Changes in Pharmacokinetics and Pharmacodynamics During Pregnancy

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Pharmacokinetics

“What the body does to the drug”

• Absorption
  – Bioavailability
    • Extent drug dose reaches the circulation unchanged

• Distribution
  • Plasma protein binding

• Metabolism
  • Termination of activity

• Elimination
Pharmacodynamics

“What the drug does to the body”

- To produce its specific biologic effects, a drug must be in appropriate concentrations at its sites of action.

- In **Phase I**: healthy volunteers
  - evaluate its safety
  - determine a safe dosage range
  - identify adverse effects doses (toxicology).

- **Phase II**: Effective (=pharmacology).

- **Phase III**: Compare to commonly used treatments.
History of Women in Clinical Trials

• Before 1993, the FDA excluded women from most clinical studies.
  – FDA guidelines
    • no women of **child-bearing potential** in Phase I and Phase II trials.

• Child bearing potential
  – any woman physiologically capable of becoming pregnant
    • regardless of sexual activity/practices and contraceptive use

• Argument for excluding women
  – Safety of the fetus if pregnancy were to occur during the trial.
  – Pregnant women, fetuses and neonates are a vulnerable population.
Thalidomide

- **1956**: a sedative prescribed in Germany for nausea and insomnia.
- **1960** Grunenthal applied to FDA for approval to sell thalidomide in U.S (rodents in pre-market studies).
- Frances Kelsey MD, PhD
  - first drug review case for FDA
    - rejected application 6 times
    - Interested in fetal safety- Had studied quinine in 1940s
      - Perhaps thalidomide could cross placenta? (rabbit study)
      - No data had been provided on human metabolism, PK
Thalidomide

• 1961: discovered that drug
  – Causes miscarriage
  – Stunts growth of fetal limbs
• 20,000 children affected
• 1962 FDA
  – Commission on Drug Safety founded
Patient Perception

• Pregnant women believe almost any drug is teratogenic.
  – Unnecessary anxiety
    • Survey: women exposed to acetaminophen and dental x-rays considered themselves to be at 24% risk (similar to thalidomide).

• Goal: focus on prevention of malformation in cases where women are exposed to known teratogens.
  – Evidence based counseling.
Obstetric Pharmacology

- Off-label drug use common
  - 50% pregnant women take at least one medication
    - 92% Prenatal Vitamins
    - 35% antibiotics
    - 8% opioids
- Most drugs used in pregnancy have no data on dosage and safety.
- NOT having accurate drug efficacy and safety data in pregnancy = higher risk than that associated with
  - women in clinical trials becoming pregnant and exposing the fetus to the trial drug.
Obstetric Pharmacology

- **1990**, the NIH directed that women and minorities be included in clinical trials.
  - “...the study of drugs used in pregnancy is one of the most neglected areas in the field of clinical pharmacology and drug research.”

- **1994** FDA created Office of Women’s Health (OWH)
  - Pendulum: moderate protectionism
    - Info on **HOW** to *include* vulnerable populations
    - Informed consent

- **2004** Obstetric-Fetal Pharmacology Research Unit (OPRU)
  - 4 Sites: UTMB, Magee, U Washington, Georgetown
  - Focus: to expand knowledge of pharmacology during pregnancy
    - Clearance for almost all drugs increases in pregnancy.
SEX DIFFERENCES

• Physiological factors
• Molecular factors
SEX DIFFERENCES

  • 9/10 were associated with greater ADRs in women over men.
    - QT prolongation
    - Hepatic toxicity
      • 2000 cases of liver failure/yr
        - ¾ are women.
• If these drugs had been evaluated in both men and women, there would have been an indication that sex differences exist.
SEX DIFFERENCES

• Physiological factors
  – The length of QT interval is androgen dependent, with QT intervals longer in women than men.
    • The longer the QT interval, the greater the likelihood of arrhythmia.
  – Generally lower
    • Body weight
    • Organ size
    • Glomerular filtration rate
  – Generally higher
    • Percentage of body fat (affects Vd: smaller for ethanol).
Pharmacokinetics
“What the body does to the drug”

Distribution-
Rate at which equilibrium between tissue and plasma concentration is achieved depends on:

- Drug’s ability to bind to proteins or tissues
- Drug lipid solubility
  - **Water soluble**
    - will cross cell membranes only if small molecular size
  - **Lipid soluble**
    - more likely to cross biological barriers
      - cell membranes
      - blood-brain barrier
      - placenta
Pharmacokinetics
“What the body does to the drug”

Metabolism-
Major determinant of drug clearance

• Drug solubility
  – Water soluble
    • Eliminated unchanged after glomerular filtration
  – Lipid-soluble
    • Series of Reactions to render drug more polar for excretion in bile or urine

• Phase I; CYP
  – responsible for inter-individual differences in drug pharmacokinetics.
    – Ethnicity
    – Gender
    – Pregnancy

• Phase II
Metabolism

• Phase I
  – Generate metabolites that are polar than the parent compound. Functional group added that can undergo phase II reaction.
  – Phase I reaction can lead to the formation of
    • Inactive metabolite
    • Prodrug $\rightarrow$ active form of drug
    • Toxic metabolites.

\[
\text{PHENYTOIN} \rightarrow \text{p-HPPH}
\]
Metabolism

• Phase II
  – Conjugation of parent molecule or phase I metabolite.
    • Glutathione

• Conjugates are more water-soluble and less active (less toxic) than nonconjugated compounds.
**Metabolism: Cytochrome P450**

- **Heme Protein**
  - Major player in oxidative metabolism.

- **Encoded by gene superfamily-hundred of genes.**

- **Substrates include**
  - Endobiotics- steroid hormones
  - Xenobiotics- inactivation of drugs
Metabolism: Cytochrome P450

- Liver
  - Hepatic microsomal enzymes (oxidation, conjugation)

- GI, lungs, kidneys
  - Extrahepatic microsomal enzymes (oxidation, conjugation)

- Hepatic non-microsomal enzymes
  (acetylation, sulfation, GSH, alcohol/aldehyde dehydrogenase, hydrolysis, ox/red)
Cytochrome P450

• Men seem to have higher activity relative to women for:
  – Cyp 1A
  – Cyp 2D
  – Cyp 2E

• Women have higher
  – Cyp 3A4 activity
    • Pregnancy increases further
Cytochrome P450

- Genetic Polymorphisms result in differences in gene expression.

- **CYP 2D6 Fast metabolizers**
  - activity increased (codeine metabolized to morphine)
  - Increased toxicity

**Case Study (Lancet 2006):** Healthy full term newborn died at 13 days from morphine poisoning.
- Mother with genetic polymorphism CYP2D6 (increased activity during pregnancy)
- Codeine was prescribed for episiotomy pain
- Breastfeeding
- Ultrarapid metabolizer
  - codeine to morphine
- Baby with extremely high blood morphine concentration

- **CYP 2D6 Poor metabolizers**
  - Activity decreased → No drug effect
  - Example= Fluoxetine (metabolized to an active compound)
    - increased dose of antidepressants needed to maintain efficacy in poor metabolizers

- Inducible expression (activity and level) by nongenetic factors
  - Dietary habits (grapefruit juice ↓ intestinal CYP3A4 → increased calcium channel blocker concentration)
  - Smoking (induces CYP1A2)
Pregnancy

Cardiovascular
Respiratory
Renal
GI
Endocrine
Blood
Skin
Weight Gain

• 2/3 of weight gain is total body water
- 40% -- fetal compartment
- 60% -- maternal compartment
• Total body water increases - up to 8 liters
• Plasma volume increases by 50%
• Maternal cardiac output increases by 30-50% during pregnancy (4.5 l/min → 6 l/min)
  – Enhances GFR/renal excretion of drugs
  – Example: atenolol clearance increases by 36%.
PK and Physiological Changes In Pregnancy

• **Ingestion**
  - **Compliance**
    - Fear that fetus may be harmed
    - Nausea, vomiting and heartburn

• **Absorption**
  - **Gastric**
    - Delayed gastric emptying
    - Gastric acid secretion is decreased by 40%
  - **Epidural space**
    - Greatly increased vascularity in epidural space
    - Demerol more rapidly absorbed

• **Distribution**
  - Decreased albumin concentration (hemodilution)

• **Metabolism**
  - Unpredictable (↑ CYP2D6, ↑CYP3A4, ↓CYP1A2)

• **Elimination**
  - 40% Increased renal blood flow,
    - Increased clearance of water-soluble drugs
    - Ex: ampicillin, lithium
Drug Effects of Pregnancy

- Caffeine increased concentration.
  - Water soluble
    - Vd increases, and concentration falls due to increased total body water
  - Metabolized by CYP1A2
    - Decreased during pregnancy

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Clearance</th>
<th>Half-Life</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>100%</td>
<td>5.3h</td>
</tr>
<tr>
<td>17</td>
<td>68%</td>
<td>9.9h</td>
</tr>
<tr>
<td>24</td>
<td>54%</td>
<td>12.6h</td>
</tr>
<tr>
<td>32</td>
<td>37%</td>
<td>10h</td>
</tr>
<tr>
<td>PP</td>
<td>100%</td>
<td>5.5h</td>
</tr>
</tbody>
</table>

- Pregnant women spontaneously reduce amt of caffeinated beverages they drink.
Principles of Teratology

- Teratogenic agent - potential to interfere with the normal functional/structural development of an embryo or fetus.
  - generally thought of as major congenital anomalies
  - also may increase risk for a spectrum of adverse pregnancy outcomes (abortion, minor structural anomalies, shortened gestational age, growth restriction, and behavioral or cognitive deficits)
- Anticonvulsants
- Antineoplastic agents
- inhibitors of angiotensinogen-angiotensin pathway
- Methylmercury
- Cocaine
- Alcohol
- Hyperthermia
- Tetracycline
- Warfarin
- Isotretinoin
1970s Wilson and Fraser, basic principles of teratology

- **species specificity**
  - thalidomide was not teratogenic in rodents

- **genetic susceptibility**
  - Polymorphisms

- **gestational timing**
  - Exposure during the formation of organ. eg, Carbamazepine (Tegretol), anticonvulsant linked to a 10-fold increased risk for neural tube defects (28 days after conception…no effect after 1st trimester).

- **dose response**
  - Higher doses cause higher frequency of defect

- **route of administration**
  - Isotretinoin (Accutane) taken orally→ potent human teratogen
  - topical retinoids →have not been associated with increased risk for adverse effects

- **spectrum of outcomes (eg, alcohol)**
  - depending on dose and timing in gestation, effects range from spontaneous abortion to major structural defects, prenatal or postnatal growth deficiency, preterm delivery and deficits in IQ

- **specific mechanisms leading to pathogenesis**
  - act on specific targets to produce a characteristic pattern of effects
    - increase the risk for neural tube defects via folate antagonism
Data on Exposures in Pregnancy

• For most exposures, reliable information is limited.

• Human safety data for US prescription medications over 20 years (Lo and Friedman)
  – There is insufficient data to rule out teratogenicity for more than 80% of drugs

• Clinical trials for prescription medications are not typically conducted in human pregnancy
  – Pharmaceutical industry has no incentive to do so.

• Animal reproductive and developmental toxicity studies are used to estimate the potential for human teratogenicity.
  – However, animal studies are not completely predictive of human pregnancy outcomes
    • Species sensitivity
    • Differences in dosing and exposure timing
Adverse Case Reports

• When new medications are marketed in the United States
  – initial reports of pregnancy exposures with adverse outcomes:
    • safety data provided to the FDA by manufacturers
    • case reports in the literature
    • voluntary reports by clinicians or patients.

• Weaknesses:
  – data sources lack information about the number of exposed pregnancies with normal outcomes
    • confuse the process of determining whether the adverse event reports represent an excess risk over the baseline for that event.
Pregnancy Registries

• Prospective collection of data re: exposures to a specific drug
  – Outcome of interest: major birth defects

• **Strengths**
  – potential for gathering *early* information about a new drug

• **Weaknesses:**
  – lack formal comparison groups (compared to background population)
  – typically have outcome data on **small numbers** of pregnancies.
  – Small sample sizes ➔ Only pick up dramatically increased birth defect rate

• Collaborative registry designs such as the **Antiepileptic Drugs in Pregnancy Registry** have demonstrated success in identifying signals or establishing higher than expected rates for major birth defects after selected exposures
Observational Cohort Studies

- Prospectively designed exposure cohort studies in which women with and without the exposure of interest are enrolled during pregnancy and followed to outcome.

  **Strengths:**
  - Goal of testing a specific hypothesis
  - Ability to evaluate a spectrum of outcomes, including major and minor malformations
  - Include a comparison group or groups, allowing for the control of key factors that may be confounders
    - Maternal age, socioeconomic status, and alcohol or tobacco use.

- Such a study design was successful identifying carbamazepine as a human teratogen.

  **Weakness:**
  - Small sample sizes ➔ Only pick up dramatically increased birth defect rate
Database Cohorts

• Historical cohort using archived information in existing databases.
  – For example, HMO claims data and records from government-supported healthcare agencies analyzed for information on pregnancies with or without specific medication exposures.

• **Strengths:**
  – cost savings for collecting data for a given number of pregnancies

• **Weaknesses:**
  – Database studies rely on information not collected primarily for research purposes
    • validation of exposure and outcome, as well as data on some key potential **confounders**, may be difficult or impossible to obtain.

• Database cohorts have been used to identify a possible link between paroxetine and congenital heart defects.
Case-Control Studies

- Pregnancies are retrospectively selected
  - specific outcome, such as a particular birth defect.
  - The frequency of exposure to an agent of interest among mothers of affected infants is compared with the frequency among mothers whose pregnancies did not result in that birth defect.

- **Strengths:**
  - With proper numbers of cases and controls,
    - provide sufficient power to detect increased risks for rare outcomes.
  - **Control group**: collects information on potential **confounding variables**
    - age, socioeconomic status, alcohol and tobacco use

- The case-control approach was used successfully to identify the association of misoprostol (used to induce abortion) with a very high risk for a rare congenital facial nerve paralysis, Möbius syndrome.

- **Weaknesses:**
  - Lag **time** inherent in collecting information on a new drug, especially if it is infrequently used by pregnant women
  - possible that women who are already aware of a negative outcome of their pregnancy may **recall** exposures more carefully (or incorrectly) than those who had a normal outcome.
Summary

• Drug disposition and response differs not only between men and women but also between pregnant and nonpregnant women.
  – More research is needed to understand how pregnancy alters the PK and PD of drugs

• Randomized trials to demonstrate efficacy
  • easier to demonstrate than safety
  – Birth defects
    • Background risk is 2-3% of population
    • To find specific birth defect that occurs at a rate of 1 in 1,000 or fewer,
      – to demonstrate drug does not produce a specific birth defect requires >100,000 pregnant women

• Evidence based counseling.
  – Preconception counseling ideal: understand and weigh the risks of complications of medical condition versus side effects of medications.
<table>
<thead>
<tr>
<th>Substance</th>
<th>Effects</th>
<th>Time Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Calvarial hypoplasia, renal dysgenesis, oligohydramnios, IUGR, and neonatal renal failure</td>
<td>second and third trimester</td>
</tr>
<tr>
<td>Alcohol</td>
<td>growth restriction, microcephaly, craniofacial dysmorphology (1–4/1000 live births); renal, cardiac, and other major malformations</td>
<td>late pregnancy use is associated with IUGR and developmental delay; incidence is 4–44% among “heavy drinkers” chronic daily ingestion of at least 2 grams alcohol/kg (8 drinks per day).</td>
</tr>
<tr>
<td>Antidepressants (SSRIs)</td>
<td>Possible cardiac defects, NTDs, omphalocele; neonatal pulmonary hypertension and withdrawal syndrome</td>
<td></td>
</tr>
<tr>
<td>Aminopterin, methotrexate</td>
<td>calvarial hypoplasia, craniofacial abnormalities, limb defects; possible developmental delay</td>
<td>Syndrome associated with methotrexate &gt;10 mg/wk</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>NTDs (1%); possible facial hypoplasia and developmental delay</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Cleft lip/palate increased threefold to sixfold; IUGR increased with high doses</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>Ebstein cardiac anomaly</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>IUGR, microcephaly, facial hypoplasia, hypertelorism, prominent upper lip (10%); possible developmental delay</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>Hearing loss, eighth nerve damage</td>
<td></td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Discoloration of deciduous teeth and enamel hypoplasia</td>
<td></td>
</tr>
<tr>
<td>Tobacco</td>
<td>Oral clefts: relative risk, 1.22–1.34; IUGR, IUFD, abruption</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>NTDs (1–2%); facial hypoplasia, possible developmental delay</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>nasal hypoplasia, stippled epiphyses, growth restriction (6%); also increased microcephaly, Dandy-Walker syndrome, IUGR, preterm birth, mental retardation</td>
<td>Greatest risk is at 6–9 wk</td>
</tr>
</tbody>
</table>
Resource

- http://www.otispregnancy.org/hm/
  - 866-626-6847
- www.reprotox.org
- www.FDA.gov
- www.CDC.gov