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Brief Report: Treating Women with Opioid Use Disorder during Pregnancy in Appalachia: Initial Neonatal Outcomes Following Buprenorphine + Naloxone Exposure

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Background and Objectives: Rising concerns regarding diversion and misuse of mono-buprenorphine for treatment of pregnant women with opioid use disorders have sparked interest in the use of buprenorphine + naloxone to reduce misuse and diversion rates. Examined the relationship of prenatal buprenorphine + naloxone exposure to neonatal outcomes.
Methods: This is a retrospective chart review of 26 mother infant dyads in comprehensive medication-assisted treatment with buprenorphine + naloxone during pregnancy.
Results: All neonatal birth outcome parameters were within normal ranges, albeit on the lower side of normal for gestational age and birth weight. Only 19% of neonates required morphine pharmacology for NAS.
Conclusions: Use of buprenorphine + naloxone shows relative safety in pregnancy.
Scientific Significance: These findings can help better guide prescribing practices for pregnant patients at risk for misuse or diversion of buprenorphine. (Am J Addict 2018;27:92–96)

INTRODUCTION

Opioid use disorder (OUD) during pregnancy is related to increased risk for maternal morbidities such as poor/late prenatal care, poor nutrition, sexually transmitted infections, and violence.[1] It is also linked to fetal growth restriction, abruption placentae, fetal death, preterm labor, and intrauterine passage of meconium.[1] Furthermore, neonates prenatally exposed to either illicit or licit opioids often experience neonatal abstinence syndrome (NAS). If severe, NAS treatment requires pharmacotherapy.

Methadone and buprenorphine are the standard of care for OUD treatment during pregnancy,[2,3] with buprenorphine being superior in regard to its office-based prescribing ability, lower drug interaction profile, lower overdose potential, and less severe NAS.[4,5]

Prenatal buprenorphine pharmacotherapy has focused almost exclusively on mono-buprenorphine rather than the combination buprenorphine + naloxone (4:1 buprenorphine:naloxone) medication, the most common buprenorphine formulation prescribed to non-pregnant individuals. Mono-buprenorphine has been preferred to limit fetal exposure to additional compounds, specifically naloxone due to concerns regarding fetal withdrawal if injected, and a potential for mixed hormonal and behavioral effects found in animal models.[6,7] However, mono-buprenorphine has a higher misuse and diversion potential than buprenorphine + naloxone.[7]

Examinations of buprenorphine + naloxone as a potential safer alternative to mono-buprenorphine, have yet to raise concerns for clinicians considering buprenorphine + naloxone pharmacotherapy for pregnant women with OUD.[7] One study found no significant differences in maternal outcomes for women prescribed buprenorphine + naloxone compared to mono-buprenorphine, methadone, or methadone-assisted withdrawal.[8] A retrospective cohort analysis found that prenatal buprenorphine + naloxone exposed neonates were less likely to be diagnosed with NAS, had lower peak NAS

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scores, and shorter overall hospitalization than prenatal methadone-exposed neonates.[9] Another retrospective cohort study found no differences between a buprenorphine + naloxone group and either an other-opioid-exposure group or a no-opioid-exposure group on birth weight, preterm delivery, congenital anomalies, and stillbirth.[10]

The present study is a retrospective chart review of 26 mother-infant dyads from a comprehensive outpatient program for pregnant women with OUD in Morgantown, WV exclusively receiving buprenorphine + naloxone during pregnancy. We examined neonatal birth outcomes and compared neonates who received pharmacotherapy for NAS with those not receiving pharmacotherapy. Finally, we examined if maintenance buprenorphine + naloxone dose during pregnancy was related to neonatal outcomes. Treatment providers want to know if prescribing buprenorphine + naloxone to pregnant women with OUD is safe for neonates. Answering this question will help clinicians engage in shared decision-making with patients about OUD medication choices during pregnancy.

METHODS

The Institutional Review Board of West Virginia University approved the study.

Participants

We used data on 26 women active in outpatient medication-assisted treatment (MAT) and their neonates. All deliveries occurred between 1/1/2016 and 5/1/2017 at Ruby Memorial Hospital in Morgantown, WV. Neonates were born to women enrolled in the Comprehensive Opioid Addiction Treatment (COAT) program during pregnancy and were initiated and maintained on buprenorphine + naloxone film for the entirety of their treatment. COAT is West Virginia's largest comprehensive outpatient, group-based program using medication and therapy, treating a predominantly rural population. Treatment consists of weekly medication management and group therapy in pregnancy-OUD specific groups, with 10–12 patients in each. Patients must attend four community based recovery meetings per week. Random urine screening is conducted during clinic visits. Use of non-prescribed substances including alcohol is prohibited. If patients voluntarily disclose relapse, they are retained in treatment unless a higher level of care is indicated.

Data Collection

Data extracted from electronic medical records included maternal age of first opioid use, criminal history, hepatitis C status, number of children, and marital status, all collected by a licensed clinical therapist in a structured interview at intake assessment. Additional background variables were extracted directly from the electronic medical record and included race, age, insurance type, duration of treatment, treatment status at time of delivery, maintenance dose of buprenorphine + naloxone, and urine drug screening test results at time of delivery.

Neonatal outcome measures included gestational age at delivery, 5-minute Apgar scores, weight, length, and head circumference at birth, NAS treatment status (treated vs. not-treated-for-NAS, defined as receiving or not receiving morphine pharmacotherapy for NAS), and total length of hospital stay in days. Preterm birth was defined as less than 37 weeks of gestation, and low birth weight as less than 2.5 kg.

Statistical Analyses

Descriptive statistics [mean and standard deviation for continuous variables, frequency (n) and percentage for categorical variables] were calculated for all variables, as appropriate. Given the small sample sizes, nonparametric tests were used to conduct all inferential analyses. Spearman's correlation was used to measure association between continuous variables. In the case of testing the association between categorical variables, Fisher's exact test was used, while testing for the association of a dichotomous variable with a continuous variable, Wilcoxon two-sample tests were used. All Wilcoxon tests of significance used exact tests to calculate p values.

RESULTS

A total of 26 women and 26 infants were included in the chart review.

Maternal Participants

The women were exclusively white, with a mean age of 28.2 (SD = 5.0), and receiving Medicaid. First exposure to opioids was fairly evenly divided among use of heroin, use of pills, or both, with a mean age of first opioid use of 18.5 (SD = 5.7) (Table 1). Route of drug administration data was not consistently available. Four of the women dropped out of treatment shortly before delivery, and they account for 4/5 buprenorphine-negative, 2/3 opioid-positive, 1/6 THC-positive, and 1/2 amphetamine-positive urine screening results. Mean length of stay in COAT for the 26 women was 129.0 days (SD = 110.0).

Buprenorphine + Naloxone Dose and Relationship to Maternal Background Variables

Mean maintenance buprenorphine + naloxone dose was 10.0 mg (SD = 2.0; range: 4–16 mg). Buprenorphine + naloxone dose was uncorrelated with any maternal background variable (all $p > .09$).

Neonatal Outcomes

The average gestational age, 5-minute Apgar, and growth parameters were all within the normal range of birth outcomes, although on the lower side. Of note, 6/26 (23%)

TABLE 1. Maternal demographic and background information for the total sample and descriptive statistics and *p* values for neonatal birth outcome variables by NAS treatment status ($N = 26$)

Maternal demographic and background variables	*N* (%)	Mean (SD)
Demographics		
Race: white	25 (100)	
Age		28.2 (5.0)
Marital status		
Single	15 (60)	
Engaged	2 (8)	
Divorced	5 (20)	
Married	3 (12)	
Number of children		1.7 (1.2)
Insurance type: medicaid	25 (96)	
Criminal history		
Current criminal activity	5 (19)	
Past criminal activity	9 (35)	
History of incarceration	5 (19)	
History of child protective services	7 (27)	
Opioid use history		
Type of opioids first used		
Heroin (route of administration not specified)	8 (31)	
Pills	11 (42)	
Both	7 (27)	
Age of first opioid use		18.5 (5.7)
Positive for hepatitis C	10 (38)	
Positive urine screening at delivery		
Buprenorphine	21 (81)	
Opioids	3 (12)	
Cocaine	1 (4)	
Benzodiazepines	1 (4)	
Amphetamines	2 (8)	
THC	6 (23)	
Any substance other than buprenorphine	9 (35)	
Current treatment status		
Maintenance buprenorphine + naloxone dose during treatment		10.0 (2.9)
Days in treatment		129.0 (110.0)
Remained in treatment until delivery	22 (85%)	

Neonatal birth outcome variables	Total sample ($N = 26$)	Treated-for-NAS ($n = 5$)	Not-treated-for-NAS ($n = 21$)	*p*
Gestational age	37.4 (3.1)	38.1 (3.4)	37.2 (3.4)	.99
Premature: Yes	6 (23.1%)	5 (83.3%)	1 (16.7%)	1.0
Apgar score at 5 minutes	8.5 (1.0)	8.3 (1.0)	8.6 (1.0)	.77
Weight (kg)	2.7 (0.8)	2.6 (2.4)	2.7 (0.8)	.65
Low birth weight: yes	10 (38%)	3 (60%)	7 (33%)	.34
Length (cm)	45.1 (6.4)	40.1 (8.1)	45.8 (6.0)	.22
Head circumference (cm)	34.8 (6.3)	37.9 (5.8)	34.1 (5.8)	.76
Hospital length of stay (days)	16.4 (23.7)	38.0 (43.9)	11.2 (13.2)	.009

Data for race and marital status were each missing for one participant, and for age at first use of opioids for two participants. Data for urine screening test results at delivery were missing for two participants. Urine screening was conducted for amphetamines, cocaine, THC, opiates, phencyclidine, benzodiazepines, tricyclic antidepressants, barbiturates, oxycodone, propoxyphene, methadone, and buprenorphine. Those not listed on the table had zero positives. Values for neonatal outcomes are Mean (Standard Deviation) except for low birth weight, for which it is frequency (percentage). Percentages are for the respective group. Apgar score at 5 minutes and length are each missing two observations in the treated-for-NAS group and 1 observation in the not-treated-for-NAS group, respectively. *p* values reflect the results of exact tests for the Wilcoxon two-sample test for all neonatal outcomes except low birth weight, which was tested with Fisher's exact test.

were premature, and 10/26 (38%) were low birth weight (Table 1).

NAS Treatment

Of the 26 neonates, 5 (19%) required morphine pharmacotherapy for NAS. The treated-for-NAS group was not significantly different from the not-treated-for-NAS group on all neonatal outcomes except for hospital length of stay (Table 1).

Maternal Buprenorphine + Naloxone Dose and Neonatal Outcomes

Buprenorphine + naloxone dose showed moderate positive associations with estimated gestational age [Spearman $r(24) = .41$, $p = .036$] and neonate length [Spearman $r(21) = .50$, $p = .015$]. Thus, higher buprenorphine + naloxone doses were associated with longer gestational age and length.

DISCUSSION

In a cohort of 26 pregnant women treated with buprenorphine + naloxone for OUD, we found that maternal demographic and background characteristics were unrelated to maternal dose, neonatal outcomes were within normal range, and those outcomes were unrelated to maternal dose.

First, this sample was similar to other pregnant women with OUD receiving mono-buprenorphine or methadone in that they were socioeconomically disadvantaged, single, often had children in the house, and legal system involvement. This sample was all White, whereas many other studies of this population have been more racially diverse. The cohort was typical of the women seen in the COAT clinic including the early onset of first opioid use and high percentage of Hepatitis C-positive.

Second, as has been reported for mono-buprenorphine,[5] findings showed neonatal outcomes within normal ranges for delivery and growth parameters. However, relatively high rates for prematurity and low birth weight are concerning. Previous studies on mono-buprenorphine with at least five participants have reported prematurity rates of 0–25%, with the majority below 10%, and average gestational ages of 38.4–40 weeks.[5,8] Moreover, mean birth weights have been mostly above 2.9 kg, with the lowest reported at 2.796 kg.[5,8] Previous studies on buprenorphine + naloxone have shown no increased risk of low birth weight or preterm birth compared to mono-buprenorphine or methadone.[7–10] It is unclear why our cohort has lower birth weight and gestational age. Unmeasured life context factors of psychiatric co-morbidity, stress, nutrition, and smoking may have contributed to these higher-than-average normal negative birth outcomes.

The NAS treatment rate of 19% was on the lower end of rates previously reported among pregnant women prescribed mono-buprenorphine (20–48%).[8] Consistent with previous research on mono-buprenorphine,[11,12] neonates requiring NAS treatment did not differ from neonates not requiring NAS treatment excepting hospital length of stay.

Finally, the average buprenorphine dose was lower than the product insert's recommended target dose (10 vs. 16 mg, respectively). Higher buprenorphine + naloxone doses were associated with longer gestational age and length. The reason for this association needs further investigation, but these results would suggest no deleterious effect due to exposure to naloxone

Limitations

This study has several limitations. First, data were collected retrospectively, and data for every variable were not available in each chart. Second, the small sample may not be representative of the larger OUD pregnant population. Third, the small sample limits power to detect small effects. Fourth, data were limited to the antenatal and neonatal period and may not reflect the long-term outcomes of buprenorphine + naloxone exposure.

CONCLUSIONS

This retrospective chart review adds to the growing literature for health care providers showing the relative safety of buprenorphine + naloxone in pregnancy, strengthening support for its use as a reasonable alternative to mono-buprenorphine, especially when there is concern for misuse or diversion. Larger, prospective studies are needed to further examine the fetal, and child safety of buprenorphine + naloxone. Longitudinal studies of the neonates prenatally exposed to buprenorphine + naloxone should also be conducted to assess developmental outcomes.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

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