Impact of Pregnancy on Ceftriaxone Pharmacokinetics and Treatment of Syphilis: A Physiologic-Based Population PK Modeling Approach

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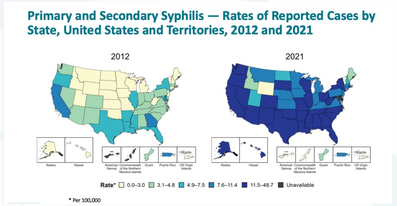
Background

- Over the last 20 years, we have seen the resurgence of syphilis in the United States (historic lows in 2000-2001).
- Cases of **Primary and Secondary syphilis**—the most infectious stages of the disease— have **increased 781%** since 2001.[1]



- **Congenital syphilis** continues to surge, **increasing 203%** in the past five years.[1]
  - In 2021, there were a total of 2,855 cases of congenital syphilis reported for a rate of 77.9 cases per 100,000 live births.[1]
- Per the CDC, during 2017 to 2021, the majority of **missed prevention opportunities**
  - NO timely prenatal care or syphilis testing (n = 2,857; 38%)
  - Timely syphilis testing but **no adequate maternal treatment** (n = 2,670; 35%).
- For pregnant women, **penicillin G benzathine** is the only endorsed treatment option[2]; however, global shortages of penicillin are restricting supply to critical populations.
- **Ceftriaxone (CTX)** is a WHO alternative treatment[3] with limited data on pharmacokinetics (PK) and optimal dosing in pregnancy.

Objectives

Our objective was to characterize expected CTX PK changes during pregnancy using a physiologic-based population PK (PopPK) model to optimize CTX dosing for syphilis treatment.

QRS Code

Study Design

- A PopPK CTX model was developed for simulations from existing literature.[4,5]
- These limited CTX PK data in pregnancy were leveraged[6,7] with established PopPK pregnancy models that utilize a large repository of anatomic, physiologic, and biologic parameters that change with gestational age, e.g., plasma volume, GFR [Table 1] [8].
- CTX compartmental PK parameters were linked with pregnancy-related physiological changes from 0 to 40 weeks gestation

Table 1 Main Anatomical, Physiological, and Biological Parameters Needed for p-PBPK Model and Equations Used to Calculate Parameter Values During Different Gestation Ages (GA) (14)

Parameter	Unit	Equation
Today body weight (kg)	kg	$TBW=61.1+0.2409\ GA+0.0038\ GA^2$
Cardiac output (CO)	L/h	$CO=301+5.916\ GA-0.086\ GA^2$
Total body fat mass (TFM)	kg	$TFM=17.14+0.1305\ GA+0.0008\ GA^2$
Weight of the uterus	g	Weight of the uterus=$80+8.2931\ GA+0.3546\ GA^2$
Fetal volume	mL	Fetal volume=$0.01\ \exp(13.6041-\exp(-0.0702GA))$
Placental volume	mL	Placenta volume=$0.0-0.0716+0.9146\ GA^2-0.0222\ GA^2$
Amniotic fluid	mL	Amniotic fluid volume=$0+1.9648\ GA-1.2956\ GA^2+0.2064GA^3-0.0061\ GA^4+0.00005\ GA^5$
Volume of fetoplacental unit	mL	Fetoplacental volume=Uterus weight+Placenta volume+Fetal volume+ Amniotic fluid volume
Blood flow of uterine	L/h	Uterine blood flow=$1.71+0.2068\ GA+0.0841\ GA^2-0.0015\ GA^3$
Plasma volume	L	Plasma volume=$2.5-0.0223\ GA+0.0042\ GA^2-0.00007\ GA^3$
Red blood cell (RBC) volume	L	RBC volume=$1.49+0.0098\ GA$
Total blood volume	L	Total blood volume=plasma volume+RBC volume
Glomerular filtration rate (GFR)	mL/min	$GFR=114+3.2367\ GA-0.0572\ GA^2$

Dallmann, Dallmann A, Ince I, Meyer M, Willmann S, Eissing T, Hempel G. Gestation-Specific Changes in the Anatomy and Physiology of Healthy Pregnant Women: An Extended Repository of Model Parameters for Physiologically Based Pharmacokinetic Modeling in Pregnancy. Clin Pharmacokinet. 2017 Nov;56(11):1303-1330. doi: 10.1007/s40262-017-0526-5. PMID: 28653279

- Steady-state CTX exposures were predicted in pregnant and non-pregnant persons with different dosing strategies:
  - 1g vs 2g IV/IM
  - q24h, q48h, vs q72h

Results

- With all dosing strategies, **concentrations were highly variable** with lower CTX concentrations in the 3rd trimester compared to non-pregnant persons (Figure 1).
- The predicted concentration of **unbound CTX trough also decreased quicker** than in non-pregnancy to <1% of non-pregnant adult levels due to non-linear binding (Figure 2).
- Following a 1g IM q24h regimen, as gestation increased, **the CTX trough decreased by 58%** to 11.7 mcg/mL, 5.9-21.5 (median, IQR) at 40 wks gestation (Figure 3).
- Cord blood troughs were predicted to be only 22% of non-pregnant plasma trough levels.
- Increasing the CTX dose to 2g did not compensate for the changes between pregnant and nonpregnant states nor allow for infrequent dosing.
- The expected median CTX trough values for pregnancy show **a significant number of very low concentrations across different dosing intervals** in pregnancy that are not apparent in non-pregnant persons (Figure 4).

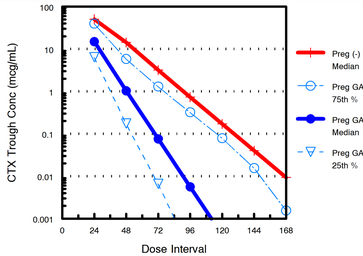


Figure 4: Steady-state CTX Concentration Troughs Following 2gm IM at Various Dose Interval

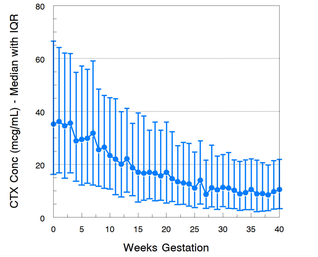


Figure 3: Steady-state CTX Concentration Troughs Following 1gm IV Q24 by Gestational Age

Results

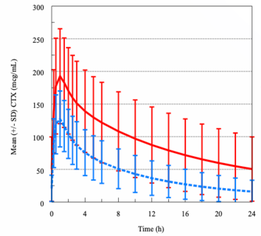


Figure 1: Steady-state CTX Concentrations Predictions Following 1gm IV Q24 by Time

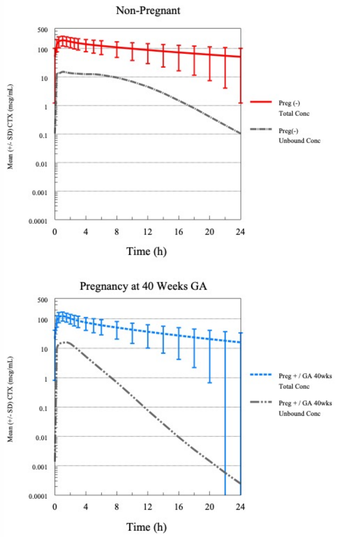


Figure 2: Comparison of Mean CTX Concentrations Following 1gm IV Q24 in Non-Pregnant Persons versus Pregnant Person at 40 weeks gestation

Conclusion

- There is a predicted **significant decrease in CTX exposure** to the mother and fetus in the **3rd trimester** regardless of dosing strategy.
- **Infrequent high dose CTX may not maintain adequate concentration** of Ceftriaxone **to treat syphilis in pregnant** and non-pregnant persons per modeling.
- Currently, effective CTX dosing in vivo is unknown against T. pallidum in pregnancy, however **late pregnancy may require different dosing approaches than non-pregnant persons to maintain adequate concentration** in the mother and fetus.
- Next Steps:
  - Continue to investigate alternatives to Benzathine Penicillin ideally has the following properties: easy admin (IM/oral), long-half-life, active against syphilis, crosses the placenta and can treat fetus, non-toxic to fetus
  - A complete understanding of the PK/PD of Benzathine Penicillin in pregnancy is necessary to design potential alternatives
    - Compare Ceftriaxone Pk/PD to Benzathine Penicillin Pk/PD with collected biologic data
    - Model with biological data a theoretical Long Acting (LA) intramuscular formulation of Ceftriaxone that can maintain appropriate trough concentrations for at least 1 week

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