

Brief Report

A retrospective, observational study on medication for opioid use disorder during pregnancy and risk for neonatal abstinence syndrome

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Abstract

Objectives: The prevalence of opioid use disorder (OUD) among pregnant women is increasing. Research consistently demonstrates the efficacy of medications for OUD (MOUD); however, researchers have called for additional studies evaluating the safety of MOUD during pregnancy, particularly the relative safety of two commonly used MOUD medications—methadone and buprenorphine. This study aimed to evaluate the consequences of MOUD exposure during pregnancy on risk for neonatal abstinence syndrome (NAS).

Methods: In a clinical sample of infants born to women with OUD, we evaluated the risk of NAS among those exposed to (i) methadone and (ii) buprenorphine compared with those unexposed to MOUD, as well as the risk of NAS among those exposed to (i) methadone compared with those exposed to (ii) buprenorphine.

Results: Compared with buprenorphine-exposed infants ($n = 37$), methadone-exposed infants ($n = 27$) were at increased risk for NAS (odds ratio [OR] = 4.67, 95% confidence interval [CI]: 1.03, 21.17). Compared with unexposed infants ($n = 43$), buprenorphine-exposed infants were at decreased risk for NAS (OR = 0.45, 95% CI: 0.14, 1.39) and methadone-exposed infants were at increased risk for NAS (OR = 2.64, 95% CI: 0.79, 8.76), though these associations were not statistically significant.

Conclusions: Our study suggests that when methadone and buprenorphine are equally appropriate options for the treatment of OUD in pregnant women, buprenorphine may add the additional benefit of reduced risk of newborn NAS.

Lay Summary

Medications for opioid use disorder (MOUD), such as buprenorphine and methadone, are effective in reducing the significant harms associated with untreated opioid use disorder (OUD) in nonpregnant and pregnant adults. While previous research clearly documents that the risks of MOUD in pregnancy are less than the risks of untreated OUD in pregnancy, researchers have called for additional studies evaluating the safety of MOUD during pregnancy, particularly the relative

Key Messages

- Research on Medications for Opioid Use Disorder (MOUD) in pregnancy is needed.
- We assessed neonatal abstinence syndrome (NAS) risk after prenatal MOUD exposure.
- The sample included infants born to 149 women with OUD in the Southeastern US.
- Buprenorphine-exposed had lower NAS risk compared to methadone-exposed infants.
- Our study supports using buprenorphine over methadone among pregnant women.

safety of methadone and buprenorphine. In a clinical sample of infants born to women with OUD, we showed that buprenorphine-exposed infants were at significantly reduced risk for neonatal abstinence syndrome compared with methadone-exposed infants. Our study adds to the growing body of evidence supporting the use of buprenorphine over methadone for the treatment of OUD among pregnant women.

Key words: addiction medicine, neonatology, obstetrics/postpartum care, substance abuse (not tobacco), women's health/gynecology

Background

Research has consistently demonstrated that the prevalence of pregnant women with opioid use disorder (OUD) is increasing. For example, a study estimated that maternal OUD rates at delivery have more than quadrupled from 1999 to 2014¹; and, a more recent study utilizing healthcare data from 47 states and the District of Columbia estimated that the rate of maternal opioid-related diagnoses increased from 3.5 per 1,000 delivery hospitalizations in 2010 to 8.2 per 1,000 delivery hospitalizations in 2017.² Given the need for OUD treatments for pregnant women, it is important to understand the safety of medications for opioid use disorder (MOUD) in pregnancy, such as methadone and buprenorphine.

Research has consistently demonstrated that the risks of MOUD during pregnancy are less than the risks of untreated OUD during pregnancy.³ The decision to choose methadone versus buprenorphine for the treatment of OUD during pregnancy is dependent upon which medication is most effective and accessible.³ However, in cases where both medications are equally likely to be effective and are available, the decision to choose one medication over the other depends on the impact of the medication on fetal and newborn health.³ Research has provided some support for the safety of MOUD during pregnancy.⁴ Some research suggests that buprenorphine may result in lower risk of some adverse obstetric outcomes compared with methadone.⁵ However, researchers have called for future studies to evaluate the relative safety of buprenorphine versus methadone.⁴ Moreover, because much of the existing observational studies on prenatal exposure to MOUD have utilized European samples and lower treatment doses of buprenorphine and methadone tend to be used in Europe versus the United States, questions remain regarding the generalizability of previous findings to the United States.⁶

Therefore, the aim of this study was to evaluate the risk for neonatal abstinence syndrome (NAS) after exposure to MOUD in a sample of infants born to women seeking treatment in a medical center in the Southeastern United States. NAS is a common clinical concern for infants prenatally exposed to substances, including methadone and buprenorphine. NAS is typically defined as constellation of signs and symptoms of withdrawal that may require pharmacologic intervention.⁷ Signs of NAS can be classified as (i) neurologic manifestations due to increased excitability (e.g. tremors, excessive/high pitch cry, seizures), (ii) gastrointestinal manifestations

(e.g. diarrhea, vomiting), and (iii) autonomic manifestations (e.g. fever, sweating, increased respiratory rate).⁸

Methods

This study was approved by the Institutional Review Board (IRB) at the Medical University of South Carolina (IRB protocol #00012855), and a waiver of written informed consent was granted by the IRB. This study was conducted from February 10, 2016 to December 27, 2020 and included 149 infants born to women with OUD who were treated by reproductive psychiatrists in the Women's Reproductive Behavioral Health Clinic at the Medical University of South Carolina during their pregnancies. We ascertained data from assessments that were completed at each appointment, as well as retrospective chart reviews of patients' electronic medical records.

We classified women according to OUD treatment status during pregnancy (i.e. prescribed methadone, prescribed buprenorphine, or not prescribed MOUD). The women not prescribed MOUD (i.e. the unexposed group) were women with OUD who declined MOUD. While MOUD was recommended for all pregnant women with OUD in this sample, some women declined this component of treatment. A shared decision-making tool was employed to assist women in understanding the risks associated with MOUD, as well as the risks associated with not taking MOUD (i.e. risk for relapse), so that all women were provided with consistent information and making an informed decision that was in line with their preferences and values.⁹

Using diagnostic interviews and urine drug screens, we also obtained information on type of OUD (i.e. involving prescription opioids versus heroin). Additionally, we obtained maternal demographic information, which included maternal age, ethnicity, race, relationship status, highest level of education completed, and annual household income.

Our outcome of interest was NAS in infants. The majority of women in the sample delivered their newborns at the academic center's delivery hospital where a standardized protocol is in place for monitoring newborns with any potential in utero substance exposure for NAS using the Finnegan Scale. Given that the patient's diagnosis of OUD was in the medical record prior to delivery, all of the newborns in our sample would have been monitored for NAS at the time of delivery using the Finnegan Scale. Cases with missing

Table 1. Maternal characteristics and infant neonatal abstinence syndrome status for 149 infants born to women with opioid use disorder who were treated in a behavioral health clinic (February 10, 2016 to December 27, 2020).

	Exposure status						Neonatal abstinence syndrome status			
	Methadone n = 35 (23.49%)		Buprenorphine n = 58 (38.93%)		Unexposed n = 56 (37.58%)		Present n = 126 (84.56%)		Missing n = 23 (15.43%)	
Maternal characteristics										
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	28.74	4.3	29.76	4.66	28.22	3.97	28.97	4.47	28.82	3.70
	n	%	n	%	n	%	n	%	n	%
Age missing	0	0.00	0	0.00	1	1.79	1	0.79	0	0.00
Prescription opioid use disorder										
Yes	27	77.14	43	74.14	45	80.36	101	80.16	14	60.87
Missing	0	0.00	0	0.00	3	5.36	1	0.79	0	0.00
Heroin use disorder	15	42.86	27	46.55	18	32.14	45	35.71	15	65.22
Ethnicity										
Not Hispanic or Latino	32	91.43	57	98.28	54	96.43	121	96.03	22	95.65
Hispanic or Latino	2	5.71	1	1.72	1	1.79	3	2.38	1	4.35
Missing	1	2.86	0	0.00	1	1.79	2	1.59	0	0.00
Race										
American Indian or Alaska Native	0	0.00	1	1.72	1	1.79	1	0.79	1	4.35
Asian	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Native Hawaiian or Other Pacific Islander	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Black or African American	1	2.86	0	0.00	6	10.71	7	5.56	0	0.00
White or Caucasian	32	91.43	56	96.55	47	83.93	113	89.68	22	95.65
Missing	2	5.71	1	1.72	2	3.57	5	3.97		0.00
Relationship status										
Married	6	17.14	21	36.21	9	16.07	32	25.40	4	17.39
Engaged	9	25.71	7	12.07	5	8.93	16	12.70	5	21.74
Living together	8	22.86	10	17.24	19	33.93	29	23.02	8	34.78
Together as a couple, but not living together	4	11.43	5	8.62	11	19.64	19	15.08	1	4.35
Not in a relationship	6	17.14	13	22.41	10	17.86	25	19.84	4	17.39
Missing	2	5.71	2	3.45	2	3.57	5	3.97	1	4.35
Education completed										
Junior high school	6	17.14	7	12.07	7	12.50	16	12.70	4	17.39
High school	16	45.71	33	56.90	39	69.64	74	58.73	14	60.87
College	9	25.71	8	13.79	4	7.14	18	14.29	3	13.04
Graduate school	1	2.86	3	5.17	1	1.79	5	3.97	0	0.00
Missing	3	8.57	7	12.07	5	8.93	13	10.32	2	8.70
Annual household income										
Less than \$12,000 per year	10	28.57	11	18.97	15	26.79	31	24.60	5	21.74
\$12,000–25,000 per year	19	54.29	23	39.66	26	46.43	62	49.21	6	26.09
\$25,000–50,000 per year	1	2.86	12	20.69	8	14.29	15	11.90	6	26.09
\$50,000–75,000 per year	3	8.57	4	6.90	4	7.14	10	7.94	1	4.35
\$75,000–100,000 per year	0	0.00	1	1.72	1	1.79	1	0.79	1	4.35
More than \$100,000 per year	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Missing	2	5.71	7	12.07	2	3.57	7	5.56	4	17.39
Infant outcome										
	n	%	n	%	n	%	n	%	n	%
Neonatal abstinence syndrome										
Yes	22	62.86	16	27.59	26	46.43	64	50.79	0	0.00
Missing	3	8.57	14	24.14	6	10.71	0	0.00	23	100

NAS were from women who delivered at a hospital outside of the academic center.

We conducted all analyses using SAS 9.4. First, we evaluated type of OUD, demographic characteristics, and prevalence of NAS stratified by OUD treatment status. Then, using logistic regression, we evaluated associations between OUD treatment and risk

of NAS in a sample with complete data on NAS while controlling for maternal characteristics. Specifically, we evaluated risk of NAS among those exposed to (i) methadone and (ii) buprenorphine compared with those unexposed to MOUD, as well as among those exposed to (i) methadone compared with those exposed to (ii) buprenorphine.

Results

Table 1 reports measures and frequency of missing data stratified by OUD treatment status, as well as measures among cases with ($n = 23$ [15%]) and without ($n = 126$ [85%]) missing NAS status.

Compared with unexposed infants ($n = 43$), infants exposed to buprenorphine ($n = 37$) were at decreased risk for NAS (odds ratio [OR] = 0.45, 95% confidence interval [CI]: 0.14, 1.39) and infants exposed to methadone ($n = 27$) were at increased risk for NAS (OR = 2.64, 95% CI: 0.79, 8.76). Of note, these associations were not statistically significant and CIs were wide, making it difficult to draw strong conclusions. Compared with buprenorphine-exposed infants, methadone-exposed infants were at a statistically significant increased risk for NAS (OR = 4.67, 95% CI: 1.03, 21.17).

Conclusions

In a clinical sample of pregnant women with OUD, we evaluated the risk of NAS following MOUD exposure. Our results demonstrated buprenorphine-exposed infants were at significantly reduced risk of NAS compared with methadone-exposed infants.

Our results are consistent with the three previous randomized control trials evaluating the influence of MOUD exposure during pregnancy on NAS. These three randomized control trials found converging evidence suggesting that methadone-exposed infants have more severe NAS than buprenorphine-exposed infants. The first randomized control trial showed that buprenorphine-exposed infants ($n = 9$) had hospital stays that were 1.3 days shorter on average than methadone-exposed infants ($n = 11$).¹⁰ In the second randomized control trial, while there were no statistically significant differences between buprenorphine-exposed ($n = 8$) and methadone-exposed ($n = 6$) infants, methadone-exposed infants tended to have earlier onset of NAS and longer treatment duration compared with buprenorphine-exposed infants.¹¹ Similarly, the most recent randomized control trial showed significantly shorter treatment durations and lower morphine doses to treat NAS among buprenorphine-exposed infants ($n = 58$) compared with methadone-exposed infants ($n = 73$).¹²

Our findings are also consistent with several observational studies, which have suggested that buprenorphine-exposed infants have lower occurrence of NAS and less severe NAS symptoms compared with methadone-exposed infants. For example, a Danish population-based study of 364 opioid-exposed infants (buprenorphine $n = 167$, methadone $n = 197$) showed that 6.6% of buprenorphine-exposed infants exhibited NAS compared with 55% methadone-exposed infants¹³; and a retrospective cohort study of 609 opioid-dependent pregnant women (buprenorphine $n = 361$, methadone $n = 248$) in the United States found that buprenorphine-exposed infants were less likely to be treated for NAS and had shorter duration of NAS treatment compared with methadone-exposed infants.¹⁴

Our findings should be considered in light of several limitations. First, our exposure was subject to measurement error as we did not have a measure of medication adherence. Second, we did not evaluate severity of NAS symptoms. Third, our findings may have been biased due to excluding 15% of our sample who had missing information on NAS as some maternal characteristics differed among infants with and without missing NAS. In particular, compared with those with complete NAS data, those with missing NAS data had mothers with a lower prevalence of prescription

OUD, higher prevalence of heroin use disorder, higher prevalence of living with a partner but lower prevalence of being in a relationship and not living with their partner, and lower prevalence of annual household income below \$25,000. Fourth, we could not make causal inferences as we did not conduct a randomized control trial or control for all potential confounding factors. Fifth, our sample size was small, which limited our statistical power. Sixth, our sample was not racially and ethnically diverse, and, therefore, findings may not generalize.

Despite these limitations, our findings have important clinical implications. Our study, which was conducted with a clinical sample of infants born to women in the Southeastern United States, along with other previous studies that utilized different samples, suggests that when methadone and buprenorphine are equally appropriate options for the treatment of OUD in pregnant women, buprenorphine may add the additional benefit of reduced risk of newborn NAS.

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Ethical approval

This study was approved by the Institutional Review Board (IRB) at the Medical University of South Carolina (IRB protocol #00012855).

Conflict of interest

None declared.

Data availability

These data are not publicly available.

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