NTP
National Toxicology Program

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

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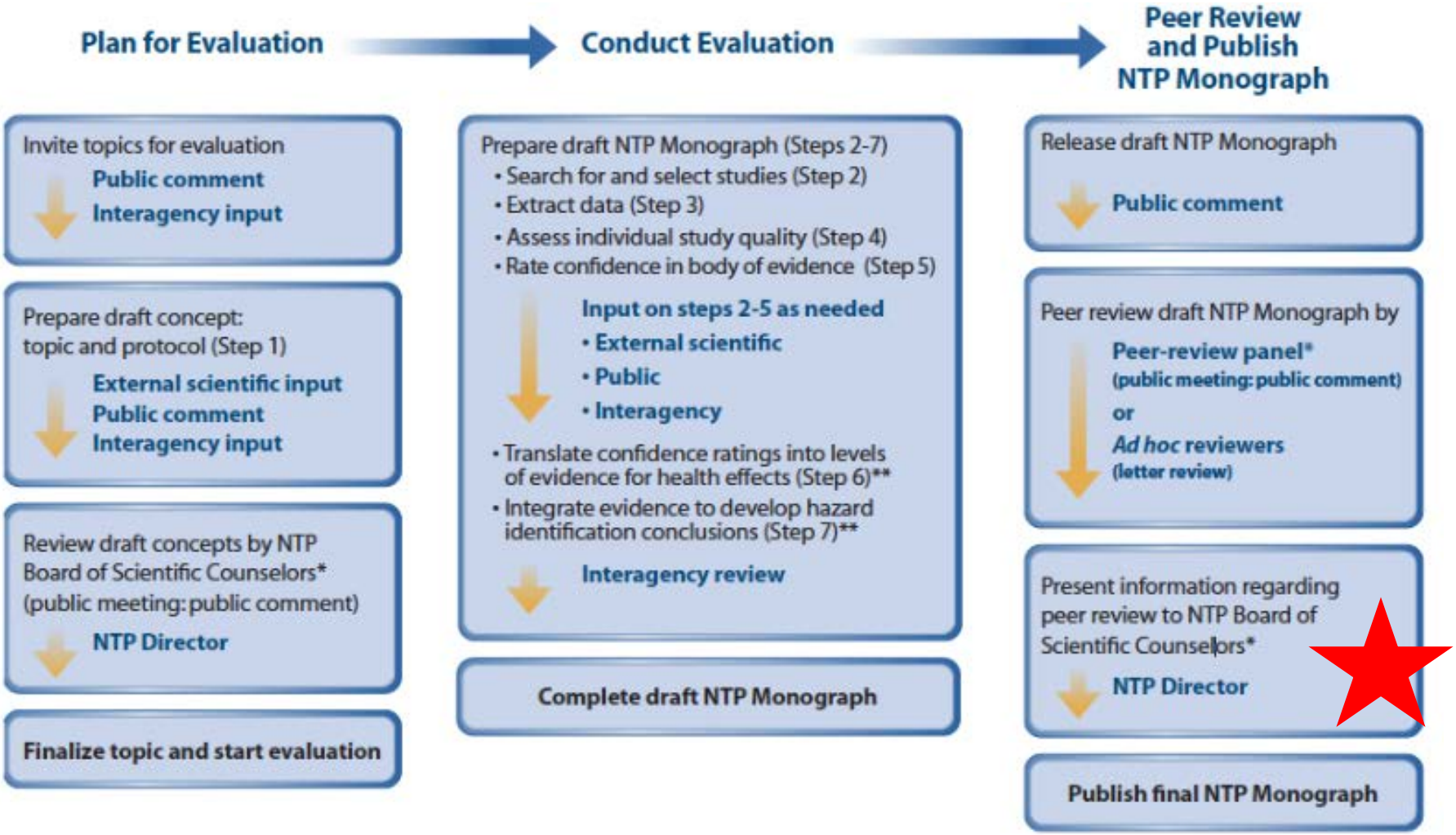
Office of Health Assessment and Translation (OHAT)

- Environmental health resource to the public and to regulatory and health agencies (Bucher et al 2011)
  - "conducts evaluations to assess the evidence that environmental chemicals, physical substances, or mixtures (collectively referred to as "substances") cause adverse health effects and provides opinions on whether these substances may be of concern given what is known about current human exposure levels.”

OHAT evaluation process



Background and rationale for the evaluation

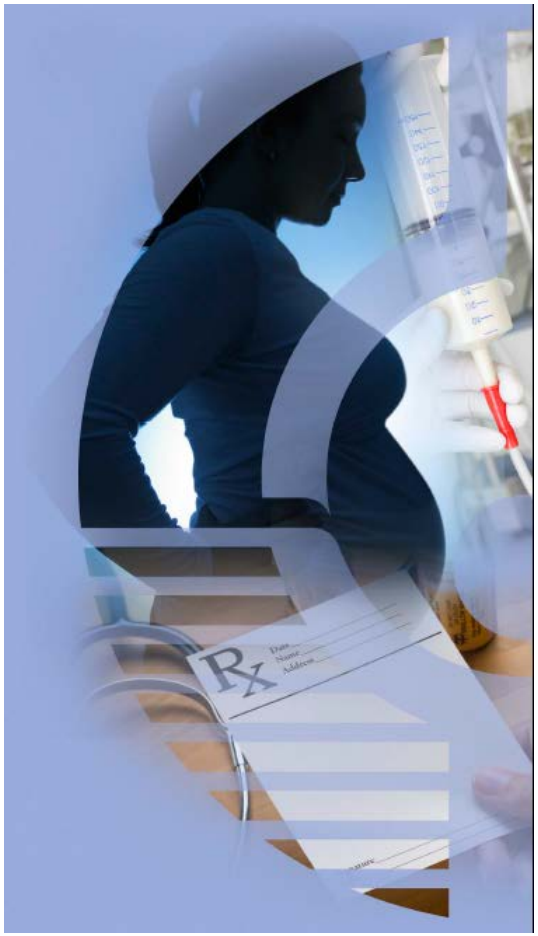
- ~17 to 100 per 100,000 women are diagnosed with cancer during pregnancy
- Patient and her medical team must determine course of treatment optimal for mom with minimal risk to fetus
  - Most treatments for cancer involve chemotherapy
  - Nearly all cancer chemotherapeutic agents have possible or demonstrable risk to the fetus
- Current medical paradigm suggests:
  - Avoid treatment during the 1st trimester, when possible
  - Treatment in 2nd and/or 3rd trimester does not appear to increase risk of major congenital malformations observed at birth
- A thorough literature review of cancer chemotherapy use during pregnancy was not available

Scope of the NTP monograph

- The monograph summarizes the effects of gestational exposure to chemotherapy on pregnancy outcomes
  - Focused on chemotherapy for treatment of cancer
    - Reviewed 56 chemotherapeutic agents with reported use during pregnancy
- The purpose of the monograph is to serve as a tool for physicians and their patients in making clinical decisions
  - Not intended as a medical advice or clinical guidance

Organization of the monograph

- Executive summary
- Introduction
- Methods
- Cancer diagnosed during pregnancy
- Effects of chemotherapy
  - Any chemotherapy (1 chapter)
  - Individual agents with >10 cases (34 chapters)
- Discussion and conclusions
- Appendices



Structure of individual chemotherapeutic agent chapters

- Mechanism of action, route of administration, and indications
- Evidence of placental and breast milk transport
- Laboratory animal developmental toxicity
- Human gestational exposure and effects 
  - Number of cases, publications and types of cancer treated
  - Termination of pregnancy
  - Spontaneous fetal death
  - Rate of occurrence of congenital malformations
  - Pregnancy complications and newborn health
  - Infant death
  - Follow-up evaluations
- Summary

Majority of publications reporting pregnancy outcomes are case reports and case series

- The monograph reviewed pregnancy outcomes of 1247 cases with 1261 pregnancies (1276 conceptuses)
  - Conceptus refers to a liveborn infant or an embryo or fetus from an induced abortion, spontaneous abortion, stillbirth, or maternal/fetal death

Study types	Number of publications	Number of conceptuses per study type
case reports	342	357
case series	90	371
case series, retrospective	9	93
cohort, retrospective	2	30
survey, retrospective	13	267
survey, registry	1	158
Total	457	1276

Limitations of the data

- Lack of referent group
- Small numbers of cases reported for most treatment regimens
- Small numbers of conceptuses reported with specific types of major malformations
- Reports with no information on the condition of the abortus or fetus
- Reports lacking information on individual cases
- Lack of follow-up examination and variable quality of the assessments
- High rate of premature birth
- Publication bias

Peer review of the draft NTP monograph

- An independent expert panel reviewed the draft Monograph during a public meeting held October 1-2, 2012 in RTP

Catherine Spong, MD FACOG (Chair)	National Institute of Child Health and Human Development (NICHHD)
Cheryl Broussard, PhD	National Center on Birth Defects and Developmental Disabilities, Center for Disease Control and Prevention (CDC)
Michael Greene, MD	Massachusetts General Hospital
Julia Lawrence, DO	Wake Forest School of Medicine
John Mulvihill, MD	The University of Oklahoma
Janine Polifka, PhD	University of Washington
Tina Rizack, MD MPH	Warren Alpert Medical School of Brown University
Judith Ann Smith, PharmD	The University of Texas MD Anderson Cancer Center
Kristel Van Calsteren, MD PhD	UZ Gasthuisberg Leuven, Belgium

Key questions addressed in NTP monograph

- Are major congenital malformations more frequently associated with chemotherapy in the 1st trimester versus the 2nd and/or 3rd trimester only?
- Is chemotherapy for the treatment of cancer during pregnancy associated with:
  - Spontaneous fetal death?
  - Pregnancy complications?
  - Effects on newborn weight and health?
  - Adverse effects on infant growth and development?

Peer review of the draft NTP monograph

- The panel generally agreed with the draft NTP findings on health effects associated chemotherapy use
- Suggested specific analysis and editorial changes
  - For example:
    - Adjust denominators for each health outcome
    - Determine SGA based on a standard growth curve
    - Reformat agent chapters and summary tables
    - Synthesize any similarities observed between human and animal developmental toxicity
    - Include contact information for the Organization of Teratology Information Specialists in the monograph

Higher risk of major malformations reported for chemotherapy exposure in the 1st trimester

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

	Rate of major malformations
During 1st trimester	14% (41/303 conceptuses)
2nd and/or 3rd trimester only	3% (21/826 conceptuses)
Timing not specified	0% (0/27 conceptuses)
General population of US from 1968 to 2003 (Correa 2007)	3%

  - 2 larger case series reported rate of major malformations similar to general population of US (Van Calsteren 2010, and Cardonick 2010).

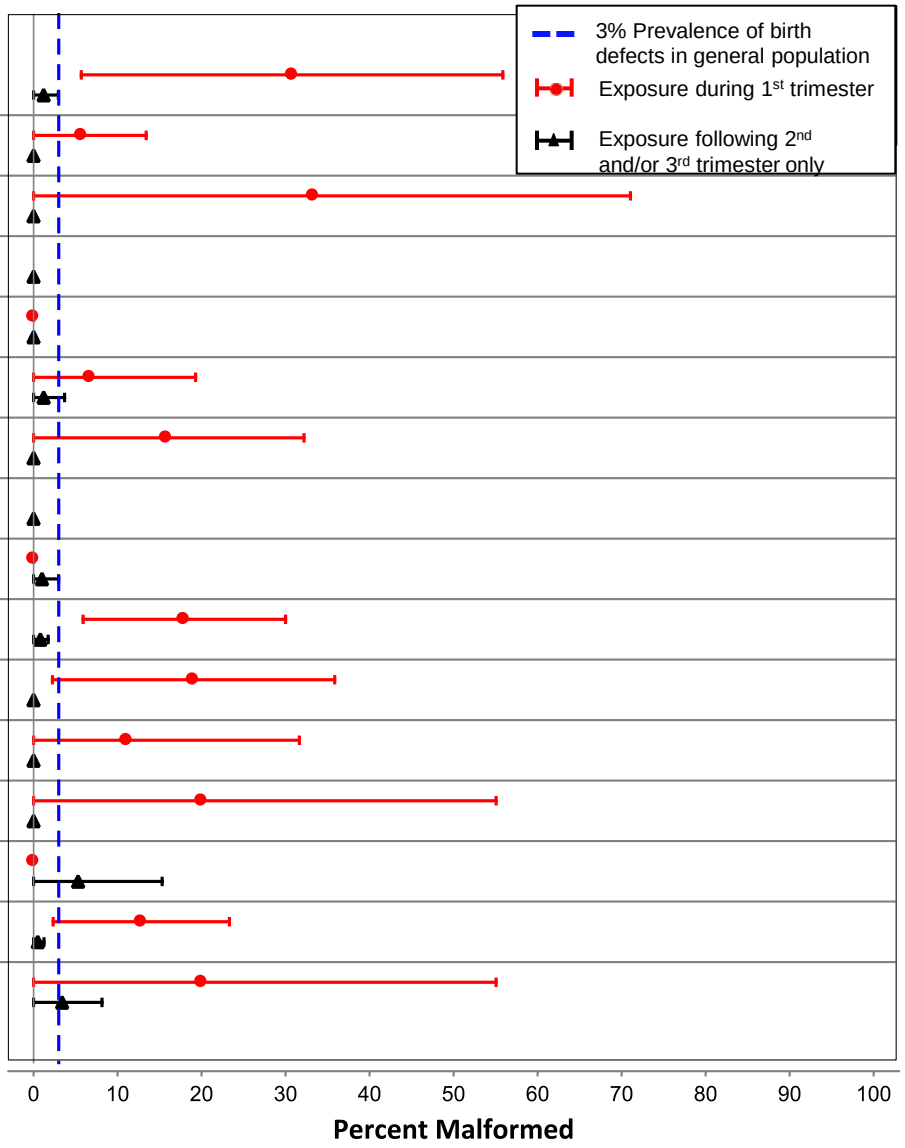
- Data are consistent with current medical practice
  - Avoid treatment during the period of organogenesis, if possible

Some malformations are not likely caused by chemotherapy use during pregnancy

- Malformations reported with exposure to chemotherapy after the critical window of development
- Malformations observed prior to chemotherapy or inherited conditions
- Malformations due to exposure to co-exposures
- After adjustment, apparent rates in the 1st trimester were not appreciably changed and apparent rates in 2nd and/or 3rd trimester were decreased

Rate of major malformations were analyzed by individual chemotherapeutic agent

Agent	Trimester Exposed	%Malformed ±CI
5-Fluorouracil	During 1st	30.8 ± 25.1 (4/13)
	2nd and/or 3rd Only	1.2 ± 1.7 (2/161)
6-Mercaptopurine	During 1st	5.7 ± 7.7 (2/35)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/41)
6-Thioguanine	During 1st	33.3 ± 37.7 (2/6)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/44)
Actinomycin D	During 1st	No Data
	2nd and/or 3rd Only	0.0 ± 0.0 (0/16)
All-trans retinoic acid	During 1st	0.0 ± 0.0 (0/2)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/24)
Bleomycin	During 1st	6.7 ± 12.6 (1/15)
	2nd and/or 3rd Only	1.3 ± 2.4 (1/80)
Busulfan	During 1st	15.8 ± 16.4 (3/19)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/6)
Carboplatin	During 1st	No Data
	2nd and/or 3rd Only	0.0 ± 0.0 (0/17)
Cisplatin	During 1st	0.0 ± 0.0 (0/5)
	2nd and/or 3rd Only	1.0 ± 2.0 (1/99)
Cyclophosphamide	During 1st	17.9 ± 12.0 (7/39)
	2nd and/or 3rd Only	0.8 ± 0.9 (3/367)
Cytarabine	During 1st	19.0 ± 16.8 (4/21)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/109)
Dacarbazine	During 1st	11.1 ± 20.5 (1/9)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/45)
Daunorubicin	During 1st	20.0 ± 35.1 (1/5)
	2nd and/or 3rd Only	0.0 ± 0.0 (0/75)
Docetaxel	During 1st	0.0 ± 0.0 (0/2)
	2nd and/or 3rd Only	5.3 ± 10.0 (1/19)
Doxorubicin	During 1st	12.8 ± 10.5 (5/39)
	2nd and/or 3rd Only	0.5 ± 0.7 (2/383)
Epirubicin	During 1st	20.0 ± 35.1 (1/5)
	2nd and/or 3rd Only	3.4 ± 4.7 (2/58)



Specific malformations may be associated exposure to certain agents

- Combinations of malformations with suggested links to certain agents:
  - Craniofacial and skeletal malformations
    - i.e., cyclophosphamide, methotrexate, or cytarabine
  - Exomphalos, skeletal malformations and/or urogenital malformations
    - i.e., imatinib
- In contrast, there was a lack of major malformations reported for other agents
  - i.e., interferon alpha, trastuzumab

Effect of exposure to chemotherapy on risk of spontaneous abortion is unclear

- Apparent rate following exposure in the 1st trimester appeared comparable to data for general population.

	Rate of spontaneous abortion
Chemotherapy exposure during 1st trimester	13% (42/327 conceptuses)
General population in US/UK (Wilcox 2010)	13% (95% CI,10-16%)

- However, there were challenges in interpreting the data:
  - Potential lack of reporting spontaneous abortions
  - Lack of detection of pregnancy and, thus, pregnancy loss

Rate of stillbirth higher with exposure to chemotherapy

- Apparent rate following exposure in the 2nd and/or 3rd trimester only appeared to be higher than data for the general population in US

	Rate of Stillbirth
Any chemotherapy agent	2% (20/836 conceptuses)
General population in US from 1990-2004 (MacDorman 2007)	0.3 to 0.4%

- Stillbirths may occur more frequently with exposure to certain agents
  - e.g., cytarabine (8%; 9/110 conceptuses) vs cyclophosphamide (1% 3/368 conceptuses)
- Hematological cancers may also increase risk of stillbirth due to elevated risk of thrombosis

Abnormally low levels of amniotic fluid (AF) may result from chemotherapy exposure

- Apparent rate for any chemotherapy exposure was comparable to rates in the general population in US

	Rate of Abnormally Low Levels of AF
Any chemotherapy	3% (32/1103 pregnancies)
Trastuzumab	72% (13/18 pregnancies)
General population in US (Casey 2000; March of Dimes)	2.3 to 4% all pregnancies

- Trastuzumab appeared to associated with low levels of AF
  - Severity of condition appears to increase with continued use, but appears to be reversible when discontinued
  - Multiple mechanisms of action hypothesized for reductions in AF by trastuzumab

Exposure to chemotherapy does not appear to induce spontaneous preterm birth

- Many of the gestationally-exposed infants were born prematurely, including medically-induced and C-sections
  - ~30% (366/1118 liveborn infants) were premature
- Apparent rate of spontaneous preterm birth was comparable to the rate in the US general population

	Rate of Spontaneous Preterm Birth	
	All data	**Normalized to reported data only**
Any chemotherapy	9% (97/1118 liveborn infants)	15% (97/661 liveborn infants)
General population in US (Martin 2011)	12% of 4,130,665 births	

Prematurity complicated the interpretation of effects of exposure to chemotherapy on offspring

- Premature birth is associated with adverse health outcomes (IOM 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

Possible risk of impaired fetal growth with exposure to chemotherapy

- Data were suggestive that chemotherapy increases the apparent rate of small for gestational age (SGA) infants

	Rate at birth	
	All data	**Normalized to reported data only**
Any chemotherapy	8% (90/1118 liveborn infants)	12% (90/723 liveborn infants)

- However, there were challenges in interpreting the data:
  - Differences in geographical location and ethnicity
  - Temporal differences (reports published from 1950-2012)
  - Information on body weight frequently (35%) not reported

Possible risk of transient myelosuppression with exposure to chemotherapy

- Data suggest that transient myelosuppression may be more prevalent with exposure to chemotherapy
  - Observed in 46 of 1118 liveborn infants
  - It generally resolved within 2-3 weeks after birth, usually without treatment
- Challenges in interpreting the data
  - Information on complete blood counts frequently not reported for gestationally-exposed infants
  - Complete blood counts are not regularly evaluated in the healthy population
- It has been suggested that myelosuppression in the newborn may be avoided by ceasing chemotherapy 3 weeks prior to birth

Effect of exposure to chemotherapy on risk of fetal/neonatal cardiotoxicity is unclear

- Data were inconclusive on whether exposure to chemotherapy induces fetal/neonatal cardiotoxicity
  - Observed in 10 of 1118 liveborn infants
- Anemia can influence cardiac function in neonates
- No overt cardiotoxicity observed at follow-up evaluation
  - One larger case series reported slight differences in cardiac morphology

Growth and development appear normal for majority of offspring exposed to chemotherapy

- Adverse health effects reported in only 3% of offspring
  - Delays in: growth (7), language and/or motor development (4)
  - Delays in growth due to major malformations (3)
  - Asperger syndrome (1; normal twin), sensorineural hearing loss (3)
  - Disease-related issues: cancer (1; normal twin), normocytic anemia (1), and leukomalacia (1)
- Challenges in interpreting the data
  - Follow-up evaluations available for only 60% of offspring
  - Age at last follow-up evaluation was usually ≤2 years of age

Conclusions

- Decision to use chemotherapy during pregnancy should be made on an individual patient basis
  - Monograph can be used as a resource
- Evaluate other populations exposed to chemotherapy
  - Medical personnel as well as maintenance workers
  - Patients with non-cancer health conditions
- Increase participation in prospective studies and registries of cancer during pregnancy
- Develop and improve consensus documents on treatment of cancer during pregnancy

Step moving forward…

- Offer the master file of all gestationally-exposed conceptuses on request
- Present the monograph at the Annual Meeting of the Teratology Society on June 25, 2013
- Publish a review paper based on monograph
- Develop a concept for a systematic review of the health effects of occupational exposures to cancer chemotherapeutic agents

Acknowledgments

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