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Analgesics in Pregnancy and Lactation

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The following chart includes information to help guide decisions regarding analgesic use in pregnancy and lactation. FDA pregnancy categories have several limitations and are not included. Topical analgesics are covered in our chart, *Topical Medications in Pregnancy and Lactation*.

NONOPIOIDS

Drug or Drug Class	Use in Pregnancy	Use in Lactation
Acetaminophen	• Generally considered the analgesic/antipyretic of choice in pregnant women, but use the lowest dose for the shortest duration necessary.[36] • For chronic use (e.g., >1 month), some (not all) limited observational studies in humans suggest an association with neurodevelopmental concerns (e.g., ADHD, autism).[1,4,11,12,22,28,29,34,35] • Some cohort evidence suggests an association with early puberty in girls, and cryptorchidism.[1,37]	• First-line analgesic for lactating patients.[17] • Amount in milk less than therapeutic doses given to infants.[2] • Case report of rash.[1]
NSAIDs and Aspirin	• Analgesic doses used around 20 weeks or later may cause perinatal renal impairment and/or oligohydramnios and its complications.[9,23] Consider ultrasound monitoring of amniotic fluid if used for >48 hours.[9] Increased risk of maternal and newborn hemorrhage.[1] • Third trimester use poses risk of premature closure of ductus arteriosus (30 weeks or later[9]) and inhibition of labor.[1] • Use of non-aspirin NSAIDs before week 20 possibly linked to miscarriage; data inconclusive.[6,7] • Modest association between use before 20 weeks and major birth defects, including heart defects, hypospadias, cleft palate +/- cleft lip, anencephaly, spina bifida, and gastroschisis.[6,8,31] If used, consider limiting use to <10 days.[31] • Low aspirin doses (e.g., 81 mg once daily) may have favorable risk/benefit for certain complicated pregnancies.[1,5,23] • There is no proof that topical NSAIDs are safter than systemic agents in pregnancy.	**Aspirin** • Hemolysis (in a glucose-6-phosphate dehydrogenase-deficient infant), metabolic acidosis, and thrombocytopenia reported.[2] • Theoretical risk of Reye's syndrome.[2] • Low-dose aspirin 81 mg once daily can be considered.[2] **NSAIDs** • Ibuprofen is the NSAID of choice: short half-life; amount in milk less than therapeutic doses given to infants.[2,17]

OPIOIDS IN PREGNANCY

- Opioids may pose teratogenic risks in the first trimester,[2] but absolute risk is generally considered low.[3,8,38] **See footnotes** b, d, and e for more information on birth defects from some large cohorts. Note there is no human data with tapentadol or oxymorphone.[1]
- Use the lowest dose that is effective for the shortest duration necessary.[3]
- Buprenorphine or methadone can be used during pregnancy for opioid use disorder.[24-26,32] Methadone has a higher risk of preterm birth than buprenorphine.[32]
- Opioid use during labor can cause fetal distress or neonatal respiratory depression.[1] Meperidine is not recommended during labor.[1] Newborns clear meperidine slowly and may experience respiratory depression or neurologic side effcts.[1]
- Although not a "typical" opioid, **tramadol** use near term is linked to respiratory depression and withdrawal in newborns.[1]
- Long-term opioid use during pregnancy may result in neonatal opioid withdrawal (abstinence) syndrome.[18] Symptoms of neonatal withdrawal include vomiting, diarrhea, poor feeding, irritability, tremor, and high-pitched crying.[18] Neonatal opioid withdrawal can be life-threatening and requires management according to protocols developed by neonatology experts.[19]

Drug	Use in LACTATION (also see footnote a)
Buprenorphine	• Poor oral absorption.[1] • Use considered "acceptable" based on use for opioid dependence.[2] • Extradural use for postpartum pain may suppress feeding.[2]
Butorphanol	• Poor oral absorption.[2] • Probably compatible with breastfeeding,[1] but no info with repeated, high, intravenous, or intranasal doses.[2] • Consider alternatives due to paucity of information, especially if nursing preterm infant or newborn.[2]
Codeine	• Not recommended (Canada: contraindicated).[15,21] Risk of fatal morphine (codeine metabolite) toxicity if the lactating person is an ultrarapid CYP2D6 metabolizer (**see footnote c**).[1]
Fentanyl	• Considered compatible with breastfeeding,[1] but try to limit use to only a few days at a low dose.[2] • Preterm infants have impaired fentanyl clearance.[2] • If used epidurally, may affect infant for first 24 hours and impair initial breastfeeding efforts if good support is not available.[2]
Hydrocodone	• Excessive sleepiness and cyanosis reported in two case reports.[2] • Active metabolite (hydromorphone) formed through CYP2D6 is more potent than oxycodone.[2] • Theoretical risk of hydromorphone (hydrocodone metabolite) toxicity if the lactating person is an ultrarapid CYP2D6 metabolizer (**see footnote c**).[2] • Limit daily dose 30 mg for 2 to 3 days.[2]
Hydromorphone	• Excreted in breast milk.[1] • Case report of excessive sleepiness, intermittent bradycardia, and apnea in infant.[2]
Meperidine	• Newborns have trouble clearing meperidine.[1] • Fentanyl preferred for intravenous or intramuscular use during lactation, especially if nursing a newborn or preterm infant.[2] • Higher risk vs morphine.[2] • Single dose for maternal anesthesia usually not problematic in older infants.[2] • Postpartum epidural PCA usually not sedating to breastfed infants.[2]
Methadone	• Probably compatible.[1] • Breast milk concentrations are too low to be relied upon to prevent neonatal abstinence syndrome.[1] • Other agents are preferred for pain control during breastfeeding.[2] • Initiation of methadone postpartum, or increasing the dose to >100 mg/day, poses a particular risk of infant sedation and respiratory depression, especially if the infant is opioid-naive.[2]
Morphine	• Newborns and young infants do not clear morphine as rapidly as adults.[2] Infant can have detectable morphine levels, which may be within the therapeutic range.[2] • Epidural administration leads to lower levels in milk than oral or intravenous administration.[2] • Limit use to 2 to 3 days at a low dose.[2]
Nalbuphine	• Poor oral absorption.[1] • Amount in milk less than therapeutic doses given to infants. Unlikely to affect infant.[2]
Oxycodone	• Accumulates in breast milk.[1] • May not be safer than codeine; one in five infants of moms taking oxycodone experience CNS depression, similar to codeine.[13] • Oxycodone elimination is impaired in young infants and varies interindividually.[2] • Theoretical risk of oxymorphone (oxycodone metabolite) toxicity if lactating person is a CYP2D6 ultrarapid metabolizer (see footnote c).[14] But oxycodone is metabolized mainly by CYP3A4 to a weak metabolite (noroxycodone).[13] • Limit daily dose to 30 mg for 2 to 3 days.[2]
Oxymorphone	• No data in humans.[1,2] • Probably excreted in breast milk.[2]
Tapentadol	• Potential to accumulate in breast milk based on physicochemical properties.[1]
Tramadol	• Not recommended (Canada: contraindicated) because tramadol and its active metabolite are excreted in breast milk.[20,30] • Tramadol has the same risks associated with ultrarapid CYP2D6 metabolism as codeine (**see codeine and footnote c**).[20,30]

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Footnotes

a. Reserve opioids for postpartum pain that can't be managed with acetaminophen or ibuprofen.[17] Use a low dose of a low-potency, short-acting opioid as needed for shortest time necessary.[17] Watch baby for limpness, difficulty feeding or breathing, or sleeping more than usual.[2]

b. Using data from the single-payer health system in Ontario, Canada, association was found between first trimester use of opioids and birth defects (2.8% vs 2% [unexposed]), including heart defects (e.g., ASD [tramadol], VSD [codeine], pulmonary artery stenosis) gastrointestinal malformations (e.g., hypertrophic pyloric stenosis), tongue tie, neoplasms (tramadol), urinary defects (tramadol), and genital defects (oxycodone).[33] Opioids represented in the study included **codeine, fentanyl, hydromorphone, meperidine, morphine, oxycodone, and tramadol**.[33]

c. Ultrarapid CYP2D6 metabolism occurs in up to 1% to 10% of white Europeans or North Americans; 3% to 4% of African Americans; 1% to 2% of Chinese, Japanese, and Koreans; and >10% of Oceanic, North African, Middle Eastern, and Puerto Rican populations, and Ashkenazi Jews.[20] In a US urban population, individuals identifying as Caucasian or Hispanic had an incidence of ~11%, with variability within subpopulations.[27]

d. The **Birth Defects Study (Pregnancy Health Interview Study)** found an odds ratio of 2.2 (95% CI 0.9 to 5.7) for risk of **neural tube defects** in women who took opioids in early pregnancy for pain.[9] The absolute risk of neural tube defects is low (four to six per 10,000 live births), so a two-fold increased risk would represent a small increase in absolute risk.[7] Opioids represented in the study included **buprenorphine, butorphanol, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, morphine, nalbuphine, oxycodone, and tramadol**.[9]

e. In the **National Birth Defects Prevention Study**, associations were found between opioid use one and three months post-conception and heart defects, hydrocephaly, spina bifida, gastroschisis, glaucoma/anterior chamber defect, and cleft palate (hydrocodone).[8,10] However, the absolute risk is likely small (e.g., 0.06% increased risk of hypoplastic left heart syndrome).[10] Opioids represented in the study included **codeine, fentanyl, hydrocodone, hydromorphone, meperidine, methadone, morphine, oxycodone, and tramadol**.

Abbreviations: ASD = atrial septal defect; VSD = ventricular septal defect

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