Pharmacokinetics and Drug Therapy in Pregnancy and Lactation

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In the late 1990s the FDA & NIH convened a series of conferences to discuss medication usage in pregnancy.

Pregnancy = special population

What is a special population?

Any group of people who share a common change in physiology that alters the pharmacokinetics sufficiently to require dosing modifications compared to healthy, young adults:

- Renal disease
- Hepatic disease
- Geriatric adults
- Pediatrics
Therapeutic Range - Efficacy

- Concentration
- Duration of action
- Therapeutic Range
- MTC
- MEC
- AUC
- Onset time
- $t_{\text{max}}$
Minimum Effective Concentration

- Non-pregnant AUC
- Pregnant AUC
Overview

- Review the changes in estradiol and progesterone that occur in pregnancy
- Discuss pharmacokinetics in pregnant women using representative medications
  - Heparins: volume of distribution, CO & renal clearance
  - Penicillins: renal clearance & drug transporters
  - Digoxin: placental drug transporters
  - Blood flow & protein binding
  - Phase II Glucuronidation - Lamotrigine & labetalol
  - Phase I metabolism – CYP1A2, 3A4, 2D6, 2C19 & 2C9
  - Drug transfer in lactation
# Endocrine Changes in Pregnancy

## Progesterone Production

<table>
<thead>
<tr>
<th>Phase</th>
<th>Site</th>
<th>Production</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular Phase</td>
<td>Ovary</td>
<td>2.5 mg/day</td>
<td>-</td>
</tr>
<tr>
<td>Luteal Phase</td>
<td>Ovary</td>
<td>25 mg/day</td>
<td>30-40 ng/mL</td>
</tr>
<tr>
<td>Term Pregnancy</td>
<td>Placenta</td>
<td>250 mg/day</td>
<td>130-150 ng/mL</td>
</tr>
</tbody>
</table>
Endocrine Changes in Pregnancy

![Graph showing changes in progesterone levels during pregnancy.](image)
Endocrine Changes in Pregnancy

Maternal Plasma Progesterone

ng/mL
200
150
100
50

Weeks of pregnancy
6  8  10  12  14  16  18  20  22  24  26  28  30  32  34  36  38  40  42
Endocrine Changes in Pregnancy

Pre-pregnancy estradiol
0.05ng/mL = 50pg/mL

Estradiol at term
25ng/mL = 25,000pg/mL
Women who require anticoagulation are switched from warfarin to heparins (UFH or LMWH) as soon as or just before she becomes pregnant. WHY?

Warfarin crosses the placenta and is a known major teratogen:

- 5-30% of exposed 1st trimester fetuses can be affected
- Fetal Warfarin Syndrome (1st trimester exposure): hypoplasia of the nasal bridge, multiple bone and limb abnormalities, hydrocephalus, agenesis of the corpus callosum, mental retardation, cleft lip and palate, and growth retardation
- Exposure during 2nd & 3rd trimesters: CNS disorders, spasticity & seizures, and eye defects
Low Molecular Weight Heparins

- *Why is the fetus not anti-coagulated when the mother is on heparin?*
- Molecules > 1000 Daltons do not easily cross the placenta
- Unfractionated heparin chains: 5000 to >40,000 Da
- Even LMWHs are too large
  - LMWHs have mass of 3600-9000 Da
Low Molecular Weight Heparins

- LMWHs are preferred in pregnancy (vs UFH)
  - Longer half-lives
  - Decreased dosing frequency
  - More predictable anticoagulant effect
  - Decreased risk of bleeding
  - Decreased need to frequently monitor coagulation parameters
  - Reduced risk of heparin-induced thrombocytopenia
Low Molecular Weight Heparins

- Anticoagulation in pregnancy
  - Estrogen increases production of multiple hepatic clotting factors
  - Risk of clotting abnormalities increases in pregnancy
  - Therapeutic index for LMWHs is narrow
  - Dosing requirements have to precisely change coagulation

- What happens to LMWH pharmacokinetics in pregnancy? How does maternal physiology change how we dose LMWHs?
  - Volume of Distribution
  - Clearance
Volume of Distribution:
- The Vd of LMWHs = ~ plasma volume
- *What happens to LMWH Vd in pregnancy?*

Increase in plasma volume:
- About 1200 - 1600 mL above the nonpregnant state, or ~ 40% greater
- Increase begins at 6 - 8 weeks’ gestation
- Increase peaks at ~ 32 weeks’ gestation
- Increase in plasma volume is related to fetal number: PV increase in triplets is almost double that in singletons
- Increase in RBC volume < blood volume: dilutional anemia
Plasma Volume Expansion

![Graph showing changes in plasma volume, total blood volume, cardiac output, and RBC volume over weeks of gestation and postpartum.](image)

- Plasma volume
- Total blood volume
- Cardiac output
- RBC Volume

Non-pregnant

Weeks of gestation

Delivery

6 months postpartum

% change

-10 0 10 20 30 40 50
<table>
<thead>
<tr>
<th>WEIGHT</th>
<th>PLASMA VOLUME</th>
<th>ECF SPACE</th>
<th>TBW</th>
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<tbody>
<tr>
<td>(kg)</td>
<td>(mL/kg)</td>
<td>(L/kg)</td>
<td>(L/kg)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NONPREGNANT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 70</td>
<td>0.189</td>
<td>0.516</td>
<td></td>
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<tr>
<td>70 – 80</td>
<td>0.156</td>
<td>0.415</td>
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<tr>
<td>&gt; 80</td>
<td>0.151</td>
<td>0.389</td>
<td></td>
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<tr>
<td></td>
<td>49</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| PREGNANT |       |           |      |
| < 70     | 0.257  | 0.572     |      |
| 70 – 80  | 0.255  | 0.514     |      |
| >80      | 0.240  | 0.454     |      |
|          | (↑37%)  |           |      |

LMWH Clearance in Pregnancy

- LMWH clearance:
  - Hepatic desulfation and depolymerization
  - Renal Clearance

- What happens to LMWH renal clearance in pregnancy?

- GFR is proportionate to cardiac output

- Cardiac output increases by 30 – 50%
  - Increase in CO begins as early as 5 weeks
  - 50% of the increase occurs by 8 weeks
  - CO peaks at about 32 weeks

- CO = Heart Rate x Stroke Volume
  - Both HR and SV increase in pregnancy

- Renal blood flow increases in pregnancy → GFR goes up
GFR during Pregnancy and Postpartum

Pregnant  Postpartum

Based on this knowledge what can we predict will happen to LMWHs in pregnancy?

- Volume of Distribution increases
  - For the same dose, the concentration will be lower in pregnant women

- LMWH renal clearance increases
  - LMWH concentrations and anticoagulant effect may not be sustained for the full dosing interval
LMWHs in Pregnancy

- Monitor anti-Factor Xa levels and adjust dose:
  - Treatment regimens: evaluate q 2-4 wks
    Peak levels: drawn 3-4 h after dose
    Periodically monitor trough to ensure adequate coverage
    Dose twice daily especially after 20 wks
    Treatment goals: peak 0.5 - 1.2
    trough 0.2 - 0.4 IU/mL

  - Prophylaxis: evaluate q trimester
    Prophylaxis goals: peak 0.2 - 0.4
    trough 0.1 - 0.3 IU/mL
LMWHs in Pregnancy

- Anticipate need to escalate dose

  - *Barbour 2004* 13 pregnancies on therapeutic dalteparin with initial dose 100 IU/Kg BID

    - 85% required one or more upward dose titrations
    - By 30 wks, 50% of women required dalteparin 140 IU/Kg BID to maintain therapeutic anti-Factor Xa levels
    - Trough levels were in the therapeutic range only 9% of the time, despite maintenance of therapeutic peak levels.
Intrapartum Management

- In anticipation of labor (≥36wks) change to UFH
  - LMWHs have longer half-lives than UFH
  - Increased risk of bleeding with epidural and cesarean section
  - Anticoagulant effects of UFH more easily reversed with protamine sulfate
- UFH can be stopped 3-6h prior to cesarean or epidural
- Restart LMWHs 6-12 h after vaginal delivery & 12-24 h after cesarean section
- Anticipate need to decrease dose as renal clearance normalizes
A pregnant woman with a URI caused by ampicillin sensitive *H. influenzae* was treated with oral ampicillin 0.5 gm qid. She failed to respond and an ampicillin level was reported as “undetectable”.

She was cured when ampicillin was given intramuscularly in the same dosage.

*Philipson A. J Inf Dis 1977;136:370-6. (Karolinska Institute)*
### Oral Ampicillin PK in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>$C_{\text{max}}$ (µg/ml)</th>
<th>AUC IV (cm$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>2.2 ± 1.0 *</td>
<td>18.6 ± 5.9 *</td>
</tr>
<tr>
<td>Nonpregnancy</td>
<td>3.7 ± 1.5</td>
<td>28.3 ± 10.2</td>
</tr>
</tbody>
</table>

* $P < 0.001$

## Cefuroxime in Pregnancy

<table>
<thead>
<tr>
<th></th>
<th>$V_d$ (L)</th>
<th>$Cl$ (ml/min)</th>
<th>$T_{1/2}$ (min)</th>
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</thead>
<tbody>
<tr>
<td>Pregnant</td>
<td>17.8 ± 1.9</td>
<td>282 ± 34 *</td>
<td>44 ± 5 *</td>
</tr>
<tr>
<td>At Delivery</td>
<td>19.3 ± 3.1</td>
<td>259 ± 35 *</td>
<td>52 ± 10</td>
</tr>
<tr>
<td>Postpartum</td>
<td>16.3 ± 2.1</td>
<td>198 ± 27</td>
<td>58 ± 8</td>
</tr>
</tbody>
</table>

* $p < 0.05$ in comparison to PP

Amoxicillin in Pregnancy

- **AUC (mcg·hr/mL)**
  - 2\textsuperscript{nd} trim: 15.2 ± 5.6
    - $P = 0.02$
  - 3\textsuperscript{rd} trim: 14.9 ± 2.8
    - $P = 0.003$
  - PP: 20.4 ± 6.6

Amoxicillin in Pregnancy

- **Amoxicillin Elimination Half-life (h)**
  - 2\textsuperscript{nd} trim: 1.2 ± 0.5 (P=0.05)
  - 3\textsuperscript{rd} trim: 1.3 ± 0.2 (P=0.01)
  - PP: 1.6 ± 0.2

- **Amoxicillin Renal Clearance (L/h/kg) \(\propto\) CrCl**
  - 2\textsuperscript{nd} trim: 0.36 ± 0.11 (P < 0.001)
  - 3\textsuperscript{rd} trim: 0.31 ± 0.05 (P = 0.001)
  - PP: 0.22 ± 0.05

- **Amoxicillin Renal Net Secretion Cl (mL/min/kg)**
  - 2\textsuperscript{nd} trim: 4.1 ± 1.7 (P=0.002)
  - 3\textsuperscript{rd} trim: 3.4 ± 0.7 (P=0.005)
  - PP: 2.5 ± 0.8

Andrew MA et al, 2007
Renal Net Secretion of Amoxicillin

Renal afferent vessel → Renal Tubule Cell

Organic Anion Transporting Polypeptide (OATP??) → Peptide transporter (PEPT1)

Progesterone decreases transcription of PEPT1 by unknown mechanisms (Watanabe 2006)

Renal afferent vessel → Urine

Renal Tubule Cell → Urine

OAT?? → PEPT2

Peptide transporter
Penicillins in Pregnancy

- **Andrew 2007:**
  Anthrax prophylaxis: after ciprofloxacin, switch to amoxicillin 500 mg po tid; however, trough levels may not be sufficient to adequately treat some strains of Anthrax with higher MICs.

- For most infections, penicillins and cephalosporins are dosed well above the necessary MIC. However, because efficacy requires free drug concentration above the MIC for 60-70% of the dosing interval, prescribing at the upper dosing range and shorter dosing frequency is recommended in pregnancy.
Cephalosporins in Pregnancy

- Cephalosporin Prophylaxis for Cesarean Delivery
  - Elkomy M et al (2014)
    - PK study in 20 women undergoing cesarean section
    - Cefazolin Clearance increased by 74% in pregnancy (CL liters/h, pregnancy 7.18 vs 4.12 post-pregnancy)
    - Cord blood concentration-to-maternal concentration ratio: 0.41 (range, 0.21 to 1.45)
    - Computer simulation showed that the probability of maintaining free cefazolin conc above 8mg/L was <50% in cord blood when <2g or when it was give <1h prior to OR.
    - Recommendations: Cefazolin 2 gm IVPB at 1 h prior to OR
Cephalosporins in Pregnancy

- Cephalosporin Prophylaxis for Cesarean Delivery in Obese Patients
  - Pevzner et al (2011)
    - 29 women undergoing cesarean section
      - BMI categories
        - Lean: BMI < 30
        - Overweight: BMI 25 – 29.9
        - Obese: BMI 30 – 39.9
        - Extremely Obese: > 40
      - 2 gm cefazolin IV between 30-60 min prior to incision
      - Sampled:
        - Adipose tissue at beginning & end of CS
        - Myometrium at time of delivery
        - Maternal blood at end of CS
      - Cefazolin theoretic breakpoint for resistance: 4 mcg/g
Cephalosporins in Pregnancy

- Cephalosporin Prophylaxis for Cesarean Delivery in Obese Patients
  - Cefazolin concentration in adipose tissue at skin incision (p<0.001)
    - lean women: $9.4 \pm 2.7$ mcg/g
    - obese women: $6.4 \pm 2.3$ mcg/g
    - extremely obese women: $4.4 \pm 1.2$ mcg/g
  - At incision, 20% of the obese & 33.3% of the extremely obese women had cefazolin adipose concentrations < 4mcg/g
  - At closure, all lean women had therapeutic adipose concentrations; but 20% of the obese & 44.5% of the extremely obese women had cefazolin adipose concentrations < 4mcg/g
  - Conclusion: 2 g cefazolin dose is inadequate in obese women
Cephalosporins in Pregnancy

- Cephalosporin Prophylaxis Guidelines 2013
  American Society of Health System Pharmacists
  Infectious Diseases Society of America
  Surgical Infection Society
  Society for Healthcare Epidemiology of America

- Recommendations
  - 2 g for women < 120 kg
  - 3 g for women ≥ 120 kg
Fetal tachyarrhythmias occur in ~ 0.5% of pregnancies
Digoxin in Pregnancy

- If untreated and present for an extended period, fetal SVT can lead to fetal cardiac failure, hydrops, and fetal or neonatal demise.

- Digoxin is the primary initial therapy
  - Slows AV transmission and decreases ventricular rate

- Treating the mom with goal of treating the infant.
Digoxin in Pregnancy

- Very difficult to get therapeutic levels of digoxin in the fetus
  - Umbilical cord digoxin 0.4 ng/mL vs maternal digoxin 3.6 ng/mL
    \((King \ 1984)\)
  - Fetal (umbilical cord) / Maternal levels: 0.1 to 0.9 with ratios frequently < 0.5
    \((Syme \ 2004)\)
- Why are fetal levels so disproportionately low?
Initially when it was discovered that the placenta was rich in CYP enzymes, it was presumed that they were there to protect the fetus by metabolizing potential maternal drug exposure.

Subsequently learned that the vast majority of the CYP 450 enzymes present are involved in placental steroid production.

Drug metabolizing CYPs (families 1, 2 & 4) are only minimally present.

Therefore: Digoxin is NOT being metabolized by the placenta.

However, there are multiple drug efflux and influx transporters that play critical roles in moving molecules in to or away from the fetus.
P-glycoprotein (Pgp)

- MDR1 gene (multi-drug resistance)
- ATP binding cassette transporter – efflux transporter
- Transports chemicals back “out” to the other side
- Binds to a large number of different drugs including digoxin
- Location: intestinal mucosa, liver, kidney, blood-brain barrier, PLACENTA: apical brush border – maternal facing
- Two-fold decline in expression between late first trimester and term
Placental Transport Systems

- Multidrug resistance-associated proteins (MRP-1, MRP-3, MRP-5)
- Multidrug resistance protein (MDR-3)
- Organic cation transporters
- Organic anion transporters

Fetal Circulation

- Organic cation transporters

Maternal Circulation

- P-glycoprotein (Pgp)
- Breast Cancer Resistance Protein (BCRP)
- Multidrug resistance-associated proteins (MRP-2 & MRP-3)
- Organic cation transporter (OCT)
- Serotonin transporter (SERT)
- Noradrenalin transporter (NET)
- Organic anion transporting peptide (OATP)
- Organic cation transporter (OCT)
Maternal Digoxin in Pregnancy

- 28-32 weeks vs 6-10 weeks postpartum
  Digoxin 0.25 mg po (Hebert, M 2008)
  - $\text{AUC}_{0\rightarrow48}$ 7.3 ± 1.6 vs 9.3 ± 2.2 ng*h/mL  P<0.006
    19% lower in pregnancy
  - $\text{Cl}_{\text{renal}}$ 181 ± 25 vs 115 ± 25 mL/min  P<0.002
    60% greater in pregnancy
    Good correlation between CrCl and digoxin renal clearance (r=0.8)
  - $\text{Cl}_{\text{secretion}}$ 73 ± 22 vs 37 ± 14 mL/min  P<0.002
    120% greater in pregnancy
  - $f_u$ 67 ± 4 vs 63 ± 5 %  P<0.002
    5.8% greater in pregnancy
Renal Secretion of Digoxin

Renal afferent vessel → Renal Tubule Cell → Urine

- Organic Anion Transporting Polypeptide (OATP)
- P-glycoprotein (Pgp)
Digoxin dosing in pregnancy pearls:

- Don’t be surprised by the high dosing requirements in pregnancy: usually greater than non-pregnant expectations for both maternal and fetal indications
- Mom can become dig-toxic trying to get adequate fetal levels
- May need to either directly treat the fetus with digoxin intramuscularly into the fetal thigh or intracordally (increased fetal risk) or add second drug: flecainide, sotalol, amiodarone
Regional Blood Flow Changes

- Increase in blood flow to uterus - 20% of CO
  • Low resistance arteriovenous shunt
  • Reduces cardiac afterload
- Increase in renal blood flow
- Increase in skin blood flow
- Increase in mammary blood flow
- Decrease in skeletal muscle blood flow
- Decrease in splanchnic blood flow
- Mixed results: hepatic blood flow changes
Hepatic Blood Flow in Pregnancy

Although % CO to liver changes, the absolute blood flow remains the same.

Robson SC 1990
What happens to albumin concentration in pregnancy?

P = total protein   A = albumin   * p < 0.05 compared with PP

Plasma Proteins in Pregnancy

- Mean Albumin concentrations
  - 2nd Trimester: 3.6 gm/dL
  - Nonpregnant: 4.2 gm/dL
  - Albumin concentrations continue to decrease during the 2nd trimester until term when they are 70-80% of normal values. (Dean M, et al 1980)

- Minimal change in total protein
  (except in pre-eclampsia, nephrotic syndrome)

- α₁-acid glycoprotein: 52% lower at 30-36 wks vs postpartum (may affect betamethasone, bupivacaine, lidocaine, lopinavir)

- Drugs with narrow TIs that are highly protein bound: monitor free fraction, NOT total drug
Lamotrigine (LTG) approved mid 1990s for:
- Partial & absence seizures
- Primary generalized seizures
- Mood stabilizer: bipolar disorders
Lamotrigine

- **Tomson 1997** Karolinska Institute
  Plasma LTG decreased as pregnancy progressed:
  Dose / plasma conc: 3.6 times higher 3rd trimester
  5.8 times higher at delivery
  compared with 5 mo postpartum
  Suggesting enhanced clearance of LTG during pregnancy

- **Fotopoulou 2009:**
  Mean increase in LTG clearance in pregnancy
  - 2nd trimester: 236%
  - 3rd trimester: 248%
  Mean increase in dosing to maintain pre-LTG levels: 250%
  CI of LTG back to pre-pregnancy rates by 3 wks postpartum
Lamotrigine

- Lamotrigine levels similarly affected by birth control pills
  - LTG levels can be reduced by >50%

- Sabers 2003:
  - Mean steady state lamotrigine plasma concentration:
    - 30 women not on COC: 28 µmol/L
    - 22 women on COC: 13 µmol/L  \( p < 0.0001 \)

- Reimers 2005:
  - LTG concentrations w/ identical LTG doses (mean ± SD)
    - COC: combined oral contraception  POP: progestin-only pills
    - LTG controls:  5.6 ± 3.1 mg/L
    - LTG POP:  5.4 ± 2.1 mg/L
    - LTG COC:  2.0 ± 1.3 mg/L  \( p < 0.001 \)
Lamotrigine

- How does estradiol affect lamotrigine clearance?
- How is lamotrigine cleared?

- Phase II hepatic metabolism
  Conjugated via N-glucuronidation
  Renal clearance
Overview of Drug Metabolism

- Phase I and Phase II Hepatic Metabolism

Phase I = chemical modification  
Phase II = biotransformation

Phase I: Conversion into potentially less toxic metabolites

Phase II: Addition of moieties that make the drug more water soluble to facilitate renal clearance: sugars, sulfates, amino acids
Phase II Hepatic Metabolism

- Multiple conjugation reactions
  - Glucuronidation – major pathway
    - O-, N-, and S-
  - Sulfation
  - Acetylation
  - Methylation
  - Amino acid conjugation – glycine, taurine, glutathione
- Catalyzed by different enzymes

- UGT: uridine 5’-diphosphate glucuronosyltransferase
  UGT – 2 subfamilies, 2 chromosomes with at least 20 isoforms
Estradiol & Glucuronidation

- Estradiol is a potent inducer of glucuronidation UGT 1A family
  1A4 and to a lesser extent 1A3
  Chen 2009: Estradiol upregulates mRNA UGT1A4
- Estrogens increase clearance of LTG via induction of UGT 1A4
How quickly does the estradiol effect go away?

- Fotopoulou 2009:
  Cl of LTG back to pre-pregnancy rates by 3 wks postpartum

- Sidhu 2006
  16 women, 2 COC cycles with & without LTG
  COC: EE 30 µg / LNG 150 µg
  LTG 300 mg qd
  Trough LTG on 3rd, 5th & 7th days of placebo
  LTG levels 27%, 63% & 116% higher, respectively
  compared when on COCs

- Because induction of UGT1A4 by EE quickly falls, women can become lamotrigine-toxic by end placebo week
- After delivery lamotrigine levels will rise as glucuronidation goes back to normal
Monitoring Lamotrigine in Pregnancy

- Establish effective pre-pregnancy LTG level
- Monitor levels every 4 weeks at the same time relative to dosing & adjust LTG dose prn
- Anticipate significant increase in dosing requirements
  - pre-pregnancy LTG 150 mg BID →
  - 3rd trimester 400 mg BID
- Begin taper down by postpartum hospital discharge with goal of returning to prepregnancy dosing by about 3 weeks’ postpartum
Labetalol in Pregnancy

- Labetalol Vd not changed in pregnancy
- Phase II metabolism via glucuronidation predominantly UGT1A1 & UGT2B7 to inactive metabolites
- Rogers 1990
  - Labetalol elimination half-life shorter in pregnancy:
    Historic nonpregnant controls: 6 – 8 h
    Pregnancy: 1.7 h
  - Recommendations:
    - Monitor trough BPs to ensure BP control
    - Dosing interval may need to be shortened from q 12h to 8h
Overview of Drug Metabolism

- Phase I and Phase II Hepatic Metabolism

  **Phase I** = chemical modification  
  **Phase II** = biotransformation

**Phase I**: Conversion into potentially less toxic metabolites  
oxidation, reduction, hydroxylation, cyclization & decyclization

**Phase II**: Addition of moieties that make the drug more water soluble to facilitate renal clearance: sugars, sulfates, amino acids
12 Families – based on amino acid homology

Drug metabolism - CYP 1, 2 & 3 families

Subfamilies A, B, C – based on homology with an additional number if more than one subfamily
1A1 & 1A2, 2C9 & 2C19, 3A4 & 5, 3A7 (fetal)

Redundancy:
- More than one enzyme catalyzes same reaction
- Some drugs are metabolized by one enzyme
- Some drugs metabolized by multiple enzymes

Pregnancy can affect the various CYP enzymes differently
Phase I Metabolism & Pregnancy

- **Tracy 2005**
  3 stages of pregnancy (14-18wks, 24-28wks, 36-40 wks)
  vs 6-8 wks postpartum
  probe medications for specific CYP activity
  CYP1A2: salivary caffeine clearance:
  CYP2D6: dextromethorphan O-demethylation
  CYP3A: dextromethorphan N-demethylation

- **CYP1A2**: progressively decreases across pregnancy
  • -32.8% +/- 22.8%, -48.1% +/- 27%, -65.2% +/- 15.3%

- **CYP2D6**: increases sequentially across pregnancy
  • 25.6% +/- 58.3%, 34.8% +/- 41.4%, 47.8% +/- 24.7%
  • Excluded from analysis: CYP2D6 poor metabolizers

- **CYP3A**: increased at all pregnancy stages by 35-38%
Caffeine Clearance during Pregnancy and Postpartum

CYP1A2 activity: theophylline, ropivacaine, lidocaine, ondansetron, olanzapine, clozapine

CYP3A

- CYP3A family: metabolizes more than 50% of medications
e.g.: alprazolam, amiodarone, amlodipine, amprenavir, buspirone, carbamazepine, cisapride, citalopram, cyclosporine, diltiazem, efavirenz, erythromycin, estrogens, felodipine, fentanyl, fluconazole, indinavir, itraconazole, ketoconazole, lidocaine, loratidine, methadone, metronidazole, midazolam, nelfinavir, nicardipine, nifedipine, omeprazole, phenobarbital, prednisolone, progesterone, quetiapine, rifampin, sirolimus, statins, tacrolimus, testosterone, trazadone, R-warfarin, zolpidem
CYP3A Activity in Pregnancy

- Hebert MF 2008
  Midazolam (probe marker for CYP3A activity)
  3rd trimester vs 6-10 wks postpartum
  - 1’OH-mid Cl\text{formation} increases by 124±63% (P=0.002)
  - AUC decreases by 46±26% (P=<0.002)
  - C\text{max} decreases by 28±32% (P=0.01)
  - Apparent oral Cl increases by 108±62% (P=0.002)
CYP3A & Midazolam

Average midazolam plasma concentration–time profiles

Hebert MF 2008
CYP3A Activity in Pregnancy

- **Indinavir:**
  - Protease inhibitor, anti-retroviral therapy
  - Metabolized by CYP3A4/5

- **Unadkat JD 2007**
  - 16 HIV+ pregnant women 14 - 28 wks’ gestation INV PK
  - Compared to same women 12 wks postpartum
  - Indinavir 800 mg tid (+ zidovudine & lamivudine)

- Mean AUC: approximately 3-fold lower in pregnancy

- Cord IDV plasma concentrations – evaluated in 8 mother/infant pairs
  - below the assay limit of quantification: for 6
  - no detectable peak: 1
  - concentration of 39.9 ng/mL: 1
CYP3A Activity in Pregnancy

- Indinavir mean AUC pregnancy vs postpartum

Unadkat JD 2007
CYP2D6

- CYP2D6: 2\textsuperscript{nd} most active CYP enzyme \(~20\%\) of drugs

\textit{eg:}
Amitriptyline, clomipramine, codeine, dextromethorphan, doxepin, flecainide, fluoxetine, fluvoxamine, haloperidol, hydrocodone, imipramine, metoprolol, nortriptyline, paroxetine, promethazine, propranolol, resperidone, venlafaxine, tamoxifen
CYP2D6 Genotype & Phenotype

<table>
<thead>
<tr>
<th>Metabolic Phenotype</th>
<th>Genotype</th>
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<tbody>
<tr>
<td>Poor metabolizer</td>
<td>No functional gene</td>
</tr>
<tr>
<td>Intermediate metabolizer</td>
<td>One active gene</td>
</tr>
<tr>
<td>Extensive metabolizer</td>
<td>Two active genes (&quot;normal&quot;)</td>
</tr>
<tr>
<td>Ultra Rapid metabolizer</td>
<td>Multiple copies of an active gene</td>
</tr>
</tbody>
</table>

- Genetically determined polymorphisms
- Activity can vary 1000-fold
CYP2D6 Allelic Activity & Ethnicity

<table>
<thead>
<tr>
<th>Allele</th>
<th>CYP2D6 activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP2D6*1</td>
<td>normal</td>
</tr>
<tr>
<td>CYP2D6*2</td>
<td>increased</td>
</tr>
<tr>
<td>CYP2D6*3</td>
<td>none</td>
</tr>
<tr>
<td>CYP2D6*4</td>
<td>none</td>
</tr>
<tr>
<td>CYP2D6*5</td>
<td>none</td>
</tr>
<tr>
<td>CYP2D6*9</td>
<td>decreased</td>
</tr>
<tr>
<td>CYP2D6*10</td>
<td>decreased</td>
</tr>
<tr>
<td>CYP2D6*17</td>
<td>decreased</td>
</tr>
</tbody>
</table>

- Caucasians 5-10% PM
- 20-25% carry CYP2D6*4
- CYP2D6*4: absent in Africans, Asians, & South Americans
- CYP2D6*10: 50% Asians partial function
- CYP2D6*17: 30% Africans partial function
- UltraRapid Metabolizers: Caucasians 1-5%
- Arabian, East Africans, Pacific populations: 10-50%
CYP2D6: dextromethorphan O-demethylation

Wadelius M 1997
17 pregnant women phenotyped for CYP2D6 & 7-11 weeks postpartum
4 poor, 7 heterozygous extensive & 6 extensive
Dextromethorphan/dextrorphan metabolic ratio

Ratio significantly reduced = increased CYP2D6 activity:
- Homozygous & heterozygous extensive metabolizers
  mean decrease 53% (P=0.0015)
- Homozygous extensive metabolizers
  mean decrease 29% (P=0.028)
- Heterozygous extensive metabolizers
  mean decrease 63% (P=0.018)

Ratio increased in poor metabolizers = decreased activity
- Homozygous poor metabolizers
  mean increase 63% (P not calculated in 4 subjects)
Metoprolol Clearance – CYP2D6

- Metoprolol – known CYP2D6 substrate
  
  *Hogstedt, S 1985*
  
  5 women with HTN
  
  metoprolol 10mg IV, then 100mg po 3 d later
  
  3rd trimester vs. 3-6 mos postpartum, 24-h PK studies

  - Bioavailability: 0.21±0.06 in pregnancy vs 0.42±0.05 postpartum
  - V_d minimally higher in pregnancy (not significantly)
  - C_max 1.8 to 8.4 times lower during pregnancy
  - AUCs 1.9 to 12.8 times lower during pregnancy
  - Apparent oral clearance 4 times higher during pregnancy
  - Mean Cl_{iv} decreased by 55 ± 12% postpartum (26 – 97%) p<0.05
CYP2C19

- CYP2C19
  - eg:
    Amitriptyline, chloramphenicol, citalopram, clomipramine, clopidogrel, cyclophosphamide, diazepam, escitalopram, esomeprazole, gliclazide, hexobarbital, imipramine, indomethacin, lansoprazole, mephenytoin, nelfinavir, omeprazole, pantoprazole, phenytoin, phenobarbital, proguanil, propranolol, sertraline, valproic acid, warfarin
  - Proguanil to cycloguanil ratio: probe for CYP2C19 activity

- Some controversy re: role of other CYPs (3A4) in its metabolism
CYP2C19

- CYP2C19 polymorphisms
  - Two primary & several minor alleles with a single nucleotide mutation have been identified that are either nonfunctional or with significantly decreased activity plus one allele with increased activity
  - Homozygous or 2 non-functional alleles: poor metabolizer
  - Heterozygous with wildtype: intermediate metabolizer
  - Homozygous wildtype CYP2C19: extensive metabolizer
  - Ethnic variation of Poor Metabolizers:
    - Caucasians: 0.9 - 7.7%
    - Mexican Americans: 3.2%
    - African Americans: 1 - 7.5%
    - Asians: (Japanese) 13 - 24%
    - Micronesia: 38 - 79%
CYP2C19 Activity in Pregnancy

- Proguanil in pregnancy
  *Wangboonskul J 1993*
  10 women during 3rd trimester
  4 also studied 2 months postpartum
  Mean proguanil /cycloguanil AUC ratios
  Proguanil /cycloguanil ratio (higher ratio=decreased activity)
  - 3rd trimester: 16.7
  - 2 mo postpartum: 7.8
  - CYP2C19 activity is decreased during pregnancy
CYP2C9

- CYP2C9 – metabolizes about 10% drugs
  - Eg:
    - Amitriptyline, celecoxib, diclofenac, flubiprofen, fluoxetine, fluvastatin, glipizide, glyburide, ibuprofen, losartan, meloxicam, naproxen, omeprazole, phenytoin, piroxicam, sulfamethoxazole, tamoxifen, tolbutamide, torsemide, valproic acid, voriconazole, S-warfarin

- At least 42 SNP polymorphisms identified
  - CYP2C9*2 & CYP2C9*3 most common; others very low frequency
  - CYP2C9*2 & CYP2C9*3 reduce activity, but varies with different drugs
  - Non-wild type alleles most common in Caucasians (& Spanish & Turks) very infrequent in Asians & African Americans

- CYP2C9 activity increases in pregnancy
CYP2C9 Activity & Pregnancy

- **Glyburide**
  Predominantly metabolized by CYP2C9 with some contribution from CYP3A4 & CYP2C19

*Hebert MF 2009*

- Glyburide concentrations 50% of non-pregnant at same dose
- Gestational increase in apparent oral clearance of free glyburide
- Gestational increase of formation clearance of OH-metabolite >2X
- Anticipate need for higher doses of glyburide in pregnancy
Pharmacokinetics in Pregnancy

- Net effect of pregnancy changes not always predictable

- \( t_{1/2} = \ln 2 \times \frac{V_d}{Cl} \)
  
  If both clearance and \( V_d \) increase, elimination half-life may stay the same or be minimally affected

- Drugs metabolized by multiple enzymes: if activity of one pathway is decreased, dominance may shift to an alternate pathway, decreasing the influence of the primary change

- Significant interpersonal variability in response to induction stimulants.
Pharmacokinetics in Pregnancy

- Changes in Vd, GFR, protein binding reflect normal pregnancy physiology, but why do changes occur in hepatic metabolism, renal secretion or other transporters?

- One hypothesis – classic enzyme induction:
  - Xenobiotic Sensing Receptors – Nuclear Receptors
    - Pregnane X-receptor (PXR)
    - Constitutive androstane receptor (CAR)

- Early Vertebrates: PXR regulates bile acid metabolism
  - evolved from an early estrogen steroid nuclear receptor
  - pre-mammalian development doubled: PXR & CAR
Xenobiotic Inducing Enzymes & Transporters

- In mammals – PXR LBD evolved to protect the organism from xenobiotics which could disrupt its endogenous steroid equilibrium (ensures reproduction)

- Up regulates transport and metabolism proteins that keep toxic chemicals out and get rid of what does get in. Mechanisms to detoxify xenobiotics also transport and metabolize modern drugs.

- Drug binds to PXR and/or CAR
  Activated PXR or CAR complexes form a heterodimer with the Retinoid X Receptor (RXR) which binds to the regulatory region of specific enzymes and transporters.

*Hypericum – St John’s wort*

*Digitalis – Fox Glove*
Orphan Nuclear Receptors

EID

CYTOPLASM

PXR / CAR

NR

PROTEIN PRODUCTS OF TARGET GENES

Drug Metabolizing Enzymes
Drug transporters

NR

TF

DNA

HRE

Hormone Responsive Element

Target gene

transcription

ucleus
# Xenobiotic Inducing Enzymes & Transporters

Representative genes controlled by PXR & CAR
Overlap of both genes upregulated as well as drugs that bind to them

### PXR
- CYP 1A1, 1A2
- CYP 2A6, 2B6
- CYP 2C8, 2C9, 2C19
- CYP 3A4, 3A7
- CYP 24A (Vit D)
- SULT 2A1
- UGT 1A1, 1A3, 1A4
- Glutathione S-transferase
- MDR1 (Pgp)
- MRP2 & 3
- AHR1
- OATP2

### CAR
- CYP 1A1, 1A2
- CYP 2A6, 2B6
- CYP 2C8, 2C9, 2C19
- CYP 3A4, 3A7
- CYP 24A (Vit D)
- SULT 2A1
- UGT 1A1, 1A3, 1A4
- Glutathione S-transferase
- Amino-N-SULT
- PAPS
- MRP1, MRP2 & 3
- AHR1
Some Drugs that bind to PXR and/or CAR
- Rifampin
- Mifepristone (RU 486)
- Estrogen (but not ethinyl estradiol)
- Progesterone & other progestins
- Phenobarbital, carbamazepine, phenytoin, oxcarbazepine
- Calcium channel blockers
- Cortisol, prednisolone
- St. John’s Wort - hyperforin
- Protease inhibitors
- Statins

What up-regulates PXR/CAR in pregnancy?
Why are some CYPs down-regulated in pregnancy?
Drugs and Lactation

- Mechanisms of drug transfer
  - Diffusion
  - Intercellular movement
  - Active transporter

- Drugs with poor bioavailability, even if present in breast milk, achieve low infant levels due to poor oral absorption

- Most drugs are safe to use with lactation

- Specific Drug Examples
Factors that affect drug transfer into the alveolar lumen

Passive Diffusion – dominant mode

- Molecular size
- Degree of ionization
- Lipid solubility
- Protein binding
- Drugs that are most readily transferred:
  - low molecular weight
  - no ionization (no electrical charge)
  - highly lipid soluble
  - low protein binding
Drug Transfer into Breastmilk

- Transcellular diffusion
  Small molecules <200-300 daltons readily diffuse across into breast milk
- Influenced by differences in:
  - pH (6.8–7.2 for milk vs. 7.4 for plasma)
  - lipids (3% for milk vs. 1% for plasma)
  - protein (1% for milk vs. 8% for plasma)
- Intercellular (paracellular) mechanism used for larger molecules, eg: maternal antibodies or monoclonal antibody drugs
- All but a few drugs transfer via simple or facilitated diffusion
General Rules

- Milk concentrations are usually lower than maternal plasma concentrations.
- There usually is a fixed ratio between milk and plasma concentrations.

Kinetic Analysis of Theophylline: Plasma and Milk Concentrations
Three methods of expressing Infant drug exposure

- Milk to Plasma Drug concentration ratios
- Relative Infant Drug
- Plasma drug concentration in the infant
Milk to Maternal Plasma Drug Concentrations

Milk to Maternal Plasma Drug Concentrations  M:P Ratio

- Drug concentration in breast milk
  Drug concentration in maternal plasma

- Most commonly used method to assess drug transfer

- Does not express other factors that can affect drug exposure:
  - How much milk/drug is infant actually getting per day
  - How much drug is being absorbed
  - How well does the infant metabolize the drug
Relative Infant Dose

- Estimation of infant drug exposure per day as a percentage of the dose to the mother:

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

- Dose to infant is based on measurement drug concentration in breast milk and total milk volume ingested per day, Milk volume estimate: 150 mL/Kg/day

\[
\text{Infant dose/day} = C_{\text{mat}} \times M/P \times V_{\text{milk}}
\]

- RID < 10% is considered relatively safe but also need to factor in medication risks
Breast Cancer Resistance Protein

- ATP efflux transporter
- Apical border of mammary cells
- Transports drug against a concentration gradient into milk
- Expressed with lactation, PRL induced
- Produces increased M/P ratios
- Unclear primary function
- No other ATP transporters present
<table>
<thead>
<tr>
<th>Medication</th>
<th>M/P Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir</td>
<td>5.1</td>
</tr>
<tr>
<td>Bupropion</td>
<td>2.5 – 8.6</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>29.3</td>
</tr>
<tr>
<td>Δ-9-THC</td>
<td>8</td>
</tr>
<tr>
<td>Diazepam</td>
<td>3.7 – 9.5</td>
</tr>
<tr>
<td>Nadolol</td>
<td>4.6</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>31.1</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>13</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>4.9</td>
</tr>
<tr>
<td>Tepotocan</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Infant Plasma Drug Concentrations

- **Nitrofurantoin Safety**
  - Even with M/P ratio of 31.1, nitrofurantoin is considered safe in lactation (in G6PD negative infants) because fetal dose remains small: *Gerk 2001* estimated that a breastfed infant would only consume 0.2 mg/kg (6% of the maternal dosage) of nitrofurantoin each day.

- **Plasma drug concentration in the infant**
  - *Drug delivery from milk*
  - Oral bioavailability in the infant
  - Drug clearance in the infant
Drug Transfer during Lactation

- Drugs generally contraindicated during lactation
  - Antineoplastics
  - Immune suppressants
  - Ergot Alkaloids
  - Gold
  - Iodine
  - Lithium carbonate
  - Radiopharmaceuticals
  - Social drugs / drugs of abuse