

But she's pregnant (or breastfeeding)!
I can't prescribe that!

Considerations for medications during the childbearing cycle

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Safe and effective

Don't take the risk if you won't gain the
benefits

Why this topic? Historical perspective

- ▶ It was once assumed that the placenta was a barrier that protected the embryo/fetus. It was also obvious that at least some substances (notably alcohol and narcotics) passed through breast milk and affected the nursing.
- ▶ The thalidomide tragedy disabused medical professionals and the public of the concept of a 'placental barrier' and the pendulum swung to completely avoiding medications in pregnancy.
- ▶ However, this tragedy also led to an explosion of understanding of how best to evaluate medications for toxicity not just in embryos and fetuses.

Timing matters, dosing matters

- ▶ Paracelsus: All substances are poisons, there is none which is not a poison. The right dose differentiates a poison from a remedy.”
- ▶ I would add that, in pregnancy and lactation, not just the dosing but the timing and the age of the embryo, fetus, or nursing that matters.
- ▶ For example, thalidomide was teratogenic for only a 4 week period of development, and its effects were specific to the gestational age at exposure.
- ▶ [Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease | Toxicological Sciences | Oxford Academic \(oup.com\)](#)

Pregnancy concerns

- ▶ Teratology (the study of malformations) www.birthdefectsresearch.org
- ▶ Does this medication cause a structural or biochemical change in the embryo or fetus aka a birth defect? This is not as easy a question to answer, as there are other environmental influences that can lead to birth defects. One example is hyperglycemia (in the untreated or undertreated diabetic pregnancy). Another might be a gene mutation (such as SALL4, which leads to birth defects nearly identical to thalidomide). Nutritional deficiencies especially folate is another example. Sorting out medication effects from baseline levels of birth defects is a challenging statistical problem.

Lactation issues

- ▶ There has been no seminal event similar to thalidomide in the consideration of medication transmission to a nursing via breastmilk. However, it was observed even 400 years ago that babies who were consuming breast milk while their wetnurse or mother was drinking alcohol would show signs of intoxication - although the milk producer would have to consume prodigious quantities to show an effect on the infant!
- ▶ Therefore there are concerns about transmission of biologically active agents across breastmilk. Some of these are reasonable, others probably not

Basic considerations for any Rx in pregnancy and lactation

- ▶ Necessity
- ▶ Risks, benefits, alternatives
- ▶ Dosing and timing of doses
- ▶ Metabolic pathways
- ▶ In pregnancy, molecular size, pharmacology, placental transport
 - ▶ Gestational age
- ▶ In lactation, how much is actually transported into the milk and for how long after dosing?
 - ▶ Age of the nursling

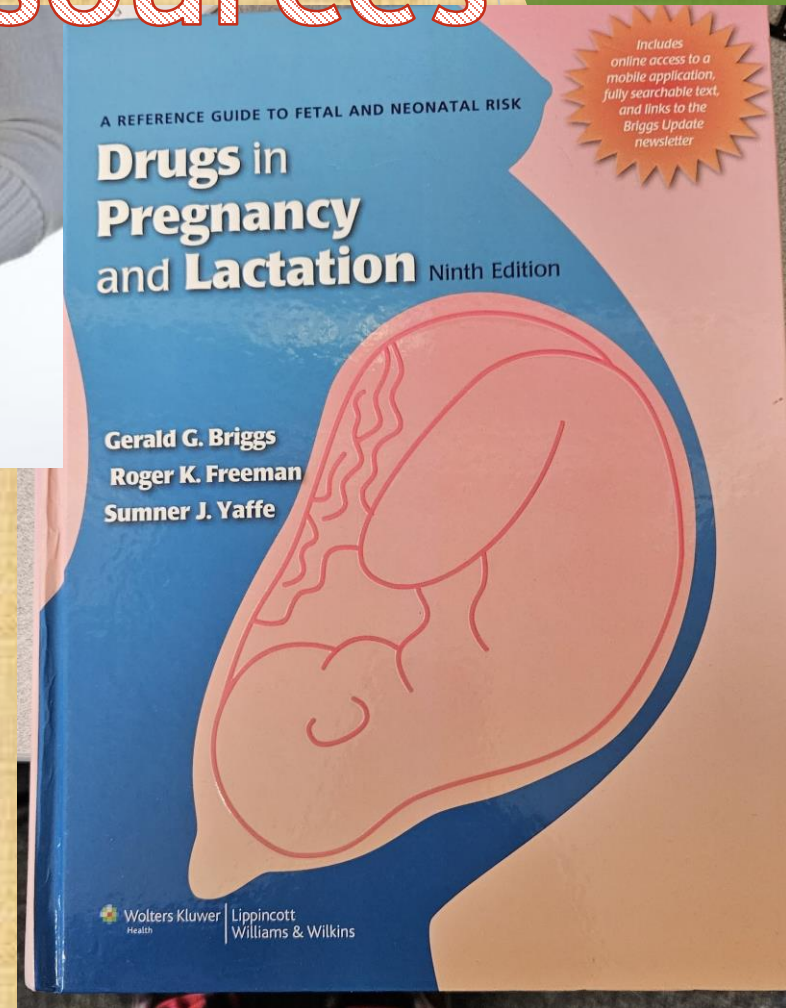
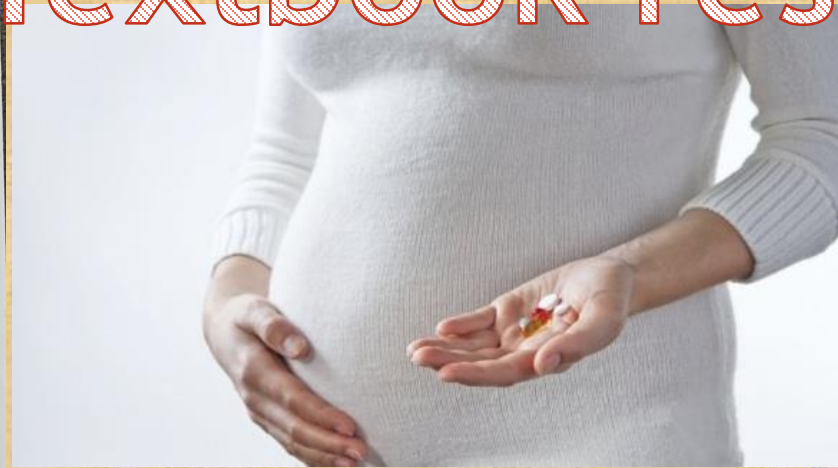
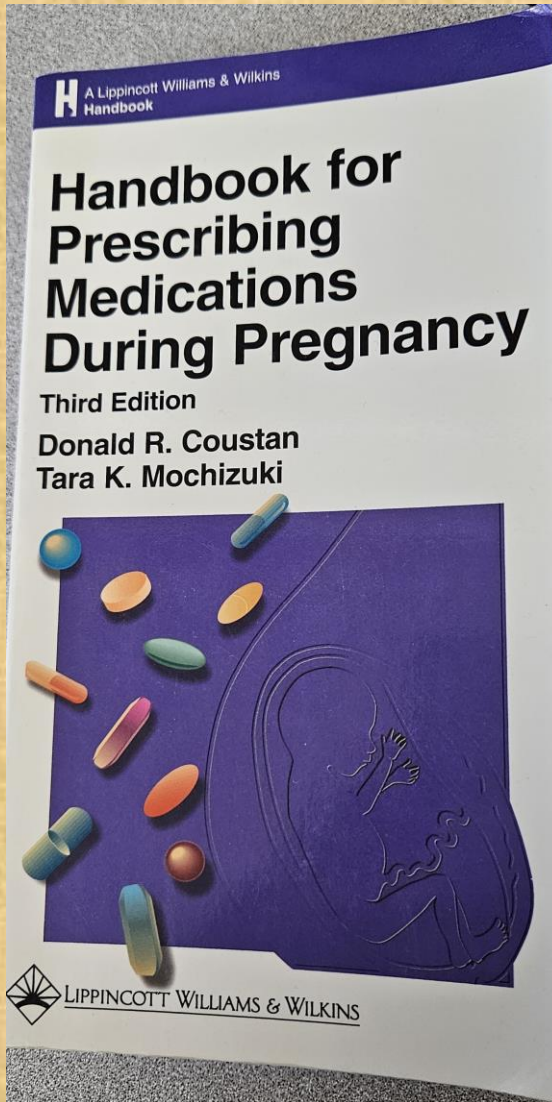
Pregnancy (before and early)

- ▶ Pre pregnancy medications - ideally any person on chronic medications should have a preconception consultation and medication review
- ▶ Stopping some medications can be riskier than continuing them. Where possible, the safest effective medication should be prescribed. For example, ACE inhibitors and ARB medications should be transitioned to another category, as this category of drug has known adverse fetal effects including fetal demise.
- ▶ Thyroid replacement and insulin should be continued during pregnancy and titrated to effective doses. Hyperglycemia is a known teratogen, and abnormal thyroid function has known risks to pregnancy.

Pregnancy

- ▶ It is difficult if not impossible to have a healthy fetus if the pregnant person is not healthy! This includes mental health as well. Questions when considering the pharmacological treatment of an illness or dysfunction in pregnancy include:
 - ▶ 1 “How would I treat this if this patient were not pregnant?”
 - ▶ 2 “Which of the proposed therapies is both effective and safe for the patient and the embryo/fetus at this stage of pregnancy and ongoing?”
 - ▶ 3 “What might happen if this is not treated? Is there an effective non drug treatment?”

Textbook resources



FDA considerations

- ▶ Until 2015, the FDA used an alphabetical labeling for medication safety in pregnancy (ABCD and X)
- ▶ This has been replaced by the Pregnancy and Lactation Labelling Rule (PLLR). Instead of using an arbitrary lettering system, the PLLR provides detailed risk summaries and more comprehensive information derived from clinical experience (if available), animal data, and concerns related to the pharmacologic activity of the drug. In addition, the label includes information on the risks associated with untreated illness. This information helps to put the potential effects of the drug into perspective with the goal of providing a more individualized risk-benefit analysis.
- ▶ It also encourages participation in pregnancy registries. See the FDA Pregnancy Registry Website for a list of applicable registries.
- ▶ The Epocrates app is free and includes all the FDA required labelling and is up to date.
- ▶ See also [DailyMed \(nih.gov\)](https://www.nlm.nih.gov/dailymed)

Some specific categories of medication

- ▶ Sex hormone therapies: in general are not encouraged during pregnancy however may be indicated for specific indications (Progesterone in particular)
- ▶ Antiepileptic drugs: seizures in pregnancy can decrease fetal oxygenation. Some seizure medications increase the risk of neural tube defects due to interference with folate metabolism. High dose folate supplements may decrease this risk.
- ▶ Asthma medications: benefits generally outweigh risks. Breathing is not optional
- ▶ Psychiatric medications: benefits generally outweigh risks but should be carefully evaluated by trimester. Some SSRIs have been associated with an increased risk of fetal cardiac anomalies. Many SSRIs may have neonatal withdrawal symptoms.

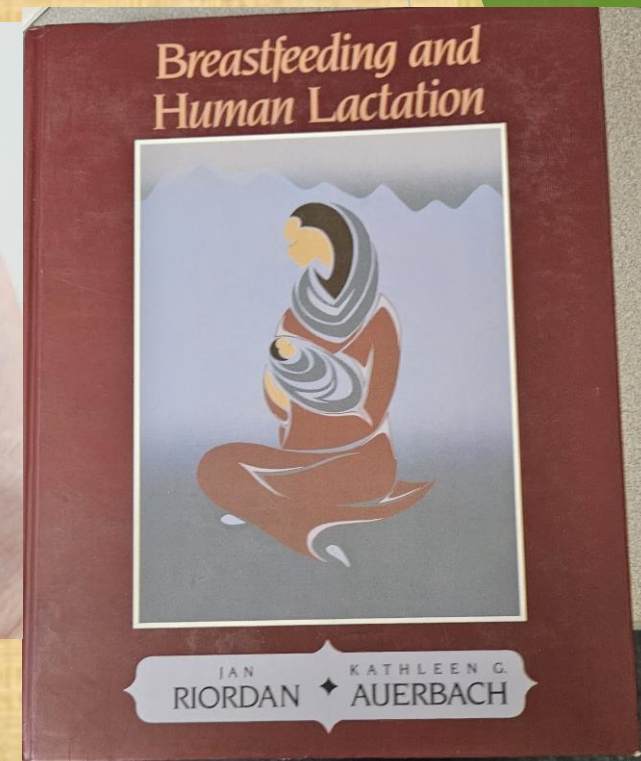
Nausea medications

- ▶ Very few have been rigorously studied in pregnancy. The one which is specifically indicated in pregnancy is a combination of doxylamine and pyridoxine, it seems to be both safe and effective for mild nausea, but does not seem to be very effective for hyperemesis gravidarum. The original formulation (Bendectin) was taken off the market for medicolegal reasons and only recently was an Rx formulation (DiClegis, returned to the market.
- ▶ Ondansetron (Zofran) remains widely used despite 1 (out of 4) studies that purported to show an increase in fetal cardiac anomalies.
- ▶ Phenergan and other sedating antihistamines seen to also be safe and somewhat effective.
- ▶ Reglan is occasionally used but often discontinued due to side effects.
- ▶ Dexamethasone and similar steroids are sometimes used for hyperemesis with varying degrees of success.

Case study

- ▶ Patient is 25 y/o G1P0 at 10 weeks who presents to initiate prenatal care. She is currently taking prenatal vitamins, an albuterol inhaler as needed, 50 mg daily of sertraline that she has been on for 3 years, and 25 mcg daily of levothyroxine that was prescribed by her PCP for subclinical hypothyroidism. She also states that she discontinued her Adderall when she stopped her pregnancy prevention. She has mild nausea but is coping with dietary interventions/
- ▶ How will you counsel her on her medications? What of any additional lab work will you recommend?

Textbook Resources for lactation issues



Considerations for prescribing in lactation

- ▶ How important is this medication to the lactating person's health?
 - ▶ Is it important enough to prescribe even if it means temporary or permanent interruption of the breastfeeding relationship? What are the alternatives?
- ▶ Is this a medication that is commonly prescribed to an infant or toddler of the nursing's age?
 - ▶ There's a big difference between a newborn who is 100% dependent on milk or formula and a toddler who is eating a broad variety of other foods.
- ▶ Is the concentration in human milk after dosing pharmacologically significant?
 - ▶ Transfer is influenced by protein binding, lipid solubility, and ionization. Bioavailability is influenced by the medication's half life etc.
- ▶ Does it directly or indirectly influence milk production or milk ejection?
 - ▶ Estrogen, for example, suppressed milk production. Metronidazole can give milk a metallic taste that might cause milk rejection by the nursing.

Resources on line

- ▶ LactMed is a comprehensive and current database
 - ▶ <http://toxnet.nlm.nih.gov>
- ▶ American Academy of Pediatrics
 - ▶ [The Transfer of Drugs and Therapeutics Into Human Breast Milk: An Update On Selected Topics | Breastfeeding Handbook for Physicians | AAP Books | American Academy of Pediatrics](#)
- ▶ The World Health Organization offers several programs and resources that address the importance of breastfeeding
 - ▶ <http://www.who.int/topics/breastfeeding/en/>
- ▶ American Academy of Breastfeeding Medicine
 - ▶ www.bfmed.org, look at protocols, most recent on is on substance use and breastfeeding

As the nursling matures, considerations change

- ▶ In the immediate postpartum period, prenatal exposures influence colostrum
- ▶ Medications for childbirth and the puerperium may include antibiotics, anesthetics, pain medications, and GI medications. Most do not seem to have a significant effect, however recent studies show that there are persons with a genetic susceptibility to codeine and tramadol that can lead to an infant overdose.
- ▶ Infants in the first few weeks may be exposed to herbs and medications taken in an effort to increase milk supply. None of these have been proven effective and their safety is relative - still the effort to support lactation warrants a conversation with the patient about risks, benefits, and alternatives
- ▶ Hormonal contraceptives are another intervention that warrants a careful conversation.
- ▶ Postpartum depression needs to be treated quickly and effectively. SSRIs are the keystone right now, but there are other effective non drug therapies.

In summary

Medications are often indicated during the childbearing cycle.

Remember the 5 rights.

- Right patient

- Right drug

- Right time

- Right dose

- Right route

Also take into consideration that an ineffective medication is WORSE than no medication - taking risks without benefits - and this is especially important when there are 2 (or more!) patients in one body.

Risks, benefits, alternatives, and side effects are an important part of medication counseling especially during this critical time of life.

Questions?



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