Drug and Alcohol Dependence 134 (2014) 414–417

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Short communication

Neonatal outcomes and their relationship to maternal buprenorphine dose during pregnancy

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ARTICLE INFO

Article history:
Received 12 July 2013
Received in revised form 6 November 2013
Accepted 7 November 2013
Available online 16 November 2013

Keywords:
Opioid use disorder
Pregnancy
Buprenorphine
Neonate
Neonatal abstinence syndrome

ABSTRACT

Background: Buprenorphine pharmacotherapy for opioid-dependent pregnant women is associated with maternal and neonatal outcomes superior to untreated opioid dependence. However, the literature is inconsistent regarding the possible existence of a dose–response relationship between maternal buprenorphine dose and neonatal clinical outcomes.
Methods: The present secondary analysis study (1) examined the relationship between maternal buprenorphine dose at delivery and neonatal abstinence syndrome (NAS) peak score, estimated gestational age at delivery, Apgar scores at 1 and 5 min, neonatal head circumference, length, and weight at birth, amount of morphine needed to treat NAS, duration of NAS treatment, and duration of neonatal hospital stay and (2) compared neonates who required pharmacotherapy for NAS to neonates who did not require such pharmacotherapy on these same outcomes, in 58 opioid-dependent pregnant women receiving buprenorphine as participants in a randomized clinical trial.
Results: (1) Analyses failed to provide evidence of a relationship between maternal buprenorphine dose at delivery and any of the 10 outcomes (all p-values > .48) and (2) significant mean differences between the untreated ($n = 31$) and treated ($n = 27$) for NAS groups were found for duration of neonatal hospital stay and NAS peak score (both p-values < .001).
Conclusions: (1) Findings failed to support the existence of a dose–response relationship between maternal buprenorphine dose at delivery and any of 10 neonatal clinical outcomes, including NAS severity and (2) that infants treated for NAS had a higher mean NAS peak score and, spent a longer time in the hospital than did the group not treated for NAS is unsurprising.

1. Introduction

Research has strongly suggested that buprenorphine pharmacotherapy for pregnant women with opioid use disorder is associated with superior maternal and neonatal outcomes relative to untreated opioid use disorder. Moreover, in terms of the relative efficacy of buprenorphine compared to methadone during pregnancy, Jones et al. (2012b) presented a systematic review of the literature in which they reported that buprenorphine and methadone have comparable maternal efficacy, that buprenorphine may produce less physiological suppression of fetal heart rate and movements than methadone, and that exposure in utero to buprenorphine results in a less severe neonatal abstinence syndrome (NAS) than methadone. A focus on NAS is of considerable current importance because its incidence in the US has increased from 1.2 to 3.4 per 1000 hospital live births from 2000 to 2009. During this same period, mean hospital charges for treatment of neonates with NAS increased more than 35%, from $39,400 to $53,400 (Patrick et al., 2012).

However, the relationship between maternal buprenorphine dose and either neonatal abstinence syndrome (NAS) incidence or severity has been inconsistent (Jones et al., 2005; Lejeune et al.,

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http://dx.doi.org/10.1016/j.drugalcdep.2013.11.006

2006), a finding also reported for methadone (Jones et al., 2013; O'Grady et al., 2013). Infant urinary concentrations of norbuprenorphine, the primary buprenorphine metabolite, have been found to correlate with infant length of hospital stay but not duration of NAS pharmacotherapy (Hytinantti et al., 2008). In line with this finding, total buprenorphine concentrations in meconium and buprenorphine/norbuprenorphine ratios were associated with the presence of a diagnosable NAS, although not necessarily one requiring pharmacotherapy (Kacinko et al., 2008). Examination of the possibility of such a dose–response relationship between maternal dose of buprenorphine and neonatal outcomes including NAS severity is of considerable clinical importance, because determination of the existence of such a relationship would have implications for the medical management of pregnant women with opioid use disorder. Such a finding would suggest the potential need to limit or restrict the buprenorphine dose for the mother in order to reduce the deleterious impact of a higher dose on the neonate. Such a restriction could be potentially disadvantageous to the treatment of the mother if the dose was insufficient to ameliorate or reduce illicit opioid use or licit opioid misuse. Moreover, knowing the extent to which buprenorphine-exposed neonates who require pharmacotherapy for NAS differ from buprenorphine-exposed neonates who do not require pharmacotherapy for NAS on clinically relevant neonatal outcomes would provide information that could be used to guide the medical management of NAS.

Research on the relationship between buprenorphine dose and neonatal clinical outcomes has largely although not entirely focused on the differences between buprenorphine and methadone in NAS occurrence or severity, and to a lesser extent on morphine dose to treat NAS, and length of hospitalization for NAS treatment. Research on the relationship between buprenorphine dose and severity of NAS has typically failed to find any such relationship (Bakstad et al., 2009; Fischer et al., 2006; Kacinko et al., 2008; Lejeune et al., 2006; O'Connor et al., 2011). Metz et al. (2011) also reported a failure to find relationships between buprenorphine dose and need for and amount of NAS medication, peak NAS score, and duration of NAS treatment in a sample of 26 neonates prenatally exposed to buprenorphine as part of comprehensive treatment program for maternal opioid use disorder.

The purpose of this secondary analysis study was twofold: (1) to examine the dose–response relationship between maternal buprenorphine and a variety of neonatal clinical outcomes and (2) to compare neonates who require pharmacotherapy for NAS to neonates who do not require such pharmacotherapy on these same outcomes, in a sample of 58 mothers with opioid use disorders who participated in a randomized clinical trial of opioid-agonist pharmacotherapy.

2. Methods

2.1. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) Study

MOTHER (Jones et al., 2010, 2012a) was a double-blind, double-dummy, flexible-dosing, parallel-group randomized clinical trial comparing outcomes for pregnant women with opioid use disorders and their neonates receiving either buprenorphine or methadone pharmacotherapy provided in the context of comprehensive care. Study findings showed that, on average, neonates in the buprenorphine condition compared to neonates in the methadone condition required significantly less morphine to treat NAS, has a shorter NAS treatment course, and spent significantly less time in the hospital. Details about the MOTHER study necessary to understanding the current analyses follow. More complete information about MOTHER is available in Jones et al. (2010, 2012a,b).

2.2. Participants

One-hundred-seventy-five pregnant women with opioid use disorders meeting eligibility criteria participated in the study. Women were randomly assigned to either the buprenorphine or the methadone condition in which double-blind, double-dummy, study medication was dispensed daily with sublingual tablets (buprenorphine or placebo) followed by oral liquid (methadone or placebo). The buprenorphine condition utilized a flexible dose range of 2–32 mg. Concomitant drug use was reduced through the use of monetary vouchers provided to participants for providing three-times-weekly urine samples testing negative for opioids (other than their study medication) and other illicit or non-prescribed drugs. One-hundred-thirty-one of the 175 maternal participants delivered neonates while enrolled in the study, of whom 58 were in the buprenorphine condition. The secondary analyses reported below use the data from the neonates of these 58 maternal participants.

2.3. Neonatal outcomes

2.3.1. Neonatal abstinence syndrome (NAS). All infants were hospitalized for a minimum of 4 days for observation for the development of NAS. Regardless of in-patient or out-patient status, neonates were assessed for NAS by trained staff for a minimum of 10 days using a modified Finnegan Scale. Oral morphine sulfate was used for NAS treatment. All pharmacotherapy for NAS was delivered to the infants during an inpatient hospital stay; no infant received medication for the treatment of NAS as an outpatient. A NAS peak score, the highest NAS score the neonate obtained during this period, was calculated for each neonate.

2.3.2. Other neonatal outcomes. Additional neonatal outcomes included estimated gestational age at delivery (weeks), Apgar scores at 1 and 5 min, neonatal head circumference (cm), length (cm), and weight at birth (g), total amount of morphine needed to treat NAS (mg), duration of treatment for NAS (days), and duration of neonatal hospital stay (days). See Jones et al. (2010) for detailed descriptions of all measures.

2.4. Statistical analyses

As in the primary outcomes paper (Jones et al., 2010), total amount of morphine needed to treat NAS (mg), infant length of stay in the hospital (days), number of days medicated for NAS (days), estimated gestational age at delivery (weeks), and Apgar scores at 1 and 5 min were analyzed with Poisson regression, allowing for overdispersion. Peak score on the MOTHER NAS scale during the assessment period, and infant head circumference, birth weight, and length were analyzed with ordinary least squares regression. Maternal buprenorphine dose (mg) at delivery, collected as part of the MOTHER trial, and site of MOTHER data collection (US Urban [Baltimore, MD; Philadelphia, PA; Detroit MI; Providence, RI] *v.* US Rural [Burlington, VT; Nashville, TN] *v.* European [Vienna]) served as the explanatory variables in all analyses.

3. Results

Maternal buprenorphine dose at delivery was 4–32 mg ($M = 16.6$, $SD = 7.3$). Table 1 contains the descriptive statistics as well as the parameter estimates and standard errors associated with the analyses of the 10 neonatal outcomes. Analyses failed to provide any evidence of a relationship between maternal buprenorphine dose at delivery and the respective outcome measure (all p's > .48).

For those infants requiring pharmacotherapy for NAS, the mean total amount of morphine (mg) was 3.5 ($SD = 3.5$), while the mean duration of treatment for NAS was 9.8 days ($SD = 5.5$). Significant mean differences between the untreated ($n = 31$) and treated ($n = 27$) for NAS groups were found for duration of neonatal hospital stay, $F(1, 54) = 15.5$, $p < .001$, [$M = 6.5$ days ($SE = 1.0$) *v.* $M = 14.1$ days ($SE = 1.6$), respectively] and NAS peak score, $F(1, 53) = 66.3$, $p < .001$, [$M = 8.5$ ($SE = .4$) *v.* $M = 13.9$ ($SE = .4$), respectively]. All other tests of mean differences between the NAS treatment status groups were nonsignificant (all p-values > .4).

4. Discussion

This secondary analysis study of data from the MOTHER trial failed to support any relationship between maternal buprenorphine dose at delivery and any of a number of clinically important neonatal outcomes. There was no relationship between maternal buprenorphine dose at delivery and NAS severity, as measured by peak NAS score, total amount of morphine needed to treat NAS, duration of treatment for NAS, or duration of neonatal hospital stay, or with any of 6 other neonatal clinical outcomes, including estimated gestational age at delivery, Apgar scores at 1 and 5 min, neonatal head circumference, length, and weight at birth. These