Pharmacokinetic Considerations for Pharmacotherapy in Pregnancy

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Learning Objectives

• Understand the scope of the problem with medication use in pregnancy

• Define the new labeling rules and application to the drug development process

• Interpret the impact of pregnancy on ADME processes and PD response to manage pharmacotherapy options in pregnant women

• Describe the concept of fetal transport of xenobiotics

• Assess the risk:benefit ratio for medication use in pregnancy
Scope of the Problem: Medication Use During Pregnancy

Medication Use During Pregnancy

Mitchell A. et al AJOG 2011
Old FDA Risk Classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Explanation</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; possibility of fetal harm appears remote.</td>
</tr>
<tr>
<td>B</td>
<td>Either animal studies do not indicate a risk to the fetus, and there are no controlled studies in women or animal studies have shown an adverse effect, but controlled studies in women failed to demonstrate a risk.</td>
</tr>
<tr>
<td>C</td>
<td>Either animal studies indicate a fetal risk, and there are no controlled studies in women, or studies in women and animals are not available.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of fetal risk, but the benefits may be acceptable despite the risk.</td>
</tr>
<tr>
<td>X</td>
<td>There is definite fetal risk based on studies in animals or humans or based on human experience, and the risk clearly outweighs any possible benefit.</td>
</tr>
</tbody>
</table>


Medication Use During Pregnancy

| Table II Drug exposures after the documentation of an initial prenatal care visit,* according to US FDA risk category (n=152,531 deliveries) |
|---|---|
| Category | Pregnancy (n)\(^1\) |
| A        | 3,520 (2.3%) |
| B        | 69,637 (45.7%) |
| C        | 50,185 (32.9%) |
| D        | 5,157 (3.4%) |
| X        | 1,653 (1.1%) |
| D (excluding female reproductive hormones)\(^2\) | 2,916 (1.9%) |
| X (excluding female reproductive hormones)\(^2\) | 178 (0.1%) |

<table>
<thead>
<tr>
<th>Trimester (n)(^1)</th>
<th>First</th>
<th>Second</th>
<th>Third</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>2,294 (1.5%)</td>
<td>3,154 (2.1%)</td>
<td>3,197 (2.1%)</td>
</tr>
<tr>
<td>B</td>
<td>24,555 (16.1%)</td>
<td>34,962 (22.9%)</td>
<td>40,868 (26.8%)</td>
</tr>
<tr>
<td>C</td>
<td>16,951 (11.1%)</td>
<td>24,919 (16.3%)</td>
<td>28,015 (18.4%)</td>
</tr>
<tr>
<td>D</td>
<td>3,198 (2.1%)</td>
<td>1,693 (1.1%)</td>
<td>2,059 (1.3%)</td>
</tr>
<tr>
<td>X</td>
<td>936 (0.6%)</td>
<td>278 (0.2%)</td>
<td>618 (0.4%)</td>
</tr>
<tr>
<td>D (excluding female reproductive hormones)(^2)</td>
<td>1,051 (0.7%)</td>
<td>1,250 (0.8%)</td>
<td>2,027 (1.3%)</td>
</tr>
<tr>
<td>X (excluding female reproductive hormones)(^2)</td>
<td>37 (0.02%)</td>
<td>52 (0.03%)</td>
<td>114 (0.1%)</td>
</tr>
</tbody>
</table>

Andrade S. et al AJOG 2004
New PLLR Labeling Requirements

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

PLLR = Pregnancy and Lactation Labeling Rule  

Medications Approved 2003-2012

• Pregnancy data:
  o 93% based on animal studies
  o 5.2% based on human pregnancy data

• Breast feeding
  o 47.9% -- No data
  o 42.7% -- animal data
  o 4.7% -- Human data

Mazar-Amirshahi M. et al. AJOG 2014
Proportion of PK Trials in Pregnancy

Problems Intrinsic to Pregnancy

- Off-label use of most drugs
- Liability discourages Pharmaceutical involvement
- Market is relatively small
- Revenue benefit is small
- Studies require long-term fetal evaluation

Discovery, Development, Approval

<table>
<thead>
<tr>
<th>Discovery/Preclinical Testing</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>FDA</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years</td>
<td>6.5</td>
<td>1.5</td>
<td>2</td>
<td>3.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Test Population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory and animal studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpose</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assess safety, biological activity, and formulations</td>
<td>Determine safety and dosage</td>
<td>Evaluate effectiveness, look for side effects</td>
<td>Confirm effectiveness, monitor adverse reactions from long-term use</td>
<td>File IND at FDA</td>
<td>Review process/approval</td>
</tr>
<tr>
<td>Success Rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5,000 compounds evaluated</td>
<td></td>
<td></td>
<td>5 enter trials</td>
<td>1 approved</td>
<td>1 approved</td>
</tr>
</tbody>
</table>

Pharma New Medicine, (October 2004), page 43.

What is needed?

- Provide incentives
  - Patent extension to Pharmaceutical companies to study drugs in pregnancy
- Encourage PK, PD, PharmacoEpi and Pediatric studies on current agents
- Expand Phase 2 and 3 sample size
- Expand post-marketing surveillance
Pregnancy Effects on Drug Behavior: ADME

PK and PD data from men and non-pregnant women cannot be extrapolated to pregnancy!

- Pregnancy is characterized by **dramatic** hemodynamic, endocrine, metabolic, and hematologic changes that affect every aspect of drug absorption, distribution, metabolism and elimination.
**ADME- Absorption & Bioavailability**

- *Absorption* is the movement of drug into the systemic circulation

- Bioavailability is how much of the administered drug reaches the systemic circulation in intact forms

- Drugs administered IV are 100% bioavailable

- Drugs administer IM, SQ, by inhalation are generally 100% bioavailable

- Drugs administered orally, intraperitoneally, dermally, rectally may not be fully bioavailable

**ADME- Absorption from Oral Route**

- For oral administered meds, stomach pH, food, gut transit time, local gut metabolism, uptake and efflux transport processes impact how much is bioavailable.

- Orally administered drugs undergo **first pass effect**.
  - Metabolism by enzymes of the GI lumen, gut wall, gut flora and liver

- Amount of drug reaching systemic circulation greatly reduced with oral route
Relative mRNA Expression of Human DMEs in Small Intestine and Liver

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Small intestine</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP3A4</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>CYP3A5</td>
<td>++++/++</td>
<td>++++/++</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>++/+</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>++/+</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2J2</td>
<td>++/+</td>
<td>++</td>
</tr>
<tr>
<td>CYP2S1</td>
<td>++/+</td>
<td>-</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>++/+</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2E1</td>
<td>++/+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Pavek and Dvorak Current Drug Metabolism, 2008

Clinical relevance of drug absorption

- The less well a drug is absorbed, the less gets into the circulation
- Difficult to gauge absorption without an easily measurable response
- Differences in absorption will cause wide variations in plasma levels with variable clinical effect and unpredictable side effects
- The greatest variability in drug absorption is seen when a medication is administered orally
Impact of Pregnancy: Absorption of PO meds

- Gastric acidity reduced in pregnancy
  - Impact depends on formulation

- Nausea & vomiting common in 1st trimester
  - Meds used to treat NVP affect gastric acidity and drug absorption

- Absorption affected by fed or fasted state

- Progesterone, a smooth muscle relaxant, slows gastric emptying and increases gut transit time about 30-50%
  - Metabolism may increase for drugs metabolized by intestinal CYP 450 enzymes

- Pregnancy impacts the DMEs in the gut

ADME - Distribution

- Once a drug enters into systemic circulation Distribution describes the reversible transfer of drug from one location to another within the body.

- Volume of distribution (V_D) used to measure degree of a drug's distribution

- Distribution Determinants
  - Perfusion of the tissue
  - Plasma protein binding
  - Lipid solubility
  - Vascular permeability
  - Tissue binding

- Distribution greater with drugs with high lipid solubility (non-polar), low rates of ionization or low plasma protein binding
Volume of Distribution ($V_D$)

- The theoretical volume into which a drug is distributed
- Smallest $V_D$ occurs if drug does not permeate outside the vascular compartment ($V_D = \text{plasma / blood volume} = 3-5 \text{L}$)
- A drug not bound to any proteins in the body will have a volume of distribution similar to total body water
- Total body water by weight is 50% for women, 60% for men and 70% for infants
- If drug is highly bound to tissues, $V_D$ can be very high
  - E.g. 15000L, chloroquine = highly lipophilic molecules that distribute into body fat

Clinical Relevance of distribution

- Impact of large volume of distribution ($V_D$)
  - Lower plasma concentration
  - More likely the drug will reach target tissue site
  - With hemorrhage little of drug lost
  - With dialysis little drug lost

$$V_D = V_P + V_T \left( \frac{fu}{fu_t} \right)$$
Impact of Pregnancy: Distribution

- Total blood volume ▲ 40-50%
- Plasma volume ▲ 40-50%
  - ~1100-1600cc
  - Linear increase from 4-6 wks, peak at 28-32 wks
- ▼ RBC volume by 10-15%
- Return to baseline ~6 weeks postpartum

Peck and Arias Obstet Gynecol 1979

Pregnancy Effects: Distribution

- Plasma volume in pregnancy increases 40-50% in singletons and 60-80% in multiples
  - Plasma drug concentrations will be lower accounting for lower AUC
  - “Dilutional effect”

- Extracellular fluid and total body water are increased dramatically (8L)

- The fetal compartment is available for distribution of many drugs

- Albumin concentration decreases 15%
Pregnancy Effects: Distribution

• Regional blood flows affects drug distribution
• Blood flow to the uterus increases from 50 to 500 mL/min at term
• Blood flow to the breasts, skin, and kidneys increases dramatically in pregnancy
• Blood flow to muscle and liver as a proportion of cardiac output decreases
• Portal venous and hepatic flow increase minimally in pregnancy

ADME- Metabolism

• Biochemical modification of pharmaceutical substances through specialized enzymatic systems
• Drug metabolism often converts lipophilic chemical compounds into more readily excreted hydrophilic products.
Metabolism of Xenobiotics

• **Phase 1 Metabolic Enzymes**
  o Transformation (oxidation, hydroxylation, reduction, hydrolysis)
    • CYP 450 enzymes
    • Flavin mono-oxygenases

• **Phase 2 Metabolic Enzymes**
  o Conjugating (acetyl, sulfate, glucuronic or amino acid)
    • UDP glucosyltransferases
    • Glutathione transferases
    • Sulfotransferases
    • N-acetyltransferases

• **Phase 1 Metabolic Enzymes**
  o Primarily in liver but also in gut, lung, kidney, and placenta

  o Three major families
    • CYP1, CYP2, CYP3

  o Majority of all drugs metabolized by CYP2C9/19, CYP2D6, and CYP3A4/5

• **Phase 2 metabolic enzymes**
  o Primarily in liver

Impact of Pregnancy: Metabolism

• Hepatic blood flow is minimally altered in pregnancy

• Gut transit is delayed

• Placental enzymes and fetal hepatic enzymes may affect how drugs are metabolized

• **Estrogen and progesterone individually and in combination have major effects on DMEs**
Clinical Relevance of Metabolism

- Metabolic enzyme activity is highly variable
  - Affected by race, ethnicity, gender, age, SNPs
- Metabolic enzyme activity is affected by co-administered medications and other substances
- Metabolic enzymes affected by pregnancy
Pregnancy Specific Changes in DMEs

- **Increased Activity**
  - CYP3A - 100% - nifedipine
  - CYP2D6 - 50% - metoprolol
  - CYP2C9 - 20% - phenytoin
  - UGT1A4 - 300% - lamotrigine
  - CYP2A6 - 54% - nicotine
  - CYP2B6 - 60% - methadone
  - UGT 1A4 - 300% - lamotrigine

- **Decreased Activity**
  - CYP1A2 - 65% - caffeine
    - $t_{1/2} = 3.4$ vs $8.3$ h
  - CYP2C19 - 50% - zoloft, prilosec

SNPs of any of these CYP enzymes may impact the response to the wild type allele

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**ADME-Elimination**

- The processes by which a drug is eliminated either in an unaltered form (unbound molecules) or modified as a metabolite

- Elimination pathways:
  - Kidney, Liver, Skin, Lungs, Feces, Glands (salivary, lacrimal, breast, sweat)
Clinical Relevance of Elimination

• Allows the body to eliminate parent drug and metabolites of drug

• Alterations in elimination lead to accumulation of parent drug or its metabolites

• Primarily kidney and liver
  o Adjust with organ failure

• Drug-drug interactions
  o Probenecid competes with excretion of penicillin, naprosyn, cephalosporins while St John’s Wort increases clearance of several drugs

Impact of Pregnancy: Elimination

• Renal blood flow is increased 40-50% in pregnancy

• Polar or water soluble drugs are excreted to a much greater degree in pregnancy

• Protein binding reduced in pregnancy, enhancing elimination
Pharmacodynamics and Assessing the Response

Pharmacodynamics

- Pharmacodynamics is the study of what a drug does to the body. This includes its biochemical and physiological effects and its mechanism of action.
Clinical Relevance of Pharmacodynamics

- PD studies required to establish proper dose or regimen

- Without PD studies, dose may be excessive and cause side effects
  - E.g. ritodrine

- Without PD studies, dose may be inadequate leading to presumed drug failure or less than optimal response
  - E.g. 17-OHPC

Impact of Pregnancy: PD

- In pregnancy AUC (exposure) is commonly lower and clearance greater than in men or NP women
Placental Transport

• Most xenobiotics cross placental barrier by simple diffusion
  o Blood-flow dependent

• Protein binding, degree of ionization, lipid solubility and molecular weight affect transport

• Molecules that will cross easily are:
  o Small (<1000 daltons)
  o Lipid soluble
  o Non-ionized
  o Poorly protein bound

• Placenta also has ability to metabolize xenobiotics

Relative mRNA Expression of Human DMEs in Placenta and Liver

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Placenta</th>
<th>Liver</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A1</td>
<td>+++/+</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>+++/+</td>
<td>+++</td>
</tr>
<tr>
<td>CYP2J2</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>CYP1B1</td>
<td>+</td>
<td>+++</td>
</tr>
</tbody>
</table>

Pavek and Dvorak Current Drug Metabolism, 2008
Placental Transport

- Fetal protection from xenobiotics provided by efflux transporters located in the apical membrane of syncytiotrophoblasts (ABC transporters)
  - p-glycoprotein (Pg-P)
  - breast cancer resistance protein 1 (BCRP1)
  - multidrug resistant protein 1 (MDRP1)

- Expression of efflux transport proteins is increased by progesterone/estrogen

<table>
<thead>
<tr>
<th>Transporter name</th>
<th>Encoding gene</th>
<th>Placental localization</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-glycoprotein</td>
<td>ABCB1/MDR1a/b</td>
<td>apical</td>
<td>fetus protection</td>
</tr>
<tr>
<td>BCRP</td>
<td>ABCG2</td>
<td>apical</td>
<td>fetus protection</td>
</tr>
<tr>
<td>MRP1</td>
<td>ABCC1</td>
<td>basolateral</td>
<td>transport of endogenous substrates</td>
</tr>
<tr>
<td>MRP2</td>
<td>ABCC2</td>
<td>apical</td>
<td>fetus protection</td>
</tr>
</tbody>
</table>
Maternal and Fetal Considerations

- The physiologic and metabolic changes accompanying pregnancy require dosing adjustments.
- Drugs eliminated primarily via the kidneys require higher doses.
- Drugs primarily metabolized by the liver may need higher or lower doses.
- Drugs affecting the fetus need to be replaced with drugs that do not.
Maternal Considerations

- Dosing adjustments are possible when drug concentrations are measured
  - AEDs

- Dosing adjustments possible when easily measurable end organ response exists
  - BP, HR, or Glucose

- Dosing adjustments not possible when end organ response not easily quantified
  - PPIs, SSRIs, asthma meds, PTB

Maternal Considerations

- With lack of response to a drug, increasing dose may create serious side effects

- Lack of response may be due to drug ineffectiveness or due to incorrect diagnosis
  - IAI not PTL, pneumonia not asthma, preeclampsia not chronic hypertension

- Lack of response may be due to drug resistance
# Fetal Considerations: Teratogens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Critical Period</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td>8th – 13th week</td>
<td>Labial fusion, clitoral hypertrophy, masculinization of female fetus</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme (ACE) inhibitor and angiotensin II receptor antagonists</td>
<td>2nd and 3rd trimester</td>
<td>Renal impairment, renal tubular dysplasia, anuria, oligohydramnios</td>
</tr>
<tr>
<td>Warfarin</td>
<td>6th – 9th week</td>
<td>Fetal Warfarin Syndrome (facial anomalies and epiphyseal stippling)</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>1st trimester</td>
<td>Neural tube defects, cardiac defects, cleft lip and palate, microcephaly, craniofacial defects</td>
</tr>
<tr>
<td>Lithium</td>
<td>3rd trimester</td>
<td>Cardiac defect (Ebstein anomaly)</td>
</tr>
<tr>
<td>Lithium</td>
<td>3rd trimester</td>
<td>Newborn toxicity</td>
</tr>
<tr>
<td>Diethylstilbestrol (DES)</td>
<td>10-13 week</td>
<td>Vaginal adenocarcinoma, abnormalities of lower mullerian tract</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>20 -36 days post conception</td>
<td>Bilateral amelia or phocomelia</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>6th – 13th weeks</td>
<td>Abortion, CNS malformations, cardiac facial dysmorphism, etc.</td>
</tr>
<tr>
<td>Iodine</td>
<td>2nd and 3rd trimester</td>
<td>Fetal hypothyroidism</td>
</tr>
</tbody>
</table>

# Fetal Considerations: Drug Toxicity

<table>
<thead>
<tr>
<th>Agent</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDS</td>
<td>Oligohydramnios, ductal closure</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>Hyperbilirubinemia</td>
</tr>
<tr>
<td>Paroxetine (Paxil)</td>
<td>Cardiac malformations, persistent pulmonary hypertension</td>
</tr>
<tr>
<td>Beta adrenergic blocker</td>
<td>Growth delay, bradycardia</td>
</tr>
<tr>
<td>Sulfonurea</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Ketamine</td>
<td>CNS depression</td>
</tr>
<tr>
<td>Narcotics</td>
<td>Addiction, withdrawal</td>
</tr>
<tr>
<td>Sedative/hypnotics</td>
<td>Hypotonia, sedation, withdrawal</td>
</tr>
</tbody>
</table>
Obstetrical-Fetal Pharmacology Summary

- Drugs intended for pregnant women should be evaluated in pregnant women.

- PK and PD studies should be performed in each trimester and under various conditions (eg fed vs fasted, twins vs singleton, long vs short duration).

- Large sample size is required to define variations in PK & PD.