DRUGS IN PREGNANCY: NEW FDA LABELING AND MORE
Objectives

- Discuss updated information regarding common teratogens and fetotoxic agents
- Discuss FDA labeling, including rules, implementation and implications
- Describe issue of chronobiology for drugs in pregnancy
Disclosure

• No potential conflict of interest
What is the most common (and costly) reason for perinatal morbidity/mortality?

Birth defects—although preterm/LBW is the most “modifiable”
Speaking of Birth Defects

What is the most common cause?
Causes of Human Malformations
from classic work by Wilson

Causes of Human Malformations

from classic work by Wilson

- Irradiation
- Infections
- Maternal Disorders
- Drugs & Chemicals
Background Incidence

3-4% of All Births
Drug Use in Pregnancy

Drugs in General Population
Half of All Pregnancies in US Unplanned
Mature Gravidas May Have Chronic Conditions
Some Drugs Once Thought Incompatible With Pregnancy
Estimated 50-80% of pregnant women use OTC drugs in pregnancy
Congenital Malformations

Difficulty in Identifying Human Birth Defects
Ex Post Facto
Questionable Data
Generalizability From Animal Data
Criteria for Human Teratogen
Timing

The effect of teratogens depends upon the timing of exposure.
The first trimester of pregnancy is the critical period of organ and limb development in the fetus.
Exposure to a teratogen during the two weeks following conception is unlikely to cause birth defects.
The fetal brain develops throughout pregnancy and can be affected at any time.
The Most Vulnerable Period
7-60 Days Postconception or
3-11 Weeks Gestational Age
Teratogenic Effects Caused by Drugs Are Unique Because They Are Preventable
NOW SHE CAN COOK BREAKFAST AGAIN

...WHEN YOU PRESCRIBE NEW MORNIDINE™

A new drug with specific effectiveness in nausea and vomiting of pregnancy, Mornidine eliminates the ordeal of morning sickness.

With its selective action on the vomiting center, or the medullary chemoreceptor "trigger zone," Mornidine possesses the advantages of the phenothiazine drugs without unwanted tranquilizing activity.

Doses of 5 to 10 mg., repeated at intervals of six to eight hours, provide excellent relief all day. In patients who are unable to retain oral medication when first used, Mornidine may be administered intramuscularly in doses of 5 mg. (1 cc.).

Mornidine is supplied in tablets of 5 mg. and as ampuls of 5 mg. (1 cc.).

Research in the Service of Medicine.
Update on Selected Drugs
Acetaminophen

• “Children exposed to acetaminophen prenatally are at increased risk of multiple behavioral difficulties, and the associations do not appear to be explained by unmeasured behavioral or social factors”


• Multiple letters to the editors questioning/criticizing methodology of study.

• Published several months later

• However, many people don’t read the letters

• Now worried about autism, decreased IQ and ADHD
Speaking of Autism

Other drugs “associated” with autism –BUT without clear causality

Antiepileptics (esp. valproate)

Beta 2 Adrenergic Receptors (e.g. albuterol)

Antidepressants (e.g. SSRI’s)

IS IT THE DISEASE OR THE DRUG?
And what about psychoactive drugs?

- PubMed reviewed for pregnancy and antidepressant drugs only—more than 1200 references in early 2017
- Suggested associations with behavioral changes, autism, and congenital anomalies
Before 2005
SSRI’s and Pregnancy

• “FDA-C “

• Do not discontinue abruptly, especially 3rd trimester—behavioral changes in newborn (neonatal abstinence issue)

• 450 exposed pregnancies and no effects
  • (Nulman, 1995; Pastuszak, 1993; Goldstein, 1995)
Paroxetine

Swedish population data—2% congenital cardiac malformations (compared to overall 1%)
Then another study 3,500 pregnant women, surprised Glaxo as previous studies had shown none.
The study showed 4 percent of women on paroxetine having children with birth defects, as opposed to 2 percent for all other women.
Regarding PPHN--the numbers were low (e.g. persistent pulmonary hypertension of the newborn is 0.1-0.2% (means 99.8% without it))

### Table 1: Risk of major congenital malformation in infants according to the antidepressant medication used maternally during the first trimester

<table>
<thead>
<tr>
<th>Drug</th>
<th>Maternal users</th>
<th>Infant malformations</th>
<th>Malformations per 1000 live births</th>
<th>Adjusted odds ratio (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>146</td>
<td>1</td>
<td>6.8</td>
<td>0.27 (0.04-1.96)</td>
</tr>
<tr>
<td>Bupropion</td>
<td>248</td>
<td>6</td>
<td>24.2</td>
<td>0.99 (0.42-2.30)</td>
</tr>
<tr>
<td>Citalopram</td>
<td>188</td>
<td>7</td>
<td>37.2</td>
<td>1.39 (0.62-3.11)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>820</td>
<td>18</td>
<td>22.0</td>
<td>0.82 (0.48-1.39)</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>41</td>
<td>1</td>
<td>24.4</td>
<td>0.94 (0.13-6.96)</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>527</td>
<td>23</td>
<td>43.6</td>
<td>2.20 (1.34-3.63)</td>
</tr>
<tr>
<td>Sertraline</td>
<td>507</td>
<td>7</td>
<td>13.8</td>
<td>0.48 (0.22-1.05)</td>
</tr>
<tr>
<td>Trazodone</td>
<td>49</td>
<td>2</td>
<td>40.8</td>
<td>1.98 (0.47-8.39)</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>129</td>
<td>2</td>
<td>15.5</td>
<td>0.59 (0.14-2.42)</td>
</tr>
<tr>
<td>&gt; 1 type of antidepressant</td>
<td>406</td>
<td>14</td>
<td>34.5</td>
<td>1.42 (0.79-2.55)</td>
</tr>
</tbody>
</table>

*Categories of specific antidepressants are mutually exclusive. Data were taken from a GlaxoSmithKline report (available at http://ctr.gsk.co.uk/summary/paroxetine/epip083.pdf [accessed 2005 Oct 26] and also at www.cmaj.ca/cgi/content/full/173/11/1320/DC1). Because no major congenital malformations were observed among the offspring of participants exposed to clomipramine, desipramine, doxepin, fluvoxamine, imipramine, mitrazapine, nortriptyline or protriptyline, data for these antidepressants are not shown. †Adjusted for age and sex of infant, calendar year of delivery and a maternal diagnosis of pre-eclampsia or eclampsia. The comparator group is the rate of malformations among infants of users of any other antidepressant in the first trimester. CI = confidence interval.

Then comes 2017

• Research failed to find any connection between antidepressants (incl. paxotine) and cardiac issues

• Systematic review concluded insufficient information (did not find consistent issue)

But....
Quebec Study 2017--SSRIs

• 18,487 pregnant women in Observational study of a cohort
• citalopram in first trimester associated with major congenital malformations (adjusted OR, (aOR) 1.36, 95% CI 1.08 to 1.73; 88 exposed cases
• Antidepressants with serotonin reuptake inhibition effect (SSRI, SNRI, amitriptyline (the most used TCA)) increased the risk of certain organ-specific defects: paroxetine increased the risk of cardiac defects (aOR 1.45, 95% CI 1.12 to 1.88), and ventricular/atrial septal defects (aOR 1.39, 95% CI 1.00 to 1.93); citalopram increased the risk of musculoskeletal defects (aOR 1.92, 95% CI 1.40 to 2.62), and craniosynostosis (aOR 3.95, 95% CI 2.08 to 7.52);
• Note: control group

Multi Country Study

• No control
• More than one half million births in observational report

• Conclusion

• “The additional absolute risk of teratogenesis associated with SSRIs, if causal, is small. However, the high prevalence of SSRI use augments its public health importance, justifying modifications to preconception care.”
And then...

SSRIs suggested associated with PTL

FDA “help” to prevent teratogenic drug use
FDA Categories: Drug Labeling

1979


Specific to pregnancy risks and teratogenic potential

Some changes in 2006, but categories remained
Current FDA Ratings for Labels of Drug Safety in Pregnancy

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Well-controlled studies in humans show no risk to the fetus</td>
</tr>
<tr>
<td>B</td>
<td>No well-controlled studies have been conducted in humans; animal studies show no risk to the fetus</td>
</tr>
<tr>
<td>C</td>
<td>No well-controlled studies have been conducted in humans; animal studies have demonstrated an adverse effect on the fetus</td>
</tr>
<tr>
<td>D</td>
<td>Evidence of human risk to the fetus exists; however, benefits may outweigh risks in certain situations</td>
</tr>
<tr>
<td>X</td>
<td>Controlled studies in animals or humans demonstrate fetal abnormalities; the risk in pregnant women clearly outweighs any possible benefit</td>
</tr>
</tbody>
</table>
Problems with A, B, C, D, X System

<table>
<thead>
<tr>
<th>FDA Use-In-Pregnancy Ratings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
</tr>
<tr>
<td>Controlled studies show no risk</td>
</tr>
<tr>
<td>B</td>
</tr>
<tr>
<td>No evidence of risk in humans</td>
</tr>
<tr>
<td>C</td>
</tr>
<tr>
<td>Risk cannot be ruled out</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>Positive evidence of risk</td>
</tr>
<tr>
<td>X</td>
</tr>
<tr>
<td>Contra-indicated</td>
</tr>
</tbody>
</table>

What They Really Mean

| A                           |
| OK to use |
| B                           |
| I don't know |
| C                           |
| I don't know |
| D                           |
| I don't know |
| X                           |
| Contra-indicated |
Problems with Current FDA Categories

Rigid categories—sometimes not clear where drug fits
Confusion about category C because it contains 2 different concepts
Limited information
  During labor and birth
  During lactation
If brief and/or accidental exposure
And Who Determines Category?

FDA?

Manufacturer?

Scientists based on interpretation of research?

And what if scientists disagree with manufacturer?
New Pregnancy Drug Labeling

Proposed Rule in 2008

Finally accepted Dec 2014

Went into effect 6/30/15

Focus on consistency

Omits letter categories
New Drug Labeling

Pregnancy AND lactation labeling

Consistent format for assessing risk and benefit

Only applicable to FDA drug applications from 2001 to current applications

Older drugs are said to be phased in, but unclear. However all older drugs must remove letter categories by 2018
What’s in the New Drug Labels

Additional Information
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
New Drug Labels: Pregnancy Information

May contain dose adjustments during perinatal period, maternal/fetal adverse effects, effects of the drug on intrapartum

Focus on potential risks of not treating a condition as well as risks of taking the drugs

More balanced than old information focused on risks of the drugs only--E.g. Hypertension, epilepsy

Information on pregnancy registry
New Drug Labels: Lactation Information

Amount of drug in breast milk (whether or not it can be determined)

Data about effect on newborn and infant

Information, when known, about long term effects

Dosing modifications
New Drug Labels: Females and Males of Reproductive Potential

New to labeling

Information regarding need for pregnancy testing

Contraceptive recommendations

Information about infertility
New Drug Labels: Clinical Considerations

Relevant information for health education of woman/family

If not discussed before, include information on
  Dosing differences
  Risks
New Drug Labels: Background Data

Information from animal and human studies that support the risk statements previously prevented

Present animal data separately from data from human studies

This is the science
Risks/Benefits of New Labels

Categories were “easy” to communicate and remember, even if not accurate.

New labels will specifically note if drug is “compatible” with lactation.

But new labels will require more reading and time than the letter categories.

And for prescribed drugs only.
Resources

FDA. FDA issues final rule on changes to pregnancy and lactation information for prescription drug and biological products

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm425317.htm

FDA. Federal Register. Content and format of labeling for human and biological products: Requirements for pregnancy and lactation labeling.

In closing--

• Some thoughts about when to administer drugs

• AKA Chronobiology
Timing: ASA Administration & Pregnancy

Double Blind Randomized Placebo Controlled

341 women, 181 primigravida

6 possible groups
  - Placebo vs. ASA (100 mg)
  - Upon awakening, 8 hours after awakening, before bedtime

Daily use, starting at 12-16 weeks gestation

Investigated intervention in regard to”
  - Preeclampsia
  - Gestational hypertension
  - IUGR
  - Preterm Birth

Incidence of Complications
Awakening Time OR 8 hours later

No statistically significant difference between ASA and Placebo

Incidence of Complications
Bedtime Timing

Therefore---

Aspirin administered at bedtime decreased complications—but ASA during awakening did not—congruent with older studies.

And here is another study with similar results:

PREGNANCY & CHRONOBIOLOGY

- the proper nutrients
- the correct time
- optimal benefits
- healthy pregnancy
Studies in process include

• Prenatal vitamin timing
• Difference in medications in breast milk
• Chronobiology/chronotherapy and pharmacokinetics for oncology drugs too

• And don’t forget pharmacogenomics