Cardiac Medications in Pregnancy and Lactation

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Objectives

• Assess pharmacokinetic changes that occur in pregnancy and the impact it has on medications
• Examine pharmacokinetic parameters that play a role in fetus and infant exposure to medications in utero and through breastfeeding
• Review selected cardiac medications with good safety data, limited data, and harmful data during pregnancy
• Discuss selected cardiac medications that can be excreted into breastmilk and the implications on the infant
History of Drugs in Pregnancy and Lactation

- Kefauver-Harris Drug Amendments Act in 1962
  - Drugs need to be safe and effective based on clinical trials
  - Drugs must be FDA approved before marketed

- Fear of causing fetal harm and death through medication use in pregnancy has resulted in lack of inclusion of this patient population in clinical research
  - Medication safety information often obtained through case reports, epidemiological studies, and animal studies
  - Pharmaceutical industry generally discourages the use of medications in pregnancy and lactation

- Clinicians and patients are left with incomplete data regarding the safety of medication use in pregnancy and lactation

Pharmacokinetic Principles in Pregnancy and Lactation
ADME

- Absorption
  - The rate and extent a medication leaves the site of administration and moves to the circulatory system
- Bioavailability
  - Fraction of an administered drug that reaches the system circulation
- Distribution
  - Relationship between the dose of a drug and the resulting systemic concentration
- Metabolism
  - Process by which drugs are converted in vivo into one or more structural derivatives
- Excretion
  - Removal of drug from the body
Drug Distribution

• Describes rate and extent of plasma transfer
• Volume of distribution (Vd) is a virtual space that relates the amount of drug administered to the measured plasma concentration
• Primary determinants are
  • Relative hydrophilicity/lipophilicity
  • Degree of protein binding of the drug

• Remember, only “free drug” can exert an effect!
Pharmacokinetic Changes in Pregnancy

• Increase in the following:
  • Plasma volume of distribution
  • Cardiac output
  • Glomerular filtration rate
  • Leads to lower circulation concentration of some medications

• Decrease in plasma albumin levels
  • Leads to increase in volume of distribution of certain highly protein bound medications
    • However, increased clearance by liver and kidney
Circulation by passive diffusion (high to low concentration)

Rate of transfer dependent upon:

- Protein binding
  - Less maternal albumin; more unbound drug, higher fetal concentrations
- Ionic dissociation
  - Fetal pH slightly more acidic compared to maternal pH
  - Medications that are weak bases are more likely to cross the placenta (and less likely to cross back over; ion trapping)
- Lipid solubility
  - Higher lipid soluble medications pass more readily through the placenta
- Molecular weight
  - < 500 Da – readily cross placenta
  - 600-1000 Da – cross the placenta slowly
  - > 1000 Da – do not cross the placenta significantly
Medication Transfer into Breastmilk

• Passive diffusion

• Factors that influence movement of medication into breast milk:
  • Protein binding
    • Medications that are highly protein bound in the mother are less likely to transfer
  • Ion dissociation
    • Breastmilk has significantly lower pH than maternal pH
      • Medications that are weak bases are more likely to transfer
  • Lipid solubility
    • Higher lipid soluble medications are more likely to transfer
  • Molecular weight
    • < 500 Da – readily transfer to breastmilk
    • 600-1000 Da – transfer slowly into breastmilk
    • > 1000 Da – do not transfer into breastmilk significantly

Exposure to Medications in Breast Milk

- Many medications enter breast milk to some degree
- Oral bioavailability of the medication in the infant’s GI tract
  - Many medications not absorbed
Calculating Infant Exposure

- Calculating infant exposure
  - Milk-to-plasma ratio
    - Unbound drug in milk/ drug in plasma
    - Most medications have a ratio of < 1
  - Relative Infant Dose (RID)
    - Assume 150 mL of milk/kg/day

\[
\text{RID} = \frac{\text{Dose infant}}{\text{Dose mother}}
\]

- \( \text{Relative Infant Dose} \)
  - \( \text{Dose infant} = \text{dose in infant/day} \)
  - \( \text{Dose mother} = \text{dose in mother/day} \)

- RID < 10% could be considered unimportant for most medications

Resources
### Table 1. FDA Pregnancy Risk Categories for Medications

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Selected Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester (and there is no evidence of risk in later trimesters), and the possibility of fetal harm appears remote.</td>
<td>Vitamins at RDA doses, thyroid hormones</td>
</tr>
<tr>
<td>B</td>
<td>Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women, or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.</td>
<td>Acetaminophen, cimetidine, aluminum hydroxide, penicillin, acyclovir, insulin, clindamycin, ibuprofen in first and second trimesters</td>
</tr>
<tr>
<td>C</td>
<td>Animal studies have shown an adverse effect (either teratogenic or embryocidal or other) and there are not well-controlled studies in pregnant women, or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women. Drug should only be given if the potential benefit justifies the potential risk to the fetus.</td>
<td>Pseudoephedrine, simethicone, clotrimazole, senna, dextromethorphan, prednisone, aspirin, hydrocortisone in second and third trimesters</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable, despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs can not be used or are ineffective).</td>
<td>Ibuprofen (in third trimester), hydrocortisone (in the first trimester), phenytoin, tamoxifen, lithium</td>
</tr>
<tr>
<td>X</td>
<td>Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities or there is evidence of fetal risk based on human experience or both. The risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The use of the product is contraindicated in women who are or who may become pregnant.</td>
<td>Vitamin A at doses exceeding RDA, triazolam, lovastatin, medroxyprogesterone</td>
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## Categorizing Risk

<table>
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<tr>
<th>Category</th>
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<td><strong>L1 Safest</strong></td>
<td>Drug that has been taken by a large number of breastfeeding mothers without any observed increase in adverse effects in the infant. Controlled studies in breastfeeding women fail to demonstrate a risk to the infant and the possibility of harm to the breastfeeding infant is remote. Or the product is not orally bioavailable in an infant.</td>
</tr>
<tr>
<td><strong>L2 Safer</strong></td>
<td>Drug that has been studied in a limited number of breastfeeding women without an increase in adverse effects in the infant and/or the evidence of a demonstrated risk that is likely to follow use of this medication in a breastfeeding woman is remote.</td>
</tr>
<tr>
<td><strong>L3 Moderately Safe</strong></td>
<td>There are not controlled studies in breastfeeding women; however, the risk of untoward effects to a breastfed infant is possible, or controlled studies show only minimal, nonthreatening adverse effects. Drugs should be given only if the potential benefit justifies the potential risk to the infant.</td>
</tr>
<tr>
<td><strong>L4 Hazardous</strong></td>
<td>There is positive evidence of risk to a breastfed infant, or to breast milk production, but the benefits from use in breastfeeding mothers may be acceptable despite the risk to the infant (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).</td>
</tr>
<tr>
<td><strong>L5 Contraindicated</strong></td>
<td>Studies in breastfeeding mothers have demonstrated that there is significant and documented risk to the infant based on human experience, or it is a medication that has a high risk of causing significant damage to an infant. The risk of using the drug in breastfeeding women clearly outweighs any possible benefit from breastfeeding. The drug is contraindicated in women who are breastfeeding an infant.</td>
</tr>
</tbody>
</table>
Categorizing Risk

• As of June 2015, package inserts for medications contain the following:
  • **Pregnancy**
    • Pregnancy Exposure Registry
    • Risk Summary
    • Clinical Considerations
    • Data
  • **Lactation**
    • Risk Summary
    • Clinical Considerations
    • Data
Resources for Pregnancy and Lactation

- LexiComp
- Briggs' Drugs in Pregnancy & Lactation
  - Pregnancy recommendation
  - Breastfeeding recommendation
- Medications and Mother’s Milk
Pregnancy Considerations Adverse events have been observed in some animal reproduction studies. Amiodarone crosses the placenta (~10% to 60%) and may cause fetal harm when administered to a pregnant woman. Reported risks include neonatal bradycardia, QT prolongation, and periodic ventricular extrasystoles; neonatal hypothyroidism (with or without goiter), neonatal hyperthyroxinemia; neurodevelopmental abnormalities independent of thyroid function; jerk nystagmus with synchronous head twitching; fetal growth retardation; and/or premature birth. Oral or IV amiodarone should be used in pregnant women only to treat arrhythmias refractory to other treatments or when other treatments are contraindicated (Page [ACC/AHA/HRS 2015]; Regitz-Zagrosek [ESG/AEP/DGesGM/ESC] 2011).

Breast-Feeding Considerations Amiodarone and its active metabolite are excreted in breast milk. Breast-feeding may lead to significant infant exposure and potential toxicity. Due to the long half-life, amiodarone may be present in breast milk for several days following discontinuation of maternal therapy (Hall 2003). The manufacturer recommends that breast-feeding be discontinued if treatment is needed.

Briggs’ Drugs in Pregnancy & Lactation

- Amiodarone

Adverse Reactions

Frequency not always defined.

Cardiovascular: Hypotension (IV: 16%, refractory in rare cases), bradycardia (2% to 5%), atrioventricular block (<2% to 5%), cardiac arrest (3%), cardiac arrhythmia (1% to 3%), cardiac failure (1% to 3%), tachycardia (2%), asystole (<2%, IV), atrial fibrillation (<2%), atrial tachycardia (2%), cardiogenic shock (<2%), tachycardia (>2%, rare), ventricular fibrillation (<2%), atioventricular dissociation, cardiac conduction disturbance, edema, flushing, peripheral thrombophlebitis (IV, with concentrations >3 mg/mL), pulseless electrical activity (PEA)

Central nervous system: Abnormal gait (4% to 40%), ataxia (4% to 40%), dizziness (4% to 40%), fatigue (4% to 40%),
Amiodarone (Briggs Drugs in Pregnancy and Lactation)

Pharmacologic Category
- Antiarhythmics

Pregnancy Recommendation
- Human and animal data suggest risk

Breast-feeding Recommendation
- Contraindicated

Pregnancy Summary
Fetal adverse effects directly attributable to amiodarone have been observed. Congenital goiter/hypothyroidism and hyperthyroidism may occur after in utero exposure. Newborns exposed to amiodarone in utero should have thyroid function studies performed because of the large proportion of iodine contained in each dose.

Fetal Risk Summary
Amiodarone is an antiarrhythmic agent used for difficult or resistant cases of arrhythmias. The drug contains about 75 mg of iodide per 200 mg dose. Amiodarone was maternally and teratogenic to rabbit fetuses (increased fetal resorptions, decreased live litter size, growth restriction, and restricted sternum and meleagropososis). In rats administered an IV infusion about 1.4 times the maximum recommended human dose based on BSA (MRHD) for lower doses about 0.4 and 0.7 times the MRHD, produced no embryo toxicity. Lower doses about 0.4 and 0.7 times the MRHD, embryo toxicity was observed at 0.3 times the MRHD and above. At about 2.7 times the MRHD, >90% of the animals aborted. No teratogenic effects were observed in any of the rabbit groups.

Amiodarone and its metabolite, desethylamiodarone, cross the placenta to the fetus in 10 infants described in these reports. Cord blood concentrations of the parent compound were 0.05-0.35 mcg/mL, representing cord/maternal ratios of 0.10-0.28 in nine cases and 0.6 in one case. Cord blood concentrations of the metabolite varied between 0.05 and 0.65 mcg/mL, about one-fourth of the maternal levels in 9 of the 10 cases. In one study, the amount of amiodarone crossing the placenta to the fetus was dependent on the degree of hydrops fetalis. The expected fetal concentrations of the drug were not achieved until substantial compensation of the fetus had occurred.

In 22 cases of amiodarone therapy during pregnancy, the antiarhythmic was administered for maternal indications. One patient in the last 3 months of pregnancy was treated with 200 mg daily for resistant atrial tachycardia. She delivered a 2780 g female infant at 40 weeks' gestation. Both the mother and the infant had a prolonged QT interval on electrocardiogram (ECG). A second woman was also treated by these investigators under similar conditions. Both infants were normal (infant sex, weight, and gestational age were not specified for the second case), including having normal thyroid function. In another report, a woman was treated at 34 weeks' gestation when amiodarone failed to control her atrial fibrillation. After an initial dose of 800 mg/day for 1 week, the dose was decreased to 400 mg/day and continued at this level until delivery at 41 weeks' gestation. The healthy 3230 g infant experienced bradycardia during labor induction (104-120 beats/minute (BPM)) and during
Cardiac Medications and Pregnancy
Anti-Hypertensives

- Preferred agents for treatment
  - Alpha agonists
    - **Methyldopa**
    - Clonidine
  - Beta blockers
    - **Labetalol**
    - Metoprolol
  - Calcium channel blockers
    - Dihydropyridine
      - **Nifedipine**
    - Non-dihydropyridine
      - Verapamil
  - Thiazide diuretics
  - Hydralazine

Anti-Hypertensives

• Agents that will likely cause harm
  • ACE inhibitors (ACEIs) and Angiotensin receptor blockers (ARBs)
    • 1st trimester - controversial
      • 2006 study → increased in fetal cardiovascular and CNS anomalies
      • 2012 metaanalysis
        • Elevated teratogenic risk not directly related to ACEIs and ARBs, but to maternal factors and diseases
  • 2nd and 3rd trimesters
    • Teratogenicity and severe fetal and neonatal toxicity
    • Fetal toxic effects: anuria, oligohydramnios, fetal hypocalvaria, intrauterine growth restriction (IUGR), prematurity, pulmonary hypoplasia, and patent ductus arteriosus
    • Stillbirth or neonatal death

Anti-Hypertensives

• Agents that may cause harm
  • Beta blocker
    • Atenolol – associated with duration of therapy
      • Intrauterine growth restriction (IUGR)
      • Smaller for gestational age
      • Pre-term labor
Anti-Hypertensives

• Diuretics
  • Volume expansion is characteristic of pregnancies → concern about diuretic-related volume depletion
• Agents considered relatively safe
  • Thiazides (hydrochlorothiazide, chlorothiazide, chlorthalidone)
    • Controversial
      • Not teratogenic
      • One large study found increase in defects, however not clear if was caused by medication exposure or maternal factors
    • Continued use recommended by ACOG
• Loops
  • Furosemide
    • Has been used in 2nd and 3rd trimester without evidence of harm to infant
    • Limited evidence with bumetanide and torsemide
• Agents that may cause harm
  • Aldosterone antagonists
    • Spironolactone
      • Limited human data; animal data suggests risk due to anti-androgen properties
Anti-Hypertensives

- Agents with limited human data:
  - Carvedilol
  - Amlodipine
Anticoagulants

- Preferred agents:
  - Heparin
    - No reports linking the use of heparin with developmental toxicity
  - LMWH (enoxaparin)
    - No reports linking the use of LMWH with developmental toxicity
    - Ease of administration

- Large molecules!
Anticoagulants

• Agents that may cause harm
  • Warfarin
    • Contraindicated – first trimester
    • Fetal warfarin syndrome
      • Nasal hypoplasia with neonatal respiratory distress (upper airway obstruction)
      • Birth weight <10th percentile for gestational age
      • Eye defects (blindness, optic atrophy, microphthalmia) when drug also used in 2nd and 3rd trimesters
      • Hypoplasia of the extremities (ranging from severe rhizomelic dwarfing to dystrophic nails and shortened fingers)
    • Developmental retardation
    • Seizures
    • Scoliosis
    • Deafness/hearing loss
    • Congenital heart disease
Anticoagulants

• Warfarin
  • 471 cases of in utero exposure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>First Trimester Exposure</th>
<th>Second Trimester Exposure</th>
<th>Total Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Infants</td>
<td>167 (63%)</td>
<td>175 (84%)</td>
<td>342 (73%)</td>
</tr>
<tr>
<td>Spontaneous Abortion</td>
<td>41 (16%)</td>
<td>4 (2%)</td>
<td>45 (10%)</td>
</tr>
<tr>
<td>Stillborn/Neonatal death</td>
<td>17 (6%)</td>
<td>19 (9%)</td>
<td>36 (8%)</td>
</tr>
<tr>
<td>FWS/CNS/other defects</td>
<td>38 (14%)</td>
<td>10 (5%)</td>
<td>48 (10%)</td>
</tr>
</tbody>
</table>

FWS – fetal warfarin syndrome; CNS – central nervous system

• Not recommended in 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester
Anticoagulants

• Agents with limited or no human data
  • DOACs
    • Likely to cross placenta to some extent given size of molecules (relatively small), partial protein binding, and longer half lives
  • Individual agents
    • No human data available
      • Apixaban
      • Dabigatran
      • Rivaroxaban
    • Edoxaban
      • Ten pregnancies were reported in a study for edoxaban for the treatment of DVT/PE
        • Estimated exposure occurred during the first trimester with duration of exposure ~6 weeks
        • Outcomes included six live births (two preterm), one first-trimester spontaneous abortion, and three elective terminations of pregnancy

Antiarrhythmics

• Agents considered relatively safe
  • Digoxin
    • No reports linking digoxin with congenital defects have been located
    • Can be administered to the fetus in utero via IM injection

• Agents that may cause harm
  • Amiodarone
    • Congenital goiter/hypothyroidism and hyperthyroidism
    • Prolonged QT interval
    • Fetal bradycardia
Lipid Medications

• Statins (HMG-CoA reductase inhibitors)
  • Contraindicated (most data with lovastatin and simvastatin)
    • Cholesterol and products synthesized by cholesterol are important during fetal development
    • Teratogen
      • Number of congenital defects reported

• Or not?
  • Earlier uncontrolled case series reported adverse events with statin therapy
  • More recent observational studies have not found increased risk of congenital abnormalities
Cardiac Medications and Lactation
Calculating Infant Exposure

- Calculating infant exposure
  - Milk-to-plasma ratio
    - Unbound drug in milk/drug in plasma
    - Most medications have a ratio of < 1
  - Relative Infant Dose (RID)
    - Assume 150 mL of milk/kg/day

\[
\text{Relative Infant Dose} = \frac{\text{Dose infant (mg/kg/day)}}{\text{Dose mother (mg/kg/day)}}
\]

\[
\text{RID} = \frac{\text{Dose infant}}{\text{Dose mother}}
\]

- RID < 10% could be considered unimportant for most medications

Anti-Hypertensives

• Agents considered relatively safe in breastfeeding
  • Beta-blockers
    • Metoprolol (RID 1.4%)
    • Propranolol (RID 0.3%)
    • Labetalol (RID 0.6%)
  • For the above beta blockers
    • None have been associated with adverse effects in infants
Anti-Hypertensives

- Agents considered relatively safe in breastfeeding
  - Calcium channel blockers
    - Nifedipine (RID 2.3%)
    - Verapamil (RID 0.15%)
    - Diltiazem (RID 0.9%)
  - For the above calcium channel blockers
    - None have been associated with adverse effects in infants
Anti-Hypertensives

- Agents considered relatively safe in breastfeeding
  - Diuretics
    - Thiazide
      - Undetectable levels in infants
    - Loop (furosemide)
      - No adverse events reported
  - Hydralazine
    - Limited amounts found in breastmilk
      - Far less than doses given in pediatrics

Anti-Hypertensives

- Agents considered relatively safe in breastfeeding
  - ACEIs – two with most data
    - Captopril
      - Twelve woman taking captopril 100 mg TID
      - Estimated RID 0.002%
      - No evidence of harm
    - Enalapril
      - Five woman taking enalapril 20 mg daily
      - Estimated RID 0.175%
      - No evidence of harm

Anti-Hypertensives

- Agents to avoid with breastfeeding
  - Beta blockers
    - Atenolol
    - Acebutolol
  - Both have been rarely associated with adverse effects in infants including:
    - Cyanosis
    - Tachypnea
    - Bradycardia
    - Hypotension
    - Low body temperature

Anti-Hypertensives

- Agents with limited data
  - ARBs
  - Beta blockers
    - Carvedilol
    - Bisoprolol

Anticoagulants

• Agents considered safe with breastfeeding
  • Heparin and LMWH (enoxaparin)
    • Large molecular weight
    • Limited passage into breastmilk
    • Any present in breastmilk is destroyed by infant GI tract (no oral bioavailability)

Anticoagulants

- Agents considered safe with breastfeeding
  - Warfarin
    - Highly protein bound (maternal)
      - Limited amounts found in breast milk
  - Case Series
    - Thirteen mothers on warfarin
    - No detectable levels of warfarin in breast milk
    - No adverse effects found in infants
  - Case Report
    - Accidental overdose of warfarin in breastfeeding mother
    - Maternal INR on presentation > 10
    - Infant INR was 1
Anticoagulants

- Agents with limited data in breastfeeding
  - DOACs
    - Likely to pass into breastmilk
      - Smaller size (most are < 500 Da)
      - Moderate plasma protein binding in mother
    - Good oral bioavailability in adults
Antiarrhythmics

- Agents considered relatively safe with breastfeeding
  - Digoxin
    - Highly protein bound in the mother
    - Limited quantities excreted in breastmilk
    - No adverse events reported

- Agents to avoid with breastfeeding
  - Amiodarone
    - Significant amounts secreted in the breastmilk
    - Potential hypothyroidism in the infant
    - Potential for bradycardia and QT prolongation

Lipid Medications

- Statins (HMG-CoA reductase inhibitors)
  - Very limited data
  - Likely excreted into breastmilk
  - Not recommended for use at this time
Take home points

• As with all medications, consider risk versus benefit
• Consider maternal factors
  • Trimester of pregnancy
• Consider infant factors
• Use your resources!
  • Look up individual medications, not classes
  • Use agents with the most safety data available
Questions?