

Draft NTP Monograph on Developmental Effects and Pregnancy Outcomes Associated with Cancer Chemotherapy Use during Pregnancy

Kembra L. Howdeshell, Ph.D. National Institute of Environmental Health Sciences

NTP Peer Review Meeting October 1-2, 2012





Main Findings

Cancer Chemotherapy Use during Pregnancy





Main Findings

- The draft NTP evaluation of cancer chemotherapy use during pregnancy focused on 5 health effects:
 - 1. Frequency of congenital malformations by trimester
 - 2. Risk of Spontaneous fetal death
 - 3. Pregnancy complications
 - 4. Newborn weight and health
 - 5. Infant growth and development



Frequency of congenital malformations by trimester

Cancer Chemotherapy Use during Pregnancy



Frequency of major malformations

- Identified as defects that adversely affect health or development (Correa 2007)
- Data analyzed by trimester exposed
 - 1st trimester
 - 2nd and/or 3rd only
- 95% confidence intervals were calculated based on pooled data for any chemotherapy exposure or individual agent exposure
- Newborns identified as normal or without a description of health were considered to have no malformations
- Total conceptuses included all fetal deaths:
 - Spontaneous abortions (47), induced abortions (79), stillbirth (24), and other fetal loss (9)
 - Reports lacking autopsy information were considered normal

Examples of major malformations associated with cancer chemotherapy exposure

- Skeletal malformations
 - Cleft lip, cleft palate, club foot, hemivertebrae, absence or syndactyly of distal digits, premature skull closure, microcephaly
- Cardiac defects
 - Ventricular septal defects, atrial septal defects, bicuspid aortic value, hypoplastic aorta
- Neural tube defects
 - Meningocele, hydrocephalus
- Other organ development
 - Pyloric stenosis, esophageal atresia, pulmonary fistula
 - Hypospadias, rectovaginal fistula or ambiguous genitalia, imperforate anus

Frequency of major malformations for all chemotherapy exposures

 Apparent rate of major malformations was higher in conceptuses exposed during the 1st trimester than those exposed in the 2nd and/or 3rd trimester only



- Data are consistent with current medical paradigm for treatment of pregnant cancer patients
- No pattern of effects observed by individual agent or specific mechanism of action

Some malformations are not likely caused by exposure to cancer chemotherapy during pregnancy

- 16 conceptuses had malformations not likely associated with cancer chemotherapy
 - Chemotherapeutic agent exposure occurred (2nd and/or 3rd trimester only) after the critical window of development (n=13 conceptuses)
 - Examples: agenesis of right kidney and ureter, Down syndrome, gastroschisis, hypospadias, meningocele, neurofibromatosis, pulmonary artery fistrula, rectal atresia, syndactyly of fingers or toes, and ventricular septal defects
 - Malformations observed prior to chemotherapy or are inherited conditions
 - Examples: Potter syndrome, familial polydactyly
- When these were excluded, apparent rate of major malformations attributed to cancer chemotherapy exposure was:
 - not appreciably changed following exposure in 1st trimester
 - lower following exposure in 2nd and/or 3rd trimester only

Minor malformations were not included in the apparent rates of major congenital malformations

- Identified as defects that do not adversely affect health or development (Rasmussen et al. 2003)
- Examples:
 - Plagiocephaly, pectus excavatum, hip subluxation, double cartilage ring in ears, patent peritoneal pit, bilateral small protuberance on phalanx 5
 - Small atrial septal defects, minor ventricular septal defects, patent ductus arteriosus, asymptomatic cardiac murmur
 - Inguinal hernia, mild glandular hypospadias
 - Microophthalmia, adherence of lens to cornea
 - Hemangioma
 - Bilateral ureteral reflex, unilateral renal dilation



Frequency of Congenital Malformations by Trimester: Conclusion

 Cancer chemotherapy use in the first trimester represents a higher apparent risk of major malformations than in the second and/or third trimesters only.



Charge questions:

1. Frequency of Congenital Malformations by Trimester

- a. Please comment on whether the scientific information in the text and Figure 1 (pages 43-44) is technically correct, clearly stated, and objectively presented. Please identify any needed improvements.
- b. Please comment on whether the draft monograph accurately identifies the limitations of the current data.
- c. Please comment on whether the evidence provided in the draft monograph supports NTP's interpretation that cancer chemotherapy use in the first trimester represents a higher apparent risk of major malformations than in the second and/or third trimester only.



Risk of Spontaneous Fetal Death

Cancer Chemotherapy Use during Pregnancy



Spontaneous Fetal Death: Spontaneous abortions

- Identified as early spontaneous fetal death; ≤22 weeks of gestation
- Apparent rate of spontaneous abortion appeared to be lower than a pooled estimate of spontaneous abortion reported in healthy women

	Rate of spontaneous abortion
Any chemotherapy agent	3.6% (46/1271 conceptuses)
Normal population in US/UK (Wilcox 2010)	13% (95%CI=10-16%)

Spontaneous Fetal Death: Stillbirths

- Identified as late spontaneous fetal death; >22 weeks of gestation
- Apparent rate of stillbirths appeared to be higher than rates of stillbirth for the general population in the U.S.

	Stillbirth
Any chemotherapy agent	1.8% (23/1271 conceptuses)
General population in US from 2003-2005 (MacDorman 2007)	0.4%

- Stillbirths appeared to occur more frequently with exposure to cytarabine (8.6%; 13/151 stillbirth and live birth conceptuses)
 - Occurred more frequently in combination therapy which included:
 - Daunorubicin (8)
 - Idarubicin (3, including one also co-treated with daunorubicin)



Spontaneous Fetal Death: Conclusions

- Cancer chemotherapy does not appear to increase the apparent risk of spontaneous abortions
- Stillbirth (spontaneous fetal loss at <22 weeks of gestation) appears to increase with use of specific agents (i.e., cytarabine in combination therapy with daunorubicin or idarubicin)

Charge questions for Main Findings

2. Risk of Spontaneous Fetal Death

- a. Please comment on whether the scientific information in the text and Table 19 is technically correct, clearly stated, and objectively presented. Please identify any needed improvements.
- b. Please comment on whether the draft monograph accurately identifies the limitations of the current data.
- c. Please comment on whether the evidence provided in the draft monograph supports NTP's interpretation that:
 - i. Cancer chemotherapy use in the first trimester does not appear to increase the apparent risk of early spontaneous fetal death (also called spontaneous abortion, ≤22 weeks of gestation).
 - ii. Cancer chemotherapy use in the second and/or third trimester only may increase the apparent risk of late spontaneous fetal death (also called stillbirth, >22 weeks of gestation).
 - iii. Apparent risk of late spontaneous fetal death is increased with use of specific agents (i.e., cytarabine in combination with daunorubicin or idarubicin).



Pregnancy Complication Associations

Cancer Chemotherapy Use during Pregnancy



Reductions in Amniotic Fluid

- Identified as: decreases in amniotic fluid, oligohydramnios, and anhydramnios; based on stillbirth and livebirth pregnancies
- Apparent rate for any chemotherapy exposure was not different than the prevalence of reductions in amniotic fluid in the general population in US
 - However, 39% of the reported reductions in amniotic fluid occurred in pregnancies exposed to trastuzumab

	Reduction in Amniotic Fluid
Any chemotherapy	2.9% (33/1128 stillborn and liveborn pregnancies)
General population in US (Casey 2000; March of Dimes)	2.3 to 4% all pregnancies

- Of pregnancies exposed to trastuzumab,
 - 68.4% experienced reduced amniotic fluid (13/19 pregnancies)
 - Severity of oligohydramnios appears to increase with continued use, but appears to be reversible when discontinued
 - Multiple mechanisms of action for reductions in amniotic fluid have been hypothesized

Spontaneous Preterm Labor

- Issue: Preterm birth (<37 weeks of gestation) occurred in a majority of patients administered chemotherapy during pregnancy
 - Including spontaneous and induced vaginal delivery as well as Caesarian-section deliveries
- Preterm spontaneous labor did not appear to be increased due to exposure to cancer chemotherapy

	Spontaneous Preterm Labor
Any chemotherapy	5.6% (63/1128 stillborn and liveborn pregnancies)
General population in US (lams and Donovan 2011)	8.4% all pregnancies (Based on preterm birth rate of 12% and 70% caused by spontaneous labor)

- Other frequently reported pregnancy complications included:
 - Premature rupture of membranes (18) and preeclampsia (17)



Pregnancy Complication Associations: Conclusions

- Trastuzumab may be responsible for reductions in amniotic fluid when administered during pregnancy.
- Cancer chemotherapy during pregnancy does not appear to be associated with spontaneous preterm labor.



Charge questions:

3. Pregnancy Complication Association

- a. Please comment on whether the scientific information in the text and Tables 20 (page 46) and 22 (page 48) are technically correct, clearly stated, and objectively presented. Please identify any needed improvements.
- b. Please comment on whether the draft monograph accurately identifies the limitations of the current data.
- c. Please comment on whether the evidence provided in the draft monograph supports NTP's interpretations of cancer chemotherapy use during pregnancy that:
 - i. Trastuzumab may be responsible for reductions in amniotic fluid when administered during pregnancy.
 - ii. Chemotherapeutic agents do not appear to be associated with spontenous preterm labor.



Effects on Newborn Weight and Health

Cancer Chemotherapy Use during Pregnancy



Newborn Weight and Health: Small for gestational age

- Data were insufficient to reach a conclusion on whether cancer chemotherapy during pregnancy increased small for gestational age newborns
 - Differences in population-based weight and growth curves (e.g. ethnicity, year of birth) prevent the cross study determination of SGA from reported birth weights
 - Small for gestational age (<10th percentile body weight) was reported in 2.2% of the total newborns exposed to cancer chemotherapy in utero (24/1112 live born infants)
- Intrauterine growth restriction estimated in fetus was not always an indicator for a small for gestational age newborn
 - Reported for 36 of 1136 total stillborn and liveborn conceptuses (3.2%)
 - Only 2 fetuses with IUGR were reported to be small for gestational age at birth
 - Possible that intrauterine growth rate may catch up when cancer chemotherapy is discontinued 2 to 3 weeks prior to birth

Newborn Weight and Health: Transient Myelosuppression

- Identified as blood measurements of pancytopenia (anemia), leukopenia, neutropenia, and/or thrombocytopenia in newborn
- Transient myelosuppression may be more prevalent following cancer chemotherapy during pregnancy
 - Frequently reported side effect in cancer patients administered chemotherapy
- Data were insufficient to reach a conclusion on whether cancer chemotherapy during pregnancy actually increased the occurrence of transient myelosuppression in newborns
 - Complete blood counts are not routinely reported for newborns exposed gestationally to cancer chemotherapy
 - Complete blood counts are not regularly evaluated in the healthy population to provide background rates (Christensen 2009)
 - Myelosuppression reported for 50 of 1112 newborns gestationally exposed to cancer chemotherapy
 - It generally resolved within 2-3 weeks after birth, usually without treatment
- It has been suggested that myelosuppression may be avoided by ceasing cancer chemotherapy 3 weeks prior to birth (Sorosky 1997)

Newborn Weight and Health: Fetal/neonatal cardiotoxicity

- Identified as arrhythmia, cardiomyopathy, tachycardia, and heart failure
- Some chemotherapeutic agents induce cardiovascular complications in patients directly administered the drug (reviewed in Gziri 2012)
 - Example: anthracycline antibiotics
 - Doxorubicin, daunorubicin, epirubicin, idarubicin, mitoxantrone
- Data were inconclusive that on whether cancer chemotherapy that induces cardiotoxicity in treated patients also induces cardiotoxicity in fetuses/neonates
 - Apparent rate of fetal/neonatal cardiotoxicity was 0.6% (7/1136 total stillborn and liveborn conceptuses)
 - No pattern by individual agent or mechanism of action
 - No cardiotoxicity observed at follow-up evaluations

Other health issues reported in newborns exposed in utero to cancer chemotherapy may be due to prematurity

- Preterm birth (<37 weeks of gestation) occurred in a majority of patients administered chemotherapy during pregnancy
- Complications associated with preterm birth include: (Institute of Medicine 2006)
 - Respiratory distress syndrome and other lung disorders
 - Immune system disorders
 - Gastrointestinal disorders
 - Apnea
 - Cardiovascular problems
 - Anemia
 - Hearing and visual impairments
 - Central nervous system disorders
- Many of these complications were reported in newborns exposed to cancer chemotherapy reviewed in the draft NTP monograph



Newborn Weight and Health: Conclusions

- Data were insufficient to reach a conclusion on whether cancer chemotherapy during pregnancy increased small for gestational age newborns
- Transient myelosuppression may be more prevalent following cancer chemotherapy during pregnancy
- Data were inconclusive that on whether cancer chemotherapy that induces cardiotoxicity in treated patients also induces cardiotoxicity in fetuses/neonates

Charge Question for Main Finding

4. Effect on Newborn Weight and Health

- a. Please comment on whether the scientific information in the text and Table 21 (page 47) is technically correct, clearly stated, and objectively presented. Please identify any needed improvements.
- b. Please comment on whether the draft monograph accurately identifies the limitations of the current data.
- c. Please comment on whether the evidence provided in the draft monograph supports NTP's interpretations of cancer chemotherapy use during pregnancy that:
 - i. It is not possible to evaluate apparent risk of small for gestational age based on current reports.
 - ii. Cancer chemotherapy use during pregnancy appears to be associated with transient myelosupression.
 - iii. Evidence is inconclusive that chemotherapy agents that induce cardiotoxicity in treated patients also induce cardiotoxicity in fetuses/neonates exposed to the same agents *in utero*.



Effects on Infant Growth and Development

Cancer Chemotherapy Use during Pregnancy



Effects on Infant Growth and Development

- Exposure to cancer chemotherapy may cause functional deficits to several organs that may not be apparent at birth
 - Ear, eye, heart, and immune, nervous, and reproductive systems
- Majority of offspring exposed in utero to cancer chemotherapy had normal growth and development in infancy and early childhood (<2 years of age)
 - Follow up data available for 63% of offspring (703/1112 infants)
 - 96% had normal growth and development (25/703 infants)
 - Adverse health effects at follow-up included:
 - Delays in growth, motor development, speech development
 - Attention deficit disorder, sensorineural hearing loss
 - Cancer (n=1 child; Zemlickis et al.1993)

Effects on Infant Growth and Development

- While certain functional deficits may not be apparent until later in life (e.g. reproductive function), most follow up evaluations are limited to the first few months or years of life
 - Example: Cyclophosphamide

Age (years)	% of children with follow up data
<2 years	42% (42/100)
2-4 years	27% (27/100)
5-12 years	13% (13/100)
12-16 years	6% (6/100)
18-22 years	3% (3/100)

Effects on Infant Growth and Development: Conclusions

• Growth and development [of offspring exposed to chemotherapy treatment for cancer during pregnancy] appear normal during infancy and early childhood (<2 years of age); however, it is important to recognize that certain functional deficits may not be apparent until later in life, e.g., effects on reproductive function.

Charge Question for Main Finding

5. Effects on Infant Growth and Development

- a. Please comment on whether the scientific information in the text is technically correct, clearly stated, and objectively presented. Please identify any needed improvements.
- b. Please comment on whether the draft monograph accurately identifies the limitations of the current data.
- c. Please comment on whether the evidence provided in the draft monograph supports NTP's interpretation that growth and development [of offspring exposed to chemotherapy treatment for cancer during pregnancy] appear normal during infancy and early childhood (<2 years of age); however, it is important to recognize that certain functional deficits may not be apparent until later in life, e.g., effects on reproductive function.





Charge Question: Main Findings

6. Are there other findings that should be highlighted? If so, please provide specific comments.