Clinical Update: Chemotherapy in Pregnancy

Meredith T. Moorman, PharmD, BCOP, CPP
Duke University Hospital
NCOP Annual Meeting
August 8, 2015

Objectives

- Describe changes in pregnancy labeling for drug and biologic products
- Understand when a fetus is at highest risk from chemotherapy administration
- Identify chemotherapy properties that contribute to risk of fetal toxicity
- Summarize data regarding specific chemotherapy agents and their risk of toxicity during pregnancy

Pregnancy Statistics

- 2013 statistics[1]:
  - 3,932,181 births were registered in the US
  - Birth rates declined for women in their 20s to record lows (by 3%)
  - Rates rose for women in their 30s and late 40s in 2013 (2% and 14%, respectively)
- About 49% of pregnancies unintended[2]
- Birth defects affect ~1 in every 33 babies born in US each year[3]

[1]Martin JA, Hamilton BE, Osterman MJK, et al. National vital statistics reports; vol 64 no 1. Hyattsville, MD: National Center for Health Statistics. 2015. [2]Finer LB and Zolna MR. Contraception 2011 Nov;84(5):478-485. [3]Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep. 2008;57(1):1-5.

Pregnancy Categories On Medication Labeling

PREGNANCY CATEGORY	DESCRIPTION
A	Adequate, well-controlled studies; failed to demonstrate risk to fetus in any trimester
B	Animal reproduction studies; failed to demonstrate risk to fetus; no adequate and well-controlled studies in pregnant women
C	Animal reproduction studies; shown adverse effect on fetus; no adequate and well-controlled studies in humans, Benefit > Risk?
D	Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, Benefit > Risk?
X	Studies in animals or humans demonstrate fetal abnormalities and/or positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, Risk > Benefit

http://chemm.nlm.nih.gov/pregnancycategories.htm

Changes in Pregnancy Labeling

- New Pregnancy and Lactation Labeling Rule (PLLR) went into effect on June 30, 2015
- Created to better facilitate communication between patient and prescriber about risks of drug therapy during all stages of pregnancy

PLLR document

What Will PLLR Look Like?

- Will apply to drug or drug products (including biological products licensed as drugs)
- Consolidation of info into 3 sections:
  1. Pregnancy (includes labor and delivery)
  2. Lactaction (replaces nursing mothers section)
  3. Females and Males of Reproductive Potential (pregnancy testing, contraception and infertility)

PLLR – Pregnancy Section

- Availability of pregnancy exposure registry
- Risk summary – based on all relevant animal and human data and pharmacology
  - Structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, alterations to growth
  - IF systemic absorption of medication, include background risk of major birth defects and miscarriage in US popn for comparison
  - Incidence of effect along with effect of dose, duration of exposure, gestational timing of exposure
- Clinical considerations – dose adjustments
- Data

PLLR – Lactation Section

- Definitions:
  - Lactation – biological state during which body produces and excretes milk
  - Breastfeeding – refers to all situations when child fed with human milk
- Includes risk summary, clinical considerations and data sections as well
  - Presence of drug/active metabolite in milk (including concentrations and estimated total daily dose)
  - Effects on breastfed child (age-related changes in ADME)
  - Effects on milk production
  - Ways to minimize exposure

ADME – absorption, distribution, metabolism, excretion

PLLR – Females and Males of Reproductive Potential Section

- Required when:
  - Requirements for pregnancy testing and/or contraception before, during, after therapy
  - Human/animal data suggesting drug-associated effects on fertility and/or pre-implantation loss effects
- Includes information on pregnancy testing, contraception, and fertility

Who Has To Follow the PLLR?

- New requirements apply to:
  - Prescription drug products with **approved** application between **06/30/2001-06/30/2006**
  - Prescription drug products with **pending** application on **06/30/2006**
  - Prescription drug products with **submitted** application **on or after June 30, 2006**
- Applications approved prior to 06/30/2001 must remove pregnancy category from labeling within 3 years of effective date of PLLR

Cancer In Pregnancy

- Estimated rate of cancer diagnosis during pregnancy is 17-100/100,000 women
- Concern about ↑ cancer rates as women delay childbearing
- Cancers most frequently diagnosed during pregnancy: breast, cervical, Hodgkin lymphoma, NHL, leukemia, ovarian cancer, melanoma

Haas JF. *Int J Cancer* 1984;34(2):229-235.
Smith LH et al. *Am J Obstet Gynecol* 2003;189(4): 1128-1135.

NHL = non-Hodgkin lymphoma

Incidence of Specific Cancers in Pregnancy

Type of Cancer	Incidence in General Popn of Women of Reproductive Potential (15-44 years) (per 100,000 women)[3]	Incidence in Pregnancy (per 100,000 women) [1, 2]
Breast	319.5	1.3-5.1
Cervical	44.7	3.6-11
Hodgkin Lymphoma	20.2	0.7-2.2
Non-Hodgkin Lymphoma	24	0.2-0.7
Leukemia	18.8	0.4-1.4
Ovarian	4.1	0.9-2.4
Melanoma	22.9	0.6-3.1

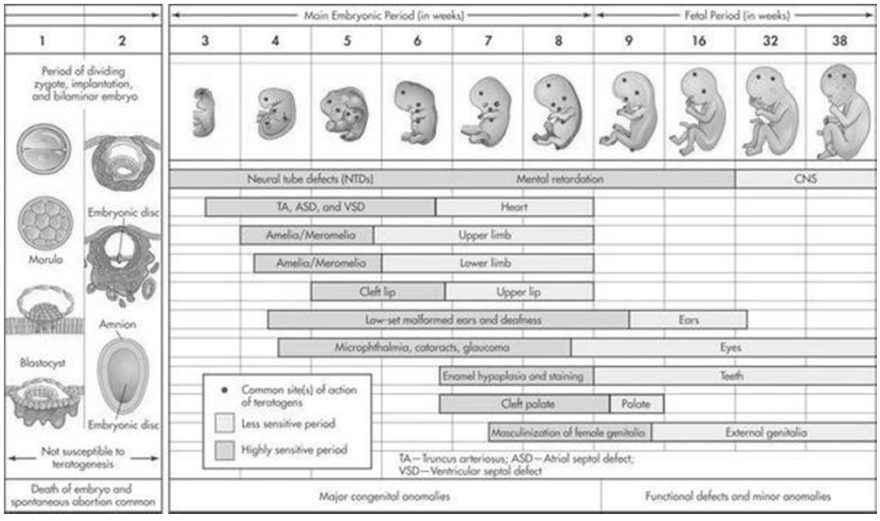
[1]Haas JF. *Int J Cancer* 1984;34(2):229-235. [2]Smith LH et al. *Am J Obstet Gynecol* 2003;189(4): 1128-1135.
[3]U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999–2011 Incidence and Mortality Web-based Report.* Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2014. Available at: www.cdc.gov/uscs.

Difficulty In Determining Toxicity Associated With Chemotherapy

- Lack of appropriate reference group to determine baseline risk
- Small numbers
  - Of cases given specific regimen
  - Of conceptuses with specific malformation
- Lack of information
  - About conceptus condition at time of death
  - Individual case data often not presented when outcomes normal
- Lack of follow-up
- High rate of pre-term birth
- Publication bias

NTP Monograph

When Is Fetus Most At Risk?



Cardonick E and Iacobucci A. Lancet Oncol 2004;5:283-91.

What Factors Contribute to Teratogenicity of a Medication?

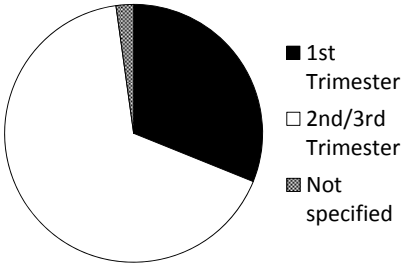
- Teratogen: exposures that irreversibly affect the normal growth, structure, or function of developing embryo or fetus
- Timing of exposure
  - ↑ rates of spontaneous abortion, fetal death, and major malformations if exposed during first trimester
- Dose
- Characteristics favoring placental transfer
  - High lipid solubility
  - Low molecular weight
  - Low levels of plasma protein binding

Koren G et al. J Obstet Gynaecol Can 2013;288:263-278.

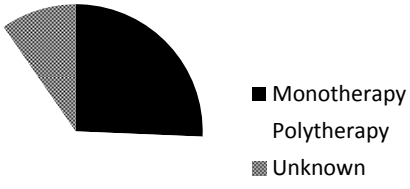
NTP Statistics

- 1247 cases → 1261 pregnancies → 1276 conceptuses

Timing of Exposure



Monotherapy vs. Polytherapy



Fetal Injury Outcomes

- Spontaneous fetal death (73 cases)
  - 48 cases ended in spontaneous abortion
    - 13% after exposure during the 1st trimester
  - 25 ended in stillbirth
    - 2% after exposure in 2nd/3rd trimester
- Overall rate of major malformations = 5%
  - 1st trimester exposure = 14%
  - 2nd/3rd trimester exposure = 3%

Pregnancy Complications

- Low levels of amniotic fluid – 3%
- Intrauterine growth restriction – 3%
- Spontaneous preterm birth – 33%
  - Early preterm birth (<34 weeks) – 16%
  - Late preterm birth (34-36 weeks) – 17%
- Infant death ~2%
  - Usually within first 4 months of life

Antimetabolites

Chemotherapy Agent	# Pregnancies Affected	Major Malformations % (n/N)	Overall Rate of Major Malformations (%)
5-Fluorouracil	N=178	1st = 31 (4/13) 2nd/3rd = 2 (3/161)	4
6-Mercaptopurine	N= 83	1st = 6 (2/35) 2nd/3rd = 0 (0/41) NS = 0 (0/3)	3
Cytarabine	N=164	1st = 19 (4/21) 2nd/3rd = 4 (4/109) NS = 0 (0/13)	6
Hydroxyurea	N=33	1st = 8 (1/13) 2nd/3rd = 14 (3/21)	12
Methotrexate	N=84	1st = 4 (1/24) 2nd/3rd = 2 (1/58)	2

NS = not specified

DNA Alkylating Agents

Chemotherapy Agent	# Cases Affected	Major Malformations % (n/N)	Overall Rate of Major Malformations (%)
Carboplatin	N=17	1st = 0 2nd/3rd = 6 (1/17)	6
Cisplatin	N=103	1st = 20 (1/5) 2nd/3rd = 4 (4/99)	5
Cyclophosphamide	N=416	1st = 18 (7/40) 2nd/3rd =1 (5/366)	3
Dacarbazine	N=56	1st = 11 (1/9) 2nd/3rd = 2 (1/45)	4

DNA Intercalating Agents

Chemotherapy Agent	# Pregnancies Affected	Major Malformations % (n/N)	Overall Rate of Major Malformations (%)
Daunorubicin	N=107	1st = 20 (1/5) 2nd/3rd = 4 (3/75) NS = 0 (0/5)	5
Doxorubicin	N=424	1st = 13 (5/39) 2nd/3rd = 2 (6/383)	2

Microtubule Function Inhibitors

Chemotherapy Agent	# Pregnancies Affected	Major Malformations % (n/N)	Overall Rate of Major Malformations (%)
Docetaxel	N=21	1st = 0 (0/2) 2nd/3rd = 11 (1/19)	10
Paclitaxel	N=36	1st = 0 (0/0) 2nd/3rd = 3 (1/38)	3
Vinblastine	N=82	1st = 31 (5/16) 2nd/3rd =5 (3/57) NS = 0 (0/8)	10
Vincristine	N=275	1st = 9 (4/44) 2nd/3rd = 1 (1/159) NS = 0 (0/1)	2

Miscellaneous/Targeted Therapies

Chemotherapy Agent	# Pregnancies Affected	Major Malformations % (n/N)	Overall Rate of Major Malformations (%)
All-trans retinoic acid	N=28	1st = 0 (0/2) 2nd/3rd = 4 (1/24)	4
Bleomycin	N=94	1st = 7 (1/15) 2nd/3rd = 5 (4/80)	5
Imatinib	N=152	1st = 12 (12/100) 2nd/3rd = 0 (0/6)	11
Interferon-alpha	N=41	1st = 6 (1/20) 2nd/3rd = 0 (0/21) NS = 0 (0/2)	2
Rituximab	N=26	1st = 20 (1/5) 2nd/3rd = 0 (0/18)	4
Tamoxifen	N=14	1st = 25 (3/12) 2nd/3rd = 0 (0/3)	20
Trastuzumab	N=19	1st = 0 2nd/3rd = 0	0

Do We Have Guidelines?

- NCCN offers some guidance in certain disease states (breast, cervical and CML guidelines)
- Lancet Oncology Review Series[1-3]
- International Consensus Guidelines for Management of Gynecologic Cancers[4]

[1]Morice P et al. *Lancet Oncol* 2012;379:558-569. [2]Amant F et al. *Lancet Oncol* 2012:379:570-579
[3]Brenner B et al. *Lancet Oncol* 2012:379:580-587.
[4]Amant F et al. *Int J Gynecol Cancer* 2014 Mar;24(3):394-403.

Long Term Outcomes In Offspring – Exposed vs. Non-Exposed

- Exposed (n=53) vs. non-exposed (n=22) children in women diagnosed with cancer
  - Developmental testing offered to mother-infant pairs enrolled in Cancer and Pregnancy Registry
  - No significant differences found in: cognitive skills, academic achievement, behavioral competence
  - Gestational age was significantly different in groups (36.7 vs. 38.2 weeks, p=0.04), but no developmental outcome differences noted
  - Results limited by small sample size but comparison of treatment vs. no treatment important

Cardonick EH et al. *Am J Obstet Gynecol* 2015;212:658.e1-8.

Long Term Outcomes In Offspring of Breast Cancer Patients

- 81 breast cancer patients treated with FAC q21-28 days until gestational week 35
- Mean values: 4.2 cycles given, gestational age 37 weeks, birth weight 2.9kg
- 28 children delivered preterm (<37 weeks)
- 30% children described as healthy, 12% with developmental milestone delays, no significant cognitive abnormalities reported

FAC = cyclophosphamide 500 mg/m2 IV D1, doxorubicin 50 mg/m2 CIVI over 72 h, 5-FU bolus 500 mg/m2 IV on Days 1&4

Murthy RK et al. *Breast Cancer Research* 2014;16:500.

Long Term Cardiac and Cognitive Outcomes

- Interim analysis of observational cohort
- Assessed 70 children at birth, 18 months, 5-6y, 8-9y, 11-12y, 14-15y, or 18y
  - Neuro exams, cognitive function tests, ECG or ECHO, general health/development questionnaire
- Median gestational age: 35.7 weeks
- Median follow-up: 22.3 months (16.8-211)
- Cognitive development scores ↓ if pre-term
- Behavior, general health, hearing, growth assessments correspond with general popn

Amant F et al. *Lancet Oncol* 2012;13:256-264.

General Recommendations

- Treatment of cancer in pregnant women should involve a multidisciplinary team
- Ultrasound prior to chemotherapy to determine if pre-existing malformations present
- Must balance welfare of mother (and lack of treatment of malignancy) and fetus (if treatment is pursued)
- Chemotherapy administration should stop ~3-4 weeks before planned delivery (no later than 35 weeks)

Conclusions

- Cancer diagnosis during pregnancy is a relatively rare phenomenon
- Chemotherapy administration should be avoided in the first trimester, if possible
- Standard of care treatments may need to be modified to limit risk to fetus
- Newer agents may have different patterns of teratogenicity when compared to traditional chemotherapy agents

Assessment Question #1

1. Which of the following changes regarding pregnancy drug labeling will occur with institution of the "Pregnancy and Lactation Labeling Rule (PLLR)"?

A. Pregnancy categories (A, B, C, D, X) will continue to be assigned to new FDA-approved products
B. No reference to pregnancy exposure registry information will be included
C. All prescription drug products should change product labeling to comply with PLLR standards by June 30, 2016
D. Information provided will be divided into 3 sections: Pregnancy, Lactation, and Females and Males of Reproductive Potential
E. All of the above

Assessment Question #2

2. The risk of major congenital malformations is highest during which gestational time period?

A. Weeks 1-2 (all-or-none period)
B. Weeks 3-8 (organogenesis)
C. Weeks 9-38 (fetal period)
D. Weeks 38+ (birth and beyond)
E. All of the above

Assessment Question #3

3. Which of the following medication-specific factors contribute to teratogenicity of chemotherapy agents?

A. Timing of exposure
B. Dose administered
C. Low molecular weight
D. Low levels of plasma protein binding
E. All of the above

Assessment Question #4

4. Exposure to this agent during pregnancy is most commonly associated with low levels of amniotic fluid:

A. Methotrexate
B. Doxorubicin
C. Trastuzumab
D. Cisplatin
E. All of the above

Clinical Update: Chemotherapy in Pregnancy

Meredith T. Moorman, PharmD, BCOP, CPP
Duke University Hospital
NCOP Annual Meeting
August 8, 2015