SESSION E5

What's New in Drug Therapy for Pregnancy? A Clinical Pharmacology Update

Mary F. Hebert, PharmD, FCCP

Session Description:

It is important to weigh the risks vs. benefits of drugs in pregnancy and FDA pregnancy categories do not correlate well with medication safety. It is important to consider the physiologic changes that occur during pregnancy when selecting and dosing medications.

Learning Objectives:

Following my presentation, participants will be able to:
1. Discuss the limitation in the FDA pregnancy categories.
2. Identify clinical pharmacology changes that occur during pregnancy.
3. Discuss the clinical implications of clinical pharmacologic changes during pregnancy.
What's New in Drug Therapy for Pregnancy – A Clinical Pharmacology Update

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UNIVERSITY of WASHINGTON

Conflict of Interest

- Mary Hebert is a consultant for Hyperion and UCB Bioscience Inc.

Off-Label Use

- Almost everything discussed in this presentation is considered off-label use because either the indication has not been approved or if the indication has been approved, the dosage in pregnancy is not described in the label.
- Although pregnancy is a condition, not a disease, the physiologic changes that occur can substantially alter the way the body handles and responds to medications and therefore may require alterations in medication selection and/or dosage.

Objectives

- Discuss the limitations in the FDA pregnancy categories
- Understand the effects of pregnancy on clinical pharmacology of drugs
- Understand the clinical implications of pharmacology changes during pregnancy

Medication Use During Pregnancy (n=578)

<table>
<thead>
<tr>
<th>Number</th>
<th>Prescription</th>
<th>OTC</th>
<th>Herbal</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.2</td>
<td>7.4</td>
<td>54.8</td>
</tr>
<tr>
<td>1</td>
<td>26.6</td>
<td>18.5</td>
<td>25.8</td>
</tr>
<tr>
<td>2</td>
<td>31.7</td>
<td>23.2</td>
<td>12.5</td>
</tr>
<tr>
<td>3</td>
<td>19.4</td>
<td>18.7</td>
<td>6.9</td>
</tr>
<tr>
<td>≥4</td>
<td>18.2</td>
<td>32.2</td>
<td></td>
</tr>
</tbody>
</table>

AJOG 2003;188:1039.
Pregnancy categories

A. Adequate and well-controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters).

B. Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no AWC studies in pregnant women, OR animal studies demonstrate a risk and AWC studies in pregnant women have not been conducted (and there is no evidence of risk in later trimesters).

C. Animal reproduction studies have shown an adverse effect on the fetus, there are no AWC studies in humans, AND the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. OR animal studies have not been conducted and there are no AWC studies in humans.

D. There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, BUT the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).

X. Studies in animals or humans have demonstrated fetal abnormalities OR there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, AND the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available).

FDA Pregnancy Categories Limitations

- Pregnancy categories are misinterpreted, misunderstood, overly simplistic, and unfortunately heavily relied upon by clinicians.
- Categories shortcomings:
  - Risks do not increase from A → B → C → D → X.
  - Do not adequately address the full range of potential developmental abnormalities, structural anomalies, functional deficits, embryo-fetal death, alterations in growth.
  - Incorrect impression that drugs in the same category have similar risk.
  - Do not differentiate severity, incidence, or type of adverse event.
  - Do not include risk/benefit analysis.
  - Do not distinguish between clinical and non-clinical supporting data.
  - Inadvertent exposure is not adequately addressed.

Risk vs Benefit Assessment

"Use in pregnancy is not recommended unless the potential benefits justify the potential risks to the fetus."

Risks to Consider
- Risk of untreated disease
  - Mother
  - Fetus
  - Neonate
- Risk of medication
  - Mother
  - Fetus
  - Neonate

Benefits to Consider
- Short term
  - Mother
  - Fetus
  - Neonate
- Long term
  - Mother
  - Neonate

Case 1

ID: 15 year old female with severe, painful cystic acne
HPI: Acne started at age 11 and progressed to severe nodular cystic acne by age 13. Patient failed benzoyl peroxide, doxycycline, minocycline, tretinoin cream, clindamycin gel and prednisone.

Meds: cephalaxin, tretinoin cream, clindamycin gel

Med/Surg: No other medical illnesses or surgeries
Pregnancy test: negative

LFTs: WNL

ROS: Negative except for severe cystic acne on face, chest and back

SH: Negative for smoking, ethanol use and recreational drugs. Not sexually active.

FH: Mother severe cystic acne as teenager and into early 20s. Father moderate non-cystic acne as teenager.

Isotretinoin

Major Human Teratogen (50%)

Women should avoid pregnancy for at least 1 month following discontinuation of isotretinoin.
Risk Evaluation and Mitigation Strategies (REMS)

Isotretinoin must only be:
- prescribed by prescribers who are registered and activated with the iPLEDGE program
- dispensed by a pharmacy registered and activated with iPLEDGE
- dispensed to patients who are registered and meet all the requirements of iPLEDGE

Prescribers or their designee must enter required information in the iPLEDGE system for patients to be qualified to receive a prescription:
- pregnancy test results
- 2 forms of contraception used
- confirmation of patient counseling

Acceptable Contraception for iPLEDGE

<table>
<thead>
<tr>
<th>Primary forms</th>
<th>Secondary forms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Tubal sterilization</td>
<td>Barrier forms (sheres used with spermicides)</td>
</tr>
<tr>
<td>• Partner’s vasectomy</td>
<td>• Diaphragm</td>
</tr>
<tr>
<td>• Intrauterine device</td>
<td>• Cervical cap</td>
</tr>
<tr>
<td>• Hormonal (combination oral contraceptives, transdermal patch, injectables, implants, or vaginal ring)</td>
<td>Barrier forms (used with or without spermicides)</td>
</tr>
<tr>
<td></td>
<td>• Male latex condom</td>
</tr>
<tr>
<td></td>
<td>Others:</td>
</tr>
<tr>
<td></td>
<td>• Vaginal sponge (contains spermicide)</td>
</tr>
</tbody>
</table>

Unacceptable Contraception for iPLEDGE

- Progesterone-only “one-pill,” e.g. 
  - Oral Mirena® Tablets
- IUD Progesterone T 
- Female condoms
- Natural family planning (rhythm method or basal body temperature)
- Fertility awareness
- Withdrawal
- Contraceptive creams

Isotretinoin Prescription Window

All patients have a specific period of time in which they can fill and pick up their prescription. This is called the “prescription window” and its start and end dates depend on the type of patient, as follows:

Female patients who can get pregnant:
- The prescription window is 7 days, and starts on the date of the last menstrual period (LMP) or date of last pregnancy test. This date is counted as DAY 1.
- To determine the end date of the 7-day prescription window, these patients should add 6 days to the date of the blood or urine sample taken.

Male patients and female patients who cannot get pregnant:
- The prescription window is 30 days, and starts on the date the prescription was written. This date is counted as DAY 1.
- To determine the end date of the 30-day prescription window, these patients should add 29 days to the date of their office visit.

After 11:59 PM Eastern Time on the last day of the prescription window, the patient can no longer fill and pick up their prescription, and must start the process over to get a new prescription window.

Some drugs should NOT be given during pregnancy

**Thalidomide**
- Major Malformations (25%)
  - Between 1956-1961 more than 10,000 infants with thalidomide birth defects.

**Mycophenolate**
- Malformations ~27%
  - Microtia, cleft lip and palate, hypoplastic nails, shortened fingers, external auditory duct atresia, diaphragmatic hernias, heart malformations

**Pregnancy Category X Drugs**

<table>
<thead>
<tr>
<th>Acitretin</th>
<th>Diethylstilbestrol</th>
<th>Leuprolide</th>
<th>Rifabutin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminopterin</td>
<td>Ergotamines</td>
<td>Medroxyprogesterone</td>
<td>Indomethacin</td>
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**Case 2**

ID: 33 year old Asian G1 PO with Class B Type 2 DM

HPI: Diabetes X 7 years. Was monitoring home glucose concentrations but discontinued due to error reading on her monitor. She also discontinued her metformin. Her HgA1C was >11% 7 months ago.

Meds: None

Allergies: NKDA

Med/Surg: No other medical illnesses or surgeries

Dating based on LMP: 6 weeks and 6 days

Dating based on U/S: 6 weeks 2 days

ROS: Negative

SH: Negative for smoking, ethanol use and recreational drugs

FHR: Mother, father and maternal grandmother had insulin dependent Type 2 DM
Maternal Complications in Diabetic Pregnancy

- Hyperglycemia
- Ketoacidosis
- Pregnancy-induced hypertension
- Preeclampsia
- Polyhydramnios
- Preterm labor

- Worsening of chronic complications:
  - Retinopathy
  - Neuropathy
  - Nephropathy
  - Cardiac Disease

Fetal and Neonatal Complications in Diabetic Pregnancy

- Asphyxia
- Birth injury
- Cardiac hypertrophy
- Heart failure
- Congenital anomalies
- Increased RBCs and hyperviscosity
- Hyperbilirubinemia
- Hypocalcemia

Glycemic Control and Risk of Spontaneous Abortions and Congenital Defects

- Caudal regression
- Spina bifida, hydrocephalus, other CNS defect
- Anecephalus
- Heart anomalies
- Anal or rectal atresia
- Renal anomalies
- Agenesis
- Cystic kidney
- Ureter duplex
- Situs inversus

http://www.idb.hr/diabetologia/99no1-1.html

**Diabetes Drugs during Pregnancy**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fetal Effect</th>
</tr>
</thead>
</table>
| **Insulin** | ○ Regular Insulin does not cross the placenta or cause congenital malformations  
○ Neither lispro nor aspart cross the placenta. Of short acting insulin, most data is with lispro which appears to be safe in pregnancy (retrospective and small prospective studies). Both lispro and aspart achieve lower postprandial glucose concentrations that regular insulin.  
○ Glargine appears to be similar to other insulin products in pregnancy outcomes. Placental perfusion study showed limited transfer across the placenta in therapeutic doses.  
○ Detemir and NPH insulin have similar maternal and fetal outcomes when used in women with Type 1 DM.  
○ A meta-analysis reported no difference in glycemic control and pregnancy outcomes when comparing multiple daily insulin injections to insulin pumps. |
| **Metformin** | ○ 1% malformation rate with metformin, 7% among disease matched controls (p<0.01) - Potential protective effect due to improvement in insulin resistance and in androgen status  
○ Use of metformin throughout pregnancy for maternal diabetes data is reassuring. |
| **Glyburide** | ○ Perfusion studies: Glyburide minimally crosses the placenta.  
○ In vivo: Umbilical cord to maternal glyburide plasma concentration ratio at the time of delivery 70%  
○ Unlikely to increase risk of malformations  
○ Glyburide shown to have comparable maternal, fetal and neonatal outcomes as insulin in the treatment of GDM  
○ GDM Meta analysis -glyburide vs insulin [Macrosomia OR (odds ratio) 1.04 (0.74-1.45), Neonatal hypoglycemia OR 1.33 (0.99-1.79)]  
| **Acarbose** | ○ Undetermined, very limited data. One small study (n=38) treating GDM that demonstrated good neonatal outcomes. |
| **Pioglitazone** | ○ Undetermined, very limited data. 7 women exposed in 1st trimester resulted in 3 healthy infants, 1 pregnancy ongoing and 3 miscarriages. |
| **Rosiglitazone** | ○ Undetermined, very limited data. 13 women exposed in 1st trimester resulted in 13 normal infants. |
| **Oxandrin** | ○ Undetermined, very limited data. 67 1st trimester exposures resulted in 5 healthy infants, 1 termination and 5 spontaneous abortions.  
○ 6 pregnancies resulted in 1 congenital malformation: Malrotation that needed surgery.  
○ Congenital cardiac defects and cleft lip and palate.  
○ 1 infant with colic subsequently found to have developmental delay. |
| **Sitagliptin** | ○ Undetermined, very limited data. 8 1st trimester exposures resulted in 5 healthy infants, 1 fetal death and 2 spontaneous abortions.  
○ 8 pregnancy exposures resulted in 2 healthy infants, 1 termination and 5 spontaneous abortions. |
| **Saxagliptin** | ○ Undetermined, very limited data. 56 1st trimester exposures resulted in 2 congenital malformations, 1 congenital heart defect and 1 translocation of the great vessels.  
○ 1 case of congenital absence of the fallopian tubes.  
○ 1 developed colic was subsequently found to have malrotation that needed surgery. |

**Pharmacokinetics**

![Pharmacokinetics Diagram](image)

**Effects of Obesity on Creatinine Clearance During Pregnancy and Postpartum**

![Graph](image)
**Atenolol Renal Clearance vs. Creatinine Clearance During Pregnancy and Postpartum**


**Metformin Concentrations during Pregnancy and Postpartum**


**CYP2C9 Activity During Pregnancy**

N=14, **p ≤ 0.025, *p ≤ 0.05**


**CYP3A Activity in Pregnancy**


**Monte Carlo Simulations**

Umbilical Cord: Maternal Plasma Glyburide Concentration Ratios

- Fetus is exposed to 70% of maternal concentration.
- Fetal safety must be considered if higher doses are used in pregnancy.


Glucose Concentrations in Pregnant and Nonpregnant Subjects


Insulin Concentrations in Pregnant and Nonpregnant Subjects


Hyperbolic relationship

Hyperbolic relationship: $\text{Insulin Secretion} \times \text{Insulin Action} = \text{Disposition Index (Constant)}$

- Disposition Index (DI): An index of beta-cell secretion that accounts for insulin sensitivity.
- Ability of the pancreatic beta-cells to compensate for insulin resistance by increasing beta-cell responsivity.


American Academy of Pediatrics
(with concurrence by WHO and Institute of Medicine)

- Recommends:
  - exclusive breastfeeding for about 6 months then
  - continued breastfeeding for 1 year or longer
- Suggested benefits in:


American Academy of Pediatrics

- Many mothers are inappropriately advised to discontinue breastfeeding or avoid taking essential medications because of fears of adverse effects on their infants

Diabetes Drugs in Breast Milk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>Infant exposure 0.2-1.1% of maternal weight-adjusted dose. Infant concentrations undetectable to 15% of maternal serum concentration. No infant adverse effects reported.</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>No data available. Molecular weight ~357. Three active metabolites. Expect transfer of pioglitazone and its metabolites into milk. Weak base, therefore expect higher concentrations in milk than maternal plasma.</td>
</tr>
<tr>
<td>Insulin, glargine</td>
<td>No data available. Insulin is excreted as a natural component of breast milk. Being a polypeptide hormone, it would be expected to be digested in the infants gut.</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Infant exposure &lt; 1.5% of maternal weight-adjusted dose. Infant concentrations not reported. No infant adverse effects reported.</td>
</tr>
<tr>
<td>Acarbose</td>
<td>No data available. Less than 2% of maternal dose is absorbed, but 30% absorbed as metabolites.</td>
</tr>
</tbody>
</table>

Depression in Pregnancy

- Affects up to 20% of pregnant women
- Suicidal ideation is associated with:
  - Unplanned pregnancy (OR 2.97)
  - Current major depression (OR 4.12)
  - Comorbid anxiety disorder (OR 4.17)
- Depression in late pregnancy is the strongest predictor for postpartum depression

- Major Depressive Disorder is associated with:
  - Less cognitive and language achievement by their children.
  - Increased behavioral problems with their children at 2-5 years

- Depression and SSRI's Effects on Preterm Birth

- Antidepressants during Pregnancy
  - Many women
  - discontinue SSRI/SNRI in pregnancy due to concerns and misinformation
  - receive small, ineffective doses
  - D/C treatment:
    - increased risk of morbidity, depression, hospitalization, drug abuse

- Antidepressants in Pregnancy

<table>
<thead>
<tr>
<th>Drug</th>
<th>Fetal Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI (Paroxetine, Fluoxetine, Sertraline)</td>
<td>Some epidemiology studies reporting increase in various malformations associated with sertraline. Overall, risk of major malformations seems unlikely. Long-term neurodevelopmental studies suggest that antenatal exposure does not adversely affect outcome. IQ, language and behavior similar to control pregnancies. Paroxetine: 0.7% incidence of cardiac malformations (similar to placebo). Poor neonatal adaptation syndrome 10-30% (discontinuation syndrome or rarely dopaminergic syndrome) Persistent pulmonary hypertension of the newborn (attributable risk &gt;1%). Increased risk of neonatal pulmonary hypertension in some but not all studies.</td>
</tr>
<tr>
<td>TCAs</td>
<td>Long-term neurodevelopmental studies suggest that antenatal exposure does not adversely affect outcome. IQ, language and behavior similar to control pregnancies. Withdral syndrome 1st month after birth: colic, cyanosis, rapid breathing, and irritability. Human data does not confirm concerns about malformations.</td>
</tr>
</tbody>
</table>


### Antidepressants in Breast Milk

<table>
<thead>
<tr>
<th>Drug</th>
<th>Infant Exposure (% of maternal weight-adjusted dose)</th>
<th>Infant Concentration (% of maternal plasma concentration)</th>
<th>Infant Concentration (% of maternal plasma concentration)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>Trazodone 0.65%, metabolites not studied</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Duloxetine 0.07-0.8%, metabolites not studied</td>
<td>&lt; 1%</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Fluoxetine 0.5-2%, norfluoxetine 0.6-4%</td>
<td>Fluoxetine 0-59%, norfluoxetine 6-39%</td>
<td>Fluoxetine 0-59%, norfluoxetine 6-39%</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Paroxetine 1.4%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Venlafaxine 3-12%, desvenlafaxine 4%</td>
<td>combine parent and metabolite concentrations were ~37%</td>
<td>combine parent and metabolite concentrations were ~37%</td>
</tr>
<tr>
<td>Sertraline</td>
<td>~0.5-0.9%</td>
<td>0-15%</td>
<td>0-15%</td>
</tr>
<tr>
<td>Escitalopram (S-isomer of citalopram)</td>
<td>Escitalopram ~4-8%, desmethylcitalopram ~2%</td>
<td>&lt; 25%</td>
<td>&lt; 25%</td>
</tr>
<tr>
<td>Citalopram</td>
<td>~3-8%</td>
<td>0-10%</td>
<td>0-10%</td>
</tr>
</tbody>
</table>

### Infant ADRs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Infant ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trazodone</td>
<td>No infant adverse effects and normal infant development</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>No infant adverse effects have been reported.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Reported ADRs: colic, decreased sleep, vomiting and watery stools, irritability, difficult to arouse, ceased rooting behavior, decreased nursing, moaning and grunting. No differences in cognitive, language or temperament development Infants exposed in utero can go through withdrawal even with breastfeeding (irritability, low body temperature, uncontrollable crying, eating and sleeping disorders)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Non-specific adverse effects with no conclusive cause-effect identified Infants exposed in utero can go through withdrawal</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>No infant adverse effects have been reported. Infants exposed in utero can go through withdrawal</td>
</tr>
<tr>
<td>Sertraline</td>
<td>1 case report of benign neonatal sleep myoclonus, 1 case of agitation, Many case reports of normal infants with normal development, infants exposed in utero can go through withdrawal</td>
</tr>
<tr>
<td>Escitalopram (S-isomer of citalopram)</td>
<td>Many infant exposures with no adverse effects and normal developmental outcomes. 1 case report of necrotizing enterocolitis.</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Reported ADRs: irritability, fussiness and sedation. Infants exposed in utero can go through withdrawal</td>
</tr>
</tbody>
</table>

### American Academy of Pediatrics

Least Problematic Antidepressants in Breast Milk

- Amitriptyline
- Paroxetine
- Sertraline