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The United States Food and Drug Administration (FDA)'s Drug Safety Communication released on April 20th 2017,¹ advised that breastfeeding mothers should not receive codeine or tramadol. This was based on evidence that the use of these medications in CYP2D6 ultra-metabolizers can result in excessive amounts of morphine in maternal breast-milk with the potential for neonatal overdose and respiratory depression.

A recent Practice Advisory developed by the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine (SMFM), and the Academy of Breastfeeding Medicine agreed with the FDA communication, however went further and raised concern that oxycodone and hydrocodone may also result in increased risks in infants breastfed by women due to genetic variability in these drug's metabolism.² The Practice Advisory based on the American Academy of Pediatrics Committee on Drugs suggested that butorphanol, morphine or hydromorphone are the preferred opioids in breastfeeding mothers because they are not metabolized by CYP2D6, and are expected to have a more predictable metabolism and less potential for breastfeeding neonatal overdose.

Following this guidance would result in a major change in the care of an estimated 1.4 million women in the United States who undergo cesarean delivery annually. Currently, the vast majority of women treated with oral opioid analgesics after cesarean delivery receive oxycodone or hydrocodone.^{3,4} Based on the available data, the Society for Obstetric Anesthesia and Perinatology (SOAP) does not believe that a shift from oral oxycodone or hydrocodone to butorphanol, morphine or hydromorphone as suggested by the Practice Advisory is warranted. Instead, we contend that this change may actually increase the risks of these medications to both mothers and infants for the following reasons:

- (1) Long history of safe use of current therapy:** In the United States, hydrocodone and oxycodone have been used safely and effectively for many years to treat pain in breastfeeding women after cesarean delivery. Despite millions of prescriptions in this setting, there is just a single case report in the literature of infant opioid overdose requiring reversal by naloxone that was that was thought to be attributable to transfer of oxycodone through breastmilk,⁵ and to our knowledge no such cases have been reported for hydrocodone. Further, while neonatal sedation has been shown to occur in association with oxycodone transferred in breastmilk,⁶ this effect is confined to maternal exposure to high doses and concomitant use of CYP3A4 inhibitors.⁷ Breastfeeding neonatal sedation has the potential to occur in association with all opioids, including butorphanol, morphine and hydromorphone. This effect is documented in a published report of a drowsy, bradypneic neonate requiring naloxone in a mother taking hydromorphone.⁸
- (2) Limited provider experience with alternative opioids:** As butorphanol, morphine and hydromorphone are not commonly used to treat post-cesarean pain,³ obstetricians and anesthesiologists may have limited experience administering these medications in this setting. This may increase the potential for under- or overdosing these medications in the mothers. The bioavailability of both oral hydromorphone and morphine is relatively low; therefore managing acute pain with oral hydromorphone or morphine may not be immediately effective, and may require large doses to achieve effect, leading to

heightened risks of excess breast milk accumulation. There is sparse clinical efficacy and safety data for breastmilk transfer for oral hydromorphone in the post-cesarean delivery setting. The primary investigation evaluating breast-milk transfer included only eight women who received intranasal hydromorphone.⁹ In addition, although not CYP-dependent, hydromorphone undergoes glucuronidation to form hydromorphone-3-glucuronide which may be neuro-excitatory.

- (3) Greater potency of substituted opioids:** At usually prescribed doses, morphine and hydromorphone are more potent opioid analgesics than either oxycodone or hydrocodone. This may increase the risk for adverse maternal opioid-related side effects, and potentially increased opioid dependence and addiction. Leftover tablets in households may carry a risk for maternal opioid misuse, diversion and overdose, therefore more potent opioids should not be the ones prescribed if leftover medication is anticipated.

In light of these considerations, the **Society for Obstetric Anesthesia and Perinatology recommends** the following approach to the management of cesarean delivery pain in breastfeeding women:

- **Multimodal analgesic strategies are key to minimizing opioid requirements after cesarean delivery.**¹⁰ Long-acting neuraxial opioids (e.g. intrathecal morphine 50-150 mcg or epidural morphine 1.5-3 mg) at the time of spinal or epidural anesthesia; as well as scheduled, fixed dose intervals of oral acetaminophen (e.g. acetaminophen 650 mg every 6 hours) and oral non-steroidal anti-inflammatory drugs (e.g. ibuprofen 600 mg every 6 hours) for up to 7-10 days postpartum should be prescribed in all women unless contraindicated. To facilitate opioid sparing in selected clinical situations, prolonged neuraxial analgesia (e.g. epidural infusion, epidural opioid re-dosing, or larger initial neuraxial opioid doses) and local anesthetic techniques (e.g. continuous wound infusions or fascial plane/nerve blocks) should be considered.
- **Oral or intravenous opioids should be used for rescue analgesia only, at the lowest effective dose, and for the shortest duration possible.** Institutional efforts should be made to reduce the maximal allowable doses of opioids (e.g. maximal daily dose of oxycodone of 30 mg). Opioids should only be prescribed post-discharge if required and desired by the mother, and limited to the fewest number of tablets required (e.g. twenty 5 mg oxycodone tablets).¹¹ Instruction for appropriate opioid drug disposal of remaining tablets should be given.
- **If needed, oral oxycodone or hydrocodone are currently the preferred rescue opioids for breakthrough pain after cesarean delivery in breastfeeding mothers.** We acknowledge that there is no optimal oral opioid to manage postpartum pain in breastfeeding women. However current data does not support a shift from oral oxycodone or hydrocodone to morphine or hydromorphone in this setting. There is sufficient evidence that codeine and tramadol should not be prescribed to breastfeeding mothers.
- **Awareness should be raised among clinician, nurses and mothers about the risk of maternal and neonatal adverse effects in all breastfeeding mothers taking opioids.** Educational initiatives should be introduced to inform women and clinicians about the importance of minimizing opioid use, and implementing appropriate assessments in women requiring high doses of opioids to identify sedated neonates.

References:

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This commentary was developed by Ruth Landau, Brian Bateman, Lisa Leffert and Brendan Carvalho, and is approved by the SOAP board. This commentary is subject to change based on emerging scientific evidence and/or changes in clinical practice. We advise checking in periodically for updates and revisions. Publications by the SOAP are protected by copyright and may not be reproduced without written permission from the SOAP.

