Special Populations: Pregnancy and Breastfeeding

Joanne C. Witsil, RN, PharmD, BCPS

Clinical Pharmacist, General Medicine/Surgery and Family Medicine
John H. Stroger Jr. Hospital of Cook County
Adjunct Clinical Assistant Professor
University of Illinois at Chicago, College of Pharmacy
Scenario 1

- A 28 year old female walks into your practice setting with a prescription that she received 4 days ago from another Practitioner for complaints of a urinary tract infection (UTI)
  - RX written as Ciprofloxacin 500 mg po every 12 hours for 7 days
Objectives

- Describe the maternal changes that occur during pregnancy and how they affect drug absorption, distribution, metabolism and clearance
- Explain the characteristics of the placenta and lactation that impact drug distribution
- State the 5 pregnancy categories
- Discuss the current treatment regimens for pregnant patients exposed to a biological, chemical or nuclear event
Stages of Pregnancy

- **First trimester (weeks 1-12)**
  - Organogenesis occurs especially 5-10th week
    - AKA: embryonic period (first 8 weeks)
- **Second trimester (weeks 13-26)**
  - Organs become functional
    - AKA: fetal period (actually starts week 9)
- **Third trimester (weeks 27-40)**
  - AKA: fetal/perinatal period

Pregnancy Physiological changes

General Changes

- Susceptibility to infections are altered
  - Overall, diminished cell-mediated immunity
  - Specifically, neutrophil chemotaxis, adherence and natural killer cell activity are decreased

- Mother and fetus are at greater risk for infections

Maternal Pharmacokinetic Changes

- **Absorption**
  - Gastrointestinal tract (GIT) motility reduced
  - Increased gastric pH
  - Increased pulmonary alveolar drug uptake

- **Key point:** May lead to increased drug absorption

Distribution

- Plasma volume increases by 50%
  - 40% distributed to maternal compartments
  - 60% distributed to amniotic fluid, placenta, fetus

- Serum albumin level
  - Decreases as weeks of gestation increase

Key point: more unbound or free drug in circulation
  - Especially drugs bound to serum albumin

Metabolism

- Increased progesterone and estradiol concentrations affect hepatic drug metabolism
  - Either increased or decreased

Clearance

- Renal blood flow and glomerular filtration rate is increased by 25-50%

Key point: appears these changes do not have clinical significance therefore no dose adjustment!

Placental Characteristics

- Historically
  - Placenta was once thought of as a barrier

- Fundamentally
  - By 5\textsuperscript{th} week of gestation it fully functions as a transporter between mother and fetus
  - Most drugs move across membranes by passive diffusion
    - Mother to fetus and then once maternal serum levels decline back to mother from fetus

Specifically

- Maternal transplacental considerations
  - Maternal dose
  - Route of administration
  - Maternal pharmacokinetics

- Drug transplacental considerations
  - High lipophilicity
  - Low ionization
  - Low molecular weight
  - Low protein binding

Timing of exposure

Teratogenicity definition

- It is the abnormal development of the fetus or fetal organs either structurally or functionally. Abnormalities can include the loss of pregnancy, structural or functional abnormalities and uterine growth impairment.

Embryonic period (2-8<sup>th</sup> week of gestation)

- Greatest potential to cause organ structural damage

Fetal period (9<sup>th</sup> week-full term)

- More subtle changes in function or behavior

Lactation Characteristics

- **Entrance into breast milk**
  - Drugs enter via passive diffusion (most common) or active transport
    - Amount of drug passing via passive diffusion in most cases is directly proportional to maternal serum concentration
    - In literature may be expressed as milk: plasma ratio (ratio of 1 means equal amount)
  - pH of breast milk is more acidic than plasma
    - Weak basic drugs enter more freely

---

Lipophilic drugs enter more freely
- Concentrate more in hind-milk versus fore-milk

Drugs that bind either to the proteins or onto the milk fat globule enter more freely

Timing and frequency of Nursing
- First few minutes of feed vs last
- Timing of drug ingestion vs onset of feed

It is still questionable how much the infant actually ingests!

# FDA Pregnancy Categories

<table>
<thead>
<tr>
<th>Pregnancy Category</th>
<th>Category Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Well-controlled studies available in humans with no adverse effects observed in human pregnancies</td>
</tr>
<tr>
<td>B</td>
<td>No adverse effects in well-controlled studies of human pregnancies with adverse effects seen in animal pregnancies OR no adverse effects in animal pregnancies without well-controlled human pregnancy data available</td>
</tr>
<tr>
<td>C</td>
<td>Human data lacking with adverse pregnancy effects seen in animal studies OR no pregnancy data available in either animals or humans</td>
</tr>
<tr>
<td>D</td>
<td>Adverse effects demonstrated in human pregnancies; benefits of drug use may outweigh the associated risks</td>
</tr>
<tr>
<td>X</td>
<td>Adverse effects demonstrated in human or animal pregnancies; the risk of drug use clearly outweigh any possible benefits</td>
</tr>
</tbody>
</table>

*Defined under 21 CFR 201.57 for the A, B, C, D, X Pregnancy Category system.*
Treatment for Bioterrorism

No treatment
- Outcomes?
- Quarantine?

Treatment
- Outcomes?
- Adverse drug effects?
## No Treatment

<table>
<thead>
<tr>
<th>Class A Agent</th>
<th>Fatality Rates in the General Population</th>
<th>Fatality Case Reports in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthrax</strong></td>
<td>Cutaneous &amp; GI -20-60%</td>
<td>3 cases – all died</td>
</tr>
<tr>
<td></td>
<td>Inhalation - &gt;80%</td>
<td></td>
</tr>
<tr>
<td><strong>Plague</strong></td>
<td>Bubonic - 60-90%</td>
<td>13/14 – fetal loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 report in 1903 – universal fetal loss</td>
</tr>
<tr>
<td><strong>Smallpox</strong></td>
<td>Major- 27-30%</td>
<td>Major-↑63%</td>
</tr>
<tr>
<td></td>
<td>Minor- ~1%</td>
<td>Prior to 25th week- 75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>stillbirths</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;25th week- 60% lost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Birth- 50% died within 2 weeks</td>
</tr>
<tr>
<td><strong>Viral hemorrhagic Fever</strong></td>
<td>Ebola- 77%</td>
<td>Ebola-↑95.5%</td>
</tr>
<tr>
<td></td>
<td>Lassa- 1-36%</td>
<td>Lassa- 30-75%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Both had fetal loss reported as 23-66%</td>
</tr>
</tbody>
</table>

Adapted from [www.idph.state.il.us/Bioterrorism/otherlinks.htm](http://www.idph.state.il.us/Bioterrorism/otherlinks.htm)
<table>
<thead>
<tr>
<th>Class B Agent</th>
<th>Fatality Rates in General Population</th>
<th>Fatality Case Reports in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brucellosis</td>
<td>5%</td>
<td>1&lt;sup&gt;st&lt;/sup&gt; &amp; 2&lt;sup&gt;nd&lt;/sup&gt; trimester- 43% fetal loss 3&lt;sup&gt;rd&lt;/sup&gt; trimester- 2% fetal loss</td>
</tr>
<tr>
<td>Q Fever</td>
<td>Low</td>
<td>Spontaneous Abortion - 22% Premature birth - 30% Growth restriction - 69% Utero fetal death - 7%</td>
</tr>
<tr>
<td>Ricin</td>
<td>High</td>
<td>1 case report- Infant born with moderate growth retardation &amp; craonio-facial dysmorphia</td>
</tr>
</tbody>
</table>
## Treatment of Class A and B Bacterial Agents

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Primary Choice</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Ciprofloxacin or doxycycline and 1 or 2 alternatives</td>
<td>rifampin, vancomycin , chloramphenicol, imipenem, clindamycin, clarithromycin, (PCN &amp; ampicillin only once sensitivities confirmed)</td>
</tr>
<tr>
<td>Plague</td>
<td>Gentamicin</td>
<td>Ciprofloxacin or doxycycline</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Gentamicin or streptomycin</td>
<td>Ciprofloxacin or doxycycline</td>
</tr>
<tr>
<td>Brucellosis</td>
<td>TMP/SMX and streptomycin or rifampin</td>
<td>None given</td>
</tr>
<tr>
<td>Glanders</td>
<td>TMP/SMX and ceftazidime if severe disease</td>
<td>TMP/SMX or tetracycline or amoxicillin/clavulanate in mild disease</td>
</tr>
<tr>
<td>Q Fever</td>
<td>Doxycycline or tetracycline</td>
<td>Quinilones, TMP/SMX chloramphenicol</td>
</tr>
</tbody>
</table>

*Dosing regimens are the same as for adults. See treatment guidelines available at IDPH or CDC.*
## Most Common Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>FDA Category</th>
<th>Placenta crossing</th>
<th>Excreted in Breast Milk</th>
<th>Adverse drug reaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>B</td>
<td>Yes</td>
<td>Yes</td>
<td>Reported association with necrotizing enterocolitis in newborns</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>BMS, Caution if used near birth, Gray-baby syndrome</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>Arthropathy</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>D</td>
<td>Yes</td>
<td>Yes</td>
<td>Fetal dental enamel hypoplasia and retarded skeletal growth. Maternal hepatic necrosis</td>
</tr>
</tbody>
</table>

*Related to maternal/ fetal effects in human data.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>FDA Category</th>
<th>Placenta crossing</th>
<th>Excreted in Breast Milk</th>
<th>Adverse drug reaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>No ototoxicity or nephrotoxicity reported in human fetuses. 1 case of renal cystic dysplasia</td>
</tr>
<tr>
<td>Penicillin</td>
<td>B</td>
<td>Yes</td>
<td>Yes</td>
<td>No↑ rate of congenital anomalies</td>
</tr>
<tr>
<td>Rifampin</td>
<td>C</td>
<td>Yes</td>
<td>Yes</td>
<td>Some reports of congenital anomalies</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>B</td>
<td>Yes</td>
<td>Yes</td>
<td>No reports of congenital anomalies. 1 report of bradycardia with rapid infusion.</td>
</tr>
</tbody>
</table>

*Related to maternal/ fetal effects in human data.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>FDA Category</th>
<th>Placenta crossing</th>
<th>Excreted in Breast Milk</th>
<th>Adverse drug reaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftazidime</td>
<td>B</td>
<td>Yes</td>
<td>Yes</td>
<td>No increased risk of congenital anomalies</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>D</td>
<td>Yes</td>
<td>Yes</td>
<td>Rare reports of irreversible deafness with fetal exposure</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>D</td>
<td>Yes</td>
<td>Yes</td>
<td>Fetal dental enamel hypoplasia and retarded skeletal growth. Reports of liver toxicity in mother.</td>
</tr>
<tr>
<td>TMP/SMX (Bactrim)</td>
<td>C/D at term</td>
<td>Yes</td>
<td>Yes</td>
<td>Reports of congenital anomalies. Kernicterus if used at birth</td>
</tr>
</tbody>
</table>

*Related to maternal/fetal effects in human data.

# Post-exposure Prophylaxis

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Primary Choice</th>
<th>Alternatives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
<td>Ciprofloxacin or doxycycline</td>
<td>Amoxicillin only after 10-14 days of primary agents</td>
</tr>
<tr>
<td>Plague</td>
<td>Ciprofloxacin or doxycycline</td>
<td>Chloramphenicol or tetracycline</td>
</tr>
<tr>
<td>Tularemia</td>
<td>Ciprofloxacin or doxycycline</td>
<td></td>
</tr>
<tr>
<td>Q Fever</td>
<td>Doxycycline or Tetracycline</td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>

No prophylaxis recommended for brucellosis or glanders.

*Dosing regimens are the same as for adults. See treatment guidelines available at IDPH or CDC.

Adapted from [www.idph.state.il.us/Bioterrorism/otherlinks.htm](http://www.idph.state.il.us/Bioterrorism/otherlinks.htm)
# Treatment of Class A Viral Agents

<table>
<thead>
<tr>
<th>Virus</th>
<th>Primary Choice</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulism</td>
<td>Supportive</td>
<td>Antitoxin trivalent (A,B,E) from CDC</td>
</tr>
<tr>
<td>Smallpox</td>
<td>Supportive</td>
<td>A few reports show in vitro activity against smallpox by Cidofovir. May consider in severe cases Antibiotics only if secondary bacterial infections</td>
</tr>
<tr>
<td>Viral Hemorrhagic Fevers</td>
<td>Supportive</td>
<td>Ribavirin, not FDA approved but could consider in severe cases</td>
</tr>
</tbody>
</table>

*Dosing regimens are the same as for adults. See treatment guidelines available at IDPH or CDC.*
## Most Common Antivirals

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>FDA Category</th>
<th>Placenta crossing</th>
<th>Excreted in Breast Milk</th>
<th>Adverse drug reaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antitoxin</td>
<td>C for A &amp; B</td>
<td>?</td>
<td>Unknown</td>
<td>Fetal malformations noted in animal studies. Hypersensitivity reactions.</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>C</td>
<td>Presumed Yes</td>
<td>Presumed Yes</td>
<td>Skeletal malformations noted in animal studies. No reports in humans</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>X</td>
<td>Presumed Yes</td>
<td>No data available</td>
<td>Teratogenic effects in nearly all animal studies</td>
</tr>
</tbody>
</table>

*Related to maternal/ fetal effects in human data.

Adapted from www.idph.state.il.us/Bioterrorism/otherlinks.htm
# Post-exposure Prophylaxis

<table>
<thead>
<tr>
<th>Virus</th>
<th>Primary Choice</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botulism</td>
<td>No prophylaxis</td>
<td></td>
</tr>
<tr>
<td>Smallpox</td>
<td>Smallpox vaccine</td>
<td></td>
</tr>
<tr>
<td>Viral Hemorrhagic Fevers</td>
<td>No prophylaxis</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from [www.idph.state.il.us/Bioterrorism/otherlinks.htm](http://www.idph.state.il.us/Bioterrorism/otherlinks.htm)
Smallpox Vaccine

- Currently, under “peaceful” times
  - CDC does NOT recommend smallpox vaccine to the following:
    - Pregnant women
    - Women who plan on becoming pregnant in 4 weeks after vaccination
    - Women who are actively breastfeeding, excretion into breast milk unknown
  - FDA pregnancy category C

www.cdc.gov/smallpox
Maternal adverse vaccine reactions
- Primary vaccinia - vesicle at site of inoculation
- Encephalitis - a few reports
- Vaccinia necrosum

Fetal complications
- Congenital defects
- Viremia
- Fetal vaccinia
  - Rare but serious complication → fetal loss

Chemical Terrorism

- **Types of Nerve Agents**
  - Tabun (GA)
  - Sarin (GB)
  - Soman (GD)
  - VX

- **Symptoms**
  - **Mild/Moderate**
    - Include localized sweating, muscle fasciculations, nausea, vomiting, weakness, dyspnea
  - **Severe**
    - Include unconsciousness, convulsions, apnea, flaccid paralysis

www.atsdr.cdc.gov/MHMI/mmg166.html
Chemical Treatment

- Protect yourself
  - Personal Protective Equipment (PPE)
- If possible
  - Get patient to remove contaminated clothing
  - Place in a plastic bag

[www.atsdr.cdc.gov/MHMI/mmg166.html](http://www.atsdr.cdc.gov/MHMI/mmg166.html)
## Agents Used

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>FDA Category</th>
<th>Placenta crossing</th>
<th>Excreted in Breast Milk</th>
<th>Adverse drug reaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine</td>
<td>C</td>
<td>Yes</td>
<td>Controversial</td>
<td>Some reports of congenital malformations</td>
</tr>
<tr>
<td>2-PAM</td>
<td>C</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown if causes fetal harm</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>D</td>
<td>Yes</td>
<td>Yes</td>
<td>Congenital malformations noted, growth retardation, central nervous defects</td>
</tr>
<tr>
<td><strong>Diazepam is most common</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Related to maternal/ fetal effects in human data.

Radioactive iodine if released into air
- It enters the body and is quickly taken up by thyroid gland

Maternal-fetal exposure
- Enters expecting mother passes through the placenta → fetus
- Can be passed through breastfeeding
- Lower radiation doses are seen in fetus
- Fetus thyroid glands are at more risk for injury
  - Severe consequences to fetus
    - Growth retardation, malformations, impaired brain function, cancer

www.bt.cdc.gov/radiation
Treatment

- **Potassium Iodide (KI)**
  - Everyone should take it
    - Pregnant women
    - Lactating women
  - How does it work?
    - Blocks radioactive iodine from entering the thyroid
    - Does not protect other parts of the body, ONLY thyroid

www.bt.cdc.gov/radiation
Dose KI (Pregnant and breastfeeding women)

- 130mg orally with tablets or Two ml of solution
- Tablets are 65mg or 130mg
- Solution- each 1 ml contains 65mg
- Protects thyroid gland for 24 hours

Adverse drug effects

- Allergic reactions (check if allergic to iodine)
- GI upset
- Rashes
- Inflammation of the salivary glands
Scenario 2

- A 28 year old female walks into your practice setting with a prescription that she received 4 days ago from another Practitioner for complaints of a cutaneous Anthrax exposure that is confirmed in your area
  - RX written as Ciprofloxacin 500mg po every 12 hours for 60 days
Questions?