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Population pharmacokinetics of rifampicin in pregnant women with tuberculosis and HIV co-infection

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Drugs in pregnancy

- "Pregnant women get sick, and sick women get pregnant"– the Second Wave Initiative

- Ethical imperative to include pregnant women in research of drug treatments: *Rationale:* need for effective treatment during pregnancy, fetal safety, harm from reticence to prescribe potentially beneficial medicines, justice and access to benefits of research participation Lyerly Int J Fem App Bioeth 2008

Drug disposition	Effect of pregnancy
Absorption	Increase gastric pH, reduced intestinal motility
Volume of distribution	Increased plasma volume Changes in protein binding (reduced albumin)
Metabolism	Increased activity of CYP3A4, CYP2D6, CYP2C9, UGT1A4, UGT2B7 Decreased activity of CYP1A2 and CYP2C19 Fetal, placental metabolizing enzymes
Renal excretion	Increased glomerular filtration rate

TB in pregnancy

- Pregnant women are at especially high risk of TB disease
  - HIV co-infection in many TB-endemic settings is very common among women of childbearing age
  - Immunologic changes of pregnancy
- In Soweto, an estimated 0.8-2.2% of pregnant women with HIV also have active TB (Gounder *et al*. 2011; Kali *et al*. 2006)
- TB is significant cause of infant and maternal morbidity and mortality, especially in areas of high HIV prevalence(Gupta *et al.*, CID 2007)

TB drugs in pregnancy

- Rifampicin drives treatment response for TB, and exposures are on the steep part of the dose-response curve. Inadequate TB treatment has serious consequences, especially for pregnant women
- First-line treatment for TB (drugs/doses) is same for pregnant women and non-pregnant adults, with exception of PZA in some settings
- Pregnant women systematically excluded from trials of new TB treatment regimens; no information on effects of pregnancy on pharmacokinetics of first-line or investigational anti-TB drugs
- Rifampin is desacetylated in the liver and excreted in the bile and urine.
- **The effects of pregnancy on the pharmacokinetics of rifampin have not been studied**

Study design

- **TSHEPISO** is a prospective cohort study among **HIV-infected pregnant women with TB (n=250 CASES) and without TB (n=500 CONTROLS),** currently enrolling in Soweto, South Africa. To date, 80 cases enrolled.
- **Antenatal clinics and obstetrics ward** at Chris Hani Baragwanath Hospital, **women at 13-34 weeks gestation**
- Impact of TB/HIV co-infection in pregnancy on maternal and infant outcomes being evaluated
- **Pregnant HIV-infected women with TB taking standard first-line TB treatment enrolled in Rifampin PK substudy, along with their infants**
- **→ We report preliminary results from women in the TSHEPISO RIF PK substudy**

Methods: TSHEPISO RIF PK Substudy

- Blood samples for RIF PK analysis were collected:
  - **Maternal: 37 weeks' gestation or delivery, then 6 weeks post-partum**;

    up to 4 samples per occasion
  - **Cord blood at delivery**
- Plasma concentrations determined by LCMS/MS†
- Post-hoc Bayesian estimates of PK parameters from **nonlinear mixed effects modeling** with allometric scaling, using NONMEM
- Maternal TB treatment outcomes and TB transmission events collected

†Clinical Pharmacology Analytical Laboratory, University of Cape Town

Results: Characteristics of study participants

CHARACTERISTIC	All (n=49)
Age in years, median (IQR)	28 (25-31)
CD4 cells/mm3 at enroll, median (IQR)	303 (200-443)
Site of TB infection, N (%)	
Pulmonary	46 (94)
Extrapulmonary	3 (6)
Both	0 (0)
Weight in kg at delivery, median (IQR)	66 (60-75)
Gestational age at delivery, median (IQR)	38 (37-40)
Weeks on TB treatment at delivery, median (IQR)	10 (7-16)
TB treatment outcome, N (%)	
Cured	2 (4)
Treatment completed	41 (84)
Death	0 (0)
Default	1 (2)
Failure	0 (0)
Lost to follow up	3 (6)

Preliminary population PK model parameter estimates (n=33) 47 PK profiles (14 both pre- and post-partum) N= 177 samples

Parameter	Typical Value	Between-subject or -occasion variability[b] [%CV]
CL [L/h]	16.2 [14.0, 18.7]	BSV: 30.2% [19.1%, 38.2%]
V_d [L]	43.3 [38.4, 48.4]	
Ka [1/h]	1.63 [1.15, 2.67]	BOV: 76.3% [49.1%, 115.0%]
MTT [h]	1.28 [1.06, 1.50]	BOV: 34.9% [21.9%, 48.3%]
NN []	55.7 [30.6, 109.5]	
BIO []	1 FIXED	BOV: 29.1% [21.2%, 33.8%]
Proportional error [%]	12.9% [7.6%, 16.6%]	
Additive error [mg/L]	0.0585 (=LLOQ/2) FIXED	
Pregnancy on CL [%]	-14.5% [-23.8%, -6.5%]	

CL and V are reported for a woman of median weight in the dataset (66 kg)
Final parameter estimates and - in brackets - the 90% CI from a non-parametric bootstrap (n=200)

Model features, key results (n=33 patients, N=177 samples)

- One-compartment model with first-order elimination and transit compartment absorption described the data well
- Allometric scaling applied to adjust for body weight
- Pregnancy decreased RIF oral clearance by 15% (yes, decreased!)
- No other covariates were found to affected PK

Maternal and cord blood RIF concentrations

Population PK model post-hoc estimates were used to predict individual AUC

Maternal PK parameter estimates, by pregnancy status

	Pregnancy (n=24)	6 weeks Post-partum (n=21)
C_{max} (mg/L)*	8.3 (7.1-9.8)	9.2 (6.7-11.2)
$AUC_{0\text{-}24h}$ (mg*h/L)	40.8 (27.3-54.1)	37.4 (29.0-50.6)

Cord blood PK parameter estimates (N=20)

- 12/20 were BLQ (<0.117 mg/L)
- Highest concentration was 2.66 mg/L
- Correlated with time after maternal dose

*Median (IQR)

TB treatment outcomes

- **Efficacy: 88% (43/49) successful maternal TB treatment outcomes**
- **Safety: No bleeding events reported**
- **Transmission: Perinatal TB**
  - **Among 47 infants born alive to 49 women with TB, one case of perinatal TB**
    - **Case Description:** Maternal TB, on continuation phase TB treatment at the time of delivery. Infant received BCG at birth & started 3mo RIF/INH prophylaxis at 8 days. At ~4months admitted for SOB, cough X5days & 1 day of fever. TB diagnosis based on CXR and initiated HREZ.

RIF exposures INCREASE in pregnancy?

- In general, drugs cleared more rapidly in pregnancy (increased cardiac output, GFR, metabolism)
- CYP1A2 and CYP2C19 downregulated in pregnancy, leading to higher concentrations of drugs metabolized by these enzyme
  - Rifamycins, though, metabolized by arylacetamide deacetylase
- Pregnancy-induced cholestasis can theoretically result in higher concentrations of drugs eliminated by hepatobiliary excretion (azithromycin?)
- Average half-life of rifampin 5.7 hours in obstructive jaundice in 1976 Harrison & Gibaldi report (competition of bilirubin for clearance vs. cholestasis?)
- Do rifampicin data help us predict what might happen with rifapentine in pregnancy?

Limitations

- Sparse PK sampling; not all participants presented for all sampling visits
- Observational study in complex setting
- Self-reported dosing time sometimes not consistent with measured concentrations
- Small sample size
- Only late pregnancy represented
- Free rifampicin concentrations not measured
- Cord blood samples of limited value
- Implications of RIF exposure in infants unknown

Summary

- First study evaluating rifampicin pharmacokinetics in pregnancy
- Rifampin clearance was (modestly) reduced rather than increased during the third trimester of pregnancy
- Mechanism unclear but may be related to estrogen-induced intrahepatic cholestasis
- Expected increases in exposures are modest, though, and unlikely to be clinically meaningful
- Rifampin detectable in cord blood but only when the dose was given shortly before delivery
- Further assessments of anti-TB drugs in pregnancy to ensure appropriate use are warranted

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