3rd Annual Critical Care Symposium 2016

OB Pharmacology Review

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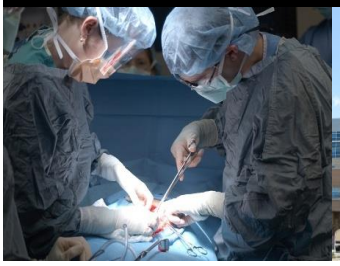


Objectives

- Review pregnancy categories and their upcoming evolution
- Discuss medication properties as they relate to pregnancy and breast feeding
- Identify common medications and doses used in acutely ill obstetric patients
- Identify certain medications to avoid during pregnancy and breast feeding

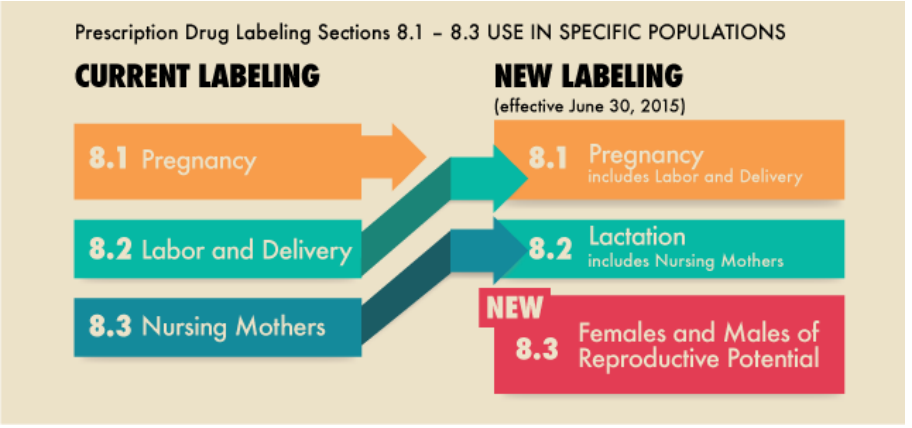
Pregnancy Categories

A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

Pregnancy and Lactation Labeling Rule (PLLR)[1]

- Published December 4, 2014
- Requires that the labeling include
  - Summary of the risks of using a drug during pregnancy and lactation
  - A discussion of the data supporting that summary
  - Relevant information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and lactation

New Labeling Requirements



Implementation Plan

	NDA's, BLA, ESs	Required Submission Date of PLLR Format
New Applications	Submitted on or after 6/30/2015	At time of submission
Older approved Applications	Approved 6/30/2001 - 6/29/2002 Approved 6/30/2005 - 6/29/2007	6/30/2018
	Approved 6/30/2007 - 6/29/2015 or pending on 6/30/2015	6/30/2019
	Approved 6/30/2002 - 6/29/2005	6/30/2020
	Applications approved prior to 6/30/2001	Not required to be in PLLR format, however must remove Pregnancy Category by 6/29/2018

Example

EMPLICITI™ (elotuzumab)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no studies with EMPLICITI with pregnant women to inform any drug associated risks. Animal reproduction studies have not been conducted with elotuzumab.

EMPLICITI is administered in combination with lenalidomide and dexamethasone. Lenalidomide can cause embryo-fetal harm and is contraindicated for use in pregnancy. Refer to the lenalidomide and dexamethasone prescribing information for additional information. Lenalidomide is only available through a REMS program.

The background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There is no information on the presence of EMPLICITI in human milk, the effect on the breast-fed infant, or the effect on milk production. Because of the potential for serious adverse reactions in breast-fed infants from elotuzumab administered with lenalidomide/dexamethasone, breastfeeding is not recommended. Refer to the lenalidomide and dexamethasone prescribing information for additional information.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Refer to the lenalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

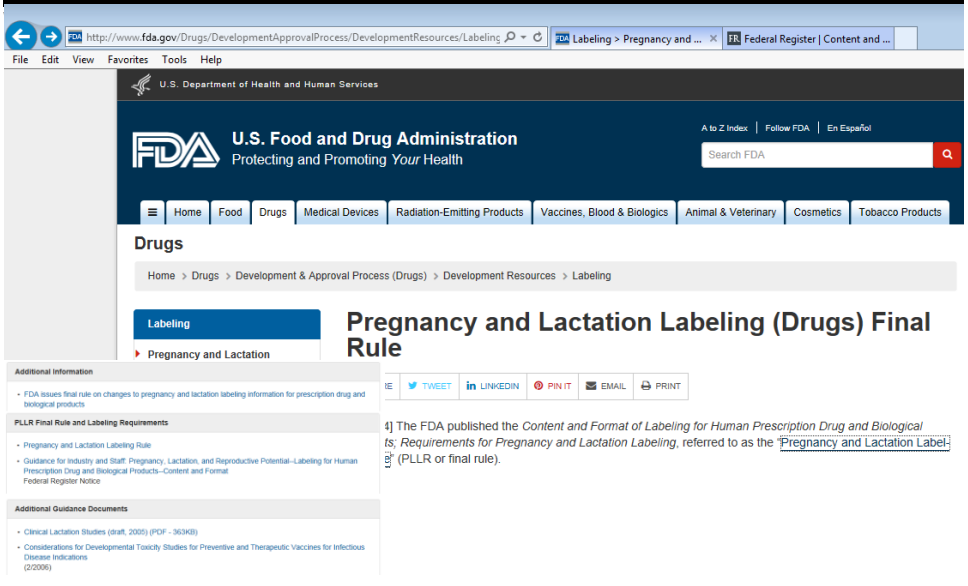
When EMPLICITI is used with lenalidomide, there is a risk of fetal harm, including severe life-threatening human birth defects associated with lenalidomide, and the need to follow requirements regarding pregnancy avoidance, including testing.

Contraception

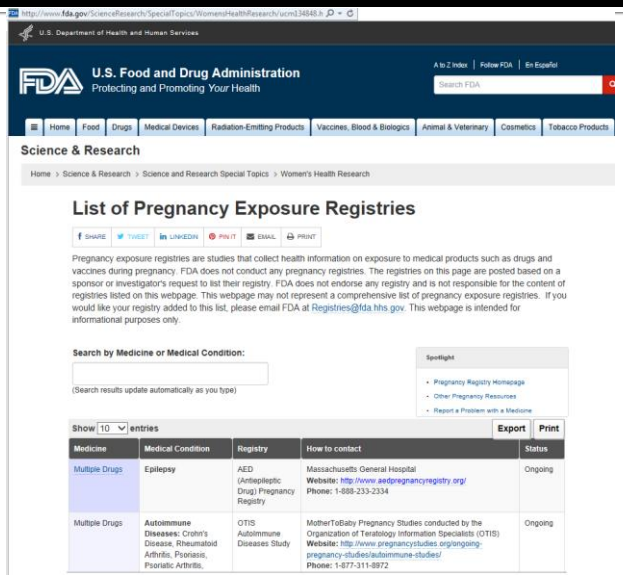
Refer to the lenalidomide labeling for contraception requirements prior to initiating treatment in females of reproductive potential and males.

Lenalidomide is present in the blood and semen of patients receiving the drug. Refer to the lenalidomide full prescribing information for requirements regarding contraception and the prohibitions against blood and/or sperm donation due to presence and transmission in blood and/or semen and for additional information.

For More Information Visit…



Pregnancy Registries



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List of Pregnancy Exposure Registries

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Pregnancy exposure registries are studies that collect health information on exposure to medical products such as drugs and vaccines during pregnancy. FDA does not conduct any pregnancy registries. The registries on this page are posted based on a sponsor or investigator's request to list their registry. FDA does not endorse any registry and is not responsible for the content of registries listed on this webpage. This webpage may not represent a comprehensive list of pregnancy exposure registries. If you would like your registry added to this list, please email FDA at Registries@fda.hhs.gov. This webpage is intended for informational purposes only.

Search by Medicine or Medical Condition:

(Search results update automatically as you type)

Spotlight

- Pregnancy Registry Homepage
- Other Pregnancy Resources
- Report a Problem with a Medicine

Show 10 entries | Export | Print

Medicine	Medical Condition	Registry	How to contact	Status
Multiple Drugs	**Epilepsy**	AED (Antiepileptic Drug) Pregnancy Registry	Massachusetts General Hospital **Website:** http://www.aedpregnancyregistry.org/ **Phone:** 1-888-233-2334	Ongoing
Multiple Drugs	**Autoimmune Diseases:** Crohn's Disease, Rheumatoid Arthritis, Psoriasis, Psoriatic Arthritis,	OTIS Autoimmune Diseases Study	MotherToBaby Pregnancy Studies conducted by the Organization of Teratology Information Specialists (OTIS) **Website:** http://www.pregnancystudies.org/ongoing-pregnancy-studies/autoimmune-studies/ **Phone:** 1-877-311-8972	Ongoing

Pharmacokinetic Changes During Pregnancy

Pharmacokinetic Properties[2]

- Increases in volume of distribution (Vd)
  - ↑ cardiac output
    - Maternal blood volume increases by 40-50%
    - Hydrophilic medications with low Vd are most affected
  - ↓ serum albumin → ↓ in plasma protein binding
    - Medications: digoxin, midazolam, phenytoin
- Alterations in drug absorption
  - Nausea/vomiting
  - Delay in gastric motility
    - Increases time to maximum concentration
  - Increases in gastric pH
    - May decrease or increase absorption pending medication properties
    - Medications: levothyroxine, iron

Pharmacokinetic Properties[2]

- Alterations in medication clearance
  - Renal blood flow and GFR ↑ 50% by 14 weeks
    - SrCr >0.8 may indicate underlying renal dysfunction
    - Medication: aminoglycosides, vancomycin, cefazolin, piperacillin, atenolol, digoxin, lithium, levetiracetam…
  - Cytochrome P450 liver enzymes
    - ↑ abundance and activity of CYP3A4 which increases metabolism of certain medications
      - Medications: nifedipine, carbamazepine, midazolam, lopinavir and ritonavir, various others…

Medications used in Pre-eclampsia/Eclampsia/HELLP

Hypertensive Medications

Medication	Dose	MOA	Onset	Duration	Adverse Effects
Hydralazine (C)	IV: 5 - 10 mg → 10 mg q 20 min	Direct vasodilation of arterioles	5-20 min	1 - 4 hours	Maternal hypotension, reflex tachycardia
Labetalol (C)	IV: 20 mg → 40 mg → 80 mg q 10 min PO: 100 - 200 mg may repeat in 30 min	α-, β1-, and β2-blocker	2-5 min (peak 5-15 min)	2 - 18 hours	Fetal bradycardia, hypoglycemia, hypotension, respiratory depression Maternal dizziness, nausea, orthostatic hypotension
Nifedipine (C)	PO: 10 mg → 20 mg after 20 min	Ca^{++} channel blocker	20 min	Depends on formulation	↑ in perinatal asphyxia, cesarean delivery, & prematurity have been described Maternal tachycardia
Nicardipine (C)	IV: 2.5 – 5 mg/hr, increase by 2.5 mg q 5 - 15 min	Ca^{++} channel blocker	Within minutes	≤8 hours	Pulmonary edema
Nitroprusside (IV infusion) (C)	Reserved for extreme emergencies and used for the shortest amount of time possible because of concerns about cyanide and thiocyanate toxicity in the mother and fetus or newborn, and increased intracranial pressure with potential worsening of cerebral edema in the mother				

Committee on Obstetric Practice. Emergent Therapy for Acute-onset, Severe Hypertension During Pregnancy and the Postpartum Period. Number 623, February 2015

Seizure Medications

Medication	Dose	MOA	Onset	Duration	Adverse Effects
Magnesium[3] (D)	IV: 4-6 gram load then 2 gram/hr IM: 5 g into each buttocks → 4 g q 4 hrs	Poorly understood	IV: Immediate IM: 1 hr	IV: 30 min-2 hr IM: 3 - 4 hrs	Use >5 days may cause fetal hypocalcemia, bone abnormalities, maternal hypotension, muscle weakness, respiratory depression and in patients with myasthenia gravis
Lorazepam (D)	IV/IM: 2 - 4 mg (q 10 - 15 min)	Enhances the inhibitory effect of GABA on neuronal excitability	IV: 2 min	IV: 6 - 8 hrs	Premature birth and low birth weight may occur; hypoglycemia and respiratory problems if given late in pregnancy; monitor for withdrawal/floppy infant syndrome
Midazolam (D)	IV/IM: 2 - 10 mg	See above	IV: 1 - 5 min	<2 hrs (dose dependent)	See above
Levetiracetam (C)	IV: 500 to 1000	GABA inhibition, modulating neurotransmitter release, inhibition calcium channels	IV: Peak effect within 5-15 min	Typically dosed q 12 hrs	Dizziness, somnolence Increased elimination noted during pregnancy[4]
Fosphenytoin (D)	15 - 20 mg/kg may repeat 10 mg/kg after 20 min	Stabilizes neuronal membranes via Na ions	IV: ~30 min	Typically dosed q 8-12 hrs	Hypotension, somnolence, hypokalemia, nystagmus Fetal cardiac defects, dysmorphic facial features, microcephaly

More on Magnesium

- Other Uses
  - Prevention and treatment of seizures in women with preeclampsia or eclampsia
  - Short-term prolongation of pregnancy (up to 48 hours) to allow for the administration of antenatal corticosteroids in pregnant women who are at risk of preterm delivery within 7 days
  - Fetal neuroprotection before anticipated early preterm (less than 32 weeks of gestation) delivery
- Follow clinical signs of toxicity rather than lab values
  - Renal patients are at risk for Mg accumulation
  - Reversal of toxic effects: calcium gluconate 1 gram IV

Steroids for Antenatal Use

- Given if pre-eclampsia develops between 24 to 34-36 weeks gestation or patient is at risk for pre-term delivery
  - Speeds up fetal lung development, may reduce other complications of pre-term birth
    - e.g. intraventricular hemorrhage, necrotizing enterocolitis, respiratory distress syndrome
  - Betamethasone
    - Dose: 12 mg IM q 24 hrs x 2 doses
      - Full benefit is at 48 hrs post first injection
  - Dexamethasone
    - Dose: 6 mg IM q 12 hrs x 4 doses
      - Preservative free or non-sulfite containing product should be used

Medications for Postpartum Hemorrhage/Severe Bleeding

Uterotonics

Medication	Dose	MOA	Onset	Duration	Adverse Effects
Oxytocin (Pitocin)	IV: 30 units/500 mL over ~1hr → 20 units/1L over ~8 hrs IM: 10 units	Binds smooth mucle receptors in uterus to cause increase in rhythmic contractions and increases uterine tone	IV: ~1 min IM: 3-5 min	IV: 1 hr IM: 2-3 hrs	Neonatal arrhythmias, bradycardia, jaundice Maternal arrhythmias, hypertension, nausea/vomiting, Qtc prolongation
Misoprostol (Cytotec)	PR: 800 mcg	Prostaglandin E1, induces uterine contractions			Maternal diarrhea, abnormal taste, nausea/vomiting, abdominal pain, dyspnea, thrombocytopenia, fever
Methylergonovine (Methergine)	IV/IM: 0.2 mg after delivery of anterior shoulder, after delivery of placenta, or during puerperium May repeat doses q 2-4 hrs as needed	Increases tone, rate and amplitude of contractions on the smooth muscles of the uterus, producing sustained contractions which shortens the 3rd stage of labor and reduces blood loss	IV: immediate IM: 2-5 min	IV: 45 min IM: 3 hrs	Maternal AV block, chest pain, brady/tachycardia, headache, hyper/hypotension, abdominal pain, diarrhea, dyspnea Should not be routinely administered IV due to potential for sudden hypertension and cerebrovascular accident
Carboprost tromethamine (Hemabate)	IM: 0.25 mg q 15-90 min up to 8 doses **or** 0.5 mg up to 3 mg **or** 0.5 mg intramyometrial	Prostaglandin F2 alpha, uterine contraction (hemostasis at the placentation site is achieved through the myometrial contractions produced by carboprost)	IM: 30 min time to peak		Chest pain, hypertension, tachycardia, anxiety, dizziness, shivering, increased temperature, dyspnea, nausea, vomiting, pulmonary edema, respiratory distress, diarrhea (consider lomotil)

Medications Affecting Hemostasis

Medication	Dose	MOA/Factors replaced	Estimated Costs	Adverse Effects
NovoSeven	10-20 mcg/kg	Recombinant factor VIIa	5 mg vial = $9000	Hypo/hypertension, bradycardia, thrombosis, decreased serum fibrinogen, fever
Kcentra (C)	IV: 25-50 units/kg	4-factor complex + protein C & S	25 unit/kg for (70 kg) = $4000	Hypo/hypertension, tachycardia, thrombosis, respiratory distress Note: Do not use in HIT patients
Bebulin (C)	IV: 25-50 units/kg	3-factor complex (II, IX, X)		Flushing, thrombosis, fever, paresthesia, dyspnea
RiaSTAP (C)	IV: 70 mg/kg if fibrinogen unknown	Fibrinogen concentrate	70 mg/kg (70 kg) = $6100	Fever, headache, thrombosis, dyspnea, MI
Tranexamic acid (B)	IV: 1000 mg	Inhibits fibrinolysis Displaces plasminogen from fibrin	1000 mg vial is ~ $50	Hypotension, headache, abdominal pain, thrombosis, renal cortical necrosis, vision changes
Aminocaproic acid (C)	IV: 4-5 g over 1 hr → 1 g/hr x ~8 hrs (NTE 30 g/24 hrs)	Inhibits fibrinolysis	5 g vial is ~ $7	Hypotension, bradycardia, thrombosis, abdominal pain, myalgia, glomerular capillary thrombosis, thrombocytopenia
Desmopressin (B)	IV: 0.3 mcg/kg over 15 minutes	Increases von Willebrand factor, factor VIII, & t-PA contributing to ↓ APTT	Dose for 70 kg pt = $500	Low birth weight Flushing, headache, hyponatremia, rhinitis, hypo/hypertension
Phytonadione (Vitamin K) (C)	IV/PO: 1-10 mg	Promotes liver synthesis of factors II, VII, IX, X	10 mg IV ~$40 10 mg PO~$130	Hypo/hypertension, pruritus, abnormal taste, dyspnea

Medications Used in the ICU

Analgesia

Medication	Dose Range	MOA	Onset	Duration	Adverse Effects
Fentanyl (C)	IV: 12.5 - 50 mcg IV infusion: 12.5 mcg/hr - 150 mcg/hr	Opioid receptor agonists	Immediate	30-60 min	Neonatal withdrawal syndrome, transient muscular rigidity Sedation, dizziness, constipation, hyponatremia, fever, cardiac arrhythmias, hyper/hypotension, thrombocytopenia
Morphine (C)	IV: 1 - 4 mg IV infusion: 1 mg - 15 mg/hr		5-10 min	3-5 hrs	Neonatal withdrawal syndrome, decreased ventilatory response to CO2, at risk for SIDS Histamine release (hypotension, flushing), constipation, hyponatremia, fever, thrombocytopenia
Hydromorphone (C)	IV: 0.5 - 1 mg 0.2 - 2 mg/hr		5 min; peak 10-20 min	3-4 hrs	Neonatal withdrawal syndrome Histamine release (hypotension, flushing), bradycardia, constipation, muscle regidity
Ketamine	IV: 0.1 - 0.5 mg/kg IV infusion: 0.1 - 0.5 mg/kg/hr	NMDA receptor antagonist	30 seconds	5-10 min	Neonatal depression, reduced APGAR scores reported Uterine contractions, hyper/hypotension, brady/tachycardia, hypertonia, DI

- Opioid IV conversion
  - 100 mcg fentanyl = 10 mg morphine = 1.5 mg hydromorphone

Sedation

Medication	Dose Range	MOA	Onset	Duration	Adverse Effects
Propofol (B)	IV: 5 to ~75 mcg/kg/min	Agonism of $GABA_A$ and NMDA receptor blockade	< 1 min	3-10 min	Neonatal depression Maternal hypotension, apnea, hypertryglyceridemia
Midazolam (D)	IV: 1 to 20 mg/hr	Benzodiazepine receptor agonist	1-5 min	< 2 hrs	Neonatal hypoglycemia, withdrawal, respiratory depression, sedation Maternal Hypotension, apnea
Ketamine	IV: 1 to 2 mg/kg IV push or continuous infusion 0.5 to 2 mg/kg/hr	NMDA receptor antagonist	30 seconds	5-10 min	Neonatal depression Uterine contractions Plasma clearance is reduced during pregnancy Bradycardia, hypertonia, hypo/hypertension, hallucinations, laryngospasm, hypersalivation
Dexmedetomidine (C)	0.2 to 1.5 mcg/kg/hr Titrated q 30 min	Selective α2-adrenoceptor agonist w/anesthetic/ sedative properties			Uterine contractions Hypotension & brady/tachy arrythmias

Paralytics

Medication	Dose Range	MOA	Onset	Recovery	Adverse Effects
Cisatracurium (B)	IV: 0.1 mg/kg IV infusion: 2.5-3 mcg/kg/min	bind to acetylcholine receptors but act as competitive antagonists	2-5 min	90 min	Maternal bradycardia, flushing, hypotension
Rocuronium (C)	IV: 1 mg/kg IV infusion: 8-12 mcg/kg/min		1-4 min	30 min	Maternal tachycardia, hyper/hypotension
Vecuronium (C)	IV: 0.1 mg/kg IV infusion: 0.8-1.7 mcg/kg/min		2.5-5 min	45-60 min	Maternal bradycardia, flushing, rash
Succinylcholine (C)	IV: 1-1.5 mg/kg	bind & activate nicotinic acetylcholine receptors → depolarization of postsynaptic membrane of striated muscle	< 1 min	4-6 min	Tachy,bradycardia, rash, hyper/hypotension, hyperkalemia, salivation, jaw rigidity, rhabomyolysis, malignant hyperthermia

- Some medications may potentiate effects of non-depolarizing neuromuscular blocking agents
  - Corticosteroids, aminoglycosides, clindamycin, polymyxins, colistin, tetracyclines

Pressor Medications

Medication	Dose Range	MOA	Onset	Duration	Adverse Effects
Norepinephrine (C)	0.5 to 30 mcg/min	Stimulates β1-& α-adrenergic receptors	Rapid	1-2 min	Vesicant Maternal bradycardia, dyspnea
Phenylephrine (C)	25 to 200 mcg/min	Direct-acting α-adrenergic agonist	Rapid	15-20 min	Fetal malformations in 1st trimester Vesicant Maternal reflex bradycardia, dyspnea
Epinephrine (C)	1 to 10 mcg/min	Stimulates alpha-, beta1-, and beta2-adrenergic receptors	Rapid	< 1 min	Uterine vasoconstriction, decreased uterine blood flow, and fetal anoxia Vesicant Maternal arrhythmias, hyperglycemia, hypokalemia, dyspnea
Vasopressin (C)	0.03 to 0.04 unit/min	Direct vasoconstrictor	within 15 min	20 min	Tonic uterine contractions Vesicant Maternal arrhythmias, hyponatremia, abdominal cramps, thrombocytopenia, tremor

- For extravasation may use phentolamine, terbutaline, or nitroglycerin 2% topical ointment

Medications and Breast Feeding

Medication Transfer into Milk[5]

- Passive diffusion from high to lower drug concentration areas
  - Maternal blood/tissue $\rightleftharpoons$ breast milk
- Drug properties
  - Size (lower molecular weight)
  - Solubility (lipophilic > hydrophobic)
  - pH (ionization)
  - Protein binding (low > higher)

Evaluation of Infant Risk[5]

- Relative Infant Dose (RID) Calculation
  - RID (%) = $\frac{\text{dose in infant (mg/kg/day)}}{\text{dose in mother (mg/kg/day)}} \times [100\%]$
    - Infant dose = Average concentration milk (mg/L) x milk intake (L/Kg/d)
    - Find RID in various published papers
  - RID of ≥10% represents a medication dosage of concern or caution
- Also consider
  - T_{max} and $t_{1/2}$ of medication
  - Oral bioavailability of medication
  - Postnatal age

Other Resources

- LactMed (NLM TOXNET, 2015)
  - http://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm
    - Free access
- The Infant Risk Center from the Texas Tech University Health Sciences Center
  - http://www.infantrisk.com
  - Various articles, subscription available for more info
- Medications and Mothers Milk
  - Available as online subscription
- Briggs Drugs in Pregnancy and Lactation
  - Accessed through Lexicomp

Medications to Avoid

In Pregnancy…

- Medications affecting angiotensin system
  - e.g. lisinopril, losartan
- Non-steroidal anti-inflammatory medications
  - Premature closure of ductus arteriosus and oligohydramnios
- Statin medications
  - e.g. simvastatin, pravastatin
- Mineral Oil, dong quai, cohosh, turmeric, sage
  - Uterine contractions
- Methotrexate
  - Folate antimetabolite
- Dronedarone

In Breast Feeding…

- Antineoplastic agents
- Amiodarone
- Chloramphenicol
- Ergotamine
- Lithium
- Tetracyclines
- Pseudoephedrine

Question 1

- Which of the following is TRUE
  a) All medications approved after 6/30/2015 need to comply with the new PLLR format
  b) All medications must remove the Pregnancy Category (A, B, C, D, X) by 6/29/2018
  c) All medications approved prior to 6/29/2015 are required to comply with the new PLLR format
  d) A and B
  e) All of the above

Question 2

- Which of the following medications should be avoided in Pregnancy
  a) ACE inhibitors/ARBs
  b) Dronedarone
  c) NSAIDs (non-steroidal anti-inflammatory)
  d) Statin medications (i.e. simvastatin, rosuvastatin)
  e) a, c, and d
  f) All of the above

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