How do we decide if a drug is “safe” during pregnancy or lactation?

Allina Health

14

Obstetric Complications: The Essentials and More

Fetal Drug Impacts during PREGNANCY

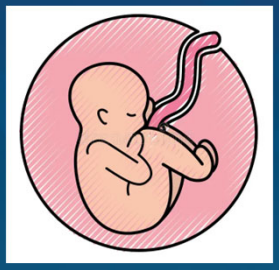
15

Absorbed into maternal circulation

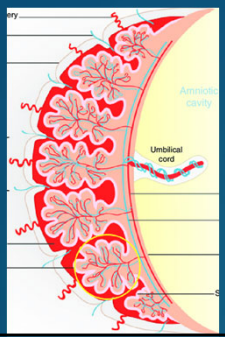
Fetal or Neonatal Impacts

Gestational age

Timing of delivery



Cross the placenta



Maternal drug metabolism

Placental or fetal drug metabolism

Gestational age changes in placental transporters

Allina Health

15

Obstetric Complications: The Essentials and More

Infant Drug Impacts during LACTATION

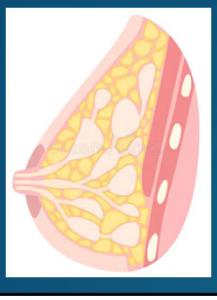
Absorbed into maternal circulation

Maternal drug metabolism

Drug half-life and feeding time

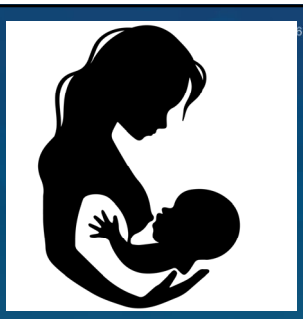
Drug equilibration or concentration in breastmilk

Transferred into breastmilk



Neonatal impacts

Age of child



Neonatal oral absorption

Impact on breastmilk supply or letdown reflex

Allina Health

16

Always consider the risks to mother and baby from NOT using the drug

Allina Health

17

CHANGES IN MATERNAL DRUG METABOLISM DURING PREGNANCY

- Delayed gastric emptying may slow drug absorption
- Volume of distribution increases
  - Increased plasma volume and increased fat stores
- Renal blood flow begins to increase at 6 weeks gestation – increased drug clearance
  - First trimester 40-50% increased GFR
  - Second trimester 60-80% increased GFR
  - Third trimester 50% increased GFR
- Hepatic enzyme function changes, increased metabolism of many drugs but some drug metabolism decreases

Eke et al, "Physiologic Changes During Pregnancy and Impact on Small Molecule Drugs, Biologic (Monoclonal Antibody) Disposition, and Response" *J Clinical Pharm* 2023 63(S1):S34-50.
Sitka C, "Principles of Obstetric Pharmacology: Maternal Physiologic and Hepatic Metabolism Changes" *Obstet Gynecol Clinic N Amer* 2023 50:1-15.

18

CHANGES IN MATERNAL DRUG METABOLISM DURING PREGNANCY

Pregnancy

Physiological changes	Impact on pharmacokinetics	ADME
▪ Gastrointestinal motility ↑ ▪ Gastric pH ↓	▪ Altered drug bioavailability ▪ Delayed time to reach peak levels (po administration)	ka
▪ Total body water and plasma volume ↑ ▪ Adipose compartment ↑	▪ ↑ Vd for hydrophilic drugs ▪ ↑ Vd for lipophilic drugs	Vd
▪ Cardiac output and blood flow ↑ ▪ Glomerular filtration rate ↑ ▪ Altered activity of drug metabolizing enzymes	▪ ↑ Elimination ▪ ↑ Renal clearance ▪ Affecting bioavailability & hepatic clearance	CL

Fetus

Physiological changes	Impact on pharmacokinetics	ADME
▪ Fetal urine enters amniotic fluid ▪ Fetal plasma pH < maternal plasma pH	▪ Reabsorption of excreted drugs by swallowing ▪ ↑ accumulation in fetal plasma (↓ backtransfer to maternal plasma due to ↑ ionization on fetal side)	ka
▪ Albumin and α_1-glycoprotein levels ↑ with GA ▪ Thickness of placental layer ↓ with GA	▪ ↑ Active drug amount (relative low protein levels) ▪ ↑ Drug transfer and fetal drug exposure	Vd
▪ Expression of metabolizing enzymes ▪ Kidney volume ↑	▪ ↓ Metabolizing capacity compared to mother ▪ Low glomerular filtration rate (immature kidney)	CL

Van Doge T et al, "Clinical Pharmacology and Pharmacometrics to Better Understand Physiological Changes During Pregnancy and Neonatal Life" *Pediatric Pharmacotherapy* 2019 325-35.

19

CASE PRESENTATION #1

18yo G1P0 @ 16w0d presents to the ED after a witnessed seizure at home

-- history of known seizure disorder

-- continued lamotrigine at her pre-pregnancy dose during the pregnancy

Obstetric Complications: The Essentials and More

AllinaHealth

20

20

LAMOTRIGINE METABOLISM IN PREGNANCY

Lamotrigine is metabolized by enzyme UGT1A4

-- increased metabolism in the presence of high estrogen levels

-- increased clearance of lamotrigine begins at 5 weeks gestation and peaks at 250-300% over baseline in the third trimester

-- enzyme function declines rapidly after delivery and returns to normal by 1-3 weeks after delivery

Obstetric Complications: The Essentials and More

AllinaHealth

21

Sitka, C "Principles of Obstetric Pharmacology: Maternal Physiologic and Hepatic Metabolism Changes" Obstet Gynecol Clinics N America 2023 50: 1-15.

21

CASE PRESENTATION #1

18yo G1P0 @ 16w0d presents to the ED after a witnessed seizure at home

-- history of known seizure disorder

-- continued lamotrigine at her pre-pregnancy dose during the pregnancy

-- lamotrigine level in ED == undetectable

-- dose increased and lamotrigine level checked monthly throughout pregnancy – required 2 additional dose increases by the third trimester

-- postpartum dose tapered down to her baseline dose by PPD#14

Obstetric Complications: The Essentials and More

AllinaHealth

22

22

SELECTED OTHER DRUGS WITH METABOLIC CHANGES DURING PREGNANCY

Ampicillin – increased renal clearance

Nifedipine – increased CYP3A metabolism

Midazolam – increased CYP3A metabolism

Lopinavir-Ritonavir (Kaletra) – increased CYP3A metabolism

Methadone – increased CYP3A4 and CYP2B6 metabolism

Caffeine – decreased CYP1A2 metabolism

Glyburide – increased CYP2C9 metabolism

Labetalol – increased UGT1A4 metabolism

Levitracitam – increased renal clearance

Obstetric Complications: The Essentials and More

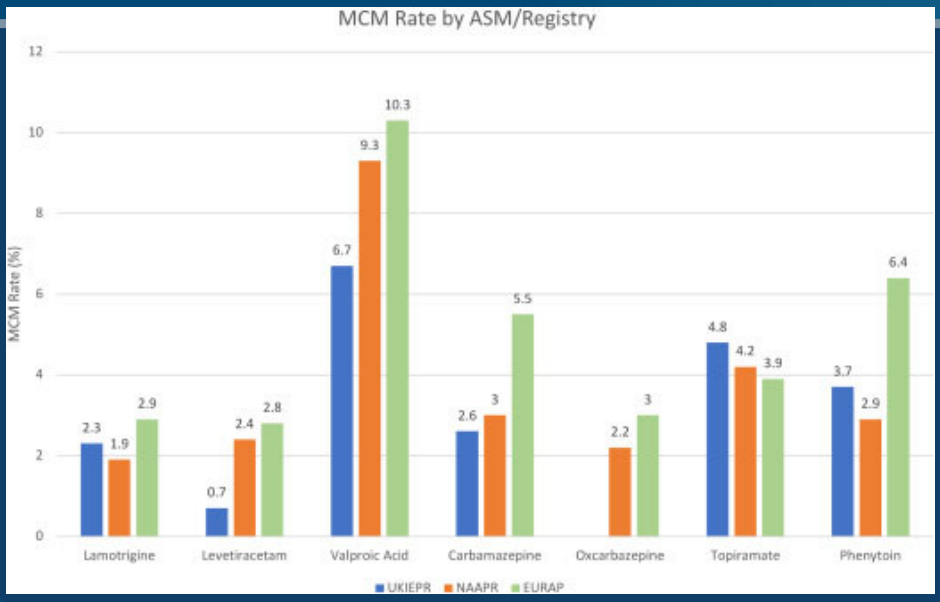
AllinaHealth

23

Sitka, C "Principles of Obstetric Pharmacology: Maternal Physiologic and Hepatic Metabolism Changes" Obstet Gynecol Clinics N America 2023 50: 1-15.

23

SAFETY OF ANTISEIZURE MEDICATIONS IN PREGNANCY



Obstetric Complications: The Essentials and More

Moise A and Gerand E "Antiseizure Medications in Pregnancy" Obstet Gynecol Clinics N America 2023 50: 251-61.

24

24

SAFETY OF ANTISEIZURE MEDICATIONS IN PREGNANCY

-- Increased risk of cognitive and behavioral changes with some antiseizure medications

-- Valproic Acid – 7-10 point IQ decrease in exposed children, dose dependent, possible increased risk of autism, decreased language processing

-- Phenobarbitol – worse language scores in exposed children

-- Topiramate – dose-dependent increase in the likelihood of neurocognitive disabilities

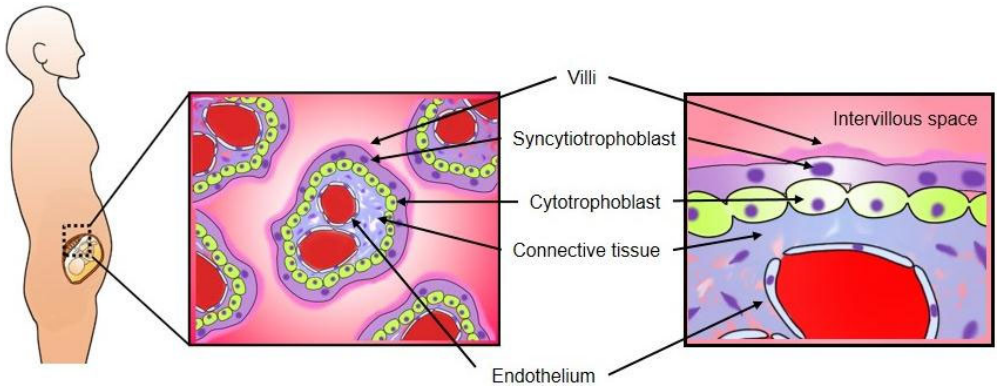
Obstetric Complications: The Essentials and More

Moise A and Gerand E "Antiseizure Medications in Pregnancy" Obstet Gynecol Clinics N America 2023 50: 251-61.

25

25

WHAT DOES IT MEAN TO "CROSS THE PLACENTA"?



Islam et al, "Omega-3 Fatty Acid Transport Through the Placenta" *As J Med and Bio Research* 2016 2(1):1.

26

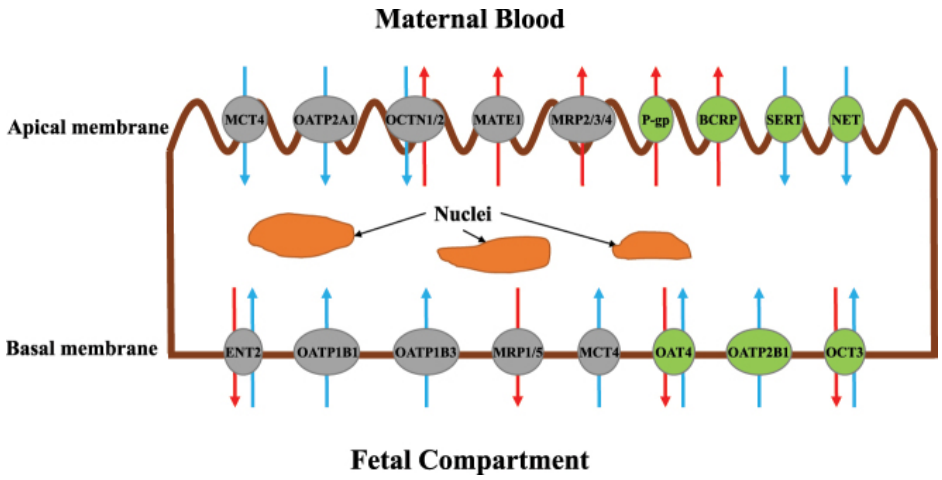
CROSSES THE PLACENTA BY PASSIVE DIFFUSION

- Lipophilic > non-lipophilic
- Un-ionized > highly-ionized
- Highly protein-bound < less protein bound
- Smaller molecular size > larger size
  - <500 readily cross by passive diffusion, >1000 poorly cross by passive diffusion

Koren G, "Special Aspects of Perinatal & Pediatric Pharmacology" in Basic and Clinical Pharmacology 15e 2021, chapter 59.

27

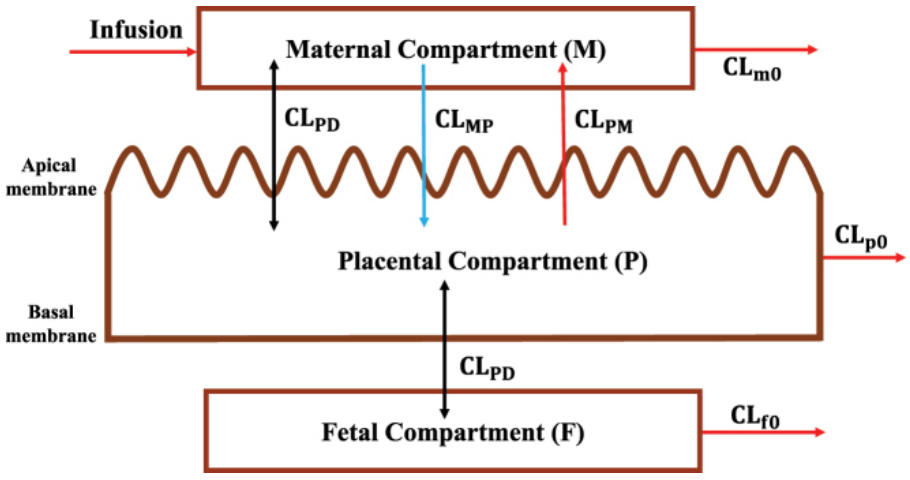
CROSSES THE PLACENTA BY ACTIVE TRANSPORT



Mao and Chen "An Update on Placental Drug Transport and its Relavance to Fetal Drug Exposure" Med Rev (Berl) 2022 2(5):501-11. 28

28

FETAL DRUG LEVELS



Mao and Chen "An Update on Placental Drug Transport and its Relavance to Fetal Drug Exposure" Med Rev (Berl) 2022 2(5):501-11. 29

29

CASE PRESENTATION #2

October 2021

30yo G2P1001 @ 28 weeks gestation admitted for respiratory distress

-- COVID test positive

-- Started on O2 via high flow nasal cannula with rapidly increasing O2 requirement

-- transferred to ICU for further care

Obstetric Complications: The Essentials and More

AllinaHealth

30

30

CASE PRESENTATION #2

ASSESSMENT OF NEW THERAPEUTICS IN PREGNANCY

October 2021

Available treatments for severe COVID with respiratory distress:

-- dexamethasone

-- remdesivir

-- tocilizumab

-- baricitinib

Obstetric Complications: The Essentials and More

AllinaHealth

Joseph N, Collier A "COVID-19 Therapeutics and Considerations for Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 50(1): 163-82.

31

31

CASE PRESENTATION #2

ASSESSMENT OF NEW THERAPEUTICS IN PREGNANCY

Dexamethasone

-- molecular weight = 392

-- 72% protein-bound

Expect dexamethasone to cross the placenta

Obstetric Complications: The Essentials and More

AllinaHealth

Joseph N, Collier A "COVID-19 Therapeutics and Considerations for Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 50(1): 163-82.

32

32

CASE PRESENTATION #2

ASSESSMENT OF NEW THERAPEUTICS IN PREGNANCY

Remdesivir

-- molecular weight 602

-- 88-93% protein-bound

-- interaction with placental receptors: unknown

Remdesivir less likely to cross the placenta

Obstetric Complications: The Essentials and More

AllinaHealth

Joseph N, Collier A "COVID-19 Therapeutics and Considerations for Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 50(1): 163-82.

33

33

CASE PRESENTATION #2

ASSESSMENT OF NEW THERAPEUTICS IN PREGNANCY

Tocilizumab

-- molecular weights: 148000

-- interaction with placental receptors: YES – monoclonal antibodies bind to placental Fc receptors starting at 16 weeks

Expect Tocilizumab not to significantly cross the placenta in the first trimester, but significant crossing in the 2nd and 3rd trimesters

Obstetric Complications: The Essentials and More

AllinaHealth

Joseph N, Collier A "COVID-19 Therapeutics and Considerations for Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 50(1): 163-82.

34

34

CASE PRESENTATION #2

ASSESSMENT OF NEW THERAPEUTICS IN PREGNANCY

Baricitinib

-- molecular weight: 371

-- 50% protein-bound

Expect Baricitinib to cross the placenta

Obstetric Complications: The Essentials and More

AllinaHealth

Joseph N, Collier A "COVID-19 Therapeutics and Considerations for Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 50(1): 163-82.

35

35

CASE PRESENTATION #2

October 2021

30yo G2P1001 @ 28 weeks gestation admitted for respiratory distress

-- COVID test positive

-- Started on O2 via high flow nasal cannula with rapidly increasing O2 requirement

-- transferred to ICU for further care

Patient received Dexamethasone, Remdesivir, Tocilizumab. Ultimately recovered and discharged home.

Obstetric Complications: The Essentials and More

AllinaHealth

36

36

WHAT IS A TERATOGEN?

-- proven exposure at critical times during human development

-- consistent dysmorphic findings recognized in well-conducted epidemiologic studies

-- specific defects or syndromes associated consistently with specific teratogens

-- rare anatomic defects associated with environmental exposure

-- proven teratogenicity in animal models

Obstetric Complications: The Essentials and More

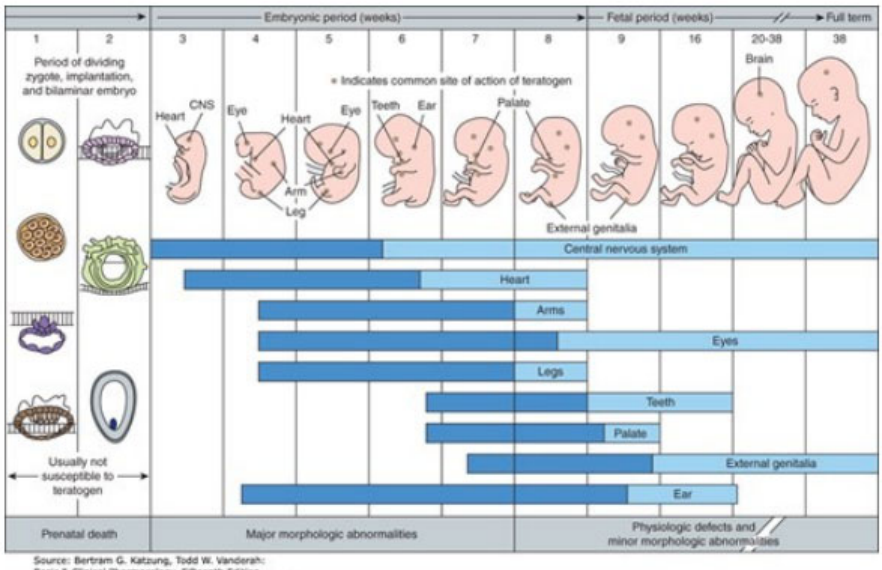
AllinaHealth

Buhimschi, C. S., & Weiner, C. P. (2009). Medications in pregnancy and lactation: part 1. Teratology. Obstetrics and gynecology, 113(1), 166–188

37

37

TIMELINE FOR FETAL TERATOGENESIS



Source: Bertram G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, Fifteenth Edition

Allina Health

38

38

MECHANISMS OF TERATOGENESIS

-- oxidative stress injury
-- changes in DNA methylation/histone acetylation
-- drug metabolic activation/toxic metabolites
-- impaired placental function
-- altered placental endocrine function
-- developmental programming changes

Obstetric Complications: The Essentials and More

Allina Health

Lu Z et al, " Developmental Toxicity and Programming Alterations of Multiple Organs in Offspring Induced by Medication During Pregnancy" *Acta Pharmaceutica Sinica B* 2022 13(2):460-77.

39

39

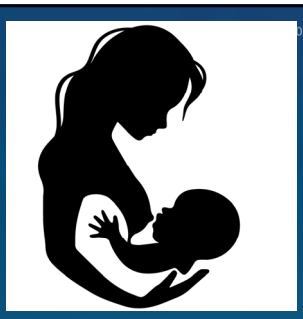
Obstetric Complications: The Essentials and More

Infant Drug Impacts during LACTATION

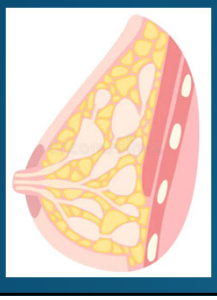
Absorbed into maternal circulation

Neonatal impacts

Age of child



Transferred into breastmilk



Maternal drug metabolism

Drug half-life and feeding time

Drug equilibration or concentration in breastmilk

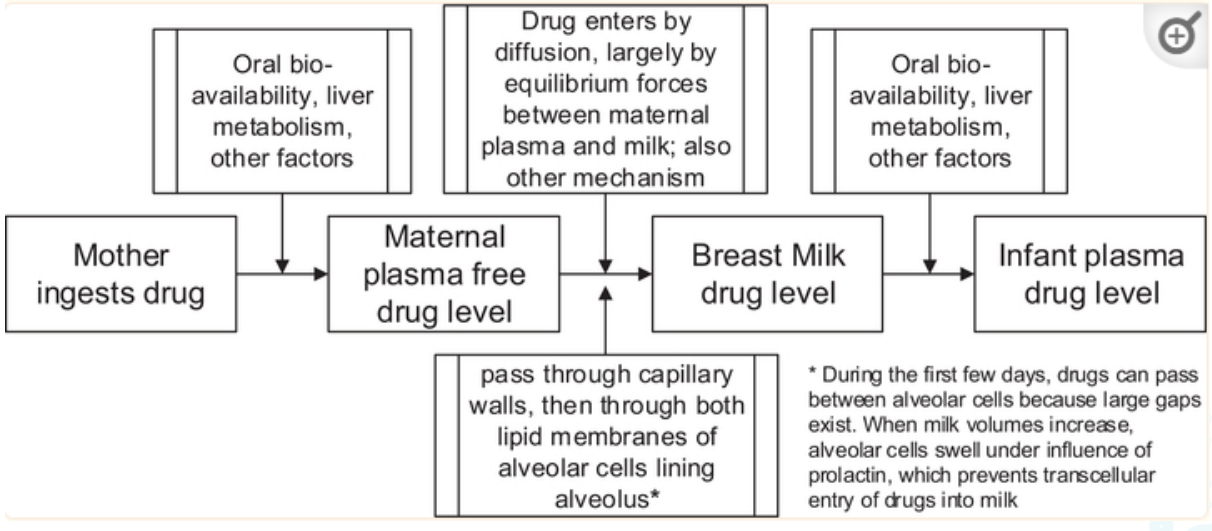
Neonatal oral absorption

Impact on breastmilk supply or letdown reflex

Allina Health

40

DRUG TRANSFER INTO BREASTMILK



Allina Health | Obstetric Complications: The Essentials and More

Sprague J et al, "Pharmacotherapy for Depression and Bipolar Disorder During Lactation: A Framework to Aid Decision-Making" *Semin Perinatol* 2020 44(3):151224.

41

41

DRUG TRANSFER INTO BREASTMILK

- Lipophilic > hydrophilic
- Highly protein-bound < less protein bound
- Smaller molecular size > larger size

- For many drugs, breastmilk levels equilibrate to maternal PLASMA levels
  - As drug is cleared from maternal plasma, it is simultaneously cleared from breastmilk
  - Drugs with higher pH may not equilibrate or become "trapped" in breastmilk

Koren G, "Special Aspects of Perinatal & Pediatric Pharmacology" in Basic and Clinical Pharmacology 15e 2021, chapter 59.
Sprague J et al, "Pharmacotherapy for Depression and Bipolar Disorder During Lactation: A Framework to Aid Decision-Making" *Semin Perinatol* 2020 44(3):151224.

DRUG TRANSFER INTO BREASTMILK

M/P = [drug in milk] / [drug in maternal plasma]

TID (mg/kg/day) = [drug in milk] x daily milk volume (~150 ml/kg/day)

RID (%) = TID (mg/kg/day) / Mother's weight adjusted dose (mg/kg/day)

- Milk/Plasma ratio >1 → the drug concentrates in breastmilk
- Relative infant dose <10% generally considered safe
  - RID 10-25% use caution but may be safe
  - RID >25% more likely to cause toxicity
- Gold standard = serum levels from breastfeeding infant (almost never available)

Koren G, "Special Aspects of Perinatal & Pediatric Pharmacology" in Basic and Clinical Pharmacology 15e 2021, chapter 59.
Sprague J et al, "Pharmacotherapy for Depression and Bipolar Disorder During Lactation: A Framework to Aid Decision-Making" *Semin Perinatol* 2020 44(3):151224.

CASE PRESENTATION #3

40yo G4P2022 on postpartum day #1 s/p SVD with shortness of breath and severe hypertension

-- pregnancy c/b chronic HTN, on lisinopril pre-preg and no antihypertensives during pregnancy

-- CXR shows pulmonary edema

-- BPs 180s-200s/100s-110s

-- transferred to the ICU

-- she is breastfeeding and strongly desires to continue nursing x 1 year

Obstetric Complications: The Essentials and More

AllinaHealth

44

44

CASE PRESENTATION #3

ACE inhibitor/Angiotensin Receptor Blocker

-- Lisinopril: 442 molecular weight, minimal protein binding

-- Enalapril: 492 molecular weight, 50-60% protein bound

relative infant dose 0.27%

-- Losartan: 422 molecular weight, highly protein bound

Beta blocker

Calcium Channel blocker

Diuretic

Obstetric Complications: The Essentials and More

AllinaHealth

DeNoble A et al, "Antihypetensive in Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 *50(1) 39-78.*

45

45

CASE PRESENTATION #3

ACE inhibitor/Angiotensin Receptor Blocker

Beta blocker

- Metoprolol – molecular weight 267; 10% protein-bound; RID 0.5%
- Carvedilol – molecular weight 406; 95% protein-bound
- Nadalol – molecular weight 309; 30% or less protein-bound; RID 5-7%
- Labetalol – molecular weight 328; 50% protein-bound; RID 0.04%

Calcium Channel blocker

Diuretic

Obstetric Complications: The Essentials and More

AllinaHealth

DeNoble A et al, "Antihypetensive in Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 *50(1) 39-78.*

46

46

CASE PRESENTATION #3

ACE inhibitor/Angiotensin Receptor Blocker

Beta blocker

Calcium Channel blocker

- Amlodipine – molecular weight 567; 93% protein-bound, 4% RID
- Nifedipine – molecular weight 346; 92% protein-bound, low milk levels but no RID
- Nicardipine – molecular weight 480, highly protein-bound, low oral bioavailability

Diuretic

Obstetric Complications: The Essentials and More

AllinaHealth

DeNoble A et al, "Antihypetensive in Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 *50(1) 39-78.*

47

47

CASE PRESENTATION #3

ACE inhibitor/Angiotensin Receptor Blocker

Beta blocker

Calcium Channel blocker

Diuretic

Furosemide (Lasix): molecular weight 331, 91-99% protein-bound

HCTZ: molecular weight 297, 40% protein-bound; undetectable serum levels in breastfed infants

*** ANY diuretic may cause a transient decrease in milk production ***

Obstetric Complications: The Essentials and More

AllinaHealth

DeNoble A et al, "Antihypetensive in Pregnancy" *Obstet Gynecol Clinics N Amer* 2023 *50(1) 39-78.*

48

48

BREASTFEEDING CONSIDERATIONS

Acronym with topics to consider when counseling about medication use in lactation.

S	Supply: Does the drug impact maternal milk supply?
A	Alternatives: consider if alternate medications are available with more data?
F	Formula: consider potential risks to baby and maternal health of not breastfeeding
E	Effectiveness of the drug for mother's condition
D	Duration of maternal treatment anticipated
L	Levels (in milk and infant): consider drug concentrations in milk and infant plasma
C	Child characteristics such as gestational age in the neonate (term/preterm), chronologic age, exposure in pregnancy or proximal to delivery, underlying health of child, special health conditions such as impaired renal clearance or liver functions
T	Talk with mother/parents to assess concerns; many women assume they cannot breastfeed due to medication use. Have an explicit conversation about all medication use during lactation.

AllinaHealth Obstetric Complications: The Essentials and More

Sprague J et al, "Pharmacotherapy for Depression and Bipolar Disorder During Lactation: A Framework to Aid Decision-Making" *Semin Perinatol* 2020 44(3):151224.

49

49

BREASTFEEDING CONSIDERATIONS

Pump and dump is (almost) NEVER the right answer

50

CASE PRESENTATION #4

21yo G2P1011 4 weeks postpartum presents to the ED with suicidal ideation

-- History of major depressive disorder, discontinued fluoxetine and aripiprazole (Abilify) when she found out she was pregnant

-- Breastfeeding baby without issue

-- After her previous delivery she was started on aripiprazole and her milk “never came in”, she was so happy with this baby that she was able to breastfeed

51

CASE PRESENTATION #4

Fluoxetine: RID 1.6%-14.6%, longer half-life

Sertraline: RID 0.2-2.4%

Escitalopram: RID 5.2-7.9%

Obstetric Complications: The Essentials and More

AllinaHealth

Sprague J et al, "Pharmacotherapy for Depression and Bipolar Disorder During Lactation: A Framework to Aid Decision-Making" *Semin Perinatol* 2020 44(3):151224.

52

52

CASE PRESENTATION #4

Aripiprazole: RID 0.7-6.44%. Known impact on prolactin levels, case reports of decreased milk supply in women started on aripiprazole during lactation

Olanzapine: RID 0.28-2.24%

Quetiapine: RID 0.02-0.1% (molecular weight 883)

**Unknown if other atypical antipsychotics also impact milk supply **

Obstetric Complications: The Essentials and More

AllinaHealth

Sprague J et al, "Pharmacotherapy for Depression and Bipolar Disorder During Lactation: A Framework to Aid Decision-Making" *Semin Perinatol* 2020 44(3):151224.

53

53

Obstetric Complications: The Essentials and More

Fetal Drug Impacts during PREGNANCY

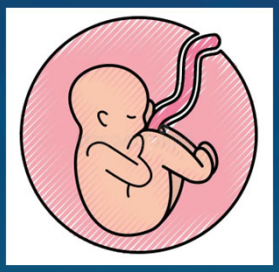
54

Absorbed into maternal circulation

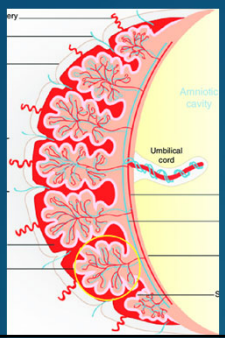
Fetal or Neonatal Impacts

Gestational age

Timing of delivery



Cross the placenta



Maternal drug metabolism

Placental or fetal drug metabolism

Gestational age changes in placental transporters

Allina Health

54

Obstetric Complications: The Essentials and More

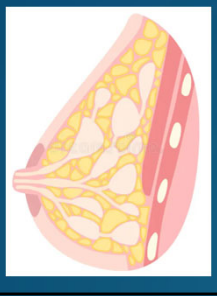
Infant Drug Impacts during LACTATION

Absorbed into maternal circulation

Neonatal impacts

Age of child

Transferred into breastmilk



Maternal drug metabolism

Drug half-life and feeding time

Drug equilibration or concentration in breastmilk

Neonatal oral absorption

Impact on breastmilk supply or letdown reflex

Allina Health

55

GENERAL PRINCIPLES

Remember that drug metabolism changes during pregnancy

Consider the risks to the mother and baby from NOT treating the disease

Consider GESTATIONAL AGE
-- likelihood that the medication crosses the placenta at that gestational age
-- likelihood that the medication causes adverse fetal or neonatal events at that gestational age

Use your resources to look up relative infant dose of medications in breastfeeding – MOST medications are safe in lactation

Remember that breastmilk is orally absorbed

Pump and Dump or weaning is (almost) NEVER the right answer

56

RESOURCES

- InfantRisk https://www.infantrisk.com/infantrisk-center-resources
  - MommyMeds app (for moms) and InfantRisk app (for health care providers)
  - Infant Risk Call Center
  - Hale's Medications and Mother's Milk textbook
- Reprotox https://reprotox.org/about
  - Requires subscription
  - Detailed information about the impact of medications, chemicals, biologics and physical agents on pregnancy, lactation, infant development, male and female fertility
- Micromedex – make sure to click on "In-Depth Answers"
  - Recommendations tend to be conservative and rely heavily on manufacturer info
  - Literature summaries are excellent – outline multiple individual studies for each medication
- UpToDate – Drug summary information tends to be overly conservative (relies heavily on manufacturer info), specific articles are more balanced.

57