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REVIEW ARTICLE

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Post-cesarean delivery pain. Management of the opioid-dependent patient before, during and after cesarean delivery

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ABSTRACT
The opioid crisis has reached an unprecedented magnitude in the United States and worldwide, and data on opioid use and misuse in the obstetric population are extremely concerning. Despite an abundant number of studies evaluating strategies to prevent neonatal opioid withdrawal syndrome in babies born to mothers who are chronic opioid users, in babies born to mothers using chronic opioids, numerous questions remain unanswered, including (1) how to optimally manage postpartum pain in opioid-dependent patients (2) how to reconcile buprenorphine and methadone use with intrapartum and post-partum analgesia, so as to avoid opioid withdrawal during and after delivery (3) how to safely and effectively provide a stepwise multimodal approach that incorporates systemic opioid-sparing approaches, such as neuraxial opioids, clonidine, ketamine, gabapentin, and regional anesthetic blocks, to ensure adequate pain relief while avoiding opioid withdrawal (4) how to optimally manage post-partum recovery and (5) how to avoid excessive opioid prescription and possibly leftover opioids that may promote persistent use, misuse and diversion.
With the recognition that an increasing number of pregnant women are taking chronic opioids, the goals of this review article are to summarize the existing literature on post-cesarean pain management in the obstetric patient with an opioid-use disorder; and to provide clinicians with a stepwise approach for management before, as well as during and after, cesarean delivery of women who have been chronically using opioids during their pregnancy.

Keywords: Opioid, dependent; Pain, post-cesarean; Methadone; Buprenorphine; Natrexone

Introduction

The opioid crisis has reached an unprecedented magnitude in the United States (US), and opioid use and misuse in the obstetric population has become alarming.[1,2]

The number of pregnant women taking opioids, whether prescribed or not, has dramatically increased, resulting in the devastating fact that in the US, every 25 minutes, a baby is born experiencing neonatal opioid withdrawal syndrome (NOWS).[3,4] The implications of an opioid use disorder (OUD) in a pregnant woman are multiple, and numerous questions remain to be resolved:[5]

- How should an opioid-dependent woman be managed early in pregnancy; and should opioid detoxification be undertaken during pregnancy without risking relapses and fetal complications, which include stillbirths?
- Which medication-assisted treatment (MAT) during pregnancy is preferable for both mothers and neonates (methadone or buprenorphine); and should naltrexone be considered?
- Can it be predicted which neonate will suffer NOWS after in utero opioid exposure, and how is it prevented?
- Will labor pain management be challenged by opioid tolerance or polysubstance use; and what is required to reconcile MAT and neuraxial labor analgesia, so as to avoid opioid withdrawal during labor and after delivery?
- What is the optimal way to successfully manage post-cesarean pain by combining the usual neuraxial analgesics with a more robust multimodal approach (neuraxial opioids, clonidine, ketamine, gabapentin, regional anesthetic blocks) and judicious opioid systemic medications, so as to provide safe and adequate pain relief while avoiding withdrawal?

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- How should postpartum recovery be managed, to avoid excessive opioid prescriptions and possibly left-over opioids that may promote persistent use, misuse and diversion?

As obstetric anesthesiologists, our ability to intervene has been perceived to be bound to the peripartum period, with a narrow window limited to managing intrapartum pain, whether during labor and vaginal delivery or intra- and postoperatively for cesarean delivery. However, with the recognition that an increasing number of pregnant women are taking chronic opioids, and the awareness that an antenatal consultation may be useful, along with enhanced monitoring at the time of delivery to prevent potential complications ranging from over-sedation to maternal cardiac arrest, the role of the anesthesiologist has expanded beyond the delivery room. This broader window offers an important opportunity to prepare women for delivery and provide optimal multimodal analgesia to those with a complex pain and analgesic "phenotype", ensuring they are neither undermanaged nor unnecessarily overtreated with opioids.

The goals of this review article are to summarize the existing literature on OUD in pregnancy, in the context of post-cesarean pain management, and to provide anesthesiologists and obstetricians with a stepwise approach for management before, as well as during and after, cesarean delivery of women who have been chronically using opioids and have continued their use during pregnancy.

The epidemiology of opioid use in women and in pregnancy

Recent data about opioid use in the US provided by the US Center for Disease Control and Prevention (CDC) are alarming; opioid prescriptions have overall increased five-fold between 1999 and 2016,[6] with similar trends reported in Australia and Europe.[7]

In 2014, an estimated 1.9 million men and women had an OUD related to prescription pain relievers and an estimated 586 000 had an OUD related to heroin use. The 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-V) states that "opiate use disorder is a problematic pattern of opioid use leading to clinically significant impairment or distress". The diagnosis is based on criteria such as the repeated occurrence within a 12-month period of two or more of 11 problems, including withdrawal, giving up important life events in order to use opioids, and excessive time spent using opioids (Box 1).[8]

Women's biological and psychosocial differences appear to influence their susceptibility to substance use disorder, which could have implications for prevention and treatment. Since 1999, women's deaths from prescription opioid overdose have quadrupled, with nearly 48 000 fatalities among women overdosing with prescription opioids between 1999 and 2010.[9] The situation in the obstetric population has mirrored that in the general population, and OUD affects pregnant women across all socio-economic, racial and ethnic groups, whether in rural or urban settings,[10] and within or outside the US.[11] The most recent data about documented OUD in delivery hospitalization in the US shows an overall four-fold increase between 1999 and 2014, with marked geographical differences.[12]

However, women who use opioids during pregnancy represent a heterogenous group of women, with some being prescribed opioids for pain management (e.g. sickle cell disease[13]), some being on MAT with methadone or buprenorphine to avoid withdrawals during pregnancy, and others misusing opioids and/or having an untreated OUD. Untreated OUD during pregnancy carries significant risks for both mothers and babies: acute maternal withdrawal results in a catecholamine

Box 1 DSM-V Opioid Use Disorder check list

1. Opioids are often taken in larger amounts or over a longer period than was intended
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid or recover from its effects
4. Craving, a strong desire or urge to use opioids
5. Recurrent opioid use resulting in failure to fulfill major role obligations at work, school, or home
6. Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use
8. Recurrent opioid use in situations in which it is physically hazardous (e.g. while driving)
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
10. Tolerance, either a need for markedly increased amounts of opioids to achieve intoxications or desired effect, or a markedly diminished effect with continued use at the same amount of an opioid
11. Withdrawal, either the characteristic opioid withdrawal syndrome or opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms (negative mood, nausea or vomiting, muscle aches, diarrhea, fever, insomnia)

DSM-V: Diagnostic and Statistical Manual of Mental Disorders, version 5.; One point is assigned to each applicable item. 2–3 points: mild opioid use disorder. 3–4 points: moderate opioid use disorder. 5–6 points: severe opioid use disorder.

surge, uterine contractions, and reduced placental blood flow and oxygen supply. Delayed placental villous maturation, a finding associated with fetal demise, has been observed in placentas exposed to opioid maintenance therapy.[14] Fluctuating levels of opioids may expose the fetus to repeated episodes of withdrawal in utero, causing motor hyperactivity, increased oxygen consumption, and increased norepinephrine levels in amniotic fluid. This combination can result in preterm labor, fetal hypoxia or fetal demise. For that reason, as well, detoxification during pregnancy is a complex process that is currently not recommended.[15] Therefore, women entering pregnancy using opioids regularly for pain management, or on opioid-maintenance treatment, will typically be maintained on a long-acting opioid (e.g. oxycodone, hydromorphone, methadone or buprenorphine).

Medication-assisted treatment

Medication-assisted treatment is a comprehensive approach that combines US Food and Drug Administration (FDA)-approved medications (currently methadone, buprenorphine, or naltrexone) with counseling and other behavioral therapies, to treat patients with OUD.[16] Opioid-agonist treatment (methadone or buprenorphine) remains the standard of care for management of OUD in pregnancy.[1,17,18] Specific to pregnancy, the goals of MAT with opioids are to suppress the debilitating symptoms of cravings and withdrawal, and prevent illicit opioid use, as this can increase the risk of fetal growth restriction, placental abruption, fetal demise and preterm labor. Medication-assisted treatment has been shown to increase adherence to prenatal care, reduce illicit drug use, and reduce infection exposure secondary to intravenous drug use.

Lack of access to gender-specific care, limited childcare availability at treatment facilities, access to providers with obstetric and addiction medicine experience, increased social stigma, and fear of criminal or child welfare consequences constitute barriers for the appropriate care of pregnant women.[19,20] Barriers are even more significant in certain US states, in the context of low income and for women of color, with fear of being reported to the police resulting in little or no prenatal care among women using opioids.[21–23]

Methadone

Methadone, a synthetic μ-opioid receptor agonist, is a potent analgesic for management of acute and chronic pain and is prescribed for the treatment of opioid dependence. The pharmacokinetic profile of methadone differs from that of morphine due to a higher oral bioavailability (70–80%), a much longer half-life, and liver-mediated metabolism involving cytochrome P450 enzymes. Of importance, the metabolism of methadone is affected by pregnancy, with significantly decreased methadone/metabolite ratios as pregnancy progresses, indicating that methadone metabolism is increased during the third trimester.[24] The clinical significance of this is that increased doses and reduced dose frequency will be needed to maintain maternal/fetal stability at term, and dose reductions will be needed postpartum as hypermetabolism reverses.[25,26] Another important factor impacting the metabolism and elimination profile of methadone is CYP2B6 genetic variability, with both constitutive variability due to CYP2B6 genetics and CYP2B6-mediated drug interactions, which can greatly modify methadone disposition, clinical effect, and drug safety.[27]

Peak plasma levels are achieved within 2–4 h. Methadone undergoes a biphasic elimination pattern: analgesia is associated with α-elimination (8–12 h) and withdrawal suppression is associated with β-elimination (30–60 h). Methadone may cause sedation, and respiratory depression. Overdoses may occur at unpredictable doses due to its long, variable metabolism due to genetic variability and variable tolerance profile. Higher methadone doses are associated with a significant prolongation of the maternal corrected QT interval (QTc) during the third trimester of pregnancy. This may result in arrhythmias, including torsade de pointes.[28]

Recommendations for peripartum use include taking the usual dose on the day of delivery and peripartum. However, due to the increased clearance and volume of distribution during pregnancy, split-dosing has also been suggested.[29] A single daily dose may indeed not be sufficient to prevent withdrawal symptoms over a 24-h period and giving the daily dose in three divided doses has been shown to provide better analgesia.[30]

Buprenorphine

Regular adherence to MAT with buprenorphine decreases opioid withdrawal symptoms and the desire to use opioids, without causing the cycle of highs and lows associated with opioid misuse or abuse. With adequate dosing, buprenorphine also decreases the pleasurable effects of other opioids, making continued opioid abuse less attractive (see Box 2).

Different formulations of buprenorphine (including generic) are available. Oral forms include a buccal film and sublingual tablets. Parenteral routes include a subdermal or subcutaneous implant, and intravenous or intramuscular injections. For chronic pain management in the general population, a transdermal patch appears to be effective.[14,31] A combined formulation of buprenorphine with naloxone, an opioid antagonist, is available to reduce diversion because if injected, buprenorphine with naloxone 4:1 (Suboxone) will cause severe withdrawal symptoms. Since naloxone is inactive by the oral route, the sublingual formulation does not cause withdrawal. Outside of pregnancy, buprenorphine is used in combina-

Box 2 Buprenorphine, methadone and naloxone pharmacology and clinical profile

	Buprenorphine ($C_{29}H_{41}NO_4$)	Methadone ($C_{21}H_{27}NO$)	Naloxone ($C_{19}H_{21}NO_4$)
Mechanism of action	• Partial μ-opioid receptor agonist • δ- and κ-opioid receptor antagonist • Partial nociception receptor (NOP; ORL-1) agonist	• Full μ-opioid receptor agonist (levo-methadone) • May be antagonist at the N-methyl-D-aspartate (NMDA) receptor (dextro-methadone; the S-enantiomer)	• Full competitive antagonist at μ-. δ- and κ-opioid receptors
Pharmacology	• High receptor binding affinity • Produces analgesia at low receptor occupancy (5–10%) • Peak plasma concentration 1–2 h after sublingual intake (onset of action) • Highly protein bound (>95%) • Long half-life (24–37 h)	• Rapid absorption after oral intake - onset in 15–45 min • Peak plasma concentration 2.5–4 h after intake • Highly protein bound (range 81%–95%; to α_1-acid glycoprotein, albumin, and globulin) • Lipophilic properties and Multicompartmental kinetics, with a volume of distribution of 4.0 L/kg (range 1.9–8.0 L/kg) • Long half-life (20–35 h), which is related to its accumulation in tissue and subsequent slow release into the blood • Steady state within 3–5 days	• Binding affinity is highest for μ->δ- >κ-opioid receptor • Onset of action IV 2 min, IM 5 min • Duration of action 45–90 min • A dose of naloxone 13 μg/kg (1 mg in an 80 kg person) will occupy 50% of available receptor sites in the human brain, in a competitive fashion
Metabolism	• Extensive first-pass effect results in poor oral biodisponibility (30% sublingual) • Phase I reactions (N-dealkylation) in the liver, into norbuprenorphine • CYP3A4 metabolism • Buprenorphine and norbuprenorphine are conjugated by phase II reactions to their glucuronide forms • Eliminated in bile and feces • Only a small amount of glucuronide metabolites excreted in the kidney (which makes it safe in patients with renal insufficiency)	• Oral bioavailability 80% (although considerable variability 36–100%), and 20% subcutaneous • Extensive hepatic metabolism • N-demethylation to 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) • CYP2B6 metabolism (& CYP3A4) • Eliminated in urine and feces	• Extensive first-pass effect results in oral availability of 2%, and intranasal 50% • Hepatic metabolism • Glucuronidation into naloxone-3-glucuronide • Eliminated in urine and bile
Formulations for MAT	• Sublingual tablets (Subutex®) • Sublingual tablets combined with naloxone (4:1 ratio) (Suboxone®) • The addition of naloxone reduces the likelihood of diversion & misuse because it induces withdrawal symptoms when injected intravenously	• Oral tablets or liquid form • Starting dose should not exceed 30 mg, with incremental increases of 5–10 mg as needed to avoid cravings (optimal dose 60–120 mg) • Split doses are suggested in pregnancy	For opioid overdose reversal: • IV • IM or SC (Evzio®; 2 mg)
Effects (advantages)	• Ceiling effect at high doses • Less euphoria and physical dependence (decrease cravings for opioids) • Lower potential for misuse and illicit opioid use • Relatively mild withdrawal profile	• Morphine-like effects (analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia and physical dependence) however onset of withdrawal symptoms is slower, the course is more prolonged and symptoms are less severe	• Reverses the effects of opioids by binding to the opioid receptors in the central nervous system, and inhibiting the typical actions of opioid analgesics, including analgesia, euphoria, sedation, respiratory depression, miosis, bradycardia, and physical dependence
Risks	• May inhibit analgesic effect of traditional opioids (dose-dependent) • May induce withdrawal symptoms in opioid-dependent patients if administered soon after the last dose of a pure agonist (e.g. fentanyl or oxycodone) • May induce hyperalgesia	• Cross tolerance with other opioids is unpredictable • Sedative effects and cognitive alteration during induction phase • Unanticipated methadone toxicity • QT prolongation	• Highly lipophilic and crosses the placenta, may cause fetal withdrawal
Overdose	• Reversal may require higher doses of naloxone than usual (2–3 mg bolus followed by 4 mg/h infusion in monitored care)	• Although methadone metabolism is significantly increased during pregnancy, and increasing doses and/or split dosing have been suggested, monitoring of serum methadone concentrations in pregnancy is not warranted	

Box 2 continued

	Buprenorphine ($C_{29}H_{41}NO_4$)	Methadone ($C_{21}H_{27}NO$)	Naloxone ($C_{19}H_{21}NO_4$)
Breastfeeding	• Women on buprenorphine are encouraged to breastfeed (if stable and without polysubstance use); it reduces the odds for pharmacological treatment of neonatal opioid withdrawal syndrome	• Low concentrations are secreted in breastmilk	• No transfer into breastmilk

MAT: medication assisted treatment.

tion with naloxone to reduce abuse and diversion. However, even though oral naloxone is not systemically absorbed, the use of buprenorphine as a single agent has been preferred during pregnancy to avoid any risk associated with prenatal naloxone exposure. The use of the combined formulation during pregnancy is likely to expand as more safety data accumulate.

Based on buprenorphine's long terminal half-life, once-daily or twice-daily dosing is typically recommended in the non-pregnant population. However, due to pharmacokinetic changes throughout pregnancy,[32] including increased clearance and volume of distribution,[33] it has been suggested that more frequent dosing (i.e. up to three- or four-times daily) may be indicated to maintain plasma concentrations above the threshold of 1 ng/mL, which will prevent withdrawal symptoms and improve adherence.[34]

Buprenorphine was shown to have significant advantages over methadone with regards to the severity of NOWS[35] in The Maternal Opioid Treatment: Human Experimental Research (MOTHER) study.[36] This was a double-blind, double-dummy, randomized, stratified, flexible-dosing clinical trial comparing methadone (20–140 mg) and buprenorphine (2–32 mg) in women enrolled between six and 30 weeks-of-gestation. Findings in this cohort of 175 mother-baby dyads randomized between 2005 and 2008 at eight international sites were numerous. In the methadone group, 10 of 89 women (11%) voluntarily discontinued the study, while 26 of 86 women (30%) did so in the buprenorphine arm (with 20/26 being dissatisfied with the medication). Babies born to mothers who successfully completed pregnancy using buprenorphine required significantly less morphine to treat NOWS and had a significantly shorter duration of hospitalization compared to methadone-exposed neonates.[35] However, the study raised many questions about how best to implement buprenorphine therapy, since attrition among women randomized to receive buprenorphine was so high.[36]

A retrospective cohort analysis including 62 pregnant women maintained with either methadone or buprenorphine with naloxone, in the period between 2011 and 2013, confirmed that newborns exposed to maternal buprenorphine and naloxone were less likely to suffer NOWS and had shorter overall length of hospitalization.[37] A systematic review including three randomized controlled trials (N=223 dyads) and 15 observational cohorts (N=1923 dyads) identified moderately strong evidence for improved neonatal outcomes, with lower risk of preterm birth, greater birth weight and larger head circumference associated with buprenorphine treatment of maternal OUD during pregnancy compared with methadone treatment, and no greater harm.[38]

Nonetheless, both buprenorphine and methadone have the disadvantage of physical opioid dependence for the fetus, such that treatment of NOWS may be needed after birth even with buprenorphine.[39] For the neonate exposed in utero to buprenorphine, the profile and withdrawal symptoms are significantly different to those occurring after methadone exposure. Buprenorphine-exposed neonates who required pharmacological treatment of NOWS did so significantly (on average 24 h) later than methadone-exposed neonates who required treatment.[40,41] Of note, in the Blinded Buprenorphine or Neonatal Morphine Solution (BBORN) trial, treatment of neonatal opioid withdrawal with sublingual buprenorphine was shown to result in a shorter duration of treatment and shorter length of hospital stay than treatment with oral morphine, with similar rates of adverse events.[42] However, these results were criticized because the buprenorphine formulation contained 30% ethanol,[43] and because a model of care with non-pharmacologic treatment should be considered to be the primary treatment, with pharmacotherapy secondary.[44] Nonetheless, a pharmacokinetic model established on a subset of participants was developed with the goal of optimizing buprenorphine dosing strategies in future clinical trials.[45]

Buprenorphine overdose, while rare, may occur.[46] Intravenous (IV) naloxone is not recommended in pregnant women with OUD unless the situation is life-threatening.[47] Treatment recommendations in the non-obstetric population for naloxone dosing to reverse buprenorphine overdose involve higher dosing (e.g. bolus dose 2–3 mg, followed by a continuous infusion of 4 mg/h).[48,49] This will cause a full reversal of the overdose within 40 to 60 minutes. A bolus dose is needed to overcome the high affinity that buprenorphine has to the μ-opioid receptor.

Although patients with chronic pain may be well managed with buprenorphine (usually transdermal patches),[14] and treatment of acute pain in opioid-naïve patients with buprenorphine is widely reported,[50] management of acute pain in patients on chronic buprenor-

phine in the context of an OUD is particularly challenging.[51] Low doses of buprenorphine will competitively displace opioid agonists from μ-opioid receptors and the displacement of buprenorphine by standard opioid agonists is only achieved with high doses. There have been few studies evaluating receptor occupancy by intake of buprenorphine or subsequent availability of the μ-opioid receptor for analgesia in an acute setting, this being hampered by buprenorphine's long half-life. Nonetheless, in an animal model, the extent and duration of receptor occupancy did not seem to exceed the duration of its antinociceptive activity, suggesting that no impairment of antinociception should be expected in the case of an opioid switch.[52] In a preliminary evaluation of three heroin-dependent male volunteers (two African-Americans and one Hispanic), buprenorphine 2 mg reduced regional cerebral μ-opioid receptor availability by 36–50% and administration of buprenorphine 16 mg was associated with reductions in μ-opioid receptor availability by between 79 and 95%.[53] Higher regional μ-opioid receptor binding potential was observed in the placebo-phase in these volunteers, in contrast to observations in three matched controls.[53]

In a cohort of five heroin-dependent volunteers successively maintained on various buprenorphine daily doses (32, 16, 2, and 0 mg), the higher doses decreased in vivo μ-opioid receptor availability and decreased hydromorphone responses. Buprenorphine significantly decreased whole-brain μ-opioid receptor availability (by 41% after 2 mg, 80% at 16 mg and 84% at 32 mg, respectively).[54] In a further study in 10 heroin-dependent volunteers maintained on buprenorphine 16 mg daily, supraspinal μ-opioid receptor availability was found to be 30% at four h, 54% at 28 h, 67% at 52 h and 82% at 76 h after buprenorphine dosing.[55]

The question whether or not to stop buprenorphine prior to elective (non-obstetrical) surgical procedures has been raised.[56,57] Different algorithms have been proposed, based on the expected severity of postoperative pain and opioid requirements, and non-opioid approaches to pain management are highly encouraged.[56] However, in the context of pregnancy the guidelines of the American Society of Addiction Medicine (ASAM) recommend that for elective cesarean deliveries, in contrast to other surgeries, buprenorphine should not be discontinued due to the risk of fetal withdrawal.[47]

Naltrexone

Naltrexone is a non-selective opioid receptor antagonist that blocks the euphoric effects of opioids and acts as a deterrent to misuse. The recently approved, injectable, long-acting form has been shown to be effective in maintaining abstinence, however the risk of relapse and treatment dropout with subsequent return to opioid use and risk of overdose, exists.[58]

Naltrexone use in pregnancy offers the advantage of avoiding in utero opioid exposure and possible NOWS,[59] but teratogenic effects, as well as short- and long-term behavioral effects on the developing brain remain to be evaluated.[60] In addition, detoxification would be required prior to naltrexone initiation. These questions have raised an interesting debate about the appropriate framework and ethics of trials evaluating naltrexone in such a vulnerable population.[61–65]

Not surprisingly, current data regarding use of naltrexone in pregnancy are scarce. A retrospective cohort study from Australia reported similar neonatal outcomes among pregnant women treated with naltrexone implants compared to women on sublingual buprenorphine, with the exception of significantly lower rates of NOWS (7.5% vs 41.8%) and shorter hospital length of stay in naltrexone-exposed neonates.[66] With regards to obstetric outcomes, while pregnancy rates were high among naltrexone-treated women, overall pregnancy losses prior to 20 weeks-of-gestation were significantly higher in naltrexone-treated women compared with buprenorphine-treated women and controls (although not compared with methadone-treated women).[67]

Post-cesarean pain management

Optimal post-cesarean pain management has been the focus of numerous studies and by design, randomized clinical trials (RCTs) consider women with chronic pain, with a history of opioid use or with an OUD, to be ineligible, so these women are not enrolled in research trials. Consequently, no RCTs to date have evaluated and compared any of the many analgesic approaches that are available for postoperative pain management - nor has any study determined which is the most effective (and safe) analgesic modality for opioid-dependent women undergoing cesarean delivery.

A recent review of the anesthetic implications of the opioid crisis in pregnancy emphasized that increased opioid doses and use of non-opioid modalities are reported to be helpful.[68] Similar to recent recommendations proposed for management of post-cesarean pain management in the opioid-naïve patient,[69–71] stepwise multimodal analgesia is key, particularly in the context of breastfeeding mothers.[72,73] One can extrapolate that the following three steps are essential to ensure safe and enhanced recovery after cesarean delivery in the opioid-dependent patient:

1. Antenatal period: plan an antenatal consultation whenever possible to establish an anesthetic plan and to reassure the patient that her needs are understood (women are often anxious about not receiving their daily opioid dose and not having postoperative pain managed adequately).

2. Intrapartum period: establish an anesthetic plan that will allow stepwise multimodal post-cesarean analgesia, maximizing neuraxial approaches rather than relying on systemic opioids (which may or may not suffice).
3. Post-partum period: propose a tailored analgesic approach for up to 72 h in a monitored environment. Ensure that a discharge plan has been made with the patient; include the chronic pain team or the addiction experts.

Despite the rising number of pregnant women with OUD on methadone or buprenorphine, there are only a handful of publications in the last 10–15 years specifically describing postpartum pain management approaches and systemic opioid intake in these women.[74–83]

Intravenous morphine patient-controlled analgesia (PCA)

A case study from 2006 reported post-cesarean pain management in two women undergoing intrapartum cesarean delivery under epidural anesthesia (mepivacaine and fentanyl 100 μg): one patient was being maintained on buprenorphine (18 mg daily) and the other on methadone (80 mg daily).[74] Neither was given epidural preservative-free morphine and both received IV morphine patient-controlled analgesia (PCA) for the first 24 h (demand bolus 1.5 mg, lockout interval 7 min and a 30 mg per four hour limit). Both women used the maximum permitted daily dose of IV morphine (180 mg). On the following days, oxycodone 5 mg plus acetaminophen 500 mg was prescribed (two tablets every four to six hours). For the buprenorphine patient, with the maximum daily dose of 60 mg of oxycodone (and 6 g of acetaminophen), pain seemed to be well managed without additional non-steroidal anti-inflammatory drugs (NSAIDs). For the methadone patient, despite the same regimen of oxycodone with acetaminophen, pain scores were moderate to severe and ibuprofen (600 mg 8 hourly) was prescribed. The authors concluded that buprenorphine and methadone can be safely continued, without interruption, through labor, delivery, and postpartum; and that multimodal analgesia, including acetaminophen and NSAIDs in combination with systemic opioids, should be prescribed.

Intrapartum neuraxial opioids among women on methadone

A retrospective case-control analysis of a cohort of women maintained on methadone during pregnancy, between 1999 to 2006 in Vermont, evaluated intrapartum and postpartum pain and analgesic consumption.[75] There were no major differences in intrapartum pain or analgesia between methadone-maintained and non-opioid dependent women. Post-cesarean pain management for women undergoing intrapartum cesarean delivery (n=33, of whom nine received long-acting intrathecal opioids) included scheduled acetaminophen 325 mg/oxycodone 5 mg in combination (one or two tablets per patient choice every four hours) and ibuprofen 400 mg every four hours for the first 48 h, then as needed for 48 h. For the first 24 h postoperatively, morphine 2–5 mg IV (at the nurse's discretion) every two hours was included for breakthrough pain, on an 'as needed' basis. After cesarean delivery both pain scores and opioid intake were significantly higher in the methadone-maintained cohort, in comparison with matched controls. The authors concluded that methadone-maintained women have similar analgesic needs and responses during labor, but use 70% more opioids after cesarean delivery than do non-opioid dependent women.

Intrapartum neuraxial opioids among women on buprenorphine

The authors performed the same assessment of pain trajectories in a subsequent case-control study among women maintained on buprenorphine during pregnancy between 2003 and 2008.[77] The results were very similar to those found in the methadone cohort. Compared with matched controls, among those delivering vaginally (n=44), there was no difference in the proportion of women choosing to receive neuraxial labor analgesia, the intrapartum management or postpartum oxycodone intake. Post-cesarean pain management for women undergoing intrapartum cesarean delivery (n=19, of whom six received long-acting intrathecal opioids, morphine or meperidine) was similar to that described for the methadone cohort. Both pain scores and oxycodone doses were significantly higher (47%) compared with matched controls. Opioid doses in excess of the standardized orders occurred more frequently among women using buprenorphine (13/19 (42.1%) compared with the controls (3/19 (8.4%), P=0.02), with most occurring within the first 24 h. Systemic opioid use was 113.9 ± 52.7 mg oxycodone equivalents in the first 24 h decreasing to 82.1 ± 40.6 mg for the next 48 h in the buprenorphine cohort. However, the non-opioid dependent controls also consumed a relatively large amount of systemic opioid (79.5 ± 19.6 mg oxycodone equivalents in the first 24 h and an additional 50.0 ± 12.5 mg across the next 48 h). Overall, because the pattern of opioid intake seemed to decrease throughout the 72-h period, the authors felt that opioid intake was motivated by pain and not the availability of opioid. Systemic opioid use was not reported to be different among the subset of women who received a dose of long-acting neuraxial opioid (although details were not provided, and the sample size was too small to draw conclusions).

In another retrospective review of 19 women on buprenorphine, three had a scheduled cesarean delivery and received intrathecal opioids, three delivered similarly and did not, and three had an intrapartum cesarean delivery and received epidural opioids.[79] Daily and total systemic opioid use (reported as an equi-analgesic hydromorphone dose in mg) as rescue analgesia was evaluated. There was wide variability but women who received neuraxial opioids (six) used higher doses postoperatively compared to those who did not, which could be attributable to opioid-induced hyperalgesia. The authors also suggested that the strong affinity of buprenorphine for μ-opioid receptors may result in standard opioids being ineffective. Whether chronic use of systemic buprenorphine causes spinal opioids to be less effective has been considered, but no study (in vitro or in an animal model) and no large clinical series support this hypothesis.

Box 3 Proposed stepwise multimodal analgesia

1. Maintain the baseline systemic opioid(s) at the same daily dose(s)
   - Consider split daily doses for methadone and buprenorphine (2-3 times daily)
2. Provide enhanced multimodal post-cesarean analgesia for at least 72 hours in a monitored environment

*In the operating room, a combined spinal-epidural (CSE) anesthetic will allow: **

- **Spinal injection (as part of the anesthetic solution):**
  1. Consider enhanced initial preservative-free morphine dose (150-300 μg)
  2. If available add clonidine 0.5-1 μg/kg (50-100 μg)

Upon arrival to recovery/step-down unit, multimodal analgesia will include:

- **Epidural analgesia (immediately postoperatively and maintained for 48-72 h):**
  1. Low-concentration local anesthetic solution (e.g. bupivacaine 0.0625% with fentanyl two μg/mL) infusion or programmed intermittent epidural bolus (PIEB) with patient controlled epidural analgesia (PCEA) 24-48 h
     - consider adding clonidine (two μg/mL) to the solution
     - when stopping the low-concentration local anesthetic solution, consider giving epidural preservative-free morphine (three to four mg) to provide additional analgesia for 12-24 h
  2. If maintaining epidural low-concentration local anesthetic solution is not possible (or patient prefers to get out of bed and ambulate), epidural preservative-free morphine (three to four mg) may be given (every 18-24 h) for 72 h
- **Systemic analgesia (until discharge)**
  1. Scheduled every six hours (given together)
     - Oral acetaminophen (650 mg)
     - Oral ibuprofen (600 mg) (or intravenous ketorolac 15-30 mg if not tolerating oral)
  2. Consider adding any of the following (or a combination of, in a monitored environment)
     - Oral gabapentin (300-600 mg every eight hours)
     - Intravenous ketamine (0.5 mg/kg bolus and two μg/kg/min infusion for 24-48 h)
     - Intravenous dexmedetomidine (infusion at 0.2-1.4 μg/kg/h, consider a bolus of one μg/kg over 10-20 min)

If prolonged epidural analgesia is not possible or if general anesthesia was provided

- **Systemic opioids should be proposed:**
  1. Intravenous opioid (hydromorphone probably preferable, particularly if patient is taking buprenorphine)
  2. Oral opioid (oxycodone five-15 mg every three hours)
- **A regional truncal block may be offered as well**

  Transversus abdominis plane (TAP) or at quadratus lumborum block (QLB) (at the end of case, or as rescue), with catheters for repeated dosing (every eight hours)

**For the patient coming to the operating room with an intrapartum epidural catheter, or if cerebrospinal fluid is not obtained during combined spinal-epidural anesthesia, epidural preservative-free morphine (3-4 mg) may be given at the end of the case, and or a low-concentration local anesthetic solution started in the recovery room/intensive care unit setting, and the catheter may be used as suggested above.*

Oral analgesics in women on methadone versus buprenorphine

In the largest retrospective cohort study, over a nine-year period from 2006 to 2014, that compares post-cesarean opioid use among women maintained on methadone (n=185; mean dose 94 ± 43 mg) versus buprenorphine (n=88; mean dose 16 ± 8 mg), there were no significant differences in systemic opioid consumption (hydromorphone), although the dose of ketorolac used was higher by 25% among women on buprenorphine.[81] Women on buprenorphine were more likely to have received a combined spinal-epidural (rather than a spinal) anesthetic and the general anesthesia rate was similar in both cohorts (3–4%). The authors concluded that buprenorphine treatment does not interfere with the management of post-cesarean pain more than methadone.

Thoracic epidural analgesia in women on buprenorphine

In a series describing post-cesarean pain management in four women maintained on buprenorphine during pregnancy, the authors proposed continuing the pre-operative baseline buprenorphine dose, offering thoracic epidural analgesia post-cesarean, and selecting traditional systemic opioids with high μ-opioid receptor affinity for rescue analgesia (for example intravenous sufentanil or hydromorphone).[80]

Multimodal approaches with ketamine, gabapentin and other adjuvants in women on buprenorphine

A case series has described the intra- and postpartum management of eight women on buprenorphine by means of various anesthetic and analgesic regimens that included ketamine, gabapentin and other adjuvants.[83] Of five women delivering via cesarean, failed neuraxial anesthesia resulted in three women requiring general anesthesia, and postoperative pain management proved to be challenging. An intravenous ketamine infusion starting intraoperatively (at 8 mg/h) and maintained for 24 h is described in one of the cases.

Epidural clonidine in women on buprenorphine

Another strategy proposed is maintenance of epidural analgesia after cesarean delivery with a local anesthetic solution (e.g. bupivacaine) containing clonidine, rather than the more commonly used adjuvant fentanyl (at 2 μg/mL).[82] This approach was reported in seven women maintained on buprenorphine (between 2–24 mg daily, taken once or twice daily) who had undergone combined spinal-epidural anesthesia. The spinal solution did not contain long-acting opioid and epidural bupivacaine 0.1% with clonidine 1.2 μg/mL was started in the recovery room at 10 mL/h for 24 hours (one patient received bupivacaine 0.0625%% with clonidine 2 μg/mL). Post-cesarean analgesia provided with clonidine 1.2 μg/mL seemed effective, and the only adverse effect noted was hypotension in the sole patient receiving the higher dose of clonidine. This episode of hypotension occurred within 60 min of initiating the epidural infusion and recovered after fluid and phenylephrine boluses. Women also received non-opioid medications (acetaminophen, ibuprofen, ketorolac) and oxycodone. Unfortunately, the authors did not report in detail the analgesic intake beyond the first 24 h, and it remains unclear why neuraxial opioids were not given initially (as part of the spinal dose); why clonidine replaced fentanyl rather than be added to it, as described in other clinical settings;[84,85] why women were not offered patient-controlled epidural analgesia; and why epidural morphine was not given before removal of the epidural catheter. Nonetheless, this report provides useful information, since epidural clonidine infusion for management of post-cesarean pain in buprenorphine-maintained patients has not previously been described.

Regional truncal blocks

Although there are no studies, either a transversus abdominis plane (TAP) block or a quadratus lumborum block (QLB) after cesarean delivery in OUD patients may be a useful approach, commenced either at the end of the case when neuraxial analgesia was unavailable (e.g. after general anesthesia) or for rescue analgesia after neuraxial anesthesia.[86,87]

Sedative adjuvants

Because of the possibility of polysubstance use, benzodiazepine dependence (e.g. alprazolam, lorazepam) or illicit drug use (e.g. cocaine, methamphetamine), concomitant administration of adjuvants with sedative properties such as intravenous dexmedetomidine[78] or ketamine, [69,83] or oral gabapentin,[69] could be beneficial. This would warrant continuous respiratory monitoring in a high-dependency or intensive care unit, particularly if neuraxial or systemic opioids (e.g. hydromorphone) are also prescribed (Box 3).

The ideal modality for respiratory monitoring (e.g. hourly nurse-assessed respiratory rate, pulse oximetry, transcutaneous carbon-dioxide monitors or capnography) to prevent opioid-related respiratory adverse events is unknown. Continuous non-invasive monitoring technology is probably the only reliable way of identifying respiratory depression in patients at higher risk, as is the case with concomitant systemic opioid and sedative intake.

In summary, contemporary post-cesarean pain management includes a stepwise pre-emptive multimodal approach, combining neuraxial anesthesia for cesarean delivery, prolonged neuraxial analgesia with neuraxial adjuvants (opioids and/or clonidine) or regional truncal

blocks and systemic adjuvants (dexmedetomidine, ketamine, gabapentin), based on a case-by-case tailored approach until 72 h after delivery, in a clinical environment with adequate continuous monitoring.

Conclusion

With the increasing application of MAT during pregnancy and with more women likely to be maintained on buprenorphine due to compelling evidence of its superiority in terms of neonatal outcomes, recommendations for post-cesarean pain management in these women are much needed but are lacking. Numerous gaps in knowledge need to be addressed.

In reviewing the scarce literature on post-cesarean pain management in women on buprenorphine maintenance therapy, there appears to be two schools of thought with regards to neuraxial opioids (fentanyl and preservative-free morphine). Some anesthesiologists omit neuraxial opioids under the premise that the high binding affinity of buprenorphine will result in limited μ-opioid receptor availability and preclude an analgesic effect. Assuming that neuraxial opioids will likely not be effective, epidural local anesthetic infusions are provided for 24 h along with adjunctive nonsteroidal anti-inflammatory drugs and acetaminophen.[79,81] Others propose that opioid-dependent women will require enhanced analgesia, and therefore maximize all multimodalities for example neuraxial local anesthetic with opioid (possibly at even higher doses and with appropriate monitoring) or with clonidine. Since there is no evidence that neuraxial opioids are ineffective in women on chronic buprenorphine treatment, nor that they are unsafe, omitting neuraxial opioids in those women most likely to experience severe post-partum pain doesn't 'seem rational'. In my opinion, all strategies that enhance analgesia while reducing systemic opioid use, including neuraxial fentanyl and preservative-free morphine, should be used. Tailored approaches, including prolonged epidural catheterization and multimodal adjuvants with adequate monitoring, remain essential until further studies determine whether neuraxial opioids provide analgesia for buprenorphine-maintained patients.

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