Pregnancy-induced anatomical and physiological changes relevant to PBPK modeling

Fetal Pharmacology and Therapeutics Workshop

FDA and University of Maryland Center of Excellence in Regulatory Science and Innovation

Oct 21-22, 2021

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Disclosure

- I have nothing to disclose.
- My presentation reflects my views only, not those of the NIH or the federal government.

Topics

- Maternal Anatomic and Physiologic Changes
- Placental Functions and Maturation
- Fetal Maturation

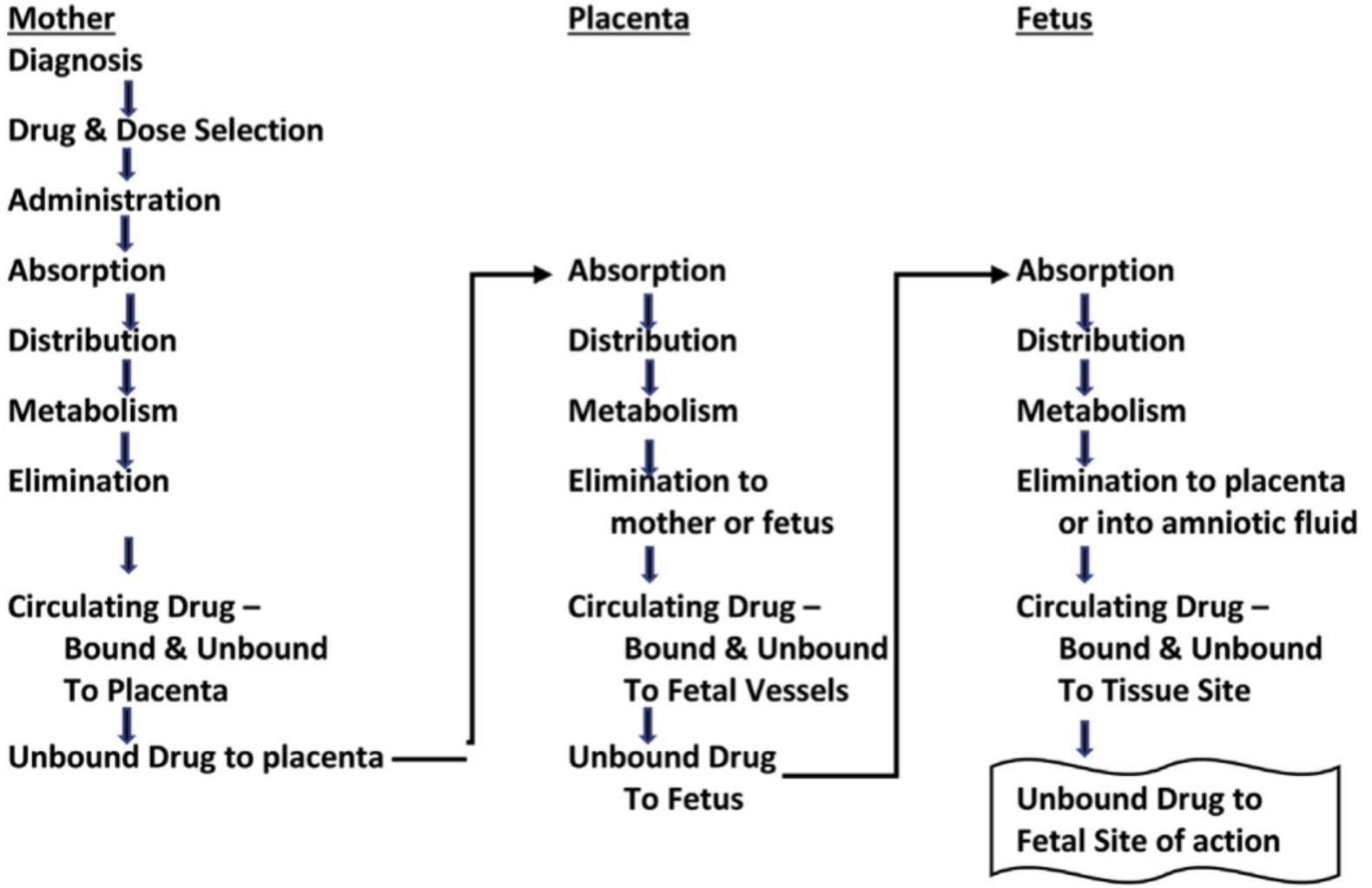
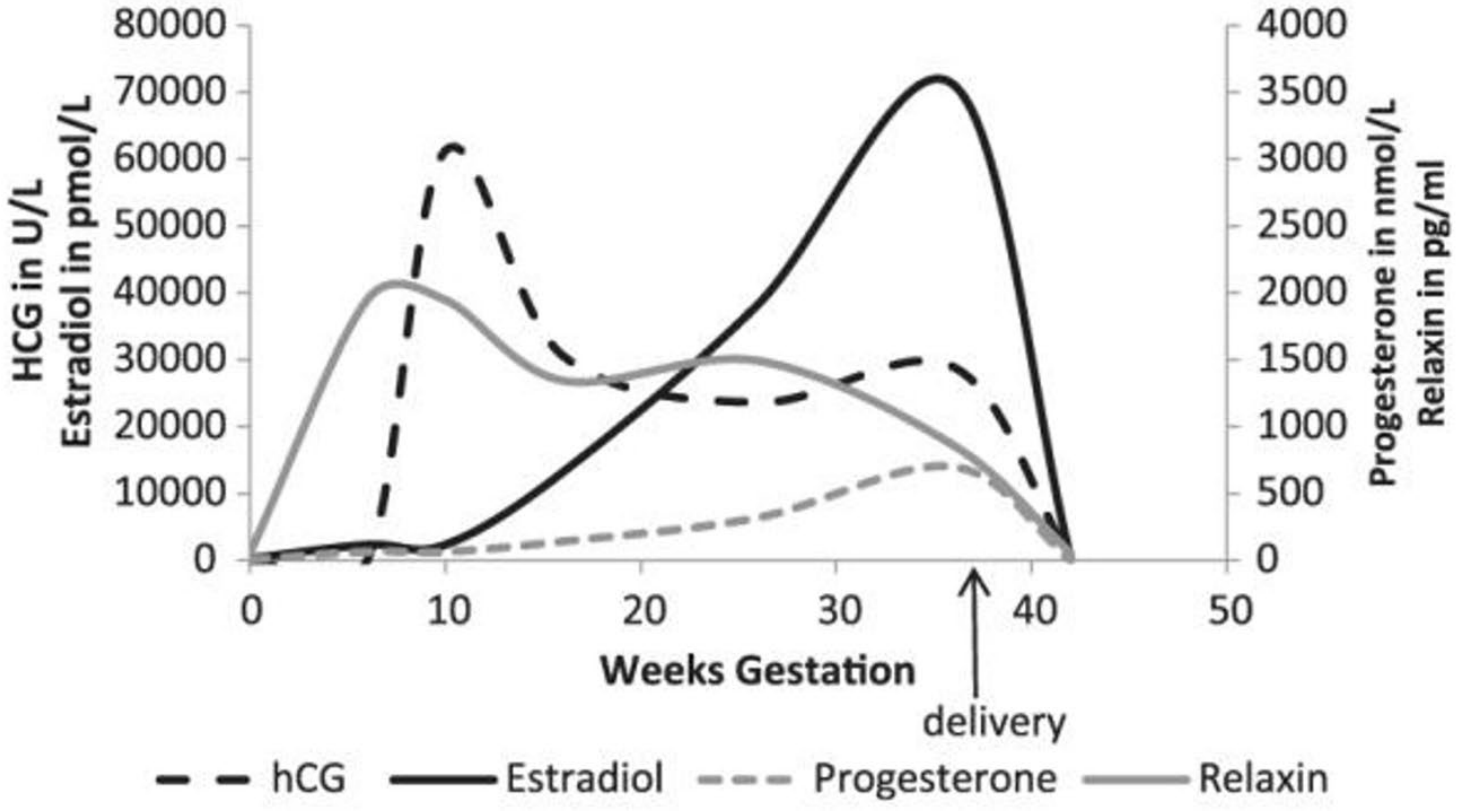


Fig. 1. Therapeutic process. Steps in the processing and transport of drugs from the mother to the proposed site of action in the fetus are shown.

Ward, R. M., & Varner, M. W. (2019). Principles of Pharmacokinetics in the Pregnant Woman and Fetus. *Clinics in perinatology*, *46*(2), 383–398. https://doi.org/10.1016/j.clp.2019.02.014



Hormonal variation throughout pregnancy and early postpartum. Mean data are of plasma human chorionic gonadotropin, estradiol, progesterone, and relaxin levels, before, during, and 6 weeks after pregnancy. Adapted from Ogueh and his colleagues.[19]

Renal Physiology of pregnancy. Cheung KL, Lafayette RA. Adv Chronic Kidney Dis 2013; 20(3):209-214. doi: 10.1053/j.ackd.2013.01.012 ; Ref 19: O. Ogueh, A. Clough, M. Hancock, M.R. Johnson. **A longitudinal study of the control of renal and uterine hemodynamic changes of pregnancy.** Hypertens Pregnancy, 30 (3) (2011), pp. 243-259

Maternal Physiologic Changes in Pregnancy

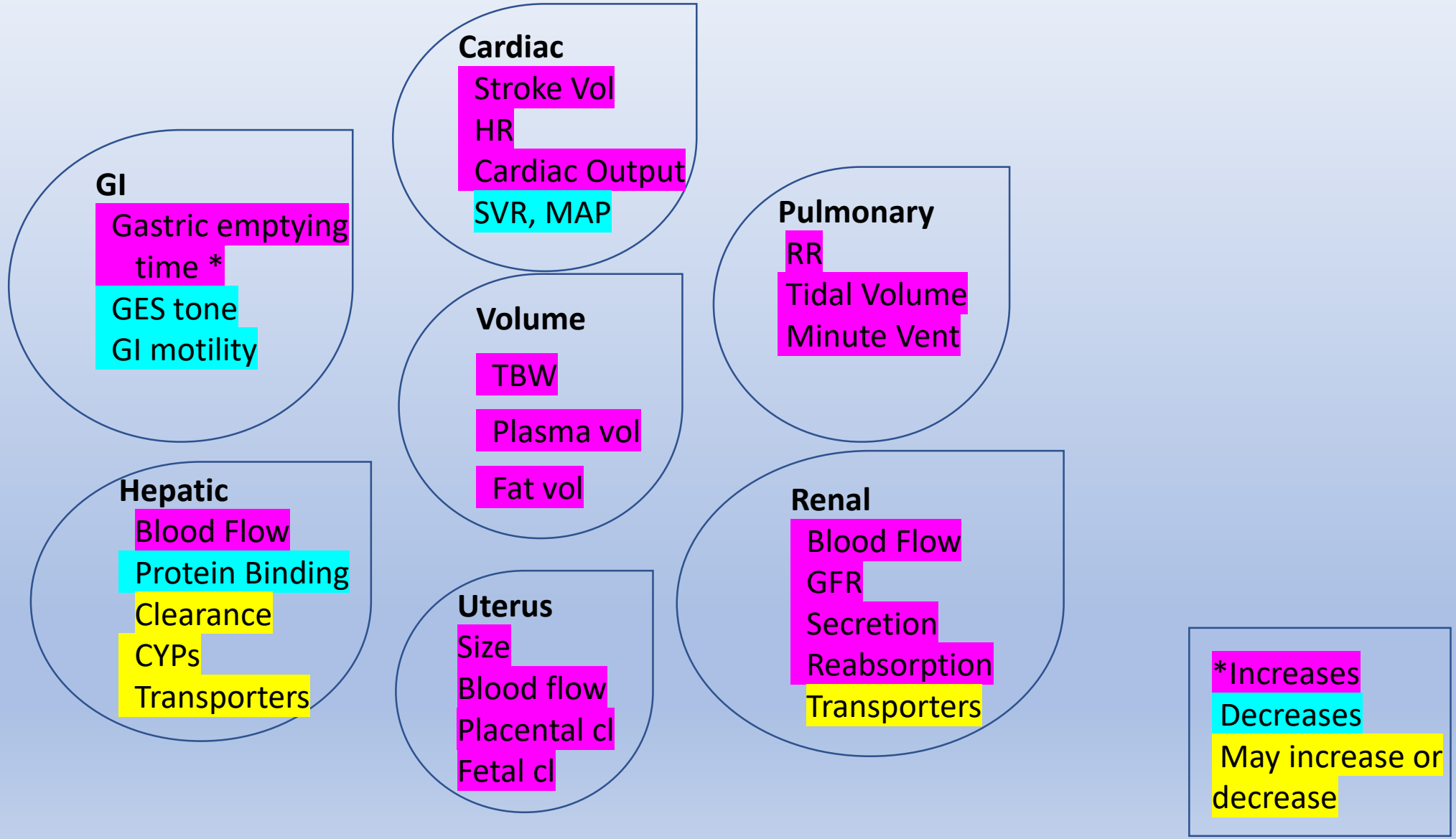


Table 2 Summary of pregnancy-induced changes in maternal physiology

Parameter	T_1[a]	T_2[a]	T_3[a]
Total body weight (kg)	↑ 6%	↑ 16%	↑ 23%
Total fat mass (kg)	↑ 11%	↑ 16%	↑ 32%
Total body water (L)	↑ 11%	↑ 27%	↑ 41%
Cardiac output (L)	↑ 18%	↑ 28%	↑ 33%
Plasma volume (L)	↑ 7%	↑ 42%	↑ 50%
Red blood cell volume (L)	↑ 4%	↑ 20%	↑ 28%
Hematocrit (%)	↓ 3%	↓ 8%	↓ 14%
Albumin (g/L)	↓ 5%	↓ 16%	↓ 31%
α1-AGP (g/L)	↓ 1%	↓ 22%	↓ 19%
Glomerular filtration rate (mL/min)[b]	↑ 19%	↑ 37%	↑ 40%
Effective renal plasma flow (L/h)	↑ 38%	↑ 48%	↑ 31%
Creatinine clearance (mL/min)	↑ 28%	↑ 58%	↑ 26%
Uterine blood flow (L/h)	↑ 923%	↑ 1,567%	↑ 2,771%
Hepatic blood flow (L/h)[c]	↔	↔	↔

↓ indicates decrease; ↑ indicates increase; ↔ indicates no effect.

[a]Mean percentage change (%) relative to prepregnancy level.

[b]Glomerular filtration rate measurement is based on inulin clearance.

[c]Literature data on hepatic blood flow are contradictory; hence, no effect is assumed.

Ke, A. B., Rostami-Hodjegan, A., Zhao, P., & Unadkat, J. D. (2014). Pharmacometrics in pregnancy: An unmet need. *Annual review of pharmacology and toxicology*, *54*, 53–69. https://doi.org/10.1146/annurev-pharmtox-011613-140009; data from Abduljalil, K., Furness, P., Johnson, T.N. *et al.* Anatomical, Physiological and Metabolic Changes with Gestational Age during Normal Pregnancy. *Clin Pharmacokinet* **51,** 365–396 (2012). https://doi.org/10.2165/11597440-000000000-00000

Other Changes during Pregnancy

- Elevated clotting factors and hypercoagulability
- Dilutional anemia
- Slight uncompensated respiratory alkalosis

TABLE 1

Summary of changes in P450 probe and sensitive marker drug disposition and in disposition of UGT markers at different stages of pregnancy

Target P450	Marker Drug	Effect on Marker Clearance during Gestation			Reference
		First Trimester	Second Trimester	Third Trimester	
CYP1A2	Caffeine, theophylline	↓	↓	↓	(Carter et al., 1986; Tracy et al., 2005)
CYP2B6	Efavirenz			↔↑[a]	(Cressey et al., 2012)
CYP2D6	Metoprolol (dextromethorphan UR)	(↑)	(↑)	↑ (↑)	(Hogstedt et al., 1985; Tracy et al., 2005)
CYP2C9	Phenytoin	↔	↑	↑	(Dickinson et al., 1989; Tomson et al., 1994)
CYP3A4	Midazolam			↑	(Hebert et al., 2008)
UGT1A4	Lamotrigine	↔	↑	↑	(Franco et al., 2008; Ohman et al., 2008)
UGT2B7	Zidovudine			↔	(Watts et al., 1991; O'Sullivan et al., 1993)

UGT, UDP glucuronosyltransferase; UR, urinary ratio.

[a]Efavirenz area under the curve was unaffected, but C_{min} was significantly decreased during the third trimester. Efavirenz is an inducer and inactivator of CYP2B6, and this may confound the findings.

Isoherranen, N., & Thummel, K. E. (2013). Drug metabolism and transport during pregnancy: how does drug disposition change during pregnancy and what are the mechanisms that cause such changes?. *Drug metabolism and disposition: the biological fate of chemicals*, *41*(2), 256–262. https://doi.org/10.1124/dmd.112.050245

TABLE 2

Summary of changes in transporter probe and sensitive marker drug disposition at different stages of pregnancy

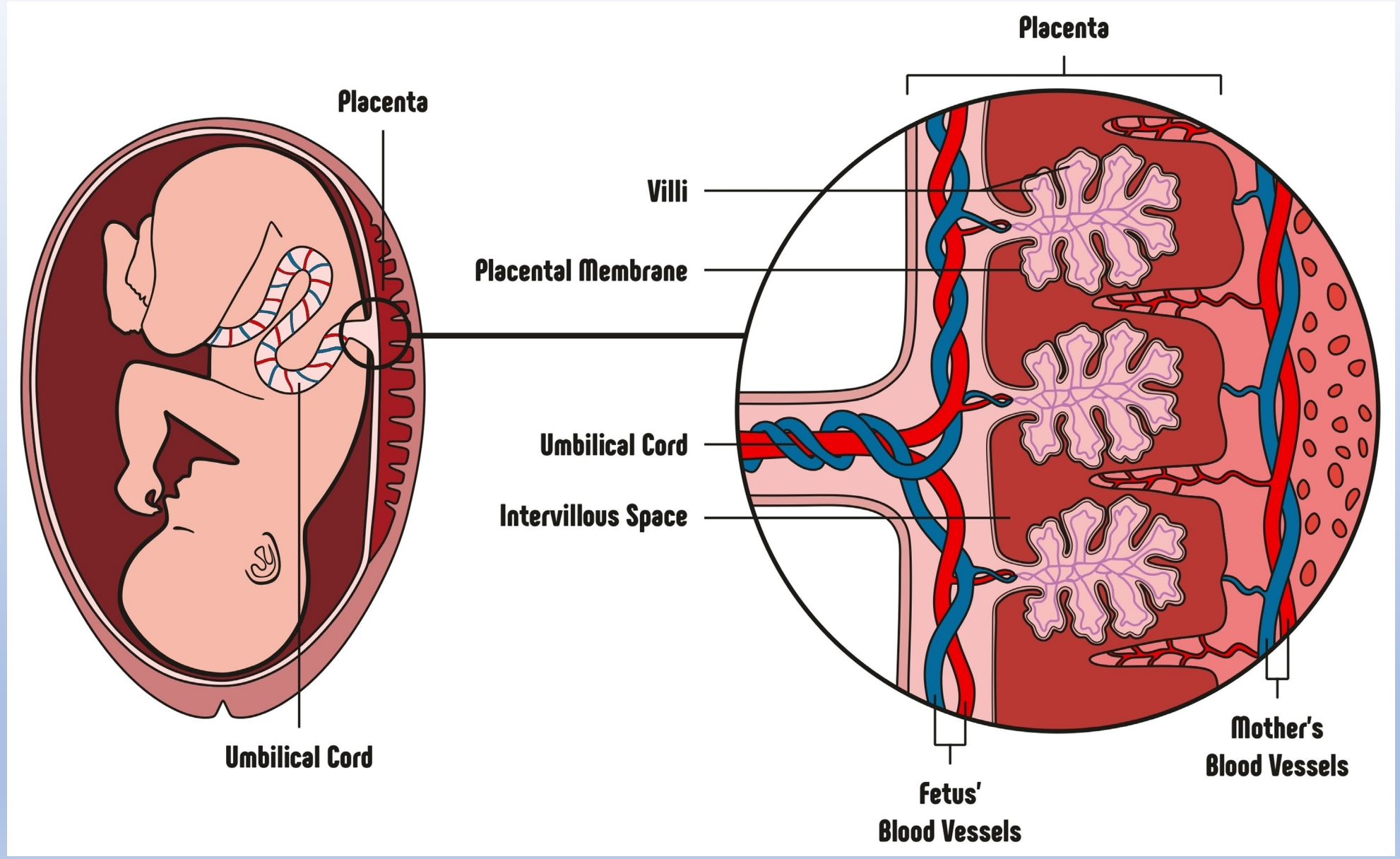
Transporter	Marker Drug	Effect on Clearance during Gestation			Reference
		First Trimester	Second Trimester	Third Trimester	
P-gp	Digoxin			↑	(Hebert et al., 2008)
OATP1B1	Glyburide[a]			↑	(Hebert et al., 2009)
OCT2	Metformin	↔	↑	↔↑[b]	(Hughes et al., 2006; Eyal et al., 2010; de Oliveira Baraldi et al., 2011)
OAT1	Zidovudine, lamivudine			↔	(Moodley et al., 1998)
OAT3	Acyclovir, zidovudine			↔	(Frenkel et al., 1991; Haddad et al., 1993)

OCT, organic cation transporter; OAT, organic anion transporter; P-gp, P-glycoprotein.

[a]While glyburide is listed as an in vivo substrate of OATP1B1, it is cleared by CYP3A4 and CYP2C9 and is a substrate of *BCRP* (breast cancer resistance protein). Hence, it is not possible to determine which enzyme is responsible for the increased clearance of glyburide during pregnancy in vivo.

[b]The secretion clearance of metformin was significantly increased during the third trimester, although oral clearance was not significantly increased.

Isoherranen, N., & Thummel, K. E. (2013). Drug metabolism and transport during pregnancy: how does drug disposition change during pregnancy and what are the mechanisms that cause such changes?. *Drug metabolism and disposition: the biological fate of chemicals*, *41*(2), 256–262. https://doi.org/10.1124/dmd.112.050245


Placenta
Placenta
Villi
Placental Membrane
Umbilical Cord
Intervillous Space
Umbilical Cord
Fetus'
Blood Vessels
Mother's
Blood Vessels

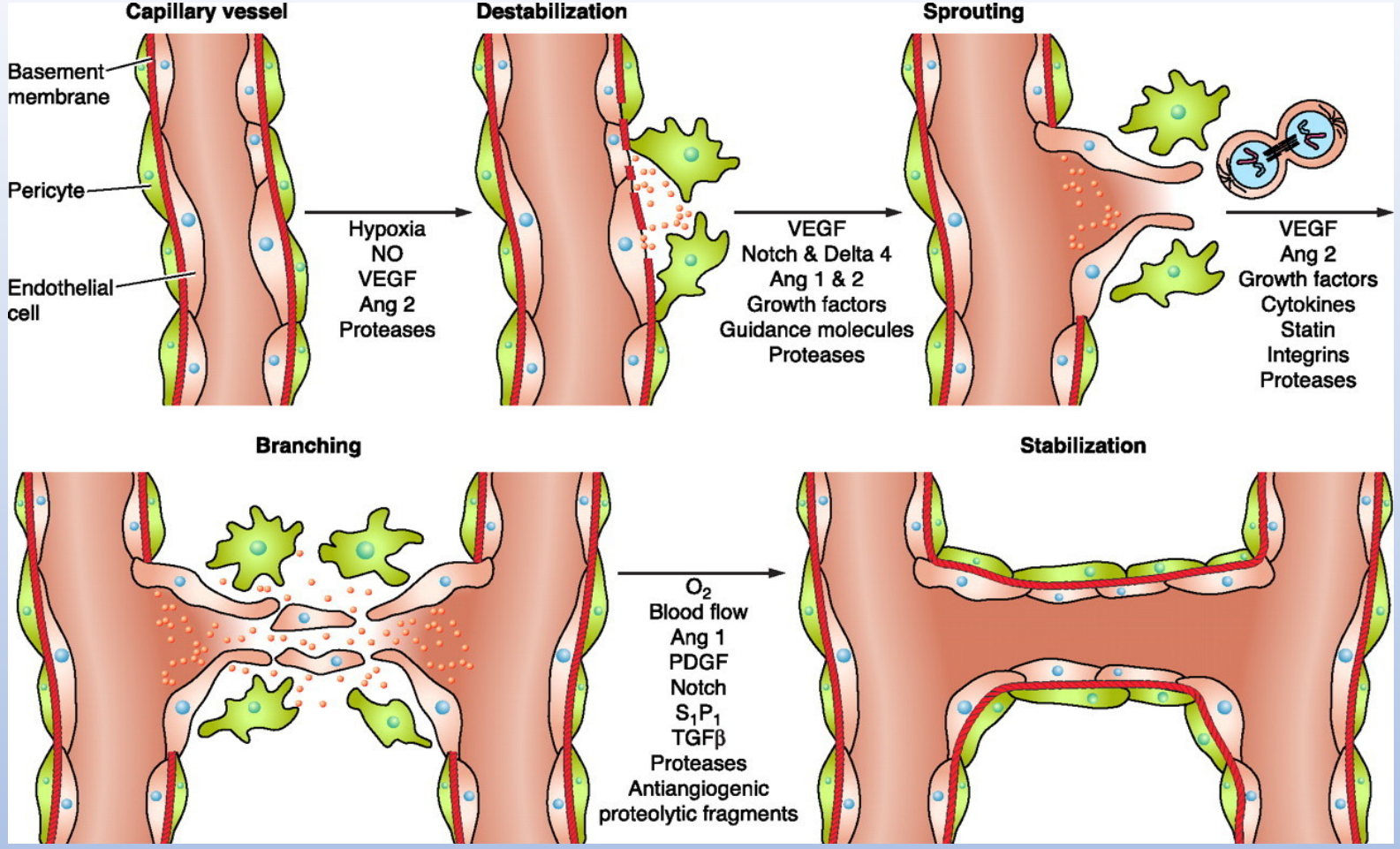
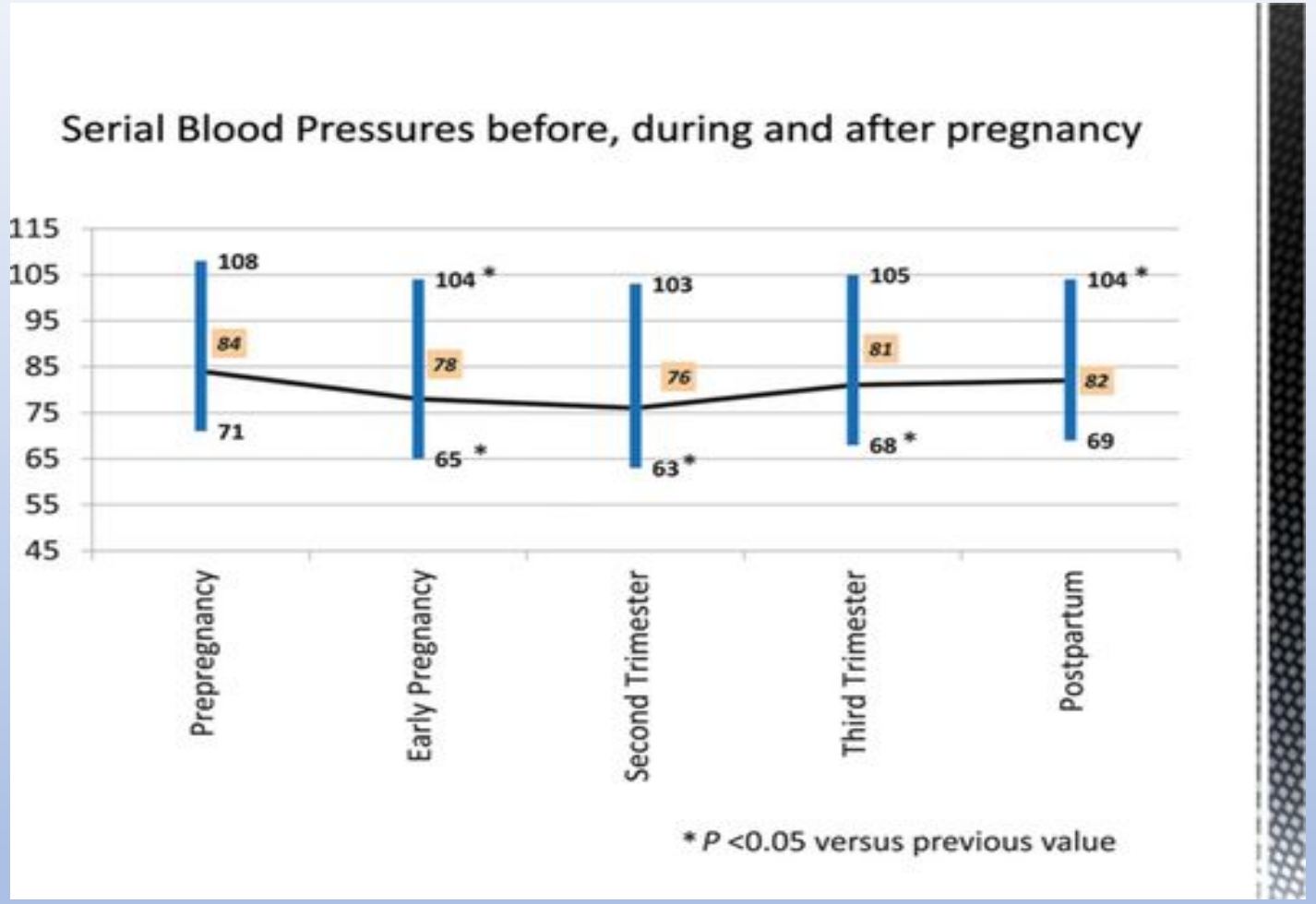
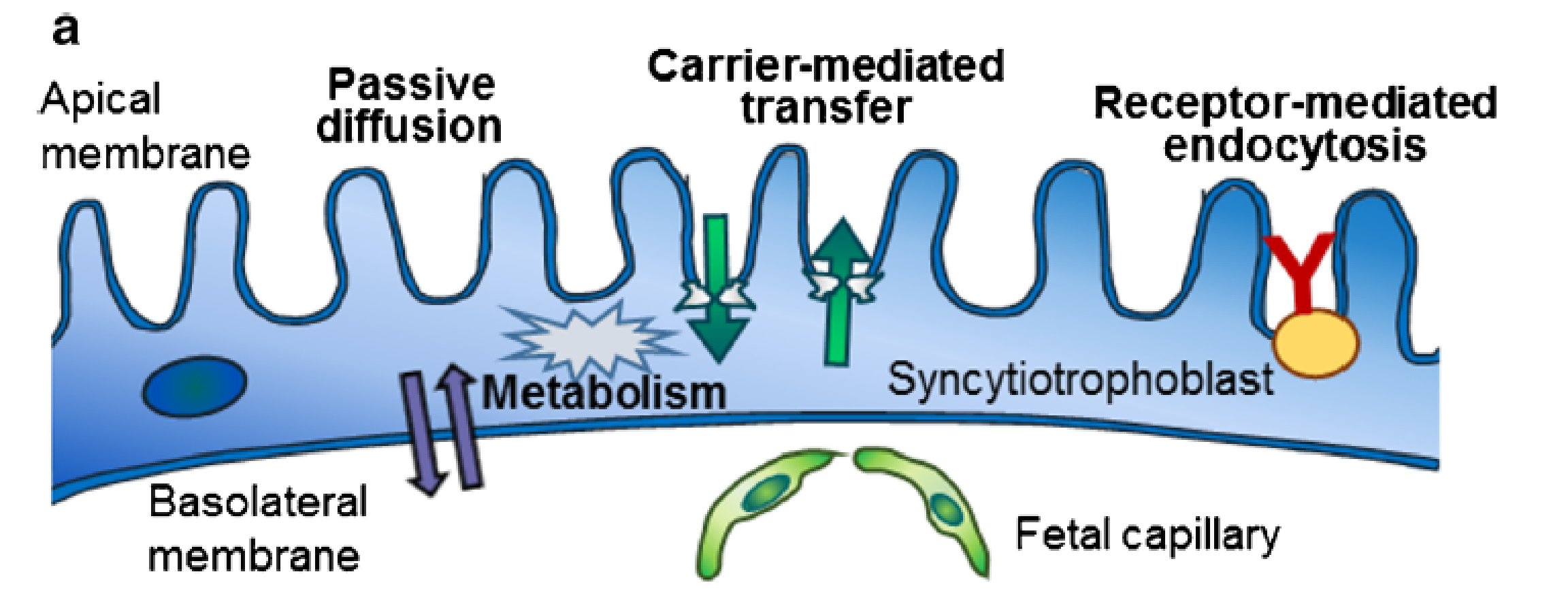


FIG. 1. The cellular steps involved in angiogenesis. Hypoxia induces the production of nitric oxide (NO) and the expression of vascular endothelial growth factor (VEGF) and angiopoietin-1 and -2 (Ang 1 and Ang 2), which interact with extracellular matrix (ECM) proteases to increase permeability of the capillary vessel wall. Destabilization then allows endothelial cells to migrate and proliferate to form tubules, aided by VEGF, angiopoietins, guidance molecules, growth factors, cytokines, and degradation of the ECM. Maturation of the newly formed vessel is accompanied by increased expression of antiangiogenic factors, many released as a result of proteolysis. PDGF, platelet-derived growth factor; S1P1, sphingosine-1-phosphate-1; TGFβ, transforming growth factor-β.

Clapp, C., Thebault, S., Jeziorski, M. C., & Martínez De La Escalera, G. (2009). Peptide hormone regulation of angiogenesis. *Physiological reviews*, *89*(4), 1177–1215. https://doi.org/10.1152/physrev.00024.2009



Monika Sanghavi. Circulation. Cardiovascular Physiology of Pregnancy, Volume: 130, Issue: 12, Pages: 1003-1008, DOI: (10.1161/CIRCULATIONAHA.114.009029)



The Placental Barrier: the Gate and the Fate in Drug Distribution
Tetro N, Moushaev S, Rubinchik-Stern M, Eyal S. Pharm Res (2018) 35: 71
https://doi.org/10.1007/s11095-017-2286-0

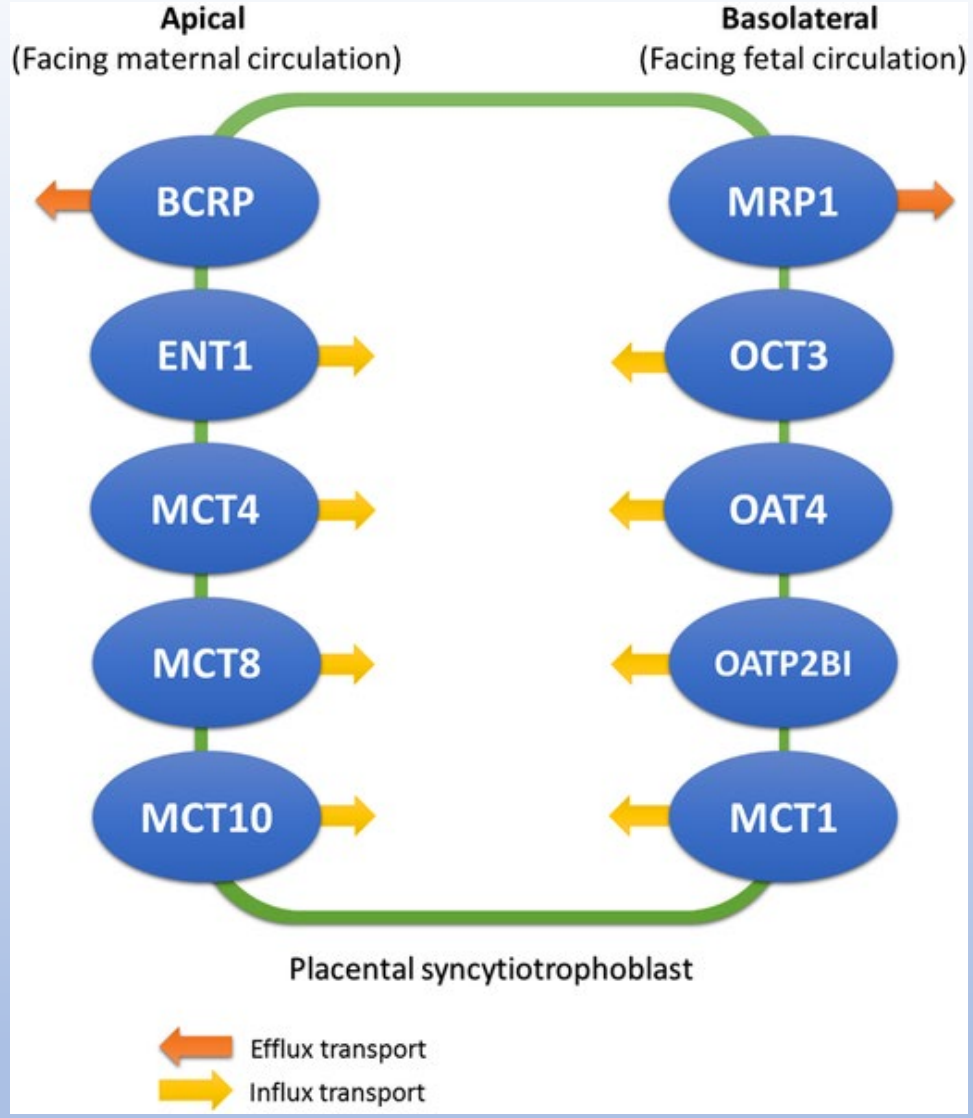
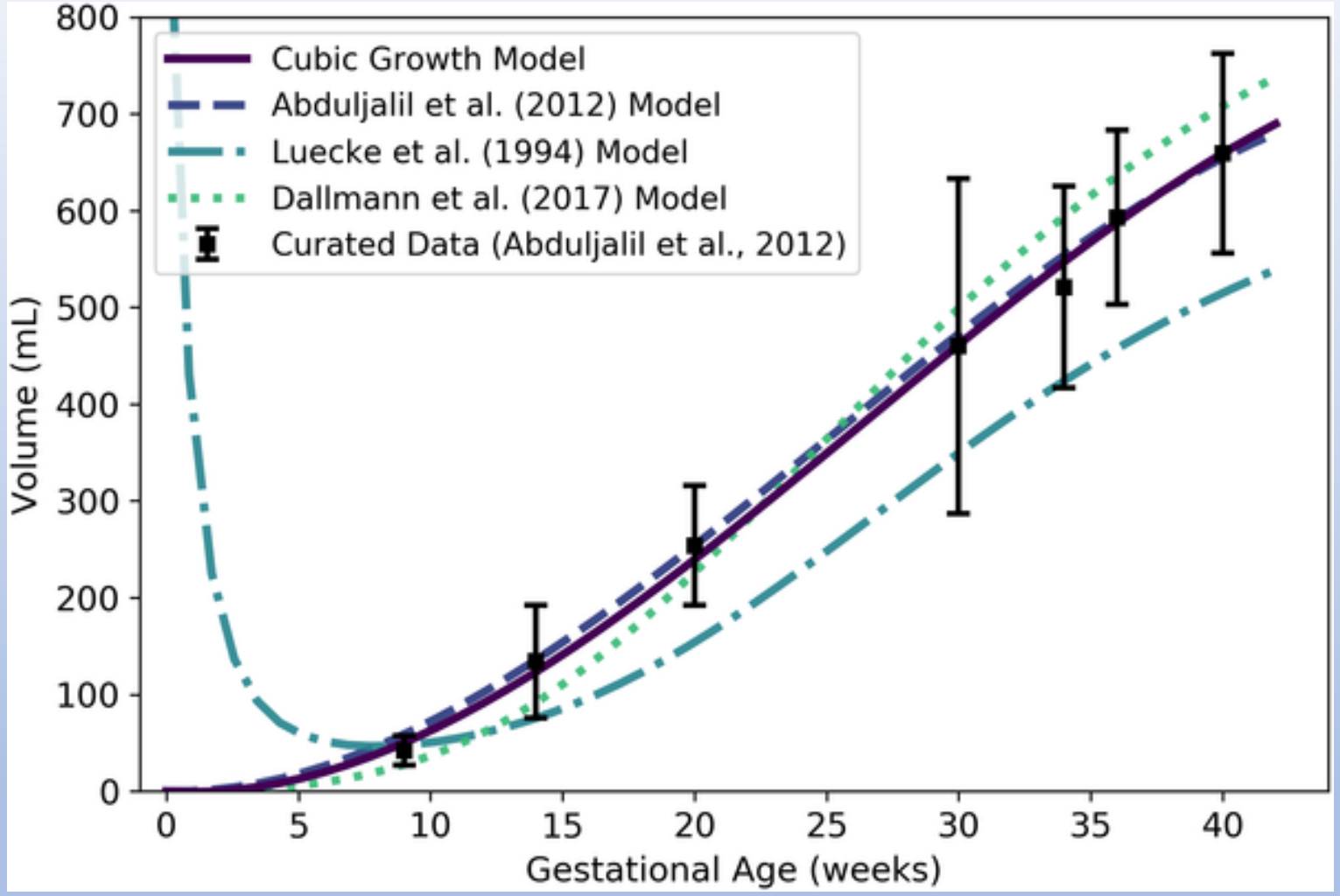


Fig 1. Placental transporter proteins are expressed on either side of the placenta.

Maternal use of drug substrates of placental transporters and the effect of transporter-mediated drug interactions on the risk of congenital anomalies.
Daud ANA, Bergman JEH, Oktora MP, Kerstjens-Frederikse WS, Groen H, et al. (2017) PLOS ONE 12(3): e0173530.
https://doi.org/10.1371/journal.pone.0173530

Fig 6. Placenta volume vs. gestational age.

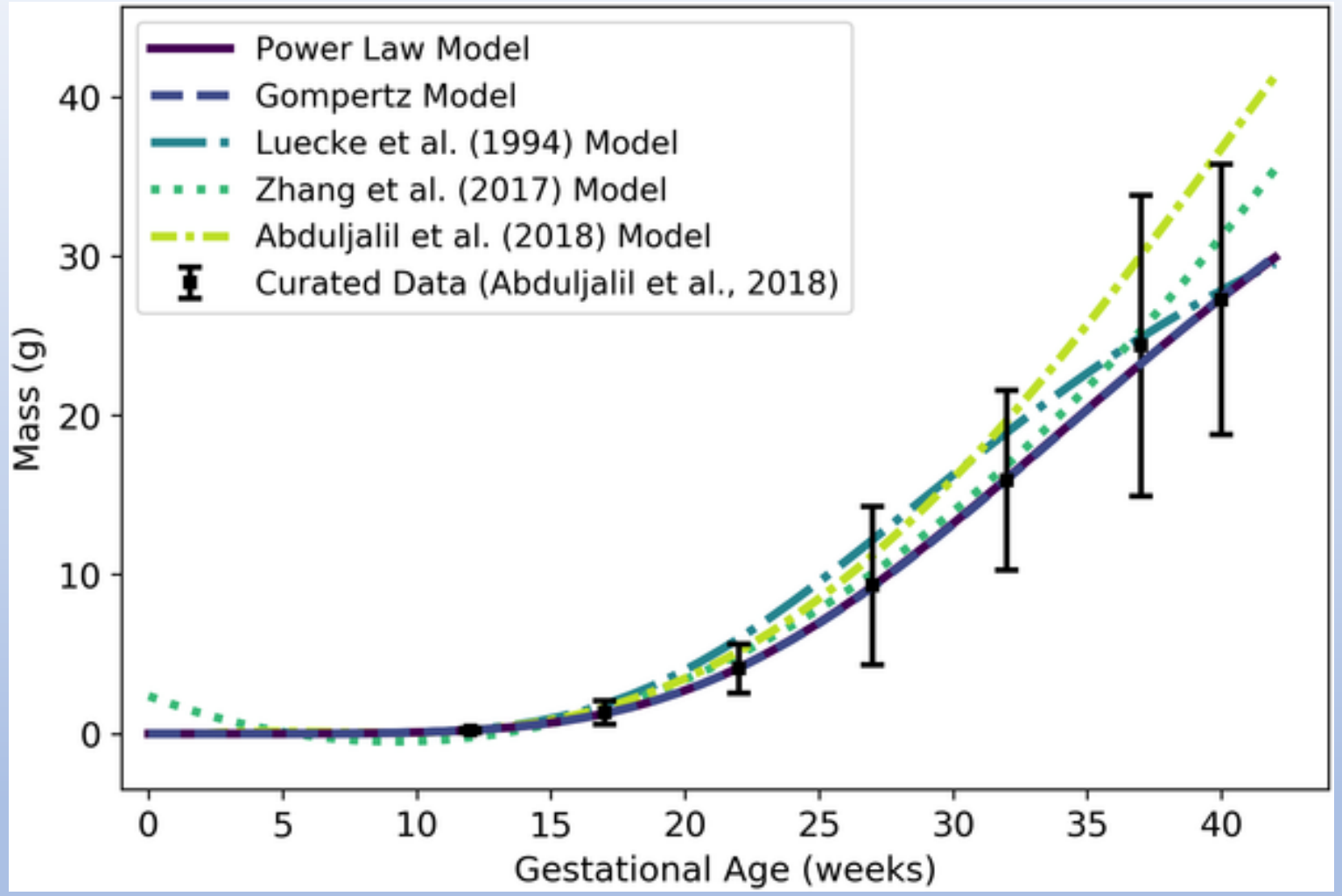


Kapraun DF, Wambaugh JF, Setzer RW, Judson RS (2019) Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation. PLOS ONE 14(5): e0215906. https://doi.org/10.1371/journal.pone.0215906
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215906

Fetal Drug Exposure

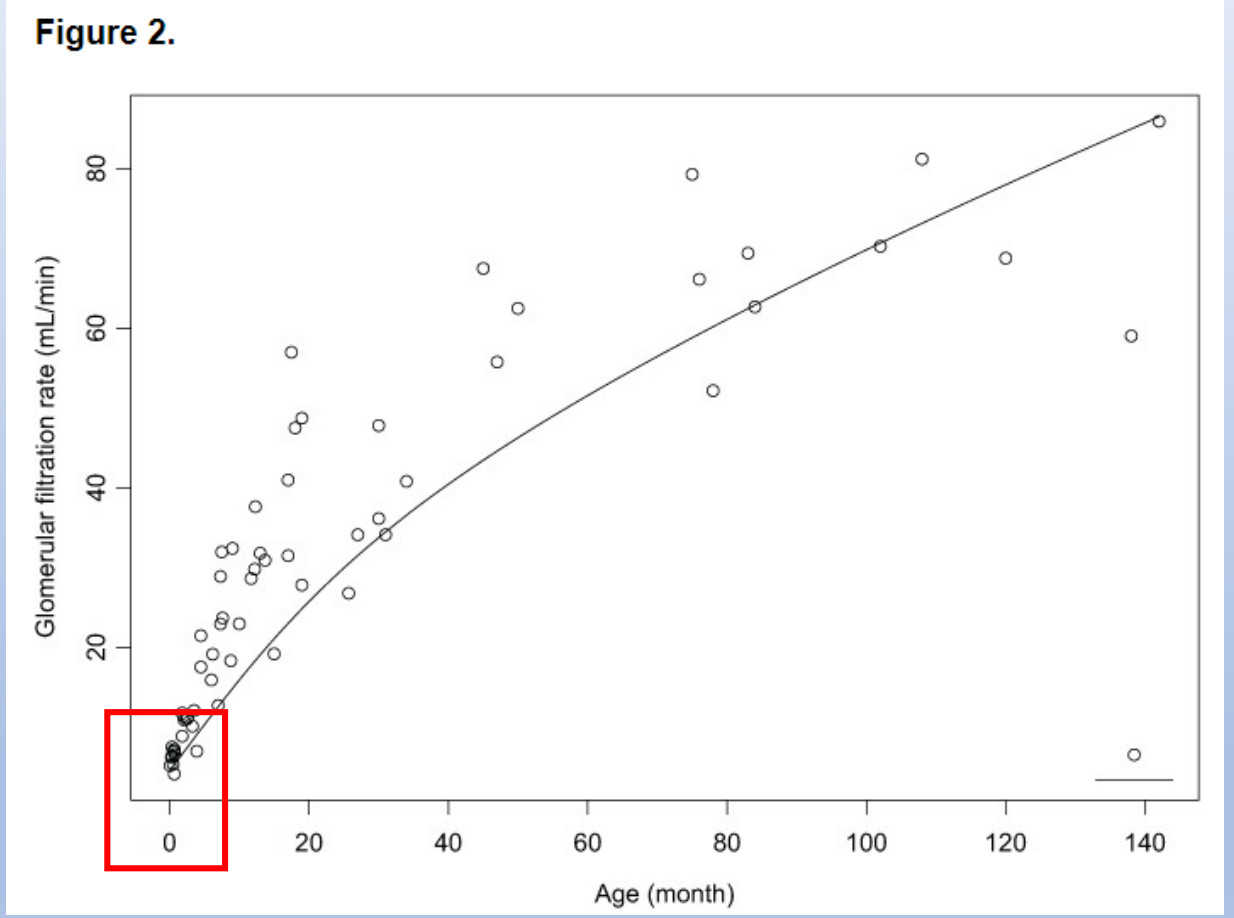
- Placental transporter/counter-transporter function
- Fetal
  - Renal function
  - Hepatic/metabolic function
  - Maturity of blood-brain barrier

Fig 17. Fetal kidney mass vs. gestational age.



Kapraun DF, Wambaugh JF, Setzer RW, Judson RS (2019) Empirical models for anatomical and physiological changes in a human mother and fetus during pregnancy and gestation. PLOS ONE 14(5): e0215906. https://doi.org/10.1371/journal.pone.0215906
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0215906

Renal Function at Birth



Lu H, Rosenbaum S. Developmental Pharmacokinetics in Pediatric Populations. J Pediatr Pharmacol Ther 2014; 19 (4): 262-276.

Fetal Hepatic Phase II Enzymes

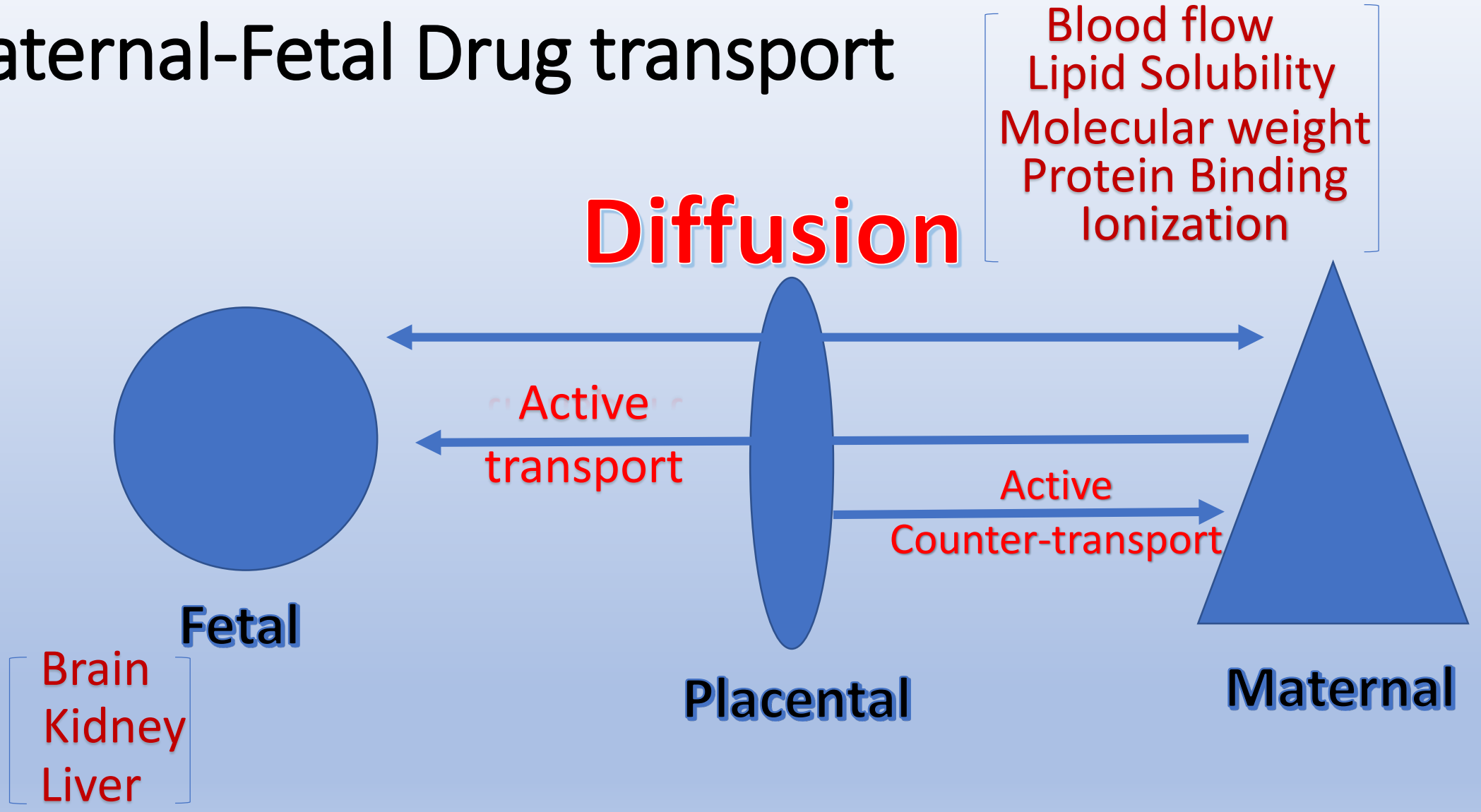
Table 2.

In Vitro Ontogeny of Human Hepatic Phase II Enzymes (Adapted From Ref.[55,56])

Isoenzyme	Fetus	Neonate (0-1 month)	1 month to 1 year	Adult	Ontogeny Facts
UDP glucuronosyltransferase (UGT)					
UGT1A1	–	+	+	+	Adult levels attained by 3-6 mo
UGT1A6	–	+	+	+	Maturation complete until puberty
UGT2B7	+	+	+	+	Adult levels attained by 2-3 mo

Lu H, Rosenbaum S. Developmental Pharmacokinetics in Pediatric Populations. J Pediatr Pharmacol Ther 2014; 19 (4): 262-276.

Maternal-Fetal Drug transport



Summary

- The maternal, placental and fetal compartments are growing and maturing interdependently over the gestation.
- Changes in maternal physiology are dramatic, and intended to increase nutrient flow to the fetus and waste from the fetal to maternal compartments.
- There are many unknowns.

Questions?

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