New FDA Pregnancy and Lactation Labelling Requirements

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Disclosures

• I have no conflicts of interest due to the absence of financial or commercial relationships with any product I mention today

Dr. Sharon Ternullo
### Current FDA Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Well-controlled studies in humans show no risk to the fetus in 1&lt;sup&gt;st&lt;/sup&gt; trimester and possibility of fetal harm appears remote. No evidence for risk in 2&lt;sup&gt;nd&lt;/sup&gt; or 3&lt;sup&gt;rd&lt;/sup&gt; trimesters.</td>
</tr>
</tbody>
</table>
| **B**    | Animal studies show no risk to fetus **BUT** no well-controlled studies in humans  
**OR** animal studies show a risk **BUT** not confirmed in controlled human studies in 1<sup>st</sup> trimester and no evidence for risk in 2<sup>nd</sup> or 3<sup>rd</sup> trimester. |
| **C**    | No well-controlled studies in humans; animal studies have demonstrated a fetal adverse effect  
**OR** no studies available |
| **D**    | Evidence of human fetal risk but **benefits may outweigh the risks in certain circumstances.** |
| **X**    | Controlled studies in humans or animals demonstrate fetal abnormalities or there is evidence based on human experience **AND** **risks outweigh any possible benefit.** |

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## Potential Effects of Medications on the Infant

<table>
<thead>
<tr>
<th>Effect on Fetus</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teratogenicity</td>
<td>Thalidomide, diethylstilbestrol, valproic acid, ethanol, phenytoin, carbamazepine, warfarin</td>
</tr>
<tr>
<td>Growth and indirectly survival and morbidities</td>
<td>Caffeine, nicotine</td>
</tr>
<tr>
<td>Post delivery withdrawal</td>
<td>Narcotics, cocaine, SSRIs, barbituates, benzodiazepines</td>
</tr>
<tr>
<td>Post delivery respiratory efforts</td>
<td>Narcotics, benzodiazepines</td>
</tr>
<tr>
<td>Interfere with nursing</td>
<td>Contraceptives, diuretics,</td>
</tr>
<tr>
<td>Initiate delivery with associated risks</td>
<td>Castor oil, Black Cohosh</td>
</tr>
<tr>
<td>Effect maturation/developmental process</td>
<td>NSAIDS: patent ductus 3rd trimester</td>
</tr>
<tr>
<td>Trimester specific</td>
<td>Beclomethasone: surfactant production 2nd and 3rd trimester</td>
</tr>
<tr>
<td>Subtle and not so subtle learning disorders</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Disease states without treatment can impact fetal health</td>
<td>Hypoxia from seizure disorder</td>
</tr>
<tr>
<td></td>
<td>LGA, meconium aspiration diabetic mothers</td>
</tr>
</tbody>
</table>
Current FDA Guidelines

**Strengths**

- Implemented in 1979 in response to thalidomide tragedy
- Focused on Teratogenicity
- Meant to guide drug choice BEFORE fetal exposure
- 2008 FDA announced they would be changed
  - Risk summary
  - Clinical considerations
  - Therapeutic alternatives

**Problematic Areas**

- Do not fully address the risk vs. benefit nature of treating pregnant and lactating woman.
- Focus on teratogenicity. Do not effectively address other reproductive effects.
- Categories are not homogenous as to risk open to misinterpretation
- No distinction made for the source of data (animal vs. human) or for NO DATA
- Misunderstanding that successive categories represent increasing severity of malformations.
- Sometimes being used to interpret exposure AFTER the fact.
- Generic statements are insufficient for after-the-fact counseling.
- Amount of time it takes to obtain meaningful data
Time Taken to Obtain Pregnancy Safety Data from Initial Time of Approval until TERIS Risk Rating

• Teratogenicity Information System
• TERIS board were unable to determine teratogenic risk in human pregnancy associated with the therapeutic use of 168 (97.7%) of 172 drug treatments approved by FDA between 2000 and 2010 *
• The mean time necessary to assign a more precise risk to treatments judged to have “undetermined” risk is approximately 27 years

Time to Change Pregnancy Categories

• Bupropion was classified initially as category B in 1985 based on animal studies
  – Moved to category C in 2006 based on withdrawal phenomena observed in humans with SSRIS

• Paroxetine came to market in 1992.
  – Moved to category D in 2006 due to cardiac anomalies in newborns.
Drugs Affected by Pregnancy and Lactation Labelling Requirements (PLLRR)

• Drugs submitted for approval after June 30, 2015 must comply immediately upon approval
  – Prescription drugs
  – Biologics

• OTC drugs are NOT affected
New Pregnancy, Lactation, and Fertility Labelling

• Rules go into effect June 30, 2015
• Applications that are pending on June 30th must comply within 4 years of June 30th or time of approval...whichever is later
• Prescription drugs approved on or after June 30, 2001 must comply within 3-5 years.
• Drugs approved before this date will need to remove the pregnancy categories by June 30, 2018.
Pregnancy and Lactation Labeling Final Rule

Below is a comparison of the current prescription drug labeling with the new PLLR labeling requirements.

Medications Approved before June 30, 2001

• Designations “Category A through X” must be removed
• Companies may keep the pregnancy information that is currently on the package insert
• These statements must be kept up to date

Information obtained personally from FDA DI
3/30/15
Pregnancy

Teratogenic Effects

*Pregnancy Category B*

There is no evidence of teratogenicity or any other adverse effect on reproduction in female rats fed erythromycin base by oral gavage at 350 mg/kg/day (approximately twice the maximum recommended human dose on a body surface area) prior to and during mating, during gestation, and through weaning. No evidence of teratogenicity or embryotoxicity was observed when erythromycin base was given by oral gavage to pregnant rats and mice at 700 mg/kg/day and to pregnant rabbits at 125 mg/kg/day (approximately 1-3 times the maximum recommended human dose).

Labor and Delivery

The effect of erythromycin on labor and delivery is unknown.

Nursing Mothers

Erythromycin is excreted in human milk. Caution should be exercised when erythromycin is administered to a nursing woman.

Pediatric Use

See [INDICATIONS AND USAGE](#) and [DOSAGE AND ADMINISTRATION](#).
Data Sources for New Labelling

• Well-conducted studies in the medical literature for drugs and biologics
• Companies will be required to include clinically relevant from these studies with the labelling
• Pregnancy exposure registries conducted by companies
Pregnancy Registries

• Have existed for decades for some drugs
• Observational study that collects health information from women who take prescription drugs or vaccines when pregnant.
• FDA can recommend or require that a drug or biologic company implement a registry based on defined criteria.
• Registry list is posted on FDA website and kept up to date by FDA Office of Women’s Health.
• Examples: cancer, epilepsy, arthritis, diabetes, and psychiatric drugs
## Pregnancy Registry Listing

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Registry Name</th>
<th>Registry Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune Diseases</td>
<td>OTIS AutoImmune Diseases Study</td>
<td>MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS) <a href="http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm">OTIS-Autoimmune Diseases In Pregnancy Study</a> Phone: 1-877-311-8972</td>
</tr>
<tr>
<td>Asthma Medications: long-acting beta agonist and short-acting beta agonist products</td>
<td>OTIS Pregnancy Outcomes and Asthma Medications in Pregnancy Study</td>
<td>MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS) <a href="http://www.pregnancystudies.org">www.pregnancystudies.org</a> Phone: 1-877-311-8972</td>
</tr>
<tr>
<td>Cancer</td>
<td>Cancer and Childbirth Registry</td>
<td>Cooper Health Phone: 1-877-635-4499 <a href="http://www.cooperhealth.org/content/pregnancyandcancer.htm">www.cooperhealth.org/content/pregnancyandcancer.htm</a></td>
</tr>
</tbody>
</table>

### Drug/Biologic

<table>
<thead>
<tr>
<th>Brand</th>
<th>Condition</th>
<th>Registry Name</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta (exenatide)</td>
<td>Type 2 Diabetes</td>
<td>Exenatide Pregnancy Registry INC Research, LLC for AstraZeneca Phone: 1-800-633-9081 <a href="http://www.exenatidepregnancyregistry.com">http://www.exenatidepregnancyregistry.com</a></td>
<td></td>
</tr>
<tr>
<td>Bydureon (exenatide)</td>
<td>Type 2 Diabetes</td>
<td>Exenatide Pregnancy Registry INC Research, LLC for AstraZeneca Phone: 1-800-633-9081 <a href="http://www.exenatidepregnancyregistry.com">http://www.exenatidepregnancyregistry.com</a></td>
<td></td>
</tr>
</tbody>
</table>
Pregnancy and Lactation Labelling

General information
Contact information if pregnancy registry available and general statement about background risk.

Fetal risk summary
Based on all available data, this section characterizes the likelihood that the drug increases the risk of developmental abnormalities in humans and other relevant risks. More than one risk conclusion may be needed. For drugs that are not systemically absorbed, there is a standard statement that states that maternal use is not expected to result in fetal exposure.

For drugs that are systemically absorbed:

- When there are human data, include a statement about the likelihood of increased risk based on these data. This statement is followed by a description of findings.
- Include a standard statement about likelihood of increased risk based on animal data.

Clinical considerations
This section provides information on the following topics:

- Inadvertent exposure: known or predicted risk to the fetus from inadvertent exposure to drug early in pregnancy.
- Prescribing decisions for pregnant women:
  - Describe any known risk to the pregnant woman and fetus from the disease or condition that the drug is intended to treat.
  - Information about dosage adjustments during pregnancy.
  - Maternal adverse reactions unique to pregnancy or increased in pregnancy.
  - Effects of dose, timing, and duration of exposure to drug during pregnancy.
  - Potential neonatal complications and needed interventions.

Data
Human and animal data are presented separately, with human data presented first.

- Describe study type, exposure information (dose, duration, timing), any identified fetal developmental abnormality, or other adverse effects.
- For human data, include positive and negative experiences, number of subjects, and duration of study.
- For animal data, include species studied, and describe doses in terms of human dose equivalents (provide basis for calculation).
Example of Drug with no Human Pregnancy Data

Table 3. Updated Pregnancy Labeling for a Fabricated Drug (Alphathon) for Which Only Animal Data Are Available for Developmental Toxicity Findings

<table>
<thead>
<tr>
<th>General information</th>
</tr>
</thead>
<tbody>
<tr>
<td>All pregnancies have a background risk of birth defect, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Alphathon’s potential to increase the risk of developmental abnormalities above the background risk.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fetal risk summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on animal data, the likelihood that Alphathon increases the risk of developmental abnormalities is predicted to be high (see Data section).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma complicates ~1% of all pregnancies, resulting in higher perinatal mortality, low-birth weight infants, preterm births, and pregnancy-induced hypertension compared to outcomes for nonasthmatic women. Because of the risks of even mild maternal hypoxia to the developing fetus, asthma should be clinically well controlled during pregnancy. There are no human studies evaluating Alphathon use in pregnant women. The time of gestation at which risk may be greatest is unknown; therefore, risks of inadvertent exposure in early gestation cannot be evaluated. Animal data suggest that Alphathon exposure may result in early fetal loss and anomalies of major organ systems. There are no data regarding dosage adjustment needs in pregnancy. Given the lack of human data and the risks suggested by animal data, prescribers should consider alternative treatments for asthma for pregnant women when possible (especially during the first trimester) and for women planning pregnancy.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human data:</td>
</tr>
<tr>
<td>• There are no data on human pregnancies exposed to Alphathon</td>
</tr>
</tbody>
</table>

| Animal data: |
| • Reproductive studies performed during early pregnancy in rats at oral doses 0.75–1.0 times the recommended human dose (adjusted for body surface area) showed implantation loss, fetal resorptions, and major congenital anomalies of the cardiac, skeletal, and renal systems without signs of maternal toxicity. |
| • Reproductive studies performed in early pregnancy in rabbits at doses ~0.33–1.0 times the recommended human dose (adjusted for body surface area) showed increased postimplantation loss. Studies at three times the human dose showed significant fetal loss without signs of maternal toxicity. |
| • The effects of Alphathon on fetal growth, labor, or postnatal complications were not evaluated in the animal studies. |

Example Lactation Labelling

Table 4. Updated Lactation Labeling for a Fabricated Drug (Gammatol) for Which Human Data are Available

Summary
Gammatol is secreted in human milk. At a maternal dose of 400 mg daily, the average milk concentration, collected over 24 hrs after dosing, was 10 mcg/ml, which is lower than maternal serum drug concentrations at steady state. Based on an average milk consumption of 150 ml/kg/day, a 2-mo-old infant would consume ~6 mg/day of Gammatol through breast milk, which is ~1.3% of the maternal dose. No studies have been performed to assess infant absorption and exposure to Gammatol from breast milk. No studies have been performed to assess the impact of Gammatol on milk production or its effects on the breastfed child.

Clinical considerations
Because Gammatol is taken once daily, mothers can reduce infant exposure by taking their Gammatol dose immediately after breastfeeding at the time of day when feedings are less frequent.

Data
A lactation study was performed in 30 women who were 2 mo postpartum and exclusively breastfeeding their infants. All women enrolled in the study were taking a single dose of Gammatol 400 mg daily. Breast milk samples were collected from each breast at the beginning and end of each feeding for 24 hrs after a Gammatol dose. An average maximum milk concentration of 20 mcg/mL occurred 3 hrs after dosing, and drug concentrations in milk rapidly declined over the next 12 hrs. The average milk concentration was 10 mcg/ml. No drug was detectable in milk samples obtained 36 hrs or later after dosing. No data are available to assess the impact of Gammatol on milk production or its effects on the breastfed child.

Summary

• Improve the ability of health care practitioners to understand risks associated with medication use
• More information available
• Critical information more easily identified
• More responsibility for interpretation on the part of pharmacists and prescribers
• Encourages the use of Pregnancy Registries
Questions?