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

Kembra L. Howdeshell, Ph.D.
Office of Health Assessment and Translation
NTP/NIEHS

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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)
  - "conduces 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

Plan for Evaluation
- Invite topics for evaluation
  - Public comment
  - Interagency input
- Prepare draft concept: topic and protocol (Step 1)
  - External scientific input
  - Public comment
  - Interagency input
- Review draft concepts by NTP Board of Scientific Counselors* (public meeting: public comment)
  - NTP Director
- Finalize topic and start evaluation

Conduct Evaluation
- Prepare draft NTP Monograph (Steps 2-7)
  - Search for and select studies (Step 2)
  - Extract data (Step 3)
  - Assess individual study quality (Step 4)
  - Rate confidence in body of evidence (Step 5)
- Input on steps 2-5 as needed
  - External scientific
  - Public
  - Interagency
- Translate confidence ratings into levels of evidence for health effects (Step 6)**
- Integrate evidence to develop hazard identification conclusions (Step 7)**
- Interagency review
- Complete draft NTP Monograph

Peer Review and Publish NTP Monograph
- Release draft NTP Monograph
  - Public comment
- Peer review draft NTP Monograph by Peer-review panel* (public meeting: public comment) or Ad hoc reviewers (letter review)
- Present information regarding peer review to NTP Board of Scientific Counselors*
  - NTP Director
- Publish final NTP Monograph
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 1\textsuperscript{st} trimester, when possible
  – Treatment in 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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

<table>
<thead>
<tr>
<th>Study types</th>
<th>Number of publications</th>
<th>Number of conceptuses per study type</th>
</tr>
</thead>
<tbody>
<tr>
<td>case reports</td>
<td>342</td>
<td>357</td>
</tr>
<tr>
<td>case series</td>
<td>90</td>
<td>371</td>
</tr>
<tr>
<td>case series, retrospective</td>
<td>9</td>
<td>93</td>
</tr>
<tr>
<td>cohort, retrospective</td>
<td>2</td>
<td>30</td>
</tr>
<tr>
<td>survey, retrospective</td>
<td>13</td>
<td>267</td>
</tr>
<tr>
<td>survey, registry</td>
<td>1</td>
<td>158</td>
</tr>
<tr>
<td>Total</td>
<td>457</td>
<td>1276</td>
</tr>
</tbody>
</table>
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 2\textsuperscript{nd} and/or 3\textsuperscript{rd} 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 1\textsuperscript{st} trimester

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

<table>
<thead>
<tr>
<th>Timing</th>
<th>Rate of major malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>During 1\textsuperscript{st} trimester</td>
<td>14% (41/303 conceptuses)</td>
</tr>
<tr>
<td>2\textsuperscript{nd} and/or 3\textsuperscript{rd} trimester only</td>
<td>3% (21/826 conceptuses)</td>
</tr>
<tr>
<td>Timing not specified</td>
<td>0% (0/27 conceptuses)</td>
</tr>
<tr>
<td>General population of US from 1968 to 2003 (Correa 2007)</td>
<td>3%</td>
</tr>
</tbody>
</table>

- 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

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

<table>
<thead>
<tr>
<th>Rate of spontaneous abortion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy exposure during 1st trimester</td>
</tr>
<tr>
<td>13% (42/327 conceptuses)</td>
</tr>
<tr>
<td>General population in US/UK (Wilcox 2010)</td>
</tr>
<tr>
<td>13% (95% CI, 10-16%)</td>
</tr>
</tbody>
</table>

• 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

<table>
<thead>
<tr>
<th></th>
<th>Rate of Stillbirth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any chemotherapy agent</td>
<td>2% (20/836 conceptuses)</td>
</tr>
<tr>
<td>General population in US from 1990-2004 (MacDorman 2007)</td>
<td>0.3 to 0.4%</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th></th>
<th>Rate of Abnormally Low Levels of AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any chemotherapy</td>
<td>3% (32/1103 pregnancies)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>72% (13/18 pregnancies)</td>
</tr>
<tr>
<td>General population in US</td>
<td>2.3 to 4% all pregnancies</td>
</tr>
</tbody>
</table>

- 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

<table>
<thead>
<tr>
<th></th>
<th>Rate of Spontaneous Preterm Birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All data</td>
</tr>
<tr>
<td>Any chemotherapy</td>
<td>9% (97/1118 liveborn infants)</td>
</tr>
<tr>
<td>General population in US</td>
<td>12% of 4,130,665 births</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th></th>
<th>Rate at birth</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All data</td>
</tr>
<tr>
<td>Any chemotherapy</td>
<td>8% (90/1118 liveborn infants)</td>
</tr>
</tbody>
</table>

- 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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The NTP Board of Scientific Counselors

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