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Maternal buprenorphine treatment and infant outcome

Lauren M. Jansson[a,*], Martha L. Velez[a], Krystle McConnell[a], Nancy Spencer[b], Michelle Tuten[c], Hendree Jones[d], Rebeca Rios[a], Van L. King[a], Neeraj Gandotra[a], Lorraine Millio[a], Janet A. DiPietro[e]

[a] Johns Hopkins University School of Medicine, Baltimore, MD, United States
[b] Johns Hopkins Bayview Medical Center, Baltimore, MD, United States
[c] University of Maryland, School of Social Work, MD, United States
[d] University of North Carolina Chapel Hill, Chapel Hill, NC, United States
[e] Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States

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ABSTRACT

Background and objectives: Maternal buprenorphine maintenance predisposes the infant to exhibit neonatal abstinence syndrome (NAS), but there is insufficient published information regarding the nature of NAS and factors that contribute to its severity in buprenorphine-exposed infants.

Methods: The present study evaluated forty-one infants of buprenorphine-maintained women in comprehensive substance use disorder treatment who participated in an open-label study examining the effects of maternal buprenorphine maintenance on infant outcomes. Modifiers of the infant outcomes, including maternal treatment and substance use disorder parameters, were also evaluated.

Results: Fifty-nine percent of offspring exhibited NAS that required pharmacologic management. Both maternal buprenorphine dose as well as prenatal polysubstance exposure to illicit substance use/licit substance misuse were independently associated with NAS expression. Polysubstance exposure was associated with more severe NAS expression after controlling for the effects of buprenorphine dose. Other exposures, including cigarette smoking and SRI use, were not related to outcomes. Maternal buprenorphine dose was positively associated with lower birth weight and length.

Conclusions: Polysubstance exposure was the most potent predictor of NAS severity in this sample of buprenorphine-exposed neonates. This finding suggests the need for interventions that reduce maternal polysubstance use during medication assisted treatment for opioid use disorder, and highlights the necessity of a comprehensive approach, beyond buprenorphine treatment alone, for the optimal care for pregnant women with opioid use disorders.

1. Introduction

Gestational illicit opioid use and licit opioid misuse are on the rise in the US, with an attendant increase in the incidence of neonatal abstinence syndrome (NAS) among exposed infants (Patrick et al., 2012; Patrick et al., 2015; Ko et al., 2016). Medication assisted treatment of maternal opioid use disorders (OUDs) with either methadone, a full mu-agonist or buprenorphine, a partial mu-agonist/antagonist during gestation is the current standard of care (WHO, 2014). Buprenorphine treatment has become more common (Krans et al., 2016) since the publication of the MOTHER study (Jones et al., 2010), which found that buprenorphine treatment of women with OUDs may confer some advantage to the infant in the form of less severe NAS. NAS requiring pharmacotherapy occurs in 22–67% (Kocherlakota, 2014) among buprenorphine-exposed infants. Substances that may potentiate NAS severity in methadone-exposed infants include polysubstance exposures (Jansson et al., 2012), heavy cigarette smoking (Choo et al., 2004) and psychiatric medication, particularly SRIs (Kaltenbach et al., 2012). It is unknown whether these substances similarly predispose the infant to more severe NAS in buprenorphine-exposed pregnancies, or if other aspects of exposure, such as maternal buprenorphine dose, potentiates NAS in exposed infants.

The purpose of this longitudinal, prospective study is to comprehensively document the outcome of buprenorphine-exposed neonates. Research questions include: 1) the extent to which there is a positive association between maternal buprenorphine dose and NAS severity; 2) whether other maternal factors, including polysubstance use, severity of opioid use, and psychiatric medications potentiate NAS outcomes;

* Corresponding author at: Johns Hopkins University School of Medicine, 4940 Eastern Avenue, D4E, Baltimore, MD, 21224, United States.
E-mail address: ljansson@jhmi.edu (L.M. Jansson).

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and 3) the relation between maternal buprenorphine dose and size at birth. A secondary analysis addressed whether any detected associations between buprenorphine dose and NAS severity is similarly present among women who do and do not use illicit/misuse licit substances during treatment.

2. Participants and methods

Participants were drawn from a population of pregnant women with OUD entering treatment at the Center for Addiction and Pregnancy (CAP) between 2012 and 2016. CAP is a comprehensive treatment facility for pregnant and parenting women and has been comprehensively described previously (Jansson et al., 1996). Women who opted for buprenorphine (monoproduct only) maintenance as part of a study evaluating fetal and infant outcomes were eligible for enrollment. Eligibility was limited to singleton pregnancies less than 34 weeks of gestation at the time of enrollment, and absence of significant medical/obstetrical comorbidities that could independently affect fetal functioning, such as gestational diabetes, growth restriction, HIV infection, disorders of thyroid functioning and hypertension. Current alcohol use as measured by the Addiction Severity Index (McLellan et al., 1992) at enrollment was exclusionary, as was more than three episodes of alcohol use during treatment. Daily benzodiazepine use at enrollment was also exclusionary due to risk for maternal seizures during inpatient induction (as determined on an individual basis by the overseeing psychiatrist) was exclusionary. Other substance use was not exclusionary, nor was maternal consumption of prescribed psychotropic medications. Participants were required to comply with study procedures, including periodic fetal monitoring, urine toxicology requirements and daily observed buprenorphine dosing at the center; more than 5 consecutive episodes of missed dosing resulted in disenrollment from the protocol. Women provided weekly research urine samples for toxicology screening which were analyzed for illicit substance use/licit substance misuse. The protocol was approved by the overseeing institutional review board and all participants provided informed written consent.

Participants either underwent a 3-day inpatient buprenorphine induction based on the MOTHER study (Jones et al., 2010) or were admitted to the protocol on a stable dose of buprenorphine that was prescribed by another provider prior to pregnancy. Participants in the latter group transferred all obstetric and psychiatric care to CAP program physicians for the duration of the pregnancy. All participants attended intensive outpatient substance use disorder treatment at the center, where they also received obstetric and psychiatric care for co-occurring disorders. Daily buprenorphine dosing was observed through tablet dissolving. Weekly urine samples were analyzed for illicit substance use/licit substance misuse including: amphetamines, barbiturates, buprenorphine, benzodiazepines, cocaine, THC, methamphetamine, methadone, opiates (morphine), and oxycodone (see Table 1 for cut-off values). Infants were delivered at a hospital on the same campus as the treatment center; pediatric care for infants was available at the center.

Infants were evaluated for symptoms/signs of NAS using a modified version of the Finnegan scoring system (Jansson et al., 2009) conducted every 3–4 h, and all were hospitalized for a minimum of 4 days after delivery for observation. Pharmacotherapy for NAS in the hospital of infant birth included oral morphine sulfate with a secondary medication (clonidine, orally) added for infants reaching maximal doses of morphine. All NAS treatment occurred during the inpatient stay; no infants were discharged home on medication. Standard of care for infants after delivery in the hospital of record included rooming in with their mothers.

2.1. Analytic plan

The primary outcome measure of NAS severity was defined as the total morphine treatment dose, in 0.10 mg increments, administered to infants during hospitalization. Maternal pharmacologic exposure was based on buprenorphine dose (mg); other substances included cigarette use (mean cigarettes per day during treatment) and exposure to illicit substance use/licit substance misuse during treatment, operationalized as the percent of positive urine toxicology tests for any substance during treatment and the percent in which only opioids were detected. A binary variable (0 = none; 1 = > 1) was also created indicating any positive toxicology screen during treatment. Additional maternal variables included maternal age and two measures of opioid use severity: age at first regular opioid use and number of years of regular use.

Negative binomial regression was used to test hypotheses, as it is appropriate for a count distribution (NAS severity, measured in 0.10 mg morphine increments) with many zero values (Allison, 2012), and overdispersion (conditional variance > conditional mean; Coxe et al., 2009). The relation of maternal buprenorphine dose at delivery and each explanatory risk factor with NAS severity was evaluated in single predictor negative binomial models. Multivariable models assessed the association of buprenorphine dose with NAS severity adjusting for maternal characteristics. To aid with interpretation of model coefficients, continuous control variables were centered at the mean (Aiken and West, 2017). In addition, exposure to illicit substance use/licit substance misuse during maternal treatment was tested as a moderator of the relation between maternal buprenorphine dose and NAS severity by entering an interaction term (substance exposure by maternal buprenorphine dose) into negative binomial models. Model fit was assessed using likelihood ratio chi-square, and Akaike (AIC) and Bayesian (BIC) information criteria were used to compare relative fit between models.

The effect of maternal buprenorphine use on birth parameter outcomes (i.e., weight, length and head circumference) was evaluated through linear regression models specified to test buprenorphine dose and other explanatory risk factors in single predictor and adjusted models. All statistical analyses were performed using SPSS version 24 (IBM Corp. Released, 2015).

3. Results

A total of 127 pregnant women provided consent for study participation; 41 completed the protocol through delivery. Participants who left the protocol did so for a variety of reasons (Fig. 1). Of the 86 participants who left the protocol for any reason, 42 remained in drug treatment but switched to methadone maintenance and 44 left drug treatment at the center. Data describing fetal neurobehavioral development in the final sample are presented elsewhere (Jansson et al., 2017).

3.1. Maternal characteristics

Maternal participants (n = 41) were predominantly Caucasian (92.7%), with a mean (*SD*) age of 26.7 (*4.6*) years, and 11.4 (*2.0*) years of education. All were multiparous; participants had on average 2.2 (*1.2*) prior deliveries at term and 4 women (9.8%) had prior preterm deliveries. Almost all (38, 92.7%) smoked cigarettes, with a mean of 9.7 (*6.7*) cigarettes smoked per day. Most had at least one psychiatric diagnosis; 25 (61.0%) depression; 6 (14.6%) anxiety, 7 (17.1%) other diagnosis. Seventeen (41.5%) received psychiatric medications during the current pregnancy, all SRIs. Nearly half (n = 18; 43.9%) had no positive urine toxicology results for illicit substance use/licit substance misuse after study enrollment, despite frequent testing (Mean number of urine toxicology testings = 17.8). Maternal substance exposure and drug treatment information is presented in Table 1. Of those with positive toxicology screens, 4 (17.4%) included opioid use only. Maternal urine toxicology screening at delivery was negative for most (38, 92.7%) participants, with 1 positive for THC and 2 for illicit opioid use.