In 2015 more than 30,000 deaths from opioid overdose were reported (FIGURE, page 10). More than 50% of the deaths were due to prescription opioids. The opioid crisis is a public health emergency and clinicians are diligently working to reduce both the number of opioid prescriptions and the doses prescribed per prescription.

In obstetrics, there is growing concern that narcotics used for the treatment of pain in women who are breastfeeding may increase the risk of adverse effects in newborns, including excessive sedation and respiratory depression. The American Academy of Pediatrics (AAP), the US Food and Drug Administration (FDA) and the American College of Obstetricians and Gynecologists (ACOG) recommend against the use of codeine and tramadol in women who are breastfeeding because their newborns may have adverse reactions, including excessive sleepiness, difficulty breathing, and potentially fatal breathing problems. Genotyping can identify some women who are ultrarapid metabolizers, but it is not currently utilized widely in clinical practice.

In the United States approximately 5% of women express high levels of CYP2D6 and are ultrarapid metabolizers of codeine, CYP2D6 gene duplication or multiplication is the cause of the increased enzyme activity. Newborn central nervous system (CNS) depression is the most common adverse effect of fetal ingestion of excessive codeine and morphine from breast milk and may present as sedation, apnea, bradycardia, or cyanosis. Multiple newborn fatalities have been reported in the literature when lactating mothers who were

Use acetaminophen and/or ibuprofen for pain management in women who are breastfeeding. If narcotic treatment is necessary consider using the lowest effective dose of morphine for the shortest time possible. 

Robert L. Barbieri, MD
Editor in Chief, OBG MANAGEMENT
Chair, Obstetrics and Gynecology
Brigham and Women’s Hospital, Boston, Massachusetts
Kate Macy Ladd Professor of Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School, Boston

Instant Poll
Will you prioritize acetaminophen and/or ibuprofen for pain management in women who are breastfeeding?
Tell us at rbarbieri@frontlinemedcom.com
Please include your name and city and state.

CONTINUED ON PAGE 9
ultrarapid metabolizers took codeine. The FDA and ACOG recommend against the use of codeine in lactating women.

**Hydrocodone**

Hydrocodone, a hydrogenated ketone derivative of codeine, is metabolized by CYP2D6 to hydromorphone. Both hydrocodone and hydromorphone are present in breast milk. In lactating mothers taking hydrocodone, up to 9% of the dose may be ingested by the breastfeeding newborn.9 There is concern that hydrocodone use by women who are breastfeeding and are ultrarapid metabolizers may cause increased fetal consumption of hydromorphone resulting in adverse outcomes in the newborn. The AAP cautions against the use of hydrocodone.2

**Oxycodone**

Oxycodone is metabolized by CYP2D6 to oxymorphone and is concentrated into breast milk.10 Oxymorphone is more than 10 times more potent than oxycodone. In one study of lactating women taking oxycodone, codeine, or acetaminophen, the rates of neonate CNS depression were 20%, 17%, and 0.5%, respectively.11 The authors concluded that for mothers who are breastfeeding oxycodone was no safer than codeine because both medications were associated with a high rate of depression in the neonate. Newborns who develop CNS depression from exposure to oxycodone in breast milk will respond to naloxone treatment.12 The AAP recommends against prescribing oxycodone for women who are breastfeeding their infants.2

In a recent communication, the Society for Obstetric Anesthesia and Perinatology (SOAP) observed that in the United States, following cesarean delivery the majority of women receive oxycodone or hydrocodone.13 SOAP disagreed with the AAP recommendation against the use of oxycodone or hydrocodone in breastfeeding women. SOAP noted that all narcotics can produce adverse effects in newborns of breastfeeding women and that there are no good data that the prescription of oxycodone or hydrocodone is more risky than morphine or hydromorphone. However, based on their assessment of risk and benefit, pediatricians prioritize the use of acetaminophen and morphine and seldom use oxycodone or hydrocodone to treat moderate to severe pain in babies and children.

**Tramadol**

Tramadol is metabolized by CYP2D6 to O-desmethyltramadol. Both tramadol and O-desmethyltramadol are excreted into breast milk. In ultrarapid metabolizers, a greater concentration of O-desmethyltramadol is excreted into breast milk. The FDA reported that they identified no serious neonatal adverse events in the literature due to the use of tramadol by women who are breastfeeding. However, given that tramadol and its CYP2D6 metabolite enter breast milk and the potential for life-threatening respiratory depression in the infant, the FDA included tramadol in its warning about codeine.3

Codeine, hydrocodone, oxycodone, and tramadol are all metabolized to more potent metabolites by the CYP2D6 enzyme. Individuals with low CYP2D6 activity, representing about 5% of the US population, cannot fully activate these narcotics. Hence they may not get adequate pain relief when treated with codeine, oxycodone, hydrocodone, or tramadol. Given their resistance to these medications they may first be placed on a higher dose of the narcotic and then switched from a high ineffective dose of one of the agents activated by CYP2D6 to a high dose of morphine or hydromorphone. This can be dangerous because they may then receive an excessive dose of narcotic and develop respiratory depression.14

**Aspirin**

There are very little high quality data about the use of aspirin in women breastfeeding and the effect on the neonate. If a mother takes aspirin, the drug will enter breast milk. It is estimated that the nursing baby receives about 4% to 8% of the mother’s dose. The World Health Organization recommends that aspirin is compatible with breastfeeding in occasional small doses, but repeated administration of aspirin in normal doses should be avoided in women who are breastfeeding. If chronic or high-dose aspirin therapy is recommended, the infant should be monitored for side effects including metabolic acidosis15 and coagulation disorders.16 The National Reye's Syndrome Foundation recommends against the use of aspirin in women who are breastfeeding because of the theoretical risk of triggering Reye syndrome.17 Acetaminophen and ibuprofen are recommended by the WHO for chronic treatment of pain during breastfeeding.16

**Acetaminophen and ibuprofen**

For the medication treatment of pain in women who are breastfeeding, the WHO recommends the use of acetaminophen and ibuprofen.16 Acetaminophen is transferred from the maternal circulation into breast milk, but it is estimated that the dose to the nursing neonate is <0.3%
of the maternal dose.\textsuperscript{18} In mothers taking ibuprofen 1600 mg daily, the concentration of ibuprofen in breast milk was below the level of laboratory detection (<1 mg/L).\textsuperscript{19} Ibuprofen treatment is thought to be safe for women who are breastfeeding because of its short half-life (2 hours), low excretion into milk, and few reported adverse effects in infants.

**Morphine**

Morphine is not metabolized by CYP2D6 and is excreted into breast milk. Many experts believe that women who are breastfeeding may take standard doses of oral morphine with few adverse effects in the newborn.\textsuperscript{20,21} For the treatment of moderate to severe pain in opioid-naive adults, morphine doses in the range of 10 mg orally every 4 hours up to 30 mg orally every 4 hours are prescribed. When using a solution of morphine, standard doses are 10 mg to 20 mg every 4 hours, as needed to treat pain. When using morphine tablets, standard doses are 15 mg to 30 mg every 4 hours.

The WHO states that occasional doses of morphine are usually safe for women breastfeeding their newborn.\textsuperscript{16} The AAP recommends the use of morphine and hydromorphone when narcotic agents are needed to treat pain in breastfeeding women.\textsuperscript{2}

**Hydromorphone**

Hydromorphone, a hydrogenated ketone derivative of morphine, is not metabolized by CYP2D6 and is excreted into breast milk. There are limited data on the safety of hydromorphone during breastfeeding. Breast milk concentrations of hydromorphone are low, and an occasional dose is likely associated with few adverse effects in the breastfeeding newborn.\textsuperscript{22} For the treatment of moderate to severe pain in opioid-naive adults, hydromorphone doses in the range of 2 mg orally every 4 hours up to 4 mg orally every 4 hours are prescribed. Like all narcotics, hydromorphone can result in central nervous system depression. If a mother ingests sufficient quantities of hydromorphone, respiratory depression in the breastfeeding newborn can occur. In one case report, a nursing mother was taking hydromorphone 4 mg every 4 hours for pain following a cesarean delivery. On day 6 following birth, her newborn was lethargic and she brought the infant to an emergency room. In the emergency room the infant became apneic and was successfully treated with naloxone, suggesting a narcotic overdose due to the presence of hydromorphone in breast milk.\textsuperscript{23} Hydromorphone should only be used at the lowest effective dose and for the shortest time possible.

**The bottom line**

Pediatricians seldom prescribe codeine, oxycodone, hydrocodone, or tramadol for the treatment of pain in newborns or children. Pediatricians generally use acetaminophen and morphine for the treatment of pain in newborns. Although data from large, high quality clinical trials are not available, expert opinion recommends that acetaminophen and ibuprofen should be prescribed as first-line medications for the
treatment of pain in women who are breastfeeding. Use of narcotics that are metabolized by CYP2D6 should be minimized or avoided in women who are breastfeeding. If narcotic medication is necessary, the lowest effective dose of morphine or hydromorphone should be prescribed for the shortest time possible. If morphine is prescribed to women who are breastfeeding, they should be advised to observe their baby for signs of narcotic excess, including drowsiness, poor nursing, slow breathing, or low heart rate.

The goal of reducing morbidity and mortality from opioid use is a top public health priority. Obstetrician-gynecologists can contribute through the optimal use of opioid analgesics. Reducing the number of opioid prescriptions and the quantity of medication prescribed per prescription is an important first step in our effort to reduce opioid-related deaths.

Dr. Barbieri reports no financial relationships relevant to this article.