Buprenorphine for Medication-Assisted Treatment of Opioid Use Disorder in Pregnancy: Relationship to Neonatal Opioid Withdrawal Syndrome

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Abstract

Objective To examine the relationship between antepartum buprenorphine dose for medication-assisted treatment (MAT) of opioid use disorder (OUD) and incident neonatal opioid withdrawal syndrome (NOWS).

Study Design We performed a prospective cohort study of pregnant women with a singleton gestation diagnosed with OUD and receiving buprenorphine for MAT at a tertiary care academic institution from July 2015 to January 2017. We divided the study cohort into two groups—pregnancies with versus without NOWS. Substance abuse patterns in pregnancy, maternal, and neonatal clinical outcomes were compared.

Results The incidence of NOWS was 31.11% ($n = 28/90$) in our study cohort. Pregnancies with NOWS had a significantly higher rate of benzodiazepine positive urine tests and number of positive urine drug screen (UDS) results for illicit opioids. The group without NOWS had significantly higher number of patients with an appropriate UDS result at delivery through postpartum. Rates of neonatal intensive care unit (NICU) admission, length of NICU stay, and maximum Finnegan score were significantly higher in the group with NOWS. Neither the initial (10.6 ± 5.2 versus 10.3 ± 4.8 mg, $p = 0.80$) nor the final buprenorphine doses (13.3 ± 5.1 versus 13.0 ± 4.6 mg, $p = 0.81$) were significantly different between study groups.

Conclusion The occurrence of NOWS was not related to buprenorphine dose used for MAT.

Keywords
- buprenorphine
- opioid use disorder (OUD)
- medication assisted treatment (MAT)
- neonatal opioid withdrawal syndrome (NOWS)

Opioid use disorder (OUD) is increasingly recognized as a national public health epidemic in the United States, leading not only to adverse perinatal outcomes, but also negative effects on childhood neurodevelopment.[1–5] The problem is further compounded by the increasing burden of healthcare costs associated with treatment of neonates exposed to opioids in utero who then experience neonatal opioid withdrawal syndrome (NOWS).[6,7] Management algorithms of OUD in pregnancy have traditionally hinged on the use of methadone as the agent of choice for pharmacotherapy—either constituted along the lines of a methadone "taper" or maintaining a steady state of methadone as a form of

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medication-assisted treatment (MAT).[8–10] However, the use of methadone for MAT during pregnancy also carries the risk of fetal exposure in utero, manifesting as NOWS, also known as neonatal abstinence syndrome (NAS).[10,11] Affected neonates exhibit a clinical profile characterized by hyperirritability, agitation, and central and/or autonomic nervous system dysfunction often necessitating intervention with pharmacologic therapy. This in turn leads to prolonged inpatient hospitalization for the neonate and the need for continued outpatient surveillance.[10–15] Recently, attention has shifted toward the use of buprenorphine as an agent of choice for MAT of OUDs in pregnancy. Buprenorphine administration was initially targeted toward women who could be followed-up at longer intervals, representing a higher level of medication adherence and compliance, without the need for daily monitoring (as is the case with methadone). Buprenorphine treatment in an office-based setting allows women to have prescriptions for their medications, longer intervals between visits, and unsupervised dosing representing a model of care consistent with other chronic medical illnesses, in contrast to methadone treatment that requires more intensive monitoring with daily supervised dosing for the first 90 days of treatment that sometimes becomes a barrier to treatment entry.[16–19] Importantly, maternal treatment with buprenorphine in pregnancy has been shown to have similar efficacy as methadone while also representing a safe and convenient option for outpatient management by allowing for prescribing through certified physician offices rather than daily attendance at methadone clinics.[16,18,20,21] While buprenorphine is generally accepted in pregnancy as a safe alternative to methadone for MAT, the extent to which buprenorphine dose correlates with the risk of NOWS remains incompletely understood, with some studies supporting a dose–response relation and others not.[1,17,20–22]

The objective of our study was to examine the relationship between antepartum buprenorphine dose among pregnant women undergoing MAT for OUD and incident NOWS.

Methods

The study was approved by the Institutional Review Board (IRB) at the University of Kentucky. Women were recruited from the Perinatal Assistance and Treatment Home (PATHways) Program at the University of Kentucky Polk Dalton clinic—an outpatient treatment program that includes group prenatal and postpartum care, MAT, and supportive services for high-risk women throughout Kentucky. We prospectively recruited and followed a cohort of pregnant women with a well-documented history of OUD, receiving prenatal care at a tertiary teaching institution from July 2015 to January 2017. Inclusion criteria included: (1) current diagnosis of opioid dependence with participation in the buprenorphine treatment program; (2) less than 30 weeks with a singleton gestation; and (3) age 18 to 49 years old. Women were excluded if they had current prisoner status, current severe mental illness (e.g., bipolar disorder with current mania, current suicidal ideation), or alcohol or sedative/hypnotic dependence that required medical intervention.

All patients received buprenorphine as the agent of choice for MAT of OUD, which was prescribed by waivered (X-licensed) maternal fetal medicine physicians with advanced training and licensure for buprenorphine administration. Buprenorphine dosing was once daily after initial buprenorphine induction, which verified objective withdrawal with the Clinical Opiate Withdrawal Scale (COWS). Medication adjustments were individualized for each patient based on healthcare provider clinical judgment, factoring in patient response and medication adherence. Patients received no more than a 2-week prescription at any given point in time. All patients received buprenorphine in the form of the commercially marketed generic formulation—Subutex (Reckitt Benckiser Pharmaceuticals, Inc, Richmond, Virginia), containing only buprenorphine, without naloxone. Pregnant patients with ongoing illicit drug use, e.g., as determined by self-report and/or urine drug testing, were managed by a customized approach centered upon escalation of care. For example, patients received increased face-to-face counseling with providers having subspecialty training in maternal fetal medicine, mental health, and addiction medicine. This was accompanied by closer follow-up and surveillance monitoring with visits ranging from once to thrice weekly. Patients were followed through delivery until 6 weeks postpartum. Patients underwent serial urine drug screens (UDS) at each prenatal visit, upon admission into the Labor & Delivery Unit and every postpartum visit. MAT was continued in all cases through the study period. Upon completion of the 6-week postpartum period, maternal and neonatal clinical outcomes data were abstracted through a review of their respective medical records. Data pertaining to maternal demographics, patterns of antenatal substance abuse, and incident pregnancy comorbidities were obtained from a thorough review of their outpatient electronic medical record. Labor and delivery–related outcomes were ascertained through a review of the inpatient electronic medical record system. The diagnosis of NOWS requiring pharmacologic management was confirmed based on documentation in the neonatal electronic medical record system. These cases were managed as per standardized institutional neonatal intensive care unit (NICU) protocols that used a modified Finnegan scale for scoring neonates for opioid withdrawal, also known as the MOTHER NAS scale.[1,14] In this system, scoring is done for any infant chronically exposed to opioids in utero or who has demonstrated signs of significant withdrawal. Scoring is performed every 3 to 4 hours and changed to every 6 to 8 hours once the infant is stable. Pharmacologic therapy was initiated when three consecutive scores were >8 or two consecutive scores were >12. We divided the study cohort into two groups—that is, pregnancies with and without incident NOWS requiring pharmacotherapy.

Details of maternal substance abuse patterns during pregnancy, as well as maternal and neonatal clinical outcomes, were compared across these two groups, using the two-sample *t*-test or Mann–Whitney U test for continuous data, as appropriate, and the chi-square test of association or Fisher's exact test for categorical data. All statistical analyses were performed using SAS version 9.4; an α level of 0.05 was used throughout.

Results

We recruited a total of 96 patients receiving buprenorphine for treatment of OUD in pregnancy. Of these, 90 patients delivered at our tertiary teaching hospital and were therefore available for follow-up of maternal and neonatal outcomes (the rest delivered at an outside hospital and hence their delivery outcomes data and neonatal data were unavailable and excluded from analyses). The incidence of NOWS was noted to be 31.11% in our cohort ($n = 28$). Demographic characteristics (►**Table 1**) were similar among the group of patients with and without incident NOWS. Interestingly, patterns of tobacco use during pregnancy (including smoking before and during pregnancy) as well as the use of smoking cessation treatment with nicotine replacement therapy were also similar in both groups ($p > 0.05$).

Substance abuse characteristics between the two groups are compared in ►**Table 2**. Patients in each group underwent buprenorphine induction at ~20 weeks gestation. Routes of substance use or age at initiation of substance misuse did not differ between the two groups. The group with NOWS was noted to have a significantly higher rate of benzodiazepine abuse—as noted in their history of substance abuse as well as detection at initial UDS. Significantly, pregnancies with NOWS were also noted to have a significantly higher number of positive UDS results (for illicit substances) over the course of pregnancy. Most importantly, neither the initial nor the final buprenorphine dose at delivery was significantly different between the two groups.

►**Table 3** compares maternal pregnancy and delivery outcomes as well as postpartum course among the two study groups. There were no significant differences in the incidence of adverse perinatal outcomes between the study groups. However, the group without NOWS had a significantly higher number of patients with an appropriate UDS result (i.e., only positive for buprenorphine) at delivery, 2, 4, and 6 weeks postpartum. Rates of NICU admission, length of NICU stay, and maximum Finnegan score were significantly higher in the group with NOWS, as seen in ►**Table 4**. The remainder of the neonatal outcomes under evaluation failed to reach statistical significance.

Discussion

Within our clinical cohort, the occurrence of NOWS was *not related* to the buprenorphine dose used for MAT of OUD in pregnancy. There were no significant differences in the initial or final buprenorphine dose in pregnancies with and without

Table 1 Demographic characteristics

	Total sample ($N = 90$) Mean ± SD, Median (IQR) or *n* (%)	NOWS ($n = 28$) Mean ± SD, Median (IQR) or *n* (%)	Non-NOWS ($n = 62$) Mean ± SD, Median (IQR) or *n* (%)	*p*
Age	28.8 ± 4.6	28.6 ± 5.1	28.9 ± 4.4	0.79
Gravidity	3 (2–5)	3 (2–4.5)	3 (2–5)	0.98
Parity (living)	2 (1–3)	2 (1–2.5)	2 (1–3)	0.86
Living children parent custody	0 (0–1)	0 (0–0.5)	0 (0–1.0)	0.29
BMI at start of care	25.1 ± 4.6	25.2 ± 4.5	25.0 ± 4.6	0.82
Race/ethnicity				
White/non-Hispanic	83 (92.2%)	25 (89.3%)	58 (93.6%)	0.67
Other	7 (7.8%)	3 (10.7%)	4 (6.4%)	
Partnered status				
Yes	33 (37.1%)	10 (37.0%)	23 (37.1%)	0.99
No	56 (62.9%)	17 (63.0%)	39 (62.9%)	
Employment				
Employed	14 (15.6%)	1 (3.6%)	13 (21.0%)	0.056
Unemployed	76 (84.4%)	27 (96.4%)	49 (79.0%)	
Nicotine replacement				
Yes	20 (24.4%)	4 (15.4%)	16 (28.6%)	0.20
No	62 (75.6%)	22 (84.6%)	40 (71.4%)	
Using tobacco at delivery				
Yes	82 (92.1%)	26 (92.9%)	56 (91.8%)	0.86
No	7 (7.9%)	2 (7.1%)	8 (8.2%)	

Abbreviations: BMI, body mass index; IQR, interquartile range; NOWS, neonatal opioid withdrawal syndrome; SD, standard deviation.
Note: *p*-Values represent comparison between the NOWS and non-NOWS group.

Table 2 Details of substance abuse patterns

	Total sample ($N = 90$) Mean ± SD, Median (IQR) or *n* (%)	NOWS ($n = 28$) Mean ± SD, Median (IQR) or *n* (%)	Non-NOWS ($n = 62$) Mean ± SD, Median (IQR) or *n* (%)	*p*
Gestational age at program initiation	21.5 ± 8.4	23.3 ± 8.4	20.6 ± 8.4	0.17
Gestational age at buprenorphine induction	21.2 ± 8.1	22.1 ± 7.6	20.8 ± 8.3	0.53
Age at first substance abuse	18.7 ± 5.0	18.5 ± 5.9	18.8 ± 4.4	0.80
History of substance abuse				
Opioids	88 (97.8%)	28 (100.0%)	60 (96.8%)	>0.99
Methamphetamine	17 (18.9%)	7 (25.0%)	10 (16.1%)	0.32
Cocaine	25 (27.8%)	9 (32.1%)	16 (25.8%)	0.53
Benzodiazepines	31 (34.4%)	13 (46.4%)	18 (29.0%)	0.11
THC	54 (60.0%)	19 (67.9%)	35 (56.5%)	0.31
Route of substance abuse				
Oral	85 (94.4%)	26 (92.9%)	59 (95.2%)	0.65
Intravenous	43 (47.8%)	16 (57.1%)	27 (43.6%)	0.23
Intranasal	68 (75.6%)	26 (92.9%)	42 (67.7%)	0.015
Substances positive on initial UDS				
Opioids	34 (37.8%)	11 (39.3%)	23 (37.1%)	0.84
Methamphetamine	7 (7.8%)	3 (10.7%)	4 (6.5%)	0.67
Cocaine	10 (11.1%)	6 (21.4%)	4 (6.5%)	0.065
Benzodiazepines	16 (17.8%)	10 (35.7%)	6 (9.7%)	**0.006**
THC	27 (30.0%)	12 (42.9%)	15 (24.2%)	0.074
Positive UDS (% yes)	69 (76.7%)	27 (96.4%)	42 (67.7%)	**0.003**
Number of positive UDS total (any substance other than buprenorphine)	4 (1–8)	9 (6–12.5)	2 (0–6)	<**0.001**
Positive UDS illicit opioids (% yes)	48 (53.3%)	23 (82.1%)	25 (40.3%)	<**0.001**
Number of positive UDS total – illicit opioids	1 (0–3)	2 (1–4)	0 (0–2)	<**0.001**
Initial buprenorphine dose	10.4 ± 4.9	10.6 ± 5.2	10.3 ± 4.8	0.80
Final buprenorphine dose	13.1 ± 4.7	13.3 ± 5.1	13.0 ± 4.6	0.81

Abbreviations: IQR, interquartile range; NOWS, neonatal opioid withdrawal syndrome; SD, standard deviation; THC, tetrahydrocannabinol; UDS, urine drug screen.
Note: *p*-Values represent comparison between the NOWS and non-NOWS group.

incident NOWS. The incidence of NOWS in our cohort was noted to be 31.11%, which is lower than the reported rates in several other contemporary studies.[1,23,24] The incidence of NOWS requiring treatment in the setting of maternal buprenorphine use has been variably reported from 22 to 63%.[21–26] Interestingly, several of these studies have focused on comparing the impact of methadone versus buprenorphine on incident NOWS. Patterns of tobacco use, including ongoing smoking and smoking cessation/nicotine replacement therapy, were similar among patients with and without incident NOWS in our study. This is in contrast to studies which show a relationship between maternal tobacco exposure and an increased likelihood of developing NOWS among women undergoing MAT for OUD in pregnancy.[27,28]

In a double-blind randomized controlled trial called the Maternal Opioid Treatment: Human Experimental Research (MOTHER) project, Jones et al compared neonatal outcomes among women undergoing MAT with methadone versus buprenorphine at eight different international sites. They found that neonates born to mothers receiving buprenorphine for MAT had a significantly shorter duration of treatment of NOWS and required significantly lesser morphine for treatment.[1] However, the total number of neonates receiving treatment for NOWS was not statistically different in the two groups in this study. The incidence of treatment requiring NOWS in the group receiving buprenorphine in the MOTHER study was 47%.

Globally, few other studies have delved into the evaluation of methadone versus buprenorphine and consequent development of NOWS. In a nonrandomized population-based Swedish study, Kakko et al compared neonatal outcomes among prospectively followed pregnancies exposed to buprenorphine with retrospectively analyzed pregnancies exposed to

Table 3 Maternal pregnancy course, delivery, and postpartum outcomes

	Total sample ($N = 90$) *n* (%)	NOWS ($n = 28$) *n* (%)	Non-NOWS ($n = 62$) *n* (%)	*p*
Preterm labor	11 (12.2%)	2 (7.1%)	9 (14.5%)	0.49
Preeclampsia	5 (5.7%)	1 (3.6%)	4 (6.7%)	>0.99
Gestational hypertension	7 (7.8%)	1 (3.6%)	6 (9.7%)	0.43
Diabetes	6 (6.7%)	4 (14.3%)	2 (3.2%)	0.073
IUGR	10 (11.1%)	1 (3.6%)	9 (14.5%)	0.16
Oligohydramnios	1 (1.1%)	0 (0.0%)	1 (1.6%)	>0.99
Polyhydramnios	1 (1.1%)	1 (3.6%)	0 (0.0%)	0.31
Hepatitis C	42 (47.2%)	14 (50.0%)	28 (45.9%)	0.72
RPR positivity	1 (1.1%)	1 (3.6%)	0 (0.0%)	0.31
Cholestasis	2 (2.9%)	2 (8.7%)	0 (0.0%)	0.11
Mode of delivery				
Primary cesarean section	10 (11.1%)	3 (10.7%)	7 (11.3%)	0.78
Repeat cesarean section	29 (32.2%)	11 (39.3%)	18 (29.0%)	
Assisted vaginal	2 (2.2%)	1 (3.6%)	1 (1.6%)	
Spontaneous vaginal	48 (53.3%)	13 (46.4%)	35 (56.5%)	
VBAC	1 (1.1%)	0 (0.0%)	1 (1.6%)	
Induction of labor				
Yes	24 (27.3%)	6 (22.2%)	18 (29.5%)	0.48
No	64 (72.7%)	21 (77.8%)	43 (70.5%)	
Augmentation of labor				
Yes	20 (27.4%)	6 (26.1%)	14 (28.0%)	0.86
No	53 (72.6%)	7 (73.9%)	36 (72.0%)	
Appropriate UDS at delivery				
Yes	59 (67.8%)	13 (46.4%)	46 (78.0%)	**0.002**
No	20 (23.0%)	13 (46.4%)	7 (11.9%)	
Not done	8 (9.2%)	2 (7.2%)	6 (10.2%)	
UDS appropriate at 2 wk postpartum ($n = 82$)	60 (73.2%)	10/24 (41.7%)	50/58 (86.2%)	**<0.001**
UDS appropriate at 4 wk postpartum ($n = 76$)	54 (71.1%)	12/23 (52.2%)	42/53 (79.3%)	**0.017**
UDS appropriate at 6 wk postpartum ($n = 58$)	33 (56.9%)	8/21 (38.1%)	25/37 (67.6%)	**0.029**

Abbreviations: IUGR, intrauterine growth restriction; NOWS, neonatal opioid withdrawal syndrome; RPR, rapid plasma reagin; UDS, urine drug screen; VBAC, vaginal birth after cesarean section.
Note: *p*-Values represent comparison between the NOWS and non-NOWS group.

methadone. In this study, treatment with buprenorphine offered the advantage of lower incidence of NOWS requiring pharmacological treatment, as well as shorter length of hospital stay for affected neonates.[23] In a similar study of a Norwegian national clinical cohort of 139 mother–neonate couplets, Welle-Strand et al compared neonatal outcomes among patients receiving methadone versus buprenorphine for MAT during pregnancy. They found that the number of neonates that received treatment for NOWS was not significantly different between both groups as was the case with the peak Finnegan score and the length of treatment.[24] Significantly, in a subgroup analysis, this group found that the concomitant benzodiazepines abuse during pregnancy while on MAT was associated with longer duration of treatment for NOWS. These findings parallel our observation wherein pregnancies affected by NOWS appear to have a significantly higher rate of benzodiazepine abuse. This also points toward the contributory role of concomitant illicit drug use (particularly benzodiazepine abuse) on possibly altering neonatal outcomes among pregnant women receiving MAT for OUD.

In a secondary analysis of the MOTHER study, Jones et al examined the relationship between buprenorphine at delivery among patients undergoing MAT and neonatal outcomes including NOWS.[29] The authors found no relationship between buprenorphine dose and any of the neonatal outcomes under study, including incident NOWS, gestational age at delivery,

Table 4 Neonatal course

	Total sample ($N = 90$) Mean ± SD, Median (IQR) or *n* (%)	NOWS ($n = 28$) Mean ± SD, Median (IQR) or *n* (%)	Non-NOWS ($n = 62$) Mean ± SD, Median (IQR) or *n* (%)	*p*
Gestational age at delivery	38.0 ± 2.2	38.5 ± 1.1	37.8 ± 2.6	0.17
Baby gender				
Male	43 (48.9%)	15 (53.6%)	32 (53.3%)	0.55
Female	45 (51.1%)	13 (46.4%)	28 (46.7%)	
APGAR score at 1 min				
< 7	9 (10.1%)	4 (14.8%)	5 (8.1%)	0.45
≥ 7	80 (89.9%)	23 (85.2%)	57 (91.1%)	
APGAR score at 5 min				
< 7	6 (6.7%)	4 (14.8%)	2 (3.2%)	0.066
≥ 7	83 (93.3%)	23 (85.2%)	60 (96.8%)	
Birth weight (g)	2804.3 ± 491.8	3013.6 ± 350.4	2709.7 ± 519.0	**0.002**
Birth weight percentile	27.6 ± 20.3	38.5 ± 23.2	23.4 ± 17.5	**0.003**
Mode of feeding				
Breastfeeding	17 (18.9%)	2 (7.1%)	15 (24.2%)	**0.049**
Bottle	48 (53.3%)	20 (71.4%)	28 (45.2%)	
Combination	25 (27.8%)	6 (21.4%)	19 (30.7%)	
NICU admission	42 (46.7%)	28 (100.0%)	14 (22.6%)	**<0.001**
Days in NICU	6.5 (0–17)	16.5 (12.5–23.5)	0 (0–5.5)	**<0.001**
Highest Finnegan score	11 (8–14)	14 (13–15)	9 (7–11)	**<0.001**
Maximum morphine dose		0.15 (0.14–0.18)		
Total number of morphine doses		97 (69–152)		
Infant UDS positive for buprenorphine	68 (80.0%)	17 (63.0%)	51 (87.9%)	**0.007**
Infant UDS positive for norbuprenorphine	75 (88.2%)	22 (81.5%)	53 (91.4%)	0.19
Maternal screen positive for buprenorphine	51 (58.6%)	14 (51.9%)	37 (67.7%)	0.39
Maternal screen positive for norbuprenorphine	74 (85.1%)	20 (74.1%)	54 (90.0%)	0.10
Breastfeeding at discharge	31 (34.8%)	4 (14.3%)	27 (44.3%)	**0.006**

Abbreviations: APGAR score, Appearance, Pulse, Grimace, Activity, and Respiration score; IQR, interquartile range; NICU, neonatal intensive care unit; NOWS, neonatal opioid withdrawal syndrome; SD, standard deviation; UDS, urine drug screen.
Note: *p*-Values represent comparison between the NOWS and non-NOWS group. All bold represents statistical significance at the 95% confidence level.

Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) scores at 1 and 5 minute, neonatal head circumference, length and birth weight at birth, amount of morphine needed to treat NOWS, duration of treatment, and length of neonatal hospital stay. Based on these findings, this group failed to support the occurrence of a dose–response relationship between maternal buprenorphine dose for MAT and neonatal outcomes including NOWS. Paralleling these results, we failed to identify a relationship between buprenorphine dose and NOWS. In our study cohort, both the initial and final buprenorphine dose was similar among pregnancies with and without the occurrence of NOWS requiring pharmacologic treatment.

As a strength of our study, it prospectively followed patients receiving buprenorphine for MAT of OUD in pregnancy to evaluate the impact on maternal and neonatal outcomes, specifically NOWS. We also performed a detailed evaluation of patterns of substance abuse in our study cohort not only based on self-report but also ascertained through objective metrics such as UDS testing. Urine drug testing was performed throughout the course of pregnancy extending through the 6-week postpartum study period, and also included neonatal urine testing. Buprenorphine dosing was also managed by a single provider with specialized training and licensure with consultation provided as needed by an addiction medicine psychiatrist.

This study has limitations—first, we did not plan a priori to test the effect of varying dose levels of buprenorphine on NOWS; thus, we are unable to draw definitive conclusions about the buprenorphine dose–response relationship with incident NOWS. While the biologic plausibility of such a relationship

seems appropriate, the current data are inadequate in addressing this question from an evidence-based standpoint. However, in our study, the buprenorphine dose was titrated to administer the most clinically appropriate dose on an individualized basis factoring in patient symptomatology and drug response, medication compliance, and UDS results. Hence, we were unable to specifically study the effect of varying dose levels. Similarly, group comparisons were not planned according to a specified level of statistical power, and post hoc power analysis is not valid.[30] Future studies in this area may benefit from larger sample sizes for more powerful group comparisons. Second, alterations in buprenorphine dose were individualized, as against adopting a protocolized approach. Given the sheer paucity of data on alterations of buprenorphine metabolism over the pregnancy time course, we chose to adopt an individualized approach to identify the dose that best suited each patient's needs. Lastly, we are unable to comment on a comparison with methadone, since this was beyond the scope of this study. However, our data support the safety for adjusting the antepartum buprenorphine dose as deemed clinically appropriate with minimal neonatal adverse effects. Interestingly, there are inconsistent data regarding the relationship between antenatal buprenorphine dose in pregnancy for MAT and the severity of NOWS.[21,25,26] In an attempt to elucidate the biologic relationship between maternal buprenorphine and dose and incident NOWS, previous research has examined the levels of buprenorphine and its metabolites in the urine and meconium of infants born to mothers receiving buprenorphine during pregnancy.[31,32] However, these studies provide limited insights into the plausibility of a relationship between antenatal buprenorphine dose and incident NOWS. In the light of these findings, our study aimed at examining the relationship between buprenorphine dose and incident NOWS among pregnant patients receiving buprenorphine for MAT of OUD during pregnancy. Based on our data, we are not able to establish a diagnosis of a relationship between buprenorphine dose in pregnancy and subsequent NOWS. However, our results suggest that women who are able to undergo MAT with buprenorphine in pregnancy without the concurrent use of illicit opioids or benzodiazepines are much less likely to have adverse neonatal outcomes as compared with their counterparts. This is important information for clinicians treating patients for OUD in pregnancy. Further studies—particularly, larger randomized prospective trials—are warranted to evaluate if a dose–response relationship exists between antenatal buprenorphine dose and the occurrence and severity of incident NOWS in pregnant patients undergoing MAT of OUD.

Conflicts of Interest

Dr. Lofwall reports grants and consulting fees from Braeburn Pharmaceuticals, consulting fees from Indivior, and honorarium from PCM Scientific, outside the submitted work.

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Statement of Authorship

See attached documents.

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Condensation

Examining the relationship between maternal buprenorphine dose for medication-assisted treatment of opioid use disorder of pregnancy and the occurrence of neonatal opioid withdrawal syndrome.

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