Designing PK Studies in Pregnancy – Part II

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May 16, 2022
Disclosures

• I have no financial conflicts of interest

• Some of the medications discussed will include unapproved or off-label indications for medications we use in obstetrics, which are supported by evidence in the literature but not formally approved by the FDA.
Objectives

• Identify: When during pregnancy should studies be conducted – trimester focused vs longitudinal

• Review: options for control or comparator groups

• Discuss: single dose and multiple dose studies in pregnancy
Pregnancy as a Special Population – Needs Then & Now

• 2000:
  Pregnancy = Special Population = “Black Box”
  Little information

• 2022:
  How can we use our understanding to inform drug prescribing?
When during pregnancy should studies be conducted?

Longitudinal vs. trimester focused
When have studies been conducted to date?
### PK Changes across Pregnancy and Postpartum

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PK Changes across Pregnancy and Postpartum
When should studies be performed?

- **Trimester focused**
  - Useful *early* in our study of a particular drug or DME – choosing the gestational age when maximum change may occur
  - More efficient: one evaluation during pregnancy and one PP
  - Appropriate when drug use is trimester-limited

- **All trimesters & early PP**
  - Drugs for maintenance therapy – studies across pregnancy
  - Drugs for shorter regimens administered at any time

Studies often proceed from trimester-focused to longitudinal
Study Evolution that informed Dosing Guidelines:
Lamotrigine
History of Lamotrigine PK studies in Pregnancy - 1

• LTG approved for epilepsy: 1991 – UK; 1994 – US
• LTG: narrow therapeutic index; existing/familiar TDM
• 1997 – 50 reports of prenatal exposure in GlaxoSmithKline pregnancy registry – but no PK evaluation in pregnancy

• Tomson, 1997 – Case Report
  Monthly trough LTG concentrations in pregnancy
  Analyzed: Dose / Concentration (D/C ~ clearance)

• Plasma LTG D/C increased as pregnancy progressed
  Plasma D/C compared to 5 mo postpartum:
    3rd trimester – 3.6 times higher
    Delivery – 5.8 times higher
History of Lamotrigine PK studies in Pregnancy – 2

• **Ohman, 2000**
  9 women & their infants
  Focus: delivery and lactation – *when did C/D return to baseline?*
  C/D: concentration normalized by dose
  - Delivery: Maternal plasma / umbilical cord [LTG]
  - 2 weeks Postpartum: Maternal plasma / breast milk / infant [LTG]
  - Maternal Controls: 2 months PP (8) or prior to conception (1)
  - Mean C/D ratios rose 170% (range 0 – 630%) between delivery and 2 weeks PP
  - C/D ratios returned to normal by 2 weeks PP
• *Pennell, 2003*
  
  6 patients
  Control/baseline: preconception
  SS trough monthly blood draws across pregnancy;
  Analyzed: D/C ~ clearance
  Significant increases with each trimester
  Peaked at 32 weeks at 350% above pre-pregnancy baseline
  Trended down until delivery
  Rapidly returned to normal PP

• **Recommended:** monthly monitoring with dose adjustments and dose tapering over 3 weeks PP
• Contraceptive Studies
  
  *Reimers 2005*
  
  LTG conc w/ identical LTG doses (mean ± SD)

  - LTG controls: 5.6 ± 3.1 mg/L
  - LTG POP: 5.4 ± 2.1 mg/L
  - LTG COC: 2.0 ± 1.3 mg/L  \( p < 0.001 \)

• **Estradiol** induces UGT1A4
  
  *Chen 2009* - HepG2 cell culture
  
  Estradiol upregulates mRNA UGT1A4
History of Lamotrigine PK studies in Pregnancy

Polepally 2014  \( CL/F = \frac{\text{Dose}}{\text{Conc}} \)

- 60 women
- 64 pregnancies
- Epilepsy & Bipolar disease
- Population-based, nonlinear, mixed-effects model
- Returned to baseline by 2 wks

77% of women: LTG CL increased by 219%
23% of women: LTG CL increased by only 21.3%
History of Lamotrigine PK studies in Pregnancy – 5

• Karanam, 2017

*How early does the increase in UGT1A4 clearance begin?*
Focus on preconception through 13 weeks

Lamotrigine apparent oral clearance (LTG-CL/F; open circles) and estradiol (closed circles) by gestational weeks.

Lamotrigine apparent oral clearance (LTG-CL/F) by gestational weeks.
History of Lamotrigine PK studies in Pregnancy

• **Karanam, 2017**

Population separated into high change or low change groups, based on average percentage change in clearance from baseline above or below a 24% cutoff.

• Changes in E2 were similar for both groups

• **Recommended: dose adjustments may be needed by 5 weeks gestation**
What is our control group?

It depends on the drug and question / hypothesis
Control Group Options

Maintenance drugs – easiest to study
e.g. antidepressants, antihypertensives, hypoglycemics, antiretrovirals
• Control = distant postpartum = “serves as their own control”
• Control = prior to pregnancy – conception unpredictable

• Postpartum Controls - Often difficult to get women to return for multiple sample periods or in-patient studies
  • Childcare / Breast feeding / Overwhelmed with new family life
  • Hormonal Contraception
  • Relocated / Lost to FU
**Fischer J et al. 2014**

57 pregnant women with cHTN on labetalol
12 wk’s gestation through delivery
12 weeks’ postpartum
Population PK study with sparse sampling

Compared to oral clearance at postpartum:
1.4-fold greater at 12 weeks’ gestation
1.6-fold greater at 40 weeks’ gestation

Because of increased clearance –
may need q 8h dosing
Control Group Options

Short-term medications – single or multi-dosed

• Pregnant participants
  - Pregnant people ≠ Healthy volunteers
    • Often difficult to enroll; Ethics?
  - Opportunistic – indicated treatment

• Postpartum Controls – Paired sampling – “their own controls”
  - Difficult to get women to return for non-indicated re-exposure
  - Same constraints with PP sampling
    • Breast feeding, childcare / chaotic new life balancing work and family/ lost to FU
    • Hormonal Contraception
Paired Pregnancy and Postpartum Controls

• Ampicillin
  - *Philipson, 1977*
    Women with asymptomatic UTIs in pregnancy
    Controls: same women 3 – 12 months PP

• Amoxicillin
  - *Andrew (& Hebert), 2007*
    Healthy pregnant volunteers: 2nd and 3rd trimesters and 3 months PP
Short-term Medications – Alternative Options

Control Options when PP re-exposure may be contraindicated

• *PK and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the US*
  
  Intensive PK study (after at least 2 days of remdesivir)
  
  • 20 pregnant women with COVID-19
  
  • 20 nonpregnant women of reproductive age with COVID-19
    
    • Significantly better than mixed gender historic controls
  
  • *Oseltamivir in Pregnancy (Beigi, 2015)*
    
    (after 48 h of oseltamivir – PK sampling)
    
    • 29 Pregnant women (all trimesters) with influenza
    
    • 35 nonpregnant female subjects with influenza
Control = Comparator Group – CYP2D6 Phenotypes

- **Paroxetine Metabolism**
  - CYP2D6 (3A4/5, 2C19, 1A2)

- **Ververs 2009**
  - 74 pregnant women on Paroxetine
  - Blood sampled at: 16-20, 27-31 and 36-40 wks’
  - EM = 43 women
  - IM = 25 women
  - PM = 5 women

- **Depressive symptoms:**
  - EM women - worsened
  - IM and PM women – no change

![Paroxetine concentrations by trimester by phenotype](image)
Single dose vs multiple dose studies
Single vs Multiple Dose Studies

- Single dose studies

**Clearance** = rate of drug removed from a fixed amount of blood in L/h (vol/time)

**Elimination Half-Life** = Time for drug concentration to drop by half

AUC = total drug exposure across time

Fig 2.5 Atkinson’s Principals of Clinical Pharmacokinetics, p.15
Single vs Multiple Dose studies

- Multiple dose studies
  - Steady state = when rate of drug administration = drug elimination

Fig 1 from Scheerans, Heinig, Mueck, in Biopharmaceutics & Drug Disposition, 2015:36(2) p 96.
Multiple Dose Studies

- Alternate PK parameters:
  - Drug concentration
    - If all participants on same dose throughout study
    - Normalized to a standard dose
- Ververs 2009
  - 74 pregnant women on paroxetine
  - Blood sampled at: 16-20, 27-31 and 36-40 wks’
  - Paroxetine concentrations normalized to a 20 mg dose
    \[ \text{Conc} \times \left[ \frac{20 \text{ mg}}{\text{dose}} \right] = \text{Conc} \]
Multiple Dose Studies

Alternate PK parameters:

- **C/D**: concentration normalized by dose
- **Dose/Concentration** \(\sim\) clearance
- Allows for
  - Comparisons between individuals on different doses
  - Dose changes within same individual
Multiple Dose Studies

• Alternate PK parameters:
  - Metabolic concentration ratio (drug/metabolite or metabolite/drug)

• *McGready 2003*
  - 45 women during 3rd trimester
  - Restudied 60 days postpartum
  - Proguanil 200 mg QD
  - Proguanil / Cycloguanil ratios 6 hours post-dose
  - CYP2C19 activity
Multiple Dose Studies

• Sparse sampling population PK studies

• *Fischer J et al.* 2014
  57 pregnant women with cHTN on labetalol
  12 wk’s gestation through 12 weeks’ postpartum
  - Population PK study with sparse sampling timed to each participant’s PN visits throughout pregnancy and until 12 wks PP
  - Assigned sampling windows throughout dosing interval – blood drawn consistently for each participant
  - Plus, once each trimester and PP, two additional samples drawn in different sampling windows.
With the goal of translating PK data into dosing guidelines -
Design appropriate studies throughout pregnancy and PP

Thank You!