

Designing PK Studies in Pregnancy – Part II

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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

Variable		Early 1 st	Late 1 st	Early 2 nd	Late 2 nd	Early 3 rd	Late 3 rd	< 8w PP	> 8w PP
Renal - CrCL	↑								
Plasma Volume / TBW	↑								
Albumin	↓							?	
α1-acid-glycoprotein	↓							?	
Hepatic Arterial Blood Flow	=	?						?	
Hepatic Portal Blood Flow	↑	?						?	
UGT1A1	↑	?						?	
UGT1A4	↑								
CYP1A2	↓	?							
CYP2B6	=	?	?	?				?	
CYP2C9	↑	?						?	
CYP2C19	↓	?	?	?	?			?	
CYP2D6 – EM/RM	↑	?	?					?	
CYP3A4/5	↑	?						?	

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CYP2C19	↓	?	?	?	?			?	
CYP2D6 – EM/RM	↑	?	?					?	
CYP3A4/5	↑	?						?	

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

History of Lamotrigine PK studies in Pregnancy – 3

- *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**

History of Lamotrigine PK studies in Pregnancy – 4

- Contraceptive Studies

Reimers 2005

LTG conc w/ identical LTG doses (mean \pm SD)

LTG controls: 5.6 \pm 3.1 mg/L

LTG POP: 5.4 \pm 2.1 mg/L

LTG COC: 2.0 \pm 1.3 mg/L $p < 0.001$

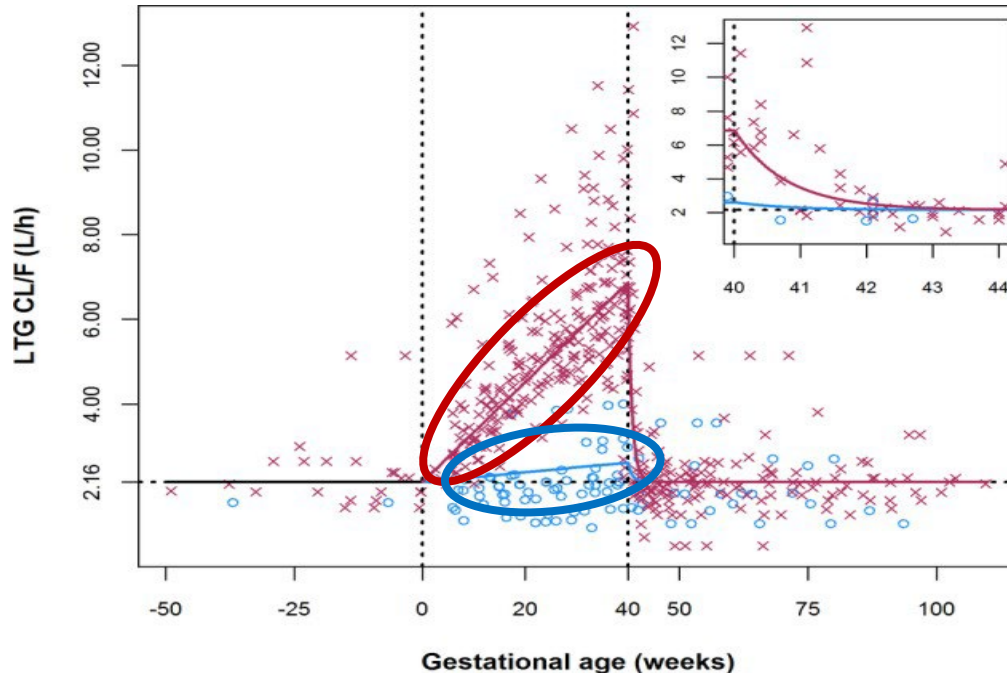
- **Estradiol induces UGT1A4**

Chen 2009 - HepG2 cell culture

Estradiol upregulates mRNA UGT1A4

History of Lamotrigine PK studies in Pregnancy – 4

Polepally 2014 $CL/F = \text{Dose} / \text{Conc}$



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%**

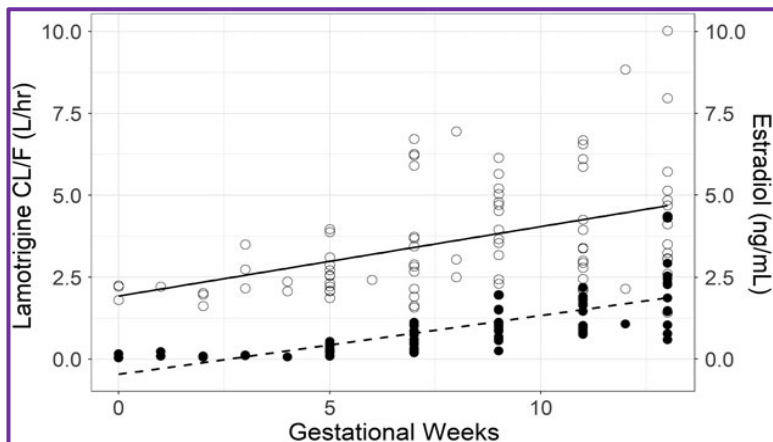
**23% of women: LTG CL increased
by only 21.3%**

History of Lamotrigine PK studies in Pregnancy – 5

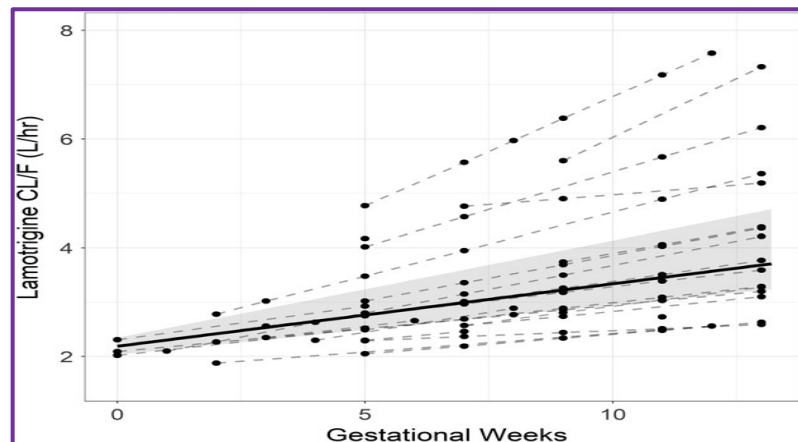
- *Karanam, 2017*

How early does the increase in UGT1A4 clearance begin?

Focus on preconception through 13 weeks



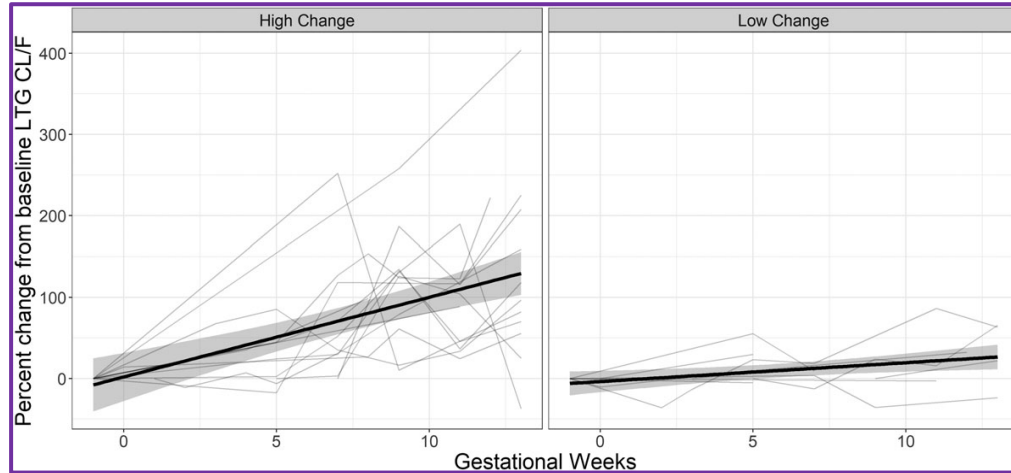
Lamotrigine apparent oral clearance (LTG-CL/F; open circles) and estradiol (closed circles) by gestational weeks.



Lamotrigine apparent oral clearance (LTG-CL/F) by gestational weeks.

History of Lamotrigine PK studies in Pregnancy – 6

- *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

Longitudinal Studies - Labetalol

Fischer J et al. 2014

57 pregnant women with cHTN on labetalol

12 wk's gestation through delivery

12 weeks' postpartum

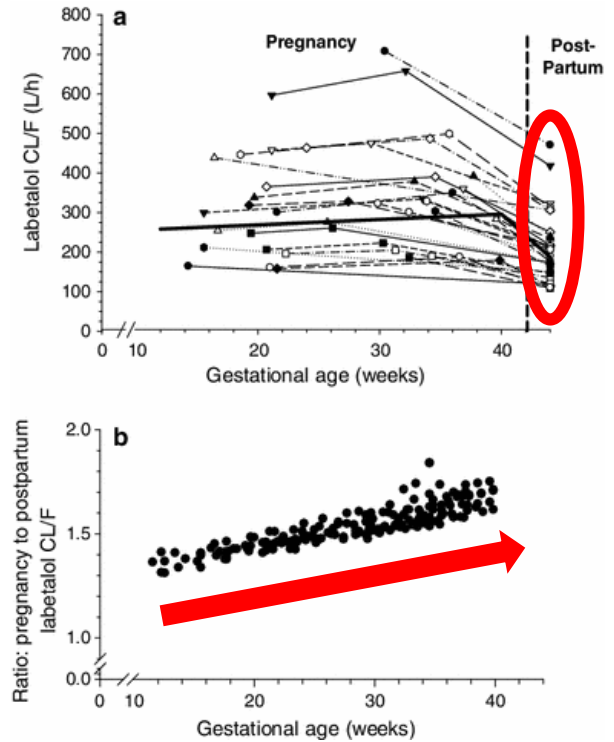
Population PK study with sparse sampling

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 \neq 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

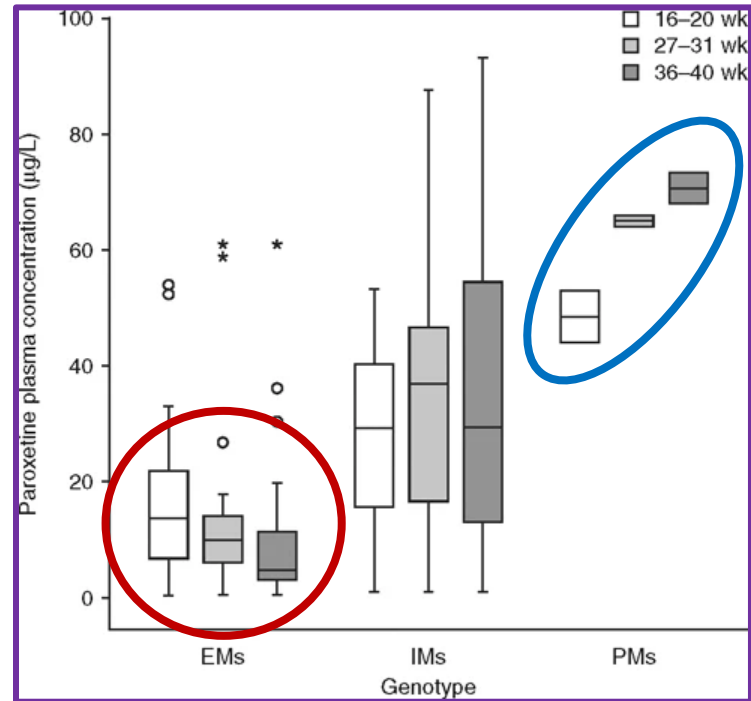
- *PK and Safety of Remdesivir for Treatment of COVID-19 in Pregnant and Non-Pregnant Women in the US*

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

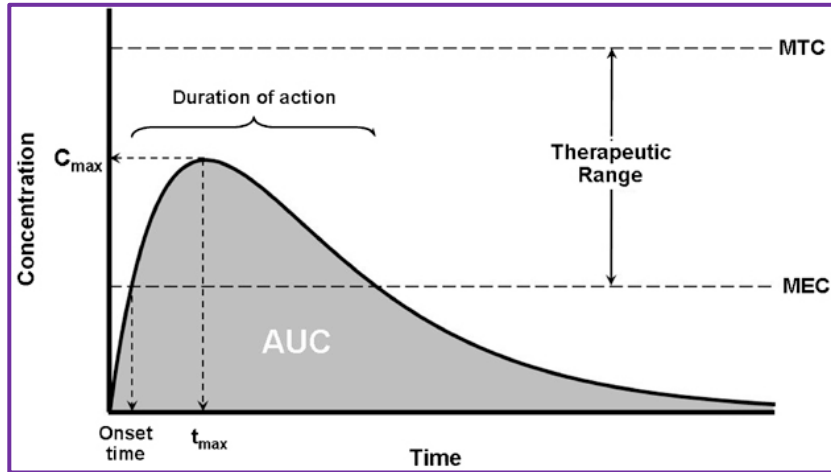


Paroxetine concentrations
by trimester by phenotype

Single dose vs multiple dose studies

Single vs Multiple Dose Studies

- Single dose studies



AUC = total drug exposure across time

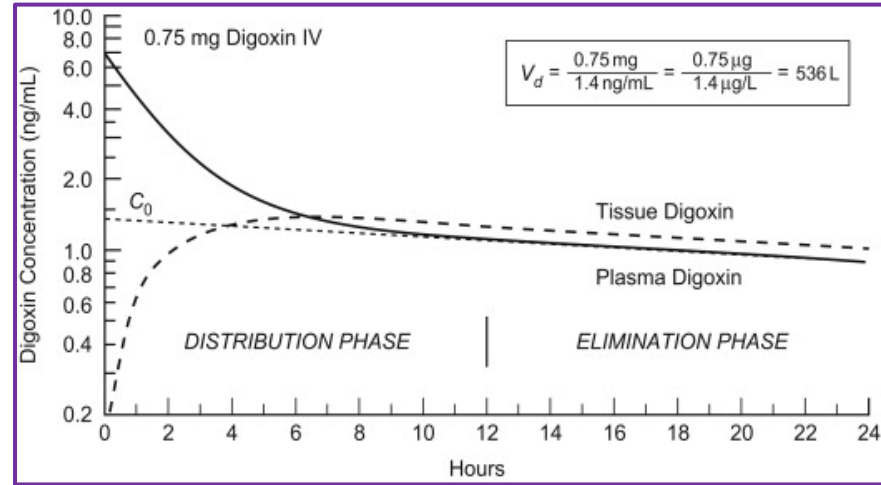


Fig 2.5 Atkinson's *Principals of Clinical Pharmacokinetics*, p.15

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

Single vs Multiple Dose studies

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

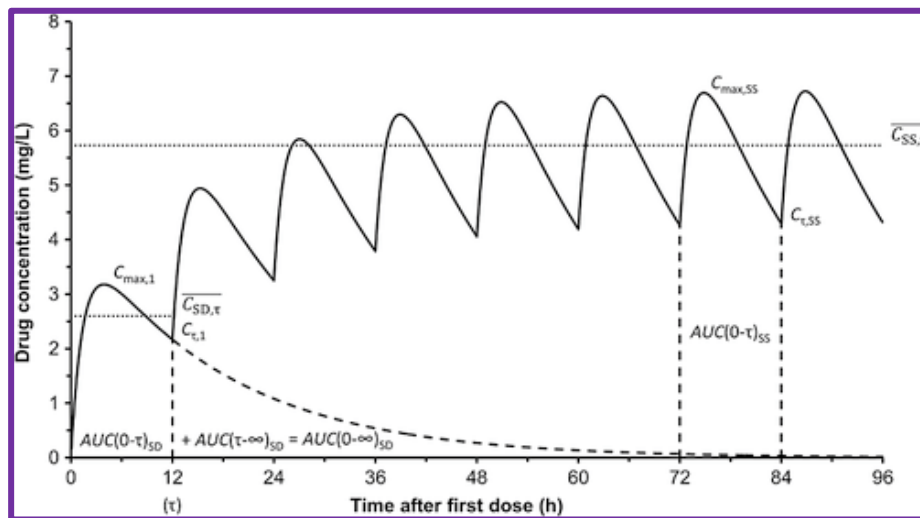


Fig 1 from Scheerans, Heinig, Mueck, in *Biopharmaceutics & Drug Disposition*, 2015:36(2) p 96.

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
 - $\text{Conc} \times [20 \text{ mg} / \text{dose}] = \text{Conc}$

Multiple Dose Studies

Alternate PK parameters:

- C/D : concentration normalized by dose
- $\text{Dose/Concentration} \sim \text{clearance}$
- 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!