Ethical Issues Related to Pharmacokinetic (PK) and Pharmacodynamic (PD) Studies in Pregnant and Postpartum Women

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Definitions

- **Pharmacokinetics** - what the body does to a drug (ADME).
  - studies require measurement of drug in some compartment usually blood or plasma

- **Pharmacodynamics** - what a drug does to the body.
  - PD studies require measurement of some target organ/tissue response and its relationship to drug concentration either in blood or in tissue.
Ethical Issues with PK Studies

Dose-normalized buprenorphine plasma concentrations during pregnancy and postpartum

- Measurement of drug in plasma/blood, saliva, urine poses little risk to mother or baby unless amount of blood withdrawn is excessive.

- Measurement of drug in other biological space may pose risk eg measurement in amniotic fluid or in fetal blood poses risk.

- Performing PK study with drug that mother or fetus do not need clinically poses an ethical challenge.

Why Give a Mother Unneeded Medications

- Pregnancy vs post partum PK studies
- Phase1/2 studies
- Metabolic cocktails – estimate in vivo cytochrome P450 and other metabolic enzyme activities

Subjects received 100 mg of caffeine (CYP1A2), 15 mg of dextromethorphan (CYP2D6 and CYP3A).
Ethical Issues in PK Studies

- Changing the dose or frequency of dosing to adapt to study design

- Asking mother to fast for an unreasonable time prior to PK study

- Asking mother to delay usual time medication taken
Why Pharmacodynamics?

The PK of a drug allows determination of how the body handles the drug but does not define what concentration achieves the desired effect.

The PD response defines how much drug is required to elicit a desired response.

Relationship between median 17-OHPC concentration within each quintile of 17-OHPC concentration and PTB Rate within each quintile

Caritis, Venkataramanan et al for the MFMU
Why are PD Studies Needed

- Off-label dosing exists for most meds used in pregnancy

- Without PD studies in pregnant women proper dosing hampered – drug may be viewed as ineffective or unsafe (ritodrine)

- Some PD endpoints may be unique to pregnancy – PTB (17-OHPC), tocolytics (nifedipine, Indomethacin), fetal lung maturity (BMX), neuroprotection (MgSO4)
Postpartum PK/PD and Breast Milk Studies

- Postpartum studies
  - Same ethical issues as PK/PD in pregnancy
  - Time commitment of mother
  - Separation of mom and baby

- Breast milk studies – maternal blood, breast milk, neonatal biological fluid usually blood
  - Blood or biological sample from baby
  - Unavailability of breast milk to baby
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