

**PHARMACOKINETICS
IN PREGNANCY;
CLINICAL
SIGNIFICANCE**

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OBJECTIVES

- To describe PK changes in pregnancy that may affect drug use
- To present cases highlighting the relevance of these changes

**P K PARAMETERS TO BE
CONSIDERED**

- Adherence
- Absorption
- Distribution
- Clearance rate
- Bioequivalence

ADHERENCE

- A 28yo woman with moderate- severe asthma
- Was put on at 8 weeks of pregnancy on Montelukast
- Was scared by family members and women's magazines that these new drugs may be "bad for the baby".
- D/C her medication at 16 wks of gestation
- At 19 wks was brought to emerg. In severe attack

ADHERENCE 2

-Died 3 hrs ago from respiratory failure
- Since the thslidomide disaster- high levels of perception of teratogenic risk= leads women not to take their medications as prescribed
- Women suffering from depression- very often under/ unprescribed
- Motherisk studies: volunteering women for PK/PD studies- take only 53% of prescribed vitamins

ADHERENCE 3

- Women with NVP cannot hold down their antiemetics=
- =will tolerate better prenatal vitamins of small size and low iron content
- Assessment of adherence is critical in evaluating poor response
- Counseling on lack of teratogenic/other adverse fetal effects is critical

ABSOPTION

- With delays in first pregnancy= many more pregnancies involve IBD:
- Impaired absorption of nutrients, vitamin B12 and potentially medications
- Nausea and Vomiting of Pregnancy:
- Delayed absorption of medicinal drugs
- Incomplete dosing due to vomiting

DISTRIBUTION

- Large increase in body weight= decrease in dose per Kg= decrease in steady state concentration
- Concentration= Dose per kg/Clearance rate
- Third trimester= decrease in serum albumin= decrease in protein binding=more free drug available for elimination

CLEARANCE RATE- ELIMINATION

- Increased activity of several CYP450
- 3A4 (protease inhibitors, midazolam)
- 2D6 (fluoxetine, other SSRI/SNRI)
- 2A6 (nicotine)
- In some cases= higher clearance- lower levels
- In other cases= active metabolite=levels not decreased (venlafaxine)

DECREASED ACTIVITY

- Decreased activity of other P450s:
- 1A2 (theophylline, caffeine)
- 2C19 (phenytoin)
- Mechanisms for changes not known
- Changes in hepatic blood flow- has not yet measured directly in humans

CLEARANCE RATE(2)

- In late pregnancy: increase in GFR up to 50%
- Increased clearance rate and decreased levels of renally eliminated drugs or metabolites (lithium, digoxin, aminoglycosides)
- Increased activity of p-glycoprotein= increased tubular secretion of digoxin
- Patient may need increased dose of drug
- Active metabolites (e.g. morphine 6 glucuronide)= patient may feel less analgesia

OSELTAMIVIR KINETICS

- **Beigi et al (2011):** Comparing pregnant to nonpregnant women:
No changes in AUC of Oseltamivir (the prodrug), but significant decrease in Oseltamivir carboxylate the active metabolite); parallel increase in apparent clearance.
- **Greer et al(2011):** 3 groups, 10 per trimester
- No differences in AUC or clearance rates of the active metabolite
- (AJOG, March 2011)

CLINICAL IMPACT OF INCREASED ELIMINATION

- The pregnant patient needs to be aware that in late pregnancy she may need higher dose of her medication= counter intuitive to her attempt to use less
- In cases of increased symptoms= may be due to increased clearance

NOVEL METHODS TO STUDY METABOLIC CHANGES IN PREGNANCY

- Hair grows 1cm/mo=long term biomarker
- Hair analysis of nicotine: cotinine in pregnancy= shows increased metabolic clearance, with higher levels of cotinine and lower levels of nicotine=50-75% increase in clearance
- This may explain failure of nicotine patch at regular dose in late pregnancy

Hair analysis of venlafaxine in late pregnancy= increased production of the active metabolite

BLOOD AND HAIR PK OF VENLAFAXINE

◦	1 st trimester	3 rd trimester
◦ Cmax(ng/ml)	422	270
◦ AUC(ng.hr/ml)	3357	1965
◦ M:P Ratio	0.9	1.96

Month of Pregnancy	M:P Ratio
3	0.44
6	1.47
9	1.69
3 mo.post partum	0.74

BIOEQUIVALENCE

Case 2:

- A company wishes to introduce a generic form of drug for the treatment of pregnancy- induced biliary cholestasis
- They compare their drug to the available compound by recruiting 20 men and studying bioequivalence
- ?????????
- They claim that “although men may have different absorption or clearance- the comparison of 2 drugs in the same man is valid for women, because gender variability in bioequivalence is similar
- Is it?

BIOEQUIVALENCE- GENDER VARIABILITY

- For many drugs - gender variability may be similar, but not for other:
- Chen(2000 studied 26 bioequivalence studies submitted to FDA.
- Using 20 difference between genders as clinically significant-
- 35% of drugs were different in peak levels
- 13% -significant differences in AUC
- Overall: in 28% of data sets= statistical differences between genders

PHARMACODYNAMICS

- Assumptions based on non pregnant women may not be valid:
e.g.
- Lower immunity in late pregnancy after viral infection (e.g. varicella)
- Lower protein binding
- Higher sensitivity to nausea and vomiting
- More depression during NVP (first trimester)
- Higher glucose levels due to corticosteroid hormones
- Higher cardiac output= more risk for heart failure in women with existing heart disease

PHARMACODYNAMICS (2)

- Be aware of the combination of metabolic changes **plus** genetic polymorphism
- e.g: CYP2D6 - increased activity in late pregnancy will lead to different changes among UM, Extensive, vs. Slow Metabolizers
- Therapy should be individualized as much as possible

CONCLUSIONS

Therapy should be individualized as much as possible, addressing kinetic changes in the context of dynamic alterations due to the medical condition
e.g. NVP with increased G-E Reflux
