

Teratogenicity & Drug-Related Pregnancy Risks



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Project Echo

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Objectives

- Review pregnancy FDA risk classification system
- Provide general principles for use of medications in treatment of maternal medical conditions

When to treat?

We may do more harm to pregnant women and their fetuses by withholding treatment for medical conditions

Risk – Benefit Ratio

Example Case

- 39 year-old G3P1102 with bipolar disorder
 - ED visit for dysuria at 11 weeks
 - Advised to stop current medications, including quetiapine, an atypical antipsychotic (Seroquel)
 - FDA class C: Risk cannot be ruled out
 - **Should only be given if potential benefits justify the potential risk**
 - (Many anti-emetics are in this class)

Example Case

- 39 year-old G3P1102 with bipolar disorder
 - Severe manic episode
 - Never returned for prenatal care
 - Poor nutrition, return to 'self-medicating' with smoking and narcotic abuse
 - Hospitalized for suicide attempt

FDA Risk Categories

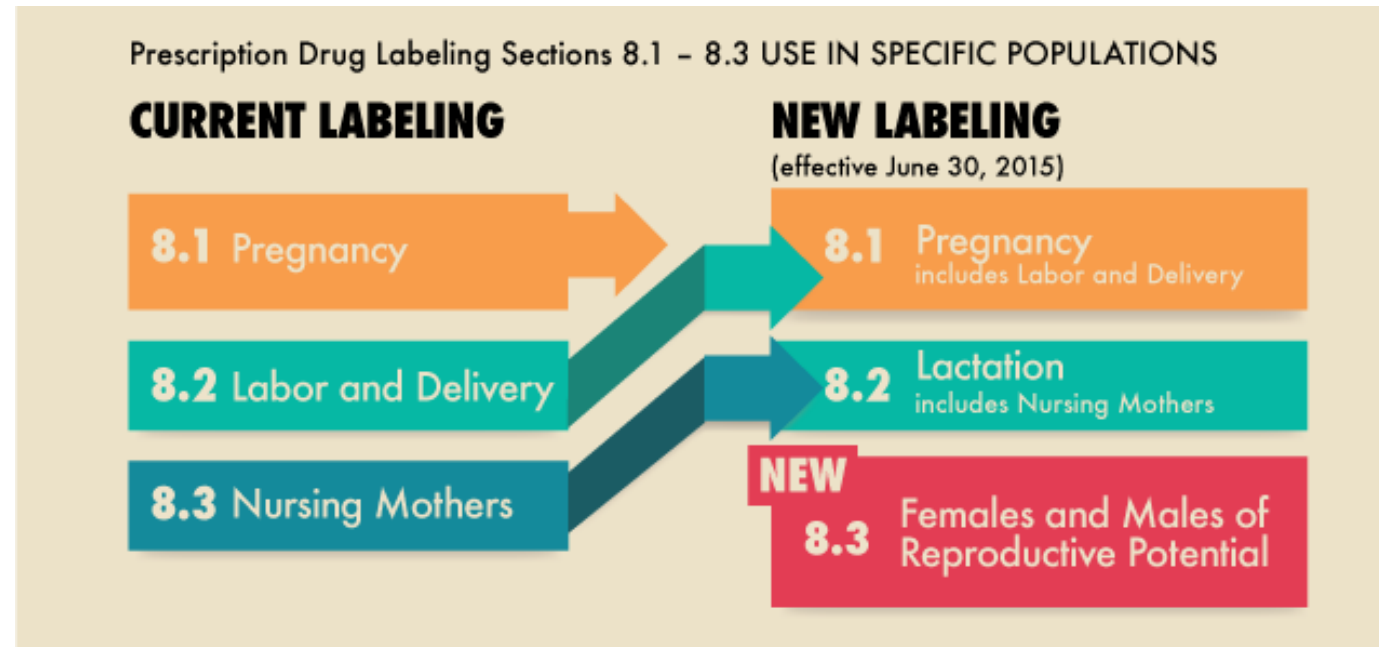
Out with the old...

Category	Interpretation
A	Controlled human studies show no risk
	Controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first trimester with no evidence of risk in later trimesters. The possibility of fetal harm appears remote.
B	No evidence of risk in studies
	Either animal reproduction studies have not demonstrated a fetal risk but there are no controlled studies in pregnant women or animal reproduction studies have shown an adverse effect (other than a decrease in fertility) that was not confirmed in controlled studies in women in the first trimester and there is no evidence of a risk in later trimesters.
C	Risk cannot be ruled out
	Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal effects or other) and there are no controlled studies in women or studies in women and animals are not available. Drugs should be given only if the potential benefits justify the potential risk to the fetus.
D	Positive evidence of risk
	There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).
X	Contraindicated in pregnancy
	Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both, and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

FDA Risk Categories

In with the new!

- Pregnancy and Lactation Labeling Rule (PLLR)
- Pregnancy risk summary replaces the previous letter designation



FDA Risk Categories

Pregnancy includes Labor and Delivery

- Contains information for a pregnancy registry if one exists
- Summary of risks of using a medication
- Describes disease-associated maternal and/or fetal risks, dose adjustments during pregnancy and postpartum, adverse reactions, fetal/neonatal adverse reactions, implications for labor/delivery
- Describe the data on which risk estimates are based

FDA Risk Categories

Lactation

includes Nursing Mothers

- Contains the data supporting excretion into breast milk
- Data on effects on the breastfed infant
- Data on effect on breast milk production
- Risk-benefit statement if systemic absorption is present
- Methods by which to minimize exposure to the infant

FDA Risk Categories

Females and Males of Reproductive Potential

- Information regarding pregnancy testing, contraception requirements before, during or after treatment
- Data regarding treatment impact on fertility

FDA Risk Categories - Label

Descovy – Used in treatment of HIV-1

Risk Summary

There are **insufficient human data on the use of Descovy during pregnancy to inform a drug-associated risk of birth defects and miscarriage**. Tenofovir alafenamide (TAF) use in women during pregnancy has not been evaluated; however, **emtricitabine (FTC) use during pregnancy has been evaluated in a limited number of women** reported to the APR. Available data from the APR show no difference in the risk of overall major birth defects for FTC (2.4%) compared with the background rate for major birth defects of 2.7% in a U.S. reference population of the Metropolitan Atlanta Congenital Defects Program (MACDP). The rate of miscarriage is not reported in the APR. The estimated background rate of miscarriage in the clinically recognized pregnancies in the U.S. general population is 15–20%. In animal studies, no adverse developmental effects were observed when the components of Descovy were administered separately during the period of organogenesis at exposures 60 and 108 times (**mice and rabbits, respectively**) the FTC exposure and at exposure equal to or 53 times (rats and rabbits, respectively) the TAF exposure at the recommended daily dose of Descovy [see [Data \(8.1\)](#)]. Likewise, no adverse developmental effects were seen when FTC was administered to **mice through lactation at exposures up to approximately 60 times the exposure at the recommended daily dose of Descovy**. No adverse effects were observed in the offspring when TDF was administered through lactation at tenofovir exposures of approximately 14 times the exposure at the recommended daily dosage of Descovy.

Medication Risk Assessment

- The old FDA classifications essentially all require a risk-benefit assessment
 - Exception: Category X
- New categories provide more information with which to counsel patients

Teratogens

Evidence of human risk; risks clearly outweigh benefits in a viable pregnancy

- Retinoic acid → miscarriage, malformations
- Androgens → virilization of female fetus
- Folic acid antagonists → malformations, placental abnormalities
- ACE-I and ARB → malformations, renal injury, sequelae of oligohydramnios

Rules for Medication Use

- Don't give medications unless indicated
- Weigh benefits of maternal treatment with risk of fetal exposure
- Choose medications with the best available safety data (not the latest and greatest)
- Use the fewest effective medications at the lowest effective dose
- Be thoughtful about medication use during the “window of teratogenesis” – first 10 weeks of pregnancy
- Do not give known teratogens in the first trimester in the setting of a viable pregnancy

Other Resources

Mother To Baby
1-801-FAT-BABY



→ Fact sheets

- <https://mothertobaby.org/fact-sheets-parent/>
- What is the medication?
- Can it cause birth defects?
- Can it cause other pregnancy complications?
- Can it be taken during breastfeeding?
- Risks if the father of the baby is taking the medication?

References

- Mother To Baby - <https://mothertobaby.org/fact-sheets-parent/>
- Use of psychiatric medications during pregnancy and lactation. ACOG Practice Bulletin No. 92. American College of Obstetricians and Gynecologists. Obstet Gynecol 2008;111:1001–20.
- FDA/CDER SBIA Chronicles. Drugs in Pregnancy and Lactation: Improved Benefit-Risk Information. January 22, 2015. Accessed May 15, 2018 at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM431132.pdf>
- Nausea and vomiting of pregnancy. ACOG Practice Bulletin No. 189. American College of Obstetricians and Gynecologists. Obstet Gynecol 2018;131:e15–30.
- ACOG Practice Advisory: FDA Boxed Warning on Immediate-Release Opioid Medications and All Prescription Opioids
- Opioid use and opioid use disorder in pregnancy. Committee Opinion No. 711. American College of Obstetricians and Gynecologists. Obstet Gynecol 2017;130:e81–94.

Thank You!

Antiemetics

- 50-80% of pregnant women experience nausea
 - 50% experience vomiting
- Treat according to symptom severity
- Escalating treatment if symptoms not improved

Antiemetics

- Ondansetron (Zofran)
 - Majority of studies have not shown a risk for birth defects
 - One study reported small increased risk for cleft palate
 - Two studies reported a small increased risk for heart defects (5-10 weeks)
- Given conflicting results recommendations have moved away from this as a first line agent during the first trimester

Antiemetics

- Promethazine (Phenergan)
 - No known association with birth defects
 - Potential for newborn sedation and respiratory depression when use late in pregnancy
- Metoclopramide (Reglan)
 - No known association with birth defects
 - Rare risks of maternal tardive dyskinesia and intermittent porphyria

Antiemetics

- Doxylamine / Pyridoxine (Diclegis)
 - No association with birth defects
 - Safe at higher doses than the formulary dose of Diclegis
- Best used as a preventive treatment

First Line Therapy: Nonpharmacologic options
 Convert prenatal vitamin to folic acid supplement only
 Ginger capsules 250 mg four times daily
 Consider P6 acupressure with wrist bands

Persistent symptoms

Pharmacologic Options*
 Vitamin B₆ (pyridoxine) 10–25 mg orally (either taken alone or in combination with Doxylamine[†] 12.5 mg orally), 3 or 4 times per day. Adjust schedule and dose according to severity of patient's symptoms.
 OR
 Vitamin B₆ (pyridoxine) 10 mg/Doxylamine 10 mg combination product, two tablets orally at bedtime initially, up to four tablets per day (one tablet in the morning, one tablet in midafternoon, and two tablets at bedtime)
 OR
 Vitamin B₆ (pyridoxine) 20 mg/Doxylamine 20 mg combination product, one tablet orally at bedtime initially, up to two tablets per day (one tablet in the morning and one tablet at bedtime)

Persistent symptoms

Add the following:
 (presented here in alphabetical order)
 Dimenhydrinate, 25–50 mg every 4–6 hours, orally as needed
 (not to exceed 200 mg per day if patient also is taking doxylamine)
 OR
 Diphenhydramine, 25–50 mg orally every 4–6 hours
 OR
 Prochlorperazine, 25 mg every 12 hours rectally
 OR
 Promethazine, 12.5–25 mg every 4–6 hours, orally or rectally

No dehydration

Persistent symptoms

Add any of the following:
 (presented here in alphabetical order)
 Metoclopramide, 5–10 mg every 6–8 hours, orally or intramuscularly
 OR
 Ondansetron, 4 mg orally every 8 hours
 OR
 Promethazine, 12.5–25 mg every 4–6 hours, orally, rectally, or intramuscularly
 OR
 Trimethoprim, 200 mg every 6–8 hours, intramuscularly

Dehydration

Intravenous fluid replacement[†]

Persistent symptoms

Add any of the following:
 (presented here in alphabetical order)
 Dimenhydrinate, 50 mg (in 50 mL saline, over 20 min) every 4–6 hours, intravenously
 OR
 Metoclopramide, 5–10 mg every 8 hours, intravenously
 OR
 Ondansetron, 8 mg, over 15 minutes, every 12 hours, intravenously
 OR
 Promethazine, 12.5–25 mg every 4–6 hours, intravenously

Persistent symptoms

Add the following:
 (presented here in alphabetical order)
 Chlorpromazine 25–50 mg intravenously or intramuscularly every 4–6 hours or 10–25 mg orally every 4 to 6 hours.
 OR
 Methylprednisolone 16 mg every 8 hours, orally or intravenously, for 3 days. Taper over 2 weeks to lowest effective dose. If beneficial, limit total duration of use to 6 weeks.

Pain Medications

- Tylenol
 - Widely used and considered safe
 - Controversial study regarding use >28 days and mild developmental delay and hyperactivity
 - Additional study evaluating children at 4 y/o did not find an association

Pain Medications

- NSAIDs
 - 1st trimester
 - Not shown to increase risk of miscarriage
 - Not enough evidence to prove association with birth defects
 - 3rd trimester
 - Not recommended due to risk of premature closure of the ductus arteriosus with subsequent risk of pulmonary hypertension
 - May also lead to oligohydramnios

Pain Medications

Opioids

- FDA black box warning: risks of misuse, abuse, addiction, overdose and death
- No known pattern of associated birth defects
- Prolonged use associated with poor fetal growth, stillbirth, preterm delivery and c-section
- Risk of withdrawal with abrupt discontinuation
 - Withdrawal associated with relapse and use of illicit substances
- Neonatal abstinence syndrome

Psychiatric Illness

- Important to achieve control of psychiatric illness during pregnancy
- Poor control associated with miscarriage, pre-eclampsia, preterm delivery, low birth weight, postpartum mood disorders

Psychiatric Illness

Table 1. Impact of Psychiatric Illness on Pregnancy Outcome				
		Impact on Outcome		
Illness	Teratogenic Effects	Obstetric	Neonatal	Treatment Options
Anxiety disorders	N/A	Increased incidence of forceps deliveries, prolonged labor, precipitate labor, fetal distress, preterm delivery, and spontaneous abortion	Decreased developmental scores and inadaptability; slowed mental development at 2 years of age	Benzodiazepines Antidepressants Psychotherapy
Major depression	N/A	Increased incidence of low birth weight, decreased fetal growth, and postnatal complications	Increased newborn cortisol and catecholamine levels, infant crying, rates of admission to neonatal intensive care units	Antidepressants Psychotherapy ECT
Bipolar disorder	N/A	See major depression	See major depression	Lithium Anticonvulsants Antipsychotics ECT
Schizophrenia	Congenital malformations, especially of cardiovascular system	Increased incidence of preterm delivery, low birth weight, small for gestational age, placental abnormalities, and antenatal hemorrhage	Increased rates of postnatal death	Antipsychotics
Abbreviations: ECT, electroconvulsive therapy; N/A, not available (eg, no studies identified)				

Antidepressants

- SSRIs
 - Sertraline (Zoloft)
 - ~10,000 pregnancies - no increased risk of birth defects
 - Paroxetine (Paxil)
 - Increased risk of heart defects (1% → 2%)
 - Fluoxetine (Prozac)
 - No report of birth defects
 - Citalopram (Celexa)
 - No report of birth defects

Antidepressants

- SNRIs
 - Venlafaxine (Effexor)
 - Study of ~700 infants, no reported birth defects
 - Small risk of neonatal withdrawal

Antidepressants

- SSRIs and SNRIs
 - Risk of neonatal withdrawal with all SSRIs
 - Unconfirmed reports of persistent pulmonary hypertension

Antidepressants

- Mirtazapine (Remeron)
 - ~1000 pregnancies studied without risk of birth defects
- Bupropion, duloxetine, venlafaxine
 - Limited data but no suggestion of increased risk of birth defects

Anxiolytics

- Benzodiazepines
 - No clear significant risk of birth defects
 - Early suggestion of increased risk of oral clefts →
 - Subsequent studies have not reproduced this risk
 - Meta-analysis - risk 6/10,000 → 7/10,000
 - Case-control study - 60, 000 women, no difference
 - Use near delivery associated with floppy infant syndrome and withdrawal

Biopolar/Schizophrenia Treatment

- Atypical antipsychotics are being used more frequently
- Olanzapine (Zyprexa)
 - ~1500 infants without reported risk of birth defects
 - Can increase the risk of gestational diabetes
- 151 pregnancies exposed to olanzapine, risperidone, quetiapine, clozapine – higher rate of low birth weight

Biopolar/Schizophrenia Treatment

- Valproic Acid (Valproate)
 - 1-3.8% risk of neural tube defects
 - Risk of craniofacial, limb and cardiovascular abnormalities
 - Fetal growth restriction
 - Developmental delay, autism spectrum disorders
 - Neonatal hepatotoxicity, coagulopathy, hypoglycemia and withdrawal

Biopolar/Schizophrenia Treatment

- Lithium
 - Some studies with an association with Ebstein's anomaly and other heart defects, not all studies have shown this conclusively
 - Meta-analysis risk ratio 1.2 – 7.7
 - Case reports of maternal hypothyroidism and goiter
 - Case reports of neonatal hypotonia, respiratory and feeding difficulty

Antibiotics

Penicillins

- Amoxicillin/Clavulanate (Augmentin)
 - Few studies in first trimester, conflicting results regarding the risk of cleft lip/palate
 - Given limited data likely a small risk with greater benefit than risk

Antibiotics

Fluoroquinolones

- Ciprofloxacin
 - Animal studies with development of arthropathy
 - Not reproduced in human studies
 - Generally not advised due to concern for adverse effect on joint development

Antibiotics

- Clindamycin
 - No reports of birth defects in first trimester data
 - Mostly studied in 2nd and 3rd trimesters
- Erythromycin
 - No confirmed associations with birth defects

Antibiotics

- Sulfamethoxazole/trimethoprim (Bactrim)
- 1st trimester use with small increased risk of birth defects
 - Sulfamethoxazole – Conflicting results, limited data
 - Trimethoprim
 - Studies showing birth defects including heart, neural tube, cleft lip or palate and urinary tract abnormalities – not reproduced in all studies
 - May decrease folic acid levels

Antibiotics

- Tetracycline
 - No association with birth defects
 - Risk of discoloration of teeth when taken after the 4th month of pregnancy
 - Concern for adverse effect on bone calcification
- Similar reports of adverse effects with doxycycline, minocycline

Antifungals

- Fluconazole
 - Miscarriage
 - Two studies (~500 women) without increased risk
 - One study showed increased risk when taken between 7-22 weeks, controversial
 - Birth defects
 - Pattern of birth defects of the head, face, bones and heart in 5 children when exposed to high doses (400 – 1200 mg per day)
 - Single low dose unlikely to cause birth defects