Background: Pain from illnesses such as cancer, pheochromocytoma, complex regional pain syndrome, or sickle cell disease can manifest during pregnancy or present as a pre-existing condition. This Fast Fact reviews safe prescribing considerations of opioids in pregnant women. Fast Facts #307 and #260 provide more information about opioid pharmacokinetics and about hepatic opioid metabolism in general.

General Analgesic Principles During Pregnancy:
• Consult with the patient’s obstetrician and a pharmacist knowledgeable in obstetrics prior to adding any analgesic; all opioids and non-opioid analgesics can pose known or unknown risks to the fetus.
• Generally, most analgesics pose less risk to the fetus in the first trimester.
• From the late 2nd trimester and onward, increased risk is associated with aspirin due to bleeding concerns; NSAIDs due to premature closure of ductus arteriosus; and opioids (see below) (1-2).

Opioids in Pregnancy and Fetal Risk: Broadly, opioids should be avoided throughout pregnancy especially during the third trimester, unless they are necessary to treat acute pain or addiction (2). Partly, this is because pregnant women are usually excluded from clinical trials, leaving opioid safety data poorly understood in pregnancy. More so, birth defects (such as congenital heart disease, spina bifida, and club foot), neonatal respiratory depression, and the neonatal abstinence syndrome (NAS) are established risks of fetal opioid exposure (3-5). The NAS is a constellation of withdrawal symptoms resulting from fetal opioid exposure such as loose stools, nasal stuffiness, irritability, increased muscle tone, tremors, excoriations of the skin from excessive movements, and hyperthermia (6).
• For short-term use, opioids are FDA category C, meaning patients and clinicians must weigh risk and benefit due to lack of data and potential harm (4).
• For chronic or high dose use, opioids are FDA category D, meaning there is evidence of fetal risk (4); however, it is not well-defined what classifies as chronic and high dose for pregnant patients.
• The fetal risk of congenital abnormalities may be more pronounced with codeine and hydrocodone, although larger studies have shown mixed results regarding this (7).
• Methadone, buprenorphine, and controlled release morphine may offer superior fetal safety for pregnant women struggling with opioid addiction (7,8). Many experts prefer buprenorphine for this indication as it may precipitate less NAS (9). Regardless, all infants exposed to opioids during pregnancy require careful observation and management for NAS.

Patient and Medication Related Factors (8,10): Several maternal and fetal factors alter the effect and dosing of commonly prescribed opioids.
• Emesis: this is an especially common symptom in the first trimester and may compel clinicians to prescribe non-oral routes. Increased cutaneous blood flow can increase absorption of transdermal opioids and thereby require dose reductions of buprenorphine and fentanyl transdermal patches.
• Slowed maternal gastrointestinal motility: prolonged time in the gut may increase absorption and slow the onset of action. Dose reductions for oral immediate release and sustained release opioids may be necessary in pregnant patients as well as counseling about the likely delayed onset of action.
• Upregulation of maternal hepatic enzymes: opioids like codeine and hydrocodone are prodrugs, that is they rely on hepatic enzymes for metabolism to be active medications. The increased hepatic metabolism associated with pregnancy can increase the amount of active codeine and hydrocodone in circulation. Hence, dose reductions of these medications may be needed.
• Decrease in maternal plasma albumin: as albumin decreases, the amount of free, active drug in the plasma increases. Higher drug levels ensue for medications with high protein binding. Opioid protein binding ranges from 8% (hydromorphone); 20% (morphine); 45% (oxycodone) to 85% (fentanyl).

Breastfeeding Considerations:
• Although all opioids are excreted in some proportion into breastmilk, most opioids are considered safe due to the low measured concentrations (1,11-12).
• Fentanyl may be the safest due to its low breastmilk concentrations and low oral bioavailability (1).
• Codeine, morphine, and oxycodone may be more dangerous due to an increased risk of infant respiratory depression and death in therapeutic concentrations (1,13).
For women taking opioid maintenance treatment (e.g. methadone or buprenorphine), there is some evidence that breastfeeding may reduce the incidence of NAS over bottle feeding (14).

Summary: Changes in physiology of the woman and fetus throughout pregnancy affect the maternal and fetal bioavailability of opioids and require ongoing dose adjustments when opioids are prescribed. Based on the limited evidence, clinicians should remember the following clinical pearls:

• Avoid codeine, oxycodone and hydrocodone due to a potential increased risk of birth defects.
• Morphine, fentanyl, or hydromorphone may be the opioids of choice for pain; methadone or buprenorphine for opioid addiction; and fentanyl for breastfeeding mothers (1,3,4).
• Opioid use longer than a few weeks may result in NAS and should be instituted with caution. If prescribed, patients should be counseled regarding the risks during pregnancy and prescribers should closely coordinate care with obstetricians, pharmacists, and neonatal specialists (4,10).

References:

Conflicts of Interest: None
Authors’ Affiliations: Cedar Sinai Medical Center, Los Angeles, CA (KM); Community Hospices, Washington, DC (RH); Georgetown University School of Medicine (HG)
Version History: Originally edited by Sean Marks MD; first electronically published in October 2017
**Fast Facts and Concepts** are edited by Sean Marks MD (Medical College of Wisconsin) and associate editor Drew A Rosielle MD (University of Minnesota Medical School), with the generous support of a volunteer peer-review editorial board, and are made available online by the [Palliative Care Network of Wisconsin](http://palliativenetworkofwisconsin.org); the authors of each individual *Fast Fact* are solely responsible for that *Fast Fact*’s content. The full set of *Fast Facts* are available at [Palliative Care Network of Wisconsin](http://palliativenetworkofwisconsin.org) with contact information, and how to reference *Fast Facts*.

**Copyright:** All *Fast Facts and Concepts* are published under a Creative Commons Attribution-NonCommercial 4.0 International Copyright ([http://creativecommons.org/licenses/by-nc/4.0/](http://creativecommons.org/licenses/by-nc/4.0/)). *Fast Facts* can only be copied and distributed for non-commercial, educational purposes. If you adapt or distribute a *Fast Fact*, let us know!

**Disclaimer:** *Fast Facts and Concepts* provide educational information for health care professionals. This information is not medical advice. *Fast Facts* are not continually updated, and new safety information may emerge after a *Fast Fact* is published. Health care providers should always exercise their own independent clinical judgment and consult other relevant and up-to-date experts and resources. Some *Fast Facts* cite the use of a product in a dosage, for an indication, or in a manner other than that recommended in the product labeling. Accordingly, the official prescribing information should be consulted before any such product is used.