Peripartum Pain Management of Women on Medication-Assisted Therapy: A Systematic Review

Abstract

Rates of opioid prescribing are at historically high levels, and, as opioid exposure increases, the number of women of childbearing age with opioid use disorder is rising. Despite this growing population, the optimal management of pain for parturients maintained on medical-assisted therapy (MAT, i.e., methadone or buprenorphine) is unknown. This systematic review is intended to evaluate patient outcomes associated with pain management strategies for parturients on MAT. Literature databases EMBASE, MEDLINE, and the Cochrane Library were searched up to September 2017. Articles were included if they discussed peripartum analgesic options for pregnant women with opioid dependence. The search identified 1,814 articles, of which, nine matched all inclusion criteria and were selected for data extraction and analysis. Articles were a mix of case series, retrospective case reviews, retrospective cohorts, and randomized controlled trials. They showed various responses ranging from no difference in analgesic requirements between MAT and non-MAT patients to MAT patients requiring higher amounts of opioids after a cesarean section. Parturients on MAT present a number of challenges for obstetric anesthesiologists, but various approaches can be used to achieve satisfactory analgesia. It is important to practice an individualized yet multidisciplinary approach to ensure the delivery of optimal patient care.

Keywords: Buprenorphine, methadone, pain management, peripartum, suboxone, subutex

Introduction

Opioid use disorder is characterized by tolerance, craving, inability to control use, and continued use despite adverse reaction. It is a chronic, debilitating, but treatable condition that can be managed successfully with a combination of medical-assisted therapy (MAT), such as methadone or buprenorphine, and substantial behavioral therapy and recovery support.[1] The number of opioid prescriptions has increased in recent years. In the United States (U.S.), health care providers wrote more than 259 million opioid prescriptions in 2012, twice the number in 1998.[2] Consequently, the rate of admissions for substance use disorder treatment was more than quadrupled between 2002 and 2012,[3] and the rate of opioid-related deaths rose approximately 400% between 2000 and 2014.[4] Heroin use in particular saw a sharp increase during this period, as overdose deaths involving heroin rose more than 300% between 2010 and 2014.[5]

Opioid use during pregnancy also has escalated dramatically in recent years, mirroring the epidemic observed in the general population. Opioids have no known direct teratogenic effects, but they are associated with multiple obstetric and neonatal complications, including intrauterine growth restriction, intrauterine fetal demise, preterm labor, placental abruption, postpartum hemorrhage, and neonatal abstinence syndrome (NAS). One study showed that antepartum maternal opioid use increased five-fold from 2000 to 2009,[6] and several states have determined that substance use is a major risk factor for pregnancy-associated deaths. This trend was also associated with a dramatic increase in NAS, from 1.5 cases per 1,000 hospital births in 1999 to 6.0 per 1,000 hospital births in 2013.[7] NAS also carries a heavy financial burden for hospitals, as the rise in number cost $316 million in the U.S. during 2012.[8]

The goals of MAT during pregnancy are to prevent illicit opioid use and promote adherence to prenatal care. Historically, methadone dispensed from a licensed

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opioid treatment program was considered the gold standard for parturients on MAT, precipitated by case reports of intrauterine fetal death associated with rapid maternal withdrawal.[9,10] However, buprenorphine has become increasingly appealing because of its availability in office-based settings,[11] and studies have shown reduced rates of NAS with buprenorphine as compared to those with methadone.[12,13]

Despite the increased rate of substance abuse in parturients, the optimal management of pain control in this population remains unknown. Few studies have focused on pain management for parturients on MAT. The purpose of this systematic review was to assess patient outcomes and recommended strategies for parturients with a history of substance abuse who are maintained on MAT.

Methods
This quantitative systematic review followed standard methodological guidelines. Searches on Cochrane, PubMed, and EMBASE databases were performed without publication date or language restriction in August 2017. Search limitations included case series, retrospective reviews, retrospective cohort studies, and randomized controlled trials (RCTs). Figure 1 and Supplementary Table 1 illustrate further details of the search strategy, including specific search items. Two reviewers independently applied the inclusion and exclusion criteria, and any differences were resolved through discussion. Included studies were assigned a level of evidence according to the National Health and Medical Research Council Hierarchy of Evidence[14] and were critically appraised for study quality according to the guidelines in the Cochrane Reviewer’s Handbook.[15]

Results
The query yielded 1,814 records in total from all three databases, including five systematic reviews from the Cochrane database. After the elimination of duplicates and non-relevant papers on the basis of the title and abstract, 181 articles received further detailed review. Of those, 16 articles were selected for data extraction. Nine were systematic reviews, case series, observational studies, and RCTs, and seven were review articles. The collected literature focused on pain management of postpartum women on opioid maintenance therapy. We searched the relevant literature for patients’ post-delivery pain scores, if any, amounts of opioid used in morphine milligram equivalents, and any non-opioid medication used. We also looked for any mention of adverse events (expected and unexpected), patient satisfaction, length of stay, and any adverse fetal outcomes. A brief summary of our findings can be found in Table 1.

Discussion
Randomized controlled trials
Two RCTs met our inclusion criteria. Silver et al.[16] compared drug-dependent women (DDW) with a control group matched for delivery date, socioeconomic status, and gravidity/parity to assess for labor complications, analgesia and anesthesia complications, and postpartum complications. The study, which was conducted from 1982 to 1984, included 112 DDW and 224 control women. Of the 112 DDW, 72% were on daily methadone maintenance. Overall, DDW had a higher incidence of medical and obstetrical complications, including higher rates of premature delivery (<37 weeks gestation), abruption placentae, hypertensive disorders, infections (thrombophlebitis, cellulitis, abscesses), history of hepatitis, breech presentation, preeclampsia, and chorioamnionitis.

Interestingly, the two groups did not differ in terms of labor length for vaginal deliveries. Equal numbers of patients in each group received systemic analgesia, but a higher percentage of patients in the DDW group received regional anesthesia with epidural or pudendal blocks. Systemic analgesia included meperidine, morphine, and butorphanol (used only in the control group). However, dosages were not reported. Therefore, we have no way of knowing how much of each drug was administered and to which groups. The authors concluded that DDW may have a greater need for pain relief during labor and delivery to avoid fetal distress but offered no suggestion of how that can be achieved.

The second RCT, by Hoflich et al.[17] compared the differences in pain management between opioid-maintained parturients and nondependent women during delivery and the postpartum period. The authors compared 40 deliveries of 37 opioid-dependent women (ODW) to a matched group of 80 nondependent women. Patients and the treatment
team were blindered to the type of opioid agonist on which the women were maintained. For vaginal deliveries, analgesia was delivered via epidural catheter with bolus and infusion as well as epidural fentanyl and possibly nalbuphine and intravenous infusions of nonsteroidal anti-inflammatory drugs (NSAIDs). For cesarean deliveries, analgesia was delivered via single shot spinal injection with or without fentanyl, intravenous NSAIDS (diclofenac, metamizol), benzodiazepines (diazepam), and opioid analgesics (tramadol, piritramid). ODW required peridural anesthesia more frequently for vaginal deliveries, reported a higher incidence of inadequate analgesia, and required a higher dosage or frequency of pain medications during labor. However, post-delivery, the two groups had similar pain management requirements. After cesarean delivery, opioid-maintained patients received fewer opioid analgesics and more NSAIDs than did the comparison group. Unlike many other studies, this study did not use the visual analogue scale to objectify pain ratings; rather, the authors depended on each patient’s judgement of whether more pain medication was needed. There were no differences in pain management or drug dosage between the two groups during the first three days after vaginal deliveries. However, among women who underwent cesarean deliveries, diclofenac use was significantly higher in the ODW group. The differences in analgesic requirements between ODW and the control group in this study were likely due to the lack of an interdisciplinary consensus on pain management protocols for ODW.

**Observational study**

In an observational study, Jones et al.\(^{[18]}\) examined acute postpartum pain management in patients maintained on methadone or buprenorphine during pregnancy. Of the 18 patients included, 8 were maintained on buprenorphine, 10 were maintained on methadone, and all had vaginal deliveries. The authors hypothesized that methadone-maintained patients would require greater doses of non-opioid medications than buprenorphine-maintained patients to achieve adequate pain control. Pain scores were collected every 4-6 hours for the first five days. Patients were ordered the following medications as needed: acetaminophen 500 mg/oxycodone 5 mg combo (AOxy) every 4-6 hours for moderate to severe pain and ibuprofen 400-600 mg every 4-6 hours for mild to moderate pain. The authors reported the administration of AOxy as a binary variable (yes or no) to indicate whether the patient received the drug because the range of doses was restricted

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**Table 1: Characteristics of included studies**

| Author (year) | Study design | Patient population | Treatment group | Control group | Outcome measure | Results |
|---------------|--------------|-------------------|-----------------|---------------|----------------|---------|
| Cassidy and Cyna (2004) | Retrospective case review | 83 patients taking opioids regularly during pregnancy | - | - | Identify overall anesthetic challenges | - |
| Gupta et al. (2013) | Retrospective cohort | 19 patients on BMT during pregnancy | Received neuraxial anesthesia | Did not receive neuraxial anesthesia | Daily amounts of peripartum rescue analgesics | - |
| Meyer et al. (2007) | Retrospective cohort | 136 patients admitted for labor | On MMT | Not on MMT, matched to MMT group | Postpartum opioid requirements | MMT patients had similar opioid needs after labor, but 70% higher after CS |
| Meyer et al. (2010) | Retrospective cohort | 126 patients admitted for labor | On BMT | Not on BMT, matched to BMT group | Postpartum opioid requirements | BMT patients had similar opioid needs after labor, but 47% higher after CS |
| Vilkins et al. (2017) | Retrospective cohort | 273 patients on MAT during pregnancy | On MMT | On BMT | Post-CS opioid requirements | No difference in opioid requirements between two groups |
| Hoffich et al. (2012) | RCT DB | 117 patients admitted for labor | On MAT | Not on MAT, matched to MAT group | Opioid requirements during delivery and postpartum period | Vaginal: no difference in opioid requirements; CS: control group required higher opioids during postpartum period |
| Silver et al. (1987) | RCT DB | 336 patients admitted for labor | DD | Not DD | Patterns of labor & analgesic requirements | DD group had premature delivery, placental abruption, gHTN, PEC, cellulitis abscesses |
| Jones et al. (2006) | Case series | 2 patients on MAT | - | - | Effectiveness of routine postpartum pain regimen | Routine postpartum pain regimen is effective in MAT patients |
| Jones et al. (2009) | Observational cohort | 18 patients on MAT | - | - | Adequacy of pain control with standard opioid regimen | Adequate pain control was achieved in MAT patients with standard protocol |

**Abbreviations:** BMT, Buprenorphine-maintenance therapy; CS, Cesarean section; DB, Double blind; DD, Drug dependent; gHTN, Gestational hypertension; MAT, Medical-assisted therapy; MMT, Methadone-maintenance therapy; PEC, Preeclampsia; RCT, Randomized control trial
by the limited number of doses that could be provided in a 24-hour period. Overall, the authors reported a decrease in pain scores and number of opioid medication doses over time in both groups. However, ibuprofen use decreased in the buprenorphine group over time but increased in the methadone group. With opioid use and pain scores decreasing over time, it is recommended that opioid analgesics be used routinely to treat acute pain in agonist-treated postpartum patients. In addition, routine pain management protocols were effective at reducing pain in this patient population. Although Jones et al.\(^\text{[18]}\) showed that routine opioid and non-opioid treatments are helpful for reducing pain scores, their small sample size limited the power of the study. Thus, prospective studies with larger sample sizes are needed to solidify this recommendation.

**Case series**

Along the same lines, Jones et al.\(^\text{[19]}\) also published a case series study in which they examined post-cesarean pain management for patients maintained on methadone or buprenorphine. This study included two patients, one on methadone and the other on buprenorphine for maintenance therapy. Both patients received epidural anesthesia for surgery and intravenous patient-controlled analgesia with morphine for postpartum analgesia along with oral opioids and NSAIDs. Given the small sample size, it is difficult to analyze a good analgesic starting point for patients on opioid maintenance therapy. It has been suggested that ODW require higher than typical doses for pain management;\(^\text{[20]}\) however, as shown by Hoflich et al.\(^\text{[17]}\), these patients do not always require opioids for appropriate analgesia.

**Retrospective case review**

Our search identified one retrospective case review and four retrospective cohort studies that met our criteria. Cassidy and Cyna\(^\text{[21]}\) reported on a cohort of 224 patients with substance abuse history, of whom 83 were opioid-dependent. The two-year study showed that 79% of opioid-consuming patients required anesthetic service, with 49% requesting labor epidural and 26% requiring pain consultation in addition to the usual analgesic regimen. These numbers were all higher than those in the control group. Twenty-three opioid-dependent patients underwent cesarean delivery, of whom 75% experienced inadequate postoperative analgesia and required higher doses of analgesic medication than non-dependent patients. The study was limited by the high number of patients using other illicit substances, which could be a confounding variable, but it highlights the challenges of managing opioid-dependent patients as they will likely have greater analgesic requirements during the perioperative period.

Different outcomes were reported by Meyer et al.\(^\text{[22,23]}\) in their two retrospective cohort studies. The first study compared 68 patients enrolled in a methadone-maintenance program to a control group during a seven-year period.\(^\text{[23]}\) The authors reported no differences between the two cohorts in admission pain score, intrapartum pain perception, rate of neuraxial analgesia request, efficacy of neuraxial anesthesia, additional intervention requirement after neuraxial analgesia, or time from admission to delivery. Methadone-maintained patients who delivered vaginally did report higher pain scores than did those in the control group, but there was no difference in frequency or amount of analgesia administered. Moreover, those who underwent cesarean delivery consumed 70% more opioid in the postoperative period than did the control group, although most of this requirement was during the first few hours.

Meyer et al.\(^\text{[23]}\) reported similar results in another study that compared 63 patients enrolled in a buprenorphine-maintenance program to patients in a control group during a five-year period. The study design was nearly identical to that of the previous study.\(^\text{[22]}\) Similarly, the authors reported no differences between the two cohorts in admission pain score, intrapartum pain perception, neuraxial request and efficacy, or additional analgesic intervention. Buprenorphine-maintained patients who delivered vaginally reported higher pain scores than did those in the control group, but no difference in frequency or amount of analgesia administered was reported. Buprenorphine-maintained patients who underwent cesarean delivery did report higher postoperative pain scores than their control counterparts and required up to 47% more opioid medication, mostly during the first 24 hours. The main limitation in both studies by Meyer et al.\(^\text{[22,23]}\) is that providers were fully aware of patients who were on opioid maintenance therapy. This knowledge could have influenced the amount of analgesics administered. Overall, these two studies allowed comparison of pain management between patients on methadone and those on buprenorphine by using similar designs and analyses. Contradicting Cassidy and Cyna’s findings, these studies showed that opioid-maintained patients, regardless of drug choice, have analgesic needs and responses during labor that are identical to those of non-dependent patients, but will likely require more analgesia immediately after cesarean delivery.

Vilkins et al.\(^\text{[24]}\) conducted a nine-year retrospective cohort study to compare analgesic requirement during cesarean delivery in 273 patients who participated in either methadone or buprenorphine maintenance programs. They found no difference between the two cohorts in the likelihood of receiving opioids or in the total amount of opioids received before, during, or after cesarean delivery. However, the buprenorphine group was 2.7 times more likely to receive neuraxial anesthesia and required significantly higher doses of ketorolac during hospitalization than did women treated with methadone. This study did not include a control group, and it was unclear how the
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decision to start methadone or buprenorphine was reached. Such uncertainty could provide additional confounding variables. Nevertheless, the study does provide insight on whether pain management should be approached in a different manner depending on the maintenance treatment of choice.

Gupta et al. performed a five-year retrospective cohort study in which they compared adequacy of peripartum pain management with and without neuraxial opioid in 19 patients on buprenorphine maintenance therapy. They found that those who received neuraxial opioid required more rescue analgesia than did those who did not receive it. Those who underwent emergent cesarean delivery after failed labor with neuraxial opioid required higher peripartum rescue analgesics than did those who underwent vaginal or elective cesarean delivery who also received neuraxial opioid. This study highlights the unexpected finding of neuraxial opioid-related hyperalgesia in this patient population. However, it focused on laboring patients who received only neuraxial anesthesia and was very underpowered with 19 patients.

It should be noted that major limitations shared by all the retrospective studies include the nature of the data collection. Evidence will benefit from randomized prospective trials in the future. The pain scores reported in all of these studies are also subjective by nature and reported by patients in numerical terms. Although the policy is to describe the numerical score to all patients in the same manner, the retrospective design does not allow for the assessment of this interaction, which could have affected the results.

Conclusion

Parturients on MAT present numerous challenges for obstetric anesthesiologists, including hyperalgesia, increased analgesic requirements, difficult intravenous access, and possible exposure to blood-borne pathogens. Our systematic review showed that this patient population can have various responses to analgesia medications and that individualization is necessary to provide safe and effective care. When caring for this patient population, it is vital to practice a multidisciplinary care model that includes social services, community health nursing, substance abuse counseling, and physicians experienced in the field of opioid use disorder.

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Conflicts of interest

There are no conflicts of interest.

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