation and variable decelerations on fetal tocogram. Female infant, 1,408 g [SGA] , Apgar scores 4, 7, and 10 at 1, 5, and 10 minutes. Newborn had hyperbilirubinemia but no dysmorphic features or major anomalies. Amniotic fluid was meconium-stained.	No	(Claahsen <i>et al.</i> 1998)
Cytarabine (Dose NS, weekly)	Case report	1	Leukemia, ALL	NS, 3 rd	6-Mercaptopurine (1 st , 2 nd) Methotrexate (1 st , 3 rd), Doxorubicin (2 nd), Vincristine (1 st , 2 nd , 3 rd)	C-section	36	Male infant: 2,400 g, Apgar scores NS. Newborn was polycythemic and jaundiced but had no congenital defects.	At 6 months, normal growth and development.	(Dara <i>et al.</i> 1981)
Cytarabine (Dose/schedule NS)	Case series	4 of 32 (Pts 12, 20, 27, 30)	Leukemia, AML	2 nd First@wk 17	Daunorubicin	C-section	28	Infant sex NS: 1,370 g, Apgar scores NS. Newborn was healthy but required intubation.		(De Carolis <i>et al.</i> 2006)
			Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 24 Last@wk 37	Doxorubicin, Cyclophosphamide, Etoposide, Bleomycin, Vincristine	C-section	35	Infant sex NS: 1,980 g, Apgar scores 8 and 9. Newborn was healthy.		
			Leukemia, AML	3 rd First@wk 28	Daunorubicin	C-section	28	Infant sex NS: 1,150 g, Apgar scores NS. Newborn had respiratory distress syndrome and hypospadias.		

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	3 rd First@wk 34 Last@wk 37	Epirubicin, Cyclophosphamide, Etoposide, Bleomycin, Vincristine	Vaginal	36	Infant sex NS: 3,020 g, Apgar scores 9 and 9. Newborn was healthy.		
Cytarabine (Pt 1 – 100 mg/m ² twice daily for 7 days, cycles NS; Pt2 – 160 mg twice daily for 7 days, cycles NS)	Case series	2 of 2	Leukemia, APL	2 nd , 3 rd First@wk 24	ATRA, Daunorubicin	Vaginal	32	Female infant: 2,300 g, Apgar scores NS. Newborn was normal.	At 10 months, she was healthy.	(Delgado-Lamas and Garces-Ruiz 2000)
			Leukemia, APL	2 nd , 3 rd First@wk20	ATRA, Daunorubicin	Vaginal	36	Female infant: 2,200 g, Apgar scores NS. Newborn had no apparent malformations but had respiratory distress that required support for 15 days.	At 5 months, growth and development were normal.	
Cytarabine (100 mg/m ² twice a day for 7 days)	Case report	1	Leukemia, APL	2 nd , 3 rd First@wk 22	Doxorubicin (2 nd), 6-Thioguanine (2 nd)	C-section	28	Intrauterine growth restriction and no response to nonstress test at 28 of wks of gestation. Male infant: 1,140 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal; placenta had multiple infarcts but no leukemia infiltration.	At 14 months, normal chromosomal study. At 20 months, normal according to physical and psychological assessment.	(D'Emilio <i>et al.</i> 1989)
Cytarabine (125 mg twice daily for 5 days, 3 cycles)	Case report	1	Leukemia, AMML	3 rd	6-Thioguanine	C-section	39	Male infant: 3,200 g, Apgar scores 6 and 9 at 1 and 5 minutes. Newborn showed no signs of bone marrow depression, and chromosome analysis was normal. There was no congenital abnormality and no evidence of leukemia in the infant or the placenta.	At 15 months, in excellent health.	(de Souza <i>et al.</i> 1982)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (Dose/schedule NS)	Case series	1 of 18 (Pt 4)	Leukemia, AML	2 nd , 3 rd	Daunorubicin, ATRA	NS	NS [~28]	Male infant: 1,050 g, Apgar scores NS. Newborn was premature with normal hematological values. He suffered respiratory distress and died after 1 day.	--	(Dilek <i>et al.</i> 2006)
Cytarabine (90 mg/m ² twice daily for 7 days; Pt 2 – 1 cycle, Pt 3 – 2 cycles)	Case series	2 of 3 (Pts 2, 3)	Leukemia, AML	2 nd	Hydroxyurea, Daunorubicin, Vincristine, 6-Thioguanine	--	--	Induced abortion at gestation wk 21. Male fetus: 308 g. Fetus had no external defects or gross abnormalities in organogenesis, and normal organ weights, except for an enlarged spleen.	--	(Doney <i>et al.</i> 1979)
				3 rd	Hydroxyurea, Daunorubicin, Vincristine, 6-Thioguanine	Vaginal	31	Spontaneous preterm labor at 4 wks after admission. Male infant: 2,130 g, Apgar scores 7 and 8 at 1 and 5 minutes. Newborn was anemic, hyponatremic, hypocalcemic, and hypoglycemic – resolved within 7 months.	At 4 months, experiencing mild infections. At 4.5 and 13.5 months, Denver Developmental Screening tests were normal. At 13.5 months, complete blood count and general physical examination were unremarkable, but growth parameters were depressed (< 3 rd percentile).	
Cytarabine (100 mg/m ² daily for 10 days, 3 cycles)	Case report	1	Leukemia, AML	3 rd First@wk 31	Vincristine	Vaginal	39	Male infant: 2,967 g, Apgar scores NS. Newborn was normal with normal blood count.	At 30 months, normal development and excellent health.	(Durie and Giles 1977)
Cytarabine (Pt 1 – 8 x 160 mg, 2 cycles, plus maintenance therapy; Pt 2 – dose/schedule NS)	Case series	2	Leukemia, AML	2 nd , 3 rd First@wk 18/19	Daunorubicin, 6-Thioguanine (2 nd), Methotrexate	Vaginal	39	Female infant: weight and Apgar scores NS. Newborn was healthy.	No	(Ebert <i>et al.</i> 1997)
				1 st Last@wk 8	Vincristine, Doxorubicin	Vaginal	NS	Female infant: weight and Apgar scores NS. Newborn had an atrial septum defect and bilateral loss of radius and fifth digit.		

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (80 mg/m ² twice a day for 7 days)	Case series	4 of 5 (Pts 1, 2, 3, 4)	Leukemia, APL	1 st First@wk 11	Vincristine, Doxorubicin	--	--	Induced abortion at gestation wk 19. Histologic and karyotypic examinations of fetus were not performed.	--	(Fassas <i>et al.</i> 1984)
			Leukemia, AML	2 nd First@wk 17	Vincristine, Doxorubicin	Vaginal	37	Spontaneous preterm labor. Male infant: 2,430 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal with no congenital abnormalities and normal blood count.	At 3-4 months, increased leukocyte count and lymphocytic with occasional red blood cells in smear. At 20 and 30 months, normal blood counts. At 37 months, normal growth and development.	
				3 rd First@wk 36	Vincristine, Doxorubicin	Vaginal	37	Male infant: 3,100 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal with normal blood count.	At 36 months, normal growth and development.	
				3 rd First@wk 31	Vincristine, Doxorubicin	C-section	38	Male infant: 3,140 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with normal blood profile. Lost to follow-up.	No	
Cytarabine (Total doses: Pt 1 – 80 mg/d x 3 days for 3 cycles, then 160 mg/d x 3 days; Pt 2 – 480 mg over 3 cycles; Pt 3 – 480 mg IV and 160 mg/day x 3 days for 1 cycle; Pt 4 and Pt 5 dose/schedule NS; cycle = 7 days)	Case series	5 of 5	Leukemia, AML	2 nd , 3 rd First@wk 26	Daunorubicin	Vaginal	39	Male infant: 2,659 g [SGA], Apgar scores 7 and 8 at 1 and 5 minutes. Newborn was normal.	At 9 years, normal growth.	(Feliu <i>et al.</i> 1988)
			Leukemia, AML	6 th month [3 rd]	Doxorubicin (1 st), Vincristine (1 st , 3 rd) Daunorubicin (2 nd), Methotrexate (1 st), 6-Mercaptopurine (1 st)	Vaginal	38	Female infant: 2,800 g, Apgar scores 8 and 10 at 1 and 5 minutes.	At 7 years, normal development.	
			Leukemia, AMML	8 th month [3 rd]	Methotrexate (1 st), 6-Mercaptopurine (1 st)	Vaginal	38	Male infant: 2,750 g, Apgar scores 6 and 8 at 1 and 5 minutes.	At 7 years, normal development.	
			Leukemia, ALL	1 st , 2 nd	Daunorubicin, Vincristine, 6-Mercaptopurine	--	--	Mother and fetus died at 23 wks of gestation. Fetal morphology was normal.	--	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	2 nd First@wk 20	Daunorubicin, 6-Thioguanine	Vaginal	32	Infant sex NS: 1,500 g, Apgar scores 6 and 7 at 1 and 5 minutes. Newborn was morphologically normal.	No	
Cytarabine (Dose/schedule NS)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd , 3 rd First@wk 21 Last@wk 28	Daunorubicin (2 nd), Mitoxantrone (3 rd)	C-section	29 + 3 days	Oligohydramnios and early intrauterine growth retardation detected at 28 wks of gestation. Fetal tachycardia at 29 wks of gestation + 3 days. Female infant: 857 g [SGA], Apgar scores 4 and 6 at 1 and 5 minutes. Newborn required resuscitation and was transferred to the NICU for mechanical ventilation and antibiotics. She showed hyponatremia, hypoglycemia, seizures, neutropenia, anemia, thrombocytopenia, and bilateral hydronephrosis with dilation of the proximal ureter of the left kidney. Hematologic derangement resolved after 7 days of therapy.	She developed failure to thrive and started to gain weight only after 3 months.	(Garcia <i>et al.</i> 1999)
Cytarabine (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd	6-Thioguanine (2 nd), ATRA (2 nd), Daunorubicin (2 nd), Mitoxantrone	Vaginal, induced	35	Female infant: 2,490 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was healthy with no physical abnormalities detected.	At 4 months, no complications with development.	(Giagounidis <i>et al.</i> 2000)
Cytarabine (160 mg daily for 5 days, 6 cycles repeated at 5-day intervals, plus 1 later cycle)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 23 Last@wk 37	Daunorubicin, 6-Thioguanine(3 rd)	Vaginal	37	Male infant: 2,880 g, Apgar scores NS. Newborn was healthy and normal.	No	(Gokal <i>et al.</i> 1976)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (Dose/schedule NS)	Case series	6 of 17 (Pts 2, 3, 5, 9, 11, 12)	Leukemia, ALL	2 nd First@wk 18	Daunorubicin, Cytarabine, Vincristine	--	--	Mother and fetus died during pregnancy [at approximately gestation wk 24]. [No fetal data reported.]	--	(Greenlund <i>et al.</i> 2001)
			Leukemia, AML	2 nd First@wk 18	Daunorubicin	NS	41	Female infant: 2,950 g, Apgar scores NS. Newborn had no malformations.		
			Leukemia, AML	2 nd First@wk 15	Daunorubicin	--	--	Fetal death [spontaneous abortion] at gestation wk 17.5. [No fetal data reported.]	--	
			Leukemia, AML	2 nd First@wk 26	Daunorubicin, 6-Thioguanine	NS	38	Male infant: 3,240 g, Apgar score 8. Newborn had no malformations.		
			Leukemia, AML	2 nd First@wk 24	Doxorubicin, Vincristine, 6-Thioguanine	NS	31.5	Female infant: 1,135 g [SGA], Apgar scores NS. Newborn had no malformations.		
			Leukemia, AML	2 nd First@wk 19	Daunorubicin, 6-Mercaptopurine	NS	36	Female infant: weight and Apgar scores NS. Newborn had no malformations.		
Cytarabine (Dose/schedule NS)	Case series, retrospective	1 of 14 from Table 1 (Case 7)	Leukemia, AML, ALL	3 rd First@wk 34	Vincristine, 6-Thioguanine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal, but had low hemoglobin.	At 26 months, constant cold, weight < 10 th percentile. Growth was 10 th percentile. Immune function test and complete blood count were normal.	(Gulati <i>et al.</i> 1986)
Cytarabine (Dose/schedule NS)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25	6-Thioguanine, Daunorubicin (3 rd)	Vaginal	37	Female infant: 2,990 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal, both physically and cytogenetically.	No	(Hamer <i>et al.</i> 1979)
Cytarabine (Dose NS, days 1-4 and 8-11, 2 cycles)	Case report	1	Leukemia, ALL	3 rd First@wk 30 Last@wk 34	Cyclophosphamide (2 nd , 3 rd), Daunorubicin (2 nd), Vincristine (2 nd , 3 rd), Asparaginase (2 nd , 3 rd), 6-Mercaptopurine, Methotrexate (intrathecal)	Vaginal	36	Transient oligohydramnios [and spontaneous preterm labor]. Male infant: 2,150 g [SGA], Apgar scores 2 and 8 at 1 and 5 minutes, respectively. Newborn was normal, with normal hematology and neurology. There was mild	No	(Hansen <i>et al.</i> 2001)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								meconium aspiration syndrome and jaundice that were successfully treated.		
Cytarabine (140 mg/day for 7 days, altered to 4.5 g/m ² /day for 3 days)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 22	Daunorubicin, Mitoxantrone, Etoposide	C-section	36	Intrauterine growth restriction. Intermittent sinusoidal fetal heart rate patterns at 36 wks of gestation. Male infant: 1,046 g [SGA], Apgar scores 2 and 7 at 1 and 5 minutes. Newborn had pancytopenia.	At 2 months, in good health.	(Hsu <i>et al.</i> 1995)
Cytarabine (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Doxorubicin, Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Aclarubicin, Vincristine, Cycloctidine, ATRA, Mitoxantrone, Idarubicin, Asparaginase	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994)†
Cytarabine (1,000 mg/m ² , 4 cycles)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd First@wk 13 Last@wk 31	Dasatinib (1 st), Hydroxyurea	Vaginal, induced	34 + 6 days	Female infant: 2,470 g, Apgar scores NS. Newborn was healthy.	At 11 months, she was healthy without structural or functional anomalies or developmental delay	(Kroll <i>et al.</i> 2010)
Cytarabine (50 mg X 6, 2 cycles)	Case report	1	Leukemia, ALL	3 rd First@wk 31 Last@wk 35	Cyclophosphamide, Methotrexate (intrathecal), Vincristine (2 nd , 3 rd), 6-Mercaptopurine (2 nd , 3 rd)	Vaginal	38	Male infant: 6 lb 8.5 oz [2,963 g], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was normal.	At 7 months, he continued to thrive and had a normal karyotype.	(Krueger <i>et al.</i> 1976)
Cytarabine (intrathecal: 70 mg on day 1; IV: 2,000 mg/m ² every 12 hrs on day 1 and 2; 2 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 26 Last@wk 29	Vincristine, Doxorubicin, Cyclophosphamide, Etoposide, Ifosfamide	C-section	32	Male infant: 1,731 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no anomalies, but was cyanotic and experienced respiratory distress.	At 1 year, mild developmental delays, but otherwise healthy.	(Lam 2006)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (120 mg daily for 5 days, 3 cycles)	Case report	1	Leukemia, AML	1 st , 2 nd First@wk 10 Last@wk 17	6-Thioguanine (1 st), Vincristine (2 nd), Daunorubicin (2 nd)	--	--	Induced abortion at gestation wk 20: Female fetus was microscopically and macroscopically with normal karyotype and had no evidence of blood dyscrasia.	--	(Lilleyman <i>et al.</i> 1977)
Cytarabine (100 mg/m ² daily for 7 days)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 17 Last@wk 34	Daunorubicin (2 nd), 6-Thioguanine	Vaginal	40	Male infant: 2,860 g [SGA], Apgar scores NS. Newborn was physically normal; no visual or hearing defects were detected; blood, bone marrow, cytogenetic analysis, and electrocardiography were all normal.	At 7 months he was normal in every respect.	(Lowenthal <i>et al.</i> 1978)
Cytarabine (intrathecal; dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 13 + 4 days	Doxorubicin, Rituximab, Cyclophosphamide, Vincristine	Vaginal	39	Female infant: 2,270 g [SGA], Apgar scores 6 and 9. Newborn was viable with low birth weight.	At 7 months, healthy.	(Magloire <i>et al.</i> 2006)
Cytarabine (100 mg/day for 7 days, 3 cycles)	Case report	1	Leukemia, AML	3 rd First@wk 28 Last@wk 33	6-Thioguanine	Vaginal	39	Female infant: 2,835 g, Apgar scores NS. Newborn was normal and healthy; chromosome studies were normal.	At 30 months, normal physical and mental development.	(Manoharan and Leyden 1979)
Cytarabine (70 mg/m ² /day on days 1-10, then 100 mg/m ² /day on days 1-7)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 26	Idarubicin (3 rd), Daunorubicin (2 nd)	C-section	32	Oligohydramnios at 32 wks of gestation. Female infant: 1,820 g, Apgar scores 6, 6, and 8 at 1, 5, and 10 minutes. Newborn showed no sign of cardiac failure, and cerebral ultrasound revealed no abnormalities. Newborn developed myelosuppression that required supportive treatment, also hepatopathy and elevated creatinine kinase. These values normalized within a wk. The baby was healthy at time of discharge.	No	(Matsuo <i>et al.</i> 2004)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (100 mg/m ² daily for 41 days)	Case report	1 (1 pt with 2 pregnancies)	Leukemia, AML	2 nd	6-Thioguanine	--	--	Induced abortion at gestation wk 24. Male fetus: 2 lb 3 oz. [992 g]. No congenital abnormalities were noted at autopsy. Tissue culture showed 2 normal male spreads, 2 spreads with trisomy C, and 1 cell with trisomy C and 1 very abnormal chromosome.	--	(Maurer <i>et al.</i> 1971)
				[1 st]	6-Thioguanine	--	--	Induced abortion. No abnormal chromosomes. [No fetal data reported.]	--	
Cytarabine (high dose, schedule NS)	Case series	1 of 2 (Pt B)	Leukemia, ALL	2 nd [First@wk18-19]	Vincristine, Asparaginase, Methotrexate (intrathecal), Daunorubicin	--	--	Stillbirth at gestation wk 22: 400 g (sex NS). [No fetal data reported.]	--	(Molkenboer <i>et al.</i> 2005)
Cytarabine (6 or more mg/kg at 2-wk intervals)	Case series	2 of 20 (only 2 pts treated during pregnancy)	Leukemia, AML	NS [at least 1 st]	6-Thioguanine	--	--	Induced abortion. [No fetal data reported.]	--	(Moreno <i>et al.</i> 1977)
			Leukemia, AML	NS [at least 1 st]	6-Thioguanine	Vaginal	Term	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	At 2 years, normal and well.	
Cytarabine (Dose/schedule NS)	Survey, retrospective	1 of 27 [27 pts received chemotherapy while pregnant; the number of pts who received cytarabine while pregnant was not provided]	Leukemia, AML	2 nd First@wk 13	Radiation therapy (1 st , 2 nd), Daunorubicin, Vincristine (2 nd , 3 rd), Cyclophosphamide (2 nd , 3 rd)	NS	NS	Infant sex, weight, and Apgar scores NS. Normal at delivery.	No	(Mulvihill <i>et al.</i> 1987)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (1 g/m ² /day, days 1-3, 2 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25	Daunorubicin, Etoposide	C-section	32	No fetal growth from 30-32 wks of gestation. Female infant: 1,460 g, Apgar scores NS. Newborn was very pale and required active resuscitation, and was anemic and neutropenic. She required ventilation for 10 hours. With treatment, the hematological abnormalities resolved by day 4. Cerebral ultrasound was normal, as was the rest of her neonatal course.	At 1 year she remained well with normal peripheral blood counts.	(Murray <i>et al.</i> 1994)
Cytarabine (Pt 1: 170 mg/24 hours for 10 days, then 40 mg every 6 hours for 5 days of 4-wk cycle; Pt 2: 140 mg/24 hours for 10 days for 2 cycles, then same dose for 4-wk cycles, 3 cycles)	Case series	2 of 2	Leukemia, acute	2 nd , 3 rd [First@wk 20]	Vincristine	C-section	[39]	Male infant: 3,460 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal.	At 4 years, normal development and good health.	(Newcomb <i>et al.</i> 1978)
				1 st , 2 nd , 3 rd [First@wk 12]	Doxorubicin, Vincristine	Vaginal	[39]	Female infant: 2,860 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn appeared normal.	At 6 wks, normal karyotype.	
Cytarabine (100 mg/m ² over 24 hours on days 1-7, then 3 g/m ² every 12 hours on days 1, 3, and 5)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 21	Idarubicin (3 rd)	C-section	37	At gestation wk 26, right ventricle mildly dilated with mild systolic dysfunction and left ventricle mildly smaller than normal with mild systolic dysfunction. Female infant: 1,710 g [SGA], Apgar scores 5 and 9 at 1 and 5 minutes. Newborn showed intrauterine growth restriction, cyanosis of the extremities, shallow sacral	At 3 months, other fetal defects [other than the heart] seen at birth seemed to have resolved. At 5 months, child recovered quickly from surgery to correct ventricular septal defect.	(Niedermeier <i>et al.</i> 2005)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								dimple, short digits and limbs, dysplastic fingernails, and prominent frontal skull with mild macrognathia, and a ventricular septal defect. Infant had normal ventricular size and function.		
Cytarabine (100 mg/m ² twice daily for 7 days)	Case series	2 of 2	Leukemia, AML	3 rd First@wk 27	Daunorubicin, 6-Thioguanine	Vaginal	40	Male infant: 5,000 g, Apgar scores NS. Newborn's blood count and karyotype were normal.	At 6 months, he remained well.	(O'Donnell <i>et al.</i> 1979)
			Leukemia, ALL	2 nd , 3 rd	Daunorubicin, 6-Thioguanine	--	--	Severe preeclamptic toxemia at gestation wk 29. Intrauterine death [stillbirth] at gestation wk 30: sex NS; no congenital abnormalities noted.	--	
Cytarabine (100 mg/m ² daily for 7 days)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 16	Idarubicin, Fludarabine (3 rd)	--	--	Fetal death [stillbirth] at gestation wk 34. [No fetal data reported.]	--	(Paşa <i>et al.</i> 2009)
Cytarabine (90-110 mg/m ² daily for 7 days, 4 cycles; 200 mg/day for 5 days, 1 cycle; 250 mg/day for 7 days, 1 cycle)	Case report	1	Leukemia, AGL	2 nd , 3 rd	6-Thioguanine, Vincristine	Vaginal	39	Infant: 2,250 g [SGA], sex and Apgar scores NS. Newborn had no abnormalities detected.	At 8 months the infant was developing normally.	(Pawliger <i>et al.</i> 1971)
Cytarabine (Dose/schedule NS)	Cohort, retrospective	3 of 14 from Tables 3 and 4 (Pts 1, 8, 10)	Hodgkin lymphoma	2 nd First@wk 26	Cisplatin, Etoposide	NS	36	Infant sex and Apgar scores NS: 2,540 g. Newborn had jaundice and non-hemolytic anemia.	No	(Peres <i>et al.</i> 2001)
			Leukemia, AML	2 nd First@wk 19	Daunorubicin	NS	39	Infant sex and Apgar scores NS: 3,000 g. Newborn had no neonatal complications.	At 9 years, normal development.	
			Leukemia, AML	NS	Idarubicin	--	--	Intrauterine growth restriction and oligohydramnios. Fetal death [stillbirth], but no malformations.	--	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (Intrathecal, 70 mg on days 1, 3, 5, 21, 45; 3.2 g/m ² IV twice daily on days 25, 16, 70, 71)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 16	Cyclophosphamide, Doxorubicin, Ifosfamide, Etoposide, Vincristine, Rituximab	--	--	Decreased amniotic fluid at gestation wk 18 and early intrauterine growth restriction at gestation wk 22; similar effects at 23.5 wks of gestation. At 68 days of treatment, vaginal bleeding, spontaneous preterm labor, and no fetal heart tones. Stillbirth at gestation wk 26. [No fetal data reported.]	--	(Peterson <i>et al.</i> 2010)
Cytarabine (Schedule NS; total doses: Pt 3 – 3,500 mg Pt 6 – 1,600 mg Pt 7 – 1,400 mg Pt 9 – 1,200 mg)	Case series	4 of 9 (Pts 3, 6, 7, 9 from Table 2)	Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Methotrexate, Cyclophosphamide, 6-Mercaptopurine	Vaginal	40	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 6 years, alive and healthy.	(Pizzuto <i>et al.</i> 1980)†
			Leukemia, ALL	1 st , 2 nd , 3 rd	6-Mercaptopurine, Methotrexate, Vincristine, Cyclophosphamide	C-section	34	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had no apparent congenital malformation but was pancytopenic.	At 21 days, died from septicemia.	
			Leukemia, ALL	2 nd , 3 rd	6-Mercaptopurine, Methotrexate, Vincristine	Vaginal	38	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 90 days, died from gastroenteritis.	
			Leukemia, AML	3 rd	Vincristine	Vaginal	38	Female infant: 3,000 g, Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 2 months, alive and healthy.	
Cytarabine (1 st pregnancy: 200 mg twice daily for 5 days, then 3 days. 2 nd pregnancy: 200 mg, then 300 mg, twice daily for 5 days, 2 or 3 cycles)	Case report	1 (1 pt with 2 pregnancies)	Leukemia, AMML	2 nd First@wk 22	6-Thioguanine	--	--	Intrauterine death [stillbirth] at gestation wk 26. No fetal abnormalities were noted.	--	(Plows 1982)
				2 nd , 3 rd	6-Thioguanine	C-section	39	Female infant: 3,133 g, Apgar scores 6 and 8. Newborn was normal.	No	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (200 mg daily for 14 days, then 200 mg weekly)	Case report	1	Leukemia, AML	2 nd , 3 rd	6-Thioguanine	Vaginal	39	Male infant: 3,540 g, Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was normal.	At 12 months he was in excellent health.	(Raich and Curet 1975)
Cytarabine (10 mg/kg on days 1 and 10, then 2 g/m ² twice daily on days 1-4, then 100 mg/m ² twice daily on days 1-3, 3 cycles)	Case series	2	Leukemia, AML	2 nd , 3 rd First@wk 25	6-Thioguanine, Daunorubicin, Mitoxantrone,	C-section	34	Male infant: 2,220 g, Apgar scores 3, 6, and 8 at 1, 5, and 10 minutes. Newborn required intubation for 7 minutes. His phenotype was rigorously normal; bone X-ray, central nervous system echography, and blood tests were all normal.	Follow-up was uneventful [age NS].	(Requena et al. 1995)
				2 nd , 3 rd First@wk 20	6-Thioguanine, Daunorubicin, Mitoxantrone,	C-section	34	Female infant: 2,100 g, Apgar scores 6, 7, and 9 at 1, 5, and 10 minutes. Newborn showed no phenotypic abnormalities; radiologic controls, sonograms, and blood tests were normal.	Follow-up has been satisfactory [age NS].	
Cytarabine (Dose/schedule NS)	Survey, retrospective	4 of 7 (Pts 2, 3, 4, 7)	Leukemia, CGL	3 rd	6-Thioguanine, Daunorubicin	Vaginal	34	[Spontaneous preterm labor.] Male infant: 2,290 g, Apgar score 9 at 5 minutes. Newborn had mild thrombocytopenia, resolved within 11 days.	At 18 months, normal growth and development.	(Reynoso et al. 1987)
			Leukemia, AML	2 nd [First@wk 25, table states 3rd]	6-Thioguanine, Daunorubicin	Vaginal	29	Spontaneous preterm labor. Male infant: 1,000 g, Apgar scores NS. Newborn had no malformations, but adherence of the iris to the cornea was diagnosed at age 2.	At 6 months, he had suffered frequent upper respiratory infections. At 3 years, normal growth and development.	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	2 nd , 3 rd	Daunorubicin, Vincristine, Cyclophosphamide	Vaginal	34	Spontaneous preterm labor. Male infant: 2,510 g, Apgar score 10 at 5 minutes. Newborn was healthy with normal peripheral blood counts and no congenital malformations.	At 7 years, healthy with weight and height in the 100 th percentile.	
			Leukemia, AML	2 nd , 3 rd	Daunorubicin, Cyclophosphamide, 6-Thioguanine, Vincristine	Vaginal, induced	39	Male infant: 3,420 g, Apgar score 10 at 5 minutes. Newborn was healthy with normal peripheral blood counts and had no congenital malformations.	At 11.5 years, healthy with normal growth and intellectual development.	
Cytarabine (100 mg/m ² on days 1-7, 2 cycles total)	Case report	1	Leukemia, AML	2 nd , 3 rd	Daunorubicin (2 nd); Mitoxantrone (2 nd , 3 rd); Idarubicin (3 rd)	--	--	Stillbirth: sex NS: 2,200 g. No obvious congenital malformations. No fetal autopsy was performed.	--	(Reynoso and Huerta 1994)
Cytarabine (Pt 1 – 175 mg/day for 2 days, 2-wk intervals, 5 cycles; Pt 4 – 200 mg/day for 5 days, 3-wk intervals, 3 cycles; Pt 5 – 200 mg/day for 5 days, 3-wk interval, 2 cycles)	Case series	3 of 7 (Pts 1, 4, 5)	Leukemia, AML	2 nd , 3 rd	Daunorubicin, 6-Mercaptopurine (3 rd)	Vaginal, Induced	32	Labor was induced because mother was seriously ill. Female infant: 2,041 g, Apgar score 9 at 1 minute. Newborn was normal.	No	(Roy <i>et al.</i> 1989)
				2 nd	Daunorubicin, 6-Thioguanine	C-section	33 (text) 34 (table)	Serial ultrasound showed poor fetal growth. Male infant: weight and Apgar score NS. Newborn had Down syndrome.		
				3 rd	Daunorubicin, 6-Thioguanine	Vaginal, induced	34	Female infant: 1,930 g, Apgar score NS. Newborn was normal.		

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (80 mg twice a day, days 1-5 of a 4-wk cycle)	Case report	1 (1 pt with 2 pregnancies)	Leukemia, acute	1 st , 2 nd , 3 rd	6-Thioguanine	C-section	38	Male infant: 2,212 g [SGA], Apgar scores 9 and 9 at 1 and 5 minutes. Physical findings were normal except for distal limb defects. The medial 2 digits of both feet were absent, with intact tarsals; the remaining lateral 3 toes and metatarsals appeared normal; the distal phalanges of both thumbs were absent, and the remnant of the right thumb was very hypoplastic.	At 2 months, normal karyotype. At 16 months, normal development and excellent health.	(Schafer 1981)
				1 st	6-Thioguanine	C-section	Term	Female infant: 2,912 g, Apgar scores 9 and 9 at 1 and 5 minutes. Physical findings were entirely normal.	At 2 months, normal karyotype. At 4 months, normal development.	
Cytarabine (1 g/m ² /day for 3 days)	Case report	1	Leukemia, AML	2 nd or 2 nd -3 rd [First@> 25 wks]	Etoposide, Daunorubicin	C-section	32	Serial ultrasounds detected reduced amniotic fluid and no fetal growth gain at 32 wks of gestation. Female infant: 1,460 g, Apgar scores NS. Newborn was very pale and required active resuscitation, also exhibited myelosuppression. She made good progress and was discharged at 46 days.	No	(Scherf and Price 1996)
Cytarabine (75 mg/m ² 4 times a day for 4 days/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Vincristine (2 nd), Asparaginase (2 nd), Daunorubicin (2 nd), Cyclophosphamide, 6-Mercaptopurine, Methotrexate (IT), Radiation therapy	Vaginal	40	Female infant: weight and Apgar scores NS. Newborn was healthy, had a full head of hair, and no abnormalities. Cytogenetic analysis of lymphocytes showed a normal karyotype but some chromosome breakage and a ring chromosome.	No	(Schleuning and Clemm 1987)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (100 mg/m ² on days 1-4, 2 cycles, 2 wks apart. One more cycle was given at half this dose.)	Case report	1	Sarcoma, granulocytic (breast)	NS	Vincristine, Daunorubicin, Cyclophosphamide	Vaginal	NS	Female infant: 7 lb 2 oz [3,232 g], Apgar scores NS. Newborn was completely normal.	No	(Sears and Reid 1976)
Cytarabine (Dose/schedule NS)	Case report	1	Leukemia, ALL	3 rd First@wk 32	Daunorubicin, Vincristine, Asparaginase, Cyclophosphamide	Vaginal, induced	~35	Female infant: 6.8 lbs [3,084 g], Apgar scores NS. Newborn was normal.	At 16 months, she was healthy with a normal blood count.	(Sigler <i>et al.</i> 1988)
Cytarabine (100 mg/m ² twice daily for 5 days, 4 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 27	6-Thioguanine	Vaginal	35	Spontaneous preterm labor Female infant: 1,430 g [SGA], Apgar scores 8 and 9. Newborn had a mildly decreased platelet count and increased bilirubin on day 4 – resolved by 2 wks; she had a normal karyotype.	At 1 year, normal weight and development. No evidence of a drug-related abnormality.	(Taylor and Blom 1980)
Cytarabine (60 mg twice daily for 5 days every 3 wks, 2 cycles)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd First@wk 24	6-Thioguanine, Daunorubicin, Doxorubicin	Vaginal	32	Spontaneous preterm labor. Female infant: 2,000 g, Apgar scores NS. Newborn had a premature appearance, but was normal with no obvious abnormalities.	At 13 months, feeding and weight gain are satisfactory; developmental milestones have been normal.	(Tobias and Bloom 1980)
Cytarabine (60 mg/m ² , then 1,000 mg/m ²)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 27 Last @wk 32	Cyclophosphamide, Daunorubicin (2 nd), Methotrexate (intrathecal), 6-Thioguanine, Vincristine (2 nd), Amsacrine (3 rd)	Vaginal	33	Spontaneous rupture of membranes. Male infant: 1,928 g [Table 2 states 1925 g], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn's physical exam was unremarkable with normal cerebral ultrasound, hearing, and echocardiography. He exhibited transient neonatal myelosuppression that was treated and resolved by day 20, including leukopenia at birth, neutropenia at day 2,	At 24 months, normal growth and development.	(Udink ten Cate <i>et al.</i> 2009)

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								anemia and thrombocytopenia at day 3. Treated for a urinary tract infection on day 7.		
Cytarabine (Dose/schedule NS)	Survey, retrospective	2 of 27 (Pts 10, 11)	Leukemia, AML	2 nd , 3 rd First@wk 27	Daunorubicin	C-section	30	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 21	Daunorubicin	C-section	37	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	
Cytarabine (100 mg/m ² twice daily for 7 days, then 500 mg/m ² twice daily for 7 days, 2 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd Last@wk 29	Doxorubicin, 6-Thioguanine (2 nd) Vincristine (3 rd)	C-section	29	Fetal suffering per ultrasonography and cardiotocography at wk 29. Female infant: 1,000 g, Apgar score 6 at 1 minute. Newborn was macroscopically normal, but had hyaline membrane disease and moderate meningeal hemorrhage that were successfully treated.	At 3.5 years, she is well with weight in normal range and normal neurological and hematological parameters.	(Veneri <i>et al.</i> 1996)
Cytarabine (Dose/schedule NS, Pt 1 – 2 cycles)	Case series	3 of 4 (Pts 1, 2, 4)	Leukemia, AML	2 nd First@wk 17 Last@wk 22	Daunorubicin, 6-Thioguanine	NS	30	Premature rupture of membranes, possibly the result of a medical evaluation of the placenta. Female infant: 1,180 g, Apgar scores NS. Placenta had myeloblastic infiltration.	At 5 years, development was normal, and health was excellent.	(Volkenandt <i>et al.</i> 1987)
			Leukemia, AML	2 nd First@wk 23	Daunorubicin, 6-Thioguanine	C-section	42	Male infant: 3,840 g, Apgar scores NS. Newborn was healthy. Newborn had 6 toes on right foot (family history of polydactyly).	At 22 months, development was normal and health was excellent.	
			Leukemia, AML	2 nd First@wk 15	Daunorubicin, 6-Thioiguanine	--	--	Intrauterine fetal death [spontaneous abortion] at 5 wks [gestation wk 20] after initiation of chemotherapy. Fetus (sex NS): 40 g. Autopsy revealed no abnormalities and no leukemic infiltration.	--	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (Dose NS, 4 consecutive days per month for 3 months)	Case report	1	Leukemia, ALL	1 st Last@wk 8	None	NS	NS [~at term]	Male infant: 2,863 g, Apgar scores NS. Newborn had deformities of the extremities and ears: bilateral microtia, bilateral atresia of the external auditory canals, right hand had a lobster claw with only 3 digits, right femur was shortened and bowed, left femur was bifid with 1 of 2 femurs extending anterior in the mid-shaft section, both lower legs contained a single bone, each foot was composed of an os calcis and only 2 lateral metatarsals.	At 10 months, motor development seemed normal.	(Wagner <i>et al.</i> 1980)
Cytarabine (200 mg/m ² /day for 7 days)	Case report	1	Leukemia, APL	3 rd	Daunorubicin	C-section	NS	Infant sex and Apgar scores NS: 2,100 g. Newborn was healthy and hematologically normal.	No	(Wallace 1989)
Cytarabine (Dose NS, 1 cycle)	Case report	1	Leukemia, AML	3 rd First@wk 30	Idarubicin	C-section	33-34	Mild uterine contractions [spontaneous preterm labor] and fetal distress. Male infant: 2,200 g, Apgar scores 2 and 6 at 1 and 5 minutes. Amniotic fluid was meconium-stained. No further information was presented.	No	(Yucebilgin <i>et al.</i> 2004)
Cytarabine (Dose/schedule NS)	Cohort, retrospective	3 of 31 (Pts 12, 15, 16)	Leukemia, CML	1 st	Daunorubicin, Hydroxyurea, 6-Thioguanine	--	--	Induced abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
			Leukemia, AML	2 nd	Doxorubicin	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	
			Leukemia, AML	2 nd	Doxorubicin, 6-Thioguanine	--	--	Stillbirth at gestation wk 26: appeared normal except for bruising and petechia over multiple areas.	--	

Appendix C Table 21. Cytarabine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Cytarabine (Table 2: Pt 2 – 1 cycle Pt 9 – 2,240 mg total Pt 36 – 2 cycles Pt 26 – 3 cycles Pt 24 – 2 cycles Pt 25 – 1 cycle)	Survey, retrospective	6 of 48 (Table 2: Pts 2, 9, 36, 26, 24, and 25)	Leukemia, AML	1 st First@wk 11 Last@wk 11	6-Thioguanine, Daunorubicin, Vincristine	--	--	Spontaneous abortion at 20 days post-chemotherapy. [No fetal data reported.]	--	(Zuazu <i>et al.</i> 1991)
			Leukemia, AML	1 st First@wk 12 Last@wk 12	Daunorubicin	--	--	Spontaneous abortion at gestation wk 15. [No fetal data reported.]	--	
			Leukemia, AML	2 nd First@wk 20 Last@wk 27	Daunorubicin, 6-Thioguanine, Vincristine	C-section	37	Infant: 2,100 g [SGA] , sex and Apgar scores NS. Newborn was premature.	At 3 years, normal.	
			Leukemia, AML	2 nd First@month 5 Last@month 6	Daunorubicin, 6-Thioguanine, Vincristine	Vaginal	NS	Infant: sex, weight, and Apgar scores NS. Newborn had normal outcome.	At 3 years, normal.	
			Leukemia, AML	3 rd First@wk 28	Daunorubicin, 6-Thioguanine, Vincristine	Vaginal	36	Infant: 2,400 g, sex and Apgar scores NS. Newborn was normal with normal karyotype.	At 4 years, normal follow-up.	
			Leukemia, AML	3 rd First@wk 29	Daunorubicin, 6-Thioguanine, Vincristine	--	--	Fetal death [stillbirth] during treatment. C-section postmortem, fetus without macroscopical anomalies.	--	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the cytarabine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). The case series reported in Pizzuto *et al.* (1980) was not included because these patients were included in Aviles *et al.* (1988).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AGL= acute granulocytic leukemia; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; AMML = acute myelomonocytic leukemia; APL = Acute promyelocytic leukemia; CGL = chronic granulocytic leukemia; CML = chronic myelogenous leukemia; ATRA = all-*trans* retinoic acid; behenoyl-ara-C = behenoyl cytosine arabinoside; IT = intrathecal; SGA = small for gestational age.

Appendix C Table 22. Dacarbazine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Dacarbazine (375 mg/m ² on days 1 and 14, 15 days between cycles, 2 cycles)	Case series	1 of 6 (Pt 1)	Hodgkin lymphoma	2 nd First@wk 21	Doxorubicin, Bleomycin, Vinblastine	C-section	29	Female infant: 2,400 g, Apgar scores NS. Newborn was healthy.	At 10 years, she remained healthy.	(Anselmo <i>et al.</i> 1999)
Dacarbazine (Dose/schedule NS)	Case series, retrospective	10 of 14 from Table II (Pts 2, 3, 4, 6, 7, 8, 11, 12, 13, 14)	Hodgkin lymphoma	2 nd [see note in reference column]	Doxorubicin, Bleomycin, Vinblastine	Vaginal	38	Male infant: 3,200 g. Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				1 st	Doxorubicin, Bleomycin, Vinblastine	Vaginal	37	Male infant: 3,800 g. Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Doxorubicin, Bleomycin, Vinblastine	C-section	34	Female infant: 2,800 g. Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Doxorubicin, Bleomycin, Vinblastine	Vaginal	35	Female infant: 2,500 g. Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Bleomycin, Vinblastine Nitrogen Mustard, Vincristine, Procarbazine	Vaginal	38	Female infant: 2,500 g [SGA]. Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Doxorubicin, Bleomycin, Vinblastine	Vaginal	37	Male infant: 3,100 g. Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 23. Dacarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd	Doxorubicin, Bleomycin, Vinblastine	Vaginal	38	Female infant: 3,000 g. Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Bleomycin, Vinblastine	Vaginal	40	Male infant: 3,500 g. Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Bleomycin, Vinblastine	C-section	40	Female infant: 3,450 g. Apgar scores NS. Newborn had no congenital malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Doxorubicin, Bleomycin, Vinblastine	Vaginal	36	Female infant: 3,200 g. Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Dacarbazine (Dose/schedule NS)	Survey, registry	20 of 31 from Table 3 [21 of 32 infants]	Hodgkin lymphoma	2 nd or 2 nd , 3 rd	Doxorubicin, Vinblastine, Bleomycin	NS	35.9 (group mean)	Infant sex NS: 2,587 g (group mean), Apgar scores NS. Nineteen newborns were normal, including 1 set of twins. Two infants had malformations: 1 had plagiocephaly, and 1 had syndactyly of the 4 th and 5 th fingers. All newborns had normal body weight for gestational age. One infant had birth weight 15%, and 3 infants had hypoglycemia.	At 0.5 to 10 years (n=20), all children were normal phenotype. At 4 to 112 months (group range, n=15), 1 child in the group had chronic broncolitis, 1 had recurrent otitis media, and 1 had asthma; group mean weight was 67 th percentile.	(Cardonick <i>et al.</i> 2010)
Dacarbazine (Dose/schedule NS)	Case series	3 of 32 (Pts 9, 18, 19)	Hodgkin lymphoma	2 nd , 3 rd First@wk 15 Last@wk 35	Doxorubicin, Bleomycin, Vinblastine	Vaginal	36	Infant, sex NS: 2,190 g, Apgar scores 6 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
				2 nd First@wk 24 Last@wk 27	Doxorubicin, Bleomycin, Vinblastine	C-section	37	Infant, sex NS: 2,850 g, Apgar scores 8 and 8. Newborn was healthy.		

Appendix C Table 23. Dacarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd First@wk 24 Last@wk 26	Doxorubicin, Bleomycin, Vinblastine	C-section	37	Infant, sex NS: 2,450 g, Apgar scores 9 and 9. Newborn was healthy.		
Dacarbazine (Dose/schedule NS)	Case series	2 of 18 (Pts 7, 10; Pt 7 had 2 pregnancies)	Hodgkin lymphoma	1 st	Doxorubicin, Vinblastine, Bleomycin	NS	NS	Male infant: 2,500 g, Apgar scores NS. Newborn had growth restriction (SGA), but was healthy and without hematological abnormalities. [Pt 7, 1 st pregnancy]	At 65 months, alive.	(Dilek <i>et al.</i> 2006)
				2 nd , 3 rd	Doxorubicin, Vinblastine, Bleomycin	--	--	Fetal death [stillbirth] in the 8 th month [Pt 7, 2 nd pregnancy; no fetal data reported.]	--	
				1 st	Doxorubicin, Vinblastine, Bleomycin	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had growth retardation (SGA) and a floating thumb malformation on the left hand (partial agenesis of a metacarpal bone and hypoplasia of 2 phalanges).	At 43 months, alive	
Dacarbazine (600 mg, 1 dose)	Case report	1	Hodgkin lymphoma	2 nd First@wk 17	Doxorubicin, Bleomycin, Vinblastine	--	--	Induced abortion after first dose. [No fetal data reported.]	--	(D'Incalci <i>et al.</i> 1983)
Dacarbazine (25 mg/m ² on days 1-3, 2 cycles)	Case report	1	Melanoma	2 nd First@wk 23 Last@wk 26.5	Carmustine, Cisplatin, Tamoxifen	C-section	30	Female infant: 1,520 g, Apgar scores NS. Newborn was healthy. Pathology revealed malignant melanoma in the placenta.	At 17 months (corrected to 15 months for early delivery), normal muscle tone and reflexes, and, overall, age-appropriate evaluations.	(DiPaola <i>et al.</i> 1997)
Dacarbazine (Dose NS, every 3-4 wks)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 25	Doxorubicin, Bleomycin, Vinblastine	C-section	38	Serial ultrasounds detected small for gestational age fetus. Male infant: 1,650 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 10 months, he remained well.	(Fadilah <i>et al.</i> 2006)

Appendix C Table 23. Dacarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Dacarbazine (250 mg/m ² for 3 days, every 4 wks)	Case report	1	Melanoma	2 nd	Cisplatin, Interferon alpha (1 st), Radiation therapy (2 nd , 3 rd ; [calendar dates and wks of gestation are inconsistent])	C-section	28 + 3 days	Intrauterine growth retardation (fetal growth at 3 rd percentile) at 28 wks of gestation. Male infant: 735 g [SGA], Apgar scores 6, 8, and 8. Newborn was healthy and without signs of metastatic melanoma.	Uneventful, age-appropriate development [age NS].	(Gottschalk <i>et al.</i> 2009)
Dacarbazine (250 mg/m ² daily for 5 days, 6 cycles at 21-day intervals) [Not clear how 6 cycles at 21-day intervals could have been given between wks 27 and 34]	Case report	1	Melanoma	2 nd , 3 rd First@wk 27	None	Vaginal	38	Male infant: 3,175 g, Apgar scores NS. Newborn was healthy.	At 4 years, examinations revealed no abnormalities.	(Harkin <i>et al.</i> 1990)
Dacarbazine (375 mg/m ² , schedule NS, 3.5 cycles)	Case report	1	Hodgkin lymphoma	2 nd First@wk 21	Bleomycin, Doxorubicin, Vinblastine,	Vaginal	41	Female infant: weight was within normal limits. Apgar score 9. Newborn was healthy.	At follow-up [age NS], no physiological or developmental abnormalities.	(Iriyama <i>et al.</i> 2011)
Dacarbazine (750 mg)	Case report	1	Melanoma	2 nd First@wk 26	Nimustine, Vincristine, Interferon beta	Vaginal	35	Male infant: 2,208 g, Apgar scores NS. Newborn was healthy.	At 32 months, no signs of melanoma.	(Ishida <i>et al.</i> 2009)
Dacarbazine (Dose/schedule NS; Sarcoma Pt – 1 cycle, Hodgkin Pts – 7-8 cycles)	Case series	1 of 18	Sarcoma, soft tissue	NS First@ wk 12-33, 22 (mean)	Cyclophosphamide, Doxorubicin, Vincristine	--	--	Spontaneous abortion at gestation wk 22. [No further fetal data reported.]	--	(Jameel and Jamil 2007)
		2 of 18	Hodgkin lymphoma		Doxorubicin, Bleomycin, Vinblastine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborns were alive and healthy; no malformations were observed.	At follow-up, normal growth patterns without physical or neurological deficits (n=5 children, oldest child is 42 months).	
Dacarbazine (Dose/schedule NS, 3 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 27	Doxorubicin, Bleomycin, Vinblastine	C-section	39	Male infant: 2,350 g [SGA], Apgar scores NS. Newborn was healthy and HIV negative (mother was HIV positive).	At 9 months the baby was clinically well and HIV negative.	(Klepfish <i>et al.</i> 2000)

Appendix C Table 23. Dacarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Dacarbazine (220 mg/m ² days 1-3, 4 monthly cycles)	Case report	1	Melanoma	1 st , 2 nd	Carmustine, Tamoxifen, Cisplatin	C-section	34	Male infant: 2,750 g, Apgar scores 10 and 10 at 1 and 5 minutes. No dysmorphism was detected on clinical examination.	At 1 year social, hearing, and gross and fine motor assessments were normal; however, he was diagnosed with microphthalmia and severe hypermetropia.	(Li <i>et al.</i> 2007)
Dacarbazine (Dose/schedule NS)	Survey, retrospective	3 of 22 (Pts 8, 9, 19)	Melanoma	3 rd	None	Vaginal	36	Female infant: 3,200 g, Apgar scores NS.	At 20 months, alive and healthy.	(Pages <i>et al.</i> 2010)
				3 rd	None	C-section	37	Male infant: 2,260 g [SGA], Apgar scores NS. Newborn had intrauterine growth restriction.	At 5 months, alive and healthy.	
				2 nd	None	C-section	26	Male infant: 990 g, Apgar scores NS. Newborn was hospitalized in the neonatal intensive care unit. He had hyaline membrane disease, bronchopulmonary dysplasia, cytomegalovirus infection, and necrotizing enterocolitis.	At 8 months, alive and healthy.	
Dacarbazine (Dose/schedule NS)	Cohort, retrospective	1 of 14 from Table 3 and 4 (Pt 14)	Hodgkin lymphoma	1 st First@wk 3 Last@wk 7	Nitrogen mustard, Vincristine, Procarbazine, Doxorubicin, Bleomycin, Vinblastine	--	--	Induced abortion in gestation wk 18. Fetus had no malformations; toxic degenerative changes were present in of the liver and kidneys, and placenta had villus degeneration and vascular toxic degeneration.	--	(Peres <i>et al.</i> 2001)
Dacarbazine (Dose/schedule NS)	Survey, retrospective	3 of 27 (Pts 15, 16, 24)	Hodgkin Lymphoma	2 nd , 3 rd First@wk 24	Doxorubicin, Bleomycin, Vinblastine	C-section	36	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 27	Doxorubicin, Bleomycin, Vinblastine	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.		
			Sarcoma, soft tissue	3 rd First@wk 32	Doxorubicin, Cyclophosphamide, Vincristine	C-section	33	Infant sex, weight, and Apgar scores NS. Newborn was premature and had low birth weight, but no congenital malformations.		

Appendix C Table 23. Dacarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Dacarbazine (Dose/schedule NS)	Cohort, retrospective	1 of 21 (Pt 8)	Melanoma	1 st	None	--	--	Induced abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the dacarbazine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 24. Daunorubicin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (96 mg daily)	Case report	1	Leukemia, APL	1 st First@wk 9	Cytarabine (2 nd , 3 rd)	Vaginal	39	Male infant: 3,050 g, Apgar scores NS. Newborn was normal, including blood count and chromosomal analysis.	At 4 months, he was physically and neurologically normal.	(Alegre <i>et al.</i> 1982)
Daunorubicin (45 mg/m ² per day, days 1-3, schedule and number of cycles NS)	Case report	1	Leukemia, ALL	3 rd	Vincristine, Cyclophosphamide, Asparaginase	C-section	33	Premature rupture of the membranes. Male infant: 1,750 g, Apgar scores 4 and 6 at 1 and 5 minutes. Newborn was morphologically normal but was pale, lethargic, tone decreased, and had respiratory distress requiring intubation (resolved by day 7).	At 6 months, growth and development were normal.	(Ali <i>et al.</i> 2009a)
Daunorubicin (45 mg/m ² ; Pt 4 – 1 cycle, Pt 5 – 2 cycles)	Case series	2 of 8 (Pts 4, 5)	Leukemia, AML	2 nd First@wk 26	Cytarabine	--	--	Spontaneous abortion [stillbirth] on 7 th day of chemotherapy. [No fetal data reported.]	--	(Ali <i>et al.</i> 2003)
				2 nd First@wk 24	Cytarabine	--	--	Intrauterine death [stillbirth] during chemotherapy. Placental and fetal morphology were normal.		
Daunorubicin (1 X 40 mg, other details NS)	Case report	1	Leukemia, AML	1 st First@wk 1 Last@wk 5	Cytarabine, 6-Thioguanine (1 st)	C-section	“At the expected date” [NS]	Polyhydramnios. Female infant: 2,800 g, Apgar scores 2, 7, and 6 at 1, 5, and 10 minutes. Newborn was treated for respiratory distress associated with choanal stenosis and pneumothorax. She also presented with mild hypotelorism, severe brachycephaly, hypoplasia of the anterior cranial base, supra-orbital structures, and naso- and oropharynx, premature closure of both coronal sutures and the metopic suture, bilateral 4-fingered hands with hypoplastic	At 13 months, she was underweight, had mild generalized hypotonia, and slightly retarded motor milestones. Fine motor development and social development were normal. Her head appeared mesocephalic.	(Artlich <i>et al.</i> 1994)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								thumbs, bilateral absent radii, and a small ostium secundum-type atrial septal defect.		
Daunorubicin (Dose/schedule NS)	Case series, retrospective	4 of 29 (Table 1)	Leukemia, acute, AML, ALL	NS	Cytarabine	NS	NS	Individual data and outcomes NS. Birth weight: 3,085 g (median); 2,500-3,675 g (range).	In a follow-up study of 84 children, ages ranging from 6 to 29 years, learning and educational performance were normal. No congenital, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001)
Daunorubicin (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd or 2 nd , 3 rd	Behenoyl-ara-C, 6-Mercaptopurine, Cytarabine, Mitoxantrone	C-section	34	Female infant: 2,960 g, Apgar scores NS. Newborn was healthy.	At 16 months, no abnormalities.	(Azuno <i>et al.</i> 1995)
Daunorubicin (60 mg/m ² /day, days 3-5, 2 cycles)	Case report	1	Leukemia, AML	2 nd	Cytarabine	C-section	28 + 1 day	Male infant: 1,130 g, Apgar scores 5-6-7. Newborn showed no malformations, and heart function was normal. Blood transfusions and granulocyte colony stimulating factor were administered for anemia. The child recovered fully and was considered healthy.	No	(Biener <i>et al.</i> 2009)
Daunorubicin (Dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Vincristine, Asparaginase, Cytarabine (intrathecal), Methotrexate (intrathecal)	C-section	30	Female infant: 1,266 g, Apgar scores 5 and 8 at 1 and 5 minutes. Newborn's physical exam, hematological parameters, sepsis assessment, and cancer screening were all normal.	No	(Bottsford-Miller <i>et al.</i> 2010)
Daunorubicin (Dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd [First@~wk 21]	Vincristine Asparaginase	C-section	NS [~30]	Male infant: weight and Apgar scores NS. Newborn was normal.	At 3 years, alive and well with no medical problems.	(Camera <i>et al.</i> 1996)
Daunorubicin (50 mg for 3 days, 1 cycle)	Case report	1	Leukemia, AML	2 nd First@wk 24	Cytarabine	C-section	29	Female infant: 1,350 g, Apgar scores 2 and 9 at 1 and 5 minutes. Newborn had respiratory distress, seizures, and bilateral pneumothorax, but these conditions stabilized.	At 14 months, she was physically and psychologically normal.	(Cantini and Yanes 1984)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (Dose/schedule NS)	Survey, registry	2 of 3 from Table 5	Leukemia, ALL	2 nd , 3 rd	Cytarabine, Cyclophosphamide, 6-Mercaptopurine, Methotrexate, Vincristine, Asparaginase	NS	35.5 (group mean)	Infant sex NS: 2,341 g (group mean), Apgar scores NS. Both newborns were normal with normal body weight for gestational age.	At 3.2 or 9 years, both had normal phenotype. At 41 to 109 months (group range, n=2), no long-term complications; group mean weight was 65 th percentile.	(Cardonick <i>et al.</i> 2010)
Daunorubicin (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd	Cytarabine, 6-Thioguanine	Vaginal, induced	34	Female infant: 2,470 g, Apgar scores 6 and 7 at 1 and 5 minutes. Newborn was normal with normal body weight for gestational age.	At 12 months, well.	(Catanzarite and Ferguson 1984)
Daunorubicin (Dose/schedule NS)	Survey, retrospective	15 of 37 from Table 1 (Pts 2, 4, 8, 10, 12, 13, 21, 22, 25, 28, 30, 31, 35, 36, 37) [see note in reference column]	Leukemia, AML	1 st (Diagnosis @wk 7) (Pt 2)	ATRA, Cytarabine	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005) [In addition, Pts 7, 9, 11, 15, 16, 18, 19, 20, 23, 26, 29, 32, and 33 were not included because it was not possible to determine if they received chemotherapy during pregnancy.]
			Leukemia, AML	1 st (Diagnosis @wk 9) (Pt 4)	ATRA, Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	1 st (Diagnosis @wk 5) (Pt 8)	ATRA, Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 23) (Pt 10)	Cytarabine	C-section	Premature	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	Evolution has been normal with regard to growth and development in those who have been followed [age NS].	

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	2 nd (Diagnosis @wk 16) (Pt 12)	Cytarabine, Etoposide	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, ALL	1 st (Diagnosis @wk 9) (Pt 13)	Vincristine, Cyclophosphamide	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	1 st (Diagnosis @wk 9) (Pt 21)	Cytarabine		--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 18) (Pt 22)	Cytarabine	Vaginal	Term	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	Evolution has been normal with regard to growth and development in those who have been followed [age NS].	
			Leukemia, AML	1 st (Diagnosis @wk 13) (Pt 25)	Cytarabine, Mitoxantrone	--	--	Spontaneous abortion due to fetal demise. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 16) (Pt 28)	Cytarabine, Mitoxantrone	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, ALL	1 st (Diagnosis @wk 10) (Pt 30)	Vincristine, Cyclophosphamide	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 19) (Pt 31)	Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, ALL	1 st (Diagnosis @wk 9) (Pt 35)	Vincristine, Cyclophosphamide	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	1 st (Diagnosis @wk 10) (Pt 36)	Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	
			Leukemia, AML	2 nd (Diagnosis @wk 22) (Pt 37)	Cytarabine	Vaginal	Term	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	Evolution has been normal with regard to growth and development in those who have been followed [age NS].	
Daunorubicin (Dose/schedule NS)	Case series	2 of 32 (Pts 12, 27)	Leukemia, AML	2 nd	Cytarabine	C-section	28	Infant: sex and Apgar scores NS, 1,370 g. Newborn was healthy but required intubation.	No	(De Carolis et al. 2006)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	3 rd First@wk 28	Cytarabine	C-section	28	Infant sex NS; 1,150 g, Apgar scores NS. Newborn had respiratory distress syndrome and hypospadias.		
Daunorubicin (Pt 1 – 45 mg/m ² daily for 3 days; Pt 2 – 60 mg daily for 3 days)	Case series	2 of 2	Leukemia, APL	2 nd First@wk 24	ATRA, Cytarabine	Vaginal	32	Female infant: 2,300 g, Apgar scores NS. Newborn was morphologically normal.	At 10 months she was healthy.	(Delgado-Lamas and Garces-Ruiz 2000)
				2 nd First@wk 20	ATRA, Cytarabine	Vaginal	36	Female infant: 2,200 g, Apgar scores NS. Newborn had no apparent malformations, but had respiratory distress that required support for 15 days.	At 5 months, growth and development were normal.	
Daunorubicin (Dose/schedule NS)	Case series	1 of 18 (Pt 4)	Leukemia, AML	3 rd	ATRA, Cytarabine	NS	NS [~28]	Male infant: 1,050 g, Apgar scores NS. Newborn was premature, had normal hematological values, suffered respiratory distress, and died of pulmonary hemorrhage at 1 day.	--	(Dilek <i>et al.</i> 2006)
Daunorubicin (70 mg/m ² daily for 3 days; Pt 2 – 1 cycle, Pt 3 – 2 cycles)	Case series	2 of 3 (Pts 2, 3)	Leukemia, AML	2 nd	Cytarabine, Vincristine, Hydroxyurea, 6-Thioguanine	--	--	Induced abortion at gestation wk 21: Male fetus: 307.8 g. Fetus had no external defects or gross abnormalities, and normal organ weights, except for an enlarged spleen..	--	(Doney <i>et al.</i> 1979)
				3 rd	Cytarabine, Vincristine, Hydroxyurea, 6-Thioguanine	Vaginal	31	Spontaneous preterm labor at 4 wks after admission. Male infant: 2,130 g, Apgar scores 7 and 8 at 1 and 5 minutes. Newborn was anemic, hyponatremic, hyperkalemic, hypocalcemic, and hypoglycemic. Anemia resolved over 7 months.	At 4 months, experiencing mild infections. At 4.5 and 13.5 months, Denver Developmental Screening tests were normal. At 13.5 months, complete blood count and general physical examination were unremarkable, but growth parameters were depressed (< 3 rd percentile).	
Daunorubicin (3 x 90 mg, 2 cycles, plus maintenance therapy)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd , 3 rd First@wk 18/19	Cytarabine, 6-Thioguanine (2 nd), Methotrexate	Vaginal	39	Female infant: weight and Apgar scores NS. Newborn was healthy.	No	(Ebert <i>et al.</i> 1997)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (Pt 1 – 40 mg/day, 3 weekly cycles; Pt 2 – 40 mg, 3 cycles; Pt 4 – dose and schedule NS; Pt 5 – dose and schedule NS)	Case series	4 of 5 (Pts 1, 2, 4, 5)	Leukemia, AML	2 nd , 3 rd First@wk 26 Last@wk 28	Cytarabine	Vaginal	39	Male infant: 2,659 g [SGA], Apgar scores 7 and 8 at 1 and 5 minutes. Newborn was normal.	At 9 years, normal growth.	(Feliu <i>et al.</i> 1988)
			Leukemia, AML	3 rd	Doxorubicin (1 st), Vincristine (1 st , 3 rd), Cytarabine (3 rd), Methotrexate (1 st), 6-Mercaptopurine (1 st)	Vaginal	38	Female infant: 2,800 g, Apgar scores 8 and 10 at 1 and 5 minutes.	At 7 years, normal development.	
			Leukemia, ALL	1 st , 2 nd	Cytarabine Vincristine, 6-Mercaptopurine	--	--	Mother and fetus died at 23 wks of gestation. Fetal morphology was normal.	--	
			Leukemia, AML	2 nd First@wk 20	Cytarabine, 6-Thioguanine	Vaginal	32	Infant sex NS: 1,500 g, Apgar scores 6 and 7 at 1 and 5 minutes. Newborn was morphologically normal.	No	
Daunorubicin (Dose/schedule NS)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd First@wk 21 Last@wk 25	Cytarabine (2 nd , 3 rd), Mitoxantrone (3 rd)	C-section	29 + 3 days	Oligohydramnios and early intrauterine growth retardation detected at 28 wks of gestation. Fetal tachycardia at 29 wks of gestation + 3 days. Female infant: 857 g [SGA], Apgar scores 4 and 6 at 1 and 5 minutes. Newborn required resuscitation and was placed on mechanical ventilation and antibiotics. She showed hyponatremia, hypoglycemia, seizures, neutropenia, anemia, thrombocytopenia, bilateral hydronephrosis with dilation of the proximal ureter of the left kidney, and an intracranial	She developed failure to thrive and started to gain weight only after 3 months.	(Garcia <i>et al.</i> 1999)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								hemorrhage (resolved after 1 month of age). Hematologic derangement resolved after 7 days of therapy.		
Daunorubicin (45 mg/m ² daily for 3 days)	Case report	1	Leukemia, AML	3 rd First@wk 29	None	--	--	Fetal death [stillbirth]. [No fetal data reported.]	--	(Germann <i>et al.</i> 2004)
Daunorubicin (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd	6-Thioguanine, ATRA, Cytarabine (2 nd , 3 rd), Mitoxantrone (2 nd , 3 rd)	Vaginal, induced	35	Female infant: 2,490 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was healthy with no physical abnormalities.	At 4 months, there were no developmental complications.	(Giagounidis <i>et al.</i> 2000)
Daunorubicin (120 mg on day 1 of 5, then 5 days rest, 6 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 23 Last@wk 37	6-Thioguanine (3 rd), Cytarabine	Vaginal	37	Male infant: 2,880 g, Apgar scores NS. Newborn was healthy and normal	At 16 months, normal growth and development.	(Gokal <i>et al.</i> 1976)
Daunorubicin (Dose/schedule NS)	Case series	5 of 17 (Pts 2, 3, 5, 9, 12)	Leukemia, ALL	2 nd First@wk 18	Cytarabine, Vincristine	--	--	Mother and fetus died during pregnancy [at ~gestation wk 24]. [No fetal data reported.]	--	(Greenlund <i>et al.</i> 2001)
			Leukemia, AML	2 nd First@wk 18	Cytarabine	NS	41	Female infant: 2,950 g, Apgar scores NS. Newborn had no malformations.	No	
			Leukemia, AML	2 nd First@wk 15	Cytarabine	--	--	Fetal death [spontaneous abortion] at gestation wk 17.5. [No fetal data reported.]	--	
			Leukemia, AML	2 nd , 3 rd First@wk 26	Cytarabine, 6-Thioguanine	NS	38	Male infant: 3,240 g, Apgar score 8. Newborn had no malformations.	No	
			Leukemia, AML	2 nd First@wk 19	Cytarabine, 6-Mercaptopurine	NS	36	Female infant: weight and Apgar scores NS. Newborn had no malformations.	No	

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (Dose NS/single treatment)	Case report	1	Leukemia, AML	3 rd	6-Thioguanine (2 nd , 3 rd), Cytarabine(2 nd , 3 rd)	Vaginal	37	Female infant: 2,990 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal, both physically and cytogenetically.	No	(Hamer <i>et al.</i> 1979)
Daunorubicin (Dose NS, 3 daily doses)	Case report	1	Leukemia ALL	2 nd First@wk 26	Cyclophosphamide (2 nd , 3 rd), Vincristine (2 nd , 3 rd), Asparaginase (2 nd , 3 rd), Methotrexate (intrathecal; 3 rd), 6-Mercaptopurine (3 rd)	Vaginal	36	Transient oligohydramnios. [Spontaneous preterm labor.] Male infant: 2,150 g [SGA] , Apgar scores 2 and 8 at 1 and 5 minutes. Newborn was physically normal, with normal WBC, hemoglobin, hematocrit, and platelet counts. Presence of meconium required intubation with continuous positive airway pressure and oxygen therapy for 4 days. Jaundice was successfully treated with phototherapy.	No	(Hansen <i>et al.</i> 2001)
Daunorubicin (Dose, Schedule NS)	Case series	1 of 3 (Pt 3)	Leukemia, ALL	3 rd	Vincristine, Asparaginase	Vaginal	NS	Male infant: 2,086 g, Apgar scores 9 and 9. Newborn was healthy and showed no signs of myelosuppression.	No	(Hurley <i>et al.</i> 2005)
Daunorubicin (60 mg/day for 3 days)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 22	Cytarabine, Mitoxantrone, Etoposide	C-section	36	Intrauterine growth restriction. Intermittent sinusoidal fetal heart rate patterns at 36 wks of gestation [fetal distress] . Male infant: 1,046 g [SGA] , Apgar scores 2 and 7 at 1 and 5 minutes. Newborn was underweight and pancytopenic.	At 2 months, he was in good health.	(Hsu <i>et al.</i> 1995)
Daunorubicin (Dose/schedule NS, 4 cycles)	Case series	1 of 18	Leukemia, ALL	NS First@wk 12-33 22 (mean)	Vincristine	--	--	Intrauterine fetal demise [stillbirth] at 35 wks. [No fetal data reported.]	--	(Jameel and Jamil 2007)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Cyclophosphamide, Behenoyl-ara-C, Vincristine, 6-Mercaptopurine, Aclarubicin, Cytarabine, Cycloctidine, ATRA, Mitoxantrone, Idarubicin, Asparaginase	NS	NS	Individual pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994)†
Daunorubicin (Rubidomycin) (80 mg, 1 time)	Case report	1	Leukemia, AML	2 nd First@wk 16 Last@wk 17	Cytarabine (1 st , 2 nd), 6-Thioguanine (1 st) Vincristine	--	--	Induced abortion at gestation wk 20. Female fetus: macroscopically and microscopically normal in size and development with normal karyotype and no blood dyscrasia.	--	(Lilleyman <i>et al.</i> 1977)
Daunorubicin (45 mg/m ² daily for 3 days)	Case report	1	Leukemia, AML	2 nd First@wk 17	6-Thioguanine (2 nd , 3 rd), Cytarabine (2 nd , 3 rd)	Vaginal	40	Male infant: 2,860 g [SGA], Apgar scores NS. Newborn was physically normal; no visual or hearing defects were detected: blood, bone marrow, cytogenetic analysis, and electrocardiography were all normal.	At 7 months, he was normal in every respect.	(Lowenthal <i>et al.</i> 1978)
Daunorubicin (Dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 26	Vincristine, Asparaginase, Methotrexate (intrathecal)	C-section	32.4	Intrauterine growth restriction. Male infant: 1,450 g [SGA], Apgar scores 4 and 8 at 1 and 5 minutes. Newborn showed no abnormality in physical examination or laboratory tests. Respiratory distress and jaundice were successfully treated.	At 28 months, growing normally.	(Matsouka <i>et al.</i> 2008)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (25 mg/m ² on days 1, 2, 5, 6, one cycle)	Case report	1	Leukemia, AML	2 nd First@wk 26	Cytarabine (2 nd , 3 rd), Idarubicin (3 rd)	C-section	32	Oligohydramnios at 32 wks of gestation. Female infant: 1,820 g, Apgar scores 6, 6, and 8 at 1, 5, and 10 minutes. Newborn showed no sign of cardiac failure, and cerebral ultrasound revealed no abnormalities. Newborn developed myelosuppression that required supportive treatment, also hepatopathy and elevated creatinine kinase. These values normalized within a wk. The baby was healthy at time of discharge.	No	(Matsuo <i>et al.</i> 2004)
Daunorubicin (Dose/schedule NS)	Case series	2 of 2	Leukemia, ALL	1 st First@wk 6	Vincristine, Asparaginase, Methotrexate (intrathecal)	--	--	Induced abortion [at ~gestation wk 11]. [No fetal data reported.]	--	(Molkenboer <i>et al.</i> 2005)
				2 nd First@wk 15 [Last@wk 18-19]	Vincristine, Asparaginase, Methotrexate (intrathecal) Cytarabine	--	--	Stillbirth at gestation wk 22: 400 g (sex NS). [No fetal data reported.]		
Daunorubicin (25 mg/m ² for 6 days, 2 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25 Last@wk 31	Behenoyl-ara-C, 6-Mercaptopurine	C-section	33 + 6 days	Intrauterine growth restriction. Premature rupture of fetal membranes. Female infant: 1,410 g [SGA], Apgar scores 1 and 8 at 1 and 5 minutes. Newborn had no visible congenital anomalies.	At 5 months, she was well with no neurologic or hematologic abnormalities.	(Morishita <i>et al.</i> 1994)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (Dose/schedule NS)	Survey, retrospective	1 of 27 [27 pts received chemotherapy while pregnant; the total number of pts who received cytarabine while pregnant was not provided]	Leukemia, AML	2 nd First@wk 13	Radiation therapy (1 st , 2 nd), Cytarabine, Vincristine (2 nd , 3 rd), Cyclophosphamide (2 nd , 3 rd)	NS	NS	Infant sex, weight, and Apgar scores NS. Normal at delivery.	No	(Mulvihill <i>et al.</i> 1987)
Daunorubicin (45 mg/m ² daily for 3 days, number of cycles NS)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25	Etoposide, Cytarabine	C-section	32	No fetal growth from 30-32 wks of gestation. Female infant: 1,460 g, Apgar scores NS. Newborn was very pale and required active resuscitation, and was anemic and neutropenic. She required ventilation for 10 hours. With treatment, the hematological abnormalities resolved by day 4. Cerebral ultrasound was normal, as was the rest of her neonatal course.	At 1 year, she remained well with normal peripheral blood counts.	(Murray <i>et al.</i> 1994)
Daunorubicin (60 mg/m ² on days 5, 6, 7)	Case series	2 of 2	Leukemia, AML	2 nd , 3 rd First@wk 27	6-Thioguanine, Cytarabine	Vaginal	40	Male infant: 5,000 g, Apgar scores NS. Newborn's blood count and karyotype were normal.	At 6 months, he remained well.	(O'Donnell <i>et al.</i> 1979)
			Leukemia, ALL	2 nd , 3 rd	6-Thioguanine, Cytarabine	--	--	Severe preeclamptic toxemia at gestation wk 29. Intrauterine death [stillbirth] at gestation wk 30. No congenital abnormalities were noted.	--	

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (60 mg/m ² daily for 2 days)	Case report	1	Leukemia, ALL	2 nd First and Last@wk 18.5	Vincristine (1 st , 2 nd), Methotrexate (intrathecal, 1 st) Cyclophosphamide, Asparaginase, 6-Mercaptopurine, Radiation therapy	C-section	34	Premature rupture of membranes. Female infant: 2,380 g, Apgar score 8 at 5 minutes. Newborn was normally developed, but hydropic and had an enlarged liver and spleen. She had a petechial rash on her abdomen and extremities and slight cardiomegaly. She experienced transient severe myelosuppression requiring transfusions (resolved after ~3 wks). She was treated with digitalis and diuretics for congestive heart failure.	At 1 year, developmental status was normal.	(Okun <i>et al.</i> 1979)
Daunorubicin (30 mg/m ² on days 8, 15, 22, 29 of a 33-day cycle)	Case report	1	Leukemia, ALL	3 rd First@wk 28	Vincristine, Asparaginase, Methotrexate (IT)	C-section	32 + 4 days	Male infant: 1,450 g, Apgar scores 4 and 8 at 1 and 5 minutes. Newborn showed no abnormalities by physical examination or laboratory tests. Respiratory distress required treatment but resolved in 3 days Jaundice was treated with phototherapy.	At 18 months, growing normally.	(Papantoniou <i>et al.</i> 2008)
Daunorubicin (Dose/Schedule NS)	Cohort, retrospective	1 of 14 from Tables 3 and 4 (Pt 8)	Leukemia, AML	2 nd First@wk 19	Cytarabine	NS	39	Infant sex and Apgar scores NS, 3,000 g. Newborn had no complications.	At 9 years, development was normal.	(Peres <i>et al.</i> 2001)
Daunorubicin (1.5 mg/kg on days 2 and 11; Pt 1 – number of cycles NS, Pt 2 – 3 cycles)	Case series	2 of 2	Leukemia, AML	2 nd , 3 rd	Cytarabine, 6-Thioguanine, Mitoxantrone	C-section	34	Male infant: 2,220 g, Apgar scores 3, 6, and 8 at 1, 5, and 10 minutes. Newborn required intubation for 7 minutes. His phenotype was rigorously normal; bone X-ray, central nervous system echography, and blood tests were all normal.	Follow-up was uneventful [age NS].	(Requena <i>et al.</i> 1995)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd	Cytarabine, 6-Thioguanine, Mitoxantrone	C-section	34	Female infant: 2,100 g, Apgar scores 6, 7, and 9 at 1, 5, and 10 minutes. Newborn had no phenotypic anomalies; radiologic controls, sonograms, and blood tests were normal.		
Daunorubicin (45 mg/m ² on days 1-3)	Case report	1	Leukemia, AML	2 nd	Cytarabine (2 nd , 3 rd), Mitoxantrone (2 nd , 3 rd), Idarubicin (3 rd)	--	--	Stillbirth: sex NS; 2,200 g. No obvious congenital malformations. No fetal autopsy performed.	--	(Reynoso and Huerta 1994)
Daunorubicin (Dose/schedule NS) [Pt 4 – Table says Daunorubicin and text says Doxorubicin]	Survey, retrospective	4 of 7 (Pts 2, 3, 4, 7)	Leukemia, CGL	3 rd	6-Thioguanine, Cytarabine	Vaginal	34	[Spontaneous preterm labor.] Male infant: 2,290 g, Apgar score 9 at 5 minutes. Newborn had no congenital malformations.	At 18 months, normal growth and development.	(Reynoso <i>et al.</i> 1987)
			Leukemia, AML	2 nd [First@wk 25, table states 3rd]	6-Thioguanine, Cytarabine	Vaginal	29	[Spontaneous preterm labor.] Male infant: 1,000 g, Apgar scores NS. Newborn showed no malformations at birth, but congenital adherence of the iris to the posterior cornea of the left eye was diagnosed at age 2.	At 6 months, he had suffered frequent upper respiratory infections. At 3 years, normal growth and development.	
			Leukemia, AML	2 nd , 3 rd	Vincristine, Cytarabine, Cyclophosphamide	Vaginal	34	Spontaneous preterm labor. Male infant: 2,510 g, Apgar score 10 at 5 minutes. Newborn was healthy with normal peripheral blood counts and no congenital malformations.	At 7 years, healthy with weight and height in the 100 th percentile.	
			Leukemia, AML	2 nd , 3 rd	Cytarabine, 6-Thioguanine, Cyclophosphamide, Vincristine	Vaginal, induced	39	Male infant: 3,420 g, Apgar score 10 at 5 minutes. Newborn was healthy with normal peripheral blood counts and no congenital malformations.	At 11.5 years, healthy with normal growth and intellectual development.	

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunomycin [Daunorubicin] (Pt 1 – 140 mg once every 2 wks, 3 cycles; Pt 4 – 45 mg once every 3 wks, 3 cycles; Pt 5 – 45 mg once every 3 wks, number of cycles NS)	Case series	3 of 6 (Pts 1, 4, 5)	Leukemia, AML	2 nd , 3 rd	Cytarabine, 6-Mercaptopurine (3 rd)	Vaginal, induced	32	Labor was induced because mother was seriously ill. Female infant: 2,041 g, Apgar score 9 at 1 minute. Newborn was normal.	No	(Roy <i>et al.</i> 1989)
				2 nd	Cytarabine, 6-Thioguanine	C-section	33 (text) 34 (table)	Serial ultrasound showed poor fetal growth. Male infant: weight and Apgar scores NS. Newborn had Down syndrome.		
				3 rd	Cytarabine, 6-Thioguanine	Vaginal, induced	34	Female infant: 1,930 g, Apgar scores NS. Newborn was normal.		
Daunorubicin (30 mg/m ² daily for 2 days)	Case report	1	Leukemia, APL	1 st	Methyl-GAG	Vaginal	34	[Spontaneous preterm labor.] Female infant: 2,200 g, Apgar scores NS. Newborn had no congenital abnormalities.	The baby grew well [age NS] .	(Sanz and Rafecas 1982)
Daunorubicin (45 mg/m ² daily for 3 days, number of cycles NS)	Case report	1	Leukemia, AML	2 nd or 2 nd , 3 rd [First@> wk 25]	Etoposide, Cytarabine	C-section	32	Serial ultrasounds detected reduced amniotic fluid and no fetal growth gain at 32 wks of gestation. Female infant: 1,460 g, Apgar scores NS. Newborn was very pale and required active resuscitation, also exhibited myelosuppression. She made good progress and was discharged at 46 days.	No	(Scherf and Price 1996)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (25 mg/m ² on days 1,8,15, 22)	Case report	1	Leukemia, ALL	2 nd First@wk 22	Vincristine, Asparaginase, Cyclophosphamide (2 nd , 3 rd), 6-Mercaptopurine (2 nd , 3 rd), Cytarabine (2 nd , 3 rd), Methotrexate (IT; 2 nd , 3 rd), Radiation therapy (2 nd , 3 rd)	Vaginal	40	Female infant: weight and Apgar scores NS. Newborn was healthy, had a full head of hair, and no abnormalities. Cytogenetic analysis of lymphocytes showed a normal karyotype but some chromosome breakage and a ring chromosome.	No	(Schleuning and Clemm 1987)
Daunorubicin (40 mg/m ² on days 1 and 2, 2 cycles, 2 wks apart. One more cycle was given at half this dose.)	Case report	1	Sarcoma, granulocytic (breast)	NS	Vincristine, Cytarabine, Cyclophosphamide	Vaginal	NS	Female infant: 7 lb 2 oz [3,232 g], Apgar scores NS. Newborn was completely normal.	No	(Sears and Reid 1976)
Daunorubicin (Dose/schedule NS)	Case report	1	Leukemia, ALL	3 rd First@wk 32	Vincristine, Cyclophosphamide, Cytarabine, Asparaginase	Vaginal, induced	~35	Female infant: 6.8 lbs [3,084 g], Apgar scores NS. Newborn was normal.	At 16 months, she was healthy with a normal blood count.	(Sigler <i>et al.</i> 1988)
Daunorubicin (90 mg single doses 3 wks apart, 2 cycles)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd First@wk 24	Cytarabine, Doxorubicin, 6-Thioguanine	Vaginal	32	Spontaneous preterm labor. Female infant: 2,000 g, Apgar scores NS. Newborn had a premature appearance, but was normal and showed no clinical abnormalities.	At 13 months, feeding and weight gain are satisfactory; developmental milestones have been normal.	(Tobias and Bloom 1980)
Daunorubicin (Total dose 220 mg, 4 cycles)	Case series	1 of 2 (Pt 1)	Leukemia, ALL	2 nd First@wk 18	Vincristine (2 nd , 3 rd), Asparaginase, 6-Mercaptopurine (2 nd , 3 rd), Methotrexate (2 nd , 3 rd)	C-section	37	Twin infants, male and female: 2,500 g (male) and 2400 g (female), Apgar scores NS. Both newborns were normal at physical examination with normal T-cell populations. At 24 hours, both newborns had diarrhea and were lethargic; the female was also hypotonic; full recovery was completed by 2 wks.	At 54 months, both children are normal with no evidence of immunologic suppression.	(Turchi and Villasis 1988)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (45 mg/m ² on days 8, 15, and 22)	Case report	1	Leukemia, ALL	2 nd First@wk 23	Cyclophosphamide (2 nd , 3 rd), Vincristine, Cytarabine (2 nd , 3 rd), Methotrexate (intrathecal; 2 nd , 3 rd), 6-Thioguanine (2 nd , 3 rd), Amsacrine (3 rd)	Vaginal	33	Spontaneous rupture of membranes. Male infant: 1,928 g [Table 2 states 1,925 g], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn's physical exam was unremarkable with normal cerebral ultrasound, hearing, and echocardiography. He exhibited transient neonatal myelosuppression that was treated and resolved by day 20, including leukopenia at birth, neutropenia at day 2, anemia and thrombocytopenia at day 3. Treated for a urinary tract infection on day 7.	At 24 months, normal growth and development.	(Udink ten Cate <i>et al.</i> 2009)
Daunorubicin (Dose/schedule NS)	Survey, retrospective	2 of 27 (Pts 10, 11)	Leukemia, AML	2 nd , 3 rd First@wk 27	Cytarabine	C-section	30	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 21	Cytarabine	C-section	37	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	
Daunorubicin (40 mg/m ² on days 8, 15, 22; 3 cycles)	Survey, retrospective	1 of 62 [62 patients received chemotherapy while pregnant; total number receiving daunorubicin is NS]	NS	2 nd , 3 rd First@wk 24 Last@wk 32	Methotrexate, Vincristine, Cyclophosphamide, Asparaginase, 6-Mercaptopurine	NS	NS	Infant sex, birth weight, and Apgar scores NS. Newborn had a hemangioma.	No	(Van Calsteren <i>et al.</i> 2010)

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Daunorubicin (Dose/schedule NS; Pt 1 had 2 cycles)	Case series	4 of 4	Leukemia, AML	2 nd First@wk 17	Cytarabine, 6-Thioguanine	NS	30	Premature rupture of membranes, possibly the result of a medical evaluation of the placenta. Female infant: 1,180 g, Apgar scores NS. Placenta had myeloblastic infiltration.	At 5 years, development was normal, and health was excellent.	(Volkenandt <i>et al.</i> 1987)
			Leukemia, AML	2 nd First@wk 23	Cytarabine, 6-Thioguanine	C-section	42	Male infant: 3,840 g, Apgar scores NS. Newborn had 6 toes on right foot (family history of polydactyly).	At 22 months, development was normal, and health was excellent.	
			Leukemia, ALL	3 rd First@wk 32	Vincristine	Vaginal, induced	37	Male infant: 2,865 g, Apgar scores NS. Newborn was healthy.	At 14 months, he was in excellent health.	
			Leukemia, AML	2 nd First@wk 15	Cytarabine, 6-Thioguanine	--	--	Intrauterine fetal death [spontaneous abortion] at 5 wks [gestation wk 20] after initiation of chemotherapy. Fetus (sex NS): 40 g. Autopsy revealed no abnormalities and no leukemic infiltration.	--	
Daunorubicin (45 mg/m ² on day 4, 5, 6, and 7)	Case report	1	Leukemia, APL	3 rd	Cytarabine	C-section	NS	Infant sex NS: 2,100 g and Apgar scores NS. Newborn was healthy and hematologically normal.	No	(Wallace 1989)
Daunorubicin (Dose/schedule NS)	Cohort, retrospective	1 of 21 (Table 1, Pt 12)	Leukemia, CML	1 st	6-Thioguanine, Hydroxyurea, Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
Daunorubicin (dose/schedule data limited) (Table 1: Pt 11 – 1 cycle Table 2: Pt 2 – 1 cycle Pt 9 – 180 mg total Pt 36 – 2 cycles Pt 14 – dose/schedule NS Pt 26 – 3 cycles Pt 24 – 2 cycles Pt 25 – 1 cycle)	Survey, retrospective	8 of 48 (8 of 56 pregnancies) (Table 1: Pt 11, Table 2: Pts 2, 9, 36, 14, 26, 24, 25)	Leukemia, AML	1 st	Methyl-GAG	NS	34	Infant: 2,200 g, sex and Apgar scores NS. Newborn was premature, but normal.	At 5 years, normal growth and development.	(Zuazu <i>et al.</i> 1991)
			Leukemia, AML	1 st First@wk 11 Last@wk 11	Cytarabine, 6-Thioguanine, Vincristine	--	--	Spontaneous abortion 20 days post-chemotherapy. [No fetal data reported.]	--	
			Leukemia, AML	1 st First@wk 12 Last@wk 12	Cytarabine	--	--	Spontaneous abortion at gestation wk 15. [No fetal data reported.]	--	
			Leukemia, AML	2 nd First@wk 20 Last@wk 27	Cytarabine, 6-Thioguanine, Vincristine	C-section	37	Infant: 2,100 g [SGA], sex and Apgar scores NS. Newborn was premature.	At 3 years, normal.	

Appendix C Table 25. Daunorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	2 nd First and last @ 5 months	None	--	--	Maternal and fetal death post-chemotherapy. [No fetal data reported.]	--	
			Leukemia, AML	2 nd First@month 5 Last@month 6	Cytarabine, 6-Thioguanine, Vincristine	Vaginal	NS	Infant: sex, weight, and Apgar scores NS. Newborn had normal outcome.	At 3 years, normal.	
			Leukemia, AML	3 rd First@wk 28	Cytarabine, 6-Thioguanine, Vincristine	Vaginal	36	Infant: 2,400 g, sex and Apgar scores NS. Newborn was normal with normal karyotype.	At 4 years, normal follow-up.	
			Leukemia, AML	3 rd First@wk 29	Cytarabine, 6-Thioguanine, Vincristine	--	--	Fetal death [stillbirth] during treatment. C-section postmortem, fetus without macroscopical anomalies.	--	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the daunorubicin timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

† Papers not included in text analysis (highlighted in light grey). One study was not included in the text analysis because of a lack of individual data on timing of exposure, co-treatments, and pregnancy outcomes (Kawamura *et al.* 1994).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL= acute lymphocytic leukemia; AML=acute myelogenous leukemia; APL=acute promyelocytic leukemia; CGL=chronic granulocytic leukemia; chronic myelogenous leukemia; ATRA = all-*trans* retinoic acid; behenoyl-ara-C = behenoyl cytosine arabinoside; methyl-GAG = methyl-glyoxal bis guanyl hydrazine; IT = intrathecal; SGA = small for gestational age.

Appendix C Table 26. Docetaxel – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Docetaxel (Dose/schedule NS)	Survey, registry	6 of 104 infants from Table 2	Breast	2 nd , 3 rd	Doxorubicin Cyclophosphamide, Paclitaxel, Epirubicin	NS	35.9 (group mean)	Infant sex NS; 2,667 g (group mean), Apgar scores NS. Four newborns were normal, 1 had neutropenia and pyloric stenosis, and 1 had suspected holoprosencephaly. All newborns had normal body weights for gestational age.	At 0.2 to 2.6 years (n=3). Two children were normal phenotype. At 2.6 years, the newborn with suspected holoprosencephaly had prominent lateral ventricles, but was otherwise normal. At 42 months (group mean, n=93), group mean weight was 48 th percentile.	(Cardonick <i>et al.</i> 2010)
Docetaxel (Dose and schedule NS)	Case series	1 of 32 (Pt 10)	Breast	2 nd , 3 rd First@wk 19 Last@wk 31	None	C-section	32	Infant, sex NS; 1,620 g, Apgar scores 8 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
Docetaxel (100 mg/m ² every 3 wks for 3 cycles)	Case report	1	Breast	2 nd , 3 rd	Vinorelbine (2 nd)	C-section	32	Female infant; 1,620 g, Apgar scores 8 and 9. Newborn was normal.	At 20 months, she had regular psychophysical development.	(De Santis <i>et al.</i> 2000)
Docetaxel (35 mg/m ² weekly for 5 wks)	Case report	1	Breast	3 rd	None	Vaginal	40	Male infant; weight and Apgar scores NS. There was no apparent toxicity to the newborn.	At 15 months, he was well and at normal milestones.	(Gainford and Clemons 2006)
Docetaxel (Dose/schedule NS)	Case series, retrospective	4 of 15 [see note in pregnancy outcome column]	Breast	2 nd and/or 3 rd	Doxorubicin	Vaginal	39	Male infant; 3,080 g, Apgar scores NS. Newborn was healthy and without malformations. [Only 15 of 17 pts treated with chemotherapy during pregnancy; individual chemotherapy regimen of 4 pts was not provided.]	At 24 months, healthy.	(Garcia-Manero <i>et al.</i> 2009)
				3 rd	Doxorubicin (2 nd and/or 3 rd)	Vaginal	40	Male infant; 3,200 g, Apgar scores NS. Newborn was healthy and without malformations.	At 36 months, healthy.	
				3 rd	Doxorubicin (2 nd and/or 3 rd)	Vaginal	34	Male infant; 2,850 g, Apgar scores were 9/10 [9 and 10 at 5 and 10 minutes] . Newborn was healthy and without malformations.	At 12 months, healthy.	

Appendix C Table 27. Docetaxel (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd and/or 3 rd	Doxorubicin	C-section	35	Male infant: 1,850 g [SGA], Apgars scores NS. Newborn was healthy and without malformations.	At 25 months, healthy.	
Docetaxel (75 mg/m ² every 3 wks, 5 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 14 + 6 days Last@wk 30	Carboplatin, Trastuzumab (2 nd)	C-section	33 + 2 days	Anhydramnios and intrauterine growth restriction at 20 wks + 4 days of gestation. Male infant: weight less than 3 rd percentile (SGA), Apgar scores NS. Newborn showed inconspicuous development and normal renal function and urinalysis.	No	(Gottschalk <i>et al.</i> 2011)
Docetaxel (4 cycles, dose and treatment schedule NS)	Case report	1	Breast	1 st , 2 nd	Doxorubicin, Cyclophosphamide	C-section	32	Male infant: weight and Apgar scores in normal limits. Newborn was healthy with no anomalies.	No	(Ibrahim <i>et al.</i> 2006) [†]
Docetaxel (40 mg/m ² on days 1 and 8, every 21 days for 4 cycles)	Case report	1	Lung	1 st , 2 nd First@wk 9 Last@wk 21	Cisplatin, Gemcitabine (2 nd)	C-section	33	Female infant: 1,490 g [SGA], Apgar scores 8, 9, and 10 at 1, 5, and 10 minutes. Newborn showed no evidence of hearing, thyroid, adrenal, hepatorenal, and hematologic dysfunction, or gross congenital malformations.	[At 2 months,] she was developing normally.	(Kim <i>et al.</i> 2008)
Docetaxel (Dose/schedule NS, 2 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 9 + 3 days Last@wk 17	Cyclophosphamide	C-section	36 + 2 days	Placenta insufficiency, IUGR, oligohydramnios, pre-eclampsia, HELLP syndrome. Pathological fetal heart rate, reverse flow in the umbilical artery, fetal centralization, and negative A wave in the venous duct. Male infant: 1,680 g (< 5 th percentile) [SGA], Apgar scores 3, 7, and 9 at 1, 5, and	No	(Massey Skatulla <i>et al.</i> 2012)

Appendix C Table 27. Docetaxel (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								10 minutes. Newborn had no malformations but required cardiopulmonary resuscitation, was hypoglycemic for 5 days, had a single focal convulsion, and was treated for thrombocytopenia. Brain ultrasound showed no abnormality and there was no evidence of periventricular leukomalacia.		
Docetaxel (100 mg/m ² every 21 days for 4 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 25 Last@wk 34	5-Fluorouracil (1 st , 2 nd), Doxorubicin (1 st , 2 nd), Cyclophosphamide (1 st , 2 nd)	Vaginal	39	Male infant: 6.8 lbs [3,084 g], Apgar scores were normal. Newborn was healthy with normal blood counts.	No	(Nieto <i>et al.</i> 2006)
Docetaxel (75 mg/m ² every 2 wks for 4 cycles (Pt 1) or every 3 wks for 6 cycles (Pt 2))	Case series	2 of 2	Breast	2 nd , 3 rd First@wk 26 Last@wk 32	Doxorubicin (2 nd), Cyclophosphamide (2 nd)	Vaginal	34	Hydrocephalus (dilated lateral and third ventricle) noted at gestation wk 17. Infant sex, weight, and Apgar scores NS. Newborn had mild hydrocephalus, which regressed spontaneously over several months.	Development was normal at 28 months.	(Potluri <i>et al.</i> 2006)
				2 nd , 3 rd First@wk 14 Last@wk 29	Doxorubicin	C-section	35	Preeclampsia at gestation wk 35. Infant sex, weight, and Apgar scores NS. Newborn was healthy with no detectable malformations.	Development was normal at 9 months.	
Docetaxel (75 mg/m ² , 4 cycles, schedule NS)	Case report	1	Ovary	2 nd , 3 rd First@wk 21	Cisplatin	C-section	34	Anhydramnios and left-sided ventriculomegaly diagnosed prior to chemotherapy; ventriculomegaly increased during chemotherapy treatment.	--	(Rouzi <i>et al.</i> 2009)

Appendix C Table 27. Docetaxel (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Female infant: 2,245 g, Apgar scores 3 and 6 at 1 and 10 minutes. Newborn died 5 days after delivery because of multiple congenital anomalies diagnosed prior to chemotherapy.		
Docetaxel (190 mg/m ² , 2 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 23 Last @wk 26	Trastuzumab	C-section	36 + 2 days	Anhydramnios and fetal growth at the 5 th percentile at 30 wks of gestation. Male infant: 2,230 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn showed no signs of deformities or respiratory abnormalities.	Subsequent development and neonatal urine output normal [age NS].	(Sekar and Stone 2007)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the docetaxel timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Paper not included in text analysis (highlighted in light grey). Abstracts were not included in the text analysis: (Ibrahim *et al.* 2006).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; IUGR = intrauterine growth retardation; HELLP = hemolysis, elevated liver enzymes, and low platelet count syndrome; SGA = small for gestational age.

Appendix C Table 28. Doxorubicin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference				
Doxorubicin (Dose/schedule NS)	Case series	5 of 13 (Pts 2, 3, 4, 9, 10)	Breast	2 nd	Cyclophosphamide	NS	36	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	(Abellar <i>et al.</i> 2009)				
			Breast	2 nd	Cyclophosphamide	NS	39	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No					
			Breast	2 nd	Cyclophosphamide	NS	33	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No					
			Adenoid cystic carcinoma	2 nd	Cyclophosphamide, Cisplatin	NS	25	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No					
			Non-Hodgkin lymphoma, diffuse large B-cell	2 nd , 3 rd	Cyclophosphamide, Vincristine	NS	32	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No					
Doxorubicin (25 mg/m ² on days 1 and 14, 2 cycles (Pt 1), 3 cycles (Pt 5), or 4 cycles (Pt 6); cycles were 15 days apart)	Case series	3 of 6 (Pts 1, 5, 6)	Hodgkin lymphoma	2 nd First@wk 21	Bleomycin, Vinblastine, Dacarbazine	C-section	29	Female infant: 2,400 g, Apgar scores NS. Newborn was healthy.	At 10 years, child is healthy.	(Anselmo <i>et al.</i> 1999)				
				2 nd First@wk 16							C-section	NS [~36]	Preeclampsia. Female infant: 2,180 g, Apgar scores NS. Newborn was healthy.	At 7 months, healthy.
				2 nd										

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, diffuse lymphoblastic	3 rd First@wk 31	Cyclophosphamide, Vincristine, Asparaginase, Cisplatin, Cytarabine	C-section	NS	Male infant: 2,600 g, Apgar scores NS.	At 2 years, no growth retardation, mental retardation, or malformation observed.	(Ataergin <i>et al.</i> 2007)
Doxorubicin (75 mg/m ² , 2 cycles, 3 wks apart)	Case report	1	Ovary	3 rd First@wk 30	Cyclophosphamide, Vincristine	C-section	37	Female infant: 2,500 g, Apgar scores NS. Newborn was healthy with no abnormality. There were multiple tumor deposits in the placenta.	No	(Ateser <i>et al.</i> 2007)
Doxorubicin (Dose/schedule NS)	Case series, retrospective	7 of 7 from Table 1 (Pts 1, 2, 3, 4, 5, 6, 7)	Leukemia, ALL	1 st [see note in reference column]	Vincristine, 6-Mercaptopurine, Methotrexate, Cyclophosphamide	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 19 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
			Leukemia, ALL	3 rd	Vincristine	Vaginal	38	Female infant: 4,300 g, Apgar scores NS. Newborn had no congenital malformations.	At 17 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, AML	1 st	6-Mercaptopurine, Cytarabine, Methotrexate	Vaginal	36	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, AML	3 rd	Cytarabine	C-section	39	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 15 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, ALL	2 nd	Vincristine, 6-Mercaptopurine, Methotrexate, Cyclophosphamide	Vaginal	38	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	1 st	Vincristine, 6-Mercaptopurine, Methotrexate, Cyclophosphamide	Vaginal	37	Male infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, AML	2 nd	6-Mercaptopurine, Cytarabine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		10 of 14 from Table 2 (Pts 2, 3, 4, 6, 7, 8, 11, 12, 13, and 14)	Hodgkin Lymphoma	2 nd	Bleomycin, Vinblastine, Dacarbazine	Vaginal	38	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Bleomycin, Vinblastine, Dacarbazine	Vaginal	37	Male infant: 3,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Bleomycin, Vinblastine, Dacarbazine	C-section	34	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Bleomycin, Vinblastine, Dacarbazine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Bleomycin, Vinblastine, Vincristine, Dacarbazine, Nitrogen mustard, Procarbazine	Vaginal	38	Female infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Bleomycin, Vinblastine, Vincristine, Dacarbazine, Nitrogen mustard, Procarbazine	Vaginal	37	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Bleomycin, Vinblastine, Dacarbazine	Vaginal	38	Female infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Bleomycin, Vinblastine, Dacarbazine	Vaginal	40	Male infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Bleomycin, Vinblastine, Dacarbazine	C-section	40	Female infant: 3,450 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Bleomycin, Vinblastine, Dacarbazine, Nitrogen mustard, Procarbazine	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		14 of 18 from Table 3 (Pts 1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14, and 15)	Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Vincristine	Vaginal	38	Female infant: 3,400 g, Apgar scores NS. Newborn had no congenital malformations.	At 18 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Vincristine, Bleomycin	C-section	39	Male infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd	Cyclophosphamide, Vincristine, Etoposide, Methotrexate	Vaginal	40	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 15 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Vincristine, Bleomycin	C-section	40	Male infant: 3,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Cyclophosphamide, Vincristine, Bleomycin	Vaginal	37	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Vincristine, Bleomycin, Cytarabine	Vaginal	37	Male infant: 2,900 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Vincristine, Bleomycin	Vaginal	38	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Vincristine	Vaginal	38	Male infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Vincristine, Bleomycin	Vaginal	38	Female infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Vincristine	Vaginal	37	Female infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Cyclophosphamide, Vincristine, Cytarabine, Methotrexate	Vaginal	39	Female infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Vincristine, Methotrexate, Etoposide	Vaginal	37	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Vincristine, Bleomycin, Cytarabine, Methotrexate, Etoposide	Vaginal	40	Female infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Vincristine, Bleomycin	C-section	38	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Doxorubicin (300 mg – Pt 1 480 mg – Pt 2 420 mg – Pt 3 480 mg – Pt 4 280 mg – Pt 5 420 mg – Pt 6 600 mg – Pt 7 180 mg – Pt 8 360 mg – Pt 9 180 mg – Pt 10 600 mg – Pt 11 280 mg – Pt 12 90 mg – Pt 13 75 mg – Pt 15 410 mg – Pt 16)	Case series	15 of 16 (Pts 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, and 16)	Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Vincristine, Methotrexate	NS	NS	Individual pregnancy outcomes are not provided. Birth weights were 2,200-3,900 g (group range). All babies were born alive, and none of the newborns showed apparent congenital malformations.	At ages ranging from 3 to 11 years, normal growth and development.	(Avilés <i>et al.</i> 1990) [†]

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Bleomycin					
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Bleomycin, Methotrexate					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Bleomycin					
				3 rd	Cyclophosphamide, Vincristine, Bleomycin, Methotrexate, Etoposide					
				1 st , 2 nd	Cyclophosphamide, Vincristine, Bleomycin					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Bleomycin, Methotrexate, 6-Mercaptopurine					
				3 rd	Cyclophosphamide, Vincristine, Methotrexate, Etoposide					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine					
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Methotrexate, Cytarabine					

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st , 2 nd	Cyclophosphamide, Vincristine, Bleomycin					
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Methotrexate, Cytarabine, Etoposide					
				3 rd	Cyclophosphamide, Vincristine, Methotrexate, Etoposide					
				3 rd	Cyclophosphamide, Vincristine					
				1 st , 2 nd	Cyclophosphamide, Vincristine, Bleomycin					
Doxorubicin (Dose/schedule NS)	Case series, retrospective	18 of 29 from Table 1	Leukemia, acute	NS	Cytarabine, Cyclophosphamide, Vincristine	NS	NS	Birth weight, group range: 2,500-3,675 g. Individual pregnancy outcomes NS. No newborns had congenital malformations.	In this long-term follow-up, ranging from 6 to 29 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001) [†]
		12 of 26 from Table 2	Hodgkin lymphoma	NS	Vincristine, Vinblastine, Bleomycin, Dacarbazine, Nitrogen mustard, Procarbazine	NS	NS	Birth weight, group range: 2,800-4,300 g. Individual pregnancy outcomes NS. No newborns had congenital malformations.		
		29 of 29 from Table 3	Non-Hodgkin lymphoma	NS	Cyclophosphamide, Vincristine, Bleomycin	NS	NS	Birth weight, group range: 2,350-4,050 g. Individual pregnancy outcomes NS. No newborns had congenital malformations.		

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS)	Case series, retrospective	12 of 20 infants from Table 1 [10 of 18 pts] (Pts 8, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19 and 20; 2 pts had 2 pregnancies: 10 and 16, and 17 and 18)	Leukemia, ALL	1 st , 2 nd , 3 rd	6-Mercaptopurine, Vincristine, Methotrexate	NS [C-section]	NS [33]	Female infant: 1,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	(Avilés and Niz 1988) [Pt 8 was first reported in Pizzuto <i>et al.</i> (1980). We counted this pt only once using Aviles <i>et al.</i> (1988).]
				1 st , 2 nd , 3 rd	6-Mercaptopurine, Vincristine, Methotrexate	NS	NS	Female infant: 2,900 g, Apgar scores NS. Newborn had no congenital malformations. [Pt A, pregnancy 1]	At 7 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				2 nd , 3 rd	Cytarabine	NS	NS	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				1 st , 2 nd , 3 rd	6-Mercaptopurine, Vincristine, Cytarabine, Methotrexate	NS	NS	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				2 nd , 3 rd	6-Mercaptopurine, Vincristine, Methotrexate, Cyclophosphamide	NS	NS	Female infant: 2,700 g, Apgar scores NS. Newborn had pancytopenia and no congenital malformations. At 4 wks, blood counts and bone marrow samples were normal.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Vincristine	NS	NS	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				1 st , 2 nd , 3 rd	6-Mercaptopurine, Vincristine, Methotrexate	NS	NS	Male infant: 2,600 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				1 st , 2 nd	6-Mercaptopurine, Vincristine, Methotrexate	NS	NS	Male infant: 2,850 g, Apgar scores NS. Newborn had no congenital malformations. [Pt A, pregnancy 2]	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				1 st , 2 nd , 3 rd	Vincristine, Cytarabine	NS	NS	Female infant: 3,250 g, Apgar scores NS. Newborn had no congenital malformations. [Pt B, pregnancy 1]	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				1 st , 2 nd	Cytarabine	NS	NS	Male infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations. [Pt B, pregnancy 2]	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				2 nd , 3 rd	Cytarabine	NS	NS	Female infant: 2,600 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
				1 st , 2 nd , 3 rd	6-Mercaptopurine, Vincristine, Methotrexate	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (50-75 mg/m ² on day 1; Pt 1 and 2 – 2 cycles, Pt 3 and 4 – 1 cycle, Pt 5 – 3 cycles)	Case series	5 of 5	Leukemia, ALL	2 nd First@wk 17 Last@wk 35	Vincristine, Asparaginase, Cyclophosphamide (2 nd , 3 rd), Methotrexate (2 nd , 3 rd), 6-Mercaptopurine (2 nd , 3 rd)	Vaginal	[~39]	Female infant: 3,200 g, Apgar scores NS. Newborn was normal.	At 40 months, normal development and growth.	(Awidi <i>et al.</i> 1983)
			Leukemia, ALL	3 rd First@~wk 35	Vincristine	Vaginal	[~39]	Male infant: 2,900 g, Apgar scores NS. Newborn was normal.	At 29 months, normal development and growth.	
			Leukemia, ALL	3 rd First@~wk 35	Vincristine	Vaginal	[~40]	Male infant: 3,300 g, Apgar scores NS. Newborn was normal.	At 32 months, normal development and growth.	
			Leukemia, AML	2 nd First@~wk 16	Vincristine, Cytarabine	--	--	Spontaneous abortion at gestation wk 17. [No fetal data reported.]	--	
			Leukemia, acute (erythroleukemia)	2 nd , 3 rd First@~wk 26	Cytarabine, 6-Thioguanine	Vaginal	[~36]	Female infant: 2,980 g, Apgar scores NS. Newborn was normal.	At 1 month, normal.	
Doxorubicin (Dose/schedule NS, 2-4 cycles)	Case series	3 of 26	Breast	2 nd	NS	NS	28-40 (group range)	Individual pregnancy outcomes were not provided. Newborns had no malformations.	Follow-up at 0 to 84 months (median=27 months), showed no significant remote adverse events.	(Azim <i>et al.</i> 2008)
Doxorubicin (20 mg/m ² weekly, 4 cycles)	Case report	1	Breast	3 rd First@wk 31	None	C-section	35.4	Male infant: 3,100 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal.	No	(Barni <i>et al.</i> 1992)
Doxorubicin (45 mg on days 1 and 8 of a 28-day cycles, 6 cycles)	Case report	1	Breast	2 nd First@wk 17	Cyclophosphamide, 5-Fluorouracil	Vaginal	NS	Male infant: weight NS, Apgar scores 8 and 9. Newborn was phenotypically normal with a full head of hair.	At 1.5 years, he was well developed.	(Barnicle 1992)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (70 mg/m ² , days 1-3, 4 cycles)	Case report	1	Leukemia, APL	2 nd First@wk 21	6-Thioguanine, Cytarabine, Vincristine	C-section	30	Preeclampsia at days 5 and 15 of chemotherapy, treated and resolved. Male infant: 1,320 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was normal with normal blood work. At 20 minutes, he experienced tachypnea and progressive respiratory failure requiring intermittent ventilation. By 3.5 hours, he had developed severe respiratory distress syndrome requiring intubation (resolved by 6 days after treated with surfactant).	At 70 days, infant discharged from the hospital in excellent condition with normal hematological values and karyotype.	(Bartsch <i>et al.</i> 1988)
Doxorubicin (50 mg/m ² , every 3-4 wks, 1-6 cycles)	Case series	24 of 24	Breast	2 nd and/or 3 rd	5-Fluorouracil, Cyclophosphamide	NS	38 (mean), 33-40 (group range)	Three patients delivered preterm because of severe preeclampsia (1 pt) or idiopathic preterm labor (2 pts). Individual pregnancy outcomes were not provided. Apgar scores were ≥ 9 in all cases. One newborn had a low birth weight for gestational age (< 10 th percentile; SGA); 23 had normal birth weight for age. Newborns had no malformations. One newborn was diagnosed with hyaline membrane disease, and 2 newborns had tachypnea (resolved by 48 hours). One newborn was born 2 days after chemotherapy and experienced transient leucopenia. Two newborns had substantial hair loss.	At 6 months to 8 years (group range), all were alive.	(Berry <i>et al.</i> 1999)
Doxorubicin (Dose/schedule NS)	Case series, retrospective	1 of 18 (Pt 1)	Sarcoma	1 st First@month 3	Cyclophosphamide, Vincristine, AMSA	NS	Term	Male infant: 6 lb 5 oz [2,863 g], Apgar scores NS. Newborn was normal, and birth weight was normal [for gestational age].	At 2.5 years, normal.	(Blatt <i>et al.</i> 1980)
Doxorubicin (Dose/schedule NS, 8 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Vincristine	Vaginal, induced	34	Infant sex NS: 3,043 g, Apgar scores 9, 9 and 9. The newborn was not compromised.	No	(Brown <i>et al.</i> 2001)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS)	Survey, registry	98 of 104 infants in Table 2	Breast	2 nd or 2 nd , 3 rd	Cyclophosphamide, 5-Fluorouracil, Paclitaxel, Docetaxel	NS	35.9 (group mean)	Infant sex NS: 2,667 g (group mean), Apgar scores NS. Ninety-six newborns were without malformations. One infant each had pyloric stenosis and suspected holoprosencephaly. Normal body weight for gestational age was observed for 90 newborns. Neonatal complications (number affected): intrauterine growth retardation (8), thrombocytopenia and died at 13 months because of a severe autoimmune disorder (1), neutropenia (1), sepsis and anemia (1), hyperbilirubinemia or jaundice (6), hypocapnia with extreme hypotonia (1), transient tachypnea (4), apnea and/or respiratory distress syndrome (2), and gastroesophageal reflux (2), or difficulty in feeding (2).	At 42 months (n=93 from Table 7), long-term complications (number affected): periventricular leukomalacia and developmental delay requiring OT and PT (hypocapnia at birth) (1), gastroesophageal reflux (1), mild speech delay (2), mild hearing loss and recurrent otitis media (1), recurrent otitis media (3), reactive airway disease (2), selective IgA deficiency not requiring treatment (1). Group mean weight was 48 th percentile.	(Cardonick <i>et al.</i> 2010)
		21 of 31 from Table 3 [22 of 32 infants]	Hodgkin lymphoma	2 nd or 2 nd , 3 rd	Bleomycin, Vinblastine, Dacarbazine	NS	35.9 (group mean)	Infant sex NS: 2,587 g (group mean), Apgar scores NS. Twenty newborns were without malformations and had normal body weight for gestational age, including 1 set of twins. Malformations observed in 2 infants: 1 had plagiocephaly, and 1 had syndactyly of the 4 th and 5 th fingers. Other health effects included 1 with birthweight < 15% and 3 with hypoglycemia (including 1 set of twins born prematurely).	At 0.5 to 10 years (n=20), all children were normal phenotype. At 4 to 112 months (group range, n=15), 1 child in the group had chronic bronchitis, 1 had recurrent otitis media, and 1 had asthma; group mean weight was 67 th percentile.	
		8 of 32 from Table 3	Non-Hodgkin lymphoma	2 nd , 3 rd	Vincristine, Cyclophosphamide, Rituximab	NS	34.0 (group mean)	Infant sex NS: 2,576 g (group mean), Apgar scores NS. One fetus died at 30 wks; autopsy was normal. Seven newborns were without malformations and had normal body weights for gestational age. Two newborns had jaundice, 1 also had anemia, and 1 also had transient tachypnea.	At 0.2 to 5.3 years (n=20), all children were normal phenotype. At 34 to 82 months (group range, n=6), 1 child in the group had a speech delay; group mean weight was 46 th percentile.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS)	Survey, retrospective, utilizing data from the rituximab global drug safety database	3 of 20	Non-Hodgkin lymphoma, B-cell	3 rd	Cyclophosphamide, Vincristine, Rituximab	NS	35	Male infant: weight and Apgar scores NS. Newborn was premature.	No	(Chakravarty <i>et al.</i> 2011) [This entry excludes 3 published cancer case reports that are already included in our table: (Herold <i>et al.</i> 2001, Decker <i>et al.</i> 2006, Friedrichs <i>et al.</i> 2006).]
			Non-Hodgkin lymphoma	2 nd First@wk 18	Cyclophosphamide, Vincristine, Rituximab	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal.		
			Non-Hodgkin lymphoma	2 nd First@wk 21	Cyclophosphamide, Vincristine, Rituximab	NS	33	Preeclampsia. Female infant: weight and Apgar scores NS. Newborn was normal.		
Doxorubicin (60 mg/m ² in 1 st cycle, 50 mg/m ² in 2 nd and 3 rd cycles, 3 cycles, 3-4 wks apart)	Case report	1	Breast	3 rd First@wk 28 Last@wk 34	5-Fluorouracil, Cyclophosphamide	Vaginal, induced	37	Mild fetal growth restriction and progressive reduction in amniotic fluid. Female infant: 2,350 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was in good condition with normal blood count.	At 24 months, healthy with weight and height in 50 th percentile and normal psychoneurological development.	(Cordoba <i>et al.</i> 2010)
Doxorubicin (45 mg/m ² , every other day for 4.5 wks)	Case report	1	Leukemia, ALL	2 nd	Vincristine (1 st , 2 nd , 3 rd), Cytarabine (3 rd), Methotrexate (1 st , 3 rd), 6-Mercaptopurine (1 st)	C-section	36	Male infant: 2,400 g, Apgar scores NS. Newborn was polycythemic and hyperbilirubinemic, with no congenital defects.	At 6 months, normal growth and development.	(Dara <i>et al.</i> 1981)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS)	Case series	7 of 32 from Table 1 (Pts 3, 4, 8, 9, 18, 19, and 20)	Breast	2 nd First@wk 20 Last@wk 23	None	Vaginal	36	Infant sex NS: 3,120 g, Apgar scores 9 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
			Breast	2 nd First@wk 14 Last@wk 22	Cyclophosphamide	Vaginal	38	Infant sex NS: 3,150 g, Apgar scores 9 and 10. Newborn was healthy.		
			Hodgkin lymphoma	3 rd First@wk 30 Last@wk 36	Bleomycin, Vinblastine	C-section	36	Infant sex NS: 2,650 g, Apgar scores 8 and 9. Newborn was healthy.		
			Hodgkin lymphoma	2 nd , 3 rd First@wk 15 Last@wk 35	Bleomycin, Vinblastine, Dacarbazine	Vaginal	36	Infant sex NS: 2,190 g, Apgar scores 6 and 9. Newborn was healthy.		
			Hodgkin lymphoma	2 nd First@wk 24 Last@wk 27	Bleomycin, Vinblastine, Dacarbazine	C-section	37	Infant sex NS: 2,850 g, Apgar scores 8 and 8. Newborn was healthy.		
			Hodgkin lymphoma	2 nd First@wk 24 Last@wk 26	Bleomycin, Vinblastine, Dacarbazine	C-section	37	Infant sex NS: 2,450 g, Apgar scores 9 and 9. Newborn was healthy.		
			Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 24 Last@wk 37	Bleomycin, Vincristine, Etoposide, Cytarabine, Cyclophosphamide	C-section	35	Infant sex NS: 1,980 g, Apgar scores 8 and 8. Newborn was healthy.		
Doxorubicin (50 mg/m ² , 6 cycles, 14 days apart)	Case report	1	Non-Hodgkin lymphoma	1 st , 2 nd	Cyclophosphamide, Vincristine, Rituximab	Vaginal	33	Spontaneous preterm labor and delivery. Female infant: weight within 50 th -90 th percentile, Apgar scores 8, 10, and 10. Newborn was healthy, but B-cells were severely diminished at birth (recovery began at 6 wks, complete by 12 wks).	Normal immunological response to vaccinations at 8 and 16 wks. At 16 months, no physiological or developmental abnormalities.	(Decker <i>et al.</i> 2006)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (25 mg/m ² for 3 days, 1 cycle)	Case report	1	Leukemia, APL	2 nd First@wk 22	6-Thioguanine, Cytarabine (2 nd , 3 rd)	C-section	28	Intrauterine growth restriction and was non-responsive to nonstress test at 28 wks of gestation. Male infant: 1,140 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal; placental pathology showed multiple infarcts but no leukemic infiltration.	At 14 months, normal chromosomal study. At 20 months, normal according to physical and psychological assessment.	(D'Emilio <i>et al.</i> 1989)
Doxorubicin (Dose/schedule NS, 4 cycles)	Case report	1	Breast	2 nd	Cyclophosphamide	Vaginal	NS	Male infant: weight and Apgar scores NS. Newborn was healthy.	No	(Diamond <i>et al.</i> 2009)
Doxorubicin (Dose/schedule NS)	Case series	4 of 21 (Pts 7, 10, 11, and 13; Pt 7 had 2 pregnancies)	Hodgkin lymphoma	1 st	Bleomycin, Vinblastine, Dacarbazine	NSI	NS	Male infant: 2,500 g, Apgar scores NS. Newborn had growth retardation (SGA), but was healthy with no hematological abnormalities. [Pt 7, 1st pregnancy]	At 65 months, alive.	(Dilek <i>et al.</i> 2006)
				2 nd , 3 rd	Bleomycin, Vinblastine, Dacarbazine	--	--	Fetal death [stillbirth] in the 8 th month of gestation. [No fetal data reported; Pt7, 2nd pregnancy]	--	
			Hodgkin lymphoma	1 st	Bleomycin, Vinblastine, Dacarbazine	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had growth retardation (SGA) and partial agenesis of a metacarpal bone and hypoplasia of 2 phalanges (floating thumb malformation) on the left hand.	At 43 months, alive	
			Hodgkin lymphoma	1 st [Text says 1st, Table says postpartum]	Cyclophosphamide, Vincristine	NS	Term	Female infant: 3,000 g, Apgar scores NS. Newborn had no pathological findings.	At 12 months, alive.	
			Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Vincristine	NS	Term	Male infant: 2,500 g, Apgar scores NS. Newborn had no hematological abnormalities.	At 35 months, alive	
Doxorubicin (40 mg, 1 dose)	Case report	1	Hodgkin lymphoma	2 nd First@wk17	Bleomycin, Vinblastine, Dacarbazine	--	--	Induced abortion after first dose. [No fetal data reported.]	--	(D'Incalci <i>et al.</i> 1983)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (50 mg/m ² on day 2, 5 cycles, 4 wks apart)	Case report	1	Breast	2 nd , 3 rd	Cyclophosphamide, 5-Fluorouracil	C-section	38	Male infant: 5 lb 4 oz [2,665 g], Apgar scores NS. Newborn developed jaundice, but was otherwise healthy with normal blood count and chemistry.	At 4 months, 50 th percentile for weight with normal blood count and chemistry. At 15 and 24 months, excellent health and normal development.	(Dreicer and Love 1991)
Doxorubicin (Dose/schedule NS)	Case series	1 of 2 (Pt 2)	Leukemia, AML	1 st Last@wk 8	Cytarabine, Vincristine	Vaginal	NS	Female infant: weight and Apgar scores NS. Newborn had an atrial septum defect and bilateral loss of radius and fifth digit.	No	(Ebert <i>et al.</i> 1997)
Doxorubicin (Dose/schedule NS, 4 cycles)	Case report	1	Neuroendocrine carcinoma, vagina	2 nd First@wk 17 Last@wk 27	Cyclophosphamide, Vincristine	C-section	29	Male infant: 1,100 g, Apgar scores 5 and 6 at 1 and 5 minutes. Newborn was viable and, because of prematurity, received intensive care for 55 days, at which time he was discharged without complications..	At 6 years, highly functional with no neurodevelopmental delays.	(EINaggar <i>et al.</i> 2012)
Doxorubicin (Dose/schedule NS, 3 cycles, 3-4 wks apart)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 25	Bleomycin, Vinblastine, Dacarbazine	C-section	38	Serial ultrasounds noted small for gestational age fetus. Male infant: 1650 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 10 months, remained well.	(Fadilah <i>et al.</i> 2006)
Doxorubicin (37.5-50 mg/m ² on day 1)	Case series	4 of 5 (Pts 1, 2, 3, and 4)	Leukemia, APL	1 st First@wk 11	Vincristine, Cytarabine	--	--	Induced abortion at gestation wk 19. Histologic and karyotypic examinations of fetus were not performed.	--	(Fassas <i>et al.</i> 1984)
			Leukemia, AML	2 nd First@wk 17	Vincristine, Cytarabine	Vaginal	37	Spontaneous preterm labor. Male infant: 2,430 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had a normal blood count and no congenital abnormalities.	At 3-4 months, increased leukocyte count and lymphocytic with occasional red blood cells in smear. At 20 and 30 months, normal blood count. At 37 months, normal growth and development.	
			Leukemia, AML	3 rd First@wk 36	Vincristine, Cytarabine	NS	[37]	Male infant: 3,100 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal with a normal blood count.	At 36 months, normal growth and development with no hematologic abnormality.	
			Leukemia, AML	3 rd	Vincristine, Cytarabine	C-section	38	Male infant: 3,140 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with a normal blood profile.	No	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (40 mg, schedule NS)	Case series	1 of 5 (Pt 2)	Leukemia, AML	1 st First and Last@ [~wk6]	6-Mercaptopurine (1 st), Methotrexate (1 st), Vincristine (1 st , 3 rd), Daunorubicin (3 rd), Cytarabine (3 rd)	Vaginal	38	Female infant: 2,800 g, Apgar scores 8 and 10 at 1 and 5 minutes.	At 7 years, normal development.	(Feliu <i>et al.</i> 1988)
Doxorubicin (Dose/schedule NS, 6 cycles, 3 wks apart)	Case report	1	Breast	2 nd	Rituximab, Cyclophosphamide, Vincristine	C-section	41	Female infant: weight and Apgar scores NS. Newborn was healthy but with complete absence of B-cells. A fast B-cell recovery was seen in the wks following birth.	At 26 months, normal growth and development.	(Friedrichs <i>et al.</i> 2006)
Doxorubicin (Dose/schedule NS, 2 cycles)	Case series	1 of 2 (Pt 2)	Non-Hodgkin lymphoma, large B-cell	3 rd First@wk 28 Last@wk 32	Cyclophosphamide Vincristine	Vaginal	33	Male infant: 1,645 g, Apgar scores 8 and 9 at 1 and 5 minutes. Developed necrotizing enterocolitis that was successfully treated and leukopenia that resolved in 2 days.	No	(Garcia <i>et al.</i> 1999)
Doxorubicin (45 mg/m ² , 4 wks apart)	Case report	1	Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Vincristine	Vaginal	NS	Male infant: 3,400 g, Apgar score 10 after 10 minutes. Newborn had a normal appearance.	At 2 months, satisfactory condition.	(Garcia <i>et al.</i> 1981)
Doxorubicin (Table 2: Pt 1 – 100 m[g]/m ² , Pt 2 – 110 m[g]/m ² , Pt 3 – 75 m[g]/m ² , Pt 4 – 130 m[g]/m ² , others – dose NS; schedule NS)	Case series, retrospective	7 of 15 [see note in pregnancy outcome column]	Breast	2 nd and/or 3 rd	5-Fluorouracil, Cyclophosphamide	NS	35 (group average) (range 32-40)	Individual pregnancy outcomes were not provided. Seven live births with no congenital malformations. No stillbirths, miscarriages, or perinatal deaths in any pregnancies treated during the 2 nd and 3 rd . [Only 15 of 17 pts treated with chemotherapy during pregnancy; individual chemotherapy regimen of 4 pts was not provided.]	No	(Garcia-Manero <i>et al.</i> 2009)
		4 of 15	Breast	2 nd and/or 3 rd	Docetaxel	Vaginal	39	Male infant: 3,080 g, Apgar scores NS. Newborn was healthy and without malformations.	At 24 months, healthy.	
					Docetaxel (3 rd)	Vaginal	40	Male infant: 3,200 g, Apgar scores NS. Newborn was healthy and without malformations.	At 36 months, healthy.	
					Docetaxel (3 rd)	Vaginal	34	Male infant: 2,850 g, Apgar scores were 9/10 [9 and 10 at 5 and 10 minutes]. Newborn was healthy and without malformations.	At 12 months, healthy.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
					Docetaxel	C-section	35	Male infant: 1,850 g [SGA], Apgar scores NS. Newborn was healthy and without malformations.	At 25 months, healthy.	
Doxorubicin (Dose/schedule NS, 3 cycles)	Case report	1	Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Vincristine	Vaginal	Full term	Female infant: Birth weight and Apgar scores NS. Newborn showed no congenital anomalies.	At 4 wks, infant weighed 2,800 g; chromosomal analysis revealed no breaks or translocation. At 26 months, doing well.	(Garg and Kochupillai 1985)
Doxorubicin (50-100 mg/m ² , 4 cycles (Pt 6 and 8) or 1 cycle (Pt 9 and 15), 15-28 days apart)	Survey, retrospective	4 of 20 (Pts 6, 8, 9, and 15)	Breast	2 nd , 3 rd First@wk 24	Cyclophosphamide, 5-Fluorouracil	Vaginal	35	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with normal body weight for gestational age.	At 60 months, alive and well.	(Giacalone <i>et al.</i> 1999)++
				2 nd , 3 rd First@wk 26	Vincristine	Vaginal	35	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with normal body weight for gestational age.	At 20 months, alive and well.	
				3 rd First@wk 27	5-Fluorouracil	C-section	35	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with normal body weight for gestational age.	At 120 months, alive and well.	
				3 rd First@wk 31	Cyclophosphamide, 5-Fluorouracil	C-section	34	Infant sex and weight NS, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with normal body weight for gestational age.	At 120 months, alive and well.	
Doxorubicin (40 mg, 2 cycles, 3 wks apart)	Case report	1	Sarcoma, Ewing	3 rd First@wk 29 Last@wk 32	Actinomycin D, Vincristine, Cyclophosphamide, Radiation therapy	Vaginal, induced	36	Female infant: 5 lb 3 oz [2,353 g], Apgar scores 9 and 9. Newborn appeared normal.	At 3 months, growing adequately with no known abnormalities.	(Gililand and Weinstein 1983)
Doxorubicin (60 mg/m ² , 4 cycles)	Case report	1	Breast	1 st , 2 nd	Cyclophosphamide, Paclitaxel (2 nd , 3 rd)	C-section	37	Preeclampsia. Male infant: 5.4 lb [2,449 g], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal, with normal blood counts.	At 12 months, normal physical growth and development.	(Gonzalez-Angulo <i>et al.</i> 2004)
Doxorubicin (Dose/schedule NS)	Case series	1 of 17 (Pt 11)	Leukemia, AML	2 nd First@wk 24	6-Thioguanine, Vincristine, Cytarabine	NS	31.5	Female infant: 1,135 g [SGA], Apgar score NS. Newborn had no congenital malformations.	No	(Greenlund <i>et al.</i> 2001)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd [First@> wk 25]	Actinomycin D, Cyclophosphamide, Bleomycin, Vincristine	C-section	34	Female infant: 1,750 g, Apgars scores 7 and 9. Infant required intravenous calcium and was treated for mild respiratory distress syndrome for 2 days. No major problems after 3 days.	Child progressing normally [age NS, > 4 years later].	(Haerr and Pratt 1985)
Doxorubicin (50 mg/m ² over 72 hours (group mean = 4 cycles), 3-4 wks apart)	Case series	40 of 57 [Data on pregnancy outcomes available for only 40 pregnancies]	Breast	NS First@wk 11-34 (range), 23 (median) Last@wk 35	Cyclophosphamide, 5-Fluorouracil	60% Vaginal; 40% C-section	37 (group mean); 29-42, (group range; n=52)	Individual pregnancy outcomes not provided. Infant sex and Apgar scores NS: group mean birth weight = 2,890 g (range = 1,289-3,977 g; n=47). No stillbirths, miscarriages, or perinatal deaths (n=55). Pregnancy outcomes provided for 40 infants (number affected): Down syndrome (1), clubfoot (1), bilateral ureteral reflux (1), breathing difficulties (11), and neutropenia, thrombocytopenia, and subarachnoid hemorrhage (1).	Follow-up on children (ages 2-157 months; n=39). All children except the one with Down syndrome were thought to have normal development by their parents. One other school-age child had attention-deficit/hyperactivity disorder.	(Hahn <i>et al.</i> 2006)
Doxorubicin (50 mg/m ² on day 3, cycles were 4 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd First@wk 21	Rituximab, Vincristine	C-section	35	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 4 months, developing well with normal B-cell population.	(Herold <i>et al.</i> 2001)
Doxorubicin (Dose/schedule NS)	Cohort, retrospective	7 of 72	Breast	2 nd or 3 rd	Cyclophosphamide, 5-Fluorouracil, Paclitaxel, Cisplatin	NS	NS	Individual pregnancy outcomes were not provided. No congenital malformations were diagnosed in the newborns.	No	(Ibrahim <i>et al.</i> 2000) [†]
Doxorubicin (Dose/schedule NS, 6 cycles)	Case report	1	Breast	1 st , 2 nd	Cyclophosphamide, Docetaxel (1 st)	C-section	32	Male infant: weight and Apgar scores were within the normal range.	No	(Ibrahim <i>et al.</i> 2006) [†] (Abstract only)
Doxorubicin (60 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Breast	2 nd First@wk 24	Cyclophosphamide	Vaginal	36.5	Female infant: 2,530 g, Apgar scores 9 and 10 and 1 and 5 minutes. Newborn was healthy and had no complications.	At 40 months, normal growth and development.	(Inbar and Ron 1996)
Doxorubicin (25 mg/m ² , schedule NS, 3.5 cycles)	Case report	1	Hodgkin lymphoma	2 nd First@wk 21	Bleomycin, Vinblastine, Dacarbazine	Vaginal	41	Female infant: weight was within normal limits. Apgar score 9. Newborn was healthy.	At follow-up [age NS], no physiological or developmental abnormalities.	(Iriyama <i>et al.</i> 2011)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS, 4 cycles)	Survey, retrospective	1 of 49 from Table 4 (Pt 2)	Breast	2 nd , 3 rd or 3 rd	Cyclophosphamide	NS	37	Infant sex, weight, and Apgar scores NS. Newborn born alive and without malformation.	No	(Ives <i>et al.</i> 2005)
Doxorubicin (Dose/schedule NS, 2 cycles)	Case series	1 of 2 (Pt 2)	Breast	2 nd First@wk 24?	None	C-section	34	Male infant: 1,900 g, Apgar score 8. No further information provided.	No	(Jakubik <i>et al.</i> 2008)
Doxorubicin (Dose/schedule NS, Breast Pts – 2-6 cycles, Hodgkin lymphoma Pts – 7-8 cycles, Sarcoma Pt – 1 cycle)	Case series	6 of 18	Breast	NS First@wk 12-33 22 (mean)	5-Fluorouracil, Cyclophosphamide	NS	NS	Infants' sex, weight and Apgar scores NS. Newborns were alive and healthy; no malformations were observed.	At follow-up, normal growth patterns without physical or neurological deficits (n=5 children, oldest child is 42 months).	(Jameel and Jamil 2007)
		2 of 18	Hodgkin lymphoma		Bleomycin, Vinblastine, Dacarbazine	NS	NS			
		1 of 18	Sarcoma, soft tissue		Cyclophosphamide, Vincristine, Dacarbazine	--	--	Spontaneous abortion at gestation wk 22. [No fetal data reported.]	--	
Doxorubicin (Dose/schedule NS)	Survey, retrospective	NS [10 of 302 pts received chemo while pregnant; the number of pts who received doxorubicin while pregnant was not provided]	Hodgkin lymphoma	NS	Vinblastine, Bleomycin, Dacarbazine	NS	NS	Individual treatments and pregnancy outcomes are not provided. In the total number of pregnancies there were 4 perinatal deaths (5.7 expected), cancer subsequently developed in 2 (1.2 expected), and 22 infants had low birthweight (13.7 expected). The excess number of low weight births occurred primarily during the period of Hodgkin disease diagnosis and treatment.	[Not clear whether infants exposed <i>in utero</i> had follow-up.]	(Janov <i>et al.</i> 1992) [†]

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (45 mg/m ² , 5 cycles (Pt 1) or 1 cycle (Pt 2))	Case series	2 of 2	Leukemia, ALL	2 nd , 3 rd	Asparaginase, Vincristine, Methotrexate (intrathecal), Radiation therapy	C-section	34	Spontaneous preterm rupture of the membranes and labor. Male infant: 2,080 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal at physical exam, and had normal blood counts.	At 30 months, developing normally.	(Karp <i>et al.</i> 1983)
			Breast	3 rd First@wk 31	Vincristine, Radiation Therapy (2 nd , 3 rd)	--	--	Spontaneous preterm labor. Stillbirth at gestation wk 31, female: 1,200 g, no abnormalities. Placenta was immature with several small areas of recent infarction, extensive endothelial damage, organizing thrombosis, and occlusion and recanalization of the chorionic vessels.	--	
Doxorubicin (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Aclarubicin, Cytarabine, Cycloctidine, ATRA, Mitoxantrone, Idarubicin, Asparaginase, Vincristine	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994)†
Doxorubicin (60 mg/m ² , 6 cycles, 3 wks apart)	Case report	1	Breast	2 nd First@wk 14	Cyclophosphamide	Vaginal	31	Male infant: 1,474 g, Apgar scores 8 and 8 at 1 and 5 minutes. Newborn had no physical abnormality, but had apnea, tachypnea, respiratory distress requiring intubation (resolved by day 2 after surfactant therapy), hyperbilirubinemia and hypoglycemia (both resolved after 5 days).	At 1 year, in good health with normal growth and development.	(Kerr 2005)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Dose/schedule NS, 2 cycles over 4 wks)	Case report	1	Leukemia, ALL	2 nd	Vincristine (2 nd , 3 rd), Asparaginase, 6-Mercaptopurine (2 nd , 3 rd), Cyclophosphamide (2 nd , 3 rd), Methotrexate (2 nd , 3 rd)	C-section	NS [at term]	Female infant: 3,800 g, Apgar scores NS. Newborn was clinically normal, with slight leucopenia (resolved after 2 wks).	At follow-up [age NS], child was progressing well with normal blood counts, and no neurological disturbance or congenital abnormality.	(Khurshid and Saleem 1978)
Doxorubicin (50 mg/m ² once a month, 2 cycles)	Case report	1	Adenoid cystic carcinoma, submandibular gland	1 st First@wk 5 Last@wk 10	Doxorubicin, Cisplatin	C-section	25	Spontaneous preterm labor. Male infant: 912 g, Apgar scores 1 and 6 at 1 and 5 minutes. Newborn had blepharophimosis, microcephaly, and hydrocephalus	No	(Kim <i>et al.</i> 1996)
Doxorubicin (Dose/schedule NS, 3 cycles)	Case report	1	Hodgkin lymphoma	3 rd First@wk 27	Bleomycin, Vinblastine, Dacarbazine	C-section	39	Male infant: 2,350 g [SGA], Apgar scores NS. Newborn was healthy and HIV negative (mother was HIV positive).	At 9 months, clinically well and HIV negative.	(Klepfish <i>et al.</i> 2000)
Doxorubicin (50 mg/m ² , 3-4 wks apart)	Case series	4 of 4	Breast	3 rd First@wk 33	Cyclophosphamide, 5-Fluorouracil	NS	36	Infant: sex, weight, and Apgar scores NS.	At 65 months, healthy with normal development.	(Kuerer <i>et al.</i> 2002)
				2 nd , 3 rd First@wk 26	Cyclophosphamide, 5-Fluorouracil	NS	40	Infant: sex, weight, and Apgar scores NS.	At 44 months, healthy with normal development.	
				2 nd , 3 rd First@wk 26	Cyclophosphamide, 5-Fluorouracil	NS	35	Preeclampsia. Infant: sex, weight, and Apgar scores NS.	At 33 months, healthy with normal development.	
				3 rd First@wk 31	Cyclophosphamide, 5-Fluorouracil	NS	36	Infant: sex, weight, and Apgar scores NS.	At 33 months, healthy with normal development.	
Doxorubicin (40 mg/m ² on day 1, 2 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 26 Last@wk 29	Cyclophosphamide, Vincristine, Cytarabine, Etoposide, Ifosfamide	C-section	32	Male infant: 1,731 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no anomalies, but was cyanotic, and experienced respiratory distress.	At 1 year, mild delayed motor skills, otherwise healthy.	(Lam 2006)
Doxorubicin (50 mg/m ² on day 1, 3 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 22 Last@wk 28	Cyclophosphamide, Vincristine, Teniposide, Bleomycin	C-section	31	Preeclampsia and fetal growth retardation at gestation wk 28. Fetal distress at gestation wk 31. Male infant: 1,380 g, Apgar scores 7 and 9 at 5 and 10 minutes. Newborn	At 18 months, normal growth with no signs of damage to any organ system that could be related to the chemotherapy.	(Lambert <i>et al.</i> 1991)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								had no neurologic or other abnormalities, but experienced transient hyperbilirubinemia (treated and resolved in 3 days). Placenta showed extensive infarction.		
Doxorubicin (Dose/ schedule NS)	Case report	1	Breast	3 rd First@wk 32 Last@wk 35	5-Fluorouracil, Cyclophosphamide	C-section	37.5	Female infant: weight and Apgar scores NS. Newborn was healthy.	No	(Logue 2009)
Doxorubicin (35 mg/m ² (first 2 cycles) or 50 mg/m ² (last 4 cycles) on day 1, 6 cycles, 2.5-3 wks apart)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd Last@wk 37	Cyclophosphamide, Vincristine, Teniposide, Bleomycin (3 rd), Methotrexate (3 rd)	Vaginal	37	Female infant: 3,750 g, Apgar score 9. Newborn was fully developed with a normal heart and blood count, no abnormality was detected.	No	(Lowenthal <i>et al.</i> 1982)
Doxorubicin (60 mg/m ² every 2 wks for 4 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 22 Last@wk 28	Cyclophosphamide, Paclitaxel (3 rd)	C-section	38	Transient uterine contractions after 2 nd cycle of chemotherapy. Twin infants, sexes NS: Baby A – 2,354 g [SGA], Apgar scores 7 and 8 at 1 and 5 minutes; Baby B – 2,426 g [SGA], Apgar scores 8 and 9 at 1 and 5 minutes. Both newborns were healthy.	At 16 months, they were in good health.	(Lycette <i>et al.</i> 2006)
Doxorubicin (Dose/schedule NS, 6 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 13 + 4 days	Cyclophosphamide, Vincristine, Rituximab, Cytarabine (IT)	Vaginal	39	Female infant: 2,270 g [SGA], Apgar scores 6 and 9. Newborn was viable with low birth weight.	At 7 months, healthy	(Magloire <i>et al.</i> 2006)
Doxorubicin (60 mg/m ² , 4 cycles)	Case report	1	Breast	2 nd First@wk 13	Cyclophosphamide	C-section	4 wks prior to due date [NS]	Female infant: 5 lb 11 oz [2,580 g], Apgar scores NS. Newborn was healthy.	No	(Mahon <i>et al.</i> 2001)
Doxorubicin (50 mg/m ² , 1 cycle (Pt 1), or 60 mg/m ² , 4 cycles (Pt 2))	Case series	2 of 4 (Pts 1 and 2)	Breast	3 rd First@wk 27	5-Fluorouracil	C-section	34	Female infant: 2,600 g, Apgar score 10 at 1 minute. Newborn had no congenital abnormality or intrauterine growth restriction.	At 17 years, no evidence of impaired intelligence quotient; physical and sexual development was normal.	(Mathelin <i>et al.</i> 2005)
				2 nd , 3 rd First@wk 21 Last@wk 31	5-Fluorouracil	Vaginal	34	Female infant: 2,820 g, Apgar score 10 at 1 minute. Newborn had no congenital abnormality or intrauterine growth restriction.	At 11 years, no evidence of impaired intelligence quotient; physical and sexual development was normal.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Moderate for 2 cycles, 20 mg/m ² daily for 3 days for last cycle)	Case report	1	Sarcoma, Ewing	3 rd	Cyclophosphamide, Vincristine, Methotrexate	C-section	~7 months	Spontaneous preterm rupture of membranes and labor. Male infant: 2,200 g, Apgar score 9. Newborn was healthy with normal blood counts.	At 10 wks, normal growth and development.	(Meador <i>et al.</i> 1987)
Doxorubicin (40 mg/m ² weekly, 3 cycles)	Case report	1	Rhabdomyosarcoma	2 nd	Actinomycin D, Cyclophosphamide	C-section	29 + 3 days	Female infant: 2,800 g, Apgar score 9. Newborn's physical exam was normal, as were blood tests.	No	(Meazza <i>et al.</i> 2008)
Doxorubicin (50 mg/m ² , 3 cycles, 3 wks apart)	Case series	1 of 7 (Pt 6)	Sarcoma, Ewing	2 nd , 3 rd First@wk 27 Last@wk 33	Ifosfamide	C-section	36	Infant sex NS: 1,300 g [SGA], Apgar scores NS. Newborn was normal.	[At 2 years, healthy.]	(Merimsky and Le Cesne 1998) [More detailed follow-up on Pt 6 was reported in Merimsky <i>et al.</i> (1999)].
Doxorubicin (50 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Sarcoma, Ewing	3 rd First@wk 27 Last@wk 33	Ifosfamide	C-section	36	Mild intrauterine growth retardation without fetal stress. Female infant: 1,300 g [SGA], Apgar scores NS.	At 2 years, small healthy baby with no chemotherapy-related late effects.	(Merimsky <i>et al.</i> 1999) [†] [This case report is follow-up on Pt 6 in Merimsky <i>et al.</i> (1998), thus this case report was not tallied in the in the text analysis.]
Doxorubicin (45 mg/m ² , 5 cycles, 4 wks apart)	Case report	1	Ovary	2 nd , 3 rd First@wk 17	Cyclophosphamide, Vincristine	Vaginal, induced	37	Female infant: 6 lb 13 oz [3,090 g], Apgar scores NS. Newborn was normal-appearing.	At 1 year, developmentally normal.	(Metz <i>et al.</i> 1989)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (50 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Breast	2 nd , 3 rd	Cyclophosphamide	C-section	35	Idiopathic preterm labor at gestation wk 30 (treated and resolved). Oligohydramnios at gestation wk 35. Female infant: 2,490 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was in good condition with no myocardial dysfunction.	Echocardiograms were conducted every 3 months after birth for 2 years; there was no evidence of myocardial damage.	(Meyer-Wittkopf <i>et al.</i> 2001)
Doxorubicin (50 mg/m ² every 3 wks; 2 cycles, except case 5 received only 1 cycle)	Case series	5 of 5	Sarcoma, Ewing	3 rd First@wk 29	Ifosfamide	Vaginal	34	Spontaneous preterm labor. Female infant: 1,400 g [SGA], Apgar scores 8 and 9 at 1 and 5 minutes. Condition of the newborn was considered "favorable."	Normal at 8 months.	(Mir <i>et al.</i> 2012)
			Osteosarcoma	3 rd First@wk 30	Ifosfamide	Vaginal	35	Female infant: 2,200 g, Apgar scores 9 and 9 at 1 and 5 minutes. Condition of the newborn was considered "favorable."	Normal at 5 years.	
			Sarcoma, Ewing	3 rd First@wk 30	Ifosfamide	Vaginal	36	Female infant: 2,200 g, Apgar scores 8 and 10 at 1 and 5 minutes. Condition of the newborn was considered "favorable."	Normal at 3 years.	
			Sarcoma, high-grade	3 rd First@wk 29	Ifosfamide	Vaginal	35 + 5 days	Male infant: 2,300 g, Apgar scores 10 and 10 at 1 and 5 minutes. Condition of the newborn was considered "favorable."	Normal at 5 years.	
			Sarcoma, high-grade	2 nd First@wk 26	Ifosfamide	C-section	29 + 5 days	Oligohydramnios detected at 29 wks. Male infant: 1,180 g, Apgar scores 10 and 10 at 1 and 5 minutes. Condition of the newborn was considered "favorable."	Normal at 5 months.	
Doxorubicin (40 mg/m ² , 5 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd Last@wk 35	Cyclophosphamide, Vincristine, Etoposide, Bleomycin	Vaginal	35.5	Spontaneous preterm labor after last chemotherapy dose. Male infant: birth weight was in the 75 th percentile for gestational age, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no apparent physical anomalies.	At 11 months, alive and well.	(Moore and Taslimi 1991)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (60 mg/m ² , 5 cycles (Pt A and B) or 4 cycles (Pt C), 3 wks apart)	Case series	3 of 5 (Pts A, B, and C)	Breast	2 nd , 3 rd	Cyclophosphamide	C-section	36	Infant sex, weight, and Apgar scores NS. Newborn was healthy with no abnormalities.	No	(Morris <i>et al.</i> 2009)
				2 nd , 3 rd	Cyclophosphamide	C-section	35	Infant sex, weight, and Apgar scores NS. Newborn was healthy with no abnormalities.	No	
				2 nd , 3 rd	Cyclophosphamide	C-section	35	Infant sex, weight, and Apgar scores NS. Newborn was healthy with no abnormalities.	No	
Doxorubicin (325 mg total, schedule NS)	Case report	1	Breast	1 st , 2 nd	Cyclophosphamide, Radiation therapy (Cobalt, 1 st)	NS	~39	Slowed fetal growth at gestation wk 27. Female infant: 2,980 g, Apgar score 9. Newborn had an imperforate anus and a rectovaginal fistula; chromosomal analysis was normal.	At follow-up, small but otherwise normal [age NS].	(Murray <i>et al.</i> 1984)
Doxorubicin (45 mg/m ² 3-weekly, 3 cycles)	Case series	1 of 2 (Pt 2)	Breast	2 nd , 3 rd	Cyclophosphamide	Vaginal, Induced	32 or 33	Male infant: 1,800 g, Apgar scores NS. Newborn was healthy.	No	(Murray and Werner 1997)
Doxorubicin (50 mg/m ² over 2 days, 3 cycles, 3 wks apart)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd First@wk 25 Last@wk 30	Ifosfamide	C-section	32	At 28 wks of gestation, mild intrauterine growth retardation and decrease in amniotic fluid. Male infant: 1,245 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn had no dysmorphic features or anomalies. Newborn required intubation for irregular respiration (resolved after 3 days) and was tube-fed for 1 month. He was treated for hyperbilirubinemia on day 2 and became anemic by day 22 (recovered after 1 month).	At 8 months, growing adequately with no known abnormalities.	(Nakajima <i>et al.</i> 2004)
Doxorubicin, (Dose/schedule NS, 12 cycles over 13 wks)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 18	Methotrexate, Bleomycin, Cyclophosphamide, Vincristine	C-section	28	Spontaneous preterm labor at 10 th wk of chemotherapy. Twin male infants: weights and Apgar scores NS. Newborns were without apparent malformation or bone marrow suppression.	At 12 months, apparently healthy.	(Nantel <i>et al.</i> 1990)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (80 mg/m ² on day 1 of a 10-day cycle, 2 cycles; then same dose for 4-wk cycle, 3 cycles total)	Case series	1 of 2 (Pt 2)	Leukemia, acute	1 st , 2 nd , 3 rd [First@wk 12]	Cytarabine, Vincristine	Vaginal	[39]	Female infant: 2,860 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn appeared normal.	At 6 wks, normal karyotype.	(Newcomb <i>et al.</i> 1978)
Doxorubicin (50 mg/m ² , 4 cycles, 3 wks apart)	Case report	1	Breast	1 st , 2 nd First@wk 13 Last@wk 25	5-Fluorouracil, Cyclophosphamide, Doxetaxel (2 nd , 3 rd)	Vaginal	39	Male infant: 6.8 lb [3,084 g], normal Apgar scores. Newborn was healthy with normal blood counts.	No	(Nieto <i>et al.</i> 2006)
Doxorubicin (10 mg for 3 days, 4 cycles)	Case report	1	Ovary	2 nd First@wk 18	Cisplatin, Cyclophosphamide	C-section	33	Male infant: 1,896 g, Apgar scores 9 and 10. Newborn appeared normal with no anomalies or deformities.	At follow-up, growth has been normal, and there are no functional dysfunctions [age NS].	(Ohara and Teramoto 2000)
Doxorubicin (35 mg/m ² , 2 cycles)	Case report	1	Hodgkin lymphoma	2 nd	Nitrogen Mustard, Vincristine, Procarbazine, Bleomycin, Vinblastine	NS	Term	Female infant: weight and Apgar scores NS. Newborn had favorable outcome. Infant administered AZT for 6 wks because mother was HIV positive.	At 2 years, child had normal height and weight, and was HIV positive.	(Okechukwu and Ross 1998)
Doxorubicin (Dose/schedule NS)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 16	5-Fluorouracil, Cyclophosphamide	Vaginal	38	Male infant: 2,400 g [SGA], Apgar scores 5 and 8 at 1 and 5 minutes. Newborn had bilateral ventriculomegaly and colpocephaly, bicuspid aortic valve, flat nasal bridge with bulbous nasal tip, high-arched palate, and multiple hand deformities. The karyotype and clinical pathology were normal.	At 15 months, he could sit without help and walk unaided. At 3 years, visual evoked potential was normal; growth and neuromotor development were delayed.	(Paskulin <i>et al.</i> 2005)
Doxorubicin (Dose/schedule NS)	Cohort, retrospective	5 of 14 from Tables 3 and 4 (Pts 4, 6, 7, 13, and 14)	Breast	3 rd First@wk 28	None	NS	31	Infant sex NS: 2,070 g, Apgar scores NS. Newborn had respiratory distress syndrome, bronchopneumonia, and neonatal sepsis.	At 6 years, normal development.	(Peres <i>et al.</i> 2001)
			Leukemia, CML	2 nd First@wk 25	Hydroxyurea (1 st), Vincristine	NS	35	Infant sex NS: 3,195 g, Apgar scores NS. Newborn had jaundice, but no malformations.	At 4 years, normal development.	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Breast	1 st , 2 nd First@wk 2 Last@wk 26	5-Fluorouracil, Cyclophosphamide	NS	34	Infant sex NS: 2,170 g, Apgar scores NS. Newborn had no neonatal complications or malformations.	No	
			Leukemia, ALL	1 st First@wk 13	Vincristine	--	--	Spontaneous abortion at gestation wk 17. [No fetal data reported.]	--	
			Hodgkin lymphoma	1 st First@wk 3 Last@wk 7	Nitrogen mustard, Vincristine, Procarbazine, Bleomycin, Vinblastine, Dacarbazine	--	--	Induced abortion during gestation wk 18. Fetus had no malformations; toxic degenerative changes were present in the liver and kidneys. The placenta showed villus degeneration and vascular toxic degeneration.	--	
Doxorubicin (75 mg/m ² (Pt 1) or 60 mg/m ² (Pt 2), 3 cycles, 3 wks apart)	Case series	2	Breast	3 rd First@wk 27	None	Vaginal, induced	36	Female infant: 3,200 g, Apgar scores NS. Newborn had a minor ventricular septal defect (resolved without intervention within 2 years – 2 of her siblings had similar VSDs).	At 30 and 36 months, normal teeth.	(Peretz and Peretz 2003)
				2 nd , 3 rd First@wk 26	Cyclophosphamide	Vaginal, induced	36	Male infant: 3,100 g, Apgar scores NS. Newborn was healthy with normal blood counts.	At 18 months, no medical problems; all teeth were sound.	
Doxorubicin (40 mg/m ² on day 1, 3 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 16	Cyclophosphamide, Ifosfamide, Etoposide, Cytarabine, Vincristine, Rituximab	--	--	Decreased amniotic fluid at gestation wk 18 and early intrauterine growth restriction at gestation wk 22; similar effects at 23.5 wks of gestation. At 68 days of treatment, vaginal bleeding, spontaneous preterm labor, and no fetal heart tones. Stillbirth at gestation wk 26. [No fetal data reported.]	--	(Peterson <i>et al.</i> 2010)
Doxorubicin (80 mg, schedule NS)	Case series	1 of 9 (Pt 8 from Table 2)	Leukemia, ALL	1 st , 2 nd , 3 rd	6-Mercaptopurine, Vincristine, Methotrexate	C-section	33	Female infant: 1,900 g, Apgar scores NS. Newborn was normal.	At 16 months, alive.	(Pizzuto <i>et al.</i> 1980)† [Pt 8 from this case series was not counted separately because it was included in Aviles <i>et al.</i> (1988).]

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (60 mg/m ² , 4 cycles, 2 wks apart (Pt 1) or 6 cycles, 3 wks apart (Pt 2))	Case series	2	Breast	2 nd First@wk 14	Cyclophosphamide, Docetaxel (2 nd , 3 rd)	Vaginal	34	Hydrocephalus (dilated lateral and 3 rd ventricle) noted at gestation wk 17. Infant sex, weight, and Apgar scores NS. Newborn had mild hydrocephalus (resolved over several months without intervention).	At 28 months, normal development.	(Potluri <i>et al.</i> 2006)
				2 nd First@wk 14	Docetaxel	C-section	35	Preeclampsia at gestation wk 35. Infant sex, weight, and Apgar scores NS. Newborn was healthy with no detectable malformations.	At 9 months, normal development.	
Doxorubicin (62 mg, schedule NS)	Case report	1	Sarcoma, Kaposi	3 rd	Vinblastine, Bleomycin	Vaginal	33-34	Female infant: 1,150 g, Apgar scores 6, 7, and 9 at 1, 5, and 10 minutes. Newborn was < 10 th percentile for weight, length, and head circumference, blood count and gases were normal, and mild hyperbilirubinemia required phototherapy.	At 4 months, apparently well and thriving.	(Rawlinson <i>et al.</i> 1984)
Doxorubicin (50 mg/m ² on day 1, 5 cycles)	Case report	1	Non-Hodgkin lymphoma, SPTCL	2 nd , 3 rd First@wk 20	Cyclophosphamide, Vincristine	Vaginal, induced	36	Female infant: 3,245 g, Apgar scores 9, 9 and 9. Newborn showed no growth retardation, or physical or neurological deficits.	No	(Reimer <i>et al.</i> 2003)
Doxorubicin (50 mg/m ² on day 1 of 3-wk cycles, 4 cycles)	Case report	1	Non-Hodgkin lymphoma, diffuse large B-cell	2 nd	Vincristine, Rituximab, Cyclophosphamide	C-section	33	Infant, sex NS: 2,500 g, Apgar scores 10, 10, and 10. Newborn was healthy.	At 35 months, completely normal growth.	(Rey <i>et al.</i> 2009)
Doxorubicin (50-60 mg/m ² on day 1, cycles were 3 wks apart)	Survey, retrospective	11 of 28	Breast	2 nd and/or 3 rd First@wk 15-33 (group range)	Cyclophosphamide	NS	37 (median); 30-40 (group range)	Intrauterine growth restriction due to placental insufficiency was observed in 1 pregnancy. Individual pregnancy outcomes were not provided. There were no congenital malformations, and none of the infants had a birthweight lower than the 10 th percentile for gestational	No	(Ring <i>et al.</i> 2005)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								age. Another child had a hemangioma on his abdomen deemed not causally related to chemotherapy. Two infants had respiratory distress.		
Doxorubicin (30 mg/m ² for 3 days)	Case report	1	Myoblastoma, malignant granular cell	2 nd First@wk 20	None	--	--	Mother died 6 wks after chemotherapy administration. No fetal autopsy was conducted.	--	(Roboz <i>et al.</i> 1979)
Doxorubicin (50 mg/m ² , 6 cycles, 2 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Vincristine, Etoposide, Bleomycin	NS	37	Male infant: 3,200 g, Apgar scores NS. Newborn was healthy.	At 21 months, well with no evidence of iatrogenic complications.	(Rodriguez and Haggag 1995)
Doxorubicin (Dose/schedule NS)	Case report	1	Adult T-cell leukemia/lymphoma	2 nd , 3 rd First@wk 26	Hydroxyurea, Cyclophosphamide, Vincristine	C-section	~28	Male infant: weight and Apgar scores NS. Newborn was healthy.	No	(Safdar <i>et al.</i> 2002)
Doxorubicin (50 mg/m ² on day 1, 3 cycles, 4 wks apart)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 25	Etoposide, Vinblastine	C-section	36	Female infant: 2,190 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 17 months, normal psychomotor development.	(Sagan <i>et al.</i> 2010)
Doxorubicin (Dose NS, days 1 and 8 every 4 wks, 2 cycles)	Case series	1 of 4 (pt 3)	Breast	3 rd First@wk 28	Cyclophosphamide, 5-Fluorouracil	Vaginal, induced	37.5	Infant sex NS: 2,200 g, [SGA] , Apgar scores NS. Newborn was normal.	No	(Schotte <i>et al.</i> 2000)
Doxorubicin (Dose NS, every 2 wks, 4 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 24	Cyclophosphamide, Paclitaxel (3 rd)	C-section	36	Oligohydramnios noted in 3 rd trimester following the 4 th treatment with paclitaxel. Infant: 5 lb 4 oz [2,381 g] , sex and Apgar scores NS. Newborn was healthy; echocardiogram and blood count were normal.	No	(Shieh and Mehta 2011)
Doxorubicin (Dose/schedule NS, 5 cycles)	Case report	1	Sarcoma, embryonal	1 st	Ifosfamide X-rays	Vaginal	40	Infant sex NS; 3,300 g, Apgar scores NS. Newborn was normal.	No	(Shufaro <i>et al.</i> 2002)
Doxorubicin (Dose/schedule NS)	Case report	1	Breast	3 rd	Cyclophosphamide	Vaginal	37	Male infant: 3,130 g, Apgar scores NS. Newborn was healthy.	At 12 months, healthy with normal development.	(Skrablin <i>et al.</i> 2007)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (60 mg/m ² every 21 days, 3 cycles)	Case report	1	Cervix, small cell carcinoma	2 nd , 3 rd First@wk 23	Cyclophosphamide	C-section	35	Male infant: 6 lb [2,721 g, normal for age], Apgar scores NS. Newborn was healthy.	No	(Smyth <i>et al.</i> 2010)
Doxorubicin (Dose NS, 3 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Vincristine	Vaginal, induced	36	Female infant: 2,400 g, Apgar scores NS. Newborn was healthy without congenital anomalies.	No	(Soliman <i>et al.</i> 2007)
Doxorubicin (68 mg, schedule NS)	Case report	1	Hodgkin lymphoma	1 st First@wk 4 Last@wk 13	Nitrogen mustard, Vincristine, Procarbazine	--	--	Induced abortion: fetus had 1 missing toe (unilateral) and no cardiac tissue was recoverable; karyotype was normal.	--	(Thomas and Andes 1982) † (abstract only)
Doxorubicin (90 mg, 2 cycles, 3 wks apart (Pt 1) or 6 wks apart (Pt 2))	Case series	2 of 2	Leukemia, AML	2 nd First@wk 24	6-Thioguanine, Cytarabine, Daunorubicin	Vaginal	32	Spontaneous preterm labor and delivery. Female infant: 2,000 g, Apgar scores NS. Newborn had a premature appearance, but was normal with no obvious abnormalities.	At 13 months, feeding and weight gain are satisfactory; developmental milestones have been normal.	(Tobias and Bloom 1980)
			Breast	2 nd , 3 rd First@wk 22 Last@wk 28	Vincristine	Vaginal	31	Spontaneous preterm labor and delivery. Male infant: 1,990 g, Apgar score 10 at 5 minutes. Newborn had a premature appearance, but was healthy with no obvious abnormalities.	At 4 months, satisfactory clinical condition.	
Doxorubicin (60 mg, 3 cycles)	Case report	1	Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Vincristine	Vaginal	Full term	Infant sex NS: 2,860 g, Apgar score 9 at 1 minute. Newborn appeared normal; but the placenta was small (350 g).	At 3 years, normal development, no physical or mental abnormalities.	(Toki <i>et al.</i> 1990)
Doxorubicin (420 mg over 6 cycles, 3 wks apart)	Case series	1 of 2 (Pt 2)	Breast	1 st , 2 nd , 3 rd First@wk 13	5-Fluorouracil, Cyclophosphamide, Methotrexate (3 rd)	C-section	35	Elevation of blood pressure to 150/100. Female infant: 2,260 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn had normal T-cell activity and no evidence of abnormality.	At 24 months, normal growth and development.	(Turchi and Villasis 1988)

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (68 mg, schedule NS, 1-4 cycles)	Survey, retrospective	10 of 17 (Pts 1, 3, 5, 15, 16, 17, 18, 19, 20, and 24 from Table 1)	Breast	3 rd First@wk 32	Cyclophosphamide, 5-Fluorouracil	C-section	36	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.	No	(Ustaalioglu <i>et al.</i> 2010)
			Breast	3 rd First@wk 34	Cyclophosphamide	C-section	39	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Breast	2 nd First@wk 24	Cyclophosphamide	Vaginal	35	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Hodgkin lymphoma	2 nd First@wk 24	Bleomycin, Vinblastine, Dacarbazine	C-section	36	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Hodgkin lymphoma	3 rd First@wk 27	Bleomycin, Vinblastine, Dacarbazine	Vaginal	35	Intrauterine growth restriction. Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Non-Hodgkin lymphoma	3 rd First@wk 29	Cyclophosphamide, Vincristine	Vaginal	35	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Non-Hodgkin lymphoma	3 rd First@wk 29	Rituximab, Cyclophosphamide, Vincristine	Vaginal	35	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Non-Hodgkin lymphoma	3 rd First@wk 32	Cyclophosphamide, Vincristine	Vaginal	40	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Non-Hodgkin lymphoma	2 nd First@wk 27	Rituximab, Cyclophosphamide, Vincristine	Vaginal	35	Infant sex, birth weights, and Apgar scores NS. Newborn did not have a congenital malformation.		
			Sarcoma, soft tissue	3 rd First@wk 32	Cyclophosphamide, Vincristine, Dacarbazine	C-section	33	Infant sex, birth weights, and Apgar scores NS. Newborn was premature and had low birth weight, but no congenital malformations.		

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (Pt 1 – 60 mg/m ² , 3 cycles; Pt 2 – 25 mg/m ² , 3 cycles; Pt 3 – 25 mg/m ² , 2 cycles; Pt 4 – 60 mg/m ² , 2 or 3 cycles)	Survey, retrospective	4 of 62 [62 pts received chemotherapy while pregnant; the number of pts who received doxorubic while pregnant was not provided]	NS	2 nd , 3 rd First@wk 26 Last@wk 32	Cyclophosphamide	NS	NS	Infant sex, birth weights, and Apgar scores NS. Newborn had hip subluxation.	No	(Van Calsteren <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 25 Last@wk 33	Nitrogen mustard, Vincristine, Procarbazine, Bleomycin, Vinblastine	NS	NS	Infant sex, birth weights, and Apgar scores NS. Newborn had pectus excavatum.	No	
				2 nd , 3 rd First@wk 26 Last@wk 30	Nitrogen mustard, Vincristine, Procarbazine, Bleomycin, Vinblastine, Radiation therapy (2 nd)	NS	NS	Infant sex, birth weights, and Apgar scores NS. Newborn had bilateral partial syndactyly of digits 2 and 3.	No	
				2 nd , 3 rd First@wk 22 Last@wk 28	Radiation therapy (1 st , 2 nd), 5-Fluorouracil, Cyclophosphamide	NS	NS	Infant sex, birth weights, and Apgar scores NS. Newborn had doubled cartilage ring in both ears.	No	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Doxorubicin (35 mg/m ² (1 st cycle) or 50 mg/m ² (2 nd cycle) on days 1-2, 2 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd Last@wk 29	Cytarabine, 6-Thioguanine (2 nd), Vincristine (3 rd)	C-section	29	Fetal suffering per ultrasonography and cardiotocography at wk 29. Female infant: 1,000 g, Apgar score 6 at 1 minute. Newborn was macroscopically normal, but had hyaline membrane disease and moderate meningeal hemorrhage, haemogram was normal.	At 3.5 years, she is well with weight in normal range and normal neurological and hematological parameters.	(Veneri <i>et al.</i> 1996)
Doxorubicin (Dose/schedule NS)	Case report	1	Sarcoma	3 rd First@wk 28	Vincristine, Cyclophosphamide	Vaginal	32.5	Spontaneous preterm rupture of membranes and labor. Female infant: 2 lb 14 oz [1,304 g; SGA], Apgar scores 9 and 9. Newborn was viable with no respiratory distress or difficulty feeding.	At 2.5 years, normal neurological and physical development.	(Webb 1980)
Doxorubicin (60 mg/m ² , 3 cycles, 3 wks apart)	Case report	1	Breast	3 rd First@wk 30 Last@wk 33	Vincristine, Methotrexate	Vaginal	33	Spontaneous preterm labor. Female infant: 2,000g, Apgar score 8. Newborn had apnea and asystole immediately after birth. At 3 days, diagnosed with hyaline membrane disease and sepsis (resolved by day 30). Chromosome analysis showed no breaks or excess numerical abnormalities. Placenta had diffuse chorioamnionitis with infiltration by polymorphonucleated cells.	At 2 years, functioning normally.	(Willems <i>et al.</i> 1990)
Doxorubicin (Dose/schedule NS)	Cohort, retrospective	4 of 21 (Pts 15, 16, 18, and 21 from Table 1)	Leukemia, AML	2 nd	Cytarabine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	(Zemlickis <i>et al.</i> 1992b)
			Leukemia, AML	2 nd	Cytarabine, 6-Thioguanine	--	--	Stillbirth at gestation wk 26. C-section postmortem: fetus had bruising and petechiae over multiple areas, otherwise normal.	--	

Appendix C Table 29. Doxorubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Breast	3 rd	5-Fluorouracil, Cyclophosphamide, Tamoxifen	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	
			Ovary	3 rd	Cyclophosphamide, Cisplatin	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight for gestational age.	No	
Doxorubicin (Dose/schedule data limited; Table 1: Pt 31 – 1 cycle Table 2: Pt 41 – 3 cycles)	Survey, retrospective	2 of 48 (Table 1: Pt 31; Table 2: Pt 41)	Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	(Zuazo <i>et al.</i> 1991)
			Non-Hodgkin lymphoma	2 nd First@wk 22	Cyclophosphamide, Vincristine	C-section	37	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	No	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the doxorubicin timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). In order to avoid counting the same cases more than once, we did not include the following studies: (Pizzuto *et al.* 1980, Avilés *et al.* 1990, Merimsky and Le Cesne 1998, Avilés and Neri 2001). The cases in Avilés *et al.* (1990) were not included in the text analysis because they were reported in a subsequent retrospective case series (Avilés *et al.* 1991). Patient #8 from Table 2 in Pizzuto *et al.* (1980) was not included because this case series was reported in Avilés *et al.* (1988). The retrospective case series Avilés and Neri (2001) was not included because it included both new cases and long-term follow-up on previously reported case series (Avilés and Niz 1988, Avilés *et al.* 1991) without individual pregnancy outcomes. The case report by Merimsky *et al.* (1999) was not included in the text tally because this patient (Case 6) was included in a case series by the authors (Merimsky and Le Cesne 1998); the text analysis did include the detailed follow-up data for this infant reported only in the case report (Merimsky *et al.* 1999). Three studies were not included in the text analysis because of a lack of individual data on timing of exposure, co-treatments, and pregnancy outcomes (Janov *et al.* 1992, Kawamura *et al.* 1994, Ibrahim *et al.* 2000). Finally, we did not include abstracts in the text analysis (Thomas and Andes 1982, Cardonick *et al.* 2007).

††Giacalone *et al.* (1999) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; CML = chronic myelogenous leukemia; SPTCL = subcutaneous panniculitis-like T-cell lymphoma; AMSA = amsacrine; ATRA = all-*trans* retinoic acid; behenoyl-ara-C = behenoyl cytosine arabinoside; IT = intrathecal; SGA = small for gestational age.

Appendix C Table 30. Epirubicin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference	
Epirubicin (90 mg/m ² every 3 wks for 5 cycles)	Case report	1	Breast	1 st , 2 nd	Tamoxifen (2 nd , 3 rd), 5-Fluorouracil, Cyclophosphamide, Radiation, analgesic (2 nd)	C-section	35	Signs of premature delivery [spontaneous preterm labor]. Female infant: 2,070 g, Apgar scores 10 at 1 and 5 minutes. Newborn was healthy. All hematological and biochemistry parameters were in normal range.	At 12 months, there was no disorder, congenital abnormality, or disease of the infant.	(Andreadis <i>et al.</i> 2004)	
Epirubicin (Dose/schedule NS)	Case series, retrospective	4 of 18 from Table III (Pts 8, 16, 17, 18)	Non-Hodgkin lymphoma	1 st	[see note in reference column]	Cyclophosphamide, Vincristine, Bleomycin, Cytarabine, Etoposide, Methotrexate	Vaginal	37	Male infant: 2,850 g, Apgar scores NS. Newborn had no malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				3 rd		Cyclophosphamide, Vincristine, Bleomycin	Vaginal	39	Male infant: 3,100 g, Apgar scores NS. Newborn had no malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st		Cyclophosphamide, Vincristine, Bleomycin, Methotrexate, Etoposide, Cytarabine	Vaginal	40	Male infant: 2,800 g [SGA], Apgar scores NS. Newborn had no malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st		Cyclophosphamide, Vincristine, Bleomycin, Cytarabine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Epirubicin (Dose/schedule NS)	Case series, retrospective	4 of 26 from Table 2	Hodgkin lymphoma	NS	Bleomycin, Vincristine, Dacarbazine	NS	NS	Birth weight, group range: 2,800-4,300 g. Infant sex and Apgar scores NS. Individual pregnancy outcomes were not provided.	At 6 to 29 years, learning and educational performances were normal. No congenital, cytogenic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001)†	

Appendix C Table 31. Epirubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Epirubicin (35 mg/m ² weekly for 10 wks)	Case report	1	Breast	2 nd , 3 rd First@wk 17 Last@wk 29	None	C-section	34	Female infant: 2,200 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy, heart and skull ultrasounds appeared normal. The baby was placed in the intensive care unit for 2 days and was sent home after 22 days in normal condition.	At 12 months, she had normal physical and behavioral development. Repeated cardiac ultrasound did not demonstrate any apparent abnormality.	Azim and Peccatori 2008)
Epirubicin (Dose/schedule NS)	Case series	23 of 26	Breast	2 nd	None	NS	28-40 (group range)	Individual pregnancy outcomes were not provided. Of the 23 infants exposed to epirubicin, all were normal except 1 with polycystic kidney.	Follow-up at 0 to 84 months (median=27 months) showed no significant remote adverse events.	(Azim <i>et al.</i> 2008)
Epirubicin (Dose/schedule NS)	Case series	3 of 5 (Pts 1, 2, 3)	Breast	2 nd , 3 rd	5-Fluorouracil, Cyclophosphamide	C-section	36	Infant, sex NS: 2,920 g, Apgar scores greater than 7 at 1 and 5 minutes. Newborn showed normal fetal development with no congenital malformations or intrauterine growth restriction.	No	(Bodner-Adler <i>et al.</i> 2007)
				2 nd , 3 rd	5-Fluorouracil, Cyclophosphamide	Vaginal	38	Infant, sex NS: 2,940 g, Apgar scores greater than 7 at 1 and 5 minutes. Newborn showed normal fetal development with no congenital malformations or intrauterine growth restriction.		
				2 nd , 3 rd	5-Fluorouracil, Cyclophosphamide	C-section	36	Infant, sex NS: 2,530 g, Apgar scores greater than 7 at 1 and 5 minutes. Newborn showed normal fetal development with no congenital malformations or intrauterine growth restriction.		

Appendix C Table 31. Epirubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Epirubicin (Dose/schedule NS)	Survey, registry	5 of 104 infants from Table 2 [The number of pregnant pts was not provided]	Breast	2 nd , 3 rd	5-Fluorouracil, Cyclophosphamide, Docetaxel	NS	35.9 (group mean)	Infant sex NS: 2,667 g (group mean), Apgar scores NS. Four newborns were normal; 1 had a hemangioma of the left eye and talipes [clubfoot] . All newborns had normal body weight for gestational age.	At 0.4 to 3.8 years (n=4), 3 children were normal phenotype; the newborn with the hemangioma had "eye squinting," but was otherwise normal. At 42 months (group mean, n=93), group mean weight was 48 th percentile.	(Cardonick <i>et al.</i> 2010)
Epirubicin (75 mg/m ² at 14-day intervals, 6 cycles)	Case series	1 of 3 (Pt 1)	Breast	2 nd [First@wk 25]	Vinorelbine, 5-Fluorouracil, Cyclophosphamide	C-section	34	Female infant: 2,320 g, Apgar scores 8, 3, and 10 at 1, 3, and 5 minutes. Newborn was normal with no dysmorphic features. Anemia at day 21, resolved.	At 35 months, growth and development were normal.	(Cuvier <i>et al.</i> 1997)
Epirubicin (Dose/schedule NS)	Case series	1 of 32 (Pt 30)	Non-Hodgkin lymphoma	3 rd First@wk 34 Last @wk 37	Cyclophosphamide, Etoposide, Cytarabine, Bleomycin, Vincristine	Vaginal	36	Infant, sex NS: 3,020 g, Apgar scores 9 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
Epirubicin (Dose/schedule NS)	Case report	1	Breast	2 nd , 3 rd First@wk 23 Last@wk 32	None	Vaginal, induced	34	Male infant: 2,510 g, Apgar scores 9 and 10. Neonate was in good condition but spent 3 days in the neonatal unit with hypoglycemia and feeding difficulties. Examination did not detect any chemotherapy-related effects.	No	(Eedarapalli <i>et al.</i> 2007)
Epirubicin (120 mg/m ² every 3 wks for 4 cycles)	Case report	1	Breast	2 nd First@wk 14 Last@wk 25	Paclitaxel (2 nd , 3 rd)	C-section	36	Female infant: 2,280 g, Apgar score 9 at 5 minutes. Newborn was normal. Blood count, chest X-ray, echocardiography, electrocardiogram, brain ultrasound, and electroencephalogram were all normal.	At 36 months, the baby showed normal development and growth.	(Gadducci <i>et al.</i> 2003)

Appendix C Table 31. Epirubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Epirubicin (mean = 70 mg/m ² , range 50-100)	Survey, retrospective	10 of 20 (Pts 1, 2, 3, 11, 12, 14, 16, 17, 19, 20)	Breast	1 st First@wk 4	5-Fluorouracil, Cyclophosphamide	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Giacalone <i>et al.</i> 1999)††
				1 st First@wk 6	Vincristine, Methotrexate	--	--	Spontaneous abortion. [No fetal data reported.]	--	
				2 nd First@wk 23	Cyclophosphamide	--	--	Stillbirth at 26 wks. [No fetal data reported.]	--	
				3 rd First@wk 28	5-Fluorouracil, Cyclophosphamide	C-section	31	Infant sex and weight NS: Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal with no malformations and normal body weight for gestational age, but died at 8 days; cause was not determined.	--	
				3 rd First@wk 29	5-Fluorouracil, Cyclophosphamide	C-section	35	Infant sex and weight NS: Apgar scores 6 and 10 at 1 and 5 minutes. Newborn was normal with no malformations and normal body weight for gestational age, but was leukopenic.	At 18 months, alive and well.	
				3 rd First@wk 31	5-Fluorouracil, Cyclophosphamide	C-section	34	Infant sex and weight NS: Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with normal body weight for gestational age.	At 10 months, alive and well.	
				3 rd First@wk 31	5-Fluorouracil, Cyclophosphamide	C-section	33	Infant sex and weight NS: Apgar scores 6 and 10 at 1 and 5 minutes. Newborn was normal with no malformations and normal body weight for gestational age, but experienced respiratory distress.	At 6 months, alive and well.	
				3 rd First@wk 31	5-Fluorouracil, Cyclophosphamide	C-section	34	Infant sex and weight NS: Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal with no malformations and normal body weight for gestational age.	At 16 months, alive and well.	

Appendix C Table 31. Epirubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd First@wk 32	Cyclophosphamide	C-section	37	Infant sex and weight NS; Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with no malformations.	At 6 months, alive and well.	
				3 rd First@wk 35	5-Fluorouracil, Cyclophosphamide	Vaginal	37	Infant sex and weight NS; Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with no malformations and normal body weight for gestational age.	At 50 months, alive and well.	
Epirubicin (60 mg/m ² every 3 wks for 4 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 23	5-Fluorouracil, Cyclophosphamide	C-section	35	Premature rupture of fetal membranes. Female infant: 3,420 g, Apgar score 8. Newborn had no congenital malformations. Mild, transient tachypnea required oxygen support. All blood exams were in normal range.	No	(Ginopoulos <i>et al.</i> 2004)
Epirubicin (100 mg on days 1, 15, 30, and 45)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 21 Last@wk 28	Vincristine	Vaginal, induced	34	Female infant: 2,320 g, Apgar scores 8 and 8 at 1 and 5 minutes. Newborn appeared normal.	At 4 years, the child appeared normal.	(Goldwasser <i>et al.</i> 1995)
Epirubicin (Dose/schedule NS)	Survey, retrospective	2 of 16 (Pts 2, 4)	Breast	2 nd , 3 rd	None	C-section	35	Infant, sex NS: 2,540 g, Apgar score NS. Newborn had rectal atresia.	No	(Halaska <i>et al.</i> 2009) [†]
				2 nd , 3 rd	None	Vaginal	39	Infant, sex NS: 3,740 g, Apgar score NS. Newborn was normal.		
Epirubicin (Dose/schedule NS, 2 cycles)	Case report	1	Breast	1 st First@wk 2 Last@wk 5	Cyclophosphamide (1 st , 2 nd), 5-Fluorouracil (1 st , 2 nd), Methotrexate (2 nd), Radiation therapy	--	--	Induced abortion at gestation wk 19: Male fetus: 280 g (50 th percentile for gestational age). Fetal examination revealed micrognathia, skin syndactyly of the 1 st and the 2 nd fingers of both hands, shortened 2 nd and 3 rd fingers, and clinodactyly of the 5 th finger; both feet had a broad forefoot with a short 1 st toe and osseous syndactyly of the 4 th and the 5 th metatarsal bones.	--	(Leyder <i>et al.</i> 2010)

Appendix C Table 31. Epirubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Epirubicin (75 mg/m ² every 3 wks for 3 cycles)	Case series	2 of 4 (Pts 3, 4)	Breast	2 nd , 3 rd First@wk 21 Last@wk 27	5-Fluorouracil	C-section	34	Female infant: 2,790 g, Apgar score 10 at 1 minute. Newborn had no congenital anomalies or intrauterine growth retardation.	At 3.5 years, physical development was normal with normal neurological, psychological, and hematological functions.	(Mathelin <i>et al.</i> 2005)
				2 nd , 3 rd First@wk 25 Last@wk 32	5-Fluorouracil	Vaginal	35	Female infant: 3,690 g, Apgar score 10 at 1 minute. Newborn had no congenital anomalies or intrauterine growth retardation.	No	
Epirubicin (50 mg/m ² , 2 cycles)	Case report	1	Breast	3 rd	Cyclophosphamide, 5-Fluorouracil	C-section	35	Eclamptic seizures at wk 35 Infant sex NS: 1,650 g [SGA], Apgar scores NS. Newborn had no malformations.	No	(Muller <i>et al.</i> 1996)
Epirubicin (35 mg/m ² , median of 12 weekly doses)	Case series	20 of 20	Breast	NS	None	NS	35 (group median) 28-40 (group range)	Individual pregnancy outcomes were not provided. Of the 20 infants exposed to epirubicin, all were normal except 1 with polycystic kidney.	Follow-up at 0 to 4 years (median = 2 years), all 20 showed normal neurological and immunological development.	(Peccatori <i>et al.</i> 2009)† [This case series was included in Azim <i>et al.</i> (2008)].
Epirubicin (Dose/schedule NS)	Cohort, retrospective	1 of 14 (Pt 9)	Leukemia, ALL	2 nd First@wk 19	Vincristine	--	--	Fetal death [stillbirth] at gestation wk 30. [No further information.]	--	(Peres <i>et al.</i> 2001)
Epirubicin (60-100 mg/m ² on day 1, every 3 wks)	Survey, retrospective	5 of 28	Breast	2 nd and/or 3 rd First@wk 15-33 (group range)	Cyclophosphamide	NS	37 (median); 30-40 (group range)	Intrauterine growth restriction due to placental insufficiency was observed in 1 pregnancy. Individual pregnancy outcomes were not provided. There were no congenital malformations, and none of the infants had a birthweight lower than the 10 th percentile for gestational age. Another child had a hemangioma on his abdomen deemed not causally related to chemotherapy. Two infants had respiratory distress.	No	(Ring <i>et al.</i> 2005)

Appendix C Table 31. Epirubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Epirubicin (100 mg, 2 cycles, 3 wks apart)	Case report	1	Breast	3 rd First@wk 31 Last@wk 34	5-Fluorouracil, Cyclophosphamide, Radiation therapy	Vaginal	36	Spontaneous preterm labor. Female infant: 1,889 g [SGA], Apgar score 9 at 5 minutes. Newborn had no congenital anomalies.	At 6 wks, she was doing well.	(Sharma <i>et al.</i> 2009)
Epirubicin (Dose/schedule NS, 3 cycles)	Survey, retrospective	1 of 27 (Pt 2)	Breast	3 rd First@wk 32	5-Fluorouracil Cyclophosphamide	C-section	40	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
Epirubicin (1 st Pt – 100 mg/m ² , 6 cycles; 2 nd Pt – dose NS, 4 cycles)	Survey, retrospective	2 of 62 [62 pts received chemotherapy while pregnant; the number of pts who received epirubicin while pregnant was not provided]	NS	2 nd , 3 rd First@wk 20 Last@wk 35	5-Fluorouracil, Cyclophosphamide	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had bilateral small protuberance on phalanx 5.	No	(Van Calsteren <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 23 Last@wk 32	None	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had rectal atresia.		

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the epirubicin timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of the fetus or infant.

†This paper was not included in the tally of pregnancy outcomes (highlighted in light grey). The 20 cases in Peccatori *et al.* (2009) were also reported among the 23 cases in Azim *et al.* (2008); thus, we did not count Peccatori *et al.* (2009). Likewise, 2 cases reported in a retrospective survey (Halaska *et al.* 2009) were not counted because they were included in a subsequent retrospective survey by Van Calsteren *et al.* (2010).

††Giacalone *et al.* (1999) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia; SGA = small for gestational age.

Appendix C Table 32. Etoposide – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Etoposide (100 mg/m ² 3 times a day per cycle, 4 28-day cycles)	Case report	1	Neuroblastoma	2 nd , 3 rd	Cisplatin	C-section	35	Intrauterine growth restriction at 35 wks of gestation. Male infant: 1,825 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn showed no evidence of neutropenia or other post-chemotherapy sequelae. A brainstem auditory-evoked response was normal.	At 20 days, normal.	(Arango <i>et al.</i> 1994)
Etoposide (Dose/schedule NS)	Case series, retrospective	5 of 18 from Table III (Pts 3, 8, 13, 14, 17)	Non-Hodgkin lymphoma	2 nd [see note in reference column]	Cyclophosphamide, Doxorubicin, Vincristine, Methotrexate	Vaginal	40	Male infant: 3,200 g Apgar scores NS. Newborn had no congenital malformations.	At 15 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				1 st	Cyclophosphamide, Epirubicin, Vincristine, Bleomycin, Cytarabine, Methotrexate	Vaginal	37	Male infant: 2,850 g Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Doxorubicin, Etoposide, Methotrexate	Vaginal	37	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Doxorubicin, Vincristine, Bleomycin, Cytarabine, Methotrexate	Vaginal	40	Female infant: 4,000 g Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st	Cyclophosphamide, Epirubicin, Vincristine, Bleomycin, Methotrexate, Cytarabine	Vaginal	40	Male infant: 2,800 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Etoposide (Treatment schedules NS; Pt 5, 700 mg Pt 8, 600 mg Pt 12, 450 mg Pt 13, 700 mg Pt 14, 650 mg)	Case series	5 of 16 (Pts 5, 8, 12, 13, 14)	Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Methotrexate	NS	35-39 (group range)	Individual pregnancy outcomes are not provided. Birth weights were 2,200-3,900 g (group range). All babies were born alive, and none of the newborns showed apparent congenital malformations.	Authors state that at ages ranging from 3 to 11 years, all showed normal growth and development.	(Avilés <i>et al.</i> 1990)†
				3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Methotrexate	NS				
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Methotrexate, Cytarabine	NS				
				3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Methotrexate	NS				
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Methotrexate	NS				

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Etoposide (Dose/schedule NS)	Case series, retrospective	1 of 20 pregnancies [1 of 18 Pts] (Case 20)	Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, 6-Mercaptopurine, Methotrexate	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	(Avilés and Niz 1988)
Etoposide (100 mg/m ² daily for 5 days, 4 cycles)	Case report	1	Ovary	2 nd	Bleomycin, Cisplatin	C-section	36	Intrauterine growth restriction. At 36 wks, severe preeclampsia. Male infant: 1,560 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no gross malformations.	At 21 months, no evidence of minor or major malformations and normal growth and development.	(Benjapibal <i>et al.</i> 2010)
Etoposide (Dose NS; given on days 1 and 2 of an 8-day regimen, 4 cycles)	Case report	1	Choriocarcinoma, uterus	NS [2 nd] [First@> 20 wks]	Methotrexate, Actinomycin D, Cyclophosphamide, Vincristine	Vaginal	32	Spontaneous preterm delivery [spontaneous preterm labor]. Female infant: 1,383 g, Apgar scores 8 and 9. Newborn was developmentally normal.	At 42 months, normal development.	(Brudie <i>et al.</i> 2011)
Etoposide (100 mg/m ² daily for 5 days at 3-4 wk intervals)	Case series	1 of 3	Ovary	2 nd , 3 rd First@wk 26	Cisplatin	Vaginal, induced	38	Oligohydramnios and probable intrauterine growth retardation at 38 wks of gestation. Female infant: 2,320 g [SGA], Apgar scores NS. Newborn was healthy. Placenta had foci of villous edema.	At 9 months, developing normally.	(Buller <i>et al.</i> 1992)
Etoposide (Dose/schedule NS)	Survey, registry	1 of 31 from Table 3	Non-Hodgkin lymphoma	3 rd	Cytarabine, Cisplatin	NS	34.0 (group mean)	Infant sex NS: 2,576 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestation age.	At 2 months, normal phenotype. At 34 to 82 months (group range, n=6), group mean weight was 46 th percentile.	(Cardonick <i>et al.</i> 2010)
		3 of 9 from Table 4	Ovary	2 nd , 3 rd	Bleomycin, Cisplatin	NS	38.1 (group mean)	Infant sex NS: 2,639 g (group mean), Apgar scores NS. Two newborns were normal with normal body weight for gestational age. One newborn	At 63.3 months (group mean, n=7), 1 child had motor/language delay; group mean weight was 35 th percentile.	

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								had a genetic hearing loss (both parents were carriers), intrauterine growth retardation, and a spontaneous mutation for neurofibromatosis.		
Etoposide (Dose/schedule NS)	Survey, retrospective	1 of 37 (Pt 12)	Leukemia, AML	2 nd (Diagnosis @wk 16)	Daunorubicin, Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005)
Etoposide (Dose/schedule NS)	Case series	2 of 32 (Pts 20, 30)	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 24 Last@wk 37	Doxorubicin, Cyclophosphamide, Cytarabine, Bleomycin, Vincristine	C-section	35	Infant, sex NS: 1,980 g, Apgar scores 8 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
				3 rd First@wk 34 Last@wk 37	Epirubicin, Cyclophosphamide, Cytarabine, Bleomycin, Vincristine	Vaginal	36	Infant, sex NS: 3,020 g, Apgar scores 9 and 9. Newborn was healthy.	No	
Etoposide (100 mg/m ² for 5 days of wk 1 of 3-wk cycle)	Case report	1	Ovary	2 nd First@wk 25 + 5 days	Cisplatin, Bleomycin	C-section	28 + 1 day	Mild to moderate bilateral ventriculomegaly at 26 wks of gestation + 5 days. Female infant: 1,085 g, Apgar scores 7 and 8. Newborn had mild to moderate respiratory distress syndrome and apnea of prematurity. Newborn also had profound ventriculomegaly and cerebral atrophy.	No	(Elit <i>et al.</i> 1999)
Etoposide (100 mg/m ² , 5 days per wk for 3 cycles)	Case report	1	Ovary	3 rd	Bleomycin, Cisplatin	C-section	36	Oligohydramnios and estimated fetal weight < 5 th percentile observed 2 wks after last dose [age NS] . Male infant: 2,000 g [SGA] , Apgar score 9-10 at 15 minutes. Newborn had a normal appearance with a mild glandular hypospadias and an otherwise normal appearance.	At 1 month, ultrasound of the brain and kidney were normal, as were hearing studies and eudiometry. At 8 months, normal physical and neurological development.	(Ghaemmaghami <i>et al.</i> 2009)

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Etoposide (100 mg/m ² for 5 days every 21 days, 5 cycles)	Case series	1 of 3 (Pt 2)	Ovary	2 nd , 3 rd First@wk 18	Bleomycin, Cisplatin	C-section	35	Premature rupture of membranes. Infant, sex NS: 2,400 g, Apgar scores 7 and 9 at 1 and 5 minutes.	At 1 year, the infant was developmentally normal.	(Ghaemmaghami and Hasanzadeh 2006)
Etoposide (100 mg/m ² for 5 days every 4 wks, 5 cycles) (2 nd patient the same but for 2 cycles)	Case series	2 of 2	Ovary	2 nd , 3 rd First@wk 22	Bleomycin, Cisplatin	Vaginal	40	Small for gestational age fetus. Male infant: 2,610 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no gross malformations.	At 1 month, brain and kidneys were normal by ultrasound. At 6 years, the child had normal physical and neurological development.	(Han <i>et al.</i> 2005)
				3 rd First@wk 30	Bleomycin, Cisplatin	Vaginal, induced	38	Male infant: 2,970 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no evidence of gross malformations.	At 7.5 months, he had an intussusception; at 26 months, normal physical and neurological development.	
Etoposide (100 mg/m ² (or 170 mg) on days 1-3 of a 28-day cycle, 3 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 21 Last@wk 29	Bleomycin, Cisplatin	Vaginal, induced	39	Mild preeclampsia. Female infant: 2,769 g, Apgar scores 4 and 7 at 1 and 5 minutes. Newborn was anemic; no fetal anomalies were identified.	Normal development as assessed by the Child Development Assessment Team [age NS].	(Horbelt <i>et al.</i> 1994)
Etoposide (100 mg/m ² daily for 5 days)	Case report	1	Leukemia, AML	2 nd , 3 rd	Daunorubicin, Cytarabine, Mitoxantrone	C-section	36	Intrauterine growth restriction. Intermittent sinusoidal fetal heart rate patterns at 36 wks of gestation [fetal distress]. Male infant: 1,046 g [SGA], Apgar scores 2 and 7 at 1 and 5 minutes. Newborn was underweight and pancytopenic.	At 2 months, child is in good health.	(Hsu <i>et al.</i> 1995)
Etoposide (100 mg/m ² for 5 days every 3 wks, 2 cycles)	Case report	1	Ovary	3 rd First@wk 29	Bleomycin, Cisplatin	C-section	39	Female infant: 3,100 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no abnormalities.	At 1 month, brain and kidneys were normal by ultrasound. At 1.5 years, the infant showed normal physical and neurological development.	(Karimi Zarchi <i>et al.</i> 2008)

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Etoposide (100 mg/m ² for 3 days every 3 wks, 4 cycles)	Case report	1	Lung	3 rd First@wk 27	Cisplatin	C-section	34	Male infant: weight not NS, Apgar scores 9 and 9. Newborn was normal.	No	(Kluetz and Edelman 2008)
Etoposide (Dose/schedule NS, 4 cycles)	Case series	3 of 27	Ovary	2 nd and/or 3 rd First@wk 22, 8-30.6 (group range)	Bleomycin, Cisplatin	NS	Full term	Individual pregnancy outcomes NS. Newborns were healthy with no congenital malformations.	No	(Kwon <i>et al.</i> 2010)
Etoposide (60 mg/m ²)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 26 Last@wk 29	Cyclophosphamide, Vincristine, Doxorubicin, Cytarabine, Ifosfamide	C-section	32	Male infant: 1,731 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no anomalies, but was cyanotic and experienced respiratory distress.	At 1 year, he was healthy with mildly delayed motor skills, thought to result from premature birth.	(Lam 2006)
Etoposide (Dose/schedule NS)	Case series	2 of 15 (Pts 9, 15)	Ovary	2 nd	Cisplatin	NS	NS	Infant sex NS: 3,190 g, Apgar scores NS. Newborn was healthy with no malformations.	No	(Machado <i>et al.</i> 2007)
				2 nd	Cisplatin	NS	NS	Infant sex NS: 2,200 g, Apgar scores NS. Newborn was healthy with no malformations.	No	
Etoposide (Dose/schedule NS)	Case series	1 of 2 (Pt 2)	Ovary	2 nd First@wk 20	Bleomycin, Cisplatin	C-section	31	Infant, sex, weight, Apgar scores NS. Newborn required intensive care for hyaline membrane disease [respiratory distress syndrome].	No	(Malhotra and Sood 2000)
Etoposide (180 mg, 5 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd Last@wk 35	Cyclophosphamide, Doxorubicin, Vincristine, Bleomycin, Methotrexate	Vaginal	35.5	Spontaneous preterm labor after last chemotherapy dose. Male infant: birth weight in the 75 th percentile for gestational age, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no apparent physical anomalies.	At 11 months, the infant was alive and well.	(Moore and Taslimi 1991)

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Etoposide (400 mg/m ² for 3 days, 2 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25	Cytarabine, Daunorubicin	C-section	32	No fetal growth from 30-32 wks of gestation. Female infant: 1,460 g, Apgar scores NS. Newborn was very pale and required active resuscitation, and was anemic and neutropenic. She required ventilation for 10 hours. With treatment, the hematological abnormalities resolved by day 4. Cerebral ultrasound was normal, as was the rest of her neonatal course.	At 1 year, she remained well with normal peripheral blood counts.	(Murray <i>et al.</i> 1994)
Etoposide (Dose/schedule NS)	Cohort, retrospective	2 of 14 (Pts 1, 11)	Hodgkin lymphoma	2 nd First@wk 26	Cisplatin, Cytarabine	NS	36	Infant sex and Apgar scores NS: 2,540 g. Newborn complications limited to jaundice and non-hemolytic anemia.	No	(Peres <i>et al.</i> 2001)
			Non-Hodgkin lymphoma	2 nd First@wk 22	Cisplatin	--	--	Fetal death [stillbirth] at gestation wk 26 . No malformations.	--	
Etoposide (60 mg/m ² for 5 days, 2 cycles)	Case report	1	Burkitt lymphoma	2 nd First@wk 16	Cyclophosphamide, Doxorubicin, Ifosfamide, Cytarabine, Vincristine, Rituximab	--	--	Fetal ultrasounds noted decreased amniotic fluid at gestation wk 18 and early intrauterine growth restriction at gestation wk 22; similar effects at 23.5 wks of gestation. At 68 days of treatment, vaginal bleeding, spontaneous preterm labor, and no fetal heart tones. Stillbirth at gestation wk 26. [No fetal data reported.]	--	(Peterson <i>et al.</i> 2010)
Etoposide (Dose/schedule NS, 2 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 23 Last@wk 31	Cisplatin	C-section	39	Male infant: 3,130 g, Apgar scores 10, 10, and 10. Newborn had a normal aspect [no malformations], and clinical examinations were normal.	No	(Poujade <i>et al.</i> 2008)††

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Etoposide (165 mg per day for 3 days)	Case report	1	Adenocarcinoma (primary not located)	2 nd First@wk 26	Bleomycin, Cisplatin	Vaginal	27	Spontaneous preterm labor. Female infant: 1,190 g, Apgar scores 3 and 8 at 1 and 5 minutes. Infant developed severe respiratory distress and pneumothorax, (on room air by day 10). Infant developed a profound leucopenia with neutropenia by day 3 (resolved by day 13). Blood transfusions for anemia associated with immaturity were required twice. Platelet count fell, but the infant never became frankly thrombocytopenic. No demonstrable neurological abnormality, and cerebral ultrasound remained normal throughout the neonatal period. At the age of 10 days, infant was noted to be losing her scalp hair, and there was an associated rapid loss of lanugo.	At 1 year, neurodevelopmental progress was normal, but there was moderate sensorineural hearing loss.	(Raffles <i>et al.</i> 1989)
Etoposide (125 mg/m ² every other wk of 2-wk cycle, 6 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Vincristine, Bleomycin	NS	37	Male infant: 3,200 g, Apgar scores NS. Newborn was healthy.	At 21 months, well with no evidence of iatrogenic complications.	(Rodriguez and Haggag 1995)
Etoposide (110 mg/m ² daily for 2 days, 3 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 25	Vinblastine, Doxorubicin	C-section	36	Female infant: 2,190 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 17 months, in good clinical condition with normal psychomotor development and no malignancies.	(Sagan <i>et al.</i> 2010)

Appendix C Table 33. Etoposide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Etoposide (400 mg/m ² for 3 days per cycle, number of cycles NS)	Case report	1	Leukemia, AML	2 nd or 2 nd , 3 rd [First@> wk 25]	Daunorubicin, Cytarabine	C-section	32	Serial ultrasounds detected reduced amniotic fluid and no fetal growth gain at 32 wks of gestation. Female infant: 1,460 g, Apgar scores NS. Newborn was very pale and required active resuscitation, also exhibited myelosuppression. She made good progress and was discharged at 46 days.	No	(Scherf and Price 1996)
Etoposide (2 oral doses of 25 mg/m ² daily for 10 consecutive days, 2 cycles)	Case report	1	Rhabdomyosarcoma, alveolar	3 rd First@wk 28 + 1 day	Idarubicin, Trofosfamide	C-section	34 + 1 day	Male infant: 1,790 g [SGA], Apgar scores 9, 9, and 9 at 1, 5, and 10 minutes. Newborn was healthy; echocardiography and ultrasound revealed no abnormalities.	At 2.25 years, no evidence of malformations and normal neurological development.	(Siepermann <i>et al.</i> 2012)
Etoposide (100 mg/m ² /day on days 1 and 4 of a 21-day cycle, 3 days)	Case report	1	Ovary	3 rd	Cisplatin	C-section	38	Intrauterine growth retardation. Male infant: 2,180 g [SGA], Apgar scores were 8 at 1 minute and 9 at 5 minutes. Newborn had no gross fetal anomalies, but did have hypoglycemia and hyperbilirubinemia.	[At age ~14 months,] normal growth.	(Tseng and ChangChien 2004)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the etoposide timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). The cases in Aviles *et al.* (1990) were not included in the text analysis because they were reported in a subsequent retrospective case series (Avilés *et al.* 1991).

††Poujade *et al.* (2008) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; SGA = small for gestational age.

Appendix C Table 34. Hydroxyurea – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Hydroxyurea (Dose/schedule NS)	Case report	1	Leukemia, CML	2 nd First@wk 19	Imatinib (2 nd , 3 rd)	Vaginal, induced	39	Male infant: 2,740 g [SGA], Apgar score 5. Newborn was healthy with blood count and biochemical analyses in normal limits.	At 10 months, growth and development were normal.	(Ali <i>et al.</i> 2009b)
Hydroxyurea (Dose/schedule NS)	Case series	3 of 10 (Pts 1, 5, 7)	Leukemia, CML	2 nd or 3 rd	Imatinib (1 st),	Vaginal	37	Male infant: 6 lb 13 oz [3,540 g], Apgar scores NS. Newborn had hypospadias at birth (surgically corrected later), but otherwise healthy.	At 53 months, growth and development were normal.	(Ault <i>et al.</i> 2006)† [These cases are included in Pye <i>et al.</i> (2008).]
			Leukemia, CML	1 st	Imatinib	Vaginal	40	Female infant: 6 lb 12 oz [3,477 g]. Newborn was healthy.	At 16 months, growth and development were normal.	
			Leukemia, CML	1 st	Imatinib	C-section	36	Twin female infants: 5 lb, 13 oz [3,086 g] and 5 lb, 5 oz [2,586 g]. Apgar scores NS. Newborns were healthy.	At 18 months, growth and development were normal.	
Hydroxyurea (1,500 mg/day)	Case report	1	Leukemia, CML	2 nd , 3 rd	Interferon-alpha (3 rd)	C-section	37	Female infant: 2,450 g, Apgar scores NS. Newborn was normal and physically healthy.	No	(Baykal <i>et al.</i> 2000)
Hydroxyurea (0.5 g twice/day, 1 st dose; increased to 0.5 g thrice/day on 1 st wk)	Case report	1	Leukemia, CML	2 nd , 3 rd	None	C-section	38	Female infant: 3,400 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn white blood count, erythrocyte and thrombocyte counts were normal	At 4 months, infant was healthy.	(Celiloglu <i>et al.</i> 2000)
Hydroxyurea (Dose/schedule NS)	Case report	1	Leukemia, CML	2 nd , 3 rd	Imatinib (1 st)	Vaginal	34	Stillborn fetus with meningocele.	--	(Choudhary <i>et al.</i> 2006)†
Hydroxyurea (Dose/schedule NS)	Case series	1 of 32 (Pt 1)	Leukemia, CML	2 nd , 3 rd First@wk 27	Interferon-alpha (2 nd)	C-section	36	Twin infants, sex NS: 2,390 g and 2,250 g, Apgar scores 8 and 9 for both infants. Newborns were healthy.	No	(De Carolis <i>et al.</i> 2006)
Hydroxyurea (1,500 mg/day)	Case series	2 of 3 (Pts 2, 3)	Leukemia, CML	1 st , 2 nd , 3 rd	None	NS	26	Eclampsia at wk 26. Stillborn male fetus with normal phenotype.	--	(Delmer <i>et al.</i> 1992)

Appendix C Table 35. Hydroxyurea (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	40	Male infant: 3,200 g, Apgar scores NS. Newborn was healthy with a normal phenotype.	No	
Hydroxyurea (Dose/schedule NS)	Case series	1 of 18 (Pt 6)	Leukemia, CML	1 st , 2 nd , 3 rd	None	C-section	28	Vaginal bleeding due to detachment of the placenta at wk 28. Male infant: 1,800 g, Apgar scores NS. Newborn had no abnormalities, with normal body weight for gestational age, and hematological values were normal. He died at 10 days of intracranial bleeding.	--	(Dilek <i>et al.</i> 2006)
Hydroxyurea (Dose/schedule NS)	Case report	1	Leukemia, CML	2 nd , 3 rd	Imatinib (1 st , 2 nd)	NS	37	Infant sex NS: 3,120 g, Apgar scores 9 and 10. Newborn was healthy and without birth defects.	At 26 months, no late side effects.	(Dolai <i>et al.</i> 2009)
Hydroxyurea (8 g [1 time])	Case series	2 of 3 (Pts 2, 3)	Leukemia, AML	2 nd	Daunorubicin, Cytarabine, Vincristine, 6-Thioguanine	--	--	Induced abortion at gestation wk 21. Male fetus: 307.8 g. Fetus had no external defects or gross abnormalities in organogenesis, and had normal organ weights, except for an enlarged spleen.	--	(Doney <i>et al.</i> 1979)
				3 rd	Daunorubicin, Cytarabine, Vincristine, 6-Thioguanine	Vaginal	31	Spontaneous preterm labor at 4 wks after admission. Male infant: 2,130 g, Apgar scores 7 and 8 at 1 and 5 minutes. During the first 2 days the premature newborn was hyponatremic, hyperkalemic, hypocalcemic, and hypoglycemic – resolved within 7 months.	At 4 months, experiencing mild infections. At 4.5 and 13.5 months, Denver Developmental Screening tests were normal. At 13.5 months, complete blood count and general physical examination were unremarkable, but growth parameters were depressed (< 3 rd percentile).	

Appendix C Table 35. Hydroxyurea (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Hydroxyurea (4 g/day for 3 wks, then 1.5-3 g/day)	Case report	1	Leukemia, CML	3 rd	None	Vaginal	38	Male infant: 2,680 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was healthy with no abnormality.	At 1 month, continued to do well.	(Fadilah <i>et al.</i> 2002)
Hydroxyurea (Dose/schedule NS)	Case report	1	Leukemia, CML	2 nd , 3 rd (1 month prior to due date)	None	C-section	Term	Male infant: 3,400 g, Apgar scores NS. Newborn had no perinatal complications.	Growth and development appeared normal to date [age NS].	(Fitzgerald and McCann 1993)
Hydroxyurea (Dose/schedule NS)	Case report	1	Leukemia, CML	3 rd	Imatinib (1 st)	Vaginal	38	Female infant: 2,820 g, Apgar scores NS. Newborn was healthy and morphologically normal. Pyloric stenosis developed at 8 wks (resolved with surgery).	At 25 months, healthy and developing normally.	(Heartin <i>et al.</i> 2004)†
Hydroxyurea (0.5 to 1.5 g/day, increased to 3.0 g/day at 20 wks)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	C-section	37	Female infant: 2,850 g, Apgar score 9 at 5 minutes. Newborn had no perinatal complications and no abnormalities.	At 5 months, development was normal.	(Jackson <i>et al.</i> 1993)
Hydroxyurea (Dose/schedule NS)	Case series	4 of 32	Leukemia, CML	NS First@wk 12-33, 22 (mean)	None	NS	NS	Infants' sex, weight and Apgar scores NS. Newborns were alive and healthy; no malformations were observed.	At follow-up, normal growth patterns without physical or neurological deficits (n=5 children; oldest child is 42 months).	(Jameel and Jamil 2007)
Hydroxyurea (1,000-3,000 mg/day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd First@wk 12	Dasatinib (1 st), Cytarabine	Vaginal, induced	34 + 6 days	Female infant: 2,470 g, Apgar scores NS. Newborn was healthy.	At 11 months, she was healthy without structural or functional anomalies or developmental delay.	(Kroll <i>et al.</i> 2010)
Hydroxyurea (500 mg, 4 times a day, later increased to 5 times a day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd First@wk 10 Last@wk 37	Imatinib (1 st)	Vaginal, induced	37	Female infant: 2,500g, Apgar scores NS. Newborn had no congenital abnormalities.	At 1 year, normal growth and development	(Martin <i>et al.</i> 2011)
Hydroxyurea (0.5-1.0 g/day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	36	Spontaneous preterm labor. Male infant: 2,670 g, Apgar scores NS. Newborn was healthy with normal blood counts and no perinatal complications.	At 26 months, he was physically and developmentally normal.	(Patel <i>et al.</i> 1991)

Appendix C Table 35. Hydroxyurea (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Hydroxyurea (Dose/schedule NS)	Cohort, retrospective	2 of 14 (Pts 5, 6)	Leukemia, CML	2 nd First@wk 22	None	NS	39	Infant sex and Apgar scores NS: 3,800 g. Newborn had no complications.	At 4 years, development was normal.	(Peres <i>et al.</i> 2001)
				1 st	Vincristine (2 nd), Doxorubicin (2 nd)	NS	35	Infant sex and Apgar scores NS: 3,195 g. Newborn had no complications apart from jaundice.	At 4 months, development was normal.	
Hydroxyurea (Dose, schedule NS)	Survey retrospective	6 of 180 [only 125 pts reported pregnancy outcomes; did not include co-treatments of normal pregnancies]	Leukemia, CML	1 st	Imatinib	[Vaginal]	[40]	One normal infant. [Reported in Ault <i>et al.</i> (2006).]	[At 16 months, normal growth and development.]	(Pye <i>et al.</i> 2008) [This survey retrospective includes: 3 cases presented by Ault <i>et al.</i> (2006), 1 case reported by Heartin <i>et al.</i> (2004); and 1 case reported by Choudhary <i>et al.</i> (2006).]
			Leukemia, CML	1st	Imatinib	[C-section]	[36]	Twins, normal. [Twins were first reported in Ault <i>et al.</i> (2006).]	[At 18 months, normal growth and development.]	
			Leukemia, CML	2 nd and/or 3rd	Imatinib (1 st)	NS	34	Stillbirth. Meningocele. [First reported in Choudhary <i>et al.</i> (2006).]	--	
			Leukemia, CML	1 st , 2 nd , 3 rd	Imatinib (1 st)	NS	NS	Live birth. Premature closure of skull sutures.	No	
			Leukemia, CML	[2 nd or 3 rd]	Imatinib (1 st)	NS	[37]	Live birth. Hypospadias. [First reported in Ault <i>et al.</i> (2006).]	[At 53 months, normal growth and development.]	
			Leukemia, CML	2 nd and/or 3rd	Imatinib (1 st)	NS	[38]	Live birth. Pyloric stenosis. [First reported in Heartin <i>et al.</i> (2004).]	No	
Hydroxyurea (1 g, schedule NS)	Case report	1	Adult T-cell leukemia/lymphoma	2 nd , 3 rd First@wk 26	Cyclophosphamide, Doxorubicin, Vincristine	C-section	~28	Male infant: weight and Apgar scores NS. Newborn was healthy.	No	(Safdar <i>et al.</i> 2002)
Hydroxyurea (0.5 g twice daily)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	Imatinib (1 st)	Vaginal	38	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 12 months, the infant was healthy.	(Suppiah and Kalaycio 2006)
Hydroxyurea (1-3 g/day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd Last@wk 37	None	C-section	38	Male infant: 3,100 g, Apgar scores NS. Newborn had normal clinical status. Hematological assessments of umbilical cord and fetal blood were normal.	At 32 months, growth and development were normal.	(Tertian <i>et al.</i> 1992)

Appendix C Table 35. Hydroxyurea (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Hydroxyurea (Dose/schedule NS, 3 cycles)	Survey, retrospective	1 of 27 (Pt 13)	Leukemia, CML	2 nd , 3 rd First@wk 25	None	Vaginal	37	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
Hydroxyurea (Dose NS, 9 days)	Cohort, retrospective	1 of 21 (Table 1, Pt 12)	Leukemia, CML	1 st	Daunorubicin, 6-Thioguanine, Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the hydroxyurea timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Paper not included in text analysis (highlighted in light grey). The following 2 case reports and 1 case series were included in a retrospective survey and thus were not tallied separately: (Heartin *et al.* 2004, Ault *et al.* 2006, Choudhary *et al.* 2006).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; CML = chronic myelogenous leukemia; AML = acute myelogenous leukemia; SGA = small for gestational age.

Appendix C Table 36. Idarubicin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Idarubicin (9 mg/m ² on days 1,2,3, and 8)	Case report	1	Leukemia, ALL	2 nd	Cyclophosphamide, Vincristine	C-section	28	Male infant: 1,024 g, Apgar scores of 6, 8, and 8 at 1, 5, and 10 minutes. Newborn had no growth restriction or gross malformations. He had complications linked to prematurity (e.g., respiratory distress, necrotizing enterocolitis, ventricular hemorrhage). Acute cardiac failure, which authors attributed to idarubicin, occurred during the first 3 days after birth. He was treated with dopamine and glycerol nitrate, and cardiac function returned to normal after 3 days.	At 18 months, neurological status was normal but he showed a slight delay in language acquisition.	(Achtari and Hohlfeld 2000)
Idarubicin (Dose/schedule NS)	Case series, retrospective	4 of 29 from Table 1	Leukemia, acute	NS	Cytarabine	NS	NS	Birth weight: 3,085 g (median), 2,500-3,675 g (range). Infants' sex and Apgar scores NS. Individual pregnancy outcomes were not provided.	In this long-term follow-up, ranging from 6 to 29 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001)
Idarubicin (10 mg/m ² on days 2, 3, 4; 1 cycle)	Case report	1	Leukemia, AML	2 nd First@wk 26 Last@wk 26	Cytarabine, Fludarabine, Gemtuzumab-ozogamicin, Mitoxantrone	C-section	33	Fetus developed cardiomyopathy, transient cerebral ventriculomegaly, mild fetal anemia, and intrauterine growth restriction after initiation of chemotherapy. Male infant: 1,695 g, Apgar scores 8 and 9 after 5 and 10 minutes. Newborn had no clinical signs of dysmorphia but was anemic and required bag mask ventilation; transcranial ultrasound and echocardiography detected no abnormalities.	At 6 months, he showed no residual signs of cardiomyopathy or hydrocephalus.	(Baumgartner <i>et al.</i> 2009)

Appendix C Table 37. Idarubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Idarubicin (12 mg/m ² on days 2, 4, 6, 8 in the first cycle; 5 mg/m ² on days 1, 2, 3, 4 in the second cycle)	Case report	1	Leukemia, APL	2 nd , 3 rd	ATRA, Cytarabine (3 rd)	C-section	34	Female infant: 1,950 g, Apgar score NS. Newborn showed no abnormalities following physical examination and routine laboratory tests.	No	(Breccia <i>et al.</i> 2002)
Idarubicin (Dose and schedule NS)	Case report	1	Leukemia, APL	2 nd	ATRA	C-section	28	Ultrasound measured fetal ascites, oligohydramnios, and high umbilical artery resistance, indicating placental insufficiency and intrauterine growth retardation. Premature rupture of membranes. Female infant: 1,475 g, Apgar scores 2, 4, and 6 at 1, 5, and 10 minutes. Newborn was in poor condition with pulmonary hypoplasia, bilateral pneumothoraces, and patent ductus arteriosus; this closed after indomethacin was given.	At 6 months, the baby continued on nasal oxygen and diuretics with significant respiratory effort and poor overall growth.	(Carradice <i>et al.</i> 2002)
Idarubicin (Dose and schedule NS)	Survey, retrospective	3 of 37 from Table 1 (Pts 3, 5, 27) [see note in reference column]	Leukemia, AML	2 nd (Diagnosis @wk 15) (Pt 3)	Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005) [Pts 6 and 24 were not included because it was not possible to determine if they received chemotherapy during pregnancy.]
				1 st (Diagnosis @wk 6) (Pt 5)	Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	
				2 nd (Diagnosis @wk 17) (Pt 27)	Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	
Idarubicin (10 mg/m ² on days 1, 3, 5; 1 cycle)	Case report	1	Leukemia, AML	2 nd First@wk 21	Cytarabine	C-section	33 + 4 days	Intrauterine growth retardation and variable decelerations on fetal tocogram. Female infant, 1,408 g [SGA], Apgar scores 4, 7, 10 at 1, 5, and 10 minutes. Newborn had	No	(Claahsen <i>et al.</i> 1998)

Appendix C Table 37. Idarubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								hyperbilirubinemia but no dysmorphic features or major anomalies. Amniotic fluid was meconium-stained.		
Idarubicin (Dose and schedule NS)	Case series	1 of 32 (Pt 15)	Leukemia, AML	2 nd First@wk 21 Last@wk 25	ATRA	C-section	34	Infant, sex NS: 1,950 g, Apgar scores 8 and 9. Newborn was healthy	No	(De Carolis <i>et al.</i> 2006)
Idarubicin (Dose and schedule NS)	Case report	1	Leukemia, APL	2 nd	ATRA	C-section	31 + 2 days	Male infant: 1,742 g, Apgar scores 5 and 7 at 1 and 5 minutes. Newborn had respiratory distress that required support, as well as jaundice that required phototherapy.	At 2 months, his general health and neurologic condition were good.	(Ganzitti <i>et al.</i> 2010)
Idarubicin (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Doxorubicin, Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Aclarubicin, Cytarabine, Cycloctidine, ATRA, Mitoxantrone, Vincristine, Asparaginase	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994) †
Idarubicin (12 mg/m ² on days 1-3, 1 cycle)	Case report	1	Leukemia, AML	3 rd First@wk 30	Cytarabine (2 nd , 3 rd), Daunorubicin (2 nd)	C-section	32	Oligohydramnios at 32 wks of gestation. Female infant: 1,820 g, Apgar scores 6, 6, and 8 at 1, 5, and 10 minutes. Newborn showed no sign of cardiac failure, and cerebral ultrasound revealed no abnormalities. Newborn developed myelosuppression that required supportive treatment, also hepatopathy and elevated creatinine kinase. These values normalized within a wk. The baby was healthy at time of discharge.	No	(Matsuo <i>et al.</i> 2004)

Appendix C Table 37. Idarubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Idarubicin (12 mg/m ² on days 1-3, 1 cycle)	Case report	1	Leukemia, AML	3 rd First@wk 21	Cytarabine (2 nd , 3 rd)	C-section	37	At gestation wk 26, right ventricle mildly dilated with mild systolic dysfunction and left ventricle mildly smaller than normal with mild systolic dysfunction. Female infant: 1,710 g [SGA], Apgar scores 5 and 9 at 1 and 5 minutes. Newborn showed intrauterine growth restriction, cyanosis of the extremities, shallow sacral dimple, short digits and limbs, dysplastic fingernails, and prominent frontal skull with mild macrognathia, and a ventricular septal defect. Infant had normal ventricular size and function.	At 3 months, fetal defects [other than the heart] seen at birth seemed to have resolved. At 5 months, child recovered quickly from surgery to correct ventricular septal defect.	(Niedermeier <i>et al.</i> 2005)
Idarubicin (12 mg/m ² daily for 3 days, 2 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 16	Cytarabine, Fludarabine (3 rd)	--	--	Fetal death [stillbirth] at gestation wk 34. [No fetal data reported.]	--	(Paşa <i>et al.</i> 2009)
Idarubicin (Dose/schedule NS)	Cohort, retrospective	2 of 14 (Pts 2, 10)	Leukemia, ALL	2 nd First@wk 24 Last@wk 28	Vincristine, Asparaginase	NS	36	Infant sex and Apgar scores NS. Newborn had no complications.	At 2 years, development was normal.	(Peres <i>et al.</i> 2001)
			Leukemia, AML	NS	Cytarabine	--	--	Intrauterine growth restriction and oligohydramnios. Fetal death [stillbirth]. No malformations.	--	
Idarubicin (10 mg/m ² on days 1 and 2)	Case report	1	Leukemia, AML	3 rd	Cytarabine (2 nd , 3 rd), Daunorubicin (2 nd), Mitoxantrone (2 nd , 3 rd)	--	--	Stillbirth: sex NS; 2,200 g. No obvious congenital malformations. No fetal autopsy was performed.	--	(Reynoso and Huerta 1994)
Idarubicin (5 mg/m ² oral on days 1, 4, 7, 10; 2 cycles)	Case report	1	Rhabdomyosarcoma, alveolar	3 rd First@wk 28 + 1 day	Etoposide, Trofosfamide	C-section	34 + 1 day	Male infant: 1,790 g [SGA], Apgar scores 9, 9, and 9 at 1, 5, and 10 minutes. Newborn was healthy; echocardiography and ultrasound revealed no abnormalities.	At 2.25 years, no evidence of malformations and normal neurological development.	(Siepermann <i>et al.</i> 2012)

Appendix C Table 37. Idarubicin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Idarubicin (12 mg/m ² on days 1-3, 4 cycles)	Case report	1	Leukemia, APL	2 nd , 3 rd First@wk 14 Last@wk 32	ATRA	C-section	36.7	Early signs of preeclampsia at 36.7 wks of gestation. Female infant: 2,720 g, Apgar scores 6 and 9 at 1 and 5 minutes. Newborn was not malformed but was treated for transient mild respiratory distress. Infant had moderate dilation of right atrium and right ventricle, 2 small secundum atrial septal defects, and a small patent ductus arteriosus.	At 1.5 months, there was adequate somatic growth and no clinical signs of congestive heart failure. The dilation of the right atrium and right ventricle resolved, the ductus arteriosus had closed, and the secundum atrial septal defects persisted, although they were hemodynamically insignificant.	(Siu <i>et al.</i> 2002)
Idarubicin (Dose NS, 1 cycle)	Case report	1	Leukemia, AML	3 rd First@wk 30	Cytarabine	C-section	33-34	Mild uterine contractions [spontaneous preterm labor] and fetal distress. Male infant: 2,200 g, Apgar scores 2 and 6 at 1 and 5 minutes. Amniotic fluid was meconium-stained.	No	(Yucebilgin <i>et al.</i> 2004)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the idarubicin timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus of infant.

†Paper not included in tally for text summary (highlighted in light grey). Kawamura *et al.* (Kawamura *et al.* 1994) was not included because it did not include individual treatment, timing of exposure, and pregnancy outcomes.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphoblastic leukemia; AML = acute myeloblastic leukemia; APL = acute promyelocytic leukemia; ATRA = all-*trans* retinoic acid; behenoyl ara-C = behenoyl cytosine arabinoside; SGA = small for gestational age.

Appendix C Table 38. Ifosfamide – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Ifosfamide (5 g per day on 2 consecutive days, 2 cycles, 4 wks apart)	Case report	1	Rhabdomyosarcoma	2 nd First@wk 23	Vincristine, Actinomycin D	C-section	29	Anhydramnios and fetal growth restriction at 4 wks after chemotherapy administration. Female infant: 720 g [SGA], Apgar scores 3, 7, and 7 at 1, 5, and 10 minutes. Newborn exhibited anuria and didn't pass urine for 7 days, at which time she died. Postnatal cerebral ultrasound detected bilateral intraventricular hemorrhage and left occipital menigeal hematoma. Autopsy found extensive cerebral lesions associated with prematurity but revealed no renal lesions or chromosome abnormality. Placenta revealed large areas of ischemic necrosis without chorioamnionitis.	--	(Fernandez <i>et al.</i> 1989)††
Ifosfamide (1,500 mg/m ² /day for 5 days)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 26 Last@wk 29	Cyclophosphamide, Vincristine, Doxorubicin, Cytarabine, Etoposide	C-section	32	Male infant: 1,731 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no anomalies, but was cyanotic and experienced respiratory distress.	At 1 year, he was healthy with mildly delayed motor skills, thought to result from premature birth.	(Lam 2006)
Ifosfamide (5 g/m ² every 3 wks for 3 cycles)	Case series	1 of 7 (Pt 6)	Sarcoma, Ewing	2 nd , 3 rd First@wk 27 Last@wk 33	Doxorubicin	C-section	36	Infant sex NS: 1,300 g [SGA], Apgar scores NS. Newborn was normal.	[At 24 months, normal.]	(Merimsky and Le Cesne 1998) [More detailed follow-up on Case 6 was reported in Merimsky <i>et al.</i> (1999)]

Appendix C Table 39. Ifosfamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Ifosfamide (5 mg/m ² every 3 wks, 3 cycles)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd First@wk 27 Last@wk 33	Doxorubicin	C-section	36	Mild intrauterine growth retardation without fetal stress. Female infant: 1,300 g [SGA], Apgar scores NS. Newborn was a small, healthy baby.	At 24 months, she showed no chemotherapy-related late effects.	(Merimsky <i>et al.</i> 1999) [†] [This case report is follow-up on Case 6 in Merimsky <i>et al.</i> (1998), thus this case report was not tallied in the in the text analysis.]
Ifosfamide (5 g/m ² over 48 hours/cycle, 2 cycles, except case 5 received only 1 cycle)	Case series	5	Sarcoma, Ewing	3 rd First@wk 29	Doxorubicin	Vaginal	34	Female infant: 1,400 g [SGA], Apgar scores 8 and 9 at 1 and 5 minutes. Condition of the newborn was considered “favorable.”	Normal at 8 months.	(Mir <i>et al.</i> 2012)
			Osteosarcoma	3 rd First@wk 30	Doxorubicin	Vaginal	35	Female infant: 2,200 g, Apgar scores 9 and 9 at 1 and 5 minutes. Condition of the newborn was considered “favorable.”	Normal at 5 years.	
			Sarcoma, Ewing	3 rd First@wk 30	Doxorubicin	Vaginal	36	Female infant: 2,200 g, Apgar scores 8 and 10 at 1 and 5 minutes. Condition of the newborn was considered “favorable.”	Normal at 3 years.	
			Sarcoma, high-grade	3 rd First@wk 29	Doxorubicin	Vaginal	35 + 5 days	Male infant: 2,300 g, Apgar scores 10 and 10 at 1 and 5 minutes. Condition of the newborn was considered “favorable.”	Normal at 5 years.	
			Sarcoma, high-grade	2 nd First@wk 26	Doxorubicin	C-section	29 + 5 days	Oligohydramnios detected at 29 wks of gestation. Male infant: 1,180 g, Apgar scores 10 and 10 at 1 and 5 minutes. Condition of the newborn was considered “favorable.”	Normal at 5 months.	

Appendix C Table 39. Ifosfamide (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Ifosfamide (2 g/m ² every 3 wks, 3 cycles)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd First@wk 25 Last@wk 30	Doxorubicin	C-section	32	At 28 wks of gestation, mild intrauterine growth retardation and decrease in amniotic fluid. Male infant: 1,245 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn showed no dysmorphic features or anomalies. He was intubated for 1 day for irregular respiratory effort. He received nasal continuous positive airway pressure for 3 days, phototherapy for hyperbilirubinemia, and erythropoietin for low hemoglobin.	At 8 months, he was growing adequately with no known abnormalities.	(Nakajima <i>et al.</i> 2004)
Ifosfamide (1,500 mg/m ² /day, days 25-29 and 70-74)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 16	Cyclophosphamide, Doxorubicin, Etoposide, Cytarabine, Vincristine, Rituximab	--	--	Fetal ultrasounds noted oligohydramnios at gestation wk 18 and early intrauterine growth restriction at gestation wk 22; similar effects at 23.5 wks of gestation. At 68 days of treatment, vaginal bleeding, spontaneous preterm labor, and no fetal heart tones. Stillbirth at gestation wk 26. [No fetal data reported.]	--	(Peterson <i>et al.</i> 2010)
Ifosfamide (Dose/schedule NS, 5 cycles)	Case report	1	Sarcoma, embryonal	1 st	Doxorubicin, X-rays	Vaginal	40	Infant, sex NS: 3,300 g, Apgar scores NS. Newborn was normal.	No	(Shufaro <i>et al.</i> 2002)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the ifosfamide timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Paper not included in text analysis (highlighted in light grey). The infant born to case 6 in Merimsky and Le Cesne (1998) was not included because the pregnancy outcome and follow-up data were described in more detail in (Merimsky *et al.* 1999).

††Fernandez *et al.* (1989) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 40. Imatinib – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Imatinib (Dose/schedule NS)	Case series	2 of 13 (Pts 12, 13)	Leukemia, CML	1 st	None	NS	41	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	(Abellar <i>et al.</i> 2009)
				3 rd	None	NS	40	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.		
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	2 nd , 3 rd First@wk 21 Last@wk 39	Hydroxyurea (2 nd)	Vaginal, induced	39	Male infant: 2,740 g [SGA], Apgar score 5. Newborn was healthy with blood count and biochemical analyses in normal limits.	At 10 months, growth and development were normal.	(Ali <i>et al.</i> 2009b)
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st Last@wk 8	None	Vaginal, induced	38	Female infant: 3,200 g, Apgar score 9. Newborn was healthy. General examination, blood count, ultrasonography (transfontanel, abdominal and hip), echocardiography and chromosomal analysis were normal.	No	(Ali <i>et al.</i> 2005)
Imatinib (Pt 1 – 400 mg/day, Pt 2 – 200 mg/day)	Case series	2 of 2 (Pt 1 had 2 pregnancies)	Leukemia, CML	1 st , 2 nd , 3 rd	None	NS	NS	Infant: 1,870 g, Apgar score was “good.” Newborn was healthy, but small. Normal complete blood count. [Pt 1, 1 st pregnancy]	Infant [age NS] was healthy with normal growth, milestones and blood counts. (Pt 1, 1 st pregnancy)	(AlKindi <i>et al.</i> 2005)
				1 st	None	--	--	Spontaneous abortion. [No fetal data.] [Pt 1, 2 nd pregnancy]	--	
				1 st , 2 nd , 3 rd	None	NS	NS	Infant sex and Apgar scores NS: 2,540 g. Newborn was healthy, but small with normal complete blood count.	No	
Imatinib (Pt: 1 – 300 mg/day 2 – 400 mg/day 3 – 600 mg/day 4 – 400 mg/day 5 – 400 mg/day 6 – 400 mg/day 7 – 400 mg/day 8 – 800 mg/day 9 – 400 mg/day 10 – 400 mg/day)	Case series	10 of 18 (Pts 1-10)	Leukemia, CML	1 st	Hydroxyurea (NS)	Vaginal	37	Male infant: 6 lb, 13 oz [3,540 g], Apgar scores NS. Newborn was healthy but with hypospadias (surgically corrected later).	At 53 months, growth and development were normal.	(Ault <i>et al.</i> 2006) [†] [These cases are included in Pye <i>et al.</i> (2008).]
				1 st	None	--	--	Induced abortion at gestation wk 4. [No fetal data reported.]	--	
				1 st	None	--	--	Spontaneous abortion at gestation wk 4. [No fetal data reported.]	--	
				1 st	Interferon (NS)	Vaginal	36	Male infant: 5 lb, 2 oz [2,398 g], Apgar scores NS. Newborn was healthy.	At 30 months, growth and development were normal.	

Appendix C Table 41. Imatinib (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st	Hydroxyurea (NS)	Vaginal	40	Female infant: 6 lb, 12 oz [3,477 g], Apgar scores NS. Newborn was healthy.	At 16 months, growth and development were normal.	
				1 st	None	Vaginal	36	Female infant: 5 lb, 6 oz [2,648 g], Apgar scores NS. Newborn was healthy.	At 11 months, growth and development were normal.	
				1 st	Hydroxyurea (NS)	C-section	36	Female infants (twins): 5 lb, 13 oz [3,086 g] and 5 lb, 5 oz [2,586 g]. Newborns were both healthy.	At 18 months, growth and development were normal.	
				1 st	None	C-section	36	Female infant: 6 lb, 11 oz [3,415 g], Apgar scores NS. Newborn was healthy.	At 5 months, growth and development were normal.	
				1 st	None	--	--	Spontaneous abortion at gestation wk 9. [No fetal data reported.]	--	
				1 st	None	C-section	39	Male infant: 7 lb, 6 oz [3,557 g], Apgar scores NS. Newborn was healthy.	At 3 months, growth and development were normal.	
Imatinib (400 mg daily)	Case report	1	Leukemia, CML	1 st Last@month 1	Dasatinib	--	--	Induced abortion at gestation wk 17. Male fetus: 166 g, Apgar scores NA. Fetus had hydrops with subcutaneous edema, plural effusion, and ascites.	--	(Berveiller <i>et al.</i> 2012)
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	2 nd , 3 rd Last@wk 9	None	Vaginal	39	Female infant: 3,200 g, Apgar scores NS. Newborn was healthy with normal complete blood count.	No	(Buyukbayrak <i>et al.</i> 2008)
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st Last@wk 6	Hydroxyurea (2 nd , 3 rd)	NS	34	Stillborn infant with meningocele.	--	(Choudhary <i>et al.</i> 2006) [†]
Imatinib (400 mg/day, 1 st pregnancy and 800 mg/day, 2 nd pregnancy)	Case report	1 (2 pregnancies in same pt)	Leukemia, CML	1 st , 2 nd Last@wk 16	Hydroxyurea (2 nd , 3 rd)	NS	37	Infant sex NS: 3,120 g, Apgar scores 9 and 10. Newborn was healthy with no birth defects, normal total blood count.	At 26 months, no apparent late side effects.	(Dolai <i>et al.</i> 2009)
				1 st , 2 nd , 3 rd	None	Vaginal	37	Infant sex NS: 2,980 g, Apgar scores 10 and 10. Newborn was healthy with no birth defects, normal total blood count.	At 9 months, no apparent late side effects.	
Imatinib (200 mg twice daily for 8 wks)	Case report	1	Leukemia, CML	3 rd First@wk 31 + 4 days	Interferon alpha	C-section	39	Female infant: 2,613 g [SGA], Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was normal.	At 5 months, growing appropriately and meeting all neurodevelopmental milestones	(Eskander <i>et al.</i> 2011)

Appendix C Table 41. Imatinib (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Imatinib (600 mg/day)	Case report		Leukemia, CML	1 st , 2 nd Last@wk 17	None	C-section	38	Preeclampsia. Female infant: 2,980 g, Apgar score 9. Newborn was healthy with normal physical examination, white blood count, hemoglobin, platelet count, and cranial ultrasonography.	Normal growth and development [age NS].	(Fogliatto and Brum 2005)† Abstract only
Imatinib (400 mg/day)	Case report	1 (1 pt, 2 pregnancies)	Leukemia, CML	1 st Last@wk 4	None	Vaginal	38	Female infant: 3,180 g, Apgar scores 10 and 10. Newborn was healthy with normal total blood count.	At 3 years, she was healthy.	(Garderet <i>et al.</i> 2007)
				1 st Last@wk 3	Interferon (3 rd)	Vaginal	39	Female infant: 2,950 g, Apgar scores 9 and 10. Newborn was healthy.	At 10 months, she was healthy.	
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st Last@wk 7	Hydroxyurea (3 rd)	Vaginal, induced	38	Female infant: 2,820 g, Apgar scores NS. Newborn was healthy. Pyloric stenosis at 8 wks (resolved with surgery).	At 25 months, she was healthy and developing normally.	(Heartin <i>et al.</i> 2004)†
Imatinib (Clinical study: all 400 mg/day, except 1 case of 600 mg/day resulting in a normal infant) (Spontaneous reports: ranged from 200-600 mg/day and 2 unknown)	Survey, retrospective	13 of 15 (Clinical trial)	Leukemia, CML	1 st or 1 st , 2 nd , or 1 st , 2 nd , 3 rd Pregnancy detected@5-22 wks (group range)	None	NS	NS	9 induced abortions. 1 spontaneous abortion. 3 liveborn infants: 2 normal pregnancies, and 1 newborn had hypospadias – infant sex, weight, and Apgar scores NS. [2 pregnancies were ongoing at time of publication and were not included in the table because of the lack of pregnancy outcomes.]	No	(Hensley and Ford 2003)† [These cases are included in Pye <i>et al.</i> (2008).]
		6 of 11 (Spontaneous reports)		1 st or 1 st , 2 nd Last@5-23 wks (group range)	None	--	--	2 induced abortions – 1 fetus had hydrocephalus, congenital heart defect and 2-vessel cord. 4 spontaneous abortions. [3 pregnancies were missing information, and 2 pregnancies were ongoing at time of publication. They were not included in the table because of the lack of pregnancy outcome.]		
Imatinib (Dose/schedule NS)	Case series	1 of 5 (Pt 3)	Leukemia, CML	1 st , 2 nd Last@wk 21	Interferon [alpha] (2 nd , 3 rd)	NS	38 or 39	Male infant: weight and Apgar scores NS. Newborn was completely healthy.	All children had normal growth and development at 11 to 96 months.	(Klamova <i>et al.</i> 2009)

Appendix C Table 41. Imatinib (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Imatinib (600 mg/day)	Case series	1 of 3 (Pt 1)	Leukemia, CML	1 st Last@wk 12	Interferon alpha (1 st , 2 nd , 3 rd)	C-section	38	Female infant: 3,280 g, Apgar scores NS. Newborn was healthy.	At 44 months, growth and development were normal.	(Koh and Kanagalingam 2006)
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st First@wk 1 Last@wk 10	Hydroxyurea (1 st , 2 nd , 3 rd)	Vaginal, induced	37	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital abnormalities.	At 1 year, normal growth and development.	(Martin <i>et al.</i> 2011)
Imatinib (400 mg/day)	Case series	1 of 2 (Pt 2)	Leukemia, CML	1 st	None	NS	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal.	No	(Mauro <i>et al.</i> 2004)
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st Last@wk 8	None	Vaginal	30	Spontaneous preterm labor. Twin female infants: 1,200 g and 1,600 g, Apgar scores NS. Twin A died at 5 days apparently because of low birth weight; no apparent deformities, dysmorphogenesis, or pseudohermaphroditism. Twin B had normal growth and development.	At 2 years, twin B showed normal growth and development; ultrasound of abdomen, CT-chest, peripheral blood smear, blood counts, and hemoglobin electrophoresis were normal.	(Meera <i>et al.</i> 2008)
Imatinib (400 mg/day, both cases)	Case series	2 of 2	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	NS	Infant: sex, weight, and Apgar scores NS. Newborn was healthy.	No	(Prabhash <i>et al.</i> 2005)
				1 st , 2 nd , 3 rd	None	Vaginal	NS	Infant: sex, weight, and Apgar scores NS.	Newborn was normal at 1 month.	
Imatinib (300 or 400 mg/day)	Survey, retrospective	125 of 180 [Only 125 of 180 cases reported pregnancy outcomes]	Leukemia, CML [majority of cases were CML; see footnote††]	1 st or 1 st , 2 nd , 3 rd or NS	--	--	--	18 spontaneous abortions. Exposure occurred during the (number of pregnancies): 1 st trimester (8); 1 st , 2 nd , 3 rd (7); and NS (3). [No fetal data reported.]	No	(Pye <i>et al.</i> 2008) [This report includes 10 cases presented by Ault <i>et al.</i> (2006), 1 case each reported by 2 case reports (Heartin <i>et al.</i> 2004, Choudhary <i>et</i>
				1 st or 1 st , 2 nd , 3 rd or NS	NS	--	--	32 induced abortions with normal fetuses. Exposure occurred during the (number of pregnancies): 1 st trimester (20); 1 st , 2 nd , 3 rd (5); and NS (7).		
				1 st	None	--	--	Induced abortion. Abnormal ultrasound, elevated alpha fetoprotein.		

Appendix C Table 41. Imatinib (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st , 2 nd , 3 rd	None (Potential confounding non-chemotherapy treatment: Warfarin)	--	--	Induced abortion. Warfarin embryopathy, depressed nasal bridge, choanal stenosis, Dandy Walker cyst, ventricular septal defect, coarctation of the aorta, gastroschisis.		<i>al.</i> 2006). Likewise, Hensely <i>et al.</i> (2003) is an earlier report of this database.]
				NS [Likely 1 st]	None	--	--	Induced abortion. Cleft palate, polydactyly.		
				1 st	Hydroxyurea (after 1 st)	--	--	Stillbirth. Meningocele. [First reported in Choudhary <i>et al.</i> (2006).]		
				1 st , or 1 st , 2 nd , or 1 st , 2 nd , 3 rd or after 1 st , or NS	NS	NS	NS	63 live births with 64 normal infants. Exposure occurred during the (number of infants): 1 st trimester (37, on account of twin pregnancy); 1 st , 2 nd (4); 1 st , 2 nd , 3 rd (18); after 1 st (1); and NS (4).		
				1 st	Hydroxyurea	NS	NS	Live birth. Premature closure of skull sutures.		
				1 st	None	NS	NS	Live birth. Scoliosis, small exomphalos.		
				1 st	NS	NS	30	Live birth. Premature; infant died at 45 minutes. Communicating hydrocephalus, cerebellar hypoplasia, atrial septal defect, overriding aorta, ascites, and pericardial effusion.		
				1 st	Hydroxyurea	NS	[37]	Live birth. Hypospadias. [First reported in Ault <i>et al.</i> (2006)]		
				1 st	None	NS	NS	Live birth. Hypospadias.		
				1 st	Hydroxyurea (after 1 st)	[Vaginal, induced]	[38]	Live birth. Pyloric stenosis. [First reported in Heartin <i>et al.</i> (2004).]		
				1 st	None	NS	NS	Live birth. Hypoplastic lungs, exomphalos, left duplex kidney, right absent kidney, hemivertebrae, and right shoulder anomaly.		
				NS [Likely 1 st]	Interferon	NS	NS	Live birth. Exomphalos, right renal agenesis, hemivertebrae.		

Appendix C Table 41. Imatinib (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Imatinib (400 mg/day, both cases)	Case series	2 of 2	Leukemia, CML	3 rd	None	Vaginal	Term	Female infant: 3,600 g, Apgar scores NS. Newborn was healthy with normal examination, clinical course, and hematologic indices.	No	(Russell <i>et al.</i> 2007)
			Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal, induced	Term	Female infant: 2,955 g, Apgar scores NS. Newborn examination, clinical course, and hematologic indices were normal, except for non-patent mid-line perineal pit.	No	
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st , 2 nd Last@wk 18	Interferon alpha (2 nd , 3 rd)	Vaginal, induced	39	Signs of placental insufficiency. Male infant: 3,160 g, Apgar scores 10, 10, and 10. Newborn was healthy, no postnatal complications, clinical examination and blood count within physiological values.	Growth and development were normal at follow-up [age NS].	(Skoumalova <i>et al.</i> 2008)
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st Last@wk 8	None	C-section	39	Female infant: weight and Apgar scores NS. Newborn was healthy.	No	(Sora <i>et al.</i> 2009)
Imatinib (400 mg/day)	Case report	1 (1 Pt, 2 pregnancies)	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	26	Preterm [spontaneous labor and] birth. Male and female infants (twins): weights and Apgar scores NS. Newborns died 48 hrs after birth because of prematurity. No abnormalities; all parameters normal for age.	No	(Sotiropoulos and Adamidou 2004) [†] Abstract only
				1 st , 2 nd , 3 rd	None	Vaginal	37	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 2 months, she was healthy with normal laboratory tests.	
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st Last@wk 6	Hydroxyurea (1 st , 2 nd , 3 rd)	Vaginal	38	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 12 months, she was healthy.	(Suppiah and Kalaycio 2006)
Imatinib (400 mg/day)	Case report	1	Leukemia, CML	1 st First@wk 1 Last@wk 5	None	Vaginal, induced	36	Male infant: 2,560 g, Apgar score 9. Newborn was healthy with normal blood count.	At 20 months, healthy and growing normally.	(Tsuzuki <i>et al.</i> 2009)

Appendix C Table 41. Imatinib (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Imatinib (400 mg/day, all cases)	Case series	3 of 3	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	Term	Infant: sex and Apgar scores NS, 2.8 kg [2,800 g]. Newborn was healthy. Polymorphic variation of heterochromatic region of chromosome 9 (qh+) in all cells – inherited; pathogenic nature uncertain.	No	(Yilmaz <i>et al.</i> 2007)
			Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	NS	Infant: sex, weight, and Apgar scores NS. Newborn was healthy.	No	
			Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	Term	Infant sex NS: 3,100 g, Apgar score “good.” Newborn was healthy.	No	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the imatinib timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus and infant.

† Papers not included (highlighted in light grey). The 10 cases from Ault *et al.* (2006) and 2 case reports (Heartin *et al.* 2004, Choudhary *et al.* 2006) were not included in the text analysis because they were reported in a survey retrospective by Pye *et al.* (2008). Likewise, 13 cases from Hensley *et al.* (2003) were not included in the text analysis because they were included in the retrospective survey by Pye *et al.* (2008). In addition, abstracts were not included in the text analysis (Sotiropoulos and Adamidou 2004, Fogliatto and Brum 2005). †† The retrospective survey by Pye *et al.* (2008) was included in the NTP monograph because the majority of the cases (147 of 180 cases) were treated for cancer; the authors reported that imatinib was used to treat 143 cases of CML, 4 cases of gastrointestinal stromal tumors, 5 miscellaneous conditions, and 28 cases in which the health conditions were not specified.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; CML = chronic myelogenous leukemia; SGA = small for gestational age.

Appendix C Table 42. Interferon alpha – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Interferon alpha (Pt 1 – 3 million IU every other day, increased to 9 million IU daily; Pt 2 – 6 million IU daily)	Case series	2 of 2	Leukemia, CML	2 nd , 3 rd First@wk 16	None	Vaginal	40	Male infant: 2,760 g [SGA], Apgar scores NS. Newborn was healthy.	No	(Al Bahar <i>et al.</i> 2004)
				1 st , 2 nd , 3 rd First@wk 7	None	Vaginal	40	Female infant: 3,100 g, Apgar scores NS. Newborn was healthy.		
Interferon alpha (Dose/schedule NS)	Case series	1 of 18 (Pt 4)	Leukemia, CML	NS	Imatinib (1 st)	Vaginal	36	Male infant: 5 lbs 2 oz [2,326 g], Apgar scores NS. Newborn was healthy.	At 30 months, growth and development were normal.	(Ault <i>et al.</i> 2006) [†] [included in Pye <i>et al.</i> (2008).]
Interferon alpha (4 million IU/m ² every other day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	40	Female infant: 3,486 g, Apgar scores NS. Newborn was healthy.	At 15 months, the infant showed normal growth and development.	(Baer 1991) [†]
Interferon alpha (Pt 1 – 5 million IU/m ² every other day, reduced to 4 million IU/m ² ; Pt 2 – 1 million IU/m ² every other day, increased to daily; Pt 3 – 3.4 million IU 3 times a wk; Pt 4 – 2 million IU daily, then 5 million IU 3 times a wk)	Case series	4 of 4	Leukemia, CML	1 st , 2 nd , 3 rd First@wk 1	None	Vaginal	40	Female infant: 3,487 g, Apgar scores NS. Newborn was healthy.	At 2 years, the child showed normal growth and development.	(Baer <i>et al.</i> 1992)
			Leukemia, CML	1 st , 2 nd , 3 rd	None	C-section	40	Female infant: 3,714 g, Apgar scores NS. Newborn was healthy.	At 6 months, the infant showed normal growth and development.	
			Leukemia, hairy cell	2 nd , 3 rd First@wk 31	None	C-section	40	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 3 years 8 months, growth and development were normal.	
			Leukemia, hairy cell	2 nd , 3 rd First@wk 22	None	Vaginal	34	Female infant: 1,587 g [SGA], Apgar scores NS. Newborn was healthy.	At 1 year, growth and development were normal.	
Interferon alpha (3 million IU/day)	Case report	1	Leukemia, CML	3 rd First@wk 28 Last@wk 31	Hydroxyurea	C-section	37	Female infant: 2,450 g, Apgar scores NS. Newborn was healthy.	No	(Baykal <i>et al.</i> 2000)
Interferon alpha (3 million IU/day, 5 days a wk)	Case report	1	Leukemia, CML	2 nd First@wk 16	None	C-section	38	Infant (sex, body weight, and Apgar scores NS). Newborn was normal. [1 st pregnancy]	No	(Conchon <i>et al.</i> 2009)
Interferon alpha (9 million IU/day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	Dasatinib (1 st)	C-section	33	Male infant: 2,100 g, Apgar score 9 at 10 minutes. Newborn was healthy with no sequelae or malformations.	No	(Conchon <i>et al.</i> 2010)

Appendix C Table 43. Interferon alpha (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Interferon alpha (3.5 million IU/day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	40	Male infant: 3,450 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no congenital anomalies.	At 8 months, growth was at the 50 th percentile for height, weight, and head circumference.	(Crump <i>et al.</i> 1992)
Interferon alpha (Dose/schedule NS)	Case series	2 of 32 (Pts 1, 22)	Leukemia, CML	2 nd First@wk 20 Last@wk 27	Hydroxyurea (2 nd , 3 rd)	C-section	36	Twin infants, sex NS: 2,390 and 2,250 g, Apgar scores of 8 and 9 for both. Both newborns were healthy.	No	(De Carolis <i>et al.</i> 2006)
			Melanoma	2 nd , 3 rd First@wk 26 Last@wk 30	None	C-section	30	Infant, sex NS: 1,630 g, Apgar scores 7 and 7. Newborn was healthy.		
Interferon alpha (3 million IU/day)	Case series	1 of 3 (Pt 1)	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	40	Male infant: 3,500 g, Apgar scores NS. Newborn had normal phenotype.	No	(Delmer <i>et al.</i> 1992)
Interferon alpha-2b (3 million IU, 3 times a wk)	Case report	1	Melanoma	1 st , 2 nd , 3 rd	None	Vaginal, induced	36	Twin infants: sex, weight, and Apgar scores NS. Both newborns were healthy.	No	(Egberts <i>et al.</i> 2006)
Interferon alpha (3 million IU daily for 4 days)	Case report	1	Leukemia, CML	3 rd First@wk 31	Imatinib	C-section	39	Female infant: 2,613 g [SGA], Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was normal.	At 5 months, growing appropriately and meeting all neurodevelopmental milestones.	(Eskander <i>et al.</i> 2011)
Interferon alpha (3 million IU, 3 times a wk)	Case report	1	Hodgkin lymphoma	1 st , 2 nd	None	Vaginal	Near term	Male infant: 3,200 g, Apgar scores NS.	At 2 years, the child had developed normally.	(Ferrari <i>et al.</i> 1995)
Interferon alpha (3 million IU, 3 times a wk)	Case report	1	Leukemia, CML	3 rd	Imatinib (1 st)	Vaginal	39	Female infant: 2,950 g, Apgar scores 9 and 10. Newborn was healthy.	At 10 months, she was perfectly healthy.	(Garderet <i>et al.</i> 2007)
Interferon alpha-2b (Dose/schedule NS)	Case report	1	Melanoma	1 st	Dacarbazine (2 nd), Cisplatin (2 nd), Radiation therapy (2 nd , 3 rd) [Calendar dates and wks of gestation are inconsistent]	C-section	28 + 3 days	Intrauterine growth retardation (fetal growth at 3 rd percentile) at 28 wks of gestation. Male infant: 735 g [SGA], Apgar scores 6, 8, and 8. Newborn was healthy without signs of metastatic melanoma.	Uneventful age-appropriate development [age NS].	(Gottschalk <i>et al.</i> 2009)

Appendix C Table 43. Interferon alpha (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Interferon alpha (Pt 1 – 8 million IU, 3 times a wk; Pt 2 – 5 million IU, 3 times a wk, increased to 8 million IU)	Case series	2 of 2	Leukemia, CML	2 nd , 3 rd	None	C-section	At term	Infant sex, weight, and Apgar scores NS. Newborn was healthy.	No	(Haggstrom <i>et al.</i> 1996)
				2 nd , 3 rd	None	Vaginal	At term	Infant sex, weight, and Apgar scores NS. Newborn was healthy.		
Interferon beta (2,500 IU)	Case report	1	Melanoma	2 nd , 3 rd First@wk 26	Dacarbazine, Nimustine, Vincristine	Vaginal	35	Male infant: 2,208 g, Apgar scores NS. Newborn was healthy.	At 32 months, he had no signs of melanoma.	(Ishida <i>et al.</i> 2009)
Interferon alpha (Pts 1, 3, 4, and 5 – 3 million IU daily; Pt 2 – 3-5 million IU daily)	Case series	5 of 5	Leukemia CML	2 nd , 3 rd	None	Vaginal	38 or 39	Female infant: birth weight and Apgar scores NS. Newborn was healthy.	At 11 to 96 months, all had normal growth and development.	(Klamova <i>et al.</i> 2009)
					None	Vaginal	38 or 39	Female infant: birth weight and Apgar scores NS. Newborn was healthy.		
					Imatinib	Vaginal	38 or 39	Male infant: birth weight and Apgar scores NS. Newborn was healthy.		
					None	Vaginal	38 or 39	Female infant: birth weight and Apgar scores NS. Newborn was healthy.		
					None	Vaginal	38 or 39	Female infant: birth weight and Apgar scores NS. Newborn was healthy.		
Interferon alpha (Pt 1 – 3 million IU, 3 times a wk increased to 6 million IU, 5 times a wk; Pt 2 – 5 million IU, 3 times a wk; Pt 3 – dose/schedule NS)	Case series	3 of 3	Leukemia, CML	1 st , 2 nd , 3 rd First@wk 12 Last@ wk 38	Imatinib (1 st)	C-section	38	Female infant: 3,280 g, Apgar scores NS. Newborn was healthy.	At 44 months, growth and development were normal.	(Koh and Kanagalingam 2006)
				1 st , 2 nd , 3 rd	None	Vaginal	38	Female infant: 3,200 g, Apgar scores NS. Newborn was healthy.	At 46 months, growth and development were normal.	
				2 nd , 3 rd First@wk 22	None	C-section	37	Male infant: 3,215 g, Apgar scores NS. Newborn was healthy.	At 4 months, growth and development were normal.	
Interferon alpha (3 million IU a day, increased to 6 million IU a day)	Case report	1	Leukemia, CML	2 nd , 3 rd First@wk 25	None	Vaginal	37	Male infant: 2,630 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy with no congenital anomalies.	At 30 months, growth and development were normal.	(Kuroiwa <i>et al.</i> 1998)
Interferon alpha-2b (4 million IU a day)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	C-section	40 + 3 days	Male infant: 3,540 g, Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was healthy.	No	(Lipton <i>et al.</i> 1996)

Appendix C Table 43. Interferon alpha (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Interferon alpha (7.5 million IU a day)	Case series	1 of 2 (Pt 1)	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	38	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 1 year, growth and development were normal.	(Mesquita <i>et al.</i> 2005)
Interferon alpha (Pt 1 – 3 million IU, 3 times a wk; Pt 2 – 2-6 million IU every other day, increased to daily; Pt 3 – 5 million IU every other day, increased to daily)	Case series	3 of 3	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	40	Female infant: 3,100 g, Apgar scores NS. Newborn was normal with transient thrombocytopenia.	At 2.5 years, development was normal.	(Mubarak <i>et al.</i> 2002)
				1 st , 2 nd , 3 rd	None	Vaginal	40	Female infant: 3,200 g, Apgar scores NS. Newborn was in good condition with no congenital malformations.	She was developing normally [age NS].	
				1 st , 2 nd , 3 rd	None	C-section	35	Fetal growth retardation and severe oligohydramnios. Female infant: 2,150 g, Apgar scores NS. Newborn was normal.	At 4 months, she was in good general condition.	
Interferon alpha (Dose, schedule NS)	Survey retrospective	2 of 180 [Only 125 of 180 cases reported pregnancy outcomes]	Leukemia, CML	NS	Imatinib [Likely 1 st]	NS	NS	Infant: sex, weight, and Apgar scores NS. Exomphalos, right renal agenesis, hemivertebrae.	No	(Pye <i>et al.</i> 2008) [Normal infant (of Pt 4) was first reported in Ault <i>et al.</i> (2006).]
			Leukemia, CML	NS	Imatinib	[Vaginal]	[36]	Infant: sex, weight, and Apgar scores NS. Newborn was normal. [First reported as infant of Pt 4 in Ault <i>et al.</i> (Ault <i>et al.</i> 2006)]	[At 30 months, growth and development were normal.]	
Interferon alpha-2a (3 million IU daily, increased to 4.5 million)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd First@wk 13	None	Vaginal	Term	Male infant: weight and Apgar scores NS. Newborn was healthy with a normal blood count.	No	(Regierer <i>et al.</i> 2006)
Interferon alpha-2c (5 million IU, 5-7 times a wk)	Case report	1	Leukemia, CML	1 st , 2 nd , 3 rd	None	Vaginal	Term	Male infant: 3,280 g, Apgar score 10 at 5 minutes. Newborn was normal.	At 3 years, growth and neurological development were normal.	(Reichel <i>et al.</i> 1992)
Interferon alpha (3 million IU, 3 times a wk)	Case report	1	Multiple myeloma	1 st	None	Vaginal	38	Male infant: 8 lbs 4 oz [3,742 g], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was healthy and showed no fetal abnormalities or abnormal function.	No	(Sakata <i>et al.</i> 1995)

Appendix C Table 43. Interferon alpha (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Interferon alpha (9 million IU a day)	Case report	1	Leukemia, CML	2 nd , 3 rd	Imatinib (1 st , 2 nd)	Vaginal	39	Male infant: 3,160 g, Apgar scores 10, 10, and 10. Newborn was healthy without postnatal complications.	Growth and development have been normal [age NS].	(Skoumalova <i>et al.</i> 2008)
Interferon [assumed to be alpha, but not clear] (Dose/ schedule NS)	Survey, retrospective	1 of 27 (Pt 27)	Melanoma	3 rd First@wk 28	None	C-section	36	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the interferon alpha timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in the text analysis (highlighted in light grey). Patient 4 from Ault *et al.* (2006) was not counted separately in the text tally because this case was subsequently reported in Pye *et al.* (2008). One case report (Baer 1991) was excluded because it was included in a subsequent case series (Baer *et al.* 1992).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; IU = international units; CML = chronic myelogenous leukemia; SGA = small for gestational age.

Appendix C Table 44. Methotrexate – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (intrathecal; dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd	Cyclophosphamide	--	--	Induced abortion in the 4th month of gestation. Fetus weighed 1,070 g and was without gross abnormality.	--	(Armitage <i>et al.</i> 1977)
Methotrexate (Dose/schedule NS)	Case series, retrospective	4 of 7 from Table I (Pts 1, 3, 5, and 6)	Leukemia, ALL	1 st [see note in reference column]	Vincristine, Doxorubicin, 6-Mercaptopurine, Cyclophosphamide	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 19 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
			Leukemia, AML	1 st	Doxorubicin, 6-Mercaptopurine, Cytarabine	Vaginal	36	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, ALL	2 nd	Vincristine, Doxorubicin, 6-Mercaptopurine, Cyclophosphamide	Vaginal	38	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st	Vincristine, Doxorubicin, 6-Mercaptopurine, Cyclophosphamide	Vaginal	37	Male infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		6 of 18 from Table III (Pts 3, 8, 12, 13, 14, and 17)	Non-Hodgkin Lymphoma	2 nd	Cyclophosphamide, Doxorubicin, Vincristine, Etoposide	Vaginal	40	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 15 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Epirubicin, Vincristine, Etoposide, Cytarabine, Bleomycin	Vaginal	37	Male infant: 2,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Cyclophosphamide, Doxorubicin, Vincristine, Cytarabine	Vaginal	39	Female infant: 3,100g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st	Cyclophosphamide, Doxorubicin, Vincristine, Etoposide	Vaginal	37	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Cyclophosphamide, Doxorubicin, Vincristine, Etoposide, Cytarabine, Bleomycin	Vaginal	40	Female infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Cyclophosphamide, Epirubicin, Vincristine, Bleomycin, Cytarabine, Etoposide	Vaginal	40	Male infant: 2,800 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Methotrexate (100-750 mg, schedule NS)	Case series	9 of 16 (Pts 1, 3, 5, 7, 8, 10, 12, 13, and 14)	Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin	NS	35-39 (group range)	Individual pregnancy outcomes were not provided. None of the newborns showed congenital malformations.	At ages ranging from 3 to 11 years, all had normal growth and development.	(Avilés <i>et al.</i> 1990) [†]
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin					
				3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Etoposide					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin					
				3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Etoposide					
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Cytarabine					

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Etoposide, Cytarabine					
				3 rd	Cyclophosphamide, Vincristine, Doxorubicin, Etoposide					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Vincristine, Bleomycin, Etoposide, Cytarabine					
Methotrexate (Dose/schedule NS)	Case series, retrospective	11 of 20 pregnancies [10 of 18 pts] (Pregnancies 2, 3, 6, 7, 8, 10, 12, 13, 15, 16, and 20; 10 and 16 are pregnancies of same pt)	Leukemia, ALL	1 st , 3 rd	6-Mercaptopurine, Cyclophosphamide	[Vaginal]	[38]	Male infant: 3,000 g, Apgar scores NS. Newborn had no malformations.	At 13 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	(Avilés and Niz 1988) [This case paper included 5 pts (2, 3, 6, 7, and 8) that were first reported in Pizzuto <i>et al.</i> (1980). We counted them only once using Aviles <i>et al.</i> (1988).]
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, Cyclophosphamide, 6-Mercaptopurine, Cytarabine	[Vaginal]	[40]	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn had no malformations.	At 12 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Cytarabine, Vincristine, Cyclophosphamide, 6-Mercaptopurine	[C-section]	[34]	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had pancytopenia and no malformations.	At 21 days, died of septicemia; blood counts were normal at time of death.	
			Leukemia, ALL	2 nd , 3 rd	Cytarabine, Vincristine, 6-Mercaptopurine	[Vaginal]	[38]	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn had no malformations.	At 90 days, died of gastroenteritis.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, 6-Mercaptopurine, Doxorubicin	[C-section]	[33]	Female infant: 1,800 g, Apgar scores NS. Newborn had no malformations.	At 8 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, 6-Mercaptopurine, Doxorubicin	NS	NS	Female infant: 2,900 g, Apgar scores NS. Newborn had no malformations. [Pt A, pregnancy 1]	At 7 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	1 st , 2 nd , 3 rd	Cytarabine, Vincristine, 6-Mercaptopurine, Doxorubicin	NS	NS	Female infant: 3,500 g, Apgar scores NS. Newborn had no malformations.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	2 nd , 3 rd	Vincristine, 6-Mercaptopurine, Doxorubicin, Cyclophosphamide	NS	NS	Female infant: 2,700 g, Apgar scores NS. Newborn had pancytopenia and no malformations. At 4 wks, blood counts and bone marrow samples were normal.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, 6-Mercaptopurine, Doxorubicin	NS	NS	Male infant: 2,600 g, Apgar scores NS. Newborn had no malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd	Vincristine, 6-Mercaptopurine, Doxorubicin	NS	NS	Male infant: 2,850 g, Apgar scores NS. Newborn had no malformations. [Pt A, pregnancy 2]	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Vincristine, 6-Mercaptopurine, Doxorubicin, Etoposide	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had no malformations.	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
Methotrexate (30 mg weekly, 2 cycles)	Case series	1 of 5 (Pt 1)	Leukemia, ALL	2 nd , 3 rd First@wk 17	Vincristine (2 nd), Asparaginase (2 nd), Cyclophosphamide, 6-Mercaptopurine, Doxorubicin (2 nd)	NS	~39	Female infant: 3,200 g, Apgar scores NS. Newborn was normal.	At 40 months, normal development and growth.	(Awidi <i>et al.</i> 1983)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (80 mg weekly, 6 cycles)	Case series	1 of 3 (Pt 2)	Breast cancer	1 st , 2 nd , 3 rd First@wk7.5 Last@wk28.5	Fluorouracil, Radiation therapy (2 nd)	NS	29	Male infant: 820g (SGA), Apgar scores NS. Newborn was small for gestational age.	At 8.5 years, hypertelorism, frontal hair whorl, an upsweep of the frontal hairline, microcephaly, low-set ears, micrognathia, and right palmar simian crease. He stutters, has verbal expressive difficulties, and has an intelligence quotient of 70.	(Bawle <i>et al.</i> 1998)
Methotrexate (Dose NS, weekly)	Case series	2 of 2	Leukemia, ALL	1 st First@wk 3 Last@wk 4	6-Mercaptopurine, Vincristine	--	--	Spontaneous abortion [at ~6 wks of gestation. No fetal data reported.]	--	(Bergstrom and Altman 1998)
				1 st , 2 nd	6-Mercaptopurine, Vincristine	Vaginal, induced	32	Preeclampsia at 32 wks of gestation. Female infant: 4 lb 15 oz [2,240 g], Apgar scores NS. Newborn was premature; she had no abnormalities.	Subsequent exams [age NS] showed no abnormalities.	
Methotrexate (intrathecal, 12 mg, schedule NS)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd [First@ month 7]	Cyclophosphamide, Vincristine	Vaginal	7 th month	Spontaneous preterm labor 1 wk after starting chemotherapy. Female infant: weight and Apgar scores NS. Newborn was premature, but healthy.	At 3 years, general growth was satisfactory. Hematological parameters, bone marrow, immunoglobulin levels, lymphocyte function, and karyotype were within normal levels.	(Berrebi <i>et al.</i> 1983)
Methotrexate (Dose/schedule NS)	Case report	1	Choriocarcinoma	2 nd First@wk 23	None	Vaginal	25	Spontaneous preterm labor Female infant: 709 g. Apgar scores NS. Newborn was alive.	At 7 years [not entirely clear], making excellent progress with the exception of her hearing.	(Bircher <i>et al.</i> 2011)
Methotrexate (Dose/schedule NS)	Case series, retrospective	1 of 18 (Pt 5)	Leukemia, ALL	3 rd	Vincristine, 6-Mercaptopurine	NS	No births were premature [Term]	Female infant: 6 lb 3 oz [2,807 g], Apgar scores NS. Birth weight was normal [for gestational age].	At 8 years, normal.	(Blatt <i>et al.</i> 1980)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (intrathecal, Dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Vincristine, Daunorubicin, Asparaginase, Cytarabine (intrathecal)	C-section	30	Female infant: 1,266 g, Apgar scores 5 and 8 at 1 and 5 minutes. Newborn's physical examination, hematologic parameters, sepsis assessment, and cancer screening were normal.	No	(Bottsford-Miller <i>et al.</i> 2010)
Methotrexate (Dose NS; given on day 1 of 8-day regimen, 4 cycles)	Case report	1	Choriocarcinoma, uterus	NS [2 nd [First @> 20 wks]	Etoposide, Actinomycin D, Cyclophosphamide, Vincristine	Vaginal	32	Spontaneous preterm [labor and] delivery. Female infant: 1,383 g, Apgar scores 8 and 9. Newborn was developmentally normal.	At 42 months, normal development.	(Brudie <i>et al.</i> 2011)
Methotrexate (intrathecal, Dose/schedule NS)	Survey, registry	1 of 3 from Table 5	Leukemia, ALL	2 nd , 3 rd	Cyclophosphamide, Daunorubicin, 6-Mercaptopurine, Vincristine, Cytarabine, Asparaginase	NS	35.5 (group mean)	Infant sex NS: 2,341 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 9 years, normal phenotype. At 41 to 109 months (group range, n=2), no long-term complications; group mean weight was 65 th percentile.	(Cardonick <i>et al.</i> 2010)
Methotrexate (2.5 mg daily, ~6 wks)	Case report	1	Leukemia, AML	2 nd [First@wk 16 Last@wk 22]	Vincristine, 6-Mercaptopurine (2 nd , 3 rd)	C-section	37	Preeclampsia. Male infant: 6 lb [2,722 g], Apgar score 7. Newborn was normal.	At 2 years, no deleterious effects of the chemotherapeutic agents.	(Cooiland <i>et al.</i> 1969)
Methotrexate (30 mg IV weekly in 1 st ; "high dose" every 3 wks (dose NS, 3 rd))	Case report	1	Leukemia, ALL	1 st , 3 rd	6-Mercaptopurine (1 st), Vincristine (1 st , 2 nd , 3 rd), Cytarabine (3 rd), Doxorubicin (2 nd)	C-section	36	Male infant: 2,400 g, Apgar scores NS. Newborn had polycythemia and hyperbilirubinemia, with no congenital defects.	At 6 months, normal growth and development.	(Dara <i>et al.</i> 1981)
Methotrexate (2.5 mg twice daily)	Case series	1 of 3 (Pt 1)	Leukemia, AML	3 rd (last 3 days of pregnancy)	6-Mercaptopurine, Vincristine	NS	34	Premature rupture of membranes. Female infant: 2,350 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had a cushingoid appearance.	At 8 wks, height and weight were normal for gestational age.	(Doney <i>et al.</i> 1979)
Methotrexate (42 mg)	Survey, retrospective	1 of 14 (Pt 1)	Breast	3 rd First@wk 37 Last@wk 38	NS	NS	41	Infant sex NS: 3,350 g, Apgar scores NS. Newborn was healthy.	At 1 month, pneumonia.	(Donnenfeld <i>et al.</i> 1994)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (Dose/schedule NS)	Case series	1 of 2 (Pt 1)	Leukemia, AML	2 nd , 3 rd First@wk 18/19	Daunorubicin, Cytarabine, 6-Thioguanine (2 nd)	Vaginal	39	Female infant: weight and Apgar scores NS. Newborn was healthy.	No	(Ebert <i>et al.</i> 1997)
Methotrexate (Dose/schedule NS)	Case series	2 of 5 (Pts 2 and 3)	Leukemia, AML	1 st First@wk 1 Last@ [~wk6]	6-Mercaptopurine, Doxorubicin (1 st), Vincristine (1 st , 3 rd), Daunorubicin (3 rd), Cytarabine (3 rd)	Vaginal	38	Female infant: 2,800 g, Apgar scores 8 and 10 at 1 and 5 minutes.	At 7 years, normal development.	(Feliu <i>et al.</i> 1988)
			Leukemia, AMML	1 st [Last@ ~month 2]	6-Mercaptopurine, Cytarabine (2 nd)	Vaginal	38	Male infant: 2,750 g, Apgar scores 6 and 8 at 1 and 5 minutes.	At 7 years, normal development.	
Methotrexate (25 mg/day for 5 days for 2 cycles)	Case report	1	Choriocarcinoma, vagina	2 nd	Chlorambucil, Actinomycin D	Vaginal	NS	Twin male infants: 1,770 g and 1,880 g, Apgar scores NS. Newborns appeared normal.	At approximately 2 years, no adverse effects of chemotherapy.	(Freedman <i>et al.</i> 1962)
Methotrexate (15 mg/day, 1 dose)	Case series	1 of 8 (Pt 6)	Leukemia, AGL	3 rd	6-Mercaptopurine (2 nd , 3 rd)	Vaginal	NS [near term]	Female infant: 5 lb 4 oz [2,381 g], Apgar scores NS. Newborn was normal, clinically and hematologically.	At 17 months, normal and doing well.	(Frenkel and Meyers 1960)
Methotrexate (20 mg IV daily for 5 days)	Case report	1	Choriocarcinoma	3rd First@wk 30	None	Vaginal	31-32	[Spontaneous preterm labor] 10 days after beginning 1 st cycle. Male infant: weight NS. Apgar score 10.	At 12 months, alive and normal.	(Gangadhara <i>et al.</i> 1994)
Methotrexate (25 mg/m ² , 1 cycle)	Survey, retrospective	1 of 20 (Pt 2)	Breast	1 st First@wk 6	Epirubicin, Vincristine	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Giacalone <i>et al.</i> 1999)††
Methotrexate (Dose/schedule NS, 5 cycles)	Case report	1	Breast	1 st , 2 nd First@wk 6 Last@wk 24	Cyclophosphamide, 5-Fluorouracil	Vaginal	30	Spontaneous preterm labor. Male infant: 1,000 g [SGA], Apgar scores NS. Newborn was 3 rd percentile for body weight, length, and head circumference. Newborn appeared normal, apart from respiratory distress and an inguinal hernia.	At 22 months, normal growth, development, and karyotype.	(Giannakopoulos <i>et al.</i> 2000)
Methotrexate (Dose/schedule NS)	Case series, retrospective	1 of 14 (Pt 11)	Leukemia, ALL	7 months [3 rd]	Vincristine	NS	38	Infant sex, weight, and Apgar scores NS. Newborn was normal but small for gestational age (SGA).	At 14 months, under 5 th percentile for height and weight.	(Gulati <i>et al.</i> 1986)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (Intrathecal, dose NS, day 1, 2 cycles, 4 wks apart)	Case report	1	Leukemia, ALL	3 rd First@wk 30 Last@wk 34	Cytarabine, 6-Mercaptopurine, Daunorubicin (2 nd), Cyclophosphamide (2 nd , 3 rd), Vincristine (2 nd , 3 rd), Asparaginase (2 nd , 3 rd)	Vaginal	36	Transient oligohydramnios. [Spontaneous preterm labor.] Male infant: 2,150 g [SGA] , Apgar scores 2 and 8 at 1 and 5 minutes. Newborn was physically normal. Mild meconium aspiration syndrome required positive airway pressure and oxygen therapy for 4 days. Jaundice was treated with phototherapy. Placenta showed mild chorionitis with multiple small infarcts.	No	(Hansen <i>et al.</i> 2001)
Methotrexate (0.2 mg/m ² on days 1 and 4 of a 7-day cycle, 3 cycles)	Case report	1	Choriocarcinoma, ovary	3 rd First@wk 30	Actinomycin D Vinblastine	Vaginal, induced	37	Male infant: 5 lb 13 oz [2,637 g] . Apgar score 10. Newborn appeared normal but developed transitory focal seizures, urinary tract infection, and was found to have unilateral talipes equinovarus (clubfoot).	At 5 months, results of physical examination were normal.	(Hutchison <i>et al.</i> 1968)
Methotrexate (Dose/schedule NS, 3 cycles)	Survey, retrospective	1 of 49 from Table 4 (Pt 10)	Breast	2 nd , 3 rd or 3 rd	Cyclophosphamide, 5-Fluorouracil	NS	37	Infant sex, weight, and Apgar scores NS. Newborn was alive.	No	(Ives <i>et al.</i> 2005)
Methotrexate (Intrathecal, dose/schedule NS)	Case series	1 of 2 (Pt 1)	Leukemia, ALL	2 nd , 3 rd	Asparaginase, Vincristine, Doxorubicin, Radiation therapy	C-section	34	Spontaneous preterm rupture of the membranes and labor. Male infant: 2,080 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal at physical exam and had normal blood counts.	At 30 months, developing normally.	(Karp <i>et al.</i> 1983)
Methotrexate (Dose NS, once every 4 wks)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Vincristine, Cyclophosphamide, 6-Mercaptopurine Doxorubicin (2 nd), Asparaginase (2 nd)	C-section	NS [at term]	Female infant: 3,800 g, Apgar scores NS. Newborn was clinically normal, with slight leucopenia (resolved after 2 wks).	At follow-up [age NS] , child was progressing well with normal blood counts and no neurological disturbances or congenital abnormality.	(Khurshid and Saleem 1978)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate, (intrathecal: 10 mg, 2 injections; schedule NS)	Case report	1	Leukemia, ALL	3 rd	Cytarabine, Cyclophosphamide, Vincristine (2 nd , 3 rd), 6-Mercaptopurine, (2 nd , 3 rd)	Vaginal	38	Male infant: 6 lb 8.5 oz [2,963 g], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was normal.	At 7 months, he continued to thrive and had a normal karyotype.	(Krueger <i>et al.</i> 1976)
Methotrexate (Dose/schedule NS, 3 cycles)	Case report	1	Breast	2 nd First@wk 16 Last@wk 19	Epirubicin (1 st), 5-Fluorouracil (1 st , 2 nd), Cyclophosphamide (1 st , 2 nd), Radiation therapy (1 st)	--	--	Induced abortion at gestation wk 19. Male fetus: 280 g (50 th percentile for gestational age). Fetal examination revealed micrognathia, skin syndactyly of the 1 st and the 2 nd fingers of both hands, shortened 2 nd and 3 rd fingers, and clinodactyly of the 5 th finger; both feet had a broad forefoot with a short 1 st toe and osseous syndactyly of the 4 th and the 5 th metatarsal bones.	--	(Leyder <i>et al.</i> 2010)
Methotrexate (intrathecal, 12.5 mg every 2-4 days, total of 7 doses)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd First@wk 35 Last@wk 37	Bleomycin, Doxorubicin (2 nd , 3 rd), Vincristine (2 nd , 3 rd), Teniposide (2 nd , 3 rd), Cyclophosphamide (2 nd , 3 rd)	Vaginal	37	Female infant: 3,750 g, Apgar score 9. Newborn was fully developed with a normal heart and blood count. No abnormality was detected.	No	(Lowenthal <i>et al.</i> 1982)
Methotrexate (intrathecal, dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 26	Vincristine, Asparaginase, Daunorubicin	C-section	32.4	Intrauterine growth restriction. Male infant: 1,450 g [SGA], Apgar scores 4 and 8 at 1 and 5 minutes. Newborn showed no abnormality in physical examination or laboratory tests. Respiratory distress and jaundice were successfully treated.	At 28 months, growing normally.	(Matsouka <i>et al.</i> 2008)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (Dose/Schedule NS for first 2 cycles, 12 mg/m ² daily for 2 days between days 43 to 45, 3rd cycle)	Case report	1	Sarcoma, Ewing	3 rd	Cyclophosphamide, Vincristine, Doxorubicin	C-section	~7 months	Spontaneous preterm rupture of membranes and labor. Male infant: 2,200 g, Apgar score 9. Newborn was healthy with normal blood counts.	At 10 wks, normal growth and development.	(Meador <i>et al.</i> 1987)
Methotrexate (intrathecal, dose/schedule NS)	Case series	2 of 2	Leukemia, ALL	1 st First@wk 6	Vincristine, Asparaginase, Daunorubicin	--	--	Induced abortion [at ~gestation wk 11]. [No fetal data reported.]	--	(Molkenboer <i>et al.</i> 2005)
				2 nd First@wk 15 [Last@wk 18-19]	Vincristine, Asparaginase, Daunorubicin, Cytarabine	--	--	Stillbirth at gestation wk 22: 400 g (sex NS). [No fetal data reported.]	--	
Methotrexate (180 mg, 5 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd Last@wk 35	Cyclophosphamide, Vincristine, Doxorubicin, Bleomycin, Etoposide	Vaginal	35.5	Spontaneous preterm labor after last chemotherapy dose. Male infant: birth weight was 75 th percentile for gestational age, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no apparent physical abnormalities.	At 11 months, alive and well.	(Moore and Taslimi 1991)
Methotrexate (1 mg/kg every other day to 4 doses, 4 cycles)	Case report	1	Choriocarcinoma	3 rd	None	Vaginal, Induced	34	Male infant: 2,000 g, Apgar scores NS. Newborn was healthy.	At 2 years, in good health.	(Nabers <i>et al.</i> 1990)
Methotrexate (Dose/schedule NS, 12 doses over 13 wks)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 18	Bleomycin, Doxorubicin, Cyclophosphamide, Vincristine	C-section	28	Spontaneous preterm labor at 10 th wk of chemotherapy. Male infants (twins): weights and Apgar scores NS. Newborns were without apparent malformation or bone marrow suppression.	At 12 months, apparently healthy.	(Nantel <i>et al.</i> 1990)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (intrathecal, 10 mg, twice in first wk of chemotherapy)	Case report	1	Leukemia, ALL	1 st First and Last@wk 12	Vincristine (1 st , 2 nd); Asparaginase (2 nd), Cyclophosphamide (2 nd), Daunorubicin (2 nd), 6-Mercaptopurine (2 nd), Radiation therapy (2 nd)	C-section	34	Premature rupture of membranes. Female infant: 2,380 g, Apgar score 8 at 5 minutes. Newborn was normally developed, but hydropic and had an enlarged liver and spleen. She had a petechial rash on her abdomen and extremities and slight cardiomegaly. She experienced transient severe myelosuppression requiring transfusions (resolved after ~3 wks). She was treated with digitalis and diuretics for congestive heart failure.	At 1 year, developmental status was normal.	(Okun <i>et al.</i> 1979)
Methotrexate (intrathecal, 12 mg, days 1, 12, and 33; 1 cycle)	Case report	1	Leukemia, ALL	3 rd First@wk 28	Vincristine, Asparaginase, Methotrexate (IT)	C-section	32+4 days	Male infant: 1,450 g, Apgar scores 4 and 8 at 1 and 5 minutes. Newborn showed no abnormalities by physical examination or laboratory tests. Respiratory distress required treatment but resolved in 3 days.	At 18 months, growing normally.	(Papantonio <i>et al.</i> 2008)
Methotrexate (Dose/schedule NS)	Cohort, retrospective	1 of 14 from Tables 3 and 4 (Pt 12)	Breast	1 st First@wk 5 Last@wk 8	Cyclophosphamide, 5-Fluorouracil	--	--	Fetal death [stillbirth] at gestation wk 25. No malformations.	--	(Peres <i>et al.</i> 2001)
Methotrexate (Schedule NS, total doses: Pt 2 – 725 mg, Pt 3 – 1,000 mg, Pt 6 – 600 mg, Pt 7 – 600 mg, Pt 8 – 150 mg)	Case series	5 of 9 from Table 2 (Pts 2, 3, 6, 7, 8)	Leukemia, ALL	1 st , 3 rd	6-Mercaptopurine, Cyclophosphamide	Vaginal	38	Male infant: 3,000 g, Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 7 years, alive and healthy.	(Pizzuto <i>et al.</i> 1980)†
				1 st , 2 nd , 3 rd	Vincristine, Cyclophosphamide, 6-Mercaptopurine, Cytarabine	Vaginal	40	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 6 years, alive and healthy.	[This case series is included in Aviles <i>et al.</i> 1988 (1988), thus we did not count

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st , 2 nd , 3 rd	Cytarabine, 6-Mercaptopurine, Vincristine, Cyclophosphamide	C-section	34	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had no apparent congenital malformations but was pancytopenic.	At 21 days, died from septicemia.	the original case series separately.]
				2 nd , 3 rd	Cytarabine, 6-Mercaptopurine, Vincristine	Vaginal	38	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 90 days, died from gastroenteritis.	
				1 st , 2 nd , 3 rd	Vincristine, Doxorubicin, 6-Mercaptopurine	C-section	33	Female infant: 1,900 g, Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 16 months, alive and healthy.	
Methotrexate (40 mg/m ² days 1 and 8, 4-8 cycles, 4 wks apart)	Survey, retrospective	1 of 28	Breast	1 st	Cyclophosphamide, 5-Fluorouracil	--	--	Spontaneous abortion after 1 st cycle of chemotherapy. [No fetal data reported.]	--	(Ring <i>et al.</i> 2005)
		11 of 28	Breast	2 nd and/or 3 rd First@wk 15-30 (group range)	Cyclophosphamide, 5-Fluorouracil	NS	37 (median; 30-40, group range)	Intrauterine growth restriction due to placental insufficiency was observed in 1 pregnancy. Individual pregnancy outcomes were not provided. There were no congenital malformations, and none of the infants had a birthweight lower than the 10 th percentile for gestational age. Another child had a hemangioma on his abdomen deemed not causally related to chemotherapy. Two infants had respiratory distress.	No	
Methotrexate (intrathecal: 10 mg/m ² on days 31, 28, 45, and 52, then oral: 20 mg/m ² weekly)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Daunorubicin (2 nd), Vincristine (2 nd), Asparaginase (2 nd), Cyclophosphamide, 6-Mercaptopurine, Cytarabine, Radiation therapy	Vaginal	40	Female infant: weight and Apgar scores NS. Newborn showed no abnormalities. Cytogenetic analysis of lymphocytes showed a normal karyotype, but some chromosome breakage and a ring chromosome.	No	(Schleuning and Clemm 1987)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (Dose NS, days 1 and 8 every 4 wks)	Case series	1 of 4 (Pt 1)	Breast	3 rd	Cyclophosphamide, 5-Fluorouracil	Vaginal	38	Infant sex, weight, and Apgar scores NS. Newborn was healthy.	At 3 years, in good health.	(Schotte <i>et al.</i> 2000)
Methotrexate (Pt 1: 15 mg oral for 5 days, 7 cycles, 2 wks apart; Pt 2: Dose/schedule NS)	Case series	2 of 2	Leukemia, ALL	2 nd , 3 rd	6-Mercaptopurine, Daunorubicin (2 nd), Vincristine, Asparaginase (2 nd)	C-section	37	Twin infants, male and female: 2,500 g (male) and 2,400 g (female), Apgar scores NS. Both newborns were normal at physical examination with normal T-cell populations. At 24 hours, both newborns had diarrhea and were lethargic, and the female was also hypotonic; full recovery was completed by 2 wks.	At 54 months, both children are normal with no evidence of immunologic suppression.	(Turchi and Villasis 1988)
			Breast	3 rd	Doxorubicin (1 st , 2 nd , 3 rd); Cyclophosphamide (1 st , 2 nd , 3 rd), 5-Fluorouracil (1 st , 2 nd , 3 rd)	C-section	35	Elevation of blood pressure to 150/100. Female infant: 2,260 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn had normal T-cell activity and showed no evidence of abnormality.	At 36 months, normal growth and development.	
Methotrexate (Intrathecal: 15 mg weekly x 3)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 27 Last @wk 30	Cyclophosphamide, Daunorubicin (2 nd), Vincristine (2 nd), Cytarabine, 6-Thioguanine, Amsacrine(3 rd)	Vaginal	33	Spontaneous rupture of membranes. Male infant: 1,928 g [Table 2 states 1,925 g], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn's physical exam was unremarkable with normal cerebral ultrasound, hearing, and echocardiography. He exhibited transient neonatal myelosuppression that was	At 24 months, normal growth and development.	(Udink ten Cate <i>et al.</i> 2009)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								treated and resolved by day 20, including leukopenia at birth, neutropenia at day 2, anemia and thrombocytopenia at day 3. Treated for a urinary tract infection on day 7.		
Methotrexate (Intrathecal: 15 mg on days 1,8,15, 29, 43; 5,000 mg/m ² IV on days 29 and 43; 25 mg/m ² oral on day 36)	Survey, retrospective	1 of 62 [62 pts received chemotherapy while pregnant; the total number of pts receiving methotrexate was not provided]	NS	2 nd , 3 rd First@wk 24 Last@wk 32	Vincristine, Daunomycin [Daunorubicin] , Cyclophosphamide, Asparaginase, 6-Mercaptopurine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had a hemangioma.	No	(Van Calsteren <i>et al.</i> 2010)
Methotrexate (40 mg/m ² for 2 days, 2 cycles, 3 wks apart)	Case report	1	Breast	3 rd First@wk 30 Last@wk 33	Vincristine, Doxorubicin	Vaginal	33	Spontaneous preterm labor. Female infant: 2,000 g, Apgar score 8. Newborn was normal but developed apnea and asytle immediately after birth. At day 3, she was diagnosed with hyaline membrane disease. All of these were successfully treated. Chromosomal analysis showed no breaks or excess numerical abnormalities. Placenta had diffuse chorioamnionitis with infiltration by polymorphonucleated cells.	At 2 years, healthy and doing well.	(Willemse <i>et al.</i> 1990)

Appendix C Table 45. Methotrexate (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methotrexate (Dose/schedule NS)	Cohort, retrospective	3 of 21 from Table 1 (Pts 1, 3, and 19)	Breast	1 st	Cyclophosphamide, 5-Fluorouracil	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
				1 st	Cyclophosphamide, 5-Fluorouracil, Vincristine, Tamoxifen	NS	NS	Infant sex, weight and Apgar scores NS. Newborn was alive and well with no malformations, and had normal body weight per gestational age.	No	
				3 rd	Cyclophosphamide, 5-Fluorouracil	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had intrauterine growth retardation (SGA), but was alive and well with no malformations.	No	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the methotrexate timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). In order to avoid counting the same cases more than once, we did not include the following studies: (Pizzuto *et al.* 1980, Avilés *et al.* 1990). The cases in Aviles *et al.* (1990) were not included in the text analysis because they were reported in a subsequent retrospective case series (Avilés *et al.* 1991). The 5 patients from Table 2 in Pizzuto *et al.* (1980) were not included because they were included Aviles *et al.* (1988).

††Giacalone *et al.* (1999) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AGL = acute granulocytic leukemia; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; AMML = acute myelomonocytic leukemia; IT = intrathecal; SGA = small for gestational age.

Appendix C Table 46. Mitoxantrone – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Mitoxantrone (Dose/schedule NS)	Case series, retrospective	3 of 29 from Table 1	Leukemia, acute	NS	Cytarabine	NS	NS	Birth weight: 3,085 g (median), 2,800-4,300 g (group range). Individual data and outcomes NS.	In this long-term follow-up of 84 children ranging from 6 to 29 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001)
Mitoxantrone (Dose/schedule NS, 1 st cycles of consolidation therapy)	Case report	1	Leukemia, APL	2 nd or 2 nd , 3 rd	Behenoyl -ara-C, Daunorubicin, 6-Mercaptopurine, Cytarabine	C-section	34	Female infant: 2,960 g, Apgar scores NS. Newborn was healthy.	At 16 months, no abnormalities.	(Azuno <i>et al.</i> 1995)
Mitoxantrone (10 mg/m ² on days 2 and 3)	Case report	1	Leukemia, AML	2 nd First@wk 22 Last@wk 22	Cytarabine, Idarubicin, Fludarabine (3 rd), Gemtuzumab-Ozogamicin (3 rd)	C-section	33	Fetus developed cardiomyopathy, transient cerebral ventriculomegaly, mild fetal anemia, and intrauterine growth restriction after initiation of chemotherapy. Male infant: 1,695 g, Apgar scores 8 and 9 at 5 and 10 minutes. Newborn was anemic and required ventilation but adapted fast and showed no abnormalities and no clinical signs of dysmorphia.	At 6 months, no residual signs of cardiomyopathy or hydrocephalus.	(Baumgartner <i>et al.</i> 2009)
Mitoxantrone (Dose/schedule NS)	Cohort, retrospective	2 of 37 from Table 1 (Pts 25, 28) [see note in reference column]	Leukemia, AML	1 st (Diagnosis @wk 13)	Daunorubicin, Cytarabine	--	--	Spontaneous abortion (fetus had died). [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005) [In addition, Pt 32 was not included because it was not possible to determine if she received chemotherapy during pregnancy.]

Appendix C Table 47. Mitoxantrone (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	2 nd (Diagnosis @wk 16)	Daunorubicin, Cytarabine	--	--	Induced abortion. [No fetal data reported.]	--	
Mitoxantrone (Dose/schedule NS)	Case series	1 of 2 (Pt 1)	Leukemia, AML	3 rd First@wk 28	Daunorubicin (2 nd), Cytarabine (2 nd , 3 rd)	C-section	29 + 3 days	Oligohydramnios and intrauterine growth restriction noted at 25 wks of gestation and fetal tachycardia at 29 wks of gestation. Female infant: 857 g [SGA], Apgar scores 4 and 6 at 1 and 5 minutes. Newborn required resuscitation and was placed on mechanical ventilation and antibiotics. She showed hyponatremia, hypoglycemia, seizures, neutropenia, anemia, thrombocytopenia, bilateral hydronephrosis with dilation of the proximal ureter of the left kidney, and an intracranial hemorrhage (resolved after 1 month of age). Hematologic derangement resolved after 7 days of therapy.	She developed "failure to thrive," but started to gain weight after 3 months.	(Garcia <i>et al.</i> 1999)
Mitoxantrone (12 mg/m ² , 2 cycles)	Survey, retrospective	2 of 20 (Pts 7, 10)	Breast	2 nd , 3 rd First@wk 25	5-Fluorouracil, Cyclophosphamide	C-section	33	Infant sex and weight NS, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no malformations and normal body weight for gestational age, but suffered respiratory distress.	At 12 months, alive and well.	(Giacalone <i>et al.</i> 1999) ⁺⁺
				2 nd , 3 rd First@wk 27	5-Fluorouracil, Cyclophosphamide	C-section	33	Infant sex and weight NS, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn had no malformations but had intrauterine growth restriction (SGA).	At 32 months, alive and well.	

Appendix C Table 47. Mitoxantrone (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Mitoxantrone (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd , 3 rd First@wk 26	6-Thioiguanine (2 nd), Cytarabine, Daunorubicin (2 nd), ATRA (2 nd)	Vaginal, induced	35	Female infant: 2,490 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was healthy with no physical abnormalities.	At 4 months, there were no developmental complications.	(Giagounidis <i>et al.</i> 2000)
Mitoxantrone (6 mg/m ² daily for 5 days)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 20	6-Mercaptopurine	C-section	35 + 4 days	Preterm labor at beginning of 3 rd trimester was treated and resolved. Premature rupture of membranes at 35 wks + 4 days of gestation. Male infant: 1,882 g [SGA], Apgar scores NS. Newborn had no anomalies or chromosome abnormalities but was thrombocytopenic and leukocytopenic.	No	(Gondo <i>et al.</i> 1990)
Mitoxantrone (7.5 mg/m ² daily for 5 days)	Case report	1	Leukemia, AML	2 nd , 3 rd	Cytarabine, Daunorubicin, Etoposide	C-section	36	Intrauterine growth restriction. Intermittent sinusoidal fetal heart rate patterns at 36 wks of gestation [fetal distress]. Male infant: 1,046 g [SGA], Apgar scores 2 and 7 at 1 and 5 minutes. Newborn was underweight and pancytopenic.	At 2 months, he was in good health.	(Hsu <i>et al.</i> 1995)
Mitoxantrone (Dose/schedule NS)	Cohort, retrospective	103	Leukemia, ALL, AML	NS	Doxorubicin, Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Aclarubicin, Cytarabine, Cycloctidine, ATRA, Vincristine, Idarubicin, Asparaginase	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994) [†]

Appendix C Table 47. Mitoxantrone (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Mitoxantrone (20 mg/day for 5 days; 3 wks later, 2 daily doses of 10 mg)	Case report	1	Non-Hodgkin lymphoma	NS [2 nd , 3 rd First @27 wk]	Cyclophosphamide, Vincristine	C-section	31	Low biophysical profile score and abnormal cardiocotogram. Male infant: 1,700 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn was viable with no evidence of hematological suppression. Respiratory distress syndrome due to prematurity was successfully treated.	At 14 months, fit and well.	(Mavrommatis <i>et al.</i> 1998)
Mitoxantrone (12 mg/m ² on days 3 and 12 of 12-day cycle)	Case series	2 of 2	Leukemia, AML	2 nd , 3 rd First@wk 25	Cytarabine, Thioguanine, Daunomycin [Daunorubicin]	C-section	34	Male infant: 2,220 g, Apgar scores 3, 6, and 8 at 1, 5, and 10 minutes. Newborn required intubation for 7 minutes. His phenotype was rigorously normal; bone X-ray, central nervous system echography, and blood tests were normal.	Follow-up was uneventful [age NS].	(Requena <i>et al.</i> 1995)
				2 nd , 3 rd First@wk 20	Cytarabine, Thioguanine, Daunomycin [Daunorubicin]	C-section	34	Female infant: 2,100 g. Apgar scores 6, 7, and 9 at 1, 5, and 10 minutes. Newborn had no phenotypic anomalies; radiologic controls, sonograms, and blood tests were normal.	Follow-up was satisfactory [age NS].	
Mitoxantrone (12 mg/m ² days 1-3)	Case report	1	Leukemia, AML	2 nd , 3 rd	Cytarabine, Daunorubicin (2 nd), Idarubicin (3 rd)	--	--	Stillbirth: sex NS: 2,200 g. No obvious congenital malformations. No fetal autopsy performed.	--	(Reynoso and Huerta 1994)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the mitoxantrone timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Paper not included in text analysis (highlighted in light grey). The retrospective cohort study by Kawamura *et al.* (1994) was not included in the text analysis because it did not include individual data on treatments or pregnancy outcomes.

††Giacalone *et al.* (1999) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; ATRA = all-*trans* retinoic acid; behenoyl-ara-C = behenoyl cytosine arabinoside; SGA = small for gestational age.

Appendix C Table 48. Nitrogen Mustard – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Nitrogen Mustard (Dose/schedule NS)	Case series, retrospective	7 of 14 from Table II (Pts 1, 5, 7, 8, 9, 10, 14)	Hodgkin lymphoma	1 st [see note in reference column]	Vincristine, Procarbazine	C-section	38	Male infant: 4,500 g. Newborn had no congenital malformations.	At 17 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				2 nd	Vincristine, Procarbazine	Vaginal	39	Male infant: 4,000 g. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	Vaginal	38	Female infant: 2,500 g [SGA]. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Vincristine, Procarbazine	Vaginal	37	Male infant: 3,100 g. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Procarbazine	Vaginal	39	Male infant: 4,000 g. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Procarbazine	Vaginal	40	Female infant: 3,200 g. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Vincristine, Procarbazine	Vaginal	36	Female infant: 3,200 g. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 49. Nitrogen Mustard (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Nitrogen Mustard (0.3 mg/kg, schedule NS)	Case series, retrospective	1 of 84 [Only 1 pt received chemotherapy during pregnancy]	Hodgkin lymphoma	1 st First@month 2	Radiation therapy	NS	NS	Infant: sex, weight, Apgar scores NS. Newborn was healthy.	At 2 months, living and well.	(Barry <i>et al.</i> 1962)
Nitrogen Mustard (Dose/schedule NS)	Case series, retrospective	2 of 24 (Pts 15 and 16)	Hodgkin lymphoma	1 st	Radiation therapy, Vincristine, Procarbazine	--	--	Induced abortion in 1 st trimester. No fetal data reported.	--	(Blatt <i>et al.</i> 1980)
			Hodgkin lymphoma	1 st	Vincristine, Procarbazine	NS	No births were premature [Term]	Male infant: 7 lb 12 oz [3,515 g], Apgar scores NS. Newborn was normal, and birth weight was normal [for gestational age].	No	
Nitrogen Mustard (0.4 mg/kg, 3 cycles)	Case series	1 of 27 [only 1 pregnant pt receiving nitrogen mustard]	Hodgkin lymphoma	1 st	None	NS	NS [~5 th month]	Infant: 1 lb 6 oz [624 g]; sex and Apgar scores NS. [No malformations reported.] Died 2 days after birth.	--	(Boland 1951)
Nitrogen Mustard (Dose/schedule NS)	Case series	1 of 14	Hodgkin lymphoma	From the 6 th month [2 nd , 3 rd]	Vincristine, Procarbazine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was premature, but normal.	No	(Carcassonne 1981)†
Nitrogen Mustard (Pt 1 – 0.6 mg/kg, 3 cycles) (Pt 2 – 0.4 mg/kg, 2 cycles)	Case series	2	Hodgkin lymphoma	2 nd	Radiation therapy	C-section	Term	Male infant: 6 lb 2 oz [2,778 g], Apgar scores NS. Newborn was normal.	At 19 months, he showed normal development.	(Deuschle and Wiggins 1953)
				2 nd	Radiation therapy	Vaginal	7 months	Female infant, 4 lb 11 oz [2,126 g], Apgar scores NS. Newborn developed jaundice, hepatomegaly, and anemia but progressively improved.	At 10 months, she appeared to have developed normally.	
Nitrogen Mustard (Dose/schedule NS)	Case series	1 of 18 (Pt 8)	Hodgkin lymphoma	1 st	Vincristine, Procarbazine	Vaginal	NS	Female infant: 3,000 g, Apgar scores NS. Newborn was healthy. At 3 months, infant died of severe gastroenteritis.	--	(Dilek <i>et al.</i> 2006)
Nitrogen Mustard (Dose/schedule NS, 6 cycles)	Case report	1	Hodgkin lymphoma	1 st	Vinblastine, Procarbazine	Vaginal	24	Male infant: weight and Apgar scores NS. Newborn had only 4 toes on each foot with webbing of the third and fourth toes of the right foot. Right pinna appeared	No	(Garrett 1974)

Appendix C Table 49. Nitrogen Mustard (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								to be slightly abnormal, and there was bowing of the right tibia. A large hemorrhage was found in the right cerebral hemisphere.		
Nitrogen Mustard (Dose/schedule NS)	Case report	1	Leukemia, ALL	1 st [First@conception]	6-Mercaptopurine (1 st)	--	--	Spontaneous abortion [within 1 month after treatment was initiated]. Fetus was grossly normal, no histological evaluation performed.	--	(Hoover and Schumacher 1966)
Nitrogen Mustard (Dose/schedule NS)	Case report	1	Hodgkin lymphoma	3 rd First@wk 28	Vinblastine, Procarbazine	Vaginal	31	Spontaneous preterm labor. Infant: 1,420 g, sex and Apgar scores NS. Newborn had mild anemia but otherwise thrived.	No	(Johnson and Filshie 1977)
Nitrogen Mustard (10 mg twice per 4-wk cycle, 2 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 26	Vincristine, Procarbazine	Vaginal	38	Male infant: 3,110 g, Apgar score 9 at 1 minute. Newborn was normal with a full head of hair.	At 3 months, he showed normal growth and development.	(Jones and Weirnerman 1979)
Nitrogen Mustard (Dose/schedule NS)	Cohort, retrospective	1 of 2	Hodgkin lymphoma	1 st	Vincristine, Procarbazine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had hydrocephaly and died at 4 hours.	--	(Lishner <i>et al.</i> 1992)†
Nitrogen Mustard (4 mg)	Case report	1	Hodgkin lymphoma	1 st	Vincristine, Procarbazine	--	--	Induced abortion [at ~gestation wk 13]. Male fetus, 89 g, with no obvious abnormalities. Internal examination revealed that the kidneys were markedly reduced in size and were malpositioned. Other organs were within normal limits.	--	(Mennuti <i>et al.</i> 1975)
Nitrogen mustard (Dose Schedule NS, 6 cycles)	Case series	1 of 17 (Pt Q)	Hodgkin lymphoma	1 st	Vincristine, Procarbazine	C-section	Term	Infant sex, weight and Apgar scores NS. Newborn was normal.	No	(Nisce <i>et al.</i> 1986)
Nitrogen Mustard (6 mg/m ² , 2 cycles)	Case report	1	Hodgkin lymphoma (Pt was also HIV positive)	2 nd	Vincristine, Procarbazine, Doxorubicin, Bleomycin, Vinblastine	Vaginal	Term	Female infant: weight and Apgar score NS. Newborn had favorable outcome. Infant administered AZT for 6 wks because mother was HIV positive.	At 2 years, child had normal weight and height for age, and was HIV positive. (Mother was HIV positive.)	(Okechukwu and Ross 1998)

Appendix C Table 49. Nitrogen Mustard (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Nitrogen Mustard (Dose/schedule NS)	Cohort, retrospective	1 of 14 (Pt 14)	Hodgkin lymphoma	1 st First@wk 3 Last@wk 7	Vincristine, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	--	--	Induced abortion in gestation wk 18. Fetus had no malformations but toxic degenerative changes were present in the liver and kidneys; placenta had villus degeneration and vascular toxic degeneration.	--	(Peres <i>et al.</i> 2001)
Nitrogen Mustard (19.25 mg over 4 days)	Case series	1 of 8 (Pt 7)	Hodgkin lymphoma	1 st	None	Vaginal	Term	Infant, sex, weight, Apgar scores NS. Newborn was normal.	No	(Riva <i>et al.</i> 1953)
Nitrogen Mustard (20 mg IV, 5 doses, and 10 mg, 1 dose)	Case series	1 of 4 (Pt 16)	Hodgkin lymphoma	2 nd , 3 rd	Chlorambucil, Radiation therapy	Vaginal	NS [~36]	Female infant: 5 lb 1 oz [2,296 g], Apgar scores NS. Newborn was normal.	At 2 months, she was well.	(Smith <i>et al.</i> 1958)
Nitrogen Mustard (12 mg)	Case report	1	Hodgkin lymphoma	1 st First@wk 4 Last@wk 12	Doxorubicin, Vincristine, Procarbazine	--	--	Induced abortion at gestation wk 14: Fetus was missing 1 digit on the right foot, no cardiac tissue was recoverable, and karyotype was normal.	--	(Thomas and Andes 1982) [†] (Abstract only) [†]
Nitrogen Mustard (6 mg/m ² , 2 or 3 cycles)	Cohort, retrospective	2 of 62	NS	2 nd , 3 rd First@wk 25 Last@wk 33	Vincristine, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had pectus excavatum.	No	(Van Calsteren <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 26 Last@wk 30	Vincristine, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Radiation therapy (2 nd)	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had bilateral partial syndactyly of digits 2 and 3.		
Nitrogen Mustard (Dose/schedule NS)	Cohort-retrospective	3 of 21 (Pts 4, 5, and 6)	Hodgkin lymphoma	1 st	Procarbazine, Vincristine	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
				1 st	Procarbazine, Vincristine	--	--	Induced abortion. [No fetal data reported.]		
				1 st First@wk 4	Procarbazine Vincristine	NS	NS	Infant, sex, weight, Apgar scores NS. Newborn died at 4 hours with hydrocephalus.		

Appendix C Table 49. Nitrogen Mustard (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Nitrogen Mustard (In 1 st trimester, 0.1 mg/kg total divided between 2 doses; in 3 rd trimester, second course divided between 3 doses)	Case report	1	Hodgkin lymphoma	1 st , 3 rd	X-rays (1 st , 2 nd , 3 rd)	C-section	>8.5 months	Male infant: 6 lbs 5 oz [2,863 g], Apgar scores NS. Newborn was bronchoscoped for excess mucous, and response was sluggish for first few hours. He then progressed very well without any gross stigmata.	At 8 months, he was apparently normal.	(Zoet 1950)
Nitrogen Mustard (Dose/schedule data limited; Table 1: Pt 33 – 4 cycles)	Survey, retrospective	1 of 48 (Table 1 – Pt 33)	Hodgkin lymphoma	1 st , 2 nd	Vincristine, Procarbazine [paper said cyclophosphamide rather than procarbazine], Vinblastine (2 nd , 3 rd)	NS	40	Infant: 3,400 g, sex and Apgar scores NS. Newborn was normal.	No	(Zuazu <i>et al.</i> 1991)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the nitrogen mustard timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis of nitrogen mustard (highlighted in light grey): (Carcassonne 1981, Lishner *et al.* 1992), and (Thomas and Andes 1982). The case report by Carcassonne *et al.* (1981) was not included because the authors provided insufficient detail regarding the individual treatments, timing of exposure, and pregnancy outcomes of patients treated for Hodgkin disease while pregnant. The retrospective cohort study by Lishner *et al.* (1992) was not included because it did not provide individual data on treatment and timing of exposure during pregnancy. Also, the infant born with hydrocephaly reported in Lishner *et al.* (1992) was previously reported by Zemlickis *et al.* (1992b), which is included in our text analysis. Abstracts only were excluded from the text analysis (Thomas and Andes 1982).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia; SGA = small for gestational age.

Appendix C Table 50. Paclitaxel – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Paclitaxel (60 mg/m ² weekly for 5+ wks)	Case report	1	Lung	2 nd , 3 rd	Carboplatin	C-section	30	Spontaneous preterm labor. Male infant: weight and Apgar scores NS. Newborn was healthy with no evidence of metastasis.	At 5 months, development was normal.	(Azim <i>et al.</i> 2009b)
Paclitaxel (175 mg/ m ² , 2 times, separated by 3 wks)	Case report	1	Breast	2 nd , 3 rd First@wk 25 + 6 days Last@wk 28 + 5 days	Trastuzumab, Radiation therapy	C-section	32	Oligohydramnios, fetal renal failure, and cessation of fetal abdominal growth. Placental function was normal. Male infant: 1,460 g, Apgar scores NS. Newborn had bacterial sepsis with hypotension, transient renal failure, respiratory failure requiring mechanical ventilation (until age 6 days), and transient hyperechodensities in renal parenchyma (resolved by age 28 days). Discharged by 6 wks of age in healthy condition.	At 12 wks, development was normal.	(Bader <i>et al.</i> 2007b)
Paclitaxel (Dose/schedule NS)	Survey, registry	8 of 104 fetuses from Table 2	Breast	2 nd , 3 rd	Doxorubicin Cyclophosphamide, 5-Fluorouracil, Docetaxel	NS	35.9 (group mean)	Infant sex NS: 2,667 g (group mean), Apgar scores NS. Seven newborns had no malformations, and 1 newborn had pyloric stenosis as well as neutropenia. Seven infants had normal body weight for gestational age, and 1 infant had intrauterine growth retardation. One infant had hyperbilirubinemia.	At 0.2 to 7.3 years (n=7), all children were normal phenotype. At 42 months (group mean, n=93), no long-term complications; group mean weight was 48 th percentile.	(Cardonick <i>et al.</i> 2010)
Paclitaxel (Dose/schedule NS)	Survey, registry	3 of 7 from Table 4 [assumed that only 1 pt had twins]	Ovary	2 nd , 3 rd	Carboplatin (2 pts) or Cisplatin (1 pt)	NS	38.1 (group mean)	Infant sex NS: 2,639 g (group mean), Apgar scores NS. Newborns were normal with normal body weight for gestational age.	At age 11, 1 child (with a normal twin) had Asbergers syndrome, attention-deficit disorder, and delays in school. At 63.3 months (group mean, n=7), group mean weight was 35 th percentile. One child had motor/language delay at 1 year of age.	(Cardonick <i>et al.</i> 2010)

Appendix C Table 51. Paclitaxel (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Paclitaxel (2 cycles over 6 wks, doses NS)	Case report	1	Tongue, squamous cell carcinoma	2 nd First@~wk 26 Last@wk 32	Cisplatin	C-section	32	Male infant: weight and Apgar scores NS. Admitted to NICU with jaundice and anemia.	At 1 year, anemic, diagnosed as hereditary spherocytosis. At 13 months, feeding and active, but was low birth weight and height for gestational age.	(Cheung <i>et al.</i> 2009)
Paclitaxel (Pt 1 – 175 mg/m ² , 3 cycles ; Pt 2 – 175 mg/m ² , 1 cycle; Pt 3 – 175 mg/m ² , 2 cycles)	Case series	3 of 3	Cervix	2 nd , 3 rd First@wk 26 Last@wk 32	Cisplatin	C-section	35 + 5 days	Female infant: 2,570 g, Apgar scores NS. Newborn showed no signs of toxicity.	At 3 months, well and healthy.	(Chun <i>et al.</i> 2010)
				3 rd First@wk 29 + 2 days	Carboplatin	C-section	33 + 3 days	Male infant: 2,190 g, Apgar scores NS. Newborn showed no signs of toxicity.	At 48 months, normal development.	
				3 rd First@wk 31 Last@wk 34	Cisplatin	C-section	36 + 5 days	Male infant: 2,600 g, Apgar scores NS. Newborn had no abnormalities.	At 5 years, normal development.	
Paclitaxel (120 mg/m ² biweekly for 5 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 24 + 5 days	Carboplatin	C-section	36 + 2 days	Female infant: 2,062 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn showed no serious effects of chemotherapy.	At 40 months, the infant remained healthy with no serious problems.	(Doi <i>et al.</i> 2009)
Paclitaxel (175 mg/m ²)	Case series	2 of 9 (Pts 3, 4)	Cervix	2 nd and/or 3 rd First@after 16 wks (median)	Cisplatin	C-section	35 (median; range 30-36)	Infant (sex NS): 2,030 g, Apgar scores NS. Newborn had no congenital malformations and required mechanical ventilation immediately after birth (resolved).	No	(Fruscio <i>et al.</i> 2012)
			Cervix	2 nd and/or 3 rd First@after 16 wks (median)	Cisplatin	C-section	35 (median; range 30-36)	Infant (sex NS): 1,900 g, Apgar scores NS. Newborn had no congenital malformations, and had an intraventricular hemorrhage. Newborn was discharged as healthy after 40 days.	No	
Paclitaxel (175 mg/m ² every 3 wks from 25 th to 32 nd wk)	Case report	1	Breast	2 nd , 3 rd First@wk 25 Last@wk 32	Epirubicin (2 nd)	C-section	36	Female infant: 2,280 g, Apgar score 9 at 5 minutes. Infant's stay in the neonatal ward was uneventful.	At 36 months, the infant showed normal development and growth.	(Gadducci <i>et al.</i> 2003)

Appendix C Table 51. Paclitaxel (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Paclitaxel (175 mg/m ² every 3 wks for 3 cycles)	Case report	1	Lung	2 nd First@wk 21 Last@wk 27	Cisplatin	C-section	30	At gestation wk 30, brain metastases led to tonic-clonic seizures in mother. Male infant: 1,720 g, Apgar scores 3 and 4 at 1 and 5 minutes. The newborn developed acute respiratory stress syndrome that warranted invasive mechanical ventilation for 24 h. A pediatric evaluation failed to demonstrate any hearing, thyroid, adrenal or congenital abnormalities in the infant.	At 15 months, infant was well with normal development and growth.	(Garcia-Gonzalez <i>et al.</i> 2008)
Paclitaxel (80 mg/m ² weekly for 12 wks)	Case report	1	Breast	2 nd , 3 rd First@wk 21 Last@wk 33	Doxorubicin (1 st , 2 nd), Cyclophosphamide (1 st , 2 nd)	C-section	37	Preeclampsia. Male infant: 5.4 lbs [2,449 g]), Apgar scores 9 at 1, 5, and 10 minutes. Newborn was normal with normal blood counts.	At 12 months, the infant revealed normal physical development and growth.	(Gonzalez-Angulo <i>et al.</i> 2004)
Paclitaxel (175 mg/m ² every 3 wks for 3 cycles [Figure 4 suggests every 4 wks])	Case report	1	Ovary	2 nd , 3 rd First@wk 25 Last@wk 32	Carboplatin	C-section	35	Male infant: 2,450 g, Apgar scores 9, 10, 10. Newborn was healthy. He showed minor respiratory distress and mild anemia, but no neurologic, psychomotor, or developmental abnormalities.	At 20 months, he showed no abnormalities.	(Hubalek <i>et al.</i> 2007)
Paclitaxel (Dose/schedule NS)	Cohort, retrospective	7 of 72	Breast	2 nd or 3 rd	Cyclophosphamide, 5-Fluorouracil, Paclitaxel, Cisplatin	NS	NS	Individual pregnancy outcomes were not provided. No congenital malformations were diagnosed in the newborns.	No	(Ibrahim <i>et al.</i> 2000)†
Paclitaxel (75 mg/m ² , 2 cycles, 2 wks apart)	Case series	2 of 2	Cervix	3 rd First@wk 28 Last@wk 30	Cisplatin	C-section	34	Spontaneous preterm labor at 29 wks of gestation + 3 days was treated, subsided. Male infant: 2,200 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no malformations and no evidence of metabolic or hematologic abnormality.	At 21 months, normal development.	(Li <i>et al.</i> 2011)
				3 rd First@wk 30 Last@wk 32	Cisplatin	C-section	34	Male infant: 2,200 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn had no malformations.	At 13 months, in good general condition.	

Appendix C Table 51. Paclitaxel (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Paclitaxel (175 mg/m ² every 2 wks for 4 cycles)	Case report	1	Breast	3 rd First@wk 30 Last@wk 36	Doxorubicin and Cyclophosphamide (2 nd , 3 rd)	C-section	38	Transient uterine contractions after 2 nd cycle of chemotherapy. Twin infants, sexes not given: 2,354 g [SGA], 2,426 g [SGA], Apgar scores 7 and 8 at 1 and 5 minutes, 8 and 9 at 1 and 5 minutes. Newborns were healthy.	At 16 months, they were in good health.	(Lycette <i>et al.</i> 2006)
Paclitaxel (175 mg/m ² day 1 q 21 [every 3 wks] for 5 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 22 Last@wk 35	None	C-section	38	Infant, sex NS: 2,490 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 16 months, the baby showed no evidence of neurologic, renal, growth, or hematologic sequelae.	(Mantovani <i>et al.</i> 2007)
Paclitaxel (175 mg/m ² every 3 wks for 6 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 16-17 Last@wk 32	Carboplatin	C-section	35.5	Infant, sex NS: 2,500 g, Apgar scores 9, 9, and 9 at 1, 5, and 10 minutes. Newborn had normal physical examination and laboratory tests.	At 15 months, the baby had no evidence of neurologic, renal, growth, or hematologic sequelae.	(Mendez <i>et al.</i> 2003)
Paclitaxel (dose and schedule NS, 4 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 22 Last@wk 35	Carboplatin	C-section	35	Male infant: 2,600 g, Apgar scores 9 at 1 and 5 minutes. Newborn was healthy.	At 6 months, the baby showed no evidence of neurologic, renal, growth, or hematologic sequel.	(Modares Gilani <i>et al.</i> 2007)
Paclitaxel (90 mg/m ² on days 1, 8, 15 of a 28-day cycle, 6 cycles)	Case series.	1 of 5 (Pt D)	Breast	3 rd	None	C-section	38	Infant sex, weight, and Apgar scores NS. Newborn was healthy.	No	(Morris <i>et al.</i> 2009)
Paclitaxel (175 mg/mq [?] in a single treatment)	Case report	1	Cervix	2 nd	Cisplatin (2 nd , 3 rd)	C-section	35	Female infant: 2,400 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn in good health and showed no sign of any metabolic or hematologic abnormality. The auditory brainstem evoked potential test was normal.	At 10 months, the infant was in good general health.	(Palaia <i>et al.</i> 2007)
Paclitaxel (135 mg/m ² every 4 wks for 5 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 14 Last@wk 29	Cisplatin	C-section	34	Persistent pregnancy-induced hypertension at 32 wks of gestation. Male infant: 1,750 g [SGA], Apgar scores NS. Newborn cried soon after birth and did well postnatally.	At 18 months, the infant showed normal growth and development and had normal milestones.	(Raghunath and Shashi 2006)

Appendix C Table 51. Paclitaxel (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Paclitaxel (175 mg/m ² , every 3 wks for 2 cycles)	Case report	1	Ovary	3 rd	Cisplatin	C-section	34	Female infant: 1,900 g, Apgar score 8 at 5 minutes. Newborn was healthy with normal lab tests.	At 73 months, normal growth and development.	(Serkes <i>et al.</i> 2011)
Paclitaxel (Dose NS; weekly, 4 cycles)	Case report	1	Breast	3 rd	Cyclophosphamide (2 nd , 3 rd) Doxorubicin (2 nd , 3 rd)	C-section	36	Oligohydramnios noted in 3 rd trimester following the 4 th treatment with paclitaxel. Infant: sex and Apgar scores NS, 5 lb 4 oz [2,381 g]. Newborn was healthy; echocardiogram and blood counts were normal.	No	(Shieh and Mehta 2011)
Paclitaxel (135 mg/m ² every 3 wks for 3 cycles)	Case report	1	Ovary	3 rd First@~wk 29 Last@~wk 35	Cisplatin	C-section	37	Female infant: 2,800 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal with no evidence of hearing, thyroid, adrenal, hematological, or congenital abnormalities.	At 30 months, normal growth and development.	(Sood <i>et al.</i> 2001)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the paclitaxel timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Paper not included in text analysis (highlighted in light grey). The cohort retrospective by Ibrahim *et al.* (2000) was not included because individual patient data on timing of exposure and treatments were not provided.

Abbreviations: NS = not specified; pt = patient; q = quaque (Latin) or every; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 52. Procarbazine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Procarbazine (Dose/schedule NS)	Case series, retrospective	7 of 14 from Table II (Pts 1, 5, 7, 8, 9, 10, 14)	Hodgkin lymphoma	1 st	Nitrogen mustard, Vincristine	C-section	38	Male infant: 4,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 17 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				2 nd	Nitrogen mustard, Vincristine	Vaginal	39	Male infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Vincristine, Nitrogen mustard, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	Vaginal	38	Female infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Nitrogen mustard, Vincristine	Vaginal	37	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Nitrogen mustard, Vincristine	Vaginal	39	Male infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Nitrogen mustard, Vincristine	Vaginal	40	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Nitrogen mustard, Vincristine	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 53. Procarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Procarbazine (Dose/schedule NS)	Case series, retrospective	12 of 26 (Table 2)	Hodgkin lymphoma	NS	Nitrogen mustard, Vincristine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	NS	NS	Individual pregnancy outcomes, birth weights, and Apgar scores were not provided. Birth weight: 3,201 g (group median), 2,800-4,300 g (group range).	In this long-term follow-up, ranging from 5 to 26 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001) [†]
Procarbazine (Dose/schedule NS)	Case series, retrospective	2 of 18 (Pts 15 and 16)	Hodgkin lymphoma	1 st	Radiation therapy, Nitrogen mustard, Vincristine	--	--	Induced abortion in 1 st trimester. [No fetal data reported.]	--	(Blatt <i>et al.</i> 1980)
				1 st	Nitrogen mustard, Vincristine	NS	No births were premature [Term]	Male infant: 7 lb 12 oz [3,515 g] , Apgar scores NS. Newborn was normal and birth weight was normal [for gestational age] .	No	
Procarbazine (Dose/schedule NS)	Case series	1 of 14	Hodgkin lymphoma	From the 6 th month [2nd, 3rd]	Nitrogen mustard, Vincristine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was premature, but normal.	No	(Carcassonne 1981) [†]
Procarbazine (100 mg/m ² on days 1-14 of a 28-day cycle, through remainder of pregnancy)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 18	Cyclophosphamide, Vincristine	NS	37	Female infant: 2,000 g [SGA] . Apgar scores NS. Newborn had no abnormalities.	At 1 year, there were no abnormalities.	(Daly <i>et al.</i> 1980)
Procarbazine (Dose/schedule NS)	Case series	1 of 18 (Pt 8)	Hodgkin lymphoma	1 st	Nitrogen mustard, Vincristine	Vaginal	NS	Female infant: 3,000 g, Apgar scores NS. Newborn was healthy. At 3 months, infant died of severe gastroenteritis.	--	(Dilek <i>et al.</i> 2006)
Procarbazine (Dose/schedule NS)	Case report	1	Hodgkin lymphoma	1 st	Nitrogen mustard, Vinblastine	NS	24	Male infant: weight and Apgar scores NS. Newborn had only 4 toes on each foot with webbing of the third and fourth toes of the right foot. Right pinna appeared to be slightly abnormal, and there was bowing of the right tibia. A large hemorrhage was found in the right cerebral hemisphere.	No	(Garrett 1974)

Appendix C Table 53. Procarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Procarbazine (Dose/schedule NS)	Case report	1	Hodgkin lymphoma	3 rd First@wk 28	Vinblastine, Nitrogen mustard	Vaginal	31	Spontaneous preterm labor. Infant sex and Apgar scores NS: 1,420 g. Newborn had mild anemia but otherwise thrived.	No	(Johnson and Filshie 1977)
Procarbazine (150 mg daily for 2 wks, followed by 2 wks rest, 2 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 26	Nitrogen mustard, Vincristine	Vaginal	38	Male infant: 3,110 g, Apgar score 9 at 1 minute. Newborn was normal with a full head of hair.	At 3 months, growth and development were normal.	(Jones and Weinerman 1979)
Procarbazine (Dose/schedule NS)	Cohort, retrospective	1 of 50	Hodgkin lymphoma	1 st	Nitrogen mustard, Vincristine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had hydrocephaly and died at 4 hours.	--	(Lishner <i>et al.</i> 1992) [†]
Procarbazine (100 mg per day for 7 days)	Case report	1	Hodgkin lymphoma	1 st	Nitrogen mustard, Vincristine	--	--	Induced abortion [at ~gestation wk 13]. Male fetus, 89 g. No obvious external abnormalities. Internal examination revealed that the kidneys were markedly reduced in size and were malpositioned. Other organs were within normal limits.	--	(Mennuti <i>et al.</i> 1975)
Procarbazine (10 g [total] during gestation wks 1-6, schedule NS)	Survey, retrospective	1 of 27 [27 pts received chemotherapy while pregnant; the total number of pts who received procarbazine while pregnant was not provided]	Hodgkin lymphoma	1 st First@wk 1 Last@wk 6	Lomustine, Vincristine, Vinblastine (1 st , 2 nd , 3 rd)	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had cleft lip and cleft palate.	No	(Mulvihill <i>et al.</i> 1987)
Procarbazine (Dose/schedule NS, 6 cycles)	Case series	1 of 17 (Pt Q)	Hodgkin lymphoma	1 st	Nitrogen mustard, Vincristine	C-section	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal.	No	(Nisce <i>et al.</i> 1986)

Appendix C Table 53. Procarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Procarbazine (100 mg/m ² , 2 cycles)	Case report	1	Hodgkin lymphoma	2 nd	Vincristine, Nitrogen mustard, Doxorubicin, Bleomycin, Vinblastine	Vaginal	Term	Female infant: weight and Apgar score NS. Newborn had favorable outcome. Infant administered AZT for 6 wks because mother was HIV positive.	At 2 years, she was HIV positive but at expected weight and height for her age. (Mother was HIV positive)	(Okechukwu and Ross 1998)
Procarbazine (Dose/schedule NS)	Cohort, retrospective	1 of 14 (Pt 14)	Hodgkin lymphoma	1 st First @wk 3 Last@wk 7	Nitrogen mustard, Vincristine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	--	--	Induced abortion in gestation wk 18. Fetus had no malformations; toxic degenerative changes were present in the liver and kidneys, and placenta had villus degeneration and vascular toxic degeneration.	--	(Peres <i>et al.</i> 2001)
Procarbazine (100 mg /m ² daily on days 1-10 of 4-wk cycle, 5 cycles)	Case report	1	Non-Hodgkin lymphoma, diffuse histiocytic	1 st , 2 nd First@wk 4 Last@wk 20	Carmustine, Streptozotocin (2 nd , 3 rd)	Vaginal	35	Male infant: 2,340 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was normal by physical examination.	No	(Schapira and Chudley 1984)
Procarbazine (Total 1,050 mg, schedule NS)	Case series	2 of 2 (Table 3)	Hodgkin lymphoma	1 st	Vinblastine, Vincristine	Vaginal	NS	Male infant: 4 lb 2 oz [1,871 g], Apgar scores NS. On day 2, developed respiratory distress and died. Post-mortem found a small secundum atrial septal defect.	--	(Thomas and Peckham 1976)
					Vinblastine	--	--	Induced abortion. [No fetal data reported.]	--	
Procarbazine (1,500 mg [total dose], schedule NS)	Case report	1	Hodgkin lymphoma	1 st First@wk 4 Last@wk 12	Doxorubicin, Nitrogen mustard, Vincristine	--	--	Induced abortion: Fetus was missing 1 digit on the right foot. No cardiac tissue was recoverable. Karyotype was normal.	--	(Thomas and Andes 1982)† (Abstract)

Appendix C Table 53. Procarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Procarbazine (100 mg/m ² per cycle)	Survey, retrospective	2 of 62 [62 pts received chemotherapy while pregnant; the number of pts who received procarbazine while pregnant was not provided]	NS	2 nd , 3 rd First@wk 25 Last@wk 33	Nitrogen Mustard, Vincristine, Doxorubicin, Vinblastine, Bleomycin	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had pectus excavatum.	No	(Van Calsteren <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 26 Last@wk 30	Radiation therapy (2 nd), Nitrogen Mustard, Vincristine, Doxorubicin, Vinblastine, Bleomycin	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had bilateral syndactyly of digits 2 and 3.		
Procarbazine (100-150 mg/m ² daily)	Case report	1	Hodgkin lymphoma	1 st (conception through ~day 38)	None	Vaginal	39	Male infant: 4,096 g, Apgar scores NS. Newborn was normal apart from a few hemangiomas on the skin.	At 13 months, growth and development were normal.	(Wells <i>et al.</i> 1968)
Procarbazine (Dose/schedule NS)	Cohort-retrospective	3 of 21 (Pts 4, 5, and 6)	Hodgkin lymphoma	1 st	Nitrogen mustard, Vincristine	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)
				1 st	Nitrogen mustard, Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	
				1 st First@wk 4	Nitrogen mustard, Vincristine	--	--	Infant, sex, weight, Apgar scores NS. Newborn died at 4 hours with hydrocephalus.	--	
Procarbazine (Dose/schedule data limited; Table 1: Pt 33 – 4 cycles [paper said cyclophosphamide rather than procarbazine]; Table 2: Pt 43 – 3 cycles Pt 6 – 1 cycle Pt 34 – 1 cycle)	Survey, retrospective	4 of 48 (4 of 56 total pregnancies) (Table 1: Pt 33; Table 2: Pt 43, 6, 34)	Hodgkin lymphoma	1 st , 2 nd	Nitrogen Mustard, Vincristine, Vinblastine (2 nd , 3 rd)	NS	40	Infant: 3,400 g, sex and Apgar scores NS. Newborn was normal.	No	(Zuazu <i>et al.</i> 1991)
			Hodgkin lymphoma	1 st	Cyclophosphamide, Vinblastine	C-Section	38	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	No	

Appendix C Table 53. Procarbazine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	1 st First@wk 12 Last@wk 12	Cyclophosphamide, Vincristine, Triethylene-melamine	--	--	Induced abortion at gestation wk 14. [No fetal data reported. Pt 6, 1st pregnancy]	--	
			Hodgkin lymphoma	3 rd First and Last@wk 30	Cyclophosphamide, Vinblastine	C-section	NS	Infant: sex, weight, and Apgar scores NS. Newborn with anemia that resolved.	At 3 years, normal at follow-up.	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the procarbazine timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). In order to avoid counting the same cases more than once, we did not include the following studies: (Lishner *et al.* 1992, Avilés and Neri 2001). The retrospective case series of Avilés and Neri (2001) was not included because it included both new cases and long-term follow-up on previously reported case series (Avilés *et al.* 1991) without individual pregnancy outcomes. The retrospective cohort study by Lishner *et al.* (1992) was not included because it did not provide individual data on treatment and timing of exposure during pregnancy, and the infant born with hydrocephaly was previously reported by Zemlickis *et al.* (1992b). Carcassone *et al.* (1981) was omitted from the text analysis because too few details were provided in the paper regarding the individual treatments, timing of exposure, and pregnancy outcomes of patients treated for Hodgkin disease while pregnant. Finally, published abstracts were not included in the text analysis (Thomas and Andes 1982).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 54. Rituximab – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Rituximab (Dose/schedule NS)	Survey, registry	4 of 31 from Table 3	Non-Hodgkin lymphoma	2 nd , 3 rd	Doxorubicin, Vincristine, Cyclophosphamide	NS	34.0 (group mean)	Infant sex NS; 2,576 g (group mean), Apgar scores NS. One fetus died [stillbirth] at 30 wks, autopsy was normal. Three newborns had normal body weight for gestational age. One newborn had jaundice and transient tachypnea.	At 3 years, normal phenotype. At 34 to 82 months (group range, n=6), group mean weight was 46 th percentile.	(Cardonick <i>et al.</i> 2010)
Rituximab (Dose/schedule NS)	Survey, retrospective – utilizing data from the rituximab global drug safety database	8 of 20 from Table 2 [only included cancer patients]	Hodgkin lymphoma	3 rd First@wk 33	NS	NS	39	Male infant: weight and Apgar scores NS. Newborn was normal.	No	(Chakravarty <i>et al.</i> 2011) [This entry excludes 3 published case reports that are already included in our table: (Herold <i>et al.</i> 2001, Kimby <i>et al.</i> 2004, Decker <i>et al.</i> 2006, Friedrichs <i>et al.</i> 2006).
			Non-Hodgkin lymphoma	3 rd First@wk 28	NS	NS	32	Female infant: weight and Apgar scores NS. Newborn had leukopenia and anemia.		
				2 nd First@wk 18	Cyclophosphamide, Doxorubicin, Vincristine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal.		
				2 nd First@wk 21	Cyclophosphamide, Doxorubicin, Vincristine	NS	33	Preeclampsia. Female infant: weight and Apgar scores NS. Newborn was normal.		
				3 rd	NS	NS	Female infant: weight and Apgar scores NS. Newborn was normal.			
			Non-Hodgkin lymphoma, B-cell	3 rd	Cyclophosphamide, Doxorubicin, Vincristine	NS	35	Male infant: weight and Apgar scores NS. Newborn was premature.		
			Non-Hodgkin lymphoma, Burkitt	2 nd First@after wk 16	NS	NS	NS	Female infant: weight and Apgar scores NS. Newborn was healthy.		
		1 st First@wk 13		"Multiagent chemotherapy"	NS	39	Female infant: weight and Apgar scores NS. Newborn was normal.			
		4 of 70 from Supplemental Data [only included cancer patients]	Non-Hodgkin lymphoma	1 st	NS	NS	41	Infant: sex, weight, and Apgar scores NS. Newborn was normal.		
				1 st and/or 2 nd	NS	NS	35	Male infant: weight and Apgar scores NS. Newborn was normal.		
				1 st	NS	Vaginal	<10 wks	Spontaneous abortion at < 10 wks of gestation. [No fetal data reported.]		
				1 st	NS	NS	38	Male infant: weight and Apgar scores NS. Newborn had ventricular septal defect, patent foramen ovale, and patent ductus arteriosus.		

Appendix C Table 55. Rituximab (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Rituximab (dose NS, 5 days)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd First@wk 28	Vincristine, Cyclophosphamide	C-section	29	Female infant: 1,263 g, Apgar scores 9 and 9 at 1 and 5 minutes. Newborn had respiratory distress and omphalitis, but no myelosuppression. Discharged at 46 days in adequate condition.	No	(Cordeiro <i>et al.</i> 2009)
Rituximab (375 mg/m ² on days 1-5 in a 14-day cycle, 6 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd	Vincristine, Doxorubicin, Cyclophosphamide	Vaginal	33	Spontaneous preterm labor. Female infant: weight within 50 th -90 th percentile, Apgar scores 8, 10, and 10. Newborn was healthy, but B-cells were severely diminished at birth; recovery began at 6 wks.	B-cell recovery complete by 12 wks. At 8 months, normal immunological response to vaccinations. At 16 months, no physiological or developmental abnormalities.	(Decker <i>et al.</i> 2006)
Rituximab (375 mg/m ² in 4 weekly cycles, followed by 4 cycles at 3-wk intervals)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd First@wk 16	Vincristine, Doxorubicin, Cyclophosphamide	C-section	41	Female infant: weight and Apgar scores NS. Newborn was healthy but with complete absence of B-cells. A fast B-cell recovery was seen in the wks following birth.	At 26 months, normal growth and development.	(Friedrichs <i>et al.</i> 2006)
Rituximab (375 mg/m ² on day 1 of 4-wk cycles, 4 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd First@wk 21	Vincristine, Doxorubicin	C-section	35	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 4 months, normal development, and B-cell population was normal.	(Herold <i>et al.</i> 2001)
Rituximab (375 mg/m ² once weekly for 4 wks)	Case report	1	Non-Hodgkin lymphoma	1 st	None	Vaginal	40	Female infant: 3,610 g, Apgar scores NS. Newborn was healthy with transient granulocytopenia and lymphopenia.	At 18 months, normal immunity and no major infections.	(Kimby <i>et al.</i> 2004)
Rituximab (Dose/schedule NS, 6 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 13 + 4 days	Cyclophosphamide, Vincristine, Doxorubicin, Cytarabine (IT)	Vaginal	39	Female infant: 2,270 g [SGA], Apgar scores 6 and 9. Newborn was viable with low birth weight.	At 7 months, healthy.	(Magloire <i>et al.</i> 2006)
Rituximab (375 mg/m ² on days 13, 18, 39, 42, 59, 62, and 89 of an 89-day course)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 16	Cyclophosphamide, Vincristine, Doxorubicin, Cytarabine, Etoposide, Ifosfamide	--	--	Decreased amniotic fluid at 18 wks of gestation, and early intrauterine growth retardation at 22 wks of gestation; similar effects at 23.5 wks of gestation. At 68 days of treatment, vaginal bleeding, spontaneous preterm labor, and no fetal heart tones. Stillbirth at gestation wk 26. [No fetal data reported.]	--	(Peterson <i>et al.</i> 2010)

Appendix C Table 55. Rituximab (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Rituximab (375 mg/m ² on day 1 of 3-wk cycles, 3 cycles)	Case report	1	Non-Hodgkin lymphoma, diffuse large B-cell	2 nd	Vincristine, Doxorubicin, Cyclophosphamide	C-section	33	Infant, sex NS: 2,500 g, Apgar scores 10, 10, and 10. Newborn was healthy.	At 35 months, completely normal growth.	(Rey <i>et al.</i> 2009)
Rituximab (Dose/schedule NS, 2 cycles)	Survey, retrospective	2 of 27 (Pts 18, 20)	Non-Hodgkin lymphoma	3 rd First@wk 29	Cyclophosphamide, Doxorubicin, Vincristine (2 nd , 3 rd)	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 27	Cyclophosphamide, Doxorubicin, Vincristine (2 nd , 3 rd)	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.		

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the rituximab timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; IT = intrathecal; SGA = small for gestational age.

Appendix C Table 56. Tamoxifen – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Tamoxifen (20 mg daily)	Case report	1	Breast	2 nd , 3 rd First@wk 20 Last@wk 35	5-Fluorouracil, Epirubicin, Cyclophosphamide, (1 st , 2 nd , 3 rd) Radiation analgesic (2 nd)	C-section	35	Signs of premature delivery [spontaneous preterm labor]. Female infant: 2,070 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was healthy with normal hematological and biochemistry parameters.	At 12 months, she showed no disorder, congenital abnormality, or disease.	(Andreadis <i>et al.</i> 2004)
Tamoxifen (Dose NS, daily)	Case report	1	Breast	1 st , 2 nd	Trastuzumab (Pt had history of opioid use. Other confounding factors: cigarettes, methadone, nifedipine tocolysis)	C-section	31	Oligohydramnios noted at 23 wks of gestation; intravenous fluids were given to mother. At 30 wks of gestation, twin A had minimal fluid re-accumulation, and twin B showed fluid re-accumulation. Preterm rupture of amniotic membranes. Male twins, fraternal: Twin A was 1,590 g, Apgar scores 5, 8, and 9 at 1, 5, and 10 minutes; twin B was 1,705 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn twin A had large (but otherwise normal) kidneys and dilated ureter at birth, intubation on first day of life only, then maintained on oxygen after extubation; chronic renal failure at 12 wks of age; and postnatal death at 13 wks of age by respiratory arrest. Newborn twin B needed oxygen at birth, but was self-ventilating by day 3; renal ultrasound scan was normal.	No	(Beale <i>et al.</i> 2009)
Tamoxifen (20 mg daily)	Case report	1	Breast	1 st Last@wk 6	None	Vaginal	32 + 3 days	At gestation wk 30, fetus diagnosed with clubfoot and questionable cleft palate. Gestational diabetes, severe preeclampsia, spontaneous pre-term labor.	No	(Berger and Clericuzio 2008)

Appendix C Table 57. Tamoxifen (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Male infant: 1,983 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn was dysmorphic with severe micro-retrognathia (hypoplastic mandibles and thin mandibular condyles), cleft palate, and glossoptosis (diagnostic of Pierre Robin sequence); also clubfoot, acetabular and sacral dysplasia, and hypoplastic mandible and thin mandibular condyles. Karyotype was normal. Airway obstruction developed, and the infant underwent tracheotomy. Family history revealed several paternal relatives with a baseline small mandible, but no clefting.		
Tamoxifen (20 mg daily)	Case report	1	Breast	1 st , 2 nd	X-rays (Mother may have smoked marijuana/cocaine 1 or 2 times per wk during first 6 wks of pregnancy)	C-section	26	Spontaneous preterm labor, chorioamnionitis, abnormal lie of the fetus. Infant, sex NS: 896 g, Apgar scores NS. Newborn had right-sided microtia, preauricular skin tags, and hemifacial microsomia consistent with Goldenhar syndrome. Karyotype was normal.	No	(Cullins <i>et al.</i> 1994)
Tamoxifen (80 mg twice daily for 7 days, 2 cycles)	Case report	1	Melanoma	2 nd First@wk 23 Last@wk 26.5	Carmustine, Cisplatin, Dacarbazine	C-section	30	Female infant: 1,520 g, Apgar scores NS. Newborn was healthy. Pathology revealed malignant melanoma in the placenta.	At 17 months (corrected to 15 months for early delivery), normal muscle tone and reflexes, and, overall, age-appropriate evaluations.	(DiPaola <i>et al.</i> 1997)

Appendix C Table 57. Tamoxifen (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Tamoxifen (20 mg daily)	Case report	1	Breast	1 st , 2 nd , 3 rd	None	C-section	31	Male infant: 1,940 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was healthy with preauricular skin tags and no other malformations. He required treatment for moderate hyaline membrane disease and enterocolitis.	At 24 months, well with normal developmental progress.	(Isaacs <i>et al.</i> 2001)
Tamoxifen (20 mg daily)	Case report	1	Breast	1 st First 4 wks	None	C-section	39	Female infant: 3,150 g, Apgar scores NS. Newborn was healthy with no congenital malformations; clinical and laboratory evaluations were normal.	At 66 months, healthy.	(Koca <i>et al.</i> 2010)
Tamoxifen (40 mg daily)	Case report	1	Melanoma	1 st , 2 nd	Carmustine, Dacarbazine, Cisplatin	C-section	34	Male infant: 2,750 g, Apgar scores 10 and 10 at 1 and 5 minutes. No dysmorphism was detected on clinical examination.	At 1 year, social, hearing, and gross and fine motor assessments were normal; however, he was diagnosed with microphthalmos and severe hypermetropia.	(Li <i>et al.</i> 2007)
Tamoxifen (Dose/schedule NS)	Case report	1	Breast	1 st	None	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was healthy.	At 27 months, the child was apparently healthy.	(Oksuzoglu and Guler 2002)
Tamoxifen (Dose/schedule NS)	Case report	1	Breast	1 st , 2 nd	None	C-section	38	Male infant: 3,205 g, Apgar scores NS. Newborn was healthy without any anomalies.	At 3 years, there were no problems associated with tamoxifen exposure.	(Simsek and Sever 2008)
Tamoxifen (20 mg daily)	Case report	1	Breast	1 st , 2 nd Last@wk 20	None	Vaginal	29	Female infant: 1,360 g, Apgar scores 8 and 8 at 1 and 5 minutes. Newborn had ambiguous genitalia. The clitoris was enlarged as a phallic-like structure. There was 1 common perineal opening (both urethra and vagina) and the posterior portion of the rugated labioscrotal folds were fused. Ultrasonography revealed a uterus and bilateral ovaries with no male structures.	At 6 months, reduction phalloplasty and reconstruction of vagina were carried out without complications.	(Tewari <i>et al.</i> 1997)

Appendix C Table 57. Tamoxifen (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Tamoxifen (20 mg daily)	Case report	1	Breast	1 st , 2 nd First@wk 7	Trastuzumab (1 st , 2 nd , 3 rd)	C-section	37	Anhydramnios detected at 28 wks of gestation; kidneys normal; bladder not observed. Female infant: 2,690 g, Apgar scores were good. Newborn showed signs of severe pulmonary hypoplasia and was intubated. X-ray revealed atelectasis. Intensive care was discontinued, and the baby died within 40 minutes.	--	(Warraich and Smith 2009)
Tamoxifen (Dose/schedule NS)	Cohort, retrospective	2 of 21 (Pts 3, 18)	Breast	1 st	5-Fluorouracil, Cyclophosphamide, Methotrexate, Vincristine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight per gestational age.	No	(Zemlickis <i>et al.</i> 1992a)
Tamoxifen (Dose/schedule NS)	Cohort, retrospective	1 of 21 (Pt 18)	Breast	3 rd	5-Fluorouracil, Doxorubicin, Cyclophosphamide	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight per gestational age.	No	(Zemlickis <i>et al.</i> 1992b)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the tamoxifen timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix C Table 58. Trastuzumab – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 wks)	Case report	1	Breast	1 st First@wk 1 Last@wk 1	None	C-section	39	Male infant: 3,550 g, Apgar scores NS. Newborn had normal renal, respiratory and cardiac functions.	At 14 months of age, normal growth and development.	(Azim <i>et al.</i> 2009a)
Trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 wks for 2 cycles)	Case report	1	Breast	2 nd , 3 rd First@wk 25 + 6 days Last@wk 28 + 5 days	Paclitaxel, Radiation therapy	C-section	32	Oligohydramnios, fetal renal failure, and cessation of fetal abdominal growth. Placental function was normal. Male infant: 1,460 g, Apgar scores NS. Newborn had bacterial sepsis with hypotension, transient renal failure, respiratory failure requiring mechanical ventilation (until age 6 days), and transient hyperechodensities in renal parenchyma (resolved by age 28 days). Discharged by 6 wks of age in healthy condition.	At 12 wks of age, normal development.	(Bader <i>et al.</i> 2007b)
Trastuzumab (Dose NS every 3 wks)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 21	Tamoxifen (Pt had history of opioid use. Other confounding factors: Cigarettes, methadone, and nifedipine tocolysis)	C-section	31	Oligohydramnios noted at 23 wks of gestation; intravenous fluids were given to mother. At 30 wks of gestation, twin A had minimal fluid re-accumulation, and twin B showed fluid re-accumulation. Preterm rupture of amniotic membranes. Male twins, fraternal: Twin A was 1,590 g, Apgar scores 5, 8, and 9 at 1, 5, and 10 minutes; Twin B was 1,705 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn Twin A had large (but otherwise normal) kidneys and dilated ureter at birth, intubation on first day of life only, then maintained on oxygen after extubation; chronic	No	(Beale <i>et al.</i> 2009)

Appendix C Table 59. Trastuzumab (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								renal failure at 12 wks of age; and postnatal death at 13 wks of age by respiratory arrest. Newborn Twin B needed oxygen at birth, but was self-ventilating by day 3; elevated creatinine peaked at day 5 then resolved. Renal ultrasound scan was normal.		
Trastuzumab (loading dose, then 2 mg/kg every 3 wks)	Case report	1	Breast	1 st First@wk 1	None	--	--	Induced abortion at gestation wk 6 due to ectopic pregnancy. No histological examination of embryo was performed.	--	(Berveiller <i>et al.</i> 2008)
Trastuzumab (6 mg/kg body weight, q21 [every 3 wks])	Case report	1	Breast	3 rd First@wk 30 Last@wk 33	Vinorelbine	C-section	33 + 5 days	Anhydramnios was detected 3 wks after start of chemotherapy. Female infant: 1,990 g, Apgar scores 8, 9, and 9 at 1, 5, and 10 minutes. She was in good health with no signs of malformation.	Follow-up examination [age NS] revealed no problems.	(El-Safadi <i>et al.</i> 2012)
Trastuzumab (4 mg/kg loading dose, then 2 mg/kg every 3 wks)	Case report	1	Breast	2 nd , 3 rd First@wk 27 Last@wk 34	Vinorelbine	Vaginal, induced	34	Oligohydramnios; amniotic fluid remained low despite intravenous fluids to mother. Male infant: 5 lb, 11oz [2,580 g], Apgar scores 9, 9, and 10. Newborn was healthy at birth.	At 6 months, healthy with normal development.	(Fanale <i>et al.</i> 2005)
Trastuzumab (Dose/schedule NS)	Case series	2	Breast	2 nd , 3 rd	None	C-section	29	Female infant: 1,220 g, Apgar scores NS. Newborn had respiratory distress syndrome, conductive hearing loss (resolved), mild hypertonia and hyperreflexia (resolved), and minimal tightening of left Achilles tendon.	At 3 years, no obvious neurological deficit, cognitively normal with height at the 50 th percentile, weight and head circumference at the 25 th percentile, and ongoing minimal tightening of left Achilles tendon.	(Goodyer <i>et al.</i> 2009)

Appendix C Table 59. Trastuzumab (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Breast	1 st Last@wk 6	None	Vaginal	39	Female infant: 2,940 g, Apgar scores NS. Newborn was healthy. Gastroenteritis at 3, 8, and 11 months of age (resolved).	At 2 years, normal growth and development. Gastroenteritis at 3, 8, and 11 months of age (resolved). At 2 years, normal growth and development.	
Trastuzumab (4 mg/kg weekly, 4 cycles)	Case report	1	Breast	2 nd First@wk 14 + 6 days Last@wk 17 + 6 days	Docetaxel (2 nd , 3 rd), Carboplatin (2 nd , 3 rd)	C-secsion	33 + 2 days	Anhydramnios and intrauterine growth restriction at 20 wks + 4 days of gestation. Male infant: weight less than 3 rd percentile (SGA), Apgar scores NS. Newborn showed inconspicuous development and normal renal function and urinalysis.	No	(Gottschalk <i>et al.</i> 2011)
Trastuzumab (390 mg, once every 3 wks)	Case report	1	Breast	1 st , 2 nd , 3 rd First@wk 1	None	Vaginal, induced	37	Oligohydramnios at 25 wks, treatment stopped and started again after 2 wks. Oligohydramnios again in 3 rd trimester. Male infant: 3,060 g, Apgar scores NS. Newborn was healthy but experienced transient tachypnea.	At 28 months, normal development.	(Mandrawa <i>et al.</i> 2011)
Trastuzumab (4,200 mg total dose)	Case report	1	Breast	1 st , 2 nd , 3 rd First@wk 1 Last@wk 30	None	Vaginal, induced	32	Low amniotic fluid at 25 wks, amniotic fluid in low end of normal range from 26-31 wks (checked weekly), and oligohydramnios at 32 wks of gestation. Female infant: 1,810 g; Apgar scores normal. Newborn was viable; renal ultrasound and echocardiogram were normal. Intubated for surfactant delivery for first 3 days of life; no further respiratory problems.	At 5 years, normal growth and development.	(Pant <i>et al.</i> 2008)

Appendix C Table 59. Trastuzumab (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Trastuzumab (Dose/schedule NS)	Case report	1	Breast	1 st , 2 nd Last@wk 21	None	Vaginal, induced	37	Male infant, 3,200 g, Apgar NS. Newborn had transient tachypnea requiring continuous positive airway pressure for 24 hours.	No	(Roberts and Auld 2010)
Trastuzumab (695 mg loading dose; 2 nd dose of 529 mg, 21 days later; 3 rd dose of 170 mg, 1 wk later)	Case report	1	Breast	2 nd First@wk 23 Last@wk 27	Docetaxel (2 nd , 3 rd)	C-section	36 + 2 days	Anhydramnios and fetal growth restriction at 30 wks of gestation. One pocket of amniotic fluid was noted at 33 wks, and small amount of clear amniotic fluid present at birth. Male infant: 2,230 g; Apgar scores 7 and 9 at 1 and 5 minutes. Newborn had no positional deformities or respiratory abnormalities at birth.	Subsequent development and neonatal urine output normal [age NS].	(Sekar and Stone 2007)
Trastuzumab (400 mg every 3 wks)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 24	None	C-section	37	Low ejection volume and mild low ejection volume [indicating decreased amniotic fluid] were observed at 18 and 24 wks of gestation, respectively. Female infant: 2,600 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy; treated for transient tachypnea for first 2 days of life.	At 2 months, infant was healthy with physical, neurological examination and developmental milestones within normal limits.	(Shrim <i>et al.</i> 2007)
Trastuzumab (736 mg loading dose, followed by 523 mg 21 days later)	Case report	1	Breast	1 st First@wk 1 Last@wk 1	None	Vaginal	Term	Female infant: body weight and Apgar scores NS. Newborn had no sequelae.	No	(Waterston and Graham 2006)

Appendix C Table 59. Trastuzumab (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Trastuzumab (588 mg loading dose, followed by 441 mg every 3 wks)	Case report	1	Breast	1 st , 2 nd , 3 rd First@wk 7 Last@wk 31	Tamoxifen, Goserelin	C-section	37	Anhydramnios detected at 28 wks of gestation; kidneys normal; bladder not observed. Female infant: 2,690 g, Apgar scores initially good. Newborn had no amniotic fluid at birth; severe pulmonary hypoplasia and atelectasis requiring intubation. Baby's condition continued to deteriorate despite intensive care. Infant died 40 minutes following extubation.	--	(Warraich and Smith 2009)
Trastuzumab (6 mg/kg, or 580 mg, every 3 wks)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 20	None	Vaginal, induced	37	Anhydramnios at 23 wks of gestation; fetal kidneys were of normal size and echogenicity; fetal bladder small. Amniotic fluid slowly increased. Female infant: 2,960 g, Apgar scores of 8 and 9. Newborn was viable with normal renal function, no pulmonary hypoplasia.	At 6 months, she was doing well with growth at 75 th percentile.	(Watson 2005)
Trastuzumab (Dose/schedule NS)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 23	None	C-section	27	Oligohydramnios noted at 23 wks of gestation. At 27 wks + 4 days of gestation, premature detachment of the placenta. Female infant: weight and Apgar scores NS. Newborn had multiple prematurity-related problems. At 3 days old, infant had non-optimal perfusion of kidneys. Dysplastic/hypoplastic left kidney and congestion of the kidneys was observed via	Infant died at 4 months of age.	(Weber-Schoendorfer and Schaefer 2008)

Appendix C Table 59. Trastuzumab (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								ultrasound. Kidney function continued to decrease. Infant also had various infections.		
Trastuzumab (6 mg/m ³ or 56 mg/kg, every 3 wks)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 27	None	C-section	27	Oligohydramnios and maternal vaginal bleeding at 26 wks of gestation. Female infant: 1,015 g, Apgar scores of 8/7/6. Newborn had an uncommonly strong capillary leak and respiratory failure necessitating intubation. Infant also had persistent infections and necrotizing enterocolitis.	Postnatal death at 21 wks due to multiple organ failure.	(Witzel <i>et al.</i> 2008)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the trastuzumab timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; q = quaque (Latin) or every; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 60. Vinblastine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinblastine (Dose/schedule NS)	Case series	1 of 13 (Pt 11)	Hodgkin lymphoma	2 nd , 3 rd	None	NS	34	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	(Abellar <i>et al.</i> 2009)
Vinblastine (6 mg/m ² on days 1 and 14; Pt 1, 2 cycles; Pt 5, 4 cycles; Pt 6, 3 cycles)	Case series	3 of 6 (Pts 1, 5, 6)	Hodgkin lymphoma	2 nd First@wk 21	Doxorubicin, Bleomycin, Dacarbazine	C-section	29	Female infant: 2,400 g, Apgar scores NS. Newborn was healthy.	At 10 years, she remained healthy.	(Anselmo <i>et al.</i> 1999)
				2 nd First@wk 16	Doxorubicin, Bleomycin	C-section	[~36]	Preeclampsia. Female infant: 2,180 g, Apgar scores NS. Newborn was healthy.	At 7 months, she remained healthy.	
				2 nd	Doxorubicin, Bleomycin	C-section	33	Female infant: 3,130 g, Apgar scores NS. Newborn was healthy.	No	
Vinblastine (5 mg/day)	Case report	1	Hodgkin lymphoma	1 st , 2 nd , 3 rd	None	Vaginal	Full term	Male infant: 7 lb 14 oz [3,572 g], Apgar scores NS. Newborn was normal.	At 2 months, he was thriving.	(Armstrong <i>et al.</i> 1964)
Vinblastine (Dose/schedule NS)	Case series, retrospective	10 of 14 (Pts 2, 3, 4, 6, 7, 8, 11, 12, 13, 14 in Table II)	Hodgkin lymphoma	2 nd [see note in reference column]	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	38	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
				1 st	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	37	Male infant: 3,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Doxorubicin, Bleomycin, Dacarbazine	C-section	34	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				3 rd	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	35	Female infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Bleomycin, Dacarbazine, Nitrogen mustard, Procarbazine, Vincristine	Vaginal	38	Female infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				3 rd	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	37	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	38	Female infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	40	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				1 st	Doxorubicin, Bleomycin, Dacarbazine	C-section	40	Female infant: 3,450 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
				2 nd	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Vinblastine (Dose/schedule NS)	Case series	1 of 14	Hodgkin lymphoma	“beginning of pregnancy”	NS	NS	NS	Infant sex, weight, and Apgar scores NS. Treatment was “without any influence on the outcome.”	No	(Carcassonne 1981)†

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinblastine (Dose/schedule NS)	Survey, registry	21 of 31 from Table 3 [22 of 32 conceptuses]	Hodgkin lymphoma	2 nd or 2 nd , 3 rd	Doxorubicin, Vinblastine, Bleomycin	NS	35.9 (group mean)	Infant sex NS: 2,587 g (group mean), Apgar scores NS. Twenty newborns had no malformations and normal body weight for gestational age, including 1 set of twins. Malformations observed in 2 infants: 1 had plagiocephaly, and 1 had syndactyly of the 4 th and 5 th fingers. Other effects: 1 infant had birthweight 15% [15 th percentile], and 3 infants had hypoglycemia.	At 0.5 to 10 years (n=20), all children were normal phenotype. At 4 to 112 months (group range, n=15), 1 child in the group had chronic broncolitis, 1 had recurrent otitis media, and 1 had asthma; group mean weight was 67 th percentile.	(Cardonick <i>et al.</i> 2010)
Vinblastine (0.12 mg/kg on days 1 and 2, 1 cycle)	Case report	1	Ovary	2 nd First@wk 19	Cisplatin, Bleomycin	Vaginal	Term	Male infant: 3,232 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn appeared healthy.	[At ~4.5 years,] normal development with a normal karyotype.	(Christman <i>et al.</i> 1990)
Vinblastine (Dose/schedule NS)	Case series	6 of 17 (only 6 pts received treatment during pregnancy)	Hodgkin lymphoma	NS	None	NS	NS	Infants' sex, weight, Apgar scores NS. Infants were normal at delivery.	At 2 to 17 years old (mean 15 years, n=17), children had no overt abnormalities.	(Connors 2008)
Vinblastine (Dose/schedule NS)	Case series	4 of 32 (Pts 8, 9, 18, 19)	Hodgkin lymphoma	3 rd First@wk 30 Last@wk 36	Doxorubicin, Bleomycin	C-section	36	Infant sex NS: 2,650 g, Apgar scores 8 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
				2 nd , 3 rd First@wk 15 Last@wk 35	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	36	Infant, sex NS: 2,190 g, Apgar scores 6 and 9. Newborn was healthy.		
				2 nd First@wk 24 Last@wk 27	Doxorubicin, Bleomycin, Dacarbazine	C-section	37	Infant, sex NS: 2,850 g, Apgar scores 8 and 8. Newborn was healthy.		
				2 nd First@wk 24 Last@wk 26	Doxorubicin, Bleomycin, Dacarbazine	C-section	37	Infant, sex NS: 2,450 g, Apgar scores 9 and 9. Newborn was healthy.		
Vinblastine (Dose/schedule NS; Pt 7 – 2 cycles 1 st pregnancy; Pt 10 – 2 cycles)	Case series	2 of 18 (Pts 7, 10; Pt 7 had 2 pregnancies)	Hodgkin lymphoma	1 st	Doxorubicin, Bleomycin, Dacarbazine	NS	NS	Male infant: 2,500 g, Apgar scores NS. Newborn had growth retardation (SGA), but was healthy and without hematological abnormalities [Pt 7, 1 st pregnancy].	At 65 months, alive.	(Dilek <i>et al.</i> 2006)

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd	Doxorubicin, Bleomycin, Dacarbazine	--	--	Fetal death [stillbirth] in the 8 th month. [No fetal data reported; Pt 7, 2 nd pregnancy]	--	
				1 st	Doxorubicin, Bleomycin, Dacarbazine	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had growth retardation (SGA) and a floating thumb malformation on the left hand (partial agenesis of a metacarpal bone and hypoplasia of 2 phalanges).	At 43 months, alive.	
Vinblastine (9 mg, 1 dose)	Case report	1	Hodgkin lymphoma	2 nd First@wk 17	Doxorubicin, Bleomycin, Dacarbazine	--	--	Induced abortion after first dose of chemotherapy. [No fetal data reported.]	--	(D'Incalci <i>et al.</i> 1983)
Vinblastine (Dose/schedule NS, 3 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 25	Doxorubicin, Bleomycin, Dacarbazine	C-section	38	Serial ultrasounds detected small for gestational age fetus. Male infant: 1,650 g [SGA], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 10 months, he remained well.	(Fadilah <i>et al.</i> 2006)
Vinblastine (Dose/schedule NS, 6 cycles)	Case report	1	Hodgkin lymphoma	1 st	Procarbazine, Nitrogen Mustard	NS	24	Male infant: weight, Apgar scores NS. Newborn had only 4 toes on each foot with webbing of the third and fourth toes of the right foot. Right pinna appeared to be slightly abnormal, and there was bowing of the right tibia. A large hemorrhage was found in the right cerebral hemisphere.	No	(Garrett 1974)
Vinblastine (0.2 mg/kg on day 1 of a 7-day cycle, 3 cycles)	Case report	1	Choriocarcinoma, ovary	3 rd First@wk 30	Actinomycin D Methotrexate	Vaginal, induced	37	Male infant: 5 lb 13 oz [2,637 g]. Apgar score 10. Newborn appeared normal but developed transitory focal seizures and a urinary tract infection, and was found to have unilateral talipes equinovarus (clubfoot).	At 5 months, results of physical examination were normal.	(Hutchison <i>et al.</i> 1968)
Vinblastine (6 mg/m ² , schedule NS, 3.5 cycles)	Case report	1	Hodgkin lymphoma	2 nd First@wk 21	Bleomycin, Doxorubicin, Dacarbazine	Vaginal	41	Female infant: weight was within normal limits. Apgar score 9. Newborn was healthy.	At follow-up [age NS], no physiological or developmental abnormalities.	(Iriyama <i>et al.</i> 2011)

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinblastine (Dose/schedule NS, 7-8 cycles)	Case series	2 of 18	Hodgkin lymphoma	NS	Doxorubicin, Bleomycin, Dacarbazine	NS	NS	Infants' sex, weight, and Apgar scores NS. Newborns were alive and healthy; no malformations were observed.	At follow-up, normal growth patterns without physical or neurological deficits (n=5 children, oldest child is 42 months).	(Jameel and Jamil 2007)
Vinblastine (Dose/schedule NS)	Survey, retrospective	NS [10 of 302 pts received chemotherapy while pregnant; the number of pts who received vinblastine while pregnant was not provided]	Hodgkin lymphoma	NS	Doxorubicin, Bleomycin, Dacarbazine	NS	NS	Individual treatments and pregnancy outcomes are not provided. In the total number of pregnancies, there were 4 perinatal deaths (5.7 expected), cancer subsequently developed in 2 (1.2 expected), and 22 infants had low birthweight (13.7 expected). The excess number of low weight births occurred primarily during the period of Hodgkin disease diagnosis and treatment.	[Not clear whether infants exposed <i>in utero</i> had follow-up.]	(Janov <i>et al.</i> 1992) [†]
Vinblastine (Dose/schedule NS)	Case report	1	Hodgkin lymphoma	3 rd First@wk 28	Procarbazine, Nitrogen mustard	Vaginal	31	Spontaneous preterm labor. Infant: 1,420 g, sex and Apgar scores NS. Newborn had mild anemia but otherwise thrived.	No	(Johnson and Filshie 1977)
Vinblastine (Dose/schedule NS)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 27	Doxorubicin, Bleomycin, Dacarbazine	C-section	39	Male infant: 2,350 g [SGA] , Apgar scores NS. Newborn was healthy and HIV negative (mother was HIV positive).	At 9 months, the baby was clinically well and HIV negative.	(Klepfish <i>et al.</i> 2000)
Vinblastine (5 mg/day on 2-6 days/wk)	Case report	1	Hodgkin lymphoma	1 st , 2 nd , 3 rd	Radiation therapy (8 th month)	Vaginal	Full term	Male infant: 6 lb 11 oz [3,033 g] , Apgar scores NS. Newborn had no abnormalities by physical exam.	At 2 months, thriving.	(Lacher 1964)
Vinblastine (5-10 mg approx weekly, 13 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 19	Cyclophosphamide (2 nd)	C-section	~37	Male infant: 3,060 g, Apgar score 9. Newborn was normal by physical examination, and blood count was normal.	At 17 months, growth and development were normal with no abnormal chromosomes.	(Lacher and Geller 1966)

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinblastine (0.25 mg/kg on days 1 and 2, 2 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 27	Bleomycin, Cisplatin	C-section	32	Male infant: 1,900 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn experienced a mild episode of transient tachypnea but was otherwise normal.	Subsequent normal development with no abnormalities [age NS].	(Malone <i>et al.</i> 1986)
Vinblastine (0.1 mg/kg on days 1 and 3, 3 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 20 Last@wk 28	Cisplatin, Bleomycin	C-section	31	Intrauterine growth restriction at 28 wks of gestation. Marked reduction in amniotic fluid at 31 wks of gestation. Maternal hypertension. Female infant: 1,070 g [SGA], Apgar scores NS. Newborn was apparently normal and healthy.	At 65 months, follow-up did not detect any sign of metabolic or hematologic abnormality.	(Motegei <i>et al.</i> 2007)
Vinblastine (Dose/schedule NS)	Survey, retrospective	3 of 27 [27 pts received chemotherapy while pregnant; the total number of pts who received vinblastine while pregnant was not provided]	Hodgkin lymphoma	1 st , 2 nd , 3 rd First@wk 9 Last@ term	Lomustine (1 st , Vincristine (1 st), Procarbazine (1 st)	NS	NS	Infant sex, weight, and Apgar scores NS. Cleft lip and cleft palate.	No	(Mulvihill <i>et al.</i> 1987)
				1 st First@wk 3	None	NS	NS	Infant sex, weight, and Apgar scores NS. Hydrocephalus.	No	
				1 st First@wk 6	None	--	--	Spontaneous abortion at gestation wk 6. [No fetal data reported.]	--	
Vinblastine (Dose/schedule NS)	Case series	2 of 17 (Pts N, P) (Pt P had 2 pregnancies)	Hodgkin lymphoma	2 nd , 3 rd	None	NS	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal.	No	(Nisce <i>et al.</i> 1986)
			Hodgkin lymphoma	1 st , 2 nd , 3 rd	None	Vaginal	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal. [Pt P, 1st pregnancy]	At 10 years, normal.	
			Hodgkin lymphoma	1 st , 2 nd , 3 rd	None	Vaginal	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal. [Pt P, 2nd pregnancy]	At 7 years, normal.	

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinblastine (7 mg, 14 mg, 30 mg, 1 wk apart)	Case report	1	Hodgkin lymphoma	3 rd	None	Vaginal	35	Septicemia, treated and resolved. Female infant: 5 lb 11 oz [2,580 g], Apgar scores NS. Newborn was healthy and normal on examination.	Child is doing well [age NS].	(Nordlund <i>et al.</i> 1968)
Vinblastine (6 mg/m ² , 2 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd	Nitrogen mustard, Vincristine, Procarbazine, Doxorubicin, Bleomycin	NS	NS	Female infant: weight and Apgar scores NS. Newborn had favorable outcome. Infant administered AZT for 6 wks because mother was HIV positive.	At 2 years, child was normal height and weight and was HIV positive.	(Okechukwu and Ross 1998)
Vinblastine (Dose/schedule NS)	Cohort, retrospective	1 of 14 (Pt 14)	Hodgkin lymphoma	1 st First@wk 3 Last@wk 7	Nitrogen mustard, Vincristine, Procarbazine, Doxorubicin, Bleomycin, Dacarbazine	--	--	Induced abortion in gestation wk 18. Fetus had no malformations, but toxic degenerative changes were present in the liver and kidneys, and placenta had villus degeneration and vascular toxic degeneration.	--	(Peres <i>et al.</i> 2001)
Vinblastine (9 mg, schedule NS)	Case report	1	Sarcoma, Kaposi	3 rd	Doxorubicin, Bleomycin	Vaginal	33-34	Female infant: 1,150 g, Apgar scores 6, 7, and 9 at 1, 5, and 10 minutes. Newborn was < 10 th percentile for weight, length, and head circumference; blood count and gases were normal; and mild hyperbilirubinemia required phototherapy.	At 4 months, apparently well and thriving.	(Rawlinson <i>et al.</i> 1984)
Vinblastine (10-20 mg monthly)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd	None	Vaginal	40	Female infant: 5 lb 15 oz [2,693 g ; SGA], Apgar scores NS. Newborn was in apparently good condition.	Child developed normally [age NS].	(Rosenzweig <i>et al.</i> 1964)
Vinblastine (6 mg/m ² on day 1, every 28 days, 3 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 25	Etoposide, Doxorubicin	C-section	36	Female infant: 2,190 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was healthy.	At 17 months, in good condition, including neurodevelopment assessed by Denver Developmental Screening test and no malignancies.	(Sagan <i>et al.</i> 2010)

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinblastine (Pt 6 – total 10 mg, Pt 13 – total 20 mg, schedules NS)	Case series	2 of 2 (Table 3; Pts 6, 13)	Hodgkin lymphoma	1 st	Vincristine, Procarbazine	Vaginal	NS	Male infant: 4 lb 2 oz [1,871 g], Apgar scores NS. On day 2, developed respiratory distress and died. Post-mortem found a small secundum atrial septal defect.	--	(Thomas and Peckham 1976)
			Hodgkin lymphoma	1 st	Procarbazine	--	--	Induced abortion. [No fetal data reported.]	--	
Vinblastine (Dose/schedule NS)	Survey, retrospective	2 of 27 (Pts 15, 16)	Hodgkin lymphoma	2 nd First@wk 24	Doxorubicin, Bleomycin, Dacarbazine	C-section	36	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
			Hodgkin lymphoma	2 nd , 3 rd First@wk 27	Doxorubicin, Bleomycin, Dacarbazine	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.	No	
Vinblastine (6 mg/m ² every 28 days)	Survey, retrospective	2 of 62 [62 pts received chemothera py while pregnant; the total number of pts who received vinblastine while pregnant was not provided]	NS	2 nd , 3 rd First @wk 25	Nitrogen Mustard, Vincristine, Procarbazine, Doxorubicin, Bleomycin	NS	NS	Infant sex, weight, and Apgar scores NS. Infant had pectus excavatum.	No	(Van Calsteren <i>et al.</i> 2010)
			NS	2 nd , 3 rd First@wk 26	Nitrogen Mustard, Vincristine, Procarbazine, Doxorubicin, Bleomycin, Radiation therapy (2 nd)	NS	NS	Infant sex, weight, and Apgar scores NS. Infant had bilateral partial syndactyly of digits 2 and 3.		
Vinblastine (Dose/schedule data limited; Table 1: Pt 33 – 4 cycles Table 2: Pt 43 – 3 cycles Pt 34 – 1 cycle)	Survey, retrospective	3 of 48 (Table 1: Pt 33; Table 2: Pts 43, 34)	Hodgkin lymphoma	2 nd , 3 rd	Nitrogen Mustard (1 st , 2 nd), Procarbazine (1 st , 2 nd), Vincristine (1 st , 2 nd)	NS	40	Infant: 3,400 g, sex and Apgar scores NS. Newborn was normal.	No	(Zuazu <i>et al.</i> 1991)

Appendix C Table 61. Vinblastine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Hodgkin lymphoma	1 st First@wk 11 Last@wk 11	Cyclophosphamide Procarbazine	C-section	38	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	No	
			Hodgkin lymphoma	3 rd First and Last@wk 30	Cyclophosphamide, Procarbazine	C-section	NS	Infant: sex, weight, and Apgar scores NS. Newborn with anemia that resolved.	At 3 years, normal at follow-up.	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the vinblastine timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not included in text analysis (highlighted in light grey). One case series was not included in the text analysis because it did not report data on the treatments, timing of exposure, and pregnancy outcomes of individual patients (Carcassonne 1981). One survey retrospective was excluded from the text analysis because it did not provide the individual treatments used or the timing of exposure and pregnancy outcomes of the 10 of 302 women who were treated with chemotherapy during pregnancy (Janov *et al.* 1992).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix C Table 62. Vincristine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS)	Case series	1 of 13 (Pt 10)	Non-Hodgkin lymphoma, diffuse large B-cell	2 nd , 3 rd	Cyclophosphamide, Doxorubicin	NS	32	Infant sex, weight, and Apgar scores NS. Newborn was within normal limits, including a normal body weight for gestational age.	No	(Abellar <i>et al.</i> 2009)
Vincristine (2 mg/m ² on days 1, 8, 15, and 22)	Case report	1	Leukemia, ALL	2 nd	Cyclophosphamide, Idarubicin	C-section	28	Male infant: 1,024 g, Apgar scores of 6, 8, and 8 at 1, 5, and 10 minutes. Newborn had no growth restriction or gross malformations. He had respiratory distress, necrotizing enterocolitis, and ventricular hemorrhage. Acute cardiac failure, attributed to idarubicin, occurred during the first 3 days after birth; infant was treated, and cardiac function returned to normal after 3 days.	At 18 months, neurological status was normal, but he showed a slight delay in language acquisition.	(Achtari and Hohfeld 2000)
Vincristine (2 mg/day on days 1,8,15, and 22)	Case report	1	Leukemia, ALL	3 rd	Daunorubicin, Cyclophosphamide, Asparaginase	C-section	33	Premature rupture of the membranes, fetal distress. Male infant: 1,750 g, Apgar scores 4 and 6 at 1 and 5 minutes. Newborn was morphologically normal but was pale, lethargic, tone decreased, and with respiratory distress requiring intubation (resolved by day 7). His condition improved, and he was discharged on day 17.	At 6 months, growth and development were normal.	(Ali <i>et al.</i> 2009a)
Vincristine (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, diffuse lymphoblastic	3 rd First@wk 31	Cyclophosphamide, Doxorubicin, Asparaginase, Cisplatin, Cytarabine	C-section	NS	Male infant: 2,600 g. Apgar scores NS. Newborn was apparently healthy.	At 2 years, no growth retardation, mental retardation, or malformations were noted.	(Ataerigin <i>et al.</i> 2007)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (1.4 mg/m ² every 3 wks, 2 cycles)	Case report	1	Ovary	2 nd , 3 rd	Doxorubicin, Cyclophosphamide	C-section	37	Female infant: 2,500 g, Apgar scores NS. Newborn was healthy with no abnormality. There were multiple tumor deposits in the placenta	No	(Ateser <i>et al.</i> 2007)
Vincristine (1 mg, 2 cycles)	Case report	1	Leukemia, ALL	2 nd	None	Vaginal	NS	Spontaneous preterm labor and delivery. Female infant: 1,400 g, Apgar scores NS. Newborn was normal.	No	(Avasthi and Agarwal 1993)
Vincristine (Dose/schedule NS)	Case series, retrospective	4 of 7 from Table I (Pts 1, 2, 5, 6)	Leukemia, ALL	1 st [see note in reference column]	Doxorubicin, 6-Mercaptopurine, Methotrexate, Cyclophosphamide	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 19 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	(Avilés <i>et al.</i> 1991) [This paper lists the beginning of treatment, but not the duration.]
			Leukemia, ALL	3 rd	Doxorubicin	Vaginal	38	Female infant: 4,300 g, Apgar scores NS. Newborn had no congenital malformations.	At 17 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, ALL	2 nd	Doxorubicin, Cyclophosphamide, Methotrexate, 6-Mercaptopurine	Vaginal	38	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 11 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st	Doxorubicin, Cyclophosphamide, Methotrexate, 6-Mercaptopurine	Vaginal	37	Male infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		7 of 14 from Table II (Pts 1, 5, 7, 8, 9, 10, 14)	Hodgkin lymphoma	1 st	Nitrogen Mustard, Procarbazine	C-section	38	Male infant: 4,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 17 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Hodgkin lymphoma	2 nd	Nitrogen Mustard, Procarbazine	Vaginal	39	Male infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Hodgkin lymphoma	1 st	Nitrogen mustard, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	Vaginal	38	Female infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Hodgkin lymphoma	3 rd	Nitrogen Mustard, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	Vaginal	37	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Hodgkin lymphoma	2 nd	Nitrogen Mustard, Procarbazine	Vaginal	39	Male infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Hodgkin lymphoma	2 nd	Nitrogen Mustard, Procarbazine	Vaginal	40	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Hodgkin lymphoma	2 nd	Nitrogen Mustard, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	Vaginal	36	Female infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
		18 of 18 from Table III	Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Doxorubicin	Vaginal	38	Female infant: 3,400 g, Apgar scores NS. Newborn had no congenital malformations.	At 18 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin, Bleomycin	C-section	39	Male infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 16 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Doxorubicin, Etoposide, Methotrexate	Vaginal	40	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 15 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin, Bleomycin	C-section	40	Male infant: 3,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 14 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Doxorubicin, Bleomycin	Vaginal	37	Female infant: 2,800 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin, Bleomycin, Cytarabine	Vaginal	37	Male infant: 2,900 g, Apgar scores NS. Newborn had no congenital malformations.	At 10 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Doxorubicin, Bleomycin	Vaginal	38	Female infant: 3,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Epirubicin, Bleomycin, Cytarabine, Etoposide, Methotrexate	Vaginal	37	Male infant: 2,850 g, Apgar scores NS. Newborn had no congenital malformations.	At 8 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin	Vaginal	38	Male infant: 2,500 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 9 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin, Bleomycin	Vaginal	38	Female infant: 4,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 7 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Doxorubicin	Vaginal	37	Female infant: 3,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Doxorubicin, Methotrexate, Cytarabine	Vaginal	39	Female infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 6 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Doxorubicin, Etoposide, Methotrexate	Vaginal	37	Male infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Doxorubicin, Bleomycin, Methotrexate, Cytarabine, Etoposide	Vaginal	40	Female infant: 4,000 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	2 nd	Cyclophosphamide, Doxorubicin, Bleomycin	C-section	38	Male infant: 3,200 g, Apgar scores NS. Newborn had no congenital malformations.	At 5 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	3 rd	Cyclophosphamide, Epirubicin, Bleomycin	Vaginal	39	Male infant: 3,100 g, Apgar scores NS. Newborn had no congenital malformations.	At 4 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Epirubicin, Bleomycin, Methotrexate, Etoposide, Cytarabine	Vaginal	40	Male infant: 2,800 g [SGA], Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide, Epirubicin, Bleomycin, Cytarabine	Vaginal	35	Female infant: 2,500 g, Apgar scores NS. Newborn had no congenital malformations.	At 3 years, physical, neurological, psychological, hematological, immune function, and cytogenetics were normal.	
Vincristine (2 mg – Pt 1 18 mg – Pt 2 24 mg – Pt 3 16 mg – Pt 4 8 mg – Pt 5 16 mg – Pt 6 16 mg – Pt 7 4 mg – Pt 8 12 mg – Pt 9 10 mg – Pt 10 14 mg – Pt 11 12 mg – Pt 12 2 mg – Pt 13 10 mg – Pt 14 12 mg – Pt 15 12 mg – Pt 16; schedule NS)	Case series	16 of 16	Non-Hodgkin lymphoma	2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Methotrexate	NS	NS	Individual pregnancy outcomes are not provided. Birth weights were 2,200-3,900 g (group range). All babies were born alive, and none of the newborns showed apparent congenital malformations.	At ages ranging from 3 to 11 years, normal growth and development.	(Avilés <i>et al.</i> 1990) [†]
				1 st , 2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Bleomycin					
				2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Bleomycin, Methotrexate					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Bleomycin					
				3 rd	Cyclophosphamide, Doxorubicin, Bleomycin, Methotrexate, Etoposide					
				1 st , 2 nd	Cyclophosphamide, Doxorubicin, Bleomycin					

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st , 2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Bleomycin, Methotrexate, 6-Mercaptopurine					
				3 rd	Cyclophosphamide, Doxorubicin, Methotrexate, Etoposide					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Doxorubicin					
				2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Methotrexate, Cytarabine					
				1 st , 2 nd	Cyclophosphamide, Doxorubicin, Bleomycin					
				2 nd , 3 rd	Cyclophosphamide, Doxorubicin, Methotrexate, Cytarabine, Etoposide					
				3 rd	Cyclophosphamide, Doxorubicin, Methotrexate, Etoposide					
				1 st , 2 nd , 3 rd	Cyclophosphamide, Bleomycin, Methotrexate, Cytarabine, Etoposide					
				3 rd	Cyclophosphamide, Doxorubicin					
				1 st , 2 nd	Cyclophosphamide, Doxorubicin, Bleomycin					

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS)	Case series, retrospective	10 of 29 from Table 1	Leukemia, ALL	NS	Doxorubicin, Cyclophosphamide, Methotrexate, 6-Mercaptopurine	NS	NS	Birth weight, group range: 2,500-3,675 g. Individual pregnancy outcomes, birth weights, and Apgar scores were not provided.	In this long-term follow-up, ranging from 5 to 26 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	(Avilés and Neri 2001) [†]
Vincristine (Dose/schedule NS)	Case series, retrospective	2 of 26 from Table 2	Hodgkin lymphoma	NS	Doxorubicin, Bleomycin, Vinblastine, Dacarbazine, Mustargen, Procarbazine	NS	NS	Birth weight, group range: 2,800-4,300 g. Individual pregnancy outcomes, birth weights and Apgar scores were not provided.	In this long-term follow-up, ranging from 5 to 26 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	
Vincristine (Dose/schedule NS)	Case series, retrospective	29 of 29 from Table 3	Non-Hodgkin lymphoma	NS	Doxorubicin, Cyclophosphamide, Bleomycin	NS	NS	Birth weight, group range: 2,350-4,050 g. Individual pregnancy outcomes, birth weights, and Apgar scores were not provided.	In this long-term follow-up, ranging from 5 to 26 years, learning and educational performances were normal, and no congenital, cytogenetic, neurological, or psychological abnormalities were observed.	
Vincristine (Dose/schedule NS)	Case series, retrospective	13 of 20 pregnancies (Pts 3, 6, 7, 8, 9, 10, 12, 13, 14, 15, 16, 17, 20); [12 of 18 patients, because 2 pts had 2 pregnancies each]	Leukemia, ALL	1 st , 2 nd , 3 rd	Methotrexate, Cyclophosphamide, 6-Mercaptopurine, Cytarabine	[Vaginal]	[40]	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn had no malformations.	At 12 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	(Avilés and Niz 1988) [Pts 3, 6, 7, 8, and 9 were first reported in Pizzuto <i>et al.</i> (1980): the cases are tallied using Aviles <i>et al.</i> (1988).]

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	1 st , 2 nd , 3 rd	Cytarabine, 6-Mercaptopurine, Methotrexate, Cyclophosphamide	[C-section]	[34]	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had pancytopenia and no malformations.	--	
			Leukemia, ALL	2 nd , 3 rd	Cytarabine, Methotrexate, 6-Mercaptopurine	[Vaginal]	[38]	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn had no malformations. At 90 days, died from gastroenteritis.	--	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Doxorubicin, Methotrexate, 6-Mercaptopurine	[C-section]	[33]	Female infant: 1,800 g, Apgar scores NS. Newborn had no malformations.	At 8 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	3 rd	Cytarabine	NS [C-section]	[38]	Female infant: 3,000 g, Apgar scores NS. Newborn had no malformations.	At 7 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Doxorubicin, 6-Mercaptopurine, Methotrexate	NS	NS	Female infant: 2,900 g, Apgar scores NS. Newborn had no malformations. [Pt A, 1 st pregnancy]	At 7 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	1 st , 2 nd , 3 rd	Cytarabine, Doxorubicin, 6-Mercaptopurine, Methotrexate	NS	NS	Female infant: 3,500 g, Apgar scores NS. Newborn had no malformations.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	2 nd , 3 rd	Doxorubicin, 6-Mercaptopurine, Methotrexate, Cyclophosphamide	NS	NS	Female infant: 2,700 g, Apgar scores NS. Newborn had pancytopenia and no malformations. At 4 wks, blood counts and bone marrow samples were normal.	At 6 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestation al age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	3 rd	Doxorubicin	NS	NS	Male infant: 3,100 g, Apgar scores NS. Newborn had no malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Doxorubicin, Methotrexate, 6-Mercaptopurine	NS	NS	Male infant: 2,600 g, Apgar scores NS. Newborn had no malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd	Doxorubicin, Methotrexate, 6-Mercaptopurine	NS	NS	Male infant: 2,850 g, Apgar scores NS. Newborn had no malformations. [Pt A, 2 nd pregnancy]	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, AML	1 st , 2 nd , 3 rd	Cytarabine, Doxorubicin	NS	NS	Female infant: 3,250 g, Apgar scores NS. Newborn had no malformations.	At 5 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Doxorubicin, Methotrexate, Etoposide, 6-Mercaptopurine	NS	NS	Female infant: 2,500 g, Apgar scores NS. Newborn had no malformations.	At 4 years, normal growth and development. Hematology, immune function, and cytogenetics were normal.	
Vincristine (2 mg weekly, 4 doses per cycle; Pt 1 and 2 – 2 cycles, Pt 3 and 4 – 1 cycle)	Case series	4 of 5 (Pts 1, 2, 3, 4)	Leukemia, ALL	2 nd First@wk 17 Last@wk 25	Doxorubicin, Asparaginase, Cyclophosphamide (2 nd , 3 rd), Methotrexate (2 nd , 3 rd), 6-Mercaptopurine (2 nd , 3 rd)	NS	~39	Female infant: 3,200 g, Apgar scores NS. Newborn was normal.	At 40 months, normal development and growth.	(Awidi <i>et al.</i> 1983)
			Leukemia, ALL	3 rd First@~wk 35	Doxorubicin	NS	~39	Male infant: 2,900 g, Apgar scores NS. Newborn was normal.	At 29 months, normal development and growth.	
			Leukemia, ALL	3 rd First@~wk 35	Doxorubicin	NS	~40	Male infant: 3,300 g, Apgar scores NS. Newborn was normal.	At 32 months, normal development and growth.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	2nd First@~wk 16	Doxorubicin, Cytarabine	--	--	Spontaneous abortion. [No fetal data reported.]	--	
Vincristine (1 mg/m ² , 4 cycles)	Case report	1	Cervix	2 nd , 3 rd First@wk 23 Last@wk 32	Cisplatin	C-section	32 + 6 days	Male infant: 1,920 g, Apgar scores 9, 10, and 10 at 1, 5, and 10 minutes. Newborn developed respiratory distress syndrome that required mechanical ventilation until day 5. He then developed normally and was discharged at 4 wks in good condition.	[At ~77 months,] he was healthy.	(Bader <i>et al.</i> 2007a)
Vincristine (1 mg/m ² on days 1 and 9)	Case report	1	Leukemia, APL	2 nd First@wk 21	6-Thioguanine, Cytarabine, Vincristine	C-section	30	Preeclampsia at days 5 and 15 of chemotherapy, treated and resolved. Male infant: 1,320 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was normal with normal blood work. At 20 minutes, he experienced tachypnea and progressive respiratory failure requiring intermittent ventilation. By 3.5 hours, he had developed severe respiratory distress syndrome requiring intubation (resolved within 6 days after treated with surfactant).	At 70 days, infant discharged from the hospital in excellent condition with normal hematological values and karyotype.	(Bartsch <i>et al.</i> 1988)
Vincristine (Dose NS, once monthly)	Case series	2 of 2	Leukemia, ALL	1 st First@wk 3 Lst@wk 4	Methotrexate, 6-Mercaptopurine	--	--	Spontaneous abortion [at ~6 wks of gestation. No fetal data reported.]	--	(Bergstrom and Altman 1998)
				1 st , 2 nd	Methotrexate, 6-Mercaptopurine	Vaginal, induced	32	Preeclampsia at 32 wks. Female infant: 4 lb 15 oz [2,240 g] , Apgar scores NS. Newborn revealed no abnormalities.	Subsequent exams [age NS] showed no abnormalities.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (2 mg, schedule NS)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd [First@ month 7]	Cyclophosphamide, Methotrexate (intrathecal)	Vaginal	7 th month	Spontaneous preterm labor 1 wk after starting chemotherapy. Female infant: weight and Apgar scores NS. Newborn was premature, but healthy.	At 3 years, general growth was satisfactory. Hematological parameters, bone marrow, Ig levels, lymphocyte function and karyotype were within normal levels.	(Berrebi <i>et al.</i> 1983)
Vincristine (Dose/schedule NS)	Case series, retrospective	4 of 24 (Pts 1, 5, 15, and 16)	Sarcoma, undifferentiated	1 st First@month 3	Cyclophosphamide, Doxorubicin, AMSA	NS	No births were premature [Term]	Male infant: 6 lb 5 oz [2,863 g], Apgar scores NS. Birth weight was normal [for gestational age].	At 2.5 years, normal.	(Blatt <i>et al.</i> 1980)
			Leukemia, AML	3 rd	Methotrexate, 6-Mercaptopurine	NS	No births were premature [Term]	Female infant: 6 lb 3 oz [2,807 g], Apgar scores NS. Newborn had no major abnormalities, and birth weight was normal [for gestational age].	At 8 years, normal.	
			Hodgkin lymphoma	1 st	Radiation therapy, Nitrogen mustard, Procarbazine	--	--	Induced abortion in 1 st trimester. [No fetal data reported.]	--	
			Hodgkin lymphoma	1 st	Nitrogen mustard, Procarbazine	NS	No births were premature [Term]	Male infant: 7 lb 12 oz [3,515 g], Apgar scores NS. Newborn was normal, and birth weight was normal [for gestational age].	No	
Vincristine (Dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Daunorubicin, Asparaginase, Cytarabine (intrathecal), Methotrexate (intrathecal)	C-section	30	Female infant: 1,266 g, Apgar scores 5 and 8 at 1 and 5 minutes. Newborn's physical examination, hematological parameters, sepsis assessment, and cancer screening were normal.	No	(Bottsford-Miller <i>et al.</i> 2010)
Vincristine Dose/schedule NS, 8 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Doxorubicin, Cyclophosphamide	Vaginal, induced	34	Infant sex NS: 3,043 g, Apgar scores 9, 9, and 9. The newborn was not compromised.	No	(Brown <i>et al.</i> 2001)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestation al age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose NS on day 8 of an 8-day regimen, 4 cycles)	Case report	1	Choriocarcinoma, uterus	NS [2 nd] [First@> wk 20]	Actinomycin D, Etoposide, Methotrexate, Cyclophosphamide	Vaginal	32	Spontaneous preterm delivery. Female infant: 1,383 g, Apgar scores 8 and 9. Newborn was developmentally normal.	At 42 months, normal development.	(Brudie <i>et al.</i> 2011)
Vincristine (Dose/schedule NS)	Case report	1	Leukemia (ALL)	2 nd , 3 rd First@wk 17	Daunorubicin, Asparaginase	C-section	NS [~30]	Male infant: weight and Apgar scores NS. Newborn was normal.	At 3 years, alive and well with no medical problems.	(Camera <i>et al.</i> 1996)
Vincristine (Dose/schedule NS)	Case series	1 of 14	Hodgkin lymphoma	From the 6 th month [2 nd , 3 rd]	Nitrogen mustard, Procarbazine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was premature, but normal.	No	(Carcassonne 1981)†
Vincristine (Dose/schedule NS)	Survey, registry	2 of 3 from Table 5	Leukemia, ALL	2 nd , 3 rd	Cytarabine, Cyclophosphamide, Daunorubicin, 6-Mercaptopurine, Methotrexate, Asparaginase	NS	35.5 (group mean)	Infant sex NS: 2,341 g (group mean), Apgar scores NS. Both newborns were normal with normal body weight for gestational age.	At 3.2 or 9 years, normal phenotype. At 41 to 109 months (group range, n=2), no long-term complications; group mean weight was 65 th percentile.	(Cardonick <i>et al.</i> 2010)
		8 of 31 from Table 3	Non-Hodgkin lymphoma	2 nd , 3 rd	Doxorubicin, Cyclophosphamide, Rituximab	NS	34.0 (group mean)	Infant sex NS: 2,576 g (group mean), Apgar scores NS. One fetus died at 30 wks; autopsy was normal. Seven newborns were normal with normal body weight for gestational age. One infant had jaundice and anemia, and 1 infant jaundice and transient tachypnea.	At 0.2 to 5.3 years (group range, n=20), all children were normal phenotype. At 34 to 82 months (group range, n=6), 1 child in the group had a speech delay; group mean weight was 46 th percentile.	
		1 of 31 from Table 3	Hodgkin lymphoma	2 nd , 3 rd	None	NS	35.9 (group mean)	Infant sex NS: 2,587 g (group mean), Apgar scores NS. Newborn had intrauterine growth retardation (SGA), but was otherwise normal.	No	
		1 of 12 from Table 6	Rhabdomyosarcoma	2 nd , 3 rd	Cyclophosphamide, Actinomycin D	C-section	33	Male infant: 2,948 g, Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 5.3 years normal phenotype.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
		1 of 12 from Table 6	Cervix	2 nd , 3 rd	Cisplatin	NS	32 (group mean)	Infant sex NS; 2,173 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 12 to 87 months (group range, n=4 [counted as n=1 in text analysis]), no long-term complications; group mean weight was 59 th percentile.	
		1 of 12 from Table 6	Lung	2 nd , 3 rd	Cisplatin, Vinorelbine, Radiation therapy	NS	36	Infant sex NS; 2,495 g, Apgar scores NS. Newborn was normal with normal body weight for gestational age; placenta had areas of infarction.	At 2 months, there were no complications.	
Vincristine (Dose/schedule NS)	Survey, retrospective – utilizing data from the rituximab global drug safety database	3 of 20 from Table 2	Non-Hodgkin lymphoma, B-cell	3 rd	Cyclophosphamide, Doxorubicin, Rituximab	NS	35	Male infant: weight and Apgar scores NS. Newborn was premature.	No	(Chakravarty <i>et al.</i> 2011) [This entry excludes 3 published case reports that are already included in our table: (Herold <i>et al.</i> 2001, Decker <i>et al.</i> 2006, Friedrichs <i>et al.</i> 2006).
				2 nd First@wk 18	Cyclophosphamide, Doxorubicin, Rituximab	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal.		
				2 nd First@wk 21	Cyclophosphamide, Doxorubicin, Rituximab	NS	33	Preeclampsia. Female infant: weight and Apgar scores NS. Newborn was normal.		
Vincristine (Dose/schedule NS)	Survey, retrospective	3 of 37 from Table 1 (Pts 13, 30, 35)	Leukemia, ALL	1 st (Diagnosis @wk 9) (Pt 13)	Daunorubicin, Cyclophosphamide	--	--	Induced abortion. [No fetal data reported.]	--	(Chelghoum <i>et al.</i> 2005) [In addition, 1 patient diagnosed in

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, ALL	1 st (Diagnosis @wk 10) (Pt 30)	Daunorubicin, Cyclophosphamide	--	--	Induced abortion. [No fetal data reported.]	--	the 3 rd trimester and treated with vincristine (Pt 34) was not included because it was not possible to determine if the pt received chemotherapy during pregnancy.]
			Leukemia, ALL	1 st (Diagnosis @wk 9)(Pt 35)	Daunorubicin, Cyclophosphamide	--	--	Induced abortion. [No fetal data reported.]	--	
Vincristine (1 mg daily, then weekly for 4 wks)	Case report	1	Leukemia, AML	2 nd [First@wk 16 Last@wk 22]	Methotrexate, 6-Mercaptopurine (2 nd , 3 rd)	C-section	37	Preeclampsia [at gestation wk 36]. Male infant: 6 lb [2,722 g], Apgar score 7. Newborn was normal.	At 2 years, no deleterious effects of the chemotherapeutic agents.	(Coopland <i>et al.</i> 1969)
Vincristine (Dose/schedule NS)	Case report	1	Kidney, Wilms tumor	2 nd	Actinomycin D	C-section	28	Female infant: 1,130 g, Apgar scores NS. Newborn had no abnormalities but suffered respiratory stress syndrome and was in the neonatology unit for 2 months.	At 10 months, healthy.	(Corapcioglu <i>et al.</i> 2004)
Vincristine (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma, Burkitt	3 rd First@wk 28	Rituximab, Cyclophosphamide	C-section	29	Female infant: 1,263 g, Apgar scores 9 and 9 at 1 and 5 minutes. Newborn had respiratory distress and omphalitis, but no myelosuppression. Discharged at 46 days in adequate condition.	No	(Cordeiro <i>et al.</i> 2009)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (2 mg (1.4 mg/m ²) on days 1 and 8 of 28-day cycle; through remainder of pregnancy)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 18	Cyclophosphamide, Procarbazine	NS	37	Female infant: 2,000 g [SGA], Apgar scores NS. Newborn had no abnormalities, and chromosomal analysis was normal.	At 1 year, no abnormalities.	(Daly <i>et al.</i> 1980)
Vincristine (Dose NS, every 3 months, then weekly)	Case report	1	Leukemia, ALL	1 st , 2 nd , 3 rd	6-Mercaptopurine (1 st), Cytarabine (3 rd), Methotrexate (1 st , 3 rd) Doxorubicin (2 nd)	C-section	36	Male infant: 2,400 g, Apgar scores NS. Newborn was polycythemic and hyperbilirubinemic, with no congenital defects.	At 6 months, normal growth and development.	(Dara <i>et al.</i> 1981)
Vincristine (Dose/schedule NS)	Case series	2 of 32 (Pts 20, 30)	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 24 Last@wk 37	Doxorubicin, Etoposide, Bleomycin, Cytarabine, Cyclophosphamide	C-section	35	Infant sex NS: 1,980 g, Apgar scores 8 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
				3 rd First@wk 34 Last@wk 37	Epirubicin, Etoposide, Cytarabine, Bleomycin, Cyclophosphamide	Vaginal	36	Infant sex NS: 3,020 g, Apgar scores 9 and 9. Newborn was healthy.	No	
Vincristine (1.4 mg/m ² /day on days 1-5, 6 cycles on 14-day schedule)	Case report	1	Non-Hodgkin lymphoma	2 nd	Doxorubicin, Rituximab, Cyclophosphamide	Vaginal	33	Spontaneous preterm labor. Female infant: weight within 50 th -90 th percentile, Apgar scores 8, 10, and 10. Newborn was healthy, but B-cells were severely diminished at birth (recovery began at 6 wks, complete by 12 wks). Normal immunological response to vaccinations at 8 and 16 wks.	At 16 months, no physiological or developmental abnormalities.	(Decker <i>et al.</i> 2006)
Vincristine (Dose/schedule NS)	Case series	3 of 18 (Pts 8, 11, 13)	Hodgkin lymphoma	1 st	Nitrogen mustard, Procarbazine	Vaginal	NS	Female infant: 3,000 g, Apgar scores NS. Newborn was healthy. At 3 months, died of severe gastroenteritis.	No	(Dilek <i>et al.</i> 2006)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Hodgkin lymphoma	1 st [Text says 1 st , Table says postpartum]	Doxorubicin, Cyclophosphamide	NS	Term	Female infant: 3,000 g, Apgar scores NS. Newborn was normal with no pathological findings.	At 12 months, she was alive.	
			Non-Hodgkin lymphoma	2 nd , 3 rd	Doxorubicin, Cyclophosphamide	NS	Term	Male infant: 2,500 g, Apgar scores NS. Newborn had low birth weight but no hematological abnormality.	At 35 months, he was alive.	
Vincristine (1.4 mg/m ² on day 1)	Case report	1	Hodgkin lymphoma	3 rd First@wk 29	Cyclophosphamide	C-section	35	Female infant: 2,300 g, Apgar scores NS. Newborn was well.	No	(D'Incalci <i>et al.</i> 1982)
Vincristine (Pt 1 – 1 mg, once; Pt 2 – 1 mg/m ² on days 1 and 7; Pt 3 – 1 mg/m ² on days 1 and 7, followed by a second cycle at 30% higher dose)	Case series	3 of 3	Leukemia, AML	3 rd	Methotrexate, 6-Mercaptopurine	Vaginal	34	Premature rupture of membranes. Female infant: 2,350 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had a cushingoid appearance.	At 8 wks, weight and height were normal for gestational age.	(Doney <i>et al.</i> 1979)
				2 nd	Hydroxyurea, Daunorubicin, Cytarabine, 6-Thioguanine	--	--	Induced abortion at gestation wk 21. Male fetus: 307.8 g. Fetus had no external defects or gross abnormalities, and had normal organ weights, except for an enlarged spleen.	--	
				3 rd	Hydroxyurea, Daunorubicin, Cytarabine, 6-Thioguanine	Vaginal	31	Spontaneous preterm labor at 4 wks after admission. Male infant: 2,130 g, Apgar scores 7 and 8 at 1 and 5 minutes. Newborn was premature and for 2 days was anemic, hyponatremic, hyperkalemic, and hypoglycemic – resolved within 7 months.	At 4 months, experiencing mild infections. At 4.5 and 13.5 months, Denver Developmental Screening tests were normal. At 13.5 months, complete blood count and general physical examination were unremarkable, but growth parameters were depressed (< 3 rd percentile).	
Vincristine (2 mg, 3 cycles)	Case report	1	Leukemia, AML	3 rd First@wk 31	Cytarabine	Vaginal	39	Male infant: 2,967 g, Apgar scores NS. Newborn was normal with normal blood count.	At 30 months, normal development and excellent health.	(Durie and Giles 1977)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS)	Case series	1 of 2 (Pt 2)	Leukemia, AML	1 st Last@wk 8	Cytarabine, Doxorubicin	Vaginal	NS	Female infant: weight and Apgar scores NS. Newborn had an atrial septum defect and bilateral loss of radius and fifth digit.	No	(Ebert <i>et al.</i> 1997)
Vincristine (Dose/schedule NS, 2 cycles)	Case report	1	Neuroendocrine carcinoma, vagina	2 nd First@wk 17 Last@wk 27	Doxorubicin, Cyclophosphamide	C-section	29	Male infant: 1,100 g, Apgar scores 5 and 6 at 1 and 5 minutes. Newborn was viable and, because of prematurity, received intensive care for 55 days, at which time he was discharged without complications.	At 6 years, highly functional with no neurodevelopmental delays.	(ElNaggar <i>et al.</i> 2012)
Vincristine (1.2 mg/m ² on day 1, 8 cycles)	Case report	1	Non-Hodgkin lymphoma	1 st , 2 nd , 3 rd First@wk 13 Last@wk 34	Bleomycin, Cyclophosphamide	Vaginal	Term	Male infant: 2,500 g, Apgar scores NS. Newborn had no signs of abnormalities.	At 1 year, normal development. Chromosomal banding studies detected no abnormalities	(Falkson <i>et al.</i> 1980)
Vincristine (Pt 1 – 2 mg on day 2, Pt 2 – 2 mg on day 2, Pt 3 – 2 mg on day 2, Pt 4 – 2 mg on day 2, Pt 5 – 2 mg/wk for 5 wks)	Case series	5 of 5	Leukemia, APL	1 st First@wk 11	Doxorubicin, Cytarabine	--	--	Induced abortion at gestation wk 19. Histologic and karyotypic examinations of fetus were not performed.	--	(Fassas <i>et al.</i> 1984)
			Leukemia, AML	2 nd First@wk 17	Doxorubicin, Cytarabine	Vaginal	37	Spontaneous preterm labor. Male infant: 2,430 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no congenital abnormalities, and blood count was normal.	At 3-4 months, increased leukocyte count and lymphocytic with occasional nucleated red blood cells in smear. At 20 and 30 months, normal blood count. At 37 months, normal growth and development.	
			Leukemia, AML	3 rd First@wk 36	Doxorubicin, Cytarabine	Vaginal	NS [37]	Male infant: 3,100 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was normal with normal blood count.	At 36 months, normal growth and development with no hematological abnormality.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	3 rd First@wk 31	Doxorubicin, Cytarabine	C-section	38	Male infant: 3,140 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with normal blood profile.	No	
			Leukemia, ALL	2 nd , 3 rd First@wk 26 Last@ wk 31	Vindesine (3 rd)	C-section	39	Male infant: 3,700 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no congenital abnormalities, and blood profile was normal.	At 1 year, normal physical and mental development and normal blood count.	
Vincristine (Pt 2 – 2 mg, schedule NS; Pt 4 – Dose NS, weekly)	Case series	2 of 5 (Pts 2, 4)	Leukemia, AML	1 st , 3 rd	Methotrexate (1 st), 6-Mercaptopurine (1 st), Doxorubicin (1 st), Daunorubicin (3 rd), Cytarabine (3 rd)	Vaginal	38	Female infant: 2,800 g, Apgar scores 8 and 10 at 1 and 5 minutes.	At 7 years, normal development.	(Feliu <i>et al.</i> 1988)
			Leukemia, AMML	1 st , 2 nd	6-Mercaptopurine (1 st), Daunorubicin, Cytarabine	--	--	Mother and fetus died at 23 wks of gestation. Fetal morphology was normal.	--	
Vincristine (2 mg/day on days 1 and 14, 2 cycles)	Case report	1	Rhabdomyosarcoma	2 nd First@wk 23	Ifosfamide, Actinomycin D	C-section	29	Anhydramnios and fetal growth restriction at 4 wks after chemotherapy administration. Female infant: 720 g [SGA], Apgar scores 3, 7, and 7 at 1, 5, and 10 minutes. Newborn exhibited anuria and didn't pass urine for 7 days, at which time she died. Postnatal cerebral ultrasound detected bilateral intraventricular hemorrhage and left occipital meningeal hematoma. Autopsy found extensive cerebral lesions associated with prematurity but revealed no renal lesions or chromosome abnormality.	--	(Fernandez <i>et al.</i> 1989)††

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								Placenta revealed large areas of ischemic necrosis without chorioamnionitis.		
Vincristine (2.0 mg IV weekly for 12 wks)	Case report	1	Ovary	2 nd , 3 rd First@wk 20 Last@wk 32	Actinomycin D, Cyclophosphamide	Vaginal	39 + 6 days	Male infant: 4,310 g, Apgar scores 8 and 9 at 1 and 5 minutes.	No	(Frederiksen <i>et al.</i> 1991)
Vincristine (Dose NS, 6 cycles at 3-wk intervals)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd	Rituximab, Doxorubicin, Cyclophosphamide	C-section	41	Female infant: weight and Apgar scores NS. Newborn was healthy, but with complete absence of B-cells. A fast B-cell recovery was seen in the wks following birth.	At 26 months, normal growth and development.	(Friedrichs <i>et al.</i> 2006)
Vincristine (1 mg/m ²)	Case series	1 of 9 (Pt 1)	Cervix	2 nd and/or 3 rd First@after 16 wks (median)	Cisplatin	C-section	35 (median; range 30-36)	Infant (sex NS): 1,330 g, Apgar scores NS. Newborn had no congenital malformations.	No	(Fruscio <i>et al.</i> 2012)
Vincristine (4 mg, 4 cycles)	Case series	1 of 15 (Pt 8)	Cervix	2 nd First@wk 23	Cisplatin	C-section	32.1	Infant sex NS: 1,690 g, Apgar scores 5 and 8 at 1 and 5 minutes. Newborn was well with no malformations, but had anemia.	Children were well and healthy at follow-up at ages 2 to 198 months.	(Gambino <i>et al.</i> 2011)
Vincristine (2 mg on day 1 of 28-day cycle)	Case report	1	Non-Hodgkin lymphoma	1 st	Doxorubicin, Cyclophosphamide	Vaginal	NS	Male infant: 3,400 g, Apgar score 10 after 10 minutes. Newborn had a normal appearance.	At 2 months, satisfactory condition.	(Garcia <i>et al.</i> 1981)
Vincristine (Dose/schedule NS, 2 cycles)	Case series	1 of 2 (Pt 2)	Non-Hodgkin lymphoma, large B-cell	3 rd First@wk 28 Last@wk 32	Cyclophosphamide Doxorubicin	Vaginal	33	Male infant: 1,645 g, Apgar scores 8 and 9 at 1 and 5 minutes. Developed necrotizing enterocolitis that was successfully treated and leukopenia that resolved in 2 days.	No	(Garcia <i>et al.</i> 1999)
Vincristine (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma	3 rd	Doxorubicin, Cyclophosphamide	Vaginal	Full term	Female infant: 2,800 g, at 4 wks, Apgar scores NS. Newborn had no congenital abnormalities.	At 4 wks, infant weighed 2,800 g; chromosomal analysis revealed no breaks or translocation. At 26 months, doing well.	(Garg and Kochupillai 1985)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestation al age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Mean dose = 2 mg/m ² ; Pt 2 received 1 cycle; Pt 8 received 4 cycles)	Survey, retrospective	2 of 20 (Pts 2, 8)	Breast	1 st First@wk 6	Epirubicin, Methotrexate	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Giacalone <i>et al.</i> 1999)††
				2 nd , 3 rd First@wk 26	Doxorubicin	Vaginal	35	Infant sex and weight NS: Apgar scores 10 and 10 at 1 and 4 minutes. Newborn was normal with normal body weight for gestational age.	At 20 months, alive and well.	
Vincristine (2 mg on day 1, 2 cycles)	Case report	1	Sarcoma, Ewing	3 rd First@wk 29 Last@wk 32	Doxorubicin, Actinomycin D, Cyclophosphamide, Radiation therapy	Vaginal, induced	36	Female infant: 5 lb 3 oz [2,353 g] , Apgar scores 9 and 9. Newborn was normal appearing.	At 3 months, growing adequately with no known abnormalities.	(Gililand and Weinstein 1983)
Vincristine (2 mg on days 1, 15, 30, 45)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 21 Last@wk 28	Epirubicin	Vaginal, induced	34	Female infant: 2,320 g, Apgar scores 8 and 8 at 1 and 5 minutes. Newborn appeared normal.	At ~4 years, seemed to be normal.	(Goldwasser <i>et al.</i> 1995)
Vincristine (Dose/schedule NS)	Case series	3 of 17 (Pts 2, 11, 15)	Leukemia, ALL	2 nd First@wk 18	Daunorubicin, Cytarabine	--	--	Mother and fetus died during pregnancy [at ~gestation wk 24; no fetal data.]	--	(Greenlund <i>et al.</i> 2001)
			Non-Hodgkin lymphoma AML	2 nd First@wk 24	Doxorubicin, Cytarabine, 6-Thioguanine	NS	31.5	Female infant: 1,135 g [SGA] , Apgar scores NS. Newborn had no malformations.		
			Non-Hodgkin lymphoma AML	2 nd First@wk 20	6-Mercaptopurine	NS	36	Male infant: 2,130 g [SGA] , Apgar scores NS. Newborn had no malformations.		
Vincristine (Dose/schedule NS)	Case series, retrospective	2 of 14 from Table 1 (Pts 7 and 11)	Leukemia, AML, ALL	3 rd First@wk 34	Cytarabine, 6-Thioguanine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal, but had low hemoglobin.	At 26 months, constant cold, weight < 10 th percentile. Growth was 10 th percentile. Immune function test and complete blood count (CBC) were normal.	(Gulati <i>et al.</i> 1986)
			Leukemia, ALL	7 months [3rd]	Methotrexate	NS	38	Infant sex, weight, and Apgar scores NS. Newborn was normal but small for gestational age (SGA).	At 14 months, under 5 th percentile for height and weight.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestation al age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS)	Case report	1	Sarcoma, Ewing	2 nd , 3 rd [First@> wk 25]	Actinomycin D, Cyclophosphamide, Bleomycin, Doxorubicin	C-section	34	Female infant: 1,750 g, Apgar scores 7 and 9. Infant required intravenous calcium and was treated for mild respiratory distress syndrome for 2 days. No major problems after 3 days.	Child progressing normally [age NS, > 4 years later].	(Haerr and Pratt 1985)
Vincristine (Dose NS, days 1,8,15,22, then days 15, 22 twice, 3 cycles)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 26 Last@wk 34	Cyclophosphamide, Asparaginase, Daunorubicin (2 nd), 6-Mercaptopurine (3 rd), Cytarabine (3 rd), Methotrexate (intrathecal, 3 rd)	Vaginal	36	Transient oligohydramnios. [Spontaneous preterm labor.] Male infant: 2,150 g [SGA], Apgar scores 2 and 8 at 1 and 5 minutes. Newborn physical examination was normal, as were blood counts. Mild meconium aspiration syndrome required positive airway pressure and oxygen therapy for 4 days. Jaundice was treated with phototherapy.	No	(Hansen et al. 2001)
Vincristine (2 mg on day 3, 4 cycles, 4 wks apart)	Case report	1	Non-Hodgkin lymphoma	2 nd First@wk 21	Rituximab, Doxorubicin	C-section	35	Female infant: weight and Apgar scores NS. Newborn was healthy.	At 4 months, developed well with normal peripheral B-cell population.	(Herold et al. 2001)
Vincristine (Dose/schedule NS)	Case series	1 of 3 (Pt 3)	Leukemia, ALL	3 rd	Daunorubicin, Asparaginase	Vaginal	NS	Male infant: 2,086 g, Apgar scores 9 and 9. Newborn was healthy and showed no signs of myelosuppression.	No	(Hurley et al. 2005)
Vincristine (1.2 mg, schedule NS)	Case report	1	Melanoma	2 nd First@wk 26	Dacarbazine, Nimustine, Interferon beta	Vaginal	35	Male infant: 2,208 g, Apgar scores NS. Newborn was healthy.	At 32 months, no signs of melanoma.	(Ishida et al. 2009)
Vincristine (Dose/schedule NS, sarcoma Pt – 1 cycle, leukemia Pt – 4 cycles)	Case series	1 of 18	Sarcoma, soft tissue	NS First@wk 12-33, 22 (mean)	Cyclophosphamide, Doxorubicin, Dacarbazine	--	--	Spontaneous abortion at gestation wk 22. [No fetal data reported.]	--	(Jameel and Jamil 2007)
		1 of 18	Leukemia, ALL		Daunorubicin	--	--	Intrauterine fetal demise [stillbirth] at 35 wks. [No fetal data reported.]	--	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (2 mg on days 1 and 8, 2 cycles)	Case report	1	Hodgkin lymphoma	2 nd , 3 rd First@wk 26	Nitrogen mustard, Procarbazine	NS	38	Male infant: 3,110 g, Apgar score 9 at 1 minute. Newborn was normal with a full head of hair.	At 3 months, normal growth and development.	(Jones and Weinerman 1979)
Vincristine (Dose/schedule NS)	Case series	2 of 2	Leukemia, ALL	2 nd , 3 rd	Doxorubicin, Asparaginase, Methotrexate (intrathecal), Radiation therapy	C-section	34	Spontaneous preterm rupture of the membranes and labor. Male infant: 2,080 g, Apgar scores 8 and 10 at 1 and 5 minutes. Newborn was vigorous at physical exam and had a full head of hair.	At 30 months, normal development.	(Karp <i>et al.</i> 1983)
			Non-Hodgkin lymphoma, undifferentiated of T-cell origin	3 rd First@wk 31	Radiation therapy (2 nd , 3 rd), Doxorubicin	--	--	Spontaneous preterm labor. Stillbirth at gestation wk 31, female: 1,200 g. No abnormalities. Placenta was immature with several small areas of recent infarction, extensive endothelial damage, organizing thrombosis, and occlusion and recanalization of the chorionic vessels.	--	
Vincristine (Dose/schedule NS)	Survey, retrospective	103	Leukemia, ALL, AML	NS	Doxorubicin, Cyclophosphamide, Behenoyl-ara-C, Daunorubicin, 6-Mercaptopurine, Aclarubicin, Cytarabine, Cycloctidine, ATRA, Mitoxantrone, Idarubicin, Asparaginase	NS	NS	Individual exposures and pregnancy outcomes are not provided. Two anomalies were observed in the infants delivered by 103 patients.	No	(Kawamura <i>et al.</i> 1994)†

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS, 2 cycles)	Case report	1	Leukemia, ALL	2 nd , 3 rd	Cyclophosphamide, 6-Mercaptopurine, Methotrexate, Doxorubicin (2 nd), Asparaginase (2 nd)	C-section	NS [at term]	Female infant: 3,800 g, Apgar scores NS. Newborn was clinically normal with slight leucopenia (resolved after 2 wks).	At follow-up [age NS], child was well with normal blood counts and no neurological disturbances or congenital abnormality.	(Khurshid and Saleem 1978)
Vincristine (weekly for 12 wks, total 26.4 mg)	Case report	1	Ovary	2 nd , 3 rd First@wk 16	Actinomycin D, Cyclophosphamide	Vaginal	37	Spontaneous preterm labor. Male infant: 2,850 g, Apgar scores NS. Newborn was entirely normal.	No	(Kim and Park 1989)
Vincristine (2 mg, 5 cycles)	Case report	1	Leukemia, ALL	2 nd , 3 rd	6-Mercaptopurine, Cyclophosphamide (3 rd), Cytarabine (3 rd), Methotrexate (intrathecal, 3 rd)	Vaginal	38	Male infant: 6 lb 8.5 oz [2,963 g], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was normal.	At 7 months, he continued to thrive and had a normal karyotype.	(Krueger <i>et al.</i> 1976)
Vincristine (1.5 mg/m ² on days 1 and 8, 1 cycle)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 26	Cyclophosphamide, Doxorubicin, Cytarabine, Etoposide, Ifosfamide	C-section	32	Male infant: 1,731 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no anomalies, but was cyanotic, and experienced respiratory distress.	At 14 months, mild delay in motor skills (thought to result from prematurity) but otherwise healthy.	(Lam 2006)
Vincristine (1.4 mg/m ² on day 1, 3 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 22 Last@wk 28	Cyclophosphamide, Doxorubicin, Bleomycin, Teniposide	C-section	31	Preeclampsia and fetal growth retardation at gestation wk 28. Fetal distress at gestation wk 31. Male infant: 1,380 g, Apgar scores 7, 9, and 10 at 1, 5, and 10 minutes. Newborn showed no neurologic, urinary tract, lung, or other abnormalities, but experienced hyperbilirubinemia (treated and resolved in 3 days). Placenta had extensive infarctions.	At 18 months, normal growth and no signs of damage that could have been related to chemotherapy.	(Lambert <i>et al.</i> 1991)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (2 mg, 1 cycle)	Case report	1	Leukemia, AMML	2 nd First@wk 16 Last@wk 17	Cytarabine (1 st , 2 nd), 6-Thioguanine (1 st), Daunorubicin	--	--	Induced abortion at gestation wk 20. Female fetus: macroscopically and microscopically normal in size and development with normal karyotype and no blood dyscrasia.	--	(Lilleyman <i>et al.</i> 1977)
Vincristine (Dose/schedule NS)	Cohort, retrospective	1 of 2	Hodgkin lymphoma	1 st	Nitrogen mustard, Procarbazine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had hydrocephaly and died at 4 hours.	--	(Lishner <i>et al.</i> 1992) [†]
Vincristine (2 mg on day 1, 6 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd Last@wk 37	Doxorubicin, Cyclophosphamide, Teniposide, Bleomycin (3 rd), Methotrexate (intrathecal, 3 rd)	Vaginal	37	Female infant: 3,750 g, Apgar score 9. Newborn was fully developed with a normal heart and blood count, no abnormality was detected.	No	(Lowenthal <i>et al.</i> 1982)
Vincristine (Dose/schedule NS, 6 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 13 + 4 days	Doxorubicin, Rituximab, Cyclophosphamide, Cytarabine (IT)	Vaginal	39	Female infant: 2,270 g [SGA], Apgar scores 6 and 9. Newborn was viable with low birth weight.	At 7 months, healthy.	(Magloire <i>et al.</i> 2006)
Vincristine (1.5 mg/m ² every 3 rd wk, 3 cycles)	Case report	1	Rhabdomyosarcoma	2 nd , 3 rd	Actinomycin D, Cyclophosphamide	Vaginal	36.5	Spontaneous preterm labor. Female infant: 2,443 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was healthy and normal on physical examination.	No	(Martin <i>et al.</i> 1997)
Vincristine (Dose/schedule NS)	Case report	1	Leukemia, ALL	2 nd , 3 rd First@wk 26	Daunorubicin, Asparaginase, Methotrexate (intrathecal)	C-section	32.4	Intrauterine growth restriction. Male infant: 1,450 g [SGA]. Apgar scores 4 and 8 at 1 and 5 minutes. Newborn showed no abnormalities by physical examination or laboratory tests. Respiratory distress and jaundice were successfully treated.	At 28 months, normal growth.	(Matsouka <i>et al.</i> 2008)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestation al age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (1.5 mg/m ² weekly for 10 wks)	Case report	1	Kidney, Wilms tumor	2 nd , 3 rd First@wk 22	Actinomycin D	C-section	33	Male infant: 2,400 g, Apgar scores 8 and 9 at 5 and 10 minutes. Newborn was healthy and adequately developed for gestational age.	At 4 years, normal development.	(Maurer <i>et al.</i> 2009)
Vincristine (2 mg on days 1 and 5, 2 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	NS [2 nd , 3 rd First @27 wk]	Mitoxantrone, Cyclophosphamide	C-section	31	Low biophysical profile score and abnormal cardiotocogram. Male infant: 1,700 g, Apgar scores 6 and 8 at 1 and 5 minutes. Newborn was viable with no evidence of hematological suppression. Respiratory distress syndrome due to prematurity was successfully treated.	At 14 months, fit and well.	(Mavrommat is <i>et al.</i> 1998)
Vincristine (Dose/schedule NS)	Case report	1	Sarcoma, Ewing	3 rd	Methotrexate, Doxorubicin, Cyclophosphamide	C-section	~7 months	Spontaneous preterm rupture of membranes and labor. Male infant: 2,200 g, Apgar scores NS. Newborn was healthy with normal blood counts.	At 10 wks, normal growth and development.	(Meador <i>et al.</i> 1987)
Vincristine (1.5 mg)	Case report	1	Hodgkin lymphoma	1 st	Procarbazine, Nitrogen mustard	--	--	Induced abortion [at ~ gestation wk 13]. Male fetus, 89 g, with no obvious external abnormalities. Internal examination revealed that the kidneys were markedly reduced in size and were malpositioned. Other organs were within normal limits.	--	(Mennuti <i>et al.</i> 1975)
Vincristine (2 mg every 4 wks, 5 cycles)	Case report	1	Ovary	2 nd , 3 rd First@wk 17	Doxorubicin, Cyclophosphamide	Vaginal, induced	37	Female infant: 6 lb 13 oz [3,090 g], Apgar scores NS. Newborn was normal-appearing.	At 1 year, normal development.	(Metz <i>et al.</i> 1989)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS)	Case series	2 of 2	Leukemia, ALL	1 st First@wk 6	Asparaginase, Daunorubicin, Methotrexate (intrathecal)	--	--	Induced abortion [at ~gestation wk 11]. [No fetal data reported.]	--	(Molkenboer <i>et al.</i> 2005)
				2 nd First@wk 15 [Last@wk 18-19]	Asparaginase, Daunorubicin, Methotrexate (intrathecal), Cytarabine	--	--	Stillbirth at gestation wk 22: 400 g (sex NS). [No fetal data reported.]	--	
Vincristine (Dose/schedule NS)	Case report	1	Ovary	2 nd , 3 rd First@wk 23 Last@wk 36	Actinomycin D, Cyclophosphamide	Vaginal	37	Female infant: 3,285 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was grossly normal.	No	(Montz <i>et al.</i> 1989)
Vincristine (2 mg/cycle, 5 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd Last@wk 35	Doxorubicin, Etoposide, Bleomycin, Methotrexate, Cyclophosphamide	Vaginal	35.5	Spontaneous preterm labor after last chemotherapy dose. Male infant: birth weight was in 75 th percentile for gestational age, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no apparent physical anomalies.	At 11 months, alive and well.	(Moore and Taslimi 1991)
Vincristine (24 mg, schedule NS)	Survey, retrospective	2 of 27 [27 pts received chemotherapy while pregnant; the total number of pts who received vincristine while pregnant was not provided]	Hodgkin lymphoma	1 st First@wk 1 Last@wk 6	Lomustine, Procarbazine, Vinblastine (1 st , 2 nd , 3 rd)	NS	NS	Infant sex, weight, and Apgar scores NS. Cleft lip and cleft palate.	No	(Mulvihill <i>et al.</i> 1987)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Leukemia, AML	2 nd , 3 rd First@wk 13	Radiation therapy (1 st , 2 nd), Daunorubicin (2 nd), Cytarabine (2 nd), Cyclophosphamide	NS	NS	Infant sex, weight, and Apgar scores NS. Normal at delivery.		
Vincristine (Dose/schedule NS)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 18	Methotrexate, Doxorubicin, Bleomycin, Cyclophosphamide	C-section	28	Spontaneous preterm labor at 10 th wk of chemotherapy. Male infants (twins): weight and Apgar scores NS. Newborns were without apparent malformations or bone marrow suppression.	At 12 months, apparently healthy.	(Nantel <i>et al.</i> 1990)
Vincristine (Pt 1: 2 mg on day 1 of 10-day cycle, then 1 mg on day 1 of 4-wk cycle; Pt2: 2 mg on day 1 of 10-day cycle for 2 cycles, then same dose on day 1 of 4-wk cycle for 3 cycles)k	Case series	2 of 2	Leukemia, acute	2 nd , 3 rd [First@wk 20]	Cytarabine	C-section	[39]	Male infant: 3,460 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal.	At 4 years, normal development and good health.	(Newcomb <i>et al.</i> 1978)
				1 st , 2 nd , 3 rd [First@wk12]	Doxorubicin Cytarabine,	NS	[39]	Female infant: 2,860 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn appeared normal.	At 6 wks, normal karyotype.	
Vincristine (Dose/schedule NS, 6 cycles)	Case series	1 of 17 (Pt Q)	Hodgkin lymphoma	1 st	Nitrogen mustard, Procarbazine	C-section	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal.	No	(Nisce <i>et al.</i> 1986)
Vincristine [1.4 mg/m ² during wk 1, 2 cycles]	Case report	1	Hodgkin lymphoma	2 nd	Nitrogen mustard, Procarbazine, Doxorubicin, Bleomycin, Vinblastine	NS	Term	Female infant: weight and Apgar scores NS. Newborn had favorable outcome. Infant administered AZT for 6 wks because mother was HIV positive.	At 2 years, child had normal weight and height for age and was HIV positive.	(Okechukwu and Ross 1998)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (2 mg weekly)	Case report	1	Leukemia, ALL	1 st , 2 nd First@wk 12	Methotrexate (intrathecal, 1 st); Asparaginase (2 nd), Cyclophosphamide (2 nd), Daunorubicin (2 nd), 6-Mercaptopurine (2 nd), Radiation therapy (2 nd)	C-section	34	Premature rupture of membranes. Female infant: 2,380 g, Apgar score 8 at 5 minutes. Newborn was normally developed, but hydropic and had an enlarged liver and spleen. She had a petechial rash on her abdomen and extremities and slight cardiomegaly. She experienced transient severe myelosuppression requiring transfusions (resolved after ~3 wks). She was treated with digitalis and diuretics for congestive heart failure.	At 1 year, developmental status was normal.	(Okun <i>et al.</i> 1979)
Vincristine (1.4 mg/m ² on days 1 and 8, 5 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 21	Cyclophosphamide, Bleomycin	Vaginal	Term	Mild uterine contractions during 3 rd course of chemotherapy, subsided. Female infant: 3,300 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn had no signs of abnormalities.	At > 1 year, normal development with no evidence of malformations.	(Ortega 1977)
Vincristine (1.5 mg/m ² on days 8, 15, 22, 29)	Case report	1	Leukemia, ALL	3 rd First@wk 28	Daunorubicin, Asparaginase, Methotrexate (IT)	C-section	32 + 4 days	Male infant: 1,450 g, Apgar scores 4 and 8 at 1 and 5 minutes. Newborn showed no abnormalities in physical examination or laboratory tests. He had respiratory distress that was treated and resolved in 3 days and jaundice that was treated with phototherapy.	At 18 months, growing normally.	(Papantonio <i>et al.</i> 2008)
Vincristine (2 mg on day 1, 2 cycles)	Case report	1	Leukemia, AGL	2 nd , 3 rd First@wk 25	Cytarabine, 6-Thioguanine	Vaginal	39	Infant sex and Apgar scores NS: 2,250 g [SGA]. Newborn had no abnormalities.	At 8 months, normal development.	(Pawlinger <i>et al.</i> 1971)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS)	Cohort, retrospective	4 of 14 from Tables 3 and 4 (Pts 2, 6, 9, 13, 14)	Leukemia, ALL	2 nd First@wk 24 Last@wk 28	Idarubicin, Asparaginase	NS	36	Infant sex and Apgar scores NS. Newborn had no complications.	At 2 years, development was normal.	(Peres <i>et al.</i> 2001)
			Leukemia, CML	2 nd First@wk 25	Hydroxyurea (1 st), Doxorubicin	NS	35	Infant sex and Apgar scores NS: 3,195 g. Newborn had jaundice, but no malformations.	At 4 months, normal development.	
			Leukemia, ALL	2 nd First@wk 19	Epirubicin	--	--	Fetal death [stillbirth] at gestation wk 30. [No fetal data reported.]	--	
			Leukemia, ALL	1 st First@wk 13	Doxorubicin	-	--	Spontaneous abortion at gestation wk 17. [No fetal data reported.]	--	
			Hodgkin lymphoma	1 st , First @wk 3 Last@wk 7	Nitrogen mustard, Procarbazine, Doxorubicin, Bleomycin, Vinblastine, Dacarbazine	--	--	Induced abortion in gestation wk 18. Fetus had no malformations; toxic degenerative changes were present in the liver and kidneys, and placenta had villus degeneration and vascular toxic degeneration.	--	
Vincristine (2 mg on day 1, 3 cycles)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd First@wk 16	Cyclophosphamide, Doxorubicin, Ifosfamide, Etoposide, Cytarabine, Rituximab	--	--	Fetal ultrasounds noted decreased amniotic fluid at gestation wk 18 and early intrauterine growth restriction at gestation wk 22; similar effects at 23.5 wks of gestation. At 68 days of treatment, vaginal bleeding, spontaneous preterm labor, and no fetal heart tones Stillbirth at gestation wk 26. [No fetal data reported.]	--	(Peterson <i>et al.</i> 2010)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Schedule NS, total doses, Pt 3 – 48 mg, Pt6 – 24 mg, Pt 7 – 16 mg, Pt 9 – 2 mg)	Case series	5 of 9 (Pts 3, 6, 7, 8, 9)	Leukemia, ALL	1 st , 2 nd , 3 rd	Methotrexate, Cyclophosphamide, 6-Mercaptopurine, Cytarabine	Vaginal	40	Female infant: 2,300 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 6 years, alive and healthy.	(Pizzuto <i>et al.</i> 1980) [†] [This case series was included in Aviles <i>et al.</i> 1988 (1988), thus we did not include the case series in the text analysis of the table.]
			Leukemia, ALL	1 st , 2 nd , 3 rd	Cytarabine, 6-Mercaptopurine, Methotrexate, Cyclophosphamide	C-section	34	Male infant: 1,000 g [SGA], Apgar scores NS. Newborn had no apparent congenital malformations but was pancytopenic. At 21 days, died from septicemia.	--	
			Leukemia, ALL	2 nd , 3 rd	Cytarabine, 6-Mercaptopurine, Methotrexate	Vaginal	38	Female infant: 2,400 g [SGA], Apgar scores NS. Newborn was normal with no apparent congenital malformations. At 90 days, died from gastroenteritis.	No	
			Leukemia, ALL	1 st , 2 nd , 3 rd	Doxorubicin, Methotrexate, 6-Mercaptopurine	C-section	33	Female infant: 1,900 g, Apgar scores NS. Newborn had no malformations.	At 8 years, she was without physical or psychological abnormalities.	
			Leukemia, AML	3 rd	Cytarabine	C-section	38	Female infant: 3,000 g, Apgar scores NS. Newborn was normal with no apparent congenital malformations.	At 2 months, alive and healthy.	
Vincristine (1.4 mg/m ² on day 1, 5 cycles)	Case report	1	Non-Hodgkin lymphoma, SPTCL	2 nd First@wk 20	Cyclophosphamide, Doxorubicin	Vaginal, induced	36	Female infant: 3,245 g. Apgar scores 9, 9, and 9. Newborn was healthy and did not show growth retardation, or physical or neurological deficits.	No	(Reimer <i>et al.</i> 2003)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (2 mg on day 1 of 3-wk cycles, 4 cycles)	Case report	1	Non-Hodgkin lymphoma, diffuse large B-cell	2 nd	Rituximab, Doxorubicin, Cyclophosphamide	C-section	33	Infant, sex NS: 2,500 g, Apgar scores 10, 10, and 10. Newborn was healthy.	At 35 months, completely normal growth.	(Rey <i>et al.</i> 2009)
Vincristine (Dose/schedule NS)	Survey, retrospective	3 of 7 (Pts 1, 4, 7)	Leukemia, ALL	2 nd , 3 rd	6-Mercaptopurine	C-section	37	Male infant: 2,960 g, Apgar score 9 at 5 minutes. Newborn had no congenital malformations.	At 4 years, he was healthy and in the 98 th percentile for height and weight.	(Reynoso <i>et al.</i> 1987)
			Leukemia, AML	2 nd , 3 rd	Daunorubicin, Cytarabine, Cyclophosphamide	Vaginal	34	Spontaneous preterm labor. Male infant: 2,510 g, Apgar score 9 at 1 minute. Newborn was healthy with normal peripheral blood counts and no congenital malformations.	At 7 years, healthy with weight and height in the 100 th percentile.	
			Leukemia, AML	2 nd , 3 rd	Daunorubicin, Cytarabine, 6-Thioguanine, Cyclophosphamide	Vaginal, induced	39	Male infant: 3,420 g, Apgar score 10 at 5 minutes. Newborn had no congenital malformations and normal peripheral blood counts.	At 11.5 years, healthy with normal growth and intellectual development.	
Vincristine (1.4 mg/m ² every other wk for 12 wks)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd	Etoposide, Cyclophosphamide, Doxorubicin, Bleomycin	NS	37	Male infant: 3,200 g, Apgar scores NS. Newborn was healthy.	At 21 months, well with no evidence of iatrogenic complications.	(Rodriguez and Haggag 1995)
Vincristine (Dose/schedule NS)	Case report	1	Adult T-cell leukemia/lymphoma	2 nd , 3 rd First@wk 26	Hydroxyurea, Cyclophosphamide, Doxorubicin	C-section	NS [~28]	Male infant: weight and Apgar scores NS. Newborn was healthy.	No	(Safdar <i>et al.</i> 2002)
Vincristine (1.5 mg/m ² /day on days 1, 8, 15, 22)	Case report	1	Leukemia, ALL	2 nd First@wk 22	Daunorubicin, Asparaginase, Cyclophosphamide (2 nd , 3 rd), Cytarabine (2 nd , 3 rd), 6-Mercaptopurine (2 nd , 3 rd), Methotrexate (IT; 2 nd , 3 rd), Radiation therapy (2 nd , 3 rd)	Vaginal	40	Female infant: weight and Apgar scores NS. Newborn was healthy, had a full head of hair, and no abnormalities. Cytogenetic analysis of lymphocytes showed a normal karyotype but some chromosome breakage and a ring chromosome.	No	(Schleuning and Clemm 1987)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestation al age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule NS)	Case report	1	Cervix	2 nd , 3 rd	Cisplatin	C-section	31	Male infant: 1,660 g, Apgar scores 7 and 8. Newborn had an uncomplicated neonatal course.	Child remained healthy [at age of approximately 4 years].	(Seamon <i>et al.</i> 2009)
Vincristine (2 mg/m ² on day 1, 2 cycles, 2 wks apart. One more cycle was given at half this dose.)	Case report	1	Sarcoma, granulocytic (breast)	NS	Cytarabine, Daunorubicin, Cyclophosphamide	Vaginal	NS	Female infant: 7 lb 2 oz [3,232 g], Apgar scores NS. Newborn was completely normal.	No	(Sears and Reid 1976)
Vincristine (Dose NS, 4 weekly cycles)	Case report	1	Leukemia, ALL	3 rd First@wk 32	Daunorubicin, Cyclophosphamide, Cytarabine, Asparaginase	Vaginal, induced	NS [~35]	Female infant: 6.8 lb [3,084 g], Apgar scores NS. Newborn was normal.	At 16 months, healthy with a normal blood count.	(Sigler <i>et al.</i> 1988)
Vincristine (Dose NS, 3 cycles, 3 wks apart)	Case report	1	Non-Hodgkin lymphoma	3 rd	Doxorubicin, Cyclophosphamide	Vaginal, Induced	36	Female infant: 2,400 g, Apgar scores NS. Newborn was healthy and without congenital anomalies.	No	(Soliman <i>et al.</i> 2007)
Vincristine (1 mg/m ² , 3 cycles (Pt 1), 4 cycles (Pt 2))	Case series	2	Cervix	2 nd First@wk 21 Last@wk 27	Cisplatin (2 nd , 3 rd)	C-section	34	Female infant: 2,160 g, Apgar scores NS. Newborn was viable and had an uneventful neonatal period.	No	(Tewari <i>et al.</i> 1998)
				2 nd , 3 rd First@wk 21 Last@wk 29	Cisplatin	C-section	32	Male infant: 1,700 g, Apgar scores NS. Newborn was viable.	At 2 years, very healthy.	
Vincristine (Dose/schedule NS, 2 doses)	Case report	1	Leukemia, ALL	3 rd First@wk 33	None	Vaginal, induced	35	Male infant: 2,648 g, Apgar scores NS. Newborn was viable.	At 22 months, healthy and growing and developing normally.	(Tewari <i>et al.</i> 1999)
Vincristine (Total 2 mg, schedule NS)	Case series	1 of 2 (Table 3)	Hodgkin lymphoma	1 st	Vinblastine, Procarbazine	Vaginal	NS	Male infant: 4 lb 2 oz [1,872 g], Apgar scores NS. On day 2, developed respiratory distress and died. Post-mortem found a small secundum atrial septal defect.	--	(Thomas and Peckham 1976)
Vincristine (4 mg total)	Case report	1	Hodgkin lymphoma	1 st First@wk 4 Last@wk 12	Doxorubicin, Nitrogen mustard, Procarbazine	--	--	Induced abortion. Fetus was missing 1 digit from the right foot. No cardiac tissue was recoverable. Karyotype was normal.	--	(Thomas and Andes 1982)†(abstract only)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (1.5 mg on days 1 and 8, 2 cycles)	Case series	1 of 2 (Pt 2)	Breast	2 nd , 3 rd First@wk 22 Last@wk 28	Doxorubicin	Vaginal	31	Spontaneous preterm labor. Male infant: 1,990 g, Apgar score 10 at 5 minutes. Newborn had a premature appearance, but was healthy and had no obvious clinical abnormalities.	At 4 months, clinical condition was satisfactory, and hair growth was normal.	(Tobias and Bloom 1980)
Vincristine (2 mg on day 1, 3 cycles)	Case report	1	Non-Hodgkin lymphoma	3 rd	Doxorubicin, Cyclophosphamide	Vaginal	Full term	Infant sex NS: 2,860 g, Apgar score 9 at 1 minute. Newborn appeared normal but the placenta was small (350 g).	At 3 years, completely normal development and no physical or mental abnormalities.	(Toki <i>et al.</i> 1990)
Vincristine (2 mg, 4 cycles)	Case series	1 of 2 (Pt 1)	Leukemia, ALL	2 nd , 3 rd First@wk 18	Daunorubicin (2 nd), Asparaginase (2 nd), Methotrexate, 6-Mercaptopurine	C-section	37	Twin infants, male and female: 2,500 g (male) and 2,400 g (female), Apgar scores NS. Both newborns were normal at physical examination with normal T-cell populations. At 24 hours, both newborns had diarrhea and were lethargic; the female was also hypotonic; full recovery was completed by 2 wks.	At 54 months, normal growth and development with no evidence of immunologic suppression.	(Turchi and Villasis 1988)
Vincristine (1.5 mg/m ² on days 8, 15, and 22)	Case report	1	Leukemia, ALL	2 nd First@ wk 23	Cytarabine (2 nd , 3 rd), Cyclophosphamide (2 nd , 3 rd), Daunorubicin, Cytarabine (2 nd , 3 rd), 6-Thioguanine (2 nd , 3 rd), Methotrexate (intrathecal, 2 nd , 3 rd), Amsacrine (3 rd)	Vaginal	33	Spontaneous rupture of membranes. Male infant: 1,928 g [Table 2 states 1,925 g], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was unremarkable by physical examination. Cerebral ultrasound and newborn hearing screening were normal, as was ventricular function. He exhibited transient neonatal myelosuppression that was treated and resolved by day 20, including leukopenia at birth, neutropenia at day 2,	At 24 months, normal growth and development.	(Udink ten Cate <i>et al.</i> 2009)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
								anemia and thrombocytopenia at day 3. Treated for a urinary tract infection on day 7.		
Vincristine (Dose/schedule NS; Pt 12 – 3 cycles Pt 17 – 2 cycles Pt 18 – 2 cycles Pt 19 – 3 cycles Pt 20 – 2 cycles Pt 24 – 1 cycle)	Survey, retrospective	6 of 27 (Pts 12, 17, 18, 19, 20, 24)	Leukemia, ALL	2 nd , 3 rd First@wk 26	None	C-section	37	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.	No	(Ustaalioglu <i>et al.</i> 2010)
			Non-Hodgkin lymphoma	3 rd First@wk 29	Doxorubicin, Cyclophosphamide	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.		
			Non-Hodgkin lymphoma	3 rd First@wk 29	Rituximab, Doxorubicin, Cyclophosphamide	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.		
			Non-Hodgkin lymphoma	3 rd First@wk 32	Doxorubicin, Cyclophosphamide	Vaginal	40	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.		
			Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 27	Rituximab, Doxorubicin, Cyclophosphamide	Vaginal	35	Infant sex, weight, and Apgar scores NS. Newborn showed no congenital malformations.		
			Sarcoma, soft tissue	3 rd First@wk 32	Doxorubicin, Dacarbazine, Cyclophosphamide	C-section	33	Infant sex, weight, and Apgar scores NS. Newborn was premature with low birth weight but no congenital malformations.		
Vincristine (Pt 1 – 1.4 mg/m ² , 3 cycles; Pt 2 – 1.5 mg/m ² on days 8, 15, 22, 29; 3 cycles; Pt 3 – 1.4 mg/m ² , 2 cycles)	Survey, retrospective	3 of 62 [Total number of patients who received vincristine while pregnant was not provided]	NS	2 nd , 3 rd First@wk 25 Last@wk 33	Nitrogen Mustard, Procarbazine, Doxorubicin, Bleomycin, Vinblastine	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn had pectus excavatum.	No	(Van Calsteren <i>et al.</i> 2010)
				2 nd , 3 rd First@wk 24 Last@wk 32	Methotrexate, Daunorubicin, Cyclophosphamide, Asparaginase 6-Mercaptopurine	NS	NS	Infant sex, weight, and Apgar scores NS. Hemangioma.		

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				2 nd , 3 rd First@wk 26 Last@wk 30	Radiation therapy (2 nd), Nitrogen mustard, Procarbazine, Doxorubicin, Bleomycin, Vinblastine	NS	NS	Infant sex, weight, and Apgar scores NS. Bilateral syndactyly of digits 2 and 3		
Vincristine (1.3 mg/m ² on day 2)	Case report	1	Leukemia, AML	3 rd First@wk 29 Last@wk 29	Doxorubicin (2 nd , 3 rd), Cytarabine (2 nd , 3 rd), 6-Thioguanine (2 nd)	C-section	29	Fetal suffering per ultrasonography and cardiocography at wk 29. Female infant: 1,000 g, Apgar score 6 at 1 minute. Newborn was macroscopically normal, but had hyaline membrane disease and moderate meningeal hemorrhage. With appropriate therapy, she improved.	At 3.5 years, she is well with weight in normal range and normal neurological and hematological parameters.	(Veneri <i>et al.</i> 1996)
Vincristine (Dose/schedule NS)	Case series	1 of 4 (Pt 3)	Leukemia, ALL	3 rd First@wk 32	Daunorubicin	Vaginal, induced	37	Male infant: 2,865 g, Apgar scores NS. Newborn was healthy.	At 14 months, in excellent health.	(Volkenandt <i>et al.</i> 1987)
Vincristine (Dose/schedule NS)	Case report	1	Sarcoma	3 rd First@wk 28	Doxorubicin, Cyclophosphamide	Vaginal	32.5	Spontaneous preterm rupture of membranes and labor. Female infant: 2 lb 14 oz [1,304 g; SGA], Apgar scores 9 and 9. Newborn was viable with no respiratory distress or difficulty feeding.	At 2.5 years, normal neurological and physical development.	(Webb 1980)
Vincristine (Dose/schedule NS)	Case report	1	Ovary	2 nd , 3 rd Last@wk 31	Actinomycin D Cyclophosphamide	Vaginal	33	Spontaneous preterm labor. Female infant: 4 lb 14 oz [1,904 g], Apgar score of 9. Newborn was healthy.	At 8 months, normal development.	(Weed <i>et al.</i> 1979)
Vincristine (2 mg weekly, 5 cycles)	Case report	1	Leukemia, ALL	3 rd	None	Vaginal	Beginning of the 9 th month	Infant sex, weight, and Apgar scores NS. Newborn had no malformations.	No	(Weinrach 1972)

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (2 mg, twice)	Case report	1	Breast	3 rd First@wk 30 Last@wk 33	Doxorubicin, Methotrexate	Vaginal	33	Spontaneous preterm labor. Female infant: 2,000 g, Apgar score 8. Newborn was normal but developed apnea and asytle immediately after birth. At day 3, she was diagnosed with hyaline membrane disease. All of these were successfully treated. Chromosome analysis showed no breaks or excess numerical abnormalities. Placenta had diffuse chorioamnionitis with infiltration by polymorphonucleated cells.	At 2 years, healthy and doing well.	(Willemse <i>et al.</i> 1990)
Vincristine (Dose/schedule NS)	Cohort, retrospective	5 of 21 (Pts 3, 4, 5, 6, and 14)	Breast	1 st	Cyclophosphamide, Methotrexate, 5-Fluorouracil, Tamoxifen	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was alive and well with normal body weight per gestational age.	No	(Zemlickis <i>et al.</i> 1992b)
			Hodgkin lymphoma	1 st	Procarbazine, Vincristine	--	--	Spontaneous abortion. [No fetal data reported.]	--	
			Hodgkin lymphoma	1 st	Procarbazine, Vincristine	--	--	Induced abortion. [No fetal data reported.]	--	
			Hodgkin lymphoma	1 st First@wk 4	Nitrogen mustard, Procarbazine	NS	NS	Infant, sex, weight, Apgar scores NS. Newborn had normal body weight per gestational age. Newborn died at 4 hours with hydrocephalus.	--	
			Non-Hodgkin lymphoma	2 nd	Cyclophosphamide,	--	--	Induced abortion. [No fetal data reported.]	--	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vincristine (Dose/schedule data limited; Table 1: Pt 13 – 3 cycles, Pt 30 – 1 cycle, Pt 31 – 1 cycle, Pt 33 – 4 cycles; Table 2: Pt 2 – 1 cycle, Pt 6 – 1 cycle, Pt 44 – 2 mg, Pt 36 – 2 cycles, Pt 41 – 3 cycles, Pt 26 – 3 cycles, Pt 24 – 2 cycles, Pt 25 – 1 cycle)	Survey, retrospective	12 of 48 (Table 1: Pts 13, 30, 31, 33; Table 2: Pts 2, 6, 44, 36, 41, 26, 24, 25)	Hodgkin lymphoma	1 st	Cyclophosphamide	NS	Term	Infant (sex, weight, and Apgar scores NS). Newborn was normal.	At 10 years, normal.	(Zuazu <i>et al.</i> 1991)
			Non-Hodgkin lymphoma	1 st	Cyclophosphamide	--	--	Spontaneous abortion at wk 6 of gestation. [No fetal data reported.]	--	
			Non-Hodgkin lymphoma	1 st	Doxorubicin, Cyclophosphamide	--	--	Induced abortion. [No fetal data reported.]	--	
			Hodgkin lymphoma	1 st , 2 nd	Nitrogen Mustard, Procarbazine, Vinblastine (2 nd , 3 rd)	NS	40	Infant: 3,400 g, sex and Apgar scores NS. Newborn was normal.	No	
			Leukemia, AML	1 st First@wk 11 Last@wk 11	Daunorubicin, Cytarabine, 6-Thioguanine	--	--	Spontaneous abortion at 20 days post-chemotherapy. [No fetal data reported.]	--	
			Non-Hodgkin lymphoma	1 st First@wk 12 Last@wk 12	Cyclophosphamide, Procarbazine, Triethylene-melamine	--	--	Induced abortion at gestation wk 14. [No fetal data reported. Pt 6, 1st pregnancy.]	--	
			Leukemia, ALL	2 nd First @wk 14 Last@wk 14	None	--	--	Induced abortion at gestation wk 16. [No fetal data reported.]	--	
			Leukemia, AML	2 nd First@wk 20 Last@wk 27	Daunorubicin, Cytarabine, 6-Thioguanine	C-section	37	Infant: 2,100 g [SGA], sex and Apgar scores NS. Newborn was premature.	At 3 years, normal.	

Appendix C Table 63. Vincristine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
			Non-Hodgkin lymphoma	2 nd First@wk 22	Cyclophosphamide, Doxorubicin	C-section	37	Infant: sex, weight, and Apgar scores NS. Newborn was normal.	No	
			Leukemia, AML	2 nd First@month 5 Last@month 6	Daunorubicin, Cytarabine, 6-Thioguanine	Vaginal	NS	Infant: sex, weight, and Apgar scores NS. Newborn had normal outcome.	At 3 years, normal.	
			Leukemia, AML	3 rd First@wk 28	Daunorubicin, Cytarabine, 6-Thioguanine	Vaginal	36	Infant: 2,400 g, sex and Apgar scores NS. Newborn was normal with normal karyotype.	At 4 years, normal.	
			Leukemia, AML	3 rd First@wk 29	Daunorubicin, Cytarabine, 6-Thioguanine	--	--	Fetal death [stillbirth] during treatment. C-section postmortem: fetus without macroscopical anomalies.	--	

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the vincristine timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Papers not incorporated into text analysis of vincristine (highlighted in light grey). In order to avoid counting the same cases more than once, we did not include the following studies: (Pizzuto *et al.* 1980, Avilés *et al.* 1990, Lishner *et al.* 1992, Avilés and Neri 2001). The cases in Avilés *et al.* (1990) were not included in the text analysis because they were reported in a subsequent retrospective case series (Avilés *et al.* 1991). Patients #3, 6, 7, 8, and 9 from Table 2 in Pizzuto *et al.* (1980) were not included because this case series was reported in Avilés *et al.* (1988). The retrospective case series Avilés and Neri (2001) was not included because it included both new cases and long-term follow-up on previously reported case series (Avilés and Neri 1988, Avilés *et al.* 1991), and it did not report individual pregnancy outcomes. Lishner *et al.* (1992) reported 1 case of hydrocephaly with early neonatal death following first trimester exposure to procarbazine; however, this was not included because it was reported in previous paper from their research group (Zemlicki *et al.* 1992b). Two studies were not included in the text analysis because of a lack of individual patient data on timing of exposure, treatments and/or co-treatments, and pregnancy outcomes (Carcassonne 1981, Kawamura *et al.* 1994). Finally, published abstracts were not included in the text analysis (Thomas and Andes 1982).

††Giacalone *et al.* (1999) and Fernandez *et al.* (1989) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AGL = acute granulocytic leukemia; ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; AMML = acute myelomonocytic leukemia; APL = acute promyelocytic leukemia; CML = chronic myelogenous leukemia; SPTCL = subcutaneous panniculitis-like T-cell lymphoma; AMSA = amsacrine; ATRA = all-*trans* retinoic acid; behenoyl-ara-C = behenoyl cytosine arabinoside; IT = intrathecal; SGA = small for gestational age.

Appendix C Table 64. Vinorelbine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinorelbine (Dose/schedule NS)	Case series	1 of 13 (Pt 1)	Rhabdomyosarcoma	1 st , 2 nd , 3 rd	Oxaliplatin, Irinotecan	NS	32	Infant sex, weight and Apgar scores NS. Newborn had cleft lip, cleft palate, tracheoesophageal fistula, and esophageal atresia. Newborn had normal body weight for gestational age. Placenta had vacuolization and nuclear pleomorphism, extravillous trophoblasts of the chorion laeve, villous hypermaturity, and multifocal villous edema.	No	(Abellar <i>et al.</i> 2009)
Vinorelbine (Dose/schedule NS)	Survey, registry	1 of 104 fetuses [1 of 99 pts] from Table 2	Breast	2 nd , 3 rd	None	NS	35.9 (group mean)	Infant sex NS: 2,667 g (group mean), Apgar scores NS. Newborn was normal with normal body weight for gestational age.	At 4 months, normal phenotype. At 42 months (group mean, n=93), group mean weight was 48 th percentile.	(Cardonick <i>et al.</i> 2010)
		1 of 12 from Table 6	Lung	2 nd , 3 rd	Vincristine, Cisplatin, Radiation therapy	NS	36	Infant sex NS: 2,495 g, Apgar scores NS. Newborn was normal with normal body weight for gestational age; placenta had areas of infarction.	At 2 months, there were no complications.	
Vinorelbine (Pt 1 – 30 mg/m ² on days 1 and 5; Pt 2 – 20 mg/m ² on days 1 and 5, 2 cycles, then 25 mg/m ² days 1 and 5, 1 cycle; Pt 3 – 30 mg/m ² on days 1 and 5, 3 cycles)	Case series	3 of 3	Breast	2 nd First@wk 24	5-Fluorouracil, Epirubicin, Cyclophosphamide	C-section	34	Female infant: 2,320 g, Apgar scores 8, 3, and 10 at 1, 3, and 5 minutes. Newborn was normal with no dysmorphic features. Anemia at day 21, resolved.	At 35 months, growth and development were normal.	(Cuvier <i>et al.</i> 1997)
				3 rd First@wk 29	5-Fluorouracil	Vaginal	37	Male infant: 3,230 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn was normal with no dysmorphic features.	At 34 months, growth and development were normal.	
				3 rd First@wk 28	5-Fluorouracil	Vaginal	41	Male infant: 3,300 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn was normal with no dysmorphic features.	At 23 months, growth and development were normal.	
Vinorelbine (25 mg/m ² , schedule NS)	Case report	1	Breast	2 nd First@wk 16	Docetaxel (2 nd , 3 rd)	C-section	32	Female infant: 1,620 g, Apgar scores 8 and 9. Newborn was normal.	She had regular psychophysical development at 20 months.	(De Santis <i>et al.</i> 2000)

Appendix C Table 65. Vinorelbine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinorelbine (30 mg/m ² weekly for about 4 wks)	Case report	1	Breast	3 rd First@wk 30 Last@wk 33	Trastuzumab	C-section	33 + 5 days	Anhydramnios was detected 3 wks after start of chemotherapy. Female infant: 1,990 g, Apgar scores 8, 9, and 9 at 1, 5, and 10 minutes. She was in good health with no signs of malformation.	Follow-up examination [age NS] revealed no problems.	(El-Safadi <i>et al.</i> 2012)
Vinorelbine (25 mg/m ² weekly for 3 wks)	Case report	1	Breast	2 nd , 3 rd First@wk 27 Last @wk 34	Trastuzumab	Vaginal, induced	34	Oligohydramnios, decreased fetal movements, and mild occasional fetal cardiac decelerations at 34 wks. Male infant: 5 lb, 11oz [2,580 g], Apgar scores 9, 9, and 10. Newborn was healthy.	At 6 months, he was healthy with normal development.	(Fanale <i>et al.</i> 2005)
Vinorelbine (30 mg/m ² on days 1 and 8, every 3 wks, 3 cycles)	Case report	1	Lung	3 rd	Cisplatin	C-section	39	Infant, sex NS: 2,910 g, Apgar score 9. Newborn was healthy.	No	(Garrido <i>et al.</i> 2008)
Vinorelbine (mean dose, 37 mg/m ²)	Survey, retrospective	4 of 20 (Pts 4, 5, 13, 18)	Breast	2 nd First@wk 24	5-Fluorouracil	C-section	34	Infant sex and weight NS: Apgar scores 8 and 10. Newborn was anemic but had no malformations and normal body weight for gestational age.	At 80 months, alive and well.	(Giacalone <i>et al.</i> 1999)†
				2 nd First@wk 24	5-Fluorouracil	Vaginal	40	Infant sex and weight NS: Apgar scores 9 and 10. Newborn was normal with no malformations and normal body weight for gestational age.	At 40 months, alive and well.	
				3 rd First@wk 30	5-Fluorouracil	Vaginal	38	Infant sex and weight NS: Apgar scores 10 and 10. Newborn was normal with no malformations and normal body weight for gestational age.	At 75 months, alive and well.	
				3 rd First@wk 32	5-Fluorouracil	C-section	35	Infant sex and weight NS: Apgar scores 10 and 10. Newborn was normal with no malformations and normal body weight for gestational age.	At 12 months, alive and well.	

Appendix C Table 65. Vinorelbine (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vinorelbine (25 mg/m ² , 1 cycle)	Case report	1	Lung	2 nd First@wk 26	Cisplatin	C-section	26 + 4 days	<p>Patient had rapidly progressive respiratory symptoms.</p> <p>Male infant: weight NS, Apgar scores 7 and 8 at 1 and 5 minutes. Newborn was healthy. At 10 days, transient decrease in white blood cell and platelet counts (recovered by 3 wks).</p>	No	(Janne <i>et al.</i> 2001)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the vinorelbine timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Giacalone *et al.* (1999) reported gestational age as weeks of amenorrhea counting from the first day of the last menstrual period; it is also called weeks of gestation.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

4.0 APPENDIX D – SUMMARY TABLES FOR CANCER CHEMOTHERAPEUTIC AGENTS WITH 10 OR FEWER REPORTED CASES

Appendix D contains data tables for chemotherapeutic agents for which there were 10 or fewer reported cases (patients) treated with chemotherapy for cancer during pregnancy.

Appendix D Table 66. Amsacrine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Amsacrine (Dose/schedule NS)	Case series, retrospective	1 of 18	Sarcoma, undifferentiated	1 st	Cyclophosphamide, Doxorubicin, Vincristine	NS	No births were premature [Term]	Male infant: 6 lb 5 oz [2,863 g], Apgar scores NS. Newborn had no major abnormalities, and birth weight was normal [for gestational age].	At 2.5 years, normal.	(Blatt <i>et al.</i> 1980)
Amsacrine (120 mg/m ² on days 3, 5, and 7, 1 cycle)	Case report	1	Leukemia, ALL	3 rd First@wk 32	Cyclophosphamide (2 nd , 3 rd), Daunorubicin (2 nd), Vincristine (2 nd), Cytarabine (2 nd , 3 rd), 6-Thioguanine (2 nd , 3 rd), Methotrexate (intrathecal; 2 nd , 3 rd)	Vaginal	33	Spontaneous rupture of membranes. Male infant: 1,928 g [Table 2 states 1,925 g], Apgar scores 9 and 10 at 1 and 5 minutes. Newborn's physical exam was unremarkable with normal cerebral ultrasound, hearing, and echocardiography. He exhibited transient neonatal myelosuppression that was treated and resolved by day 20, including leukopenia at birth, neutropenia at day 2, anemia and thrombocytopenia at day 3. Treated for a urinary tract infection on day 7.	At 24 months, normal growth and development.	(Udink ten Cate <i>et al.</i> 2009)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the AMSA timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia; AMSA = amsacrine.

Appendix D Table 67. Behenoyl cytosine arabinoside – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Behenoyl cytosine arabinoside (Dose/schedule NS)	Case report	1	Leukemia, APL	2 nd or 2 nd , 3 rd	Daunorubicin, 6-Mercaptopurine, Cytarabine, Mitoxantrone	C-section	34	Female infant: 2,960 g, Apgar scores NS. Newborn was healthy.	At 16 months, no abnormalities.	(Azuno <i>et al.</i> 1995)
Behenoyl cytosine arabinoside (170 mg/m ² /day for 10 days, 3 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 20	Mitoxantrone, 6-Mercaptopurine	C-section	35 + 4 days	Preterm labor at beginning of 3 rd trimester was treated and resolved. Premature rupture of membranes at 35 wks of gestation + 4 days. Male infant: 1,882 g [SGA], Apgar scores NS. Newborn was thrombocytopenic and leukocytopenic but had neither anomalies nor chromosomal abnormalities.	No	(Gondo <i>et al.</i> 1990)
Behenoyl cytosine arabinoside (170 mg/m ² /day for 10 days, 2 cycles)	Case report	1	Leukemia, AML	2 nd , 3 rd First@wk 25 Last@wk 31	Daunorubicin, 6-Mercaptopurine	C-section	33 + 6 days	Intrauterine growth restriction. Premature separation of placenta. Female infant: 1,410 g [SGA], Apgar scores 1 and 8 at 1 and 5 minutes. Newborn showed no visible congenital anomalies but was severely premature.	At 5 months, known to be well with no neurologic or hematologic abnormalities.	(Morishita <i>et al.</i> 1994)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the behenoyl cytosine arabinoside timing.

*** Delivery route: C-section = Cesarean-section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AML = acute myelogenous leukemia; APL = Acute promyelocytic leukemia; behenoyl-ara-C = behenoyl cytosine arabinoside; SGA = small for gestational age.

Appendix D Table 68. Capecitabine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Capecitabine (Dose/schedule NS)	Survey, registry	1 of 12 from Table 6	Colorectal	1 st	Oxaloplatin	NS	NS	Infant sex NS: Birth weight and Apgar scores NS. Newborn was normal with normal body weight for gestational age.	No	(Cardonick <i>et al.</i> 2010)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the capecitabine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 69. Carmustine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Carmustine (150 mg/m ² on day 1, 2 cycles)	Case report	1	Melanoma	2 nd First@wk 23 Last@wk 26.5	Tamoxifen, Cisplatin, Dacarbazine	C-section	30	Female infant: 1,520 g, Apgar scores NS. Pathology revealed a malignant melanoma in the placenta.	At 17 months (corrected to 15 months for early delivery), normal muscle tone and reflexes, and, overall, age-appropriate evaluations.	(DiPaola <i>et al.</i> 1997)
Carmustine (100 mg/m ² on day 1 of an every-other-monthly cycle,	Case report	1	Melanoma	1 st , 2 nd	Dacarbazine, Cisplatin, Tamoxifen	C-section	34	Male infant: 2,750 g, Apgar scores 10 and 10 at 1 and 5 minutes. Newborn showed no dysmorphism at clinical examination.	At 1 year, social, hearing, gross and fine motor assessments were normal; however, he was diagnosed with microphthalmos and severe hypermetropia.	(Li <i>et al.</i> 2007)
Carmustine (110 mg on day 1, every 4 wks)	Case report	1	Non-Hodgkin lymphoma, diffuse histiocytic	1 st , 2 nd	Procarbazine, Streptozotocin (2 nd , 3 rd)	Vaginal	35	Male infant: 2,340 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn physical examination was entirely normal, as was the karyotype.	No	(Schapira and Chudley 1984)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the carmustine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 70. Chlorambucil – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Chlorambucil (2 mg/day on days 1, 3, and 5, every wk for 3 months)	Case report	1	Leukemia, CLL	1 st , 2 nd Last@wk 20	None	C-section	36	Male infant: 2,235 g, Apgar score 9. Newborn was healthy with normal blood count, biochemical, ultrasonographic, and echocardiographic analyses.	At 3 months, normal growth and development.	(Ali <i>et al.</i> 2009c)
Chlorambucil (4 mg/day)	Case report	1	Leukemia, CLL	1 st Last@wk 5	None	Vaginal	41	Male infant: 7 lb 6 oz [3,345 g], Apgar Scores NS. Newborn appeared normal.	At 2.5 years, in good health and of normal height and weight; his blood had no abnormalities.	(Baynes <i>et al.</i> 1968)
Chlorambucil (Dose/schedule NS)	Case series	1 of 32 (Pt 14)	Non-Hodgkin lymphoma	2 nd First@wk 20 Last@wk 24	None	C-section	39	Infant sex NS: 3,020 g, Apgar scores 9 and 9. Newborn was healthy.	No	(De Carolis <i>et al.</i> 2006)
Chlorambucil (20 mg daily)	Case report	1	Choriocarcinoma, vagina	2 nd	Methotrexate, Actinomycin D	Vaginal	NS	Twin infants (sex NS): 1,770 and 1,880 g; Apgar scores NS. Both newborns and placenta appeared normal.	At approximately 2 years, no adverse effects of chemotherapy.	(Freedman <i>et al.</i> 1962)
Chlorambucil (6 mg/day, schedule NS)	Case series	1 of 3 (Pt 3)	Non-Hodgkin lymphoma	1 st	Radiation therapy	--	--	Induced abortion at gestation wk 14. Fetus was stillborn, but morphologically normal.	--	(Ioachim 1985)
Chlorambucil (2 mg/day)	Case series	1 of 15 (Pt 0)	Hodgkin lymphoma	1 st , 2 nd , 3 rd	None	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal.	No	(Jacobs <i>et al.</i> 1981)
Chlorambucil (6 mg/day for 6 wks)	Case report	1	Hodgkin lymphoma	1 st	Radiation therapy	--	--	Induced abortion at gestation wk 18. Male fetus: 165 g. Externally normal; left kidney and ureter were absent.	--	(Shotton and Monie 1963)
Chlorambucil (Pt 16 – 2 cycles, 1 wk apart: 130 mg over 11 days, then 300 mg over 30 days; Pt 17 – 378 mg over 3 wks)	Case series	2 of 4 from Addendum (Pts 16 and 17)	Hodgkin lymphoma	2 nd , 3 rd	Nitrogen mustard, Radiation therapy (3 rd)	Vaginal	NS [~36]	Female infant: 5 lb 1 oz [2,296 g], Apgar scores NS. Newborn was normal.	At 2 months, doing well.	(Smith <i>et al.</i> 1958)
			Hodgkin lymphoma	3 rd	None	NS	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal.	At 10 months, in excellent health.	

Appendix D Table 71. Chlorambucil (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Chlorambucil (Table 2: Pt 6 – 10 mg/day)	Survey, retrospective	1 of 48 (Table 1: Pt 6)	Non-Hodgkin lymphoma	1 st Last@month 2	None	NS	NS	Infant (sex NS): 3,400 g, Apgar scores NS. Newborn was normal. [Pt 6, 2nd pregnancy]	At 20 months, normal growth and development.	(Zuazu <i>et al.</i> 1991)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the chlorambucil timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; CLL = chronic lymphocytic leukemia.

Appendix D Table 72. Dasatinib – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Dasatinib (100 mg daily)	Case report	1	Leukemia, CML	1 st , 2 nd First@wk 5 Last@wk 17	Imatinib	--	--	Induced abortion at gestation wk 17. Male fetus: 166 g, Apgar scores NA. Fetus had hydrops with subcutaneous edema, plural effusion, and ascites. Autopsy found no congenital malformations. Levels of dasatinib were detected in fetal serum and amniotic fluid.	--	(Berveiller <i>et al.</i> 2012)
Dasatinib (50 mg twice a day)	Case report	1	Leukemia, CML	1 st	Interferon alpha (2 nd , 3 rd)	C-section	33	Male infant: 2,100 g, Apgar score 9 at 10 minutes. Newborn was healthy with no sequelae or malformations.	At 8 months, normal growth and development with no evidence of congenital malformations.	(Conchon <i>et al.</i> 2010)
Dasatinib (Pt D – 180 mg/day Pt E – 200 mg/day Pt F – 140 mg/day Pt G – 140 mg/day)	Survey, Post-marketing data	7 of 8 (Pts A, B, C, D, E, F, G) (Pt H was still pregnant at time of publication)	Leukemia, CML	1 st	--	--	--	Induced abortion. [No fetal data reported.]	--	(Cortes <i>et al.</i> 2008) [†] (Abstract only)
				1 st	--	--	--	Induced abortion. [No fetal data reported.]	--	
				1 st	--	--	--	Induced abortion. [No fetal data reported.]	--	
				1 st Last@wk 5	--	--	--	Spontaneous abortion. [No fetal data reported.]	--	
				1 st Last@wk 9	--	--	--	Spontaneous abortion. [No fetal data reported.]	--	
				1 st Last@wk 7	NS	NS	NS	Infant sex, weight, and Apgar scores NS. Newborn was normal and healthy.	No	

Appendix D Table 73. Dasatinib (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
				1 st Last@wk 4	NS	C-section	7 months	Infant sex, weight, and Apgar scores NS. Newborn was "small for date" but without obvious birth defects.	No	
Dasatinib (70 mg/day)	Case report	1	Leukemia, CML	1 st Last@wk 5	Hydroxyurea (1 st , 2 nd , 3 rd), Cytarabine, (1 st , 2 nd , 3 rd)	Vaginal, induced	34 + 6 days	Female infant: 2,470 g, Apgar scores NS. Newborn was healthy.	At 11 months, she was healthy without structural or functional anomalies or developmental delay.	(Kroll <i>et al.</i> 2010)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the dasatinib timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

†Paper not included in text analysis (highlighted in light grey). No abstracts were included in the tallies for the pooled data on any chemotherapy exposure (Cortes *et al.* 2008).

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; CML = chronic myelogenous leukemia.

Appendix D Table 74. Erlotinib – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Erlotinib (150 mg once daily)	Case report	1	Lung	1 st , 2 nd , 3 rd First@wk 2	None	C-section	33	Oligohydramnios and intrauterine growth restriction at gestation wk 33. Female infant: 1,600 g, Apgar scores 8 at 1 minute and 10 at 5 minutes. Newborn had no congenital malformations.	At 4 months, good health and growth at 25 th percentile (based on data for Columbia).	(Rivas <i>et al.</i> 2012)
Erlotinib (100 mg/day)	Case report	1	Lung, non-small cell	1 st Last@month 2	None	C-section	42	Female infant: 3,940 g, Apgar scores 9 and 10 at 1 and 10 minutes, respectively. Newborn had no congenital malformation and normal hearing, thyroid, adrenal, hepatorenal, and hematological functions. Placenta had no disease.	No	(Zambelli <i>et al.</i> 2008)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the erlotinib timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 75. Fludarabine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Fludarabine (30 mg/m ² on days 2-6)	Case report	1	Leukemia, AML	3 rd First@wk 28	Cytarabine (2 nd), Mitoxantrone (2 nd), Idarubicin, Gemtuzumab-ozogamicin	C-section	33	Fetus developed cardiomyopathy, transient cerebral ventriculomegaly, mild fetal anemia, and intrauterine growth restriction after initiation of chemotherapy. Male infant: 1,695 g, Apgar scores 8 and 9 at 5 and 10 minutes. Newborn was anemic and required intermittent bag mask ventilation; transcranial ultrasound and echocardiography detected no abnormalities, and there were not clinical signs of dysmorphism.	At 6 months, no residual signs of cardiomyopathy or hydrocephalus.	(Baumgartner <i>et al.</i> 2009)
Fludarabine (30 mg/m ² on days 1-5)	Case report	1	Leukemia, AML	3 rd	Idarubicin (2 nd , 3 rd), Cytarabine (2 nd , 3 rd)	--	--	Fetal death [stillbirth] in gestation wk 34. [No fetal data reported.]	--	(Paşa <i>et al.</i> 2009)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the fludarabine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AML = acute myelogenous leukemia.

Appendix D Table 76. Gemcitabine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Gemcitabine (Dose/schedule NS)	Survey, registry	1 of 12 from Table 6	Pancreas	2 nd , 3 rd	None	NS	30	Infant sex NS: Birth weight and Apgar scores NS. Newborn had anemia and respiratory distress, but had normal body weight for gestational age.	At 1.5 years, normal; group mean body weight was 70 th percentile (n=2).	(Cardonick <i>et al.</i> 2010)
Gemcitabine (1,000 mg/m ² on days 1 and 8, 1 cycle)	Case report	1	Lung	2 nd First@wk 25	Carboplatin	C-section	28 + 4 days	Female infant: 1,040 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn was anemic, required surfactant treatment and a conventional ventilator for 29 days, and developed sepsis on day 36, from which she recovered well.	At 8 months, she was weaned from oxygen therapy and was on high-calorie formula milk. Her neurodevelopment was age appropriate.	(Gurumurthy <i>et al.</i> 2009)
Gemcitabine (1,250 mg/m ² on days 1 and 8 of 3-wk cycle, 2 cycles)	Case report	1	Lung	2 nd	Docetaxel (1 st , 2 nd), Cisplatin (1 st , 2 nd)	C-section	33	Female infant: 1,490 g, Apgar scores 8, 9, and 10 at 1, 5, and 10 minutes. Newborn was normal with normal karyotype, blood counts, thyroid, hearing, adrenal, hepatorenal, and hematology findings.	[At 2 months,] normal development.	(Kim <i>et al.</i> 2008)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the gemcitabine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 77. Gemtuzumab-ozogamicin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Gemtuzumab-ozogamicin (3 mg/m ² on day 1)	Case report	1	Leukemia, AML	3 rd First@wk 28	Cytarabine (2 nd , 3 rd), Mitoxantrone (2 nd), Idarubicin), Fludarabine	C-section	33	Fetus developed cardiomyopathy, mild fetal anemia, transient cerebral ventriculomegaly, mild fetal anemia, and intrauterine growth restriction after initiation of chemotherapy. Male infant: 1,695 g, Apgar scores 8 and 9 at 5 and 10 minutes. Newborn was anemic and required ventilation but adapted fast and showed no abnormalities and no clinical signs of dysmorphism.	At 6 months, no residual signs of cardiomyopathy or hydrocephalus.	(Baumgartner <i>et al.</i> 2009)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the gemtuzumab-ozogamicin timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 78. Irinotecan – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Irinotecan (Dose/schedule NS)	Case series	1 of 13 (Pt 1)	Rhabdomyosarcoma	1 st , 2 nd and 3 rd	Oxaliplatin, Vinorelbine	NS	32	Infant sex NS: weight and Apgar scores NS. Newborn had cleft lip, cleft palate, tracheoesophageal fistula, and esophageal atresia. Newborn had normal body weight for gestational age. Placenta had vacuolization and nuclear pleomorphism, extravillous trophoblasts of the chorion laeve, villous hypermaturity, and multifocal villous edema.	No	(Abellar <i>et al.</i> 2009)
Irinotecan (Dose/schedule NS, 10 cycles, 2 wks apart)	Case report	1	Ovary	2 nd First@wk 18 Last@wk 36	5-Fluorouacil	Vaginal	37 + 5 days	Female infant: 5 lb 14 oz [2,665 g], Apgar scores 9 and 9 at 1 and 5 minutes. Newborn was born without complications.	At 4 months, development was normal with no teratogenic effects.	(Taylor and Blom 1980)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the irinotecan timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 79. Lapatinib – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Lapatinib (750 mg daily)	Case report	1	Breast	1 st , 2 nd First@wk 1 Last@wk 14	None	Vaginal, induced	36	Female infant: 2,600 g, Apgar scores 8 and 9 at 1 and 5 minutes. Newborn was healthy.	At 18 months, she had reached all developmental milestones on schedule.	(Kelly <i>et al.</i> 2006)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the lapatinib timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 80. Lomustine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Lomustine (780 mg, schedule NS)	Survey, retrospective	1 [Note: 27 pts received chemotherapy while pregnant; the number of patients who received lomustine while pregnant was not provided.]	Hodgkin Lymphoma	1 st First@wk 1 Last@wk 6	Vincristine, Procarbazine, Vinblastine (1 st , 2 nd , 3 rd)	NS	NS	Infant: sex, weight and Apgar scores NS. Newborn had a cleft palate and cleft lip.	No	(Mulvihill <i>et al.</i> 1987)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the lomustine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 81. Melphalan – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Melphalan (Dose/schedule NS)	Case series	2 of 2	Breast	1 st First@wk 2 Last@wk 9	5-Fluorouracil	--	--	Induced abortion at gestation wk 10. [No fetal data reported.]	--	(Jochimsen <i>et al.</i> 1981)
			Breast	1 st First@wk 1 Last@wk 7	5-Fluorouracil	--	--	Spontaneous abortion at gestation wk 10. [No fetal data reported.]	--	
Melphalan (Dose/schedule NS)	Cohort, retrospective	1 of 21 (Pt 2)	Breast	1 st	None	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Zemlickis <i>et al.</i> 1992b)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the melphalan timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 82. Methyl-GAG – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Methyl-GAG (Dose/schedule NS)	Case series	1 of 17 (Pt 17)	Leukemia, AML	3 rd First@wk 29	6-Mercaptopurine	NS	36	Female infant: 2,530 g, Apgar score 6. Newborn had no malformations.	No	(Greenlund <i>et al.</i> 2001)
Methyl-GAG (250 mg/m ² on days 3, 5, and 8)	Case report	1	Leukemia, APL	1 st	Daunorubicin	Vaginal	34	[Spontaneous preterm labor.] Female infant: 2,200 g, Apgar scores NS. Newborn had no congenital abnormalities.	The baby grew well [age NS].	(Sanz and Rafecas 1982)
Methyl-GAG (150 mg, 1 dose)	Case report	1	Leukemia, AML	2 nd , 3 rd First@month 7	Colcemid, 6-Mercaptopurine (1 st , 2 nd , 3 rd)	Vaginal	NS (> 7 months)	Male infant: 1,730 g, Apgar scores NS. Newborn showed no evidence of developmental abnormalities.	No	(Stevenson <i>et al.</i> 1966)
Methyl-GAG (Dose/schedule NS; Table 1: Pt 11 – 1 cycle)	Survey, retrospective	1 of 48 (1 of 56 pregnancies) (Table 1: Pt 11)	Leukemia, AML	1 st	Daunorubicin	NS	34	Infant: 2,200 g, sex and Apgar scores NS. Newborn was premature, but normal.	At 5 years, normal growth and development.	(Zuazu <i>et al.</i> 1991)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the methyl-GAG timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; AML = acute myelogenous leukemia; APL = acute promyelocytic leukemia; methyl-GAG = methyl-glyoxal bis guanyl hydrazone.

Appendix D Table 83. Nilotinib – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Nilotinib (200 mg BID [twice daily])	Case report	1 (1 of 2 pregnancies of same pt)	Leukemia, CML	1 st Last@wk 7.4	None	C-section	33	Male infant: 3,200 g, Apgar score 9 at 10 minutes. Newborn was healthy. [2 nd pregnancy]	At 5 months, healthy and developing normally.	(Conchon <i>et al.</i> 2009)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the nilotinib timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: BID = bis in die (Latin) or twice daily; NS = not specified; pt = patient; wk = week; wks = weeks; CML = chronic myelogenous leukemia.

Appendix D Table 84. Nimustine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Nimustine (75 mg, schedule NS)	Case report	1	Melanoma	2 nd , 3 rd First@wk 26	Dacarbazine, Vincristine, Interferon beta	Vaginal	35	Male infant: 2,208 g, Apgar scores NS. Newborn was healthy.	At 32 months, he had no signs of melanoma.	(Ishida <i>et al.</i> 2009)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the nimustine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 85. Oxaliplatin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Oxaliplatin (Dose/schedule NS)	Case series	1 of 13 (Pt 1)	Rhabdomyosarcoma	1 st , 2 nd , 3 rd	Irinotecan, Vinorelbine	NS	32	Infant sex NS: weight and Apgar scores NS. Newborn had cleft lip, cleft palate, tracheoesophageal fistula, and esophageal atresia. Newborn had normal body weight for gestational age. Placenta had vacuolization and nuclear pleomorphism, extravillous trophoblasts of the chorion laeve, villous hypermaturity, and multifocal villous edema.	No	(Abellar <i>et al.</i> 2009)
Oxaliplatin (Dose/schedule NS)	Survey, registry	1 of 12 from Table 6	Colorectal	1 st	Capecitabine	NS	NS	Infant sex NS: Birth weight and Apgar scores NS. Newborn was normal with normal body weight for gestational age.	No	(Cardonick <i>et al.</i> 2010)
Oxaliplatin (85 mg/m ² , 6 biweekly cycles)	Case report	1	Rectal	2 nd , 3 rd First@wk 20 Last@wk 30	5-Fluorouracil	Vaginal, induced	33.6	Female infant: 5 lb 6 oz [2,438 g], Apgar scores 8 and 8 at 1 and 5 minutes. Newborn was normal.	At 3.5 years, no deficits and at 60 th percentile for height and 45 th percentile for weight.	(Gensheimer <i>et al.</i> 2009)
Oxaliplatin (85 mg/m ² 2-hour infusion, 10 cycles)	Case report	1	Colon	1 st , 2 nd , 3 rd First@wk 13	5-Fluorouracil	C-section	33	Premature rupture of membranes. Twins, male and female infants: 2,200 g each, Apgar scores 10 at 1 minute for both. Both were healthy with no malformations.	At 2 years, both were developing normally.	(Jeppesen and Osterlind 2011)

Appendix D Table 86. Oxaliplatin (continued)

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Oxaliplatin (100 mg/m ² every 2 wks, 4 cycles)	Case report	1	Colorectal	2 nd , 3 rd [First@> wk 23]	5-Fluorouracil	C-section	31.5	Female infant: 1,175 g [SGA], Apgar scores 8 and 9 at 1 and 5 minutes. Newborn spent 33 days in the neonatal unit, 1 day on a ventilator. She was hypothyroid.	At 11.75 months of age (adjusted for prematurity), there were no abnormal physical findings apart from a flaky red spot on the top of her head. She was beginning to walk, had normal blood parameters, a normal Denver Developmental Screening Test, and was being treated for gastro-esophageal reflux and hypothyroidism.	(Kanate <i>et al.</i> 2009)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the oxaliplatin timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix D Table 87. Streptozotocin – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Streptozotocin (800 mg for 3 days, 3 cycles, 4 wks apart)	Case report	1	Non-Hodgkin lymphoma, diffuse histiocytic	2 nd , 3 rd First@wk 24 Last@wk 33	Procarbazine (1 st , 2 nd), Carmustine (1 st , 2 nd)	NS	35	Male infant: 2,340 g, Apgar scores 7 and 9 at 1 and 5 minutes. Newborn appeared normal, and had normal blood work and chromosome studies (karyotype and sister chromatid exchange).	No	(Schapira and Chudley 1984)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the streptozotocin timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 88. Teniposide – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Teniposide (60 mg/m ² once every 21 days, 3 cycles)	Case report	1	Non-Hodgkin lymphoma	2 nd , 3 rd First@wk 22 Last@wk 28	Cyclophosphamide, Doxorubicin, Vincristine, Bleomycin	C-section	31	Preeclampsia and fetal growth retardation at gestation wk 28. Fetal distress at gestation wk 31. Male infant: 1,380 g, Apgar scores 7, 9, and 10 at 1, 5, and 10 minutes. Newborn showed no neurologic, urinary tract, lung, or other abnormalities. Phototherapy was used for 3 days for hyperbilirubinemia.	At 18 months, normal growth.	(Lambert <i>et al.</i> 1991)
Teniposide (75 mg/m ² , 1 st and 2 nd cycles, 100 mg/m ² next 4 cycles, 6 cycles at 2.5-3 wks apart)	Case report	1	Non-Hodgkin lymphoma, Burkitt	2 nd , 3 rd Last@wk 37	Doxorubicin, Cyclophosphamide, Vincristine, Bleomycin (3 rd), Methotrexate (intrathecal, 3 rd)	Vaginal	37	Female infant: 3,750 g, Apgar score 9. Newborn was fully developed with a normal heart and blood counts. No abnormalities were detected.	No	(Lowenthal <i>et al.</i> 1982)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the teniposide timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks.

Appendix D Table 89. Triethylenemelamine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Triethylenemelamine (5 mg every 4-6 days for 8 wks, then 5 mg every 3 days for the last 2 wks)	Case report	1	Leukemia, ALL	3 rd	Radiation therapy (2 nd)	C-section	One month from term [NS]	Infant sex, weight, and Apgar scores NS. At birth, the infant had a depressed leukocyte count, but the blood counts became normal immediately after birth.	At 1 year, normal blood counts.	(Bierman <i>et al.</i> 1956)
Triethylenemelamine (Dose/schedule NS)	Case series	1 of 35 in text (1 of 39 in Table II; 1 pt treated with chemotherapy during pregnancy)	Hodgkin lymphoma	NS	None	NS	NS	Infant sex, weight and Apgar scores NS. Normal delivery.	Of the 1 patient treated with triethylenemelamine and 8 patients treated with X-rays during early pregnancy, therapy had no effect on the offspring followed up to 12 years, with the exception that 1 child proved to be mentally retarded.	(Hennessy and Rottino 1963)
Triethylenemelamine (16 mg over 8 days)	Case series	1 of 4 from the Addendum (Pt 18)	Hodgkin lymphoma	1 st	None	NS	Term	Infant sex, weight, and Apgar scores NS. Newborn was normal.	No	(Smith <i>et al.</i> 1958)
Triethylenemelamine (5 mg/day for 3 days, 4 cycles over 85 days; maintenance therapy (1-3 mg/day) for remainder)	Case series	1 of 71 from Table V (Pt 9 – 2 pregnancies)	Hodgkin lymphoma	1 st	None	--	--	Spontaneous abortion. [No fetal data reported.]	--	(Wright <i>et al.</i> 1955)
				1 st	None	--	--	Spontaneous abortion. [No fetal data reported.]	--	
Triethylenemelamine (4 mg/schedule NS)	Survey, retrospective	1 of 48 (Table 2: Pt 6)	Non-Hodgkin lymphoma	1 st First@wk 12	Cyclophosphamide, Vincristine, Procarbazine	--	--	Induced abortion at 14 wks of gestation. [No fetal data reported. Pt 6, 1 st pregnancy.]	--	(Zuazu <i>et al.</i> 1991)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the triethylenemelamine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

-- No data due to death of fetus or infant.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia.

Appendix D Table 90. Trofosfamide – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Trofosfamide (2 oral doses of 75 mg/m ² daily for 10 consecutive days, 4 cycles)	Case report	1	Rhabdomyosarcoma, alveolar	3 rd First@wk 28 + 1 day	Idarubicin, Etoposide	C-section	34 + 1 day	Male infant: 1,790 g [SGA], Apgar scores 9, 9, and 9 at 1, 5, and 10 minutes. Newborn was healthy, echocardiography and ultrasound revealed no abnormalities.	At 2.25 years, no evidence of malformations and normal neurological development.	(Siepermann <i>et al.</i> 2012)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the trofosfamide timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; SGA = small for gestational age.

Appendix D Table 91. Vindesine – Summary of pregnancy outcomes following cancer chemotherapy while pregnant

Chemotherapy agent	Study type	# of cases	Cancer type	Timing of treatments*	Co-treatment (timing**)	Delivery route***	Gestational age at delivery, wks	Pregnancy complications and outcome	Follow-up evaluation	Reference
Vindesine (2 mg every 20 days)	Case series	1 of 5 (Pt 5)	Leukemia, ALL	3 rd First@wk 31 Last@wk 39	Vincristine (2 nd , 3 rd)	C-section	39	Male infant: 3,700 g, Apgar scores 9 and 10 at 1 and 5 minutes. Newborn had no congenital malformations, and his blood profile was normal.	At 1 year, normal physical and mental development and normal blood count.	(Fassas <i>et al.</i> 1984)

* Timing of chemotherapy exposure: 1st = first trimester (beginning of last menstrual period (week 1) through week 13), 2nd = second trimester (week 14 through week 27), and 3rd = third trimester (week 28 to delivery); when specified, the first and last gestational weeks of chemotherapy treatment are indicated.

** Timing of co-treatment is listed only if it is different from the vindesine timing.

*** Delivery route: C-section = Cesarean section and Vaginal = vaginal birth.

Abbreviations: NS = not specified; pt = patient; wk = week; wks = weeks; ALL = acute lymphocytic leukemia.

5.0 APPENDIX E – REGISTRIES AND CLINICAL TRIALS

Registries of cancer during pregnancy:

- Toronto Hospital of Sick Children, Toronto, Ontario, Canada (www.MotherRisk.com)
- Cooper University Hospital, Camden, New Jersey, USA (Coordinator: Dr. Elyce Cardonick; www.cancerandpregnancy.com)
- University of Oklahoma Medical Center, Oklahoma City, Oklahoma, USA (Coordinator: Dr. John Mulvihill)
- University of Texas MD Anderson Cancer Center, Houston, USA (Coordinators: Drs. Richard Theriault and Jennifer Litton)
- University of Frankfurt and German Breast Group, Frankfurt, Germany (Coordinator: Dr. Sybille Loibl; http://germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft/english-summary-.html?lang=de_DE.UTF-8%2C+de_CH.U)

Ongoing clinical trials for pregnant women with cancer (www.clinicaltrials.gov):

- The German Breast Group (http://germanbreastgroup.de/studien/adjuvant/brustkrebs-in-der-schwangerschaft/english-summary-.html?lang=de_DE.UTF-8%2C+de_CH.U) is an observational study with the title "Prospective and Retrospective Register Study of the German Breast Group (GBG) for Diagnosis and Treatment of Breast Cancer in Pregnancy." The start date was April 2003, and the target data collection end date was April 2010 for the collection of retrospective and prospective data. Their target was 500 cases. They are tentatively scheduled to complete their report by April 2011. (Status is listed as recruiting, accessed April 6, 2012).
- The MD Anderson Cancer Center has an observational study based on retrospective and prospective case reports of patients seen at MD Anderson for any type of cancer during pregnancy. It is titled "Collection of Outcomes Data for Pregnant Patients With Cancer." Their target is 200 patients. It began in December 2005 and is tentatively scheduled for data collection on December 2019; they may finish sooner depending on the number of patients.
- The MD Anderson Cancer Center has a study that is tracking patients taking Imatinib for Chronic Myeloid Leukemia titled "Chart Review Study of Chronic Myelogenous Leukemia (CML) Patients Treated With Imatinib Outside of a Clinical Trial." A secondary focus of this trial will be to evaluate the pregnancy outcomes of patients administered Imatinib during pregnancy. Started June 2005 and targeted to run through June 2012 in an effort to collect data on 850 cases (observational model: case control; retrospective study).
- The MD Anderson Cancer Center effort has a study testing a combination chemotherapy treatment for efficacy and pregnancy outcomes in women with breast cancer. It is titled "Multimodality Treatment of Primary Breast Cancer Occurring Concomitant With Pregnancy." It is an interventional study with a target of 100 patients to be seen at the MD Anderson Cancer Center. The study should start in August 2010 and tentative be completed by August 2011.
- The UZ Gasthuisberg, Katholieke Universiteit Leuven is studying the offspring of women taking cancer treatment (chemotherapy and radiation) during pregnancy titled "Oncological Treatment During Pregnancy: Pharmacokinetics of Chemotherapy and Long Term Follow up of the Offspring." (It has an unclear study design.) Study design is observational model: cohort. Study start date was August 2005, and tentative completion date is April 2020. The target is 100 cases, and they are recruiting.

6.0 APPENDIX F – OCCUPATIONAL EXPOSURE TO CANCER CHEMOTHERAPY

Sources of additional information on this topic include:

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