FDA Workshop
Evaluating Immunosuppressive Effects of In Utero Exposure to Drug and Biologic Products.
Fetal Transfer of Small Molecules
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Pregnancy Team:

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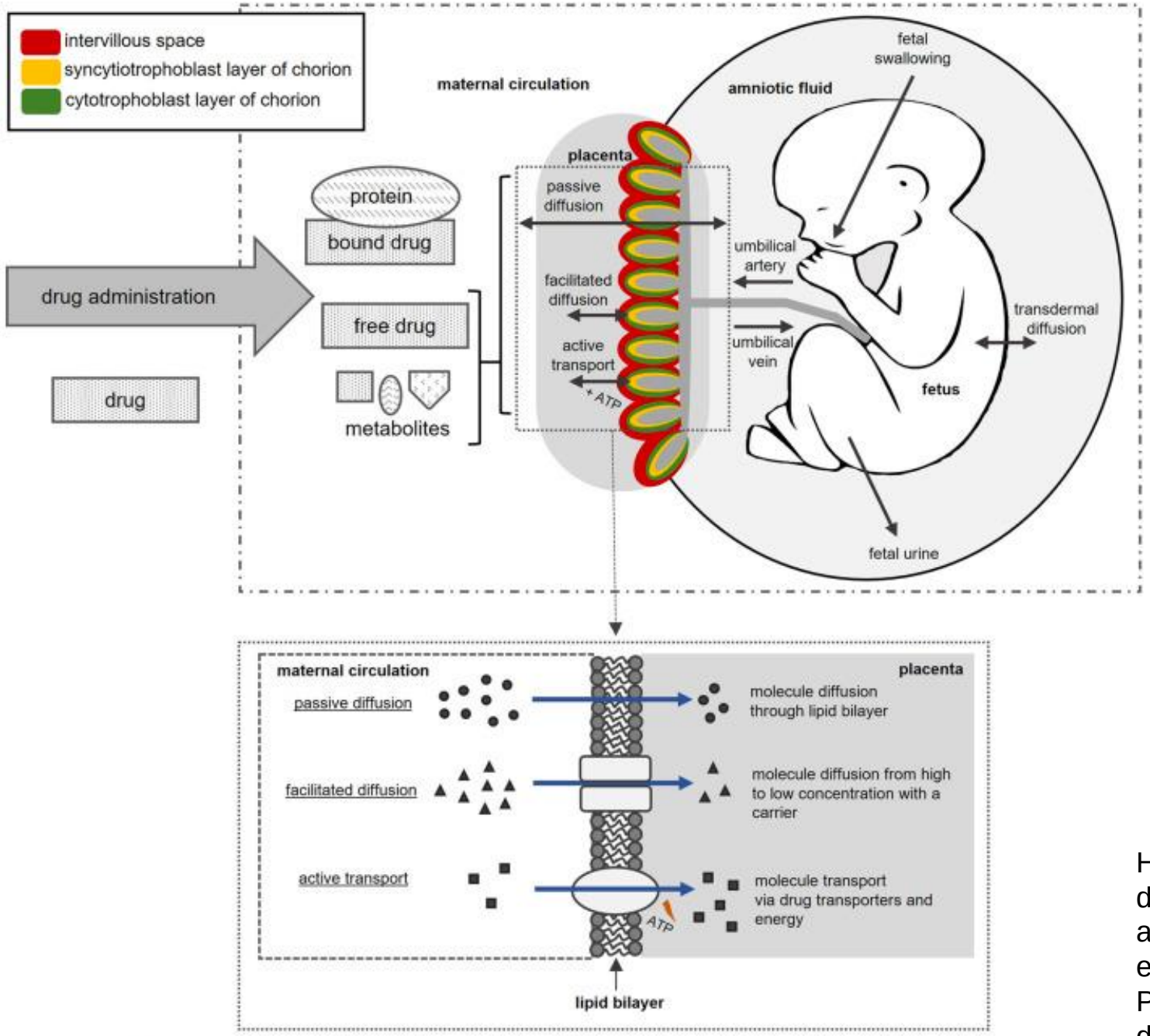
Drug Use in Pregnancy and Post Partum

1. **SAFETY, EFFICACY, EXPOSURE in the MOTHER.**

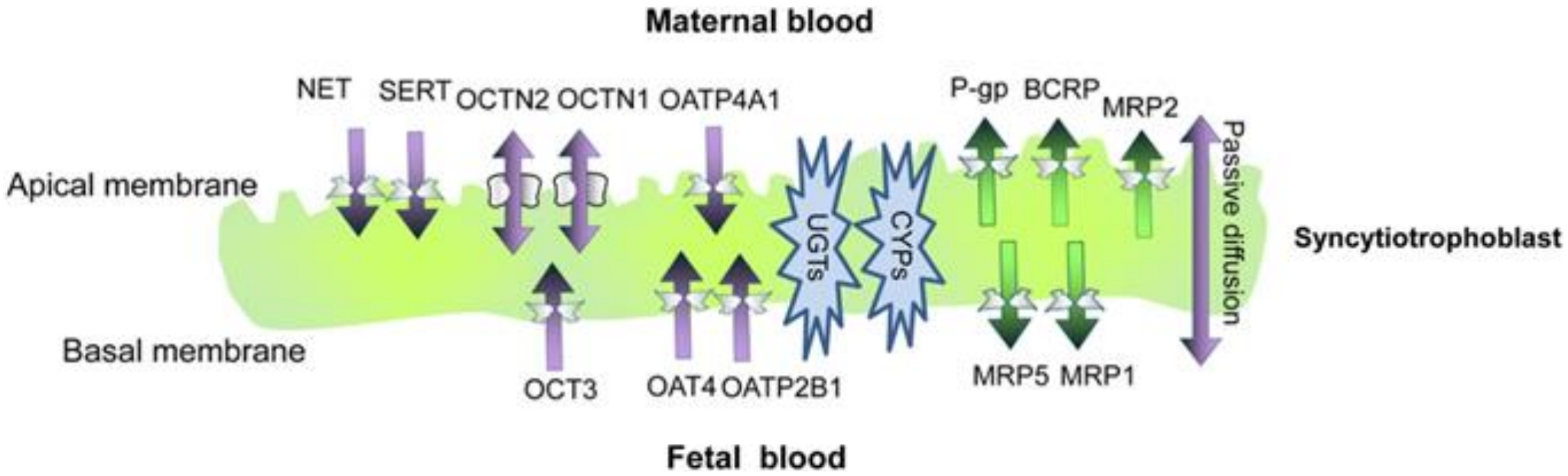
2. **SAFETY, EXPOSURE, Occasionally efficacy in the FETUS.**

3. **SAFETY, EXPOSURE, Occasionally efficacy in the NEONATES.**



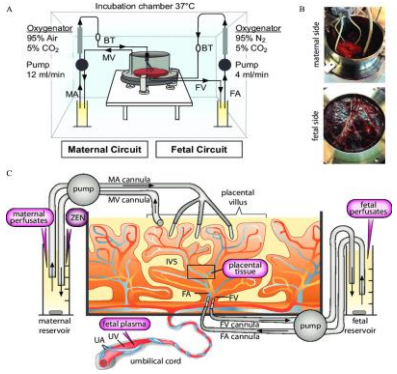
ATP adenosine triphosphate

Hudson RE, Metz TD, Ward RM, et al. Drug exposure during pregnancy: Current understanding and approaches to measure maternal-fetal drug exposure. Front Pharmacol. 2023;14:1111601. Published 2023 Mar 23. doi:10.3389/fphar.2023.1111601



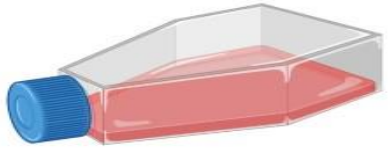
Fate of drugs in the placenta - Syncytiotrophoblast

Various Options Are Available to Study Exposure, Response and Safety in Pregnancy

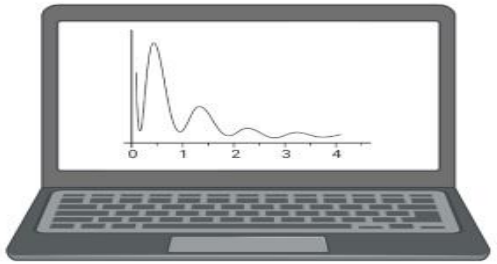


Ex-Vivo models

Clinical studies in pregnant women



In-vitro models



Computational models

Animal models

Drug Exposure, Response, Safety Studies in Pregnancy

- **In Vitro cell culture based:**
  - Static system; drug uptake-permeability parameters; impact on placenta
- **Placenta on a chip:**
  - Promising; hemodynamics; multicell layers; suitable for effect on placental cells
- **Ex vivo placental perfusion:**
  - Valuable; difficult to set up; may overestimates placental uptake; physical adsorption loss
- **Animal Models of Pregnancy:**
  - Mechanistic information; species differences in drug exposure (pharmacokinetics) and response and physiological differences in pregnancy
- **Clinical Study:**
  - Ideal; Intensive sampling in a dosing interval; Difficult to perform longitudinal studies

Methods/Models used (Exposure – Safety)

Clinical - Fetal Exposure:

Cord Tissue concentration (one time)

Cord blood/maternal only at delivery

Cord venous / Maternal blood or plasma ratio

Cord arterial / Maternal blood or plasma ratio

(rarely measured; can provide fetal metabolic capacity)

Total drug vs Unbound drug (unbound rarely measured)

Concentration depends on - Drug dosing/Sample time; assay

Other specimens:

Amniotic Fluid, meconium Concentrations (not always practical; one time)

Methods/Models used (Exposure – Safety)

Clinical - Placental concentration of drugs:

Placenta/maternal blood or plasma ratio
(typically, at delivery; rarely other times - termination of pregnancy;
sample site dependent; assay method dependent)

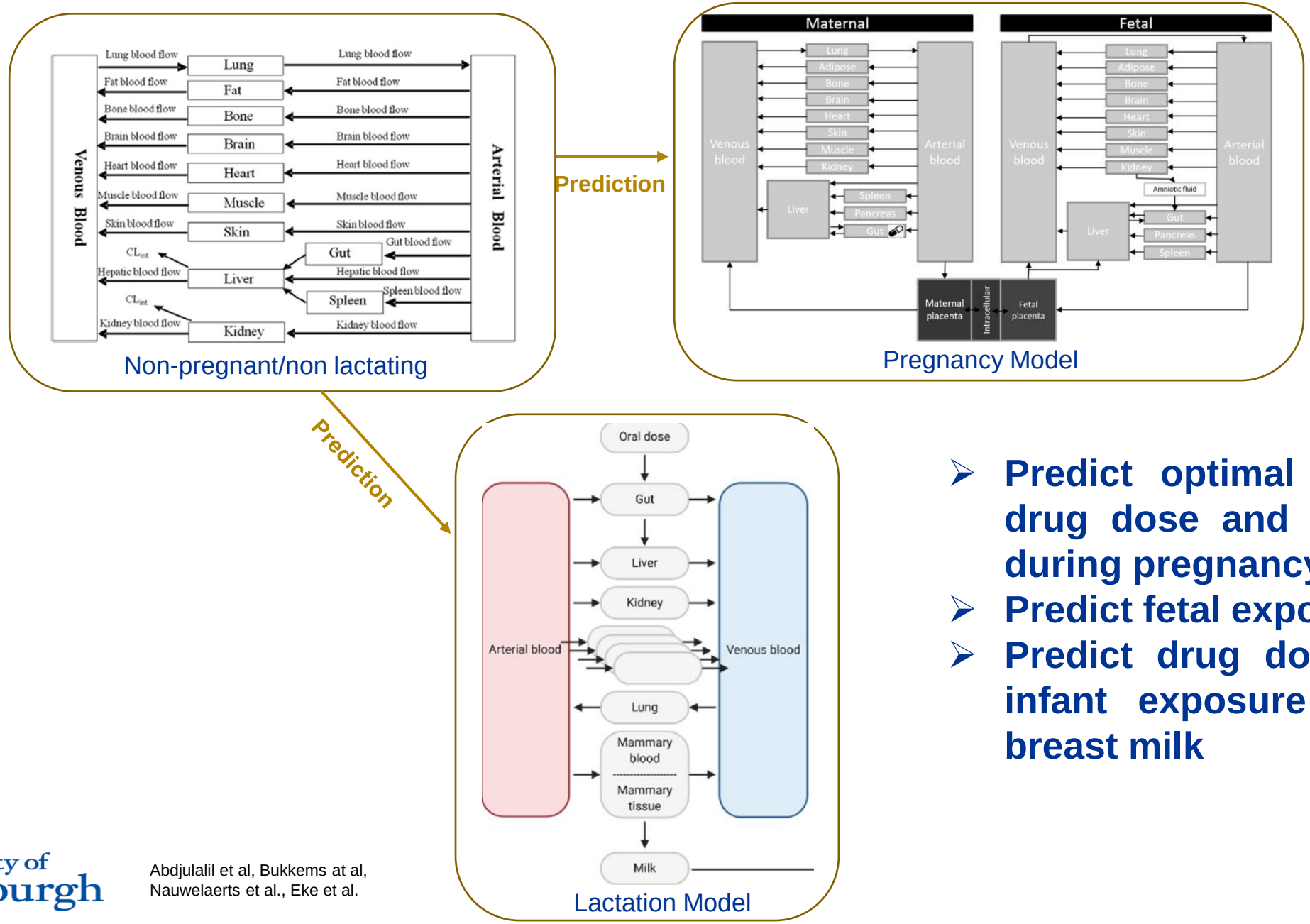
Neonates:

Blood/plasma (heel stick) –concentrations – half life
Other biospecimens (hair, nail, meconium)
Maternal milk content (Cmax and AUC ratios milk/plasma;
Relative Infant dose (RID); Upper 95% area ratio (UAR)

Computational Models:

Physiologically based pharmacokinetics-PBPK; Population Pharmacokinetics (PopPK)
Can predict time course (total and unbound concentration;
AUC total; AUC unbound); neonatal/maternal AUC ratio
Not as extensively utilized; increasingly being applied.

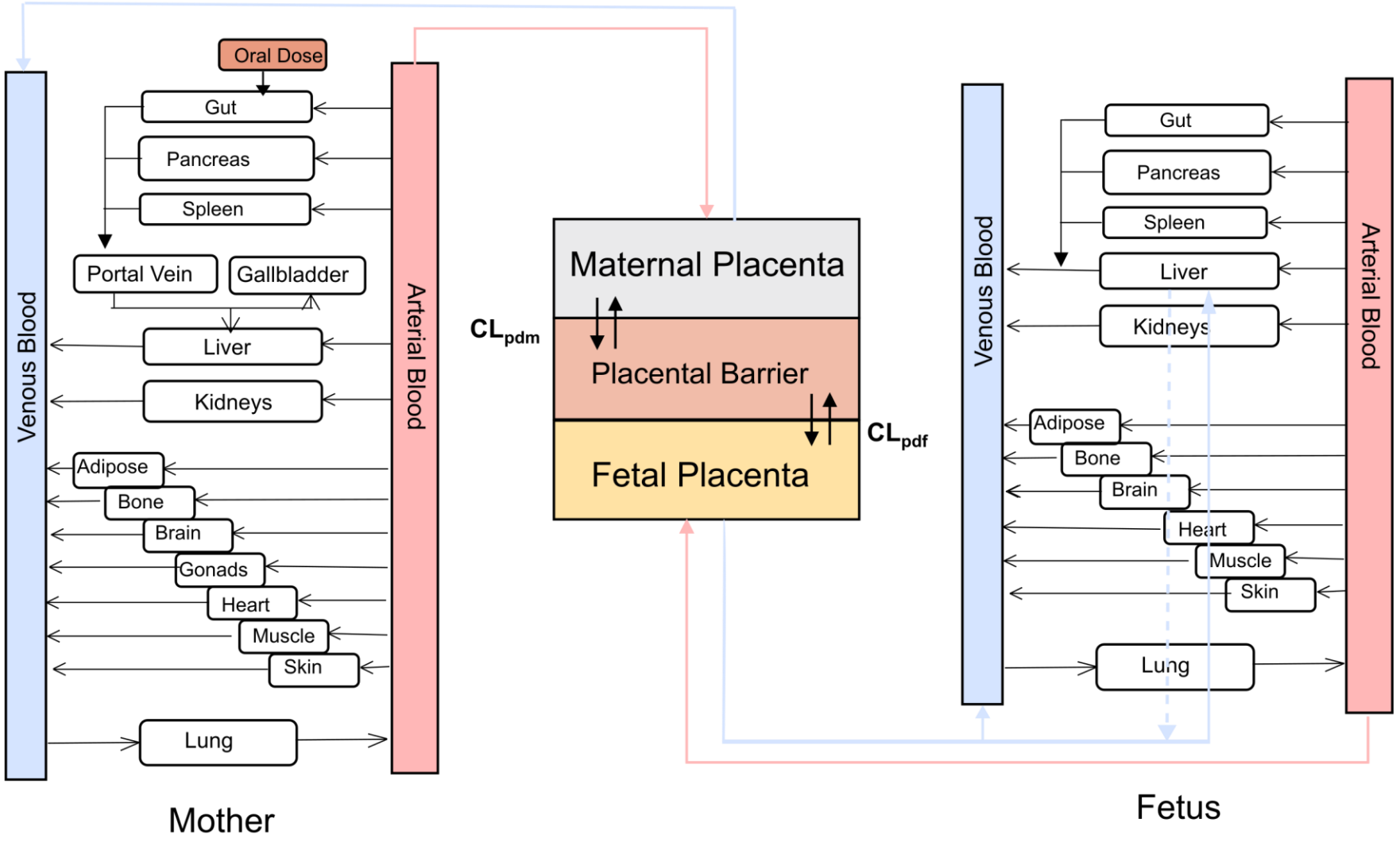
Maternal-fetal and lactation PBPK - Exposure



- **Predict optimal maternal drug dose and exposure during pregnancy**
- **Predict fetal exposure**
- **Predict drug dosing and infant exposure through breast milk**

University of Pittsburgh

Abdjulalil et al, Bukkems at al, Nauwelaerts et al., Eke et al.



Maternal-Fetal PBPK Model

Maternal-Fetal Model Structure along with Permeability-limited Placental Model. Solid arrows indicate tissue blood flows, whereas dashed arrows indicate clearances. f/F, fetal; pd, passive diffusion; m, maternal; p, placental.

Adapted from Bukkems et al. Clin Pharmacokinet. 2022;61(8):1129-1141

Methods / Models Used (Safety)

Ideal; should be performed whenever possible.

Effect on placental cell function
Effect on immune cells:
    Fetal immune development; Neonatal immune ontogeny

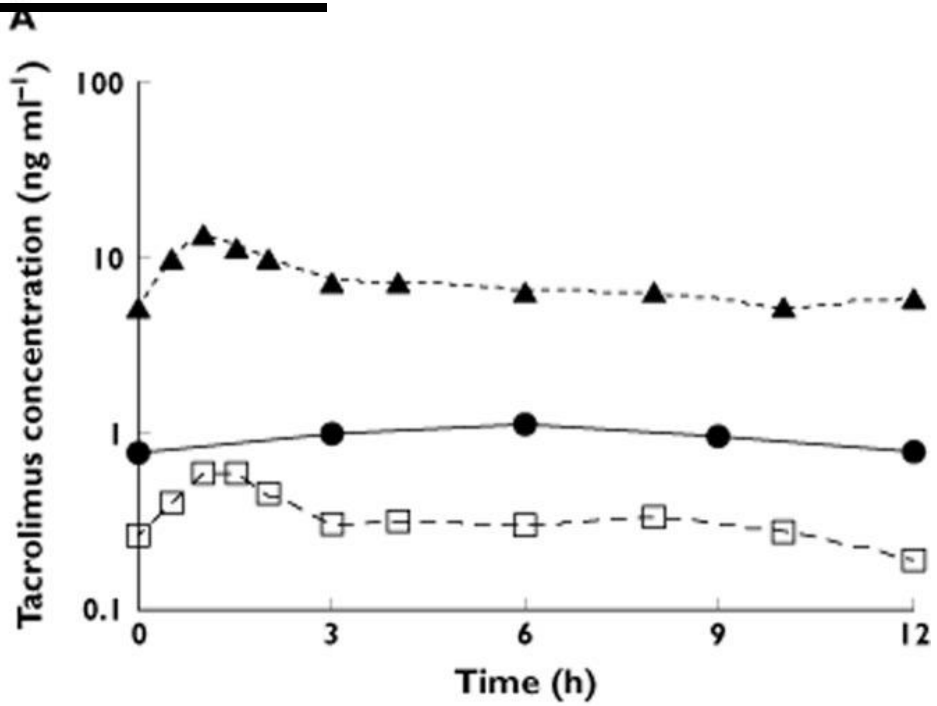
Effects on birth related outcomes of newborn:
    Prematurity; C-sections; birth weight

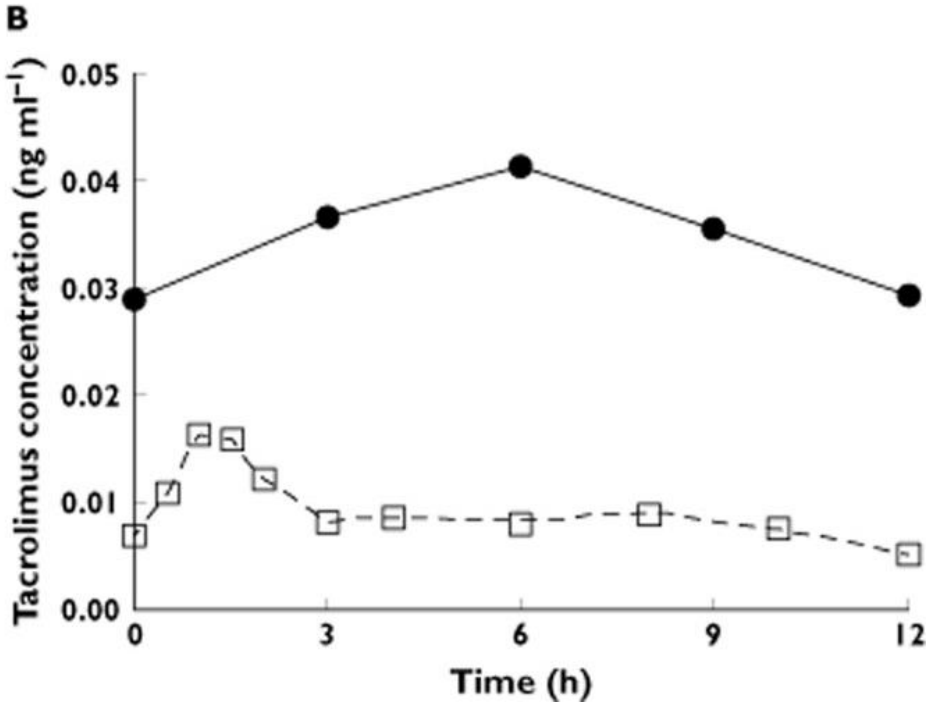
Neonates:
    Physical development; Growth and mental development; neurological
    renal outcomes
    Effects on post natal infections; Myelosuppression
    Response to immunization

Medications:
Tacrolimus - MW: 804; Log P 3.3; Highly bound to RBC

Placental Perfusion:	**Placental accumulation (113)** No fetal transfer (Likely due to placental Pgp) (Over estimation due to no RBC in medium; Drug loss in device)
Placental tissue:	**placental/maternal = >3; 10-20** sample site dependent – uneven distribution.
Cord/maternal blood:	**Generally low (< 1)**
Infant exposure through milk:	**Milk/blood < 0.2; milk/plasma = 2** **RID < 1% of maternal dose based on BW** Negligible ingestion of tacrolimus from milk in neonates
Infant clearance:	**Similar decline of TAC** in neonates (breast fed vs bottle fed low bioavailability)

Tacrolimus concentration in maternal blood, plasma and human milk





A. Steady-state unbound tacrolimus concentrations in maternal plasma and breast milk

, milk; , plasma; , blood;

B. One subject over a single dosing interval. The subject was treated with 1.5 mg of tacrolimus twice daily for immunosuppression

, milk unbound drug; , plasma unbound drug

Zheng S et al. Tacrolimus placental transfer at delivery and neonatal exposure through breast milk. Br J Clin Pharmacol. 2013;76(6):988-996.

Tacrolimus - MW: 804; Log P 3.3; Highly bound to RBC

Relatively safe; no pattern of malformation; normal development; no major negative effect.

Reports of Intrauterine growth retardation; prematurity; low birth weight.

Neonates: **Transient hyperkalemia / increase in creatinine –** resolving in 24-48 hrs.

Mostly normal GFR (dose dependent)

Neonatal Immune cells:

At high concentrations, dose dependent inhibition of cytokine production;

without affecting innate immune response

no data on functional immaturity of neonatal immune cells
pediatric transplant patients have no issues.

adequate immunogenicity after vaccination.

Satisfactory growth and development; normal physical and mental development.

Kaines et al 200; Tendon et al 2002; Ostensen et al 2006; Jain et al 1997;

Cyclosporine MW: 1202; Log P 2.9; Highly bound to RBC

Transfers through placenta

Placental concentrations higher than maternal (5-10)

Umbilical cord / Maternal ratio: High

Metabolites observed in placenta

Ex vivo:

< 5% transfer

Milk: Milk/blood < 1

RID < 2%

Cyclosporine and its metabolites in mother and child[a]

	Maternal blood (ng/ml)	Cord blood (ng/ml)	Placenta (ng/g)	Umbilical cord (ng/g)
CyA	90, 105	53, 55	506, 318	2641, <25
M-17	134, 132	159, 162	481, 184	137, 97
M-21	<25, 0	0, 0	<25, 0	0, 0
M-1	89, 63	28, 0	229, 89	28, 0
M-18	0, <25	0, 0	0, 0	0, 0

[a]The first value was observed in patient 1 and the second value was observed in patient 2.

Cyclosporine MW: 1202; Log P 2.9; Highly bound to RBC

Relatively safe; no embryo or fetotoxicity; no pattern of malformation; IQ no difference compared to non transplant control-no long term adverse neurocognitive effects

Reports of Intrauterine growth retardation, prematurity; abortions; still births; low birth weight (depends on time of pregnancy after transplantation) **(over all similar to TAC)**

Infants born:

- Normal renal function – GFR; normal psychomotor development
- some fetal kidney toxicity in rats/mice
- Immune cell function: some T and B cell development and maturation delay observed.
- **No overt clinical immunodeficiency**

Mycophenolic Acid – MW 320; Log P-1.6 High albumin binding (Inhibitor of IMPDH activity) – de novo purine synthesis

Experimental animal studies: **Teratogenic effects**

Clinical: **Cleft lip and palate; bilateral microtia**; atretic external auditory canals; chorioretinal coloboma, hypertelorism, micrognathia; fetal hydrops

32% spontaneous abortions;

27% structural malformations-ear deformation

Higher incidence with later cessation of MPA in pregnancy

Must be avoided

Milk: No data; avoided.

- Pergola et al 2001; Armenti et al 2004; Le Ray et al 2004; Sifontis et al. 2006; Sifontis et al 2006; Tjeertes et al 2007; Perez-Aytes et al 2007

Prednisone/prednisolone
MW: 358; Log P: 1.6 Highly bound to plasma protein

Drug Exposure:

Crosses placenta

Metabolized by placental hydrogenase

Minimal fetal exposure cord: maternal < 1

Milk: Detected but low; milk / plasma: 0.6;

RID < 1-5%

OK to breast feed

Not teratogenic; Some cleft palate cleft lip

At High dose: Associated with higher spontaneous abortion; fetal death
Fetal Adrenal suppression

Azathioprine
MW: 277; low protein binding

Low placental concentration: 64-93% of maternal
Fetal exposure: **1-< 5% of maternal**

Milk: Low concentrations; **RID: < 1%**
No Impact on breast feeding:

No major teratogenic effect; **normal development** (contrast with animal studies)

Spontaneous abortions; prematurity; IUGR; LBW reported

Normal blood counts; **no increased susceptibility to infection**; normal growth rate

Dose related myelosuppression

Sirolimus (MW: 914; log P; 4.3)
Everolimus (MW: 958)

Limited observations.

No teratogenicity; mutagenicity; carcinogenicity

Cord blood to maternal blood: limited data

Milk: Trace concentrations; RID: < 1%

Prematurity; fetal hypotrophy observed

Generally contraindicated

Confounding – Limiting Factors

Nature of original disease in mother

Co-morbid conditions increasing pregnancy risks

hypertension; renal dysfunction; diabetes

Combination therapy commonly used - difficult in attributing effect to a drug

Previous and later pregnancies with other agents – normal delivery (MPA as example).

Cord Blood:

Sample Timing issues: Cord/maternal not drawn at same time

Cord/maternal **sample time** with reference to drug dosing impacts ratio

Total vs unbound concentration impact and interpretation

Confounding – Limiting Factors

In Vitro placental perfusion:

Normal placenta vs patient placenta;

Difference in ex vivo vs patient (not steady state – acute study; saturation?)

Perfusate has no blood; higher placenta to perfusate levels observed.

Placental changes due to drug accumulation with time and gestation

Placental cytotrophoblasts, syncytiotrophoblasts, endothelial cells, placental lymphocyte function and maturation – **limited data**

Milk: Compositional change; sampling time issues; milk volume.

Neonatal immune system (short term-long term): **Limited data**

Conclusions

Healthy Moms – Healthy Babies – Healthy Society

Pregnancy Stress; post-partum depression – impacts mom, fetus and neonates

Recommendations: 1 year post transplant; with stable allografts; no proteinuria; no recent episodes of rejection/infections; well controlled medical conditions (hypertension/diabetes)

Maternal risk: graft loss low due to pregnancy

Neonates: No increase in malformation in transplant patients on **cyclosporine, steroids and tacrolimus** (similar to general population-3%). **No to MPA.**

Prematurity; low birth weight-but normal weight by year 2; earlier gestational age; more C-sections; some renal dysfunction - generally short lived; some immune cell effects; No difference between CYA and TAC; no long-term effect.

Milk exposure: Limited exposure; small RID; **safe to breast feed**.

Societal Responsibilities:

Support efforts towards healthy moms

Better access to health care for all moms

Health Professional Responsibilities:

Provide education to subjects; Collect data

Patients Responsibilities:

Ask questions; facilitate data generation

Funding Agencies:

Understudied population-more funding needed

Need for National Registries for organized data collection

Life Lessons:

1. We are all fortunate to be where we are and what we do; acknowledge and appreciate that. Not everyone in this world is as fortunate as we are. Let us resolve to do some thing for those who have not. Make a difference in some one's life.

2. Take advantage of the opportunities that you come across and find your passion and pursue it.

3. Real motivation comes from within. Opportunities to achieve greatness is within you.

4. It is Ok to make mistakes, but we should learn from the mistakes that we make.

5. We have to take responsibility for our actions. No one else is to be blamed for our actions.

6. Acknowledge the sacrifices of our parents/family. We have to be thankful for what we have – to our parents, to our spouse, to our family and to friends; express your appreciation at every chance that you get.

7. Attitude is a choice, the most important choice that one can ever make.

8. Success is being the best that one is capable of - as a human being we are successful if we do some thing to leave the planet world better than we found it.

9. Successful people do not find time, they make time.

10. It is not just what happens to us, it is how we react to what happens to us that will ultimately decide how we live.

11. Don't just wait for the perfect moment in life; take the moment and make it perfect.