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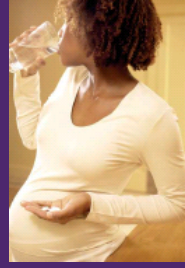

The Role of the Placenta in Fetal Exposure to Drugs

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Presented on behalf of the
University of Washington Program on Pharmacokinetics of Drugs of Abuse in Pregnancy (UWPKDAP)

https://sop.washington.edu/department-of-pharmaceutics/program-on-pharmacokinetics-of-drugs-of-abuse-during-pregnancy-uwpkdap/

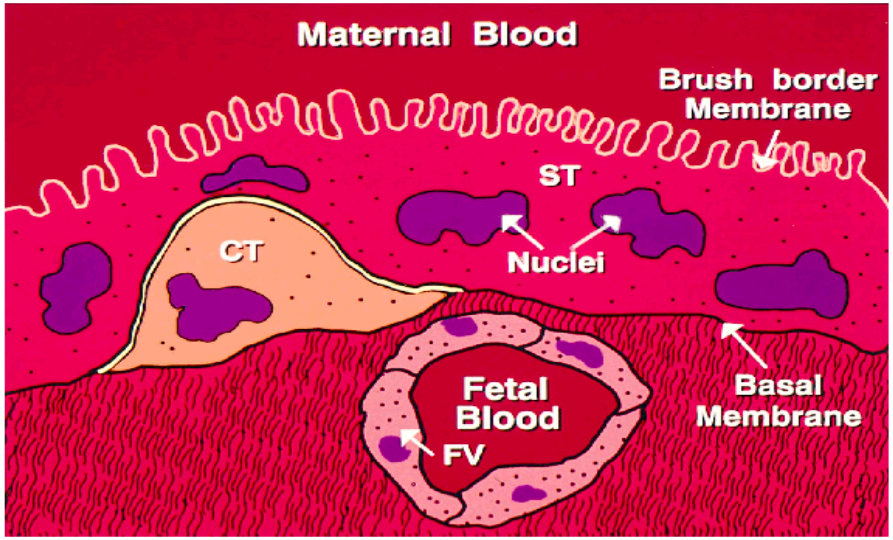
Background

- During pregnancy women take :
  - at least one prescription drug - ~96%
  - over-the-counter medications - 92.6%
  - herbal medications - 45.2%
- The fetus is de facto exposed to the drug
- Neither feasible nor desirable to perform maternal-fetal PK studies of all drugs taken by pregnant women
- Therefore study model/probe drugs to elucidate the magnitude of and mechanisms by which the fetus is exposed to drugs
- Mechanistic studies allow:
  - Extrapolation beyond the drugs (i.e. model/probe drugs) studied using a systems pharmacology approach

What Determines Fetal Drug Exposure?

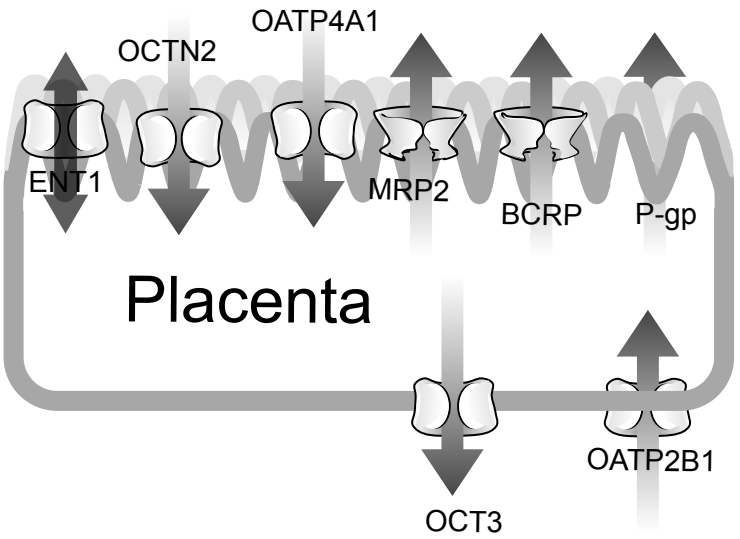
1. Maternal conc.
2. Transport (influx or effux) and/or diffusion across the placenta
3. Placental/fetal metabolism

Syncytiotrophoblast of the placenta



Ganapathy, J Pharmacol Exp Ther 2000

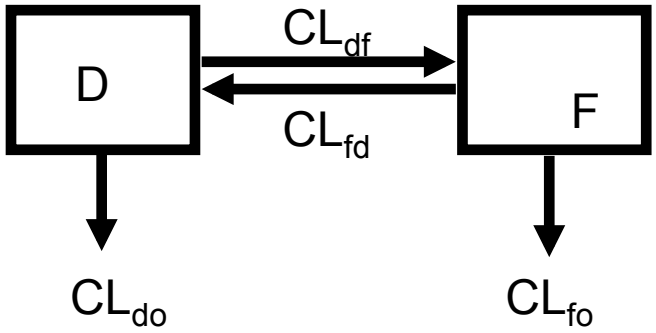
Syncytiotrophoblast is Richly Endowed with Transporters

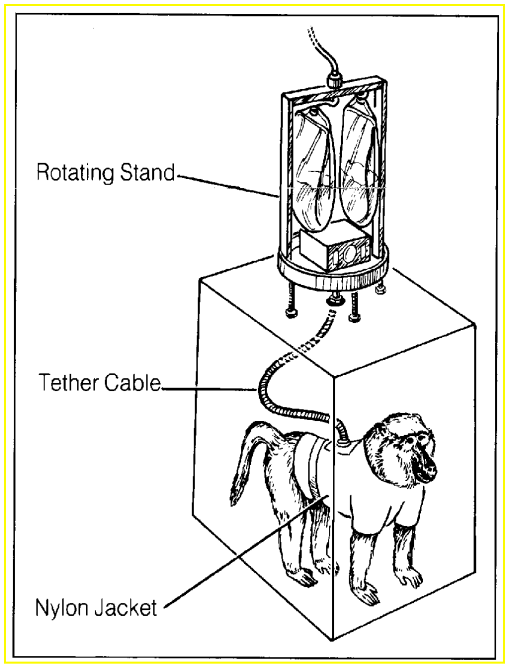


Mechanistic Studies on Placental Transport of Drugs

1. Are HIV nucleoside drugs (AZT, DDI, D4T, DDC) transported across the placenta? Nucleoside transporters are expressed in the placenta.

2. Studies in the chronically-catheterized maternal-fetal macaque model (1991-1996)



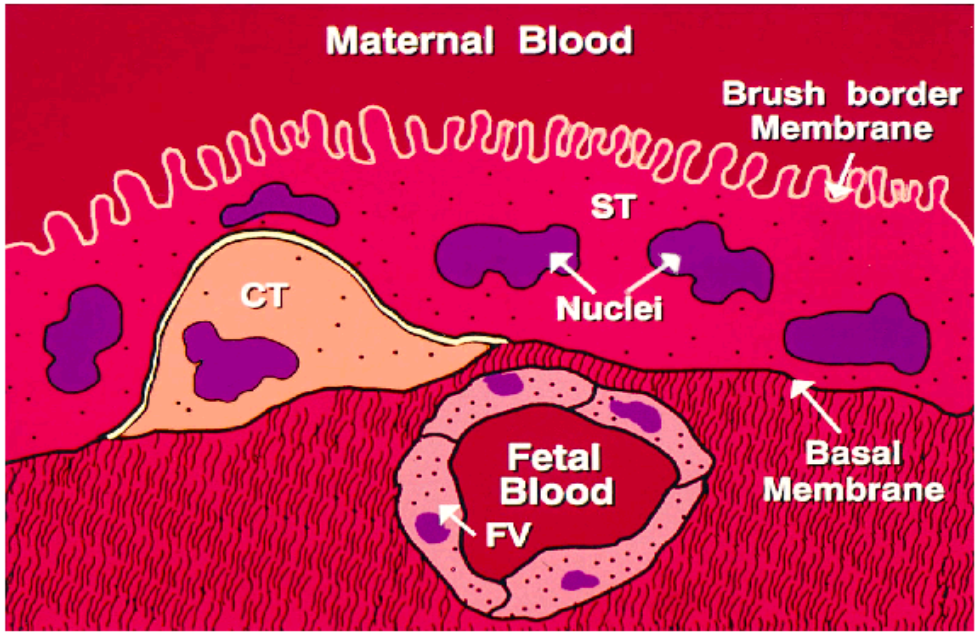


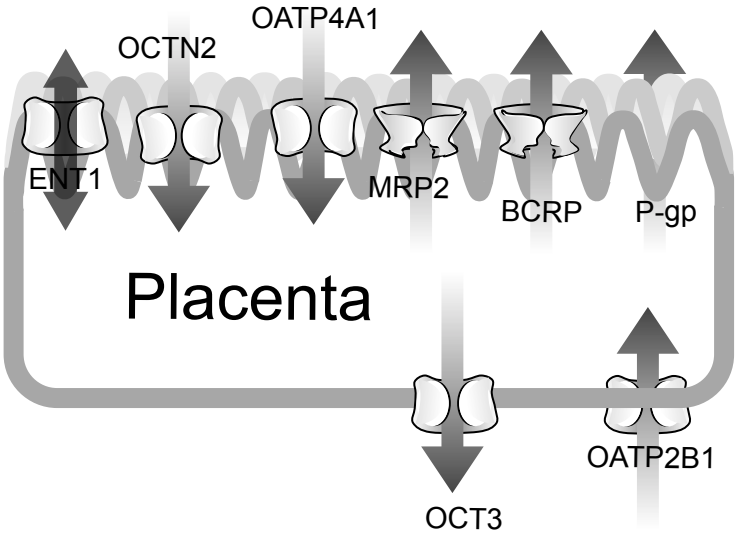
3. Surprisingly, these nucleoside drugs are NOT transported across the placenta!

Tuntland et al., J Pharmacol Exp Ther. 1998 Apr;285(1):54-62.
Odinecs et al., Antimicrob Agents Chemother. 1996 Jun;40(6):1569-71.
Tuntland et al., Am J Obstet Gynecol. 1996 Mar;174(3):856-63.
Odinecs et al., Antimicrob Agents Chemother. 1996 Jan;40(1):196-202.
Pereira et al., Antimicrob Agents Chemother. 1995 Feb;39(2):343-5.
Pereira et al., Antimicrob Agents Chemother. 1994 Apr;38(4):781-6.
Lopez-Anaya et al., J Acquir Immune Defic Syndr. 1990;3(10):959-64.

Placenta is Richly Endowed with Transporters

HIV protease inhibitors are excellent substrates of the efflux transporter, P-gp





Ganapathy, J Pharmacol Exp Ther 2000

P-gp in the Placenta Protects the Fetus from Avermectin Toxicity

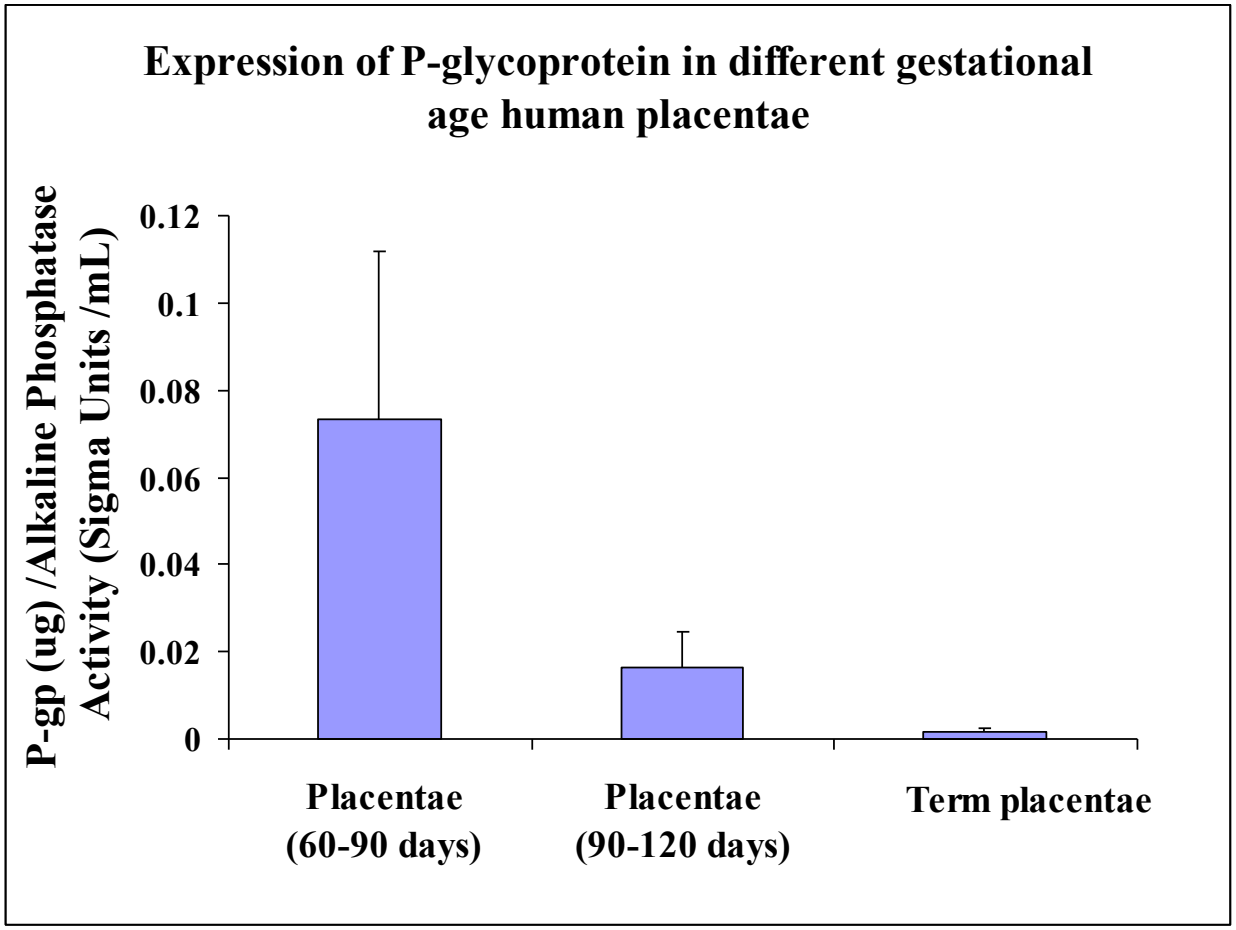
Table 2. Association between fetal P-glycoprotein genotype and induced cleft palate in CF-1 mice

Fetal Pgp genotype	Fetuses genotyped	Percent fetuses with cleft palate
+/+	70	0
+/−	70	~30
−/−	30	100

All fetuses in four, seven, and five selected L-652,280-treated litters corresponding to (+/+ × +/+), (+/− × +/+), and (+/− × −/−) matings, respectively, were analyzed for Pgp genotype following external examination for cleft palate.

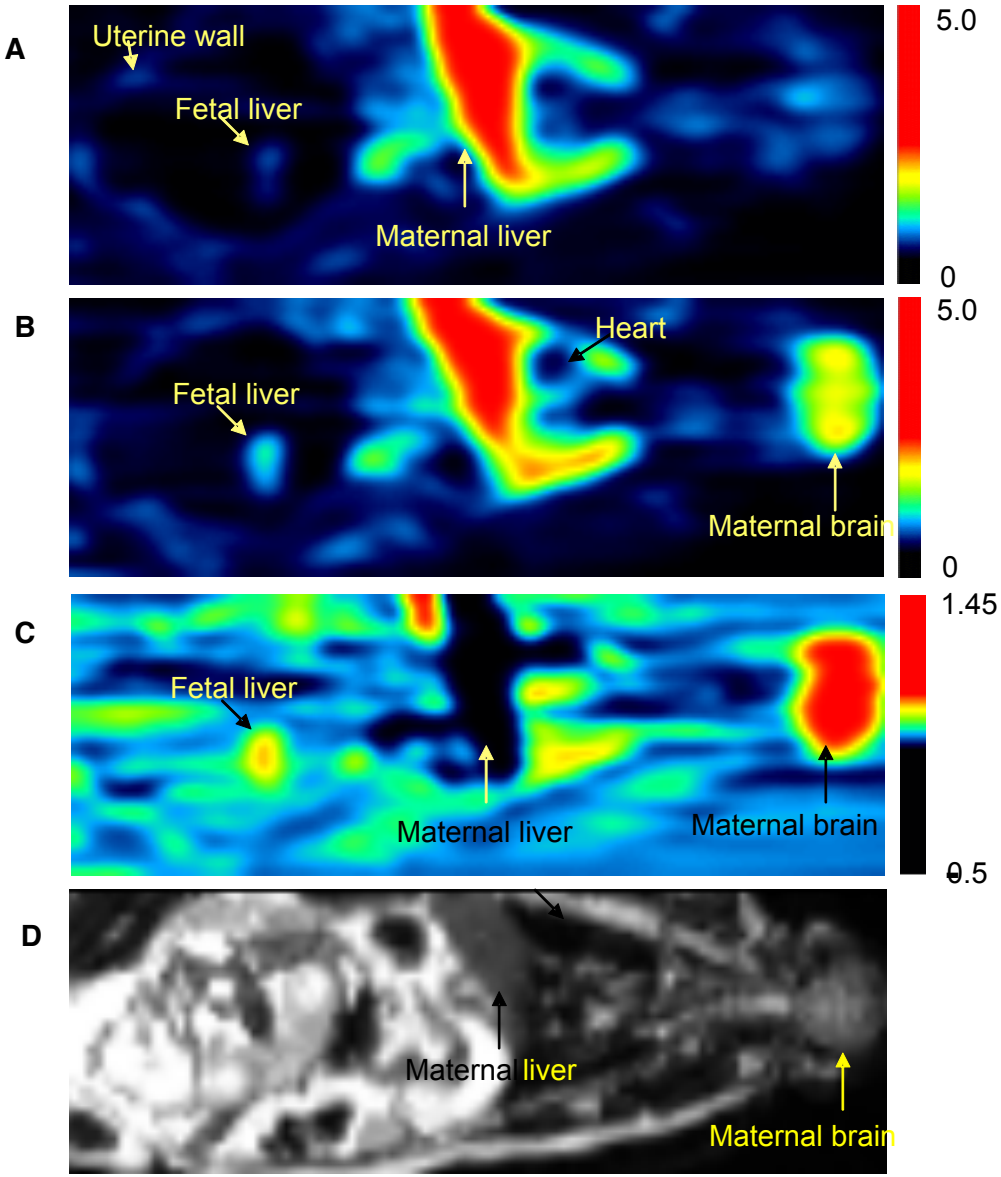
Pregenotyped mice were mated and females received vehicle or 1.5 mg/kg/d L-652,280 on Gestation Days 6 through 15. On Gestation Day 18, animals were euthanized, and the fetuses were examined for cleft palate. Lankas et al., Reprod Toxicol 1998, 12(4):457-63

P-gp Expression in the Human Placenta Decreases Dramatically with Gestational Age



Mathias et al.,
Am J Physiol Regul Integr Comp Physiol. 2005 289:R963-9.

Efflux of ^{11}C-Verapamil by Placental P-gp in the Nonhuman Primate



Eyal et al.,
J Nucl. Med, 2009
Chung et al., Br J Pharmacol, 2010

UWPKDAP

University of Washington Program on Pharmacokinetics of Drug Abuse

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PD: Jash Unadkat, PhD

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Joanne Wang, PhD

Nina Isoherranen, PhD

Project 3 – Bupropion PK and PBPK simulations

Co-PIs

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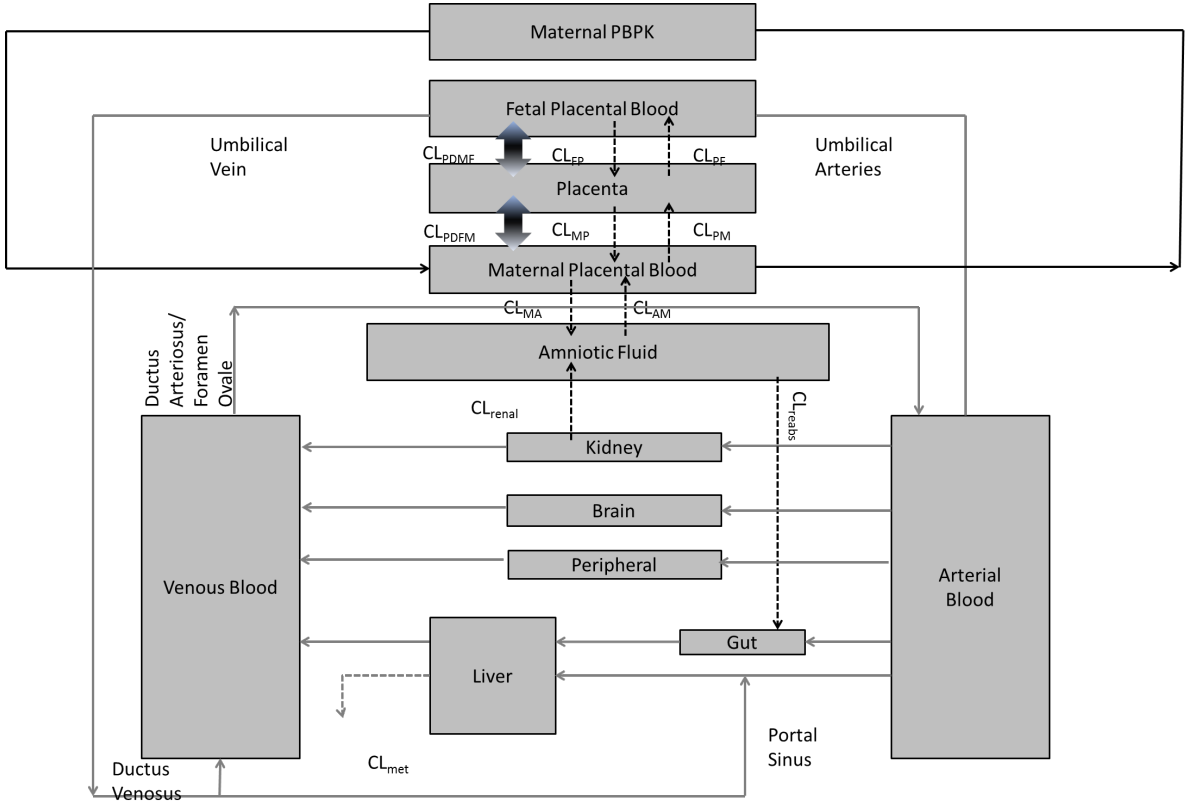
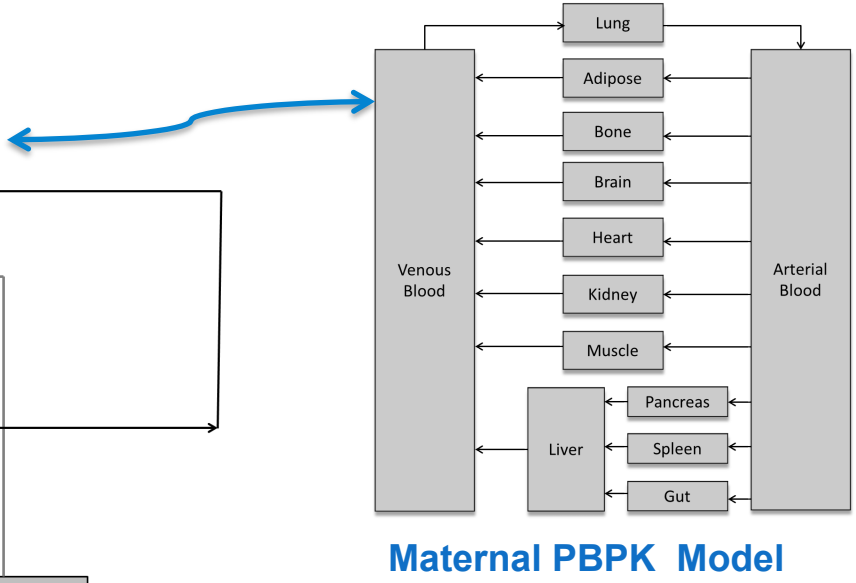
Jash Unadkat, PhD

https://sop.washington.edu/department-of-pharmaceutics/program-on-pharmacokinetics-of-drugs-of-abuse-during-pregnancy-uwpkdap/

Physiologically-Based Pharmacokinetic Model

Fetal PBPK Model

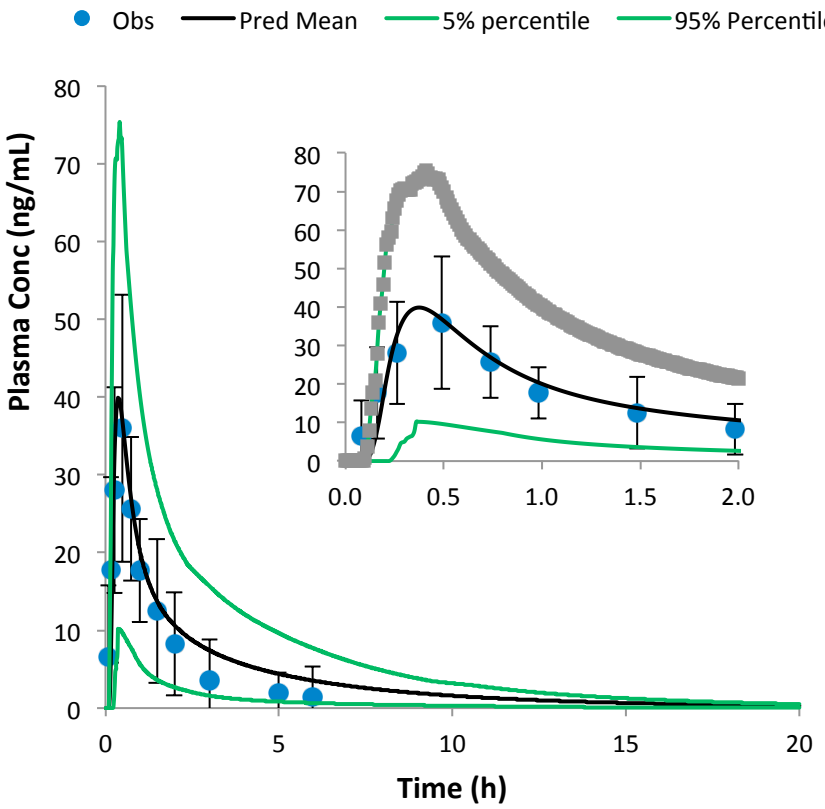




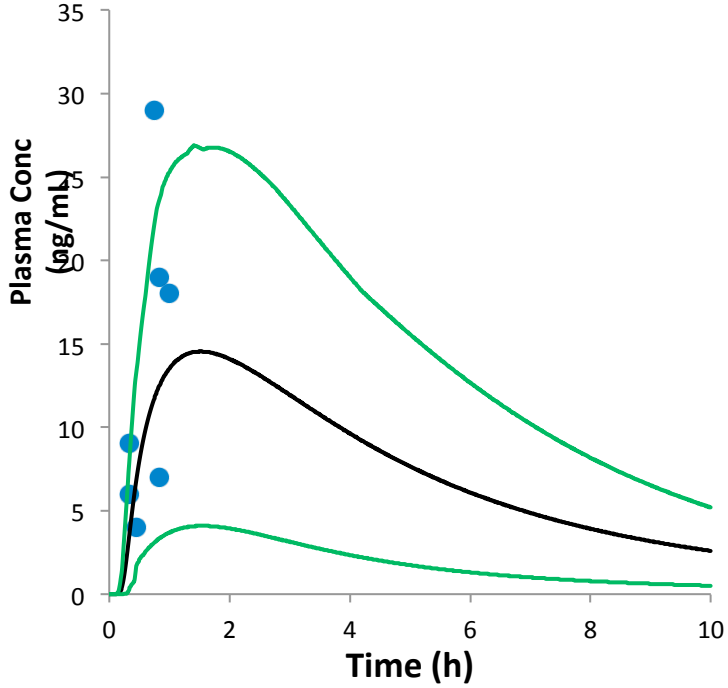
Maternal PBPK Model

Maternal-Fetal Disposition of Midazolam is Well-Predicted by the PBPK Model

Maternal



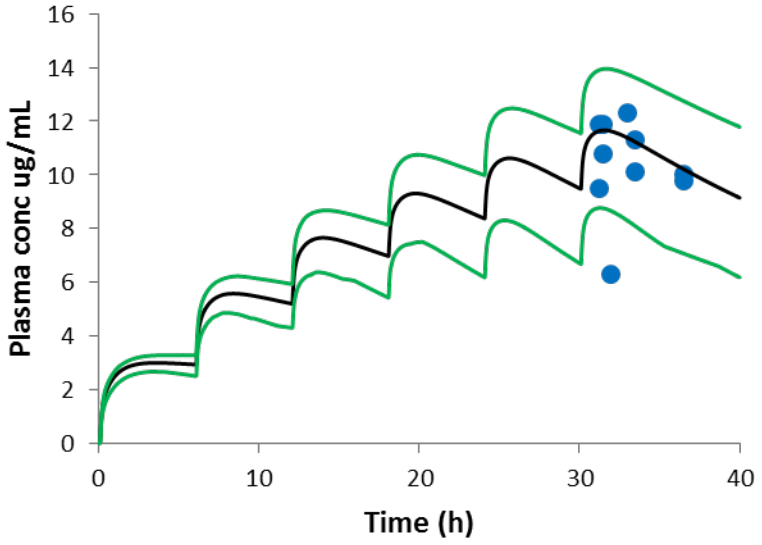
Fetal (at delivery)



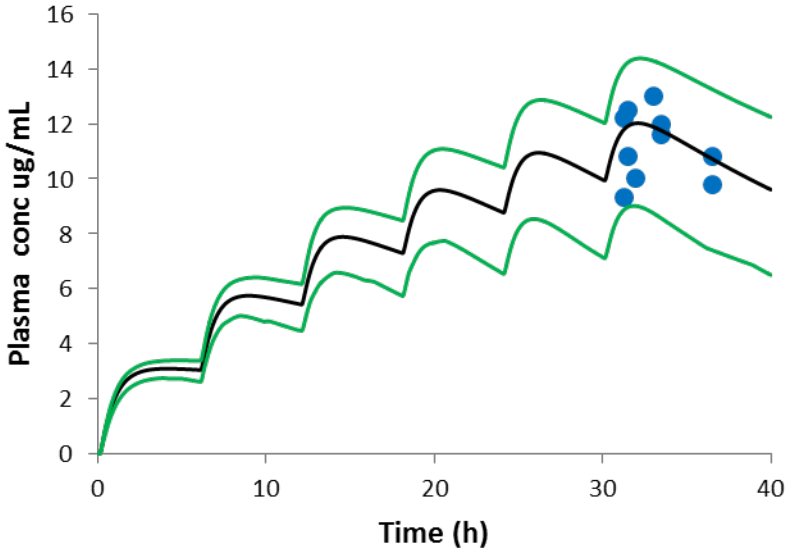
Kanto et al orally administered 15 mg midazolam to pre C-section women (n of 8)

Maternal-Fetal Disposition of Theophylline is Well-Predicted by the PBPK Model

Maternal

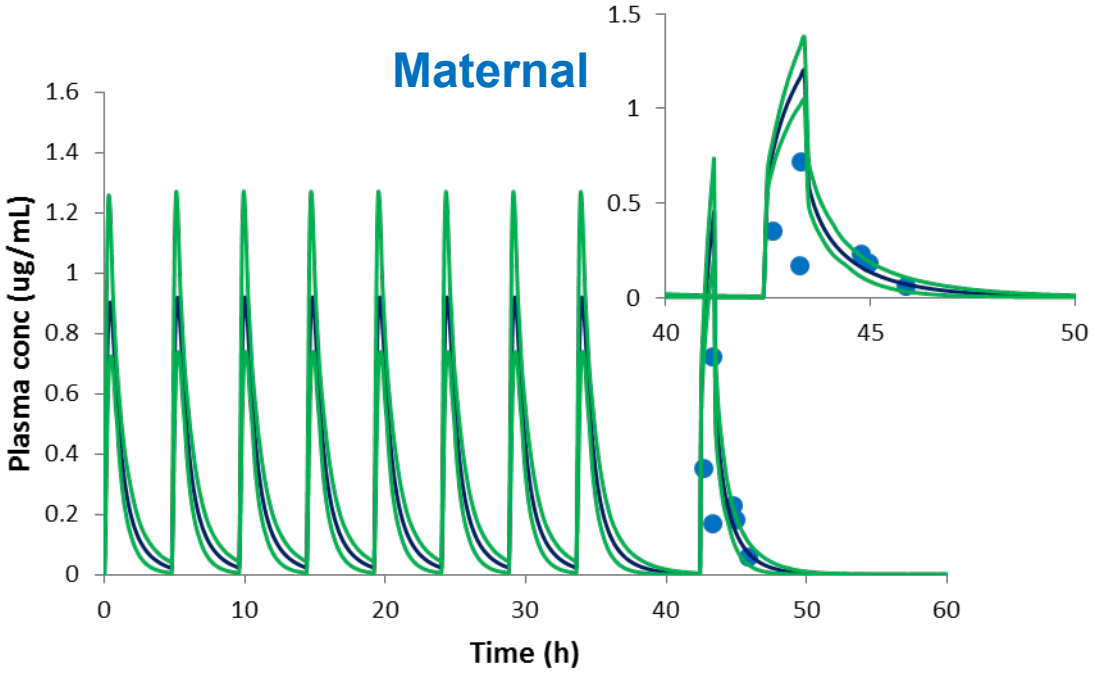


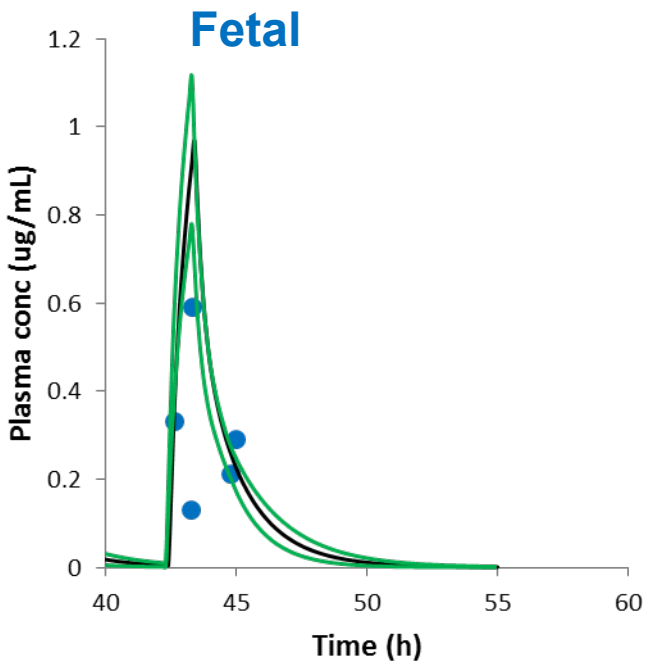
Fetal (at delivery)



Ron et al dosed 200mg oral theophylline every 6 h to asthmatic women with otherwise uncomplicated pregnancies before C-section

Maternal-Fetal Disposition of Zidovudine (AZT) is Well-Predicted by the PBPK Model





O'Sulllivan et al dosed oral AZT 200mg five times per day, followed by 1-h infusion during C-section

Conclusions and Significance

- PBPK modeling well-predicted fetal exposure to drugs that diffuse across the placenta

- Incorporation of placental transporters in our PBPK model should allow prediction of fetal exposure to drugs that are transported

UWPKDAP research should result in tools to predict drug dosing regimens for pregnant women that maximize drug efficacy while minimizing maternal-fetal toxicity

Acknowledgments

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- Project PIs, co-PIs and co-inv. of UWPKDAP
- Former graduate students and postdoctoral fellows of the Unadkat laboratory
- Funding by several past NIH grants and the present P01 DA032507

P-gp is Functional in the Perfused Human Placenta

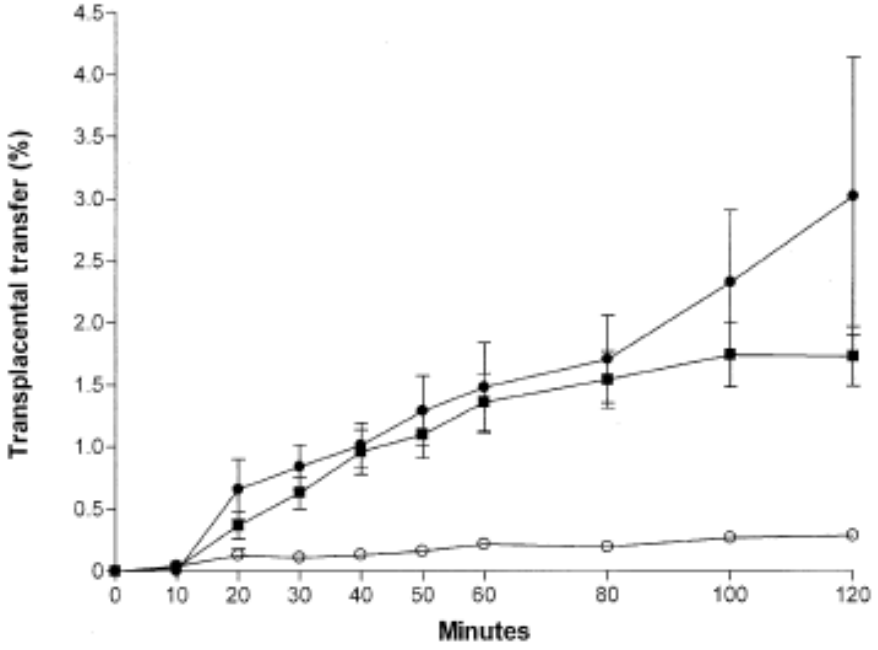
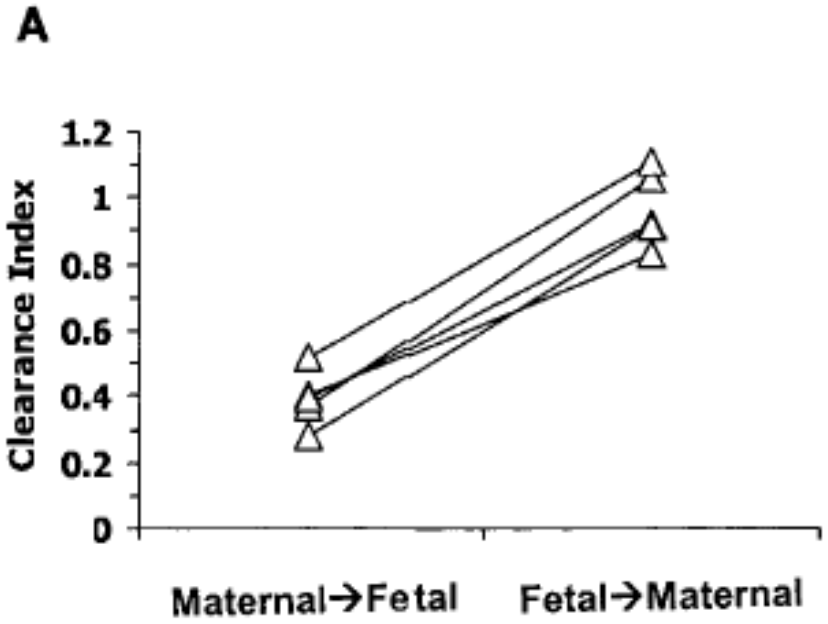


Fig 1. Transplacental transfer of saquinavir in control perfusions with saquinavir only (*open circles*) or after preperfusion with P-glycoprotein inhibitor PSC833 (*solid circles*) or GG918 (*squares*).

Molsa et al., Clin Pharmacol Ther. 2005 78:123-31



Transplacental clearance index of (A) indinavir determined in the maternal-to-fetal and fetal-to-maternal directions for each placenta. Lines join data from the same placenta.
Sudhakaran et al, Antimicrob Ag Chemo2005, 49:1023–1028