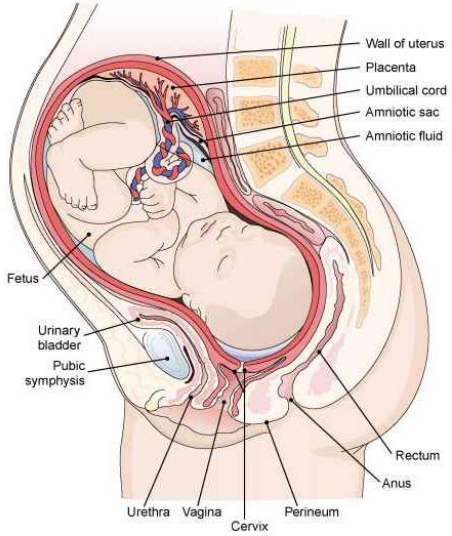
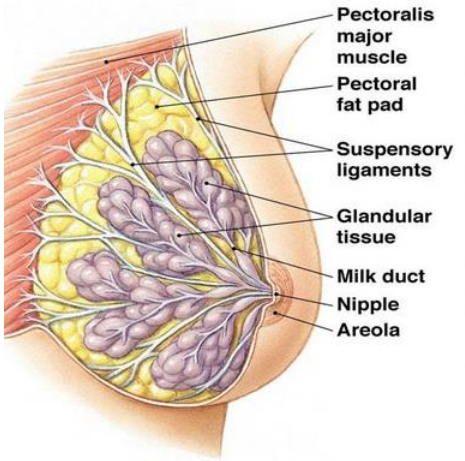




Baby on Board! Considerations in Treating the Pregnant and Post-partum Inpatient

Nicole E. Cieri-Hutcherson, PharmD, BCPS
April 13, 2019

Disclosure

➔ No conflicts of interest to disclose

Objectives: Pharmacists

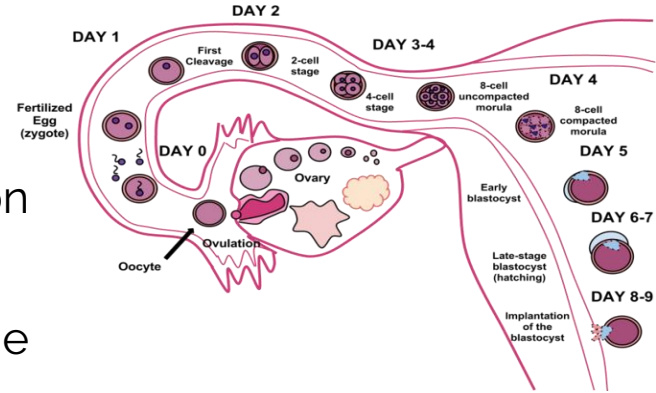
- ➔ Explain medication properties influencing placental drug transfer and drug transfer via breastmilk
- ➔ Examine various cases of pregnant patients admitted to the hospital and make recommendations for pharmacologic therapy for diseases states considering gestational age, medication properties and teratogenic potential
- ➔ Examine a postpartum patient case and make recommendations for pharmacologic therapy for diseases states considering medication properties and potential for infant harm during lactation
- ➔ Recommend helpful resources for information about medication use in pregnancy and lactation

Objectives: Technicians

- ➔ List medication properties that may increase placental drug transfer
- ➔ List medication properties that may increase drug transfer via breast milk
- ➔ Recommend helpful resources for information about medication use in pregnancy and lactation

Physiology of Pregnancy

- Fertilization occurs when sperm attaches to the outer layer of the egg, penetrates and the sperm and egg combine to create a new single cell known as a **zygote**. Male and female chromosomes join in the zygote and organize for cellular division
  - Fertilization usually occurs in the fallopian tube
  - 6 days after fertilization the cells are termed a **blastocyte**
  - hCG is now produces in appreciable amounts
- Implantation begins with the blastocyte resting on and beginning growth into the endometrial wall
- By day 10 the blastocyte is implanted under the endometrial surface and received nutrients by the maternal blood supply
- On the first day of the third week post fertilization the cells are known as an **embryo**



Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.

Physiology of Pregnancy

➔ Definitions

- Parity - The number of deliveries after 20 weeks gestation
- Gravida - The number of pregnancies regardless of outcome

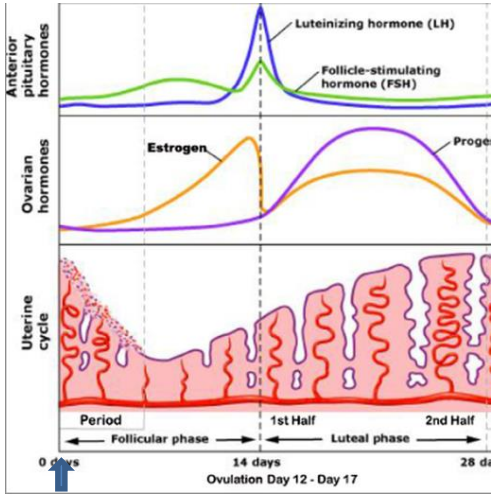
➔ Pregnancy

- Full term is considered 40 weeks gestation
- 3 Trimesters* (Gestational Age) - Trimesters vary depending on source
  - 1st trimester – week 1 to end of week 13
  - 2nd trimester – week 14 to end of week 26
  - 3rd trimester – week 27 until birth
  - *not as useful for helping assess medication use – use actual weeks
  - A medication 'safe' in one trimester may not be safe in another

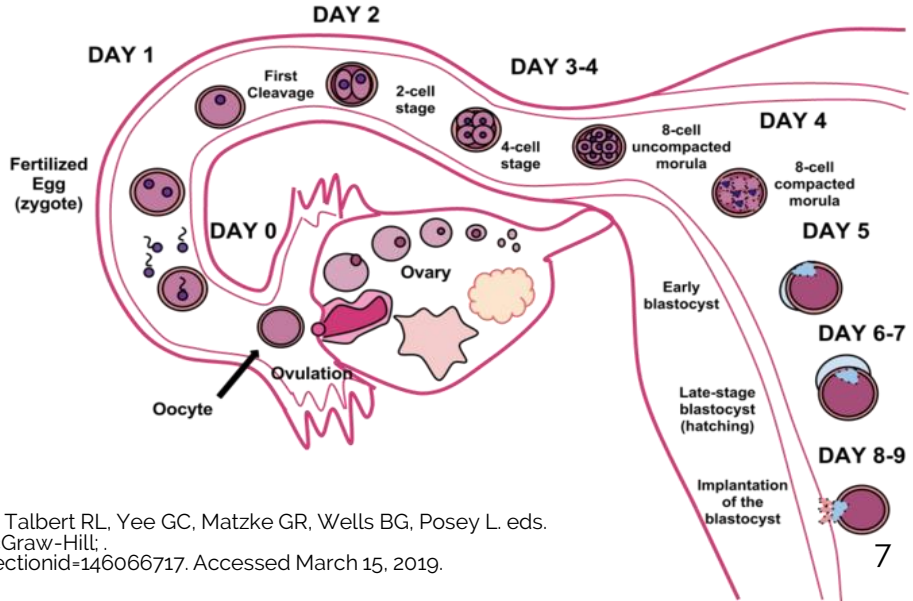
Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.

Determining Gestational Age

- For patients with a normal cycle
  - Day 1 of pregnancy (Gestational Age) starts from the first day of menses, even though conception has not taken place yet.



Day 1 of pregnancy



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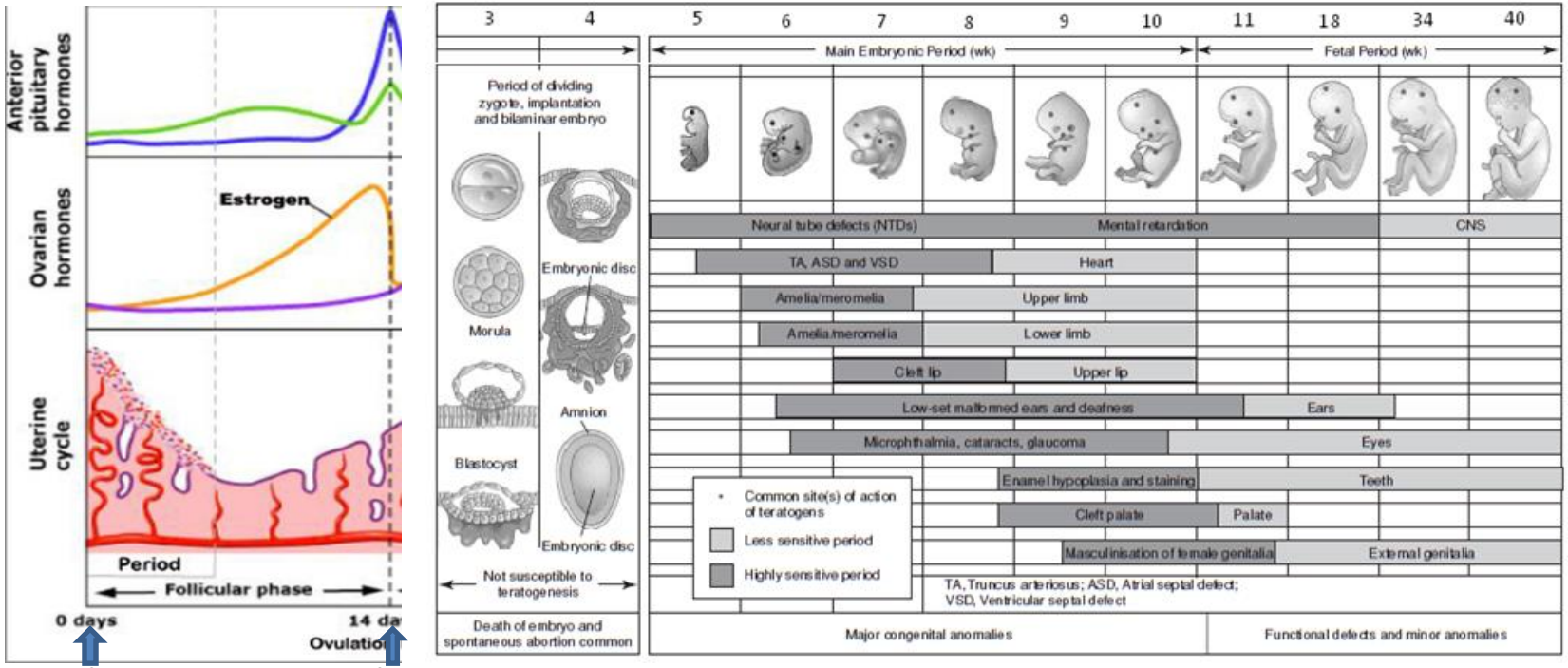
Fetal Development



Day 1 of pregnancy 2 weeks of pregnancy

Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.

Fetal Development

➔ **Does fetal stage of development matter?**

➔ Risk of harming the fetus at:

- Gestational age weeks 3 & 4: Fetal exposure may be all or none effect (destroy the embryo or have no ill effects) death of the embryo and spontaneous abortion most common
- Gestational age weeks 5 to 10: Major congenital anomalies likely
- Gestational age week 11 to birth: Functional defects and minor anomalies possible

Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.

Pharmacokinetic Changes During Pregnancy

Change	Effect on Medications
Maternal plasma volume, cardiac output and GFR increase by ≥30-50%	Lowers concentration of renally cleared medications
Increase in body fat	Increased Vd of fat soluble medications
Decrease in plasma albumin concentration	Increased Vd of highly protein bound medications; unbound drugs cleared more rapidly by the liver and kidney so little effect on concentration
Hepatic perfusion increases	Increased hepatic extraction of drugs
Nausea and vomiting	Altered absorption
Delayed gastric emptying	Altered absorption
Increase in gastric pH	Absorption of weak acids and bases affected
Increased estrogen and progesterone levels	Altered liver enzymatic activity (increase or decrease removal)

Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.

Fetal Harm

➔ **What can harm the fetus?**

➔ Rate of “naturally occurring” congenital anomalies - **3%–6%; 3% considered severe**

➔ Other causes of congenital anomalies

- Genetic/chromosomal 15-25%
- Environmental 10%
- Unknown 65-75%
- Medications <1%

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Teratogens

➔ Definition: Exposure to an agent of factor that causes malformation of an embryo

Exposure during organogenesis (weeks 5-11) resulting in structural abnormalities	Exposure after 11 weeks may result in growth retardations, CNS, other abnormalities or death
Methotrexate	NSAIDs
Cyclophosphamide	
Diethylstilbestrol	
Lithium	
Retinoids	Tetracycline
Thalidomide	
Antiepileptic drugs (AEDs)	
Coumadin	

Drugs in Pregnancy and Lactation.: A Reference Guide to Fetal and Neonatal Risk, 11th edition

Fetal Harm: Mechanisms

➔ How can medications harm the fetus?

- Act directly on the fetus, causing damage, abnormal development (leading to birth defects), or death.
  - Damaged differentiating cells more likely to result in permanent organ damage
- Alter the function of the placenta, usually by causing blood vessels to narrow (constrict) and thus reducing the supply of oxygen and nutrients to the fetus from the mother
- Cause the muscles of the uterus to contract forcefully, indirectly injuring the fetus by reducing its blood supply or triggering preterm labor and delivery.

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Methods for Determining Drug Safety in Pregnancy

➔ Estimating Risk

- Consider the quality of evidence
- Safety data from randomized, controlled trials most desirable; other types of data may be all that is available
  - Extrapolation of animal studies may not be relied upon
    - Example: Thalidomide found to be safe in animal models but teratogenic in humans
  - Case Studies: Birth defect may have developed by chance or due to the medication
- Principles for drug use during pregnancy include:
  - Selecting drugs that have been used safely for a long time
  - Prescribing doses at the lower end of the dosing range
  - Eliminating nonessential medication and discouraging self-medication
  - Avoiding medications known to be harmful (teratogens)

Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.

Pregnancy Categories

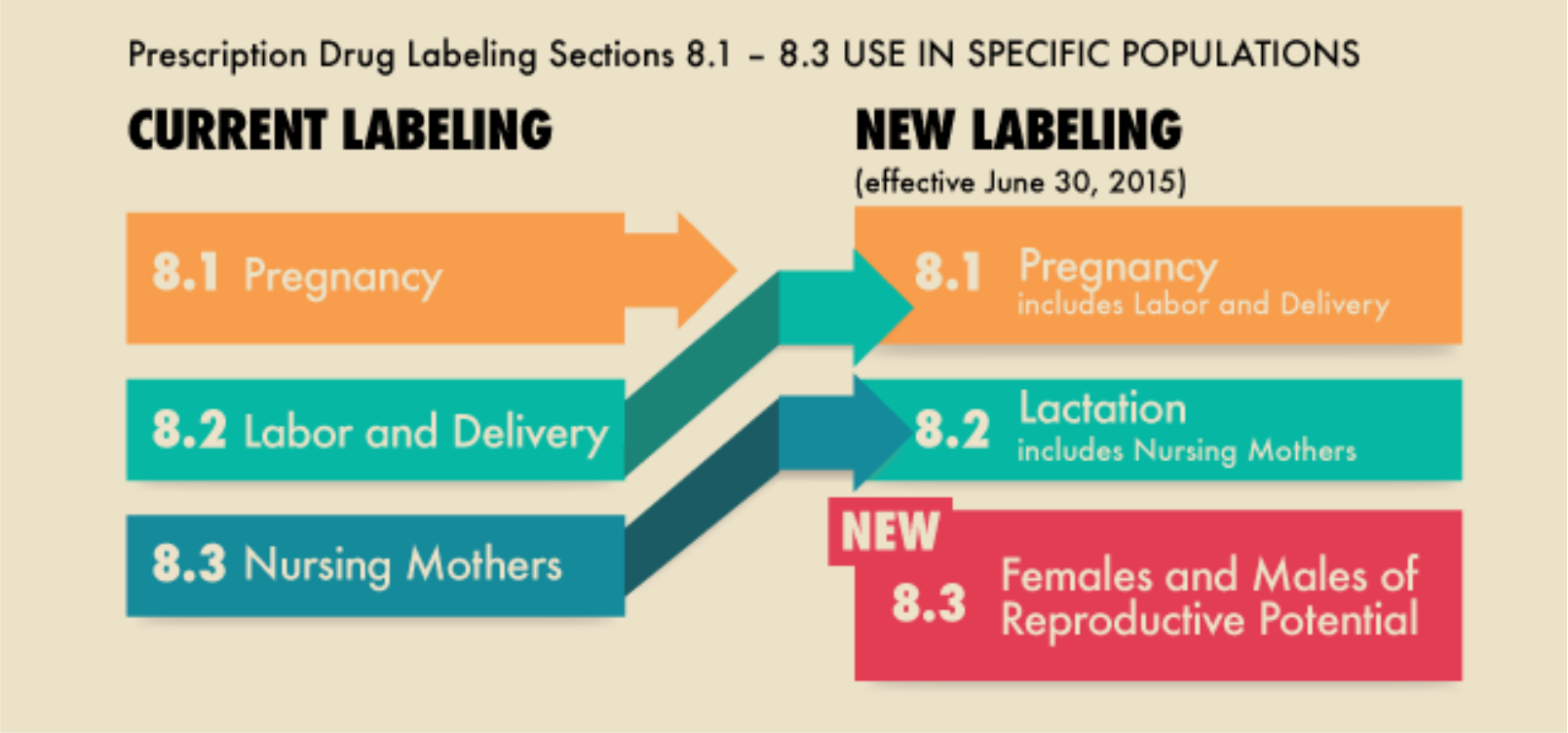
- ➔ Interpret the information:
  - FDA made a final rule in 12/2014 and is transitioning from the MISLEADING A-X categories for existing medications and not allowing them on new medication approvals effective June 2015. The labels will now contain:
    - Fetal Risk Summary: What is the risk of the medication to the fetus and is the data human or animal?
    - Clinical Consideration: Explains the risks to the woman who took the medication before learning she was pregnant
    - Data: Available about the drug in human and animal studies
- ➔ **NEVER USE:** Pregnancy Categories
  - **What do these actually mean?**

US Food and Drug Administration. Pregnancy and lactation labeling (drugs) final rule. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. Accessed March 15, 2019.

Pregnancy Categories

DO NOT USE

New Prescription Drug Labeling



US Food and Drug Administration. Pregnancy and lactation labeling (drugs) final rule. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm. Accessed March 15, 2019.

New Prescription Drug Labeling

Table 1. Timeline of Product Labeling Changes.[a]

Drug Approval Date	Deadline for Manufacturers to Submit Updated Labeling to FDA for Approval
On or after June 30, 2015	Use new format immediately
Pending application on June 30, 2015	4 Years after the effective date of pregnancy final rule or at time of approval, whichever is later
Any time from June 30, 2007, up to and including June 30, 2015	4 Years after the effective date of pregnancy final rule
Any time from June 30, 2005, up to and including June 29, 2007	3 Years after the effective date of pregnancy final rule
Any time from June 30, 2002, up to and including June 29, 2005	5 Years after the effective date of pregnancy final rule
Any time from June 30, 2001, up to and including June 29, 2002	3 Years after the effective date of pregnancy final rule
Prior to June 30, 2001	Remove previous pregnancy category but use of the new format is not required

[a]Adapted from table 1, Implementation Plan, Food and Drug Administration (FDA) Final Rule.[2] Applies to all prescription drugs and biological products; over-the-counter agents are not affected by the new labeling.

Annals of Internal Medicine. 2018;52(8):810-818

Methods for Determining Drug Safety in Pregnancy

➔ **Resources:**

- www.Motherisk.org
- www.toxnet.nlm.nih.gov

➔ **What if the information is not in the resource? What other information can help make a decision?**

- Can the medication get to the baby?

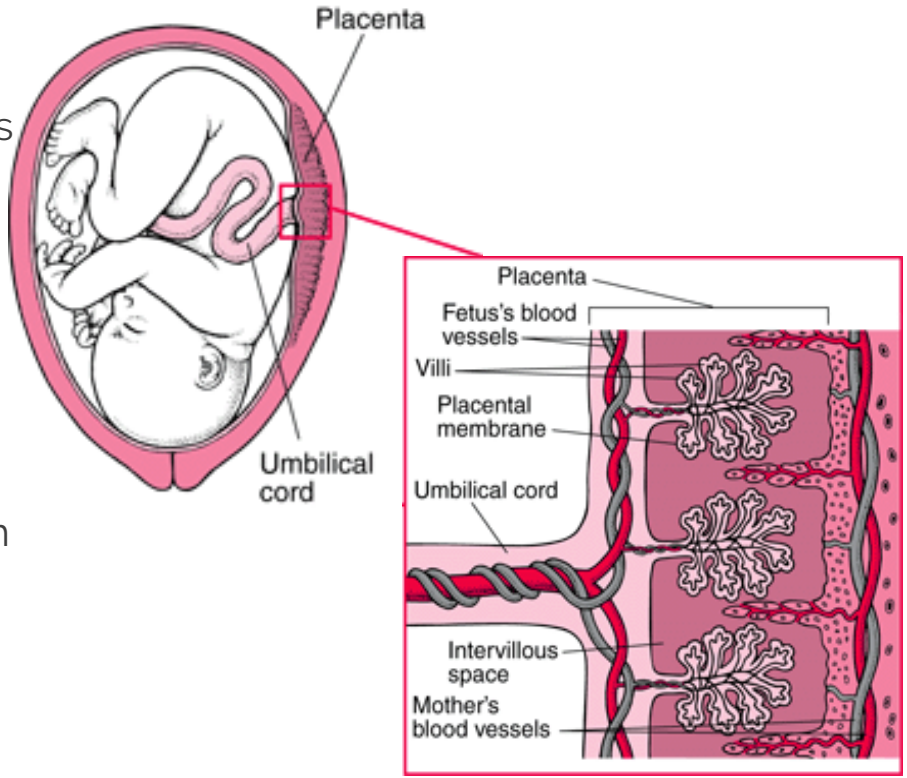
Placenta

➔ What is the placenta?

- An organ of exchange for a number of substances including medications between mother and fetus
- Most drugs move from maternal to fetal circulation by DIFFUSION
  - Certain placental properties may impact this

➔ What are the functions of the placenta?

- Transfers oxygen and nutrients from mother to fetus
- Permits release of carbon dioxide and waste from the fetus



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Placental Drug Transfer: Mechanisms

Drug Property	Increased Transfer to the Fetus
Lipophilicity	Highly lipophilic medications will cross more readily due to the lipid membrane of the placenta
Molecular Weight	Molecular weight <500Da readily cross the placenta
Protein Binding	**Unbound** drug crosses more easily. Highly **protein** bound drugs cross more easily as pregnancy progresses due to increases in fetal albumin and decreases in maternal albumin as pregnancy progresses
pH	Fetal pH is slightly more acidic than maternal pH. **Weak bases** more easily cross, once in fetal circulation the drug becomes ionized and less likely to diffuse back into maternal circulation

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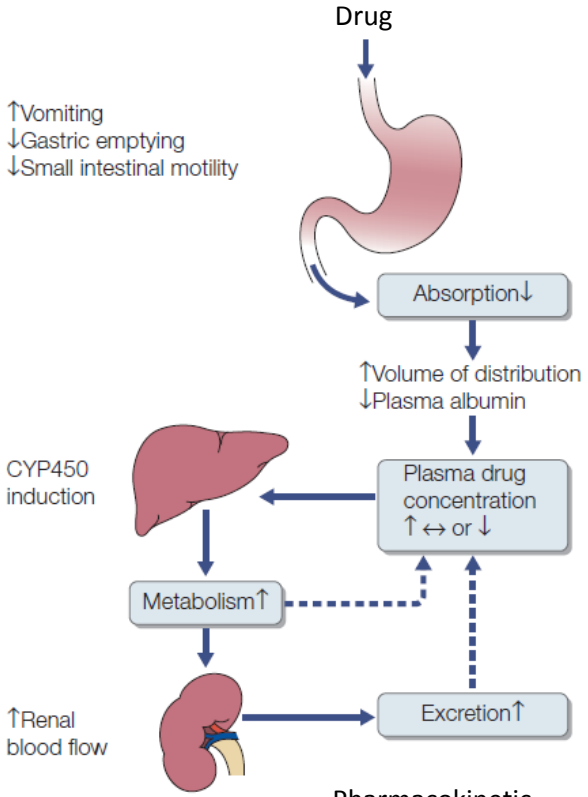
Methods for Determining Drug Safety in Pregnancy

- **What else needs to be considered after assessing safety of the medication to the fetus? What if the medication has some risks to it?**

- Are there alternatives?
  - Assess the alternatives as above
- What is the overall RISK VS BENEFIT (disease and medication)
  - What if the disease is left untreated?
  - If mom is healthy, the fetus will be more likely healthy

Methods for Determining Drug Safety in Pregnancy

- **Even if a medication is deemed safe or unlikely to affect the fetus, what are additional considerations when assessing medication use in pregnancy women?**



Pharmacokinetic changes in pregnancy

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Pregnancy Summary

➔ Pregnancy Medication Considerations

- Consider drug /disease risks/benefits on mother **AND** fetus
- Do not make recommendations solely on pregnancy categories!

Maternal	Fetal
Will the medication harm the mother?	Is the medication teratogenic or able to cause fetal adverse outcomes?
Will the medication need dosing or frequency changes due to maternal PK/PD?	Which trimester & how many weeks gestation is the infant?
How will an untreated disease impact the health the mother and the fetus?	

Patient Case and Self-Assessment Questions

Patient 1 is a 23-yr-old African American female presenting in pain-crisis due to Sickle Cell anemia.

HPI: Pt. 1 recently found out she is pregnant, 7 weeks gestational age. She has started suffering from nausea/vomiting of pregnancy and has been getting dehydrated over the last week. She has been taking her home pain medications almost around the clock but she has been unable to manage the pain.

PMH: Sickle cell disease (SS); anemia; G2P1

PTA Medications:

- Hydroxyurea 1000mg po daily (stopped after pregnancy test was positive)
- Folic Acid 1 mg po daily
- Hydromorphone 4mg tablets, 1 po q4h PRN pain (has been taking ATC for the last 2 days
- Docusate 100mg, 1 po daily PRN constipation

Allergies: penicillin (hives)

Vitals: BP 124/80mmHg; HR 84bpm; RR 20, 99% on room air; temperature 37º; Ht 160cm; Wt 54kg

Patient Case and Self-Assessment Questions

Labs:

Parameter	Result
WBC	$10.8x10^9/L$
Hgb	7.7g/dL
HCT	20.8%
PLT	$480x10^9/L$
MCV	$110\mu m^3$
Retic	18.2%
Sodium	144mmol/L
Potassium	4.5mmol/L
Chloride	96mmol/L
Carbon Dioxide	35mmol/L
BUN	50mg/dL
Creatinine	1.4mg/dL
Calcium	9.3mg/dL
Bilirubin	0.6mg/dL
Alk Phos	135unit/L
AST	35unit/L
ALT	28unit/L
Albumin	3.5g/dL
Glucose	96mg/dL
Total Bilirubin	5mg/dL
Direct Bilirubin	0.8mg/dL

➔ Inpatient Medications:

- Folic Acid 1 mg po daily
- Hydromorphone 2mg IV q2h PRN pain
- Docusate/Senna, 1 po BID
- Prenatal vitamin, 1 po daily
- Enoxaparin 40mg SQ daily

➔ Clinical Question:

- Provider on your team would like to consider adding ketorolac to provide a multimodal pain approach for the patient's pain crisis. Could this be added for the patient?

Kahoot!

- ➔ To win a gift card, go to Kahoot.it on your phone, laptop or tablet; enter the code on the screen; select a short user name (can be anything!)
- ➔ Answer questions
- ➔ The number of correct answers and the speed to which you answer will give you points
- ➔ The highest points receives the gift card

Patient Case and Self-Assessment Questions

Kahoot: Which fetal stage of development regarding exposure to medications most applies to Patient 1?

A. Fetal exposure may be all or none effect
B. Major congenital anomalies likely
C. Functional defects and minor anomalies possible
D. No major anomalies or defects likely

Patient Case and Self-Assessment Questions

Kahoot: In general, which of the following is NOT a possible mechanisms of medication-induced harm to the fetus?

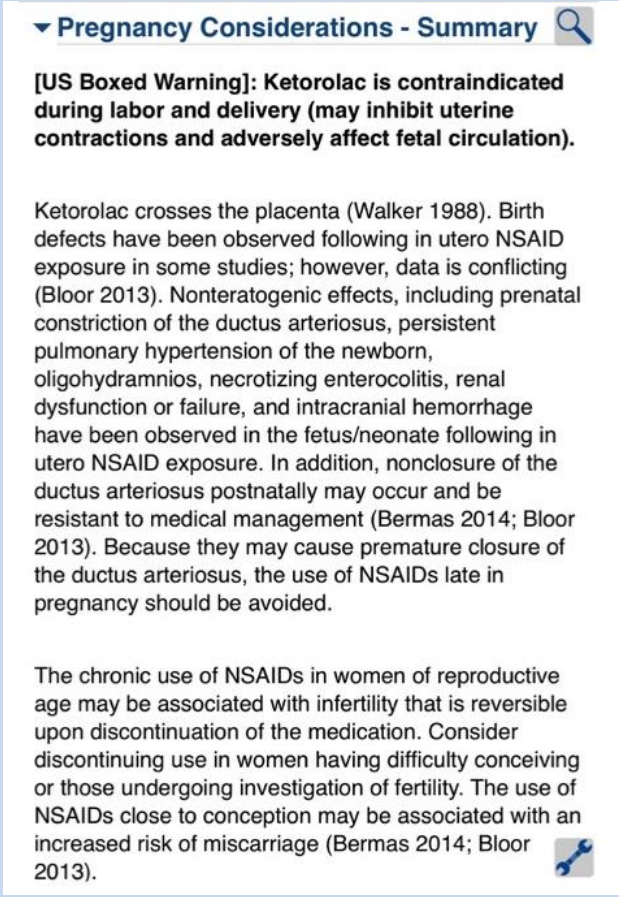
A. Act directly on the fetus, causing damage, abnormal development (leading to birth defects), or death.
B. Alter the function of the placenta thus reducing the supply of oxygen and nutrients to the fetus from the mother
C. Cause the muscles of the uterus to contract forcefully, indirectly injuring the fetus by reducing its blood supply or triggering preterm labor and delivery.
D. Cause constriction of the umbilical cord, indirectly injuring the fetus by reducing its blood supply or triggering preterm labor and delivery.

Patient Case and Self-Assessment Questions

Estimating Risk:

Ketorolac Pregnancy Considerations Summary in Lexicomp:

➔ References Briggs “Drugs in Pregnancy and Lactation”



Pregnancy Considerations - Summary

[US Boxed Warning]: Ketorolac is contraindicated during labor and delivery (may inhibit uterine contractions and adversely affect fetal circulation).

Ketorolac crosses the placenta (Walker 1988). Birth defects have been observed following in utero NSAID exposure in some studies; however, data is conflicting (Bloor 2013). Nonteratogenic effects, including prenatal constriction of the ductus arteriosus, persistent pulmonary hypertension of the newborn, oligohydramnios, necrotizing enterocolitis, renal dysfunction or failure, and intracranial hemorrhage have been observed in the fetus/neonate following in utero NSAID exposure. In addition, nonclosure of the ductus arteriosus postnatally may occur and be resistant to medical management (Bermas 2014; Bloor 2013). Because they may cause premature closure of the ductus arteriosus, the use of NSAIDs late in pregnancy should be avoided.

The chronic use of NSAIDs in women of reproductive age may be associated with infertility that is reversible upon discontinuation of the medication. Consider discontinuing use in women having difficulty conceiving or those undergoing investigation of fertility. The use of NSAIDs close to conception may be associated with an increased risk of miscarriage (Bermas 2014; Bloor 2013).

Lexicomp Ketorolac Monograph. Accessed March 15, 2019

Patient Case and Self-Assessment Questions

Kahoot: Which of the following is the most appropriate summary of the risk to the fetus with ketorolac exposure in Patient 1?

A. It is pregnancy category C, potential benefit may outweigh risk
B. Ketorolac should be avoided in the last trimester due to premature closure of the ductus arteriosus
C. Non-teratogenic effects such as renal failure have been reported with NSAID exposure *in utero*
D. NSAID use has been associated with infertility

Patient Case and Self-Assessment Questions

Ketorolac PK/PD

- ➔ 99% protein bound
- ➔ MW: 255 Daltons

- ➔ Lipophilicity and acidity not readily available without extensive search

Lexicomp Ketorolac Monograph. Accessed March 15, 2019

Patient Case and Self-Assessment Questions

Kahoot: In general, which of the following increases likelihood that a medication may cross the placenta?

A. High lipophilicity
B. High molecular weight
C. High protein binding
D. Strong base

Patient Case and Self-Assessment Questions

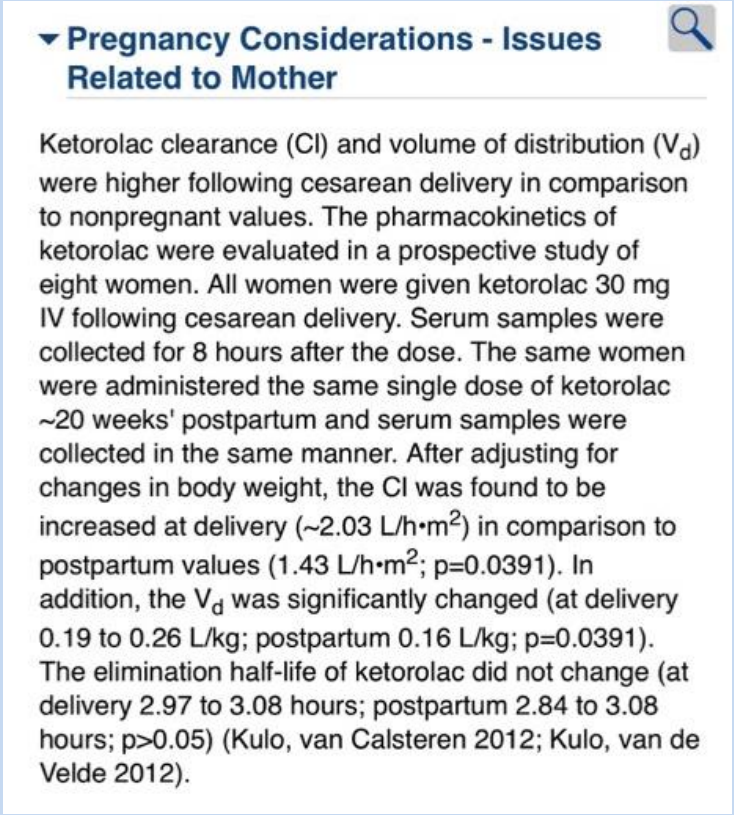
Are there alternatives?

What is the overall risk vs. benefit?

What are additional considerations when assessing medication use in pregnancy women?

Patient Case and Self-Assessment Questions

PK/PD changes in pregnancy affecting Ketorolac:



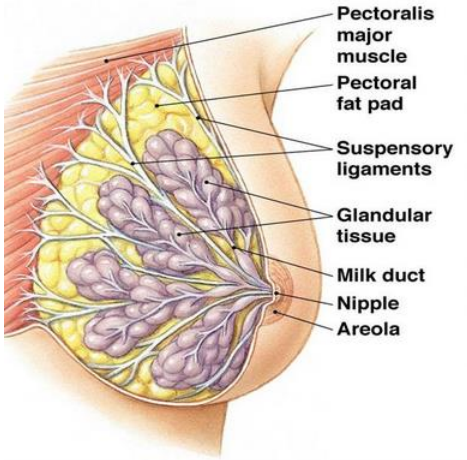
Pregnancy Considerations - Issues Related to Mother

Ketorolac clearance (Cl) and volume of distribution (V_d) were higher following cesarean delivery in comparison to nonpregnant values. The pharmacokinetics of ketorolac were evaluated in a prospective study of eight women. All women were given ketorolac 30 mg IV following cesarean delivery. Serum samples were collected for 8 hours after the dose. The same women were administered the same single dose of ketorolac ~20 weeks' postpartum and serum samples were collected in the same manner. After adjusting for changes in body weight, the Cl was found to be increased at delivery (~2.03 L/h•m^2) in comparison to postpartum values (1.43 L/h•m^2; p=0.0391). In addition, the V_d was significantly changed (at delivery 0.19 to 0.26 L/kg; postpartum 0.16 L/kg; p=0.0391). The elimination half-life of ketorolac did not change (at delivery 2.97 to 3.08 hours; postpartum 2.84 to 3.08 hours; p>0.05) (Kulo, van Calsteren 2012; Kulo, van de Velde 2012).

Lexicomp Ketorolac Monograph. Accessed March 15, 2019

Lactation

- Current recommendations from the CDC:
  - Exclusive breastfeeding for about the first 6 MONTHS
  - Breastfeeding in combination with the introduction of complementary foods until at least 12 MONTHS
  - Continuation of breastfeeding for as long as mutually desired by mother and baby



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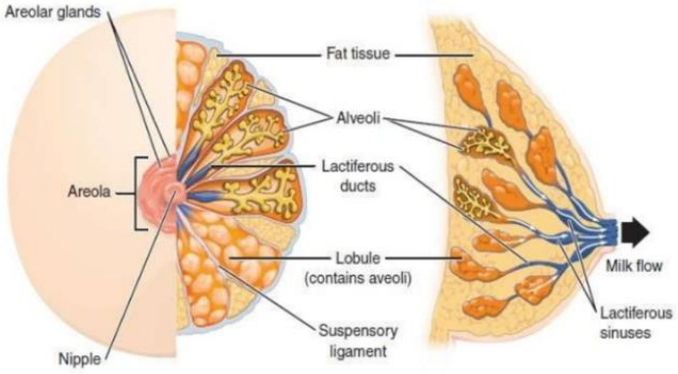
Breastmilk Composition

- ➔ Colostrum – “liquid gold” – first 3 days
  - Very rich in nutrients and antibodies to protect the baby
  - Yellow color, thick in consistency, and is high in protein and low in fat and sugar
- ➔ Mature milk – 3 to 5 days after birth
  - Has just the right amount of fat, sugar, water, and protein to help babies continue to grow
  - Foremilk - The first milk the baby receives at start of breastfeeding session. It is thin and watery with a light blue tinge.
  - Hind-milk - Released after several minutes of nursing. It is similar in texture to cream and has the highest concentration of fat.

Methods for Determining Drug Safety in Lactation

➔ **Can the medication get into the breastmilk?**

- Passive diffusion is the primary mechanism for drug transfer into breastmilk
- Greater amounts of drugs are present in colostrum, however the amount received by the nursing infant is minimal because of the limited volume of colostrum produced
- A greater volume of mature milk is produced, but drug transfer into mature milk is lower because of tight cell-to-cell junctions



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Lactation Drug Transfer: Mechanisms

Drug Property	Likelihood of Transfer
Protein Binding (maternal)	The degree of protein binding to maternal plasma proteins is one of the most significant factors affecting drug transfer to breast milk; **low bound transfer in higher amounts,** highly bound medications transfer in low amounts
Molecular Weight	**Low-molecular-weight drugs (up to 800-1000Da) passively diffuse into breast milk;** larger molecules are not likely to transfer in large amounts
Lipid solubility/Corresponding Fat Content of Milk	**Higher lipid solubility** of drugs also increases the likelihood of transfer
Plasma Concentration (maternal)	The **higher the concentration** of drug in the mother's serum, the higher the concentration will be in the breast milk. As the drug is metabolized and excreted by the mother, the mother's serum concentration drops, and the drug in the breast milk may redistribute back into the mother's bloodstream.
Half Life	Drugs with **longer half-lives** are more likely to maintain higher levels in breast milk, resulting in greater exposure to the infant.
pH	Maternal plasma pH is 7.4, while the pH of breast milk ranges between 6.8 and 7. **Weak bases are not ionized in the maternal circulation and easily transfer to breast milk.** In the lower pH of breast milk, molecules become ionized and are less likely to diffuse back into maternal circulation ("ion trapping").

Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.
Mothersmik.com Accessed March 15, 2019.

Relative Infant Dose (RID)

➔ What does RID tell you?

- Does NOT communicate safety of the medication in breastfeeding.
- Relative infant doses <10% are considered safer and are preferred.
  - Most drugs have a RID <1%
- RID >25% generally not considered safe (i.e. breastfeeding should be avoided)

Hale RW. Hale's Medications and Mothers' Milk 2019
Mothersmik.com Accessed March 15, 2019.

Relative Infant Dose (RID)

➔ EXAMPLE: Metronidazole

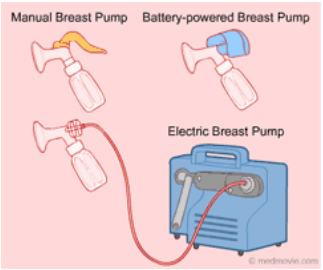
- Maternal dose: metronidazole 2000mg/day, 70kg mom = (2000mg/day divided by 70kg = 28.6mg/kg/day)
- Highest average milk concentration 45mcg/mL
- Infant dose: 45mcg/mL *150mL/kg/day = 6750 mcg/kg/day = 6.75mg/kg/day
- RID = $\frac{\text{Infant Dose (mg/kg/day)}}{\text{Maternal Dose (mg/kg/day)}} = \frac{6.75\text{mg/kg/day}}{28.6\text{mg/kg/day}} = 23.6\%$

Lactation Categories

DO NOT USE

Reducing Risk to the Breastfeeding Infant

- ➔ Selection of medications that would be considered safe for use in the infant (use pediatric resources)
- ➔ Drugs with shorter half-lives accumulate less, and those that are more protein bound do not cross into breast milk as well as those that are less protein bound.
- ➔ Drugs with lower oral bioavailability and lower lipid solubility are good choices.
- ➔ If the mother is using a once-daily medication, administration before the infant's longest sleep period may be advised to increase the interval to the next feeding.
- ➔ For medications taken multiple times per day, administration immediately after breastfeeding provides the longest interval for back diffusion of drug from the breast milk to the mother's serum.
- ➔ During short-term drug therapy, the mother can pump and discard milk to preserve her milk-producing capability if the medication is not considered compatible with breastfeeding.



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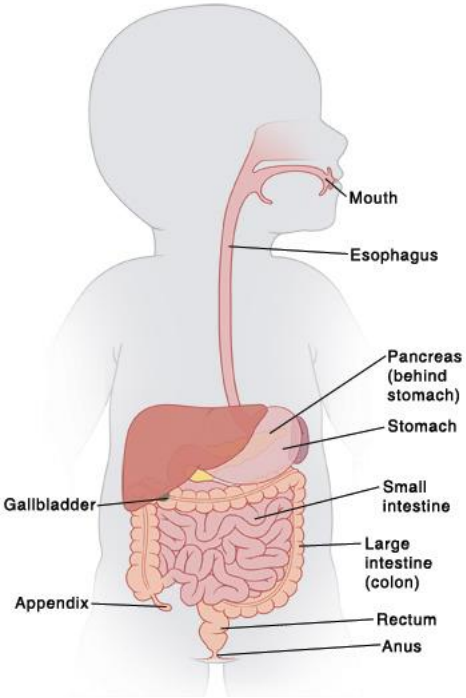
Mothersmik.com Accessed March 15, 2019.

Infant Factors

➔ What factors influence infant exposure to a medication?

- Infant-related factors may also influence the amount of drug ingested through breastfeeding.
- Both the frequency of feedings and the amount of milk ingested are important considerations.
  - Exclusively breastfed infants are more likely to ingest larger amounts of drugs than older infants who receive other foods
- Drugs unstable in gastric acid (aminoglycosides, PPIs, heparin, and insulin) are less likely to be absorbed by infants
- Infants may vary in their ability to metabolize and excrete ingested medication.
  - Premature and full-term infants may not have full renal and liver function.



Ward KE. Pregnancy and Lactation: Therapeutic Considerations. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. Pharmacotherapy: A Pathophysiologic Approach, 10e New York, NY: McGraw-Hill; . http://accesspharmacy.mhmedical.com/content.aspx?bookid=1861&sectionid=146066717. Accessed March 15, 2019.
Mothersmik.com Accessed March 15, 2019.

Methods for Determining Drug Safety in Lactation

➔ Resources for Health Care Providers

- www.mothertobaby.org → Fact Sheets
- Medsmilk.com/ Hale's Medications and Mothers' Milk
- LactMed https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- Lexicomp → Briggs Drugs in Pregnancy and Lactation
- ACOG Breastfeeding Toolkit
- CDC resources: https://www.cdc.gov/nutrition/infantandtoddlernutrition/breastfeeding/index.html

➔ Resources for Patients

- La Leche League
- KellyMom.com
- Nursing Mothers Advisory Council
- Breastfeeding USA
- The Office on Women's Health

Lactation Summary

➔ Lactation Medication Considerations

- Consider drug /disease risks/benefits on mother **AND** breastfed child

Mother	Infant
Is the medication appropriate for the mother? Is there an alternative or alternative dosing form?	Is the medication likely to cause harm if the infant is exposed to the medication?
Will the medication impact the production of breastmilk?	How much medication will the infant be exposed to (RID)?
How will an untreated disease impact the health the mother and the infant?	

Patient Case and Self-Assessment Questions

Patient 2 is a 30-yr-old Hispanic female presenting with an acute asthma exacerbation.

HPI: Pt. 2 recently moved to New York from North Carolina, she has been staying with her two children (3 years and 6 weeks; currently breastfeeding) with her sister in her apartment. She states the apartment has black mold but the landlord hasn't done anything about it. She was utilizing her albuterol very frequently and called EMS when she was unable to catch her breath to complete sentences. She was treated with IV methylprednisolone, ipratropium/albuterol nebulization and IV magnesium sulfate in the ED and has subsequently been transferred to the general medicine floor.

PMH: Severe asthma (last intubation 3 years ago), hospitalized twice in the last year for poorly controlled asthma, treated with oral systemic corticosteroids

PTA Medications:

- Albuterol (ProAir) 90 mcg/actuation 1-2 puffs every 4-6 hours PRN
- Budesonide (Pulmicort Flexhaler) 180 mcg/actuation two times daily
- Norethindrone 0.35mg po daily
- Prenatal vitamin, 1 po daily

Allergies: penicillin, levofloxacin, clindamycin, fish, peanut, soy, grass, mold, dust, ragweed, trees, cats, dogs

Vitals: BP 116/76mmHg; HR 90bpm; RR 20, 99% on room air; temperature 37º; Ht 160cm; Wt 54kg

Patient Case and Self-Assessment Questions

Labs:

Parameter	Result
WBC	11.8x10^9/L
Hgb	13g/dL
HCT	41%
PLT	310x10^9/L
Sodium	141mmol/L
Potassium	3.1mmol/L
Chloride	104mmol/L
Carbon Dioxide	29mmol/L
BUN	16mg/dL
Creatinine	0.7mg/dL
Calcium	9.3mg/dL
Bilirubin	0.6mg/dL
Alk Phos	135unit/L
AST	35unit/L
ALT	28unit/L
Albumin	3.5g/dL
Glucose	96mg/dL

➔ Inpatient Medications:

- Prednisone 60mg po daily
- Albuterol 90 mcg/actuation 1-2 puffs every 4-6 hours PRN
- Prenatal vitamin, 1 po daily
- Heparin 5000U SQ q8h

➔ Patient provided with medical grade breast pump

➔ Clinical Question:

- Provider on your team would like to consider adding ketorolac as the patient is complaining of significant soreness due to work of breathing

Patient Case and Self-Assessment Questions

Ketorolac PK/PD

- ➔ 99% protein bound
- ➔ MW: 255 Daltons
- ➔ 100% oral bioavailability
- ➔ Half life: ~5 hours

- ➔ Lipophilicity and acidity not readily available without extensive search

Patient Case and Self-Assessment Questions

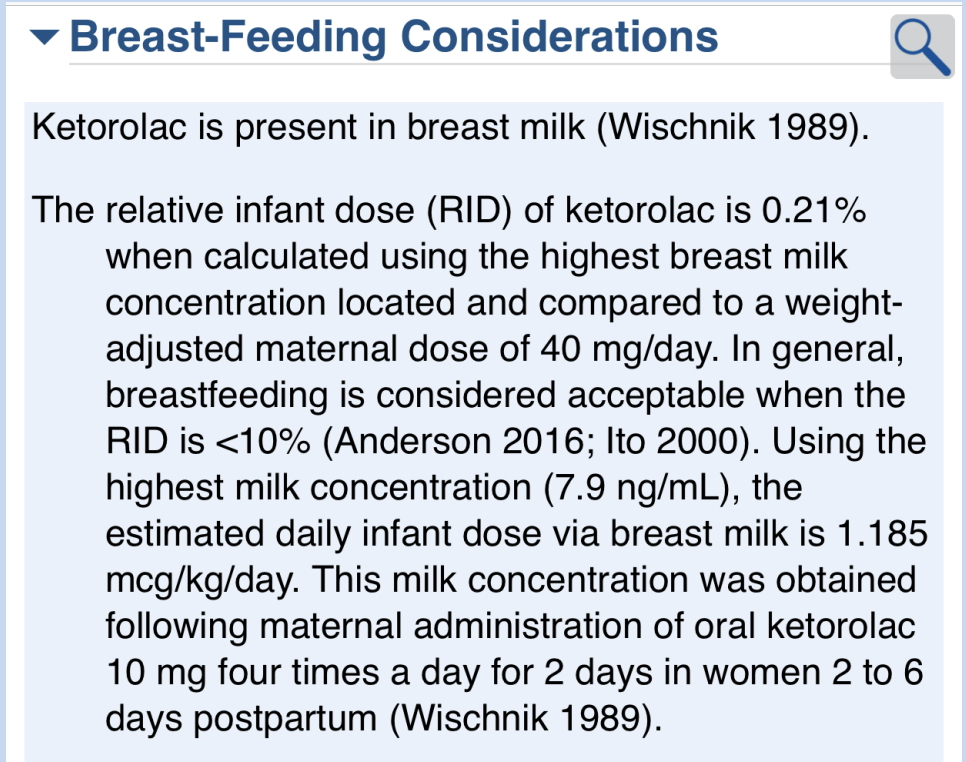
Kahoot: In general, which of the following factors increases likelihood that a medication may cross into breastmilk?

A. High lipophilicity
B. High molecular weight
C. High protein binding
D. Strong base

Patient Case and Self-Assessment Questions

Ketorolac RID

0.21%



Breast-Feeding Considerations

Ketorolac is present in breast milk (Wischnik 1989).

The relative infant dose (RID) of ketorolac is 0.21% when calculated using the highest breast milk concentration located and compared to a weight-adjusted maternal dose of 40 mg/day. In general, breastfeeding is considered acceptable when the RID is <10% (Anderson 2016; Ito 2000). Using the highest milk concentration (7.9 ng/mL), the estimated daily infant dose via breast milk is 1.185 mcg/kg/day. This milk concentration was obtained following maternal administration of oral ketorolac 10 mg four times a day for 2 days in women 2 to 6 days postpartum (Wischnik 1989).

Lexicomp Ketorolac Monograph. Accessed March 15, 2019

Patient Case and Self-Assessment Questions

Kahoot: What does the RID of Ketorolac tell you?

A. As the RID is <10% it is considered safer and preferred
B. Ketorolac is absolutely safe to use in breastfeeding
C. As the RID is <10% breastfeeding should be avoided
D. Patient 2 should pump and discard all breastmilk

Patient Case and Self-Assessment Questions

Kahoot: Which of the following factors influence infant exposure to a medication?

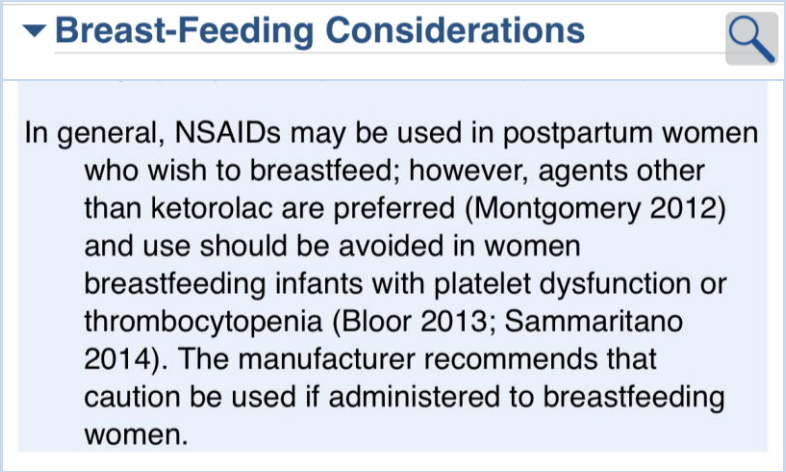
A. Frequency of right breast feedings
B. Frequency of naps for the infant
C. Medication taste
D. Oral bioavailability

Patient Case and Self-Assessment Questions

Estimating Risk:

Ketorolac Lactation Considerations Summary in Lexicomp:

➔ References Briggs “Drugs in Pregnancy and Lactation”



Lexicomp Ketorolac Monograph. Accessed March 15, 2019

Patient Case and Self-Assessment Questions

Kahoot: Which of the following is the most appropriate summary of the risk to the infant with ketorolac exposure in Patient 2?

A. It is pregnancy category L1, compatible with breastfeeding
B. Ketorolac is generally considered safe
C. Ketorolac should not be used due to risk of thrombocytopenia
D. NSAID use has been associated with infertility

Clinical Pearls

- ➔ Specific guidelines are often available for management of acute disease states, including those specific to pregnancy and lactation
- ➔ Pharmacists should equip themselves with the necessary tools needed to evaluate medication use in these special populations
- ➔ Pharmacists should familiarize themselves with the new FDA labeling and phase out use of pregnancy and lactation category labeling

References/Resources:

- Griffin BL, Stone RH, El-Ibiary SY, et al. Guide for drug selection during pregnancy and lactation: what pharmacists need to know for current practice. *Annals of Internal Medicine.* 2018;52(8):810-818.
- Lexicomp → Briggs Drugs in Pregnancy and Lactation
- www.Motherisk.org
- Mothersmilk.com/ Hale's Medications and Mothers' Milk
- www.toxnet.nlm.nih.gov
- www.mothertobaby.org → Fact Sheets
- LactMed https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
- ACOG Breastfeeding Toolkit
- CDC resources: https://www.cdc.gov/nutrition/infantandtoddlernutrition/breastfeeding/index.html