Peripartum Pain Control In the Opioid Dependent Parturient

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Introduction

There has been a sharp increase in opioid use within the first decade of the twenty-first century.\textsuperscript{1-4} According to the 2013 National Survey on Drug Use and Health, 11.8 million people aged 12 years and older misused opioids within the prior year. Included were 11.5 million individuals misusing analgesics and 948,000 heroin users.\textsuperscript{5} Another study found a substantial increase in opioid abuse between 1998 and 2011 within the age range of 20-34 year-old women.\textsuperscript{2} Not only has opioid use increased within the female population, but it has increased in a particularly concerning cohort as well, pregnant women. According to a study of 534,000 US women between 2005 and 2011, 14\% received at least one dose of opioids during pregnancy.\textsuperscript{1} Another study of 1.1 million women found that one in five women filled an opioid prescription during pregnancy.\textsuperscript{6} The use and misuse of opioids during pregnancy has increased from 1.2 per 1000 live births in 2000 to 5.6 per 1000 in 2009.\textsuperscript{3} According to the National Center for Health Statistics, pregnancy rates in 2009 were 102 live births per 1000 women.

There are several reasons practitioners prescribe opioids to pregnant women, including back pain, abdominal pain, migraine, joint pain, fibromyalgia.\textsuperscript{1} The most frequently prescribed opioids are hydrocodone, codeine, oxycodone, propoxyphene, tramadol, meperidine, hydromorphone, morphine, fentanyl, buprenorphine, methadone, pentazocine, tapentadol, and oxymorphone.\textsuperscript{1} Managing opioid dependent women’s analgesic levels during the peripartum period can be challenging for the anesthesia team.

Opioid dependent pregnant women are multifaceted patients whose lives are often complicated by physiological and psychological factors.\textsuperscript{3} Psychological conditions associated with opioid dependence such as depression and anxiety, are factors that influence the unpredictability of prenatal care. Studies have found opioid dependent parturients also often misuse other illicit drugs, alcohol, and tobacco. Compounding psychological afflictions with opioid dependence makes maternal and fetal care unpredictable.\textsuperscript{2,4,7} Opioid dependent women can also have problems with difficult intravenous (IV) access, Hepatitis C or HIV/AIDS, other blood borne infectious diseases, social stressors and malnutrition that can increase strain on the surgical and anesthesia teams.\textsuperscript{4,7}
The Joint Consensus Statement of the American Academy of Pain Medicine, the American Pain Society, and the American Society of Addiction Medicine has defined addiction, physical dependence and tolerance. Addiction is a primary, chronic, neurobiological disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by impaired control over drug use, compulsive use, continued use despite harm, and craving.” The statement also clarifies that a behavioral component is included in addiction. Physical dependence is a state of adaptation that is manifested by withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level, and/or administration of an antagonist.” An individual may have a physical dependence but not have an addiction. “Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a decrease of one or more of the drug’s effects over time.” Tolerance will affect the analgesic response to an opioid as well as the side effects.

Medication-Assisted Treatment

The most common medication-assisted treatments for opioid addiction include either methadone or buprenorphine. Methadone is most frequently prescribed for opioid abuse and chronic pain syndromes. Methadone is the treatment of choice for maintenance therapy in opioid dependent pregnant patients. Methadone can be safely started in any trimester. Higher doses than normal may be prescribed during pregnancy because of accelerated metabolism, but doses should be reduced to pre-pregnancy doses following delivery. Methadone and buprenorphine therapy have been studied, and both were found to be safe for use during pregnancy. Methadone or buprenorphine should be continued throughout the pregnancy and into the post-delivery phase.

Buprenorphine and methadone are used during pregnancy to increase adherence to prenatal care, to prevent cravings and withdrawal symptoms, and to ultimately prevent relapse. Management doses of methadone should not be assumed to supply analgesia to the parturient during the peripartum process. There are reports which suggest that the daily dose of methadone should be omitted while the patient is in labor because giving other opioids in combination with the methadone can precipitate respiratory depression. There are multiple other reports that strongly state that methadone or buprenorphine...
treatment should not be discontinued during the peripartum period because withdrawal symptoms can be triggered which can be detrimental to the mother and fetus. It is important to maintain plasma levels of either methadone or buprenorphine because decreasing doses or co-administering an agonist-antagonist medication can cause onset of withdrawal symptoms.\(^5\) Withdrawal symptoms involve activation of the maternal sympathetic nervous system resulting in tachycardia, hypertension, sweating, tachypnea, and restlessness. Withdrawal during pregnancy is associated with higher rates of fetal morbidity and mortality.\(^3,4,7,9\)

There are reports that buprenorphine is a safer choice during pregnancy due to a lower incidence of neonatal abstinence syndrome (NAS).\(^4,7,9,10,12\) The caveat with buprenorphine is its strong affinity for the mu receptor. Buprenorphine could complicate pain control with other pure mu agonists by antagonizing the effects of previously administered opioids or blocking the effects of subsequently administered opioids.\(^9,13,14\) This is a theoretical concern and studies have found that buprenorphine does not interfere with another pure agonist.\(^15\) Nor was buprenorphine therapy found to be associated with any statistically significant difference in opioid administration when compared to methadone therapy.\(^14\)

Suboxone is a medication that has the ability to provide pain relief without introducing euphoria. Suboxone, a combination of buprenorphine and naltrexone, is an agonist/antagonist, but is not recommended during labor or postpartum because of the possibility of withdrawal.\(^3,13\) There is evidence, albeit small, that indicates naltrexone implants can be used in the pregnant heroin user without risk to mother or fetus.\(^7\) Naltrexone implants pose a significant problem for pain management due to its constant opioid antagonistic properties.

**Long Term Opioid Use**

Patients who use opioids long term can begin to experience the phenomenon referred to as opioid induced hyperalgesia.\(^7,12\) Chronic opioid use or abuse has pain altering effects. Studies have found people taking methadone are clinically less able to tolerate pain, report higher pain scores and have higher opioid requirements.\(^8\) Neuroadaptive changes including fluctuations in receptor density and signal transduction pathways can occur.\(^7\) The hyperalgesia results from activation of the N-methyl-D-aspartate (NMDA)
system and an increase in the spinal endorphin concentration. A study found that alpha 2 agonists have a preventative effect for the hyperalgesia. Also, cox inhibitors reduce the spinal release of excitatory neurotransmitters and act synergistically with NMDA receptor antagonists. The hyperalgesia is worse for those abusing opioids rather than those on a regimented methadone or buprenorphine treatment. It would not be surprising that methadone patients have higher narcotic requirements and lower pain tolerance than non-opioid dependent patients. There are also theories of the pain altering effects of nicotine which contributes to the difficulties of pain management, as many opioid dependent women are also addicted to nicotine. The pain-altering effects of opioid addiction contribute to difficulty with pain management in all aspects of the peripartum process.

Detoxification is not recommended during pregnancy. One study conducted in Pittsburg evaluated 95 pregnant women who elected inpatient opioid detoxification during pregnancy and 42 relapsed and used illicit drugs prior to delivery. If methadone discontinuation is requested or another circumstance warranted the discontinuation of methadone, studies suggest a dose reduction and eventual discontinuation is safe during pregnancy with the optimal time within the second and third trimesters. There is limited research evaluating buprenorphine detoxification during pregnancy, but there is a single case report which does not describe adverse maternal or fetal outcomes. Symptoms of opioid withdrawal can be treated with non-opioid medications such as clonidine, doxepin, and diphenhydramine.

Opioid abuse during pregnancy can have harmful maternal and fetal outcomes. There are well documented cases that demonstrate fetal harm and neonatal abstinence syndrome. Maternal complications from opioid abuse include increased risks for death, preterm labor, oligohydramnios, cerebral vascular accidents, cesarean delivery, transfusion, stillbirth, and increased hospital stays. There are grave maternal and fetal risks but the study, albeit small, did not find any significant anesthetic complications.

Labor Analgesia

Pain management in the opioid dependent woman poses a challenge during the labor process. The challenges not only include maternal and fetal safety but also hyperdynamic pain control.
combined spinal epidural (CSE) techniques are safe options for the opioid dependent parturient, provided there are no signs of hemodynamic instability, coagulopathy, or infection/sepsis. HIV positive status is not a contraindication to regional anesthesia techniques. Most experts state methadone or buprenorphine should be continued through pregnancy and throughout the intraoperative process. The epidural provides pre-emptive sensory blockade with an early application of a labor epidural. Higher doses of epidural bupivacaine may prevent the sensitization of the pro-nociceptive pain pathways in the opioid dependent peripartum patients whom are highly susceptible to opioid-induced hyperalgesia. Women found to be using explicit opioids frequently requested regional anesthesia and required more parenteral analgesia during labor.

The efficacy of epidural techniques in this highly unpredictable population has had limited study. It has been reported that a larger proportion of opioid dependent women request an epidural for labor than the general obstetric population, but there was not a statistically significant difference. An Australian study reported 20 of 70 opioid dependent women in labor reported problems with the labor epidurals. Problems consisted of inadequate labor analgesia (9 women), dural puncture, difficult epidural insertion due to movement, delivery prior to requested epidural, toothache, eye splash of body fluids from a Hepatitis C infected patient to anesthetist’s eye, and blood in epidural catheter. There were 40 epidurals placed and although none had failed, frequent analgesic supplementation was administered.

Neuraxial analgesia appears to be effective within this population, but possible adjuncts can be added with the goal of reducing the amount of analgesic supplementation needed. Adding neuraxial opioids to either a CSE or an epidural was determined not to induce hyperanalgesic response. Albeit these findings are from a rather small study of 19 women on buprenorphine therapy. The study found women who received neuraxial opioids required more rescue opioids, but there was not a statistically significant difference between the control and buprenorphine group.

Post-delivery pain management offers an additional challenge. A small retrospective study of eight women illustrates the range of presentations, unpredictable analgesic requirements and discusses the alternative pain management options for opioid dependent women. Three of the eight women had vaginal
deliveries with a CSE without issues and whose pain scales during labor were 0-7, 0-6 and 0-4 respectively. Post-delivery analgesic management consisted of oral acetaminophen, ibuprofen, oxycodone, suboxone or buprenorphine. All three women reported a range of 24-hour post-delivery pain scales including 0-7, 0-4 and 2-7.\textsuperscript{18}

Anesthesia for Cesarean Section

An anesthetic for cesarean section (CS) can be managed with spinal, CSE, epidural or general anesthesia, and all are selected based on varying patient complexities. Ideally regional anesthesia is used to provide sensory blockade and anesthetic management while avoiding the use of opioids. There is a greater need for additional analgesic interventions during regional anesthesia for CS in opioid dependent women.\textsuperscript{7,12} A multimodal approach including acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), IV or epidural/intrathecal opioids, and regional anesthesia is recommended in addition to the patient’s routine methadone regimen.\textsuperscript{7} The literature reports supplemental analgesia was most commonly nitrous and IV fentanyl, but also included ketamine and midazolam\textsuperscript{13}, diclofenac/metamizole, diazepam and tramadol/piritramide.\textsuperscript{12} Administration of neuraxial opioids in opioid dependent women may have a negative effect on their pain control. A small study of women receiving buprenorphine therapy found that those that received neuraxial opioids during labor and/or CS did have increased administration of opioids as rescue analgesics, although a statistically significant difference was not found. The authors noted the small number of subjects likely was the reason a significant difference was not found.\textsuperscript{10}

The rate of c-section in opioid dependent women has not been found to be significantly different when compared to a control group. Additional surgical procedures done during a CS might require an additional use of rescue analgesics. For instance, one study reports two cases where women had a tubal ligation during their CS under regional anesthesia. One woman had a spinal anesthetic, and one had a CSE with both reporting significant pain during the tubal ligation.\textsuperscript{13}

Pain Management Post CS

Ideally regional anesthesia in combination with patient-controlled analgesia (PCA) and possibly adjunct analgesics such as ketamine or gabapentin are analgesics used for post CS pain.\textsuperscript{18} A retrospective
study found that women maintained on buprenorphine or methadone had similar intrapartum analgesic needs, but those on methadone experienced more postpartum pain and required more analgesics post CS. This trend was supported with other findings that reported a higher, up to 74% higher, incidence of inadequate postoperative pain relief after CS. An evaluation of opioid dependent women on methadone found there was a 70% increase in opioid analgesic requirements; in women on buprenorphine there was a 47% increase in analgesic requirements following a CS.

Opioid dependent women are multifaceted and each has a unique analgesic requirement. A study which implemented multimodal pain management found that 17 of 23 opioid dependent patients who underwent a CS complained of inadequate analgesia postoperatively. The patient’s post-operative analgesia was most often provided different modalities. A morphine or fentanyl PCA, intrathecal morphine (150-200 mcg), an epidural infusion of local anesthetic plus fentanyl, or intermittent epidural meperidine (25-50 mg) every 2 hours combined with oral analgesics such as acetaminophen, acetaminophen with codeine, dextropropoxyphene, or oxycodone were medications used to provide analgesia. The most common non-opioids analgesics were acetaminophen and diclofenac administered IV or orally. In the first two days postpartum there were no differences seen with NSAID administration, but on the third day there was a higher proportion of opioid dependent women receiving NSAIDs. Although this significance dissipated when smoking status was controlled for. Administration of opioids via tramadol drops varied greatly between the two groups, as the control group women received significantly more opioids than the opioid dependent women in the immediate post-partum period.

Another study which included a multimodal pain regimen compared the analgesic requirements of women on buprenorphine or methadone. Post operatively both groups were managed with 30 mg IV ketorolac every 6 hours for 48-72 hours, and oral hydromorphone 4-6 mg every 4 hours on an as needed basis. If the patient had an epidural it was removed immediately after the CS. There were no statistically significant differences in the likelihood of receiving opioids before, during or after the CS. There was no statistically significant difference in morphine-equivalent dose requirements pre-operatively, intraoperatively or postoperatively. There was no statistically significant difference in postoperative
complications or length of stay. Women treated with buprenorphine were more likely to receive a CSE or an epidural than those treated with methadone. Women on buprenorphine treatment were statistically more likely to receive ketorolac than those on methadone.

A retrospective study of 8 pregnant women on buprenorphine requiring anesthetic management for labor and/or CS delivery was published in 2018. Five of the 8 women had a CS, each received a CSE, except one patient who requested general anesthesia. Two of the CSEs failed to provide adequate anesthesia for the CS and were converted to general anesthesia. Analgesic management post-CS included acetaminophen, ibuprofen, oxycodone, hydromorphone, continued epidural infusion, PCA, IV ketamine and continuation of the baseline buprenorphine therapy. Pain scores in the 5 women were extremely varied, the lowest score being 0 and the highest score being 9. It is important to appreciate the variability and unpredictable nature of the opioid dependent woman’s pain. Most importantly the anesthesia provider needs to have multiple analgesic techniques available and to explain all of the possible risks to the patient.

Conclusion

There has been an increase in opioid use among pregnant women, and it poses a challenge to the obstetric team, especially in terms of peripartum analgesia. It can easily be said that opioid dependent women would benefit from an antenatal plan for analgesia with the anesthesia staff. The multifactorial social and psychological complexities that are associated with the opioid dependent parturient can make care inconsistent and unpredictable.

There are techniques available that have been used successfully in opioid dependent women. Further research is needed to determine whether neuraxial opioids are beneficial. Many studies have found that pain can be unpredictable and complicated from patient to patient. Research shows administration of multimodal analgesics especially including NSAIDs are very helpful in controlling pain while avoiding the use of opioids.

Anesthesia for CSs is more complicated than vaginal delivery, but many case studies and retrospective studies found regional anesthesia with epidural or CSE was helpful for surgical anesthesia. Despite all the research and clinical findings there remains no guideline to aid peripartum pain.
management in opioid dependent women. Pain during the procedure can be unpredictable, and alternative analgesics need to be available. Research on post CS pain control offers a diverse array of analgesic alternatives. Continuing the patient’s methadone or buprenorphine treatment into the post-delivery phase helps maintain a baseline from which additional analgesics can be added. A fentanyl or hydromorphone PCA, oral opioids, and IV rescue opioids all need to be administered with caution in this population, due to the risk of respiratory depression. Oral and IV NSAIDs appear to offer a lower-risk analgesic in this circumstance. Maintaining a scheduled pain medication regimen is also beneficial for these patients.
References


