

Peripartum and Postpartum Analgesia and Pain in Women Prescribed Buprenorphine for Opioid Use Disorder Who Deliver by Cesarean Section

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ABSTRACT

AIM: Little is known about whether pain can be effectively managed in pregnant women with opioid use disorder (OUD) during delivery hospitalization, particularly those undergoing surgery and taking buprenorphine as medication for OUD (MOUD). To address this question, we compared pain scores and opioid analgesic utilization during delivery hospitalization in women taking their pre-hospital dose of buprenorphine who delivered by cesarean section to matched controls. To inform future research efforts, we also began to explore opioid analgesic utilization and pain scores by type of anesthesia as this variable is often not included in related literature.

METHODS: Retrospective matched cohort study of 46 women prescribed buprenorphine during pregnancy who delivered by cesarean section during a 7-year period.

RESULTS: When compared to matched controls, women taking their pre-hospital dose of buprenorphine undergoing cesarean section utilized more opioid analgesics as measured by morphine milligram equivalents (MME) (mean MME first 48 hours 153.0 mg vs 175.1 mg, respectively, $P < .01$) but had similar pain scores during delivery hospitalization. There was no difference in MME utilization by maternal dose of buprenorphine though sample sizes were small. Women on buprenorphine who received spinal anesthesia with morphine had mean pain scores that were 1.4 points lower ($P = .01$) during the first 48 hours than women on buprenorphine receiving other methods of anesthesia.

DISCUSSION AND CONCLUSIONS: Pregnant women taking their pre-hospital dose of buprenorphine throughout their surgical delivery hospitalization were able to achieve pain relief similar to women not on MOUD but had higher MME requirements. Our results add to the emerging body of evidence suggesting that individuals on MOUD can achieve adequate post-surgical pain management without adjusting their pre-hospital dose of buprenorphine. Further research is required to fully understand the optimal buprenorphine dosing regimen during surgical hospitalizations. Our results also provide important preliminary evidence that spinal anesthesia containing opioids can be used effectively in individuals with OUD requiring surgical intervention.

KEYWORDS: Analgesia, buprenorphine, opioid use disorder, postpartum, pregnancy, cesarean

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Introduction

From 1999 to 2014, the US national prevalence of opioid use disorder (OUD) increased from 1.5 to 6.5 cases per 1000 delivery hospitalizations, an average annual increase of 0.4 per 1000 delivery hospitalizations per year ($P < .05$).¹ Treatment during pregnancy with buprenorphine, a partial agonist with a high affinity to the mu opioid receptor, increased from 15.8% of pregnant women with OUD in 2009 to 30.9% in 2015 whereas methadone utilization declined.² Despite the increased prevalence of women with OUD on buprenorphine during pregnancy, there is little evidence to guide peripartum and postpartum management of pain in this population. Pregnant women with OUD are typically excluded from prospective studies.

Recommendations as to whether patients should be continued on buprenorphine during surgical hospitalizations have evolved over time. Until recently, experts recommended stopping buprenorphine prior to surgical procedures and transitioning patients to full agonist opioids, such as methadone or morphine.^{3,4} Experts sometimes recommended a risk stratification approach to stopping or continuing buprenorphine based upon surgical characteristics (eg, elective vs emergent, expected postoperative opioid requirement).⁴ Stopping buprenorphine was associated with a myriad of challenges including precipitated withdrawal and the risk of drug overdose if buprenorphine was not re-initiated prior to discharge and/or when patients no longer required pain control.⁵



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More recent evidence suggests that full agonist opioids can be used to treat postsurgical pain in patients maintained on buprenorphine throughout hospitalization. However, some specialists have suggested reducing the daily dose of buprenorphine prior to surgery⁶ whereas 2 systematic reviews suggested that buprenorphine could be continued perioperatively at doses ≤ 16 mg daily.^{7,8} A recent multidisciplinary workgroup suggested that there was a moderate level of evidence that patients on buprenorphine should be continued at their home dose during the preoperative period and that multimodal analgesia including short-acting full agonist opioids could be used during the postoperative phase.⁹

Within the pregnant population, Meyer et al compared postpartum pain control and opioid utilization following vaginal and cesarean deliveries and found no differences in intrapartum pain or analgesic utilization between patients prescribed buprenorphine and their matched controls that were not on medications for OUD (MOUD).¹⁰ However, those undergoing cesarean section deliveries (19 women) experienced more postpartum pain and required 47% more opioid analgesics than their matched controls.¹⁰ Reno et al found that maternal dose of buprenorphine was not correlated to maximum daily pain scores or opioid consumption in the first 24 hours following cesarean section.¹¹

While there is some preliminary evidence about postsurgical analgesia utilization in women with OUD, anesthetic details are not typically reported. There is ongoing debate as to whether neuraxial opioids (such as fentanyl or morphine) should be utilized as some believe that buprenorphine's high affinity for the mu opioid receptor limits receptor availability, precluding any analgesic effect.¹² Others believe that neuraxial opioids (sometimes at doses higher than those of opioid naïve subjects) should be utilized as pregnant women with OUD require enhanced analgesia.¹²

The objective of this study is to compare pain scores and opioid analgesic utilization during the peri- and postpartum period in women taking their pre-hospital dose of buprenorphine who delivered by cesarean section to matched controls to determine whether pain can be effectively managed in this population. Second, we began to explore whether the method of anesthesia was associated with analgesic utilization and pain scores to inform future research efforts.

Methods

We conducted a retrospective cohort study of all pregnant women with OUD treated with buprenorphine at a rural family medicine residency program who underwent a cesarean section from 2011 to 2017. The MaineGeneral Medical Center IRB approved the study. We collected maternal age at delivery, smoking status, gestational age at delivery, infant birth weight, indication for cesarean section (scheduled vs urgent/emergent), length of hospital stay, primary insurance and daily buprenorphine dose at delivery. We selected a control group at random

and matched for maternal age (within 5 years), primary insurance, and indication for cesarean section. Only singleton gestation pregnancies were included.

We adjusted for smoking status as, when compared to non-smokers, patients who smoke tend to report higher levels of postsurgical pain¹³ and this variable appears to have a particularly strong influence among women with OUD.¹⁴ Women with chronic pain diagnoses as well as those who were prescribed opioid analgesics during the third trimester were excluded from the study. Women were excluded from the control group if chart documentation revealed a high index of suspicion for untreated OUD. We considered that maternal psychiatric co-morbidities and history of trauma may impact pain scores, but these are not consistent findings among postpartum women with OUD¹⁵ and are not reliably recorded in the medical record therefore were not part of our inclusion or exclusion criteria.

Data regarding type of anesthesia, opioid and non-opioid analgesic utilization and pain scores at rest were collected throughout delivery hospitalization. Opioid utilization during hospitalization was recorded from the medication and anesthesia records. Per routine nursing protocol, a numeric pain score of 0 to 10 was used to measure pain (with 10 being the worst pain). During the perioperative and postoperative phase, a variety of analgesic options were utilized including fentanyl 25 to 100 mcg IV for rescue, hydromorphone 0.2 to 0.5 mg IV for rescue or 2 to 4 mg by mouth every 4 hours (if not on the intravenous formulation), morphine 2 to 5 mg for rescue, oxycodone 5 to 10 mg by mouth every 4 hours, acetaminophen up to 1000 mg IV loading dose or up to 650 mg by mouth every 4 hours (if not on the intravenous formulation), ibuprofen 30 to 60 mg IV and up to 600 mg by mouth every 6 hours (if not on the intravenous formulation). All opioid analgesics were converted to morphine milligram equivalents (MME) using a ratio of 1 mg PO morphine = 0.333 mg IV morphine = 0.091 mg IV hydromorphone = 0.01 mcg (0.00001 mg) IV fentanyl = 1.5 mg PO oxycodone.¹⁶ Intravenous ibuprofen was converted to oral ibuprofen equivalent using 60 mg IV = 800 mg PO.

All women on buprenorphine were continued on their prenatal dose throughout delivery hospitalization. Buprenorphine was not included in daily MME total.^{6,10} Maternal daily dose of buprenorphine was categorized as low (≤ 10 mg), medium (11–15 mg) or high (≥ 16 mg).

Types of anesthesia included epidurals, spinal anesthesia with and without morphine, and general anesthesia. Epidurals were, at times, placed for labor analgesia in anticipation of vaginal delivery. If the decision was made to proceed with a cesarean section and timing allowed, the anesthesia team would determine whether the epidural was functioning well and, if so, a bolus of 2% lidocaine was used. If the epidural was not functioning well, it was removed, and a spinal was utilized using 0.75% bupivacaine with dextrose. If a labor epidural was not placed prior to the decision to proceed with a cesarean section, then a spinal would be the first choice of primary anesthetic.

Table 1. Characteristics of Women on Buprenorphine versus Controls.

	BUPRENORPHINE N = 46	CONTROL N = 46	P-VALUE
Continuous variables	Mean (std dev)	Mean (std dev)	
Maternal age at birth (years)	27.9 (3.85)	27.2 (4.35)	.409
Maternal buprenorphine dose (mg)	14.6 (5.93)	–	n/a
Maternal length of stay (days)	3.67 (1.21)	3.35 (0.674)	.115
Birthweight (g)	3094.7 (642.5)	3279.2 (506.3)	.130
Gestational age (weeks)	38.7 (1.71)	39.1 (0.954)	.167
Categorical variables	No. (%)	No. (%)	
Anesthesia type			.072
Spinal without opioids	27 (58.7)	23 (50.0)	
Spinal with morphine	9 (19.6)	4 (8.7)	
Epidural	4 (8.7)	13 (28.3)	
General	6 (13.0)	6 (13.0)	
TAPP block	9 (19.6)	7 (15.2)	.582
PCA	3 (6.52)	3 (6.52)	1.00

If the cesarean section was a true emergency, general anesthesia was used. Variables in choice of anesthesia for the cesarean section that could affect pain include epidural with only local anesthetic, spinals with only local anesthetic, spinal with local anesthetic mixed with an opioid, or general anesthesia. In all cases, intravenous opioids may have been used and were recorded appropriately. On occasion, a transverse abdominis plane block (TAP block), a regional technique for postoperative pain control, was used.

Due to the longitudinal nature of the variables, mixed-effects models were used. Initial models included fixed effects for exposure status, time, indicator variables for anesthesia type, and time-by-exposure and time-by-anesthesia-type interactions. Random intercepts and slopes were found to be necessary. Secondary models in women on buprenorphine examined similar fixed effects and included buprenorphine dose and the dose-by-time interaction. All model parameters were estimated via maximum likelihood estimation, and all achieved stable estimates.

Results

As illustrated in Table 1, 46 women prescribed buprenorphine delivered by cesarean section. Nearly 85% of these women smoked during pregnancy and all but one had Medicaid as their primary insurance. Half of the women (50%) had an urgent/emergent cesarean section. There were no differences in maternal age, length of stay, gestational age or birthweight between the buprenorphine and control groups. There were also no significant differences in type of anesthesia utilized

though the sample sizes were small. The mean daily dose of buprenorphine at delivery was 14.6 mg (range 4–32 mg).

Results from mixed-effects models with random intercepts and slopes showed that pain scores during the delivery hospitalization did not differ when comparing women on buprenorphine versus matched controls ($P = .47$). Mean pain score in the time interval 12 to 24 hours following cesarean section was 5.03 (SD = 1.54) among women on buprenorphine and 4.53 (SD = 1.90) among controls. Mean pain score in the interval 36 to 48 hours post-cesarean section was virtually the same (4.397 [SD = 2.009] among exposed women on buprenorphine and 4.401 [SD = 2.010] among controls).

As illustrated in Figure 1, women prescribed buprenorphine had higher MME utilization over the course of the delivery hospitalization when compared to controls (mean MME first 48 hours 175.1 mg vs 153.0 mg, respectively, $P < .01$). While women on buprenorphine started with lower MME requirements than matched controls, this changed early in the postpartum period and women on buprenorphine maintained higher MME requirements throughout the remainder of the hospitalization. While the sample sizes were small, there was no significant difference in MME utilization by maternal dose of buprenorphine (MME for those on low dose of ≤ 10 mg buprenorphine daily of 195.0 mg [n = 12], medium dose of 11 to 15 mg buprenorphine daily of 178.6 mg [n = 12], and high dose of ≥ 16 mg of buprenorphine daily of 163.1 mg [n = 22]).

While the objective was to analyze utilization of opioid analgesics, we gathered all analgesic information and found that both ibuprofen and acetaminophen utilization were lower

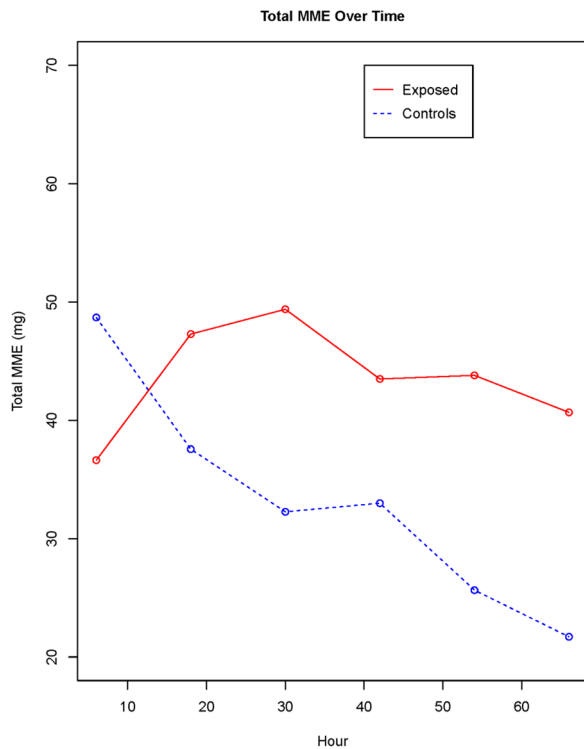


Figure 1. Plots total mean morphine milligram equivalents (MME) in milligrams over time for exposed women, or those on buprenorphine, versus controls, or women not on buprenorphine during pregnancy.

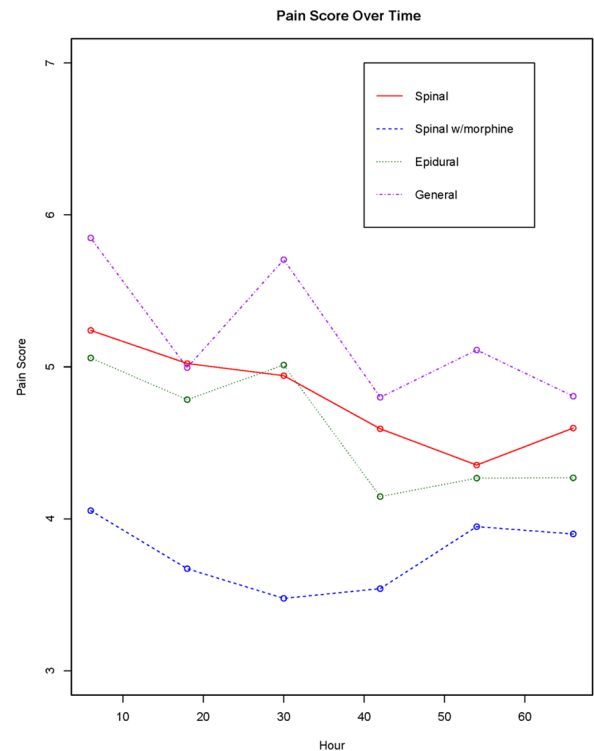


Figure 2. Highlights mean pain scores over time (in hours) by each anesthesia type (spinal, spinal with morphine, general, and epidural) for women on buprenorphine.

among women on buprenorphine when compared to the control group (mean ibuprofen first 48 hours 2906.7 mg vs 3466.3 mg, respectively, $P < .01$; mean acetaminophen first 48 hours 2319.4 mg vs 5140.2 mg, respectively, $P = .01$).

Within the population of women on buprenorphine, we compared anesthesia options and determined that there were no differences in opioid utilization by type of anesthesia. However, we found that women on buprenorphine who received spinal anesthesia with morphine reported pain scores that were, on average, 1.4 points lower ($P = .01$) than women on buprenorphine who received other types of anesthesia, resulting in a parallel but significantly lower pain trajectory (Figure 2). We then analyzed only women receiving spinal anesthesia with morphine and found that the mean pain scores over time for those on buprenorphine were equal to controls. This suggests that the analgesic effect of neuraxial opioids may not be inhibited by buprenorphine though this warrants further study as sample sizes were small. To assess the role that this finding may have had on our results regarding MME utilization, we analyzed women receiving all types of anesthesia except spinal with morphine and found that the MME gap in the first 48 hours post-surgery widened for those on buprenorphine relative to controls (192.2 mg vs 155.6 mg, $P = .12$).

Discussion

Pregnant women taking their pre-hospital dose of buprenorphine throughout their delivery hospitalization following

cesarean section were able to achieve pain relief similar to women not on MOUD but had higher MME requirements. Overall, pain scores were lower than might be expected among patients with OUD undergoing major surgery and compared favorably to mean pain scores of women on buprenorphine and delivering by cesarean in previous studies (mean pain score of 5.5 in first 24 hours and 4.7 in hours 25-72).¹⁰ Our results add to the emerging body of evidence suggesting that individuals on MOUD can achieve adequate post-surgical pain management without adjusting their pre-hospital dose of buprenorphine. Further research is required to fully understand the optimal buprenorphine dosing regimen during surgical hospitalizations.

Women on buprenorphine in our study utilized 14.4% more MME analgesia (175.1 mg vs 153.0 mg, $P < .01$) than controls whereas previous authors found that women on buprenorphine and requiring cesarean section utilized 47% to 76% more MME than their opioid naïve controls.^{10,17} Importantly, the women on buprenorphine in these studies also reported significantly more pain than controls.^{10,17} The higher MME requirements for women with OUD are likely the result of opioid tolerance and hyperalgesia, an increased sensitivity to painful stimuli, both of which can result from chronic opioid exposure, as well as buprenorphine's high affinity and slow dissociation from the mu opioid receptor which potentially limits the number of receptors available to bind with opioid analgesics.¹⁸

We found no significant difference in MME utilization by maternal dose of buprenorphine, which supports the findings of previous authors.¹¹ While not significant, the downward trend in MME utilization as maternal dose of buprenorphine increased suggests that the buprenorphine might provide some analgesic benefit. If this downward trend were found to be significant in a larger study, it would conflict with prior expert opinion that those on higher doses of buprenorphine will likely require more post-surgical opioids as more receptors are occupied by the partial agonist buprenorphine rather than full agonist opioid analgesics. Whether it would be beneficial to alter the buprenorphine regimen prior to surgery requires further research.

While there were no differences in MME utilization by anesthesia type among women on buprenorphine, pain scores were lower among those receiving spinals with morphine, suggesting that it may be a promising approach for managing surgical pain in women with OUD. Case reports have demonstrated the effectiveness of neuraxial analgesia (in addition to IV and PO analgesics) in managing post-operative pain in 1 woman undergoing cesarean section¹⁹ and in 3 male patients with OUD and on buprenorphine undergoing major surgeries.²⁰ However, authors of a study of 19 women on buprenorphine for OUD delivering by elective cesarean section found that women receiving neuraxial opioids required more parenteral opioids than those that did not receive neuraxial analgesia (16.4 mg (SD = 21.1) vs 5.3 mg (SD = 3.6), $P = .42$).²¹ However, the small sample size and large variance from the mean make it difficult to draw conclusions and further supports the need for additional research.

The difference in the utilization of non-opioid analgesics was an unexpected finding. Analysis of the markedly higher acetaminophen utilization among controls showed that they were transitioned to oral opioid/acetaminophen combinations (rather than intravenous opioids) earlier. A regimen of scheduled acetaminophen post cesarean should be considered in women with OUD as it has been associated with decreased opioid use.²² Similar to the acetaminophen findings, it appears that women in the control group were transitioned to oral rather than intravenous ibuprofen more quickly than women on buprenorphine. Previous literature indicates that the plasma ibuprofen level using the intravenous formulation is twice that of oral ibuprofen and is associated with decreased pain and opioid use.²³

Unfortunately, we were not able to determine the reason women in the control group utilized more non-opioid analgesia and were transitioned to oral formulations earlier. It is possible that nursing preferentially selected opioids (from a range of pain treatment options) for women on buprenorphine due to concern that pain would not be adequately managed in this population or that women not on buprenorphine preferentially selected non-opioid pain relief due to fear of developing a use disorder after taking opioids. It is also possible that women in the control group were more eager to transition to oral analgesics, a necessary step prior to discharge, as women with OUD

often remain (at least as a boarder) at the hospital while their infant completes the required 5-day minimum hospital stay so that they can be monitored for withdrawal.

Our study has several strengths. The sample size is larger than most previous work, we utilized matched controls and included women who had both routine and emergent cesarean sections. Our study also involved only one type of surgery, which allowed for a more robust analysis than previous studies that included multiple different types of surgeries, which may or may not be associated with similar levels of postsurgical pain. Finally, in contrast to previous authors, we also analyzed anesthetic options and were able to begin to evaluate the outcomes of different types of anesthesia in women with OUD undergoing surgery.

Several limitations should be noted. Conclusions drawn from retrospective studies are inherently limited. Buprenorphine dosing was not observed prior to hospitalization, limiting our ability to confirm that women were taking their prescribed daily dose. However, urine toxicology testing was completed at least twice per month prenatally in the exposed group and all were positive for buprenorphine. There was a large standard deviation in MME utilization in women on buprenorphine, suggesting significant heterogeneity and the need for larger, prospective studies.

The perioperative phase is an especially vulnerable period for pregnant women with OUD. Many women have concerns about receiving adequate pain relief or experiencing unexpected opioid withdrawal and worry that these issues might contribute to a return to illicit opioid use. Our results indicate that pregnant women taking their pre-hospital dose of buprenorphine throughout their surgical delivery hospitalization were able to achieve similar pain relief to women not on MOUD, though women on OUD had higher MME requirements. Our findings add to the emerging body of evidence suggesting that individuals on MOUD can achieve adequate post-surgical pain management without adjusting their pre-hospital dose of buprenorphine, thereby avoiding several potential risks and pitfalls associated with stopping buprenorphine. Further research is needed to fully understand the optimal buprenorphine dosing regimen during surgical hospitalizations and whether there are benefits or risks associated with reducing the pre-hospital dose.


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Author Contributions

ABO and JS designed and directed the project. All authors contributed in the development of the theoretical framework. JS, KL, and NB collected data. LMO performed the statistical analyses. All authors analyzed results. ABO was the primary author of the manuscript.

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