Prescribing for Pregnancy and Lactation

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Objectives

- Review the FDA pregnancy and lactation medications labeling.
- Discuss the risks and benefits of medications during pregnancy and breastfeeding
Pregnancy and Lactation Labeling Rule (PLLR)

FDA
FDA Pregnancy Risk Categories

Based on available animal and/or human studies
- Animal toxicology
- Retrospective
- Case reports

Definitions published in 1979 and apply to drugs marketed after December 1983
FDA Pregnancy Risk Categories

- Statements often considered ambiguous and difficult to interpret
- Failed to advise prescribers on the potential harm of withholding treatment
- Incorrect assumptions that drugs in the same category carry similar risks
- Incorrectly interpreted as grading systems where risk increased from lowest to highest
## FDA Pregnancy Risk Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>No evidence in women of fetal harm</td>
</tr>
<tr>
<td>B</td>
<td>Either animal studies have demonstrated no risk and there is no human data; or animal data demonstrated an adverse effect that was not confirmed in humans</td>
</tr>
<tr>
<td>C</td>
<td>Either animal studies have shown adverse effects and there are no human studies; or studies in animals or humans are not available</td>
</tr>
<tr>
<td>D</td>
<td>Positive evidence of fetal risk, although benefits may outweigh risks</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities; or there is evidence of fetal risk based on human experience, or both, AND the risk clearly outweighs the benefit</td>
</tr>
</tbody>
</table>
The rule finalizes provisions proposed in May 2008, finalized in December 2014 and was put into effect June 30, 2015.

Replaces the current letter categories A, B, C, D and X with 3 detailed sections that describe risks.
FDA Changes: Pregnancy and Lactation Labeling Rule

Prescription Drug Labeling Sections 8.1 – 8.3 USE IN SPECIFIC POPULATIONS

**CURRENT LABELING**

8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers

**NEW LABELING**
(effective June 30, 2015)

8.1 Pregnancy includes Labor and Delivery
8.2 Lactation includes Nursing Mothers
8.3 Females and Males of Reproductive Potential
Pregnancy (includes labor and delivery)
- Fetal risk summary, clinical considerations, and data

Lactation (includes nursing mothers)
- Risk summary, clinical considerations, and data

Females and Males Reproductive Potential
- Pregnancy testing, contraception, and infertility

New Labeling: Pregnancy

- Pregnancy Registry (Omitted if not available)
- Risk summary (Non-Systemically absorbed drugs)
  - Label states that maternal use is not expected to result in fetal exposure

New Labeling: Pregnancy

- Risk summary (Systemically absorbed drugs)
  - When there are human data, there is a statement about the likelihood of increased risk followed by a description of findings
  - When there is only animal data, there is a standard statement about the likelihood of increased risk but no description
  - A statement about the estimated background risk of major birth defects and miscarriage in the general population or the estimated background risk in the diseased population
  - A statement about the mechanism of action of the medication and the potential associated risk when the drug has a well-understood MOA

Clinical considerations

- Known or predicted risk to the fetus from inadvertent exposure to drug early in pregnancy
- Any known risk to the pregnant women and fetus from the disease or condition that drug is intended to treat
- Dosing adjustments during pregnancy and the post-partum period
- 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
- Effect on labor and delivery
New Labeling: Pregnancy

- Data
  - Description of the studies
  - Human Data
    - Number of Subjects
    - Study duration
    - Exposure duration
    - Limitations
  - Animal Data
    - Animal Species
    - Dosing human equivalents
    - Presence or absence of maternal toxicity

New Labeling: Lactation

- Risk summary
  - If appropriate, include statement that the use of the drug is compatible with breast-feeding
  - Effects of the drug on milk production
  - Whether the drug is present in human milk, and if so, how much
  - The effect of the drug on the breast fed child
New Labeling: Lactation

- Clinical considerations
  - Ways to minimize exposure to the breast-fed child
  - Potential drug effects in the child and recommendation for monitoring or responding to these effects
  - Dosing adjustments during lactation

- Data
  - Overview of the data on which the risk summary and clinical considerations were based

Timeline

- All drugs and biological products (approved since June 30, 2001) must revise the content and format of their pregnancy and lactation sections

- Application from June 30, 2015 and beyond
  - Immediate compliance

- Applications between June 30, 2001 and June 29, 2015
  - Changes will be phased in gradually over 3-5 years

- Applications before June 30, 2001
  - Required to remove pregnancy category within 3 years but not required to conform to labeling rule

- OTC medications are not affected by the rule

Patient Cases
Case 1: Antibiotics

- 18 year old G1P0 at 25 weeks gestation admitted to the hospital with pyelonephritis. Urine culture revealed *Citrobacter freundii* sensitive only to ciprofloxacin and sulfamethoxazole/trimethoprim

- Is sulfamethoxazole/trimethoprim a reasonable option for treatment in this patient?
Case 1: Antibiotics

- Is sulfamethoxazole/trimethoprim a reasonable option for treatment in this patient?
  - Answer: Depends on timing, in this case YES

- First Trimester: increased risk of congenital malformations
- Second Trimester: OK if necessary
- Third Trimester: May cause kernicterus in newborn
Sulfamethoxazole/Trimethoprim (Bactrim® or Septra®) and Pregnancy

In every pregnancy, a woman starts out with a 3-5% chance of having a baby with a birth defect. This is called her background risk. This sheet talks about whether exposure to sulfamethoxazole/trimethoprim may increase the risk for birth defects over that background risk. This information should not take the place of medical care and advice from your healthcare provider.

What are sulfamethoxazole and trimethoprim?
Sulfamethoxazole and trimethoprim are medications that are used to treat bacterial infections. These two medications are usually given together and called Bactrim® or Septra®.

The combination of these antibiotics is used to treat a variety of infections, including urinary tract infections (UTIs). UTIs are common among women during pregnancy.

I am taking sulfamethoxazole/trimethoprim, but I would like to stop taking it before becoming pregnant. How long do these medications stay in my body?
These medications should be mostly cleared from your body about three days after your last dose. Do not stop taking your medication without first speaking with your healthcare provider.

Can taking sulfamethoxazole/trimethoprim during my pregnancy cause birth defects?
Overall, the increased risk, if any, with sulfamethoxazole/trimethoprim use during pregnancy appears to be small. There are not many well controlled studies on sulfamethoxazole use alone in human pregnancy. Sulfamethoxazole is a member of the sulfonamide class. Some studies have suggested the use of sulfonamides during the first trimester may be associated with an increased risk for birth defects while other studies have not.

Concern has also been raised with the use of trimethoprim in pregnancy. This concern with trimethoprim has been the focus of studies involving several hundred women using this medication at anytime in pregnancy. Some studies have not found an increased risk for birth defects. However, a few studies looking at trimethoprim used with a sulfonamide during the first trimester have found an increased risk for birth defects. The birth defects that were seen included heart defects, neural tube defects (opening in the spine), cleft lip or palate, and urinary tract defects.

Trimethoprim may decrease the level of folic acid in your body. Folic acid is a B vitamin that helps the body make new healthy cells and may help reduce the risk of certain birth defects, like spina bifida, in the baby. It is recommended that pregnant women consume between 400-800 micrograms of folic acid each day from foods or vitamin supplements.

If sulfamethoxazole/trimethoprim is taken during the first trimester, your healthcare provider may suggest that you take an additional folic acid. Use of sulfamethoxazole and trimethoprim after the first trimester is not associated with a higher risk of birth defects in the baby.

I was prescribed sulfamethoxazole and trimethoprim for a UTI. Should I take this medication?
Yes. It is important to treat most infections during pregnancy. Untreated UTIs could lead to severe kidney infection for the mother, preterm birth and pre-eclampsia (dangerously high blood pressure).

Are there any other risks with sulfamethoxazole/trimethoprim use in pregnancy?
One study has suggested that women who take medications that may decrease levels of folic acid are at a greater risk for pregnancy complications such as preeclampsia, placenta abruption (when the placenta breaks away from the wall of the uterus) and fetal growth restriction. Exposure to sulfamethoxazole/trimethoprim has been associated
with preterm birth and low birth weight. However, this medication is frequently used to treat UTIs, and pregnant women with UTIs are at a greater risk for some of the same complications. Therefore it is difficult to determine whether it is the medication, the decrease in folic acid, the underlying infection, or other factors which are increasing the risk for these complications.

Is it OK to take sulfamethoxazole/trimethoprim in the 3rd trimester?
Some authors have recommended not taking sulfonamides such as sulfamethoxazole after 32 weeks gestation. There is a theoretical concern that sulfonamide use near the end of pregnancy can increase the risk for severe jaundice (a problem with liver function) and related complications in the baby. In this situation, your health care provider can help to suggest a medication that is right for you.

Can I take sulfamethoxazole/trimethoprim while breastfeeding?
Sulfamethoxazole and trimethoprim pass into breast milk in small amounts. There is some concern about taking sulfamethoxazole and trimethoprim while breastfeeding if the baby is premature, has severe jaundice, or a condition known as glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency). In those situations, it is not always necessary to stop breastfeeding while taking these medications. Be sure to talk to your health care provider about all your choices for breastfeeding.

What if the father of the baby takes sulfamethoxazole/trimethoprim?
A sulfamethoxazole and trimethoprim combination was found to decrease sperm production in men who were taking it continuously for one month. A lowered sperm count may affect a man’s ability to father a child. There are no studies looking at risk for birth defects when the father takes sulfamethoxazole/trimethoprim. In general, exposures that fathers have are unlikely to increase risks to a pregnancy. For more information, please see the MotherToBaby fact sheet Paternal Exposures and Pregnancy at http://www.mothertobaby.org/files/paternal.pdf.

References Available By Request April 2014.

April, 2014
Organogenesis and Drug Exposure

- Timing of drug/substance exposure is critical
- Exposure at time of conception and implantation (first 2 weeks after conception) may kill embryo without realization of pregnancy
- OR cells may completely regenerate and embryo is not damaged
- Exposure during this time produces an all or none effect (die vs regenerate)
First Trimester

- Classic teratogenic period is a critical six weeks (31-70 days from last menstrual period)
  - First trimester; period of organogenesis
  - Major morphologic changes
- Later exposure (>70 days from LMP) may result in functional or behavioral defects

Second and third trimester exposures
<table>
<thead>
<tr>
<th>Main Embryonic Period (in weeks)</th>
<th>Fetal Period (in weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
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<td>9</td>
<td>16</td>
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<td>32</td>
<td>38</td>
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</tbody>
</table>

**Neural tube defects (NTDs)**

- TA, ASD, and VSD
- Amelia/Meromelia
- Amelia/Meromelia
- Cleft lip
- Low-set malformed ears and deafness
- Microphthalmia, cataracts, glaucoma
- Enamel hypoplasia and staining
- Cleft palate

**Mental retardation**

- Heart
- Upper limb
- Lower limb
- Upper lip
- Ears
- Eyes
- Teeth
- Palate
- External genitalia

**Common site(s) of action of teratogens**

- Less sensitive period
- Highly sensitive period

**Major congenital anomalies**

**Functional defects and minor anomalies**

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Frequency of Malformations

- Major malformations occur at a rate of 2-3% (includes defects incompatible with survival or requiring major surgery, e.g. congenital heart disease, cleft palate, etc.)
- Minor malformations include hernias, ear tags, extra digits, hypospadias, hydroceles, etc.
- Major plus minor malformations occur at a rate of 7-10%
- Stillbirths and spontaneous abortions frequently not included in epidemiologic data
Frequency of Malformations

- Drugs account for 2-3% of all defects; 25% are genetically based; cause of most of the anomalies is unknown (>60%)

- Exact magnitude unknown (birth vs delayed)
Case 1: Antibiotics

- 18 year old currently nursing a 6 month old infant. She presents with a UTI. Urine culture revealed *Citrobacter freundii* sensitive only to ciprofloxacin and sulfamethoxazole/trimethoprim

- Is Ciprofloxacin a reasonable option for treatment in this patient?
Ciprofloxacin

CASRN: 85721-33-1

**FULL RECORD DISPLAY**
Displays all fields in the record.
For other data, click on the Table of Contents

**Drug Levels and Effects:**

**Summary of Use during Lactation:**

Fluoroquinolones such as ciprofloxacin have traditionally not been used in infants because of concern about adverse effects on the infants' developing joints. However, studies indicate little risk.\(^1\) The calcium in milk might decrease absorption of the small amounts of fluoroquinolones in milk;\(^2\) but, insufficient data exist to prove or disprove this assertion. Use of ciprofloxacin is acceptable in nursing mothers with monitoring of the infant for possible effects on the gastrointestinal flora, such as diarrhea or candidiasis (thrush, diaper rash). Avoiding breastfeeding for 3 to 4 hours after a dose should decrease the exposure of the infant to ciprofloxacin in breastmilk.

Maternal use of an ear drop or eye drop that contains ciprofloxacin presents negligible risk for the nursing infant. To substantially diminish the amount of drug that reaches the breastmilk after using eye drops, place pressure over the tear duct by the corner of the eye for 1 minute or more, then remove the excess solution with an absorbent tissue.
Drug Levels:

Maternal Levels: Ten lactating women (time postpartum not stated) were given ciprofloxacin 750 mg orally every 12 hours for 3 doses. Milk ciprofloxacin was measured after the third dose. The highest levels averaging 3.79 mg/L occurred 2 hours after the dose. Average milk levels then fell as follows: 2.26 mg/L at 4 hours; 0.85 mg/L at 6 hours; 0.51 mg/L at 9 hours; 0.2 mg/L at 12 hours; and 0.02 mg/L at 24 hours after the dose [3] Using the peak milk level data from this study, an exclusively breastfed infant would receive an estimated maximum of 0.57 mg/kg daily with this maternal dosage regimen. This dosage is much lower than the 10 to 40 mg/kg daily used in treating newborn infants.[1]

One mother who was recovering from acute renal failure was given a single dose of ciprofloxacin 500 mg orally with a prenatal vitamin and ferrous sulfate which would be expected to decrease ciprofloxacin bioavailability. Milk levels were 3.5 mg/L at 4, 8 and 12 hours after the dose and 2.3 mg/L 16 hours after the dose [4] Levels were probably elevated and elimination prolonged by the woman's impaired renal function.

A woman took ciprofloxacin 500 mg daily orally for 10 days. At 10 hours and 40 minutes after the last dose, ciprofloxacin was 0.99 mg/L in breastmilk.[5]

Infant Levels: A woman took ciprofloxacin 500 mg daily orally for 10 days. Her infant, who breastfed once 8 hours after the dose, had no detectable ciprofloxacin (<30 mcg/L) in her serum 2.7 hours after nursing [5].

Effects in Breastfed Infants:

A case of pseudomembranous colitis in a 2-month-old breastfed infant with a history of necrotizing enterocolitis was probably caused by maternal self-treatment with ciprofloxacin.[6]

Ciprofloxacin was used as part of multi-drug regimens to treat three pregnant women with multidrug-resistant tuberculosis throughout pregnancy and postpartum. Their three infants were breastfed (extent and duration not stated). At age 12.5, 1.8 and 3.9 years, the children were developing normally except for one who had failure to thrive, possibly due to tuberculosis contracted after birth.[7]

Effects on Lactation and Breastmilk:

Relevant published information was not found as of the revision date.

Alternate Drugs to Consider:
Case 1: Antibiotics

- Is Ciprofloxacin a reasonable option for treatment in this patient?
  - Answer: Yes
Stepwise Approach to Minimizing Infant Exposure

- Withhold the drug
- Delay therapy
- Choose drugs that pass poorly into milk
- Choose drugs for which data are available regarding safety in infants and/or pharmacodynamics in breastfeeding
- Choose and alternative route of administration
Stepwise Approach to Minimizing Infant Exposure

- Avoid nursing at times of peak concentration (generally 1-3 hours after an oral dose)
- Administer drug before infant’s longest sleep period
- Use caution with preterm infants because of potentially immature organ systems
- Temporarily withhold breastfeeding (1-2 half-lives for typical agents; 4-5 half-lives if toxic compound)
- Discontinue nursing (last resort)
Key Message

- **Women:** pregnant or thinking of becoming pregnant? Don’t stop or start taking any medication without first talking with a healthcare provider.

- **Provider:** discuss the potential risk and benefits of (XYZ) medication use with women of reproductive age, prior to prescribing. You might be treating for two...
Treating for Two

- At least 9/10 of women will take at least one medication during pregnancy
  - 5.4 million pregnancies are exposed to medications each year
- Fewer than 10% of medications have enough information to determine their safety for use in pregnancy
- CDC Prescription for the problem
  - Better research
  - Reliable guidance
  - Informed Decisions
Absence of evidence is not evidence of absence