Does Maternal Buprenorphine Dose Affect Severity or Incidence of Neonatal Abstinence Syndrome?

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Original Research

Objectives: To measure the incidence, onset, duration, and severity of neonatal abstinence syndrome (NAS) in infants born to mothers receiving buprenorphine and to assess the association between buprenorphine dose and NAS outcomes.

Methods: We reviewed charts of all mother–infant pairs maintained on buprenorphine who delivered in our hospital from January 1, 2000 to April 1, 2016.

Results: In 89 infants, NAS incidence requiring morphine was 43.8%. Means for morphine-treated infants included: 55.2 hours to morphine start, 15.9 days on morphine, and 20 days hospital stay. NAS requiring morphine treatment occurred in 48.5% and 41.4% of infants of mothers receiving ≤8 mg/d buprenorphine versus >8 mg/d, respectively (P = 0.39). We found no significant associations of maternal buprenorphine dose with peak NAS score, NAS severity requiring morphine, time to morphine start, peak morphine dose, or days on morphine. Among the other factors examined, only exclusive breastfeeding was significantly associated with neonatal outcomes, specifically lower odds of morphine treatment (odds ratio 0.24, P = 0.003).

Conclusions: These findings suggest higher buprenorphine doses can be prescribed to pregnant women receiving medication therapy for addiction without increasing NAS severity. Our finding of reduced risk of NAS requiring morphine treatment also suggests breastfeeding is both safe and beneficial for these infants and should be encouraged.

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According to the American College of Obstetricians and Gynecologists in 2012, 1% of pregnant women reported nonmedical use of opioid medication and 0.1% reported use of heroin in the 30 days before being surveyed ([ACOG, 2012]). Currently, the standard of care for maternal opioid use disorder (OUD) in pregnancy is methadone, which has been shown in multiple studies to improve both maternal and fetal outcomes, including mortality, compared with no treatment or detoxification ([Stimmel and Adamsons, 1976 ; Kandall, 1993 ; Kakko et al., 2008 ; Peles et al., 2012 ; Pierce et al., 2016]).

Although outcomes for both mother and baby are improved, as with any chronic opioid exposure during pregnancy, maternal opioid treatment can result in neonatal abstinence syndrome (NAS), characterized by hyperirritability of the central nervous system, gastrointestinal tract, and respiratory tract ([Finnegan et al., 1975]). NAS frequently requires prolonged hospitalization and medical monitoring, and interferes with maternal and infant bonding in the newborn period. Between 2000 and 2012, the incidence of neonatal abstinence syndrome increased 383% in the United States ([Ko et al., 2016]).

In 2000, buprenorphine was approved for use in the United States as a treatment for OUD and provides an alternative to methadone. The largest randomized controlled trial comparing buprenorphine and methadone use in pregnancy found infants exposed to buprenorphine required less and shorter treatment courses with morphine to treat NAS compared with neonates exposed to methadone in pregnancy ([Jones et al., 2010]), making buprenorphine very promising.

Unfortunately, there is limited understanding of what factors influence severity of NAS, especially with infants exposed to buprenorphine. Does maternal dose of buprenorphine affects NAS severity is an important question, as this has substantial implications for dose decisions made by patients and providers. The majority of studies looking for a relationship between maternal buprenorphine dose to NAS incidence and severity have not found an association ([Lejeune et al., 2006 ; Kacinko et al., 2008 ; Bakstad et al., 2009 ; O'Connor et al., 2011 ; Kaltenbach et al., 2012 ; Jones et al., 2014 ; Jansson et al., 2017]), but have been limited by small study populations with n < 58, or significant confounding factors such as maternal methadone use (studies grouping both methadone or buprenorphine maintained patients), illicit maternal drug use at time of delivery, different treatments for NAS, or lack of information about potential confounders like tobacco and selective serotonin reuptake inhibitor (SSRI) use ([Lejeune et al., 2006 ; Kaltenbach et al., 2012 ; Jansson et al., 2017]), bringing up concern for missing relationships or relationships being masked by confounding factors. There remains debate around tapering buprenorphine at the end of pregnancy, putting the mother at risk of relapse ([Welle-Strand et al., 2015 ; Bell et al., 2016]). Additional data are needed to examine if there is any relationship between maternal buprenorphine dose and infant NAS severity.

When considering other factors that could influence severity of NAS, even less data are available. A handful of studies have looked for other influencing factors, including breastfeeding ([O'Connor et al., 2013a, 2013b ; Cirillo and Francis, 2016]), tobacco use ([Jones et al., 2013]), sex ([O'Connor et al., 2013a, 2013b]), and SSRIs ([O'Connor et al., 2016]), but again were constrained by small study populations, with most studies looking at methadone rather than buprenorphine. Although the above studies suggested trends, results did not reach significance for buprenorphine-exposed infants when looking at modifiable factors like tobacco, SSRI use, and breastfeeding. O'Connor et al., however, did find significance for sex, with male infants having higher mean peak NAS scores and higher likelihood of requiring medication treatment for NAS (P = 0.005) ([O'Connor et al., 2013a, 2013b]).

To help address the paucity of data, we undertook a retrospective analysis of a cohort of mother–infant dyads treated with buprenorphine at our medical center from 2000 to 2016.

METHODS

Study Design and Population

The design is a retrospective cohort study based on electronic medical records. We audited charts of all pregnant women aged 18 to 53 years of age (and their infants) with *Diagnostic and Statistical Manual of Mental Disorders, Fourth edition* diagnosed opioid dependency with prenatal care from the High Risk OB Outreach Clinic at Swedish Cherry Hill and/or Swedish Ballard Addiction Recovery Services, who delivered at Swedish Medical Center First Hill Campus from January 1, 2000 to April 1, 2016. Exclusion criteria were opioid use relapse leading to transition to methadone maintenance, no drug screen performed at the time of delivery, and inappropriate maternal urine drug screen at the time of delivery (defined as urine drug screen positive for opiates, amphetamines, methamphetamines, cocaine, benzodiazepines, MDMA, PCP, oxycodone, and/or methadone, or negative for buprenorphine). A positive marijuana test did not result in exclusion.

The study was approved by the Institutional Review Board of Swedish medical Center, IRB 5982 S-16.

Procedures

Data reflecting routine antenatal and neonatal care were collected from the electronic medical records system of Swedish Medical Center. All pregnant women were started on and maintained on buprenorphine with daily dose range of 2 to 24 mg. Before delivery, patients were seen every 7 to 14 days for regular prenatal care and urine drug screening. All pregnant women were admitted for labor at the same medical facility, and their buprenorphine dosing was continued throughout labor, delivery, and discharge. All neonates were admitted to the same hospital where they were observed and assessed for NAS every 3 hours by trained nursing staff using the Finnegan scale (Finnegan et al., 1975) for a minimum of 96 hours. Oral morphine sulfate was started for neonates who had 3 consecutive Finnegan scores with a total of 24 or greater. In those infants requiring morphine, morphine was given every 3 hours, starting at 0.05 mg/kg/dose. Morphine doses were increased by 0.02 mg/kg if the infant had 3 further consecutive scores totaling 24 or more. Morphine doses were considered stable when all Finnegan scores for 48 continuous hours were 8 or less, at which time a morphine wean was started. Weans were started at 10% of peak morphine dose and performed every 24 hours as long as average Finnegan scores over the preceding 24 hours were less than 8, there were no scores of 10 or greater in the last 24 hours, and no breakthrough or extra doses of morphine were given in the last 24 hours. Infants were eligible for discharge after 48 hours of observation from last morphine dose.

Measures

Primary outcomes were requirement for morphine treatment (yes/no), peak NAS score, peak morphine dose, time to morphine start, days on morphine, and total duration of hospital stay. Our key independent variable was maternal buprenorphine dose at the time of delivery. Maternal covariates were age, number of pregnancies, number of live births, number of prenatal visits, duration of buprenorphine prior to delivery, urine drug screen results at time of delivery, tobacco use, and SSRI use. Neonatal covariates were gestational age, sex, birth weight, breastfeeding status (exclusive breast feeding defined as milk from the breast only versus non exclusive breast feeding, meaning use of formula or both formula and breast milk), and APGAR scores at 1 and 5 minutes.

Statistical Analyses

T tests were done comparing mother–infants dyads requiring morphine and those who did not. Correlation coefficients (*r* values), confidence intervals (CIs), and regressions (multiple for continuous outcomes, logistic for binary outcomes) were calculated for each NAS severity marker to further assess correlation between maternal buprenorphine dose and

peak NAS score, time to morphine start, peak morphine dose, and days on morphine theray. Regression analysis examined both forward and backward stepwise procedures, retaining only results which were consistent with both. All analyses were performed with IBM SPSS 19.

RESULTS

Whole Sample (n = 89)

We reviewed records of 152 pregnant women admitted to the hospital for labor and delivery, and prescribed buprenorphine during their pregnancy. Forty-two women were excluded for relapse to illicit opioids during pregnancy and/or transition to methadone by time of delivery. Other reasons for exclusion were patients self-tapering themselves off buprenorphine by time of delivery (n = 3), inappropriate urine drug screens at time of admission to the hospital for delivery (n = 7), no urine drug screen done at time of admission (n = 3), and transfer of prenatal care to providers outside our system (n = 8). A total of 89 women met all eligibility criteria for study inclusion. On day of admission to labor and delivery, 85 women had urine drug screens positive for buprenorphine only and 4 had drug screens positive for buprenorphine and marijuana. Table 1 shows maternal and infant demographics.

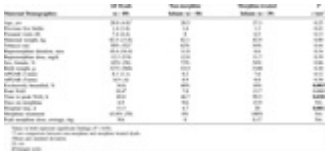

TABLE 1

Incidence of NAS requiring medication overall was 43.8% (39 out of 89 infants). Average peak NAS score in infants with NAS requiring medication was 13.7. Average start time for morphine initiation in infants with NAS requiring medication was 55.2 hours of life, with an average peak morphine dose of 0.17 mg morphine/per dose. Treated infants averaged 15.9 days on morphine with a total hospital stay of 20 days. Infants who did not require medication for NAS had an average stay of 4.7 days. As expected, infants who received morphine required longer hospital stays ($P = 0.001$) and increased time to reach peak NAS scores ($P = 0.030$).

When women were stratified based on their dose of buprenorphine, 33 women had buprenorphine doses at time of delivery of 8 mg/d or less and 56 women had buprenorphine doses above 8 mg/d. The incidence of NAS requiring medication was 48.5% for the infants of mothers who took 8 mg/d or less of buprenorphine and 41.4% for the infants of mothers who took more than 8 mg/d of buprenorphine, a difference which was not statistically significant ($P = 0.50$).

Logistic regression across our whole sample (n = 89) predicting infant need for morphine found exclusive breastfeeding to be the only significant predictor ($P = 0.002$, odds ratio [OR] 0.24). Logistic analysis permitted stepwise entry of maternal buprenorphine dose, buprenorphine duration, previous live births, weight, prenatal visits, tobacco use, and infant birth weight, APGAR scores and sex, but no other variable were significant predictors or modified the relationship between breastfeeding and morphine treatment. Among exclusively breastfed infants, 23% needed morphine treatment, compared with 55% of nonexclusively breastfed infants requiring morphine ($P = 0.003$). Exclusively breastfeeding mothers and nonexclusively breastfeeding mothers did not differ in buprenorphine dose (12.4 mg/d for exclusively breastfeeding mothers vs 12.2 mg/d for nonexclusive breastfeeders).

Given the observed negative relationship between breastfeeding and the need for morphine treatment, we conducted further comparisons of the exclusively breastfed and other infants (Table 2) and found a number of differences. Exclusively breastfeeding mothers had more prenatal visits, smoked fewer cigarettes daily, and had less SSRI use. During pregnancy, no mother who exclusively breastfed had pre-eclampsia, whereas 9% (n = 5) of the other mothers did ($P = 0.09$). Infants who were exclusively breastfed had longer gestation periods and higher APGAR scores at 1 and 5 minutes. Hospital stay for exclusively breastfed infants was 7.7 days versus 13.3 days for other infants ($P = 0.01$).

	Nonexclusively Breastfed (n = 58)	Exclusively Breastfed (n = 31)	P*
Gestation, wks	38.8	40.1	0.001
Female, %	57%	80%	0.032
Prenatal visits	6.4	9.2	0.005
Tobaccoid	1.9	0.64	0.052
SSRI use	12%	0%	0.044
Pre-eclampsia	9%	0%	0.092
APGAR-1	7.9	8.4	0.041
APGAR-5	8.8	9.1	0.001
Hospital LOS	13.3	7.7	0.011

*T test and chi-square comparisons.

TABLE 2

We then used logistic regression across our whole sample to determine the unique predictors of exclusive breastfeeding, using the potential predictors in Table 2. Our final logistic regression equation found that exclusively breastfed infants had longer gestational periods (40.1 vs 38.8 weeks; $P = 0.004$) and were more likely to be female (80% vs 57%; $P = 0.014$).

Morphine-treated Infants (n = 39)

As shown in Fig. 1, there were no significant relationship between maternal buprenorphine dose to peak Finnegan NAS score ($r = -0.07$, $P = 0.66$, 95% CI −0.38 to 0.25), peak morphine dose ($r = 0.20$, $P = 0.24$, 95% CI −0.12 to 0.48), time to morphine start ($r = -0.22$, $P = 0.18$, 95% CI −0.50 to 0.10), or days on morphine ($r = 0.31$, $P = 0.058$, 95% CI −0.01 to 0.57).

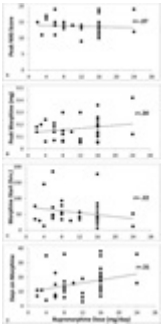

FIGURE 1

When exclusive breastfeeding status was examined in morphine-treated infants, there were no statistically significant effects of exclusive breastfeeding on peak morphine dose, days on morphine or hospital stay when looking only at those infants already on morphine.

However, sex differences were noted for peak morphine dose in morphine-treated infants, with males having a higher peak morphine dose (0.20 mg/dose for males, SD = 0.11 vs 0.14 mg/dose for females, $r = 0.34$, $P = 0.036$). No other variable among maternal buprenorphine dose, buprenorphine duration, previous live births, weight, prenatal visits, tobacco use and infant birth weight, or APGAR scores significantly added to the variance accounted for by gender when regression was done.

DISCUSSION

Our study suggests there is no relationship between maternal buprenorphine dose and NAS incidence and severity, as measured by peak NAS score, time to morphine start, peak morphine dose, or days on morphine. This is in agreement with prior smaller studies, and should reassure clinicians caring for pregnant women with OUD that it is safe to titrate buprenorphine dose to the amount needed to keep women comfortable, engaged in treatment, and minimize their risk of relapse without fear of increasing NAS incidence or severity in the infant.

It is possible the lack of association between maternal buprenorphine dose and incidence and severity of NAS is due to varying maternal and/or infant metabolism. Other studies have found correlations between norbuprenorphine, the major metabolite of buprenorphine, and NAS severity, but also noted that maternal dose of buprenorphine does not correlate well to norbuprenorphine levels (Hytinantt et al., 2008 ; Kacinko et al., 2008 ; Concheiro et al., 2010). This may be due to the complexity of buprenorphine metabolism in pregnancy, potentially influenced by maternal, fetal, and placental factors.

Our study also showed exclusive breastfeeding to be significantly associated with a lower incidence of NAS requiring morphine and shorter length of stay. Studies show very little maternal buprenorphine passes into breast milk and infant plasma levels are low or undetectable (Jansson et al., 2016), suggesting this practice is safe. A recent systematic review of published studies from 2000 to 2016 yielded 10 studies looking at breastfeeding and NAS severity, and 8 of them showed benefits for breastfeeding; however, only 2 studies included mothers maintained on buprenorphine (Cirillo and Francis, 2016). There has also been growing research showing beneficial effects of rooming in and other nonpharmacological therapies for NAS, of which breast feeding is only one component (Macmillan et al., 2018 ; Ryan et al., 2018). Given that breastfeeding is a low-cost measure with known benefits outside of NAS and limited literature showing beneficial results in NAS, larger clinical trials of interventions to increase breastfeeding appear warranted. Future studies on whether partial breastfeeding confers beneficial results similar to exclusive breastfeeding is also warranted, as our study compared only exclusive breast feeding versus nonexclusive breastfeeding, and also if it is breastfeeding versus other nonpharmacologic factors that accompany breast feeding (infant maternal physical contact, rooming in, etc) that improve outcomes.

Our study has several strengths. With sample size of 89, this study is larger than most other studies and has greater power to detect differences in NAS severity based on maternal buprenorphine dose. Prior published studies focused on buprenorphine alone range in numbers from 12 to 58 patients (Bakstad et al., 2009 ; O'Connor et al., 2011 ; Jones et al., 2014 ; Jansson et al., 2017) or included methadone patients (Kaltenbach et al., 2012). In addition, our study addresses potential confounding factors that other studies did not. The study excluded inappropriate maternal drug screens at time of delivery, removing a confounding factor in results (Jansson et al., 2017), and examined many other potential confounders including breastfeeding, sex, gestational age, APGAR scores, SSRIs, and tobacco use that other studies did not account for. Thus, we believe the lack of observed relationships between maternal buprenorphine dose and NAS severity is reliable, and not a result of "masking" by a confounding variable. We also believe our results can be applied to most populations, as buprenorphine doses ranged from 2 to 24 mg/d, and we believe virtually all pregnant women receive dosing in this range.

Our cohort study is subject to a number of limitations. The sample size, while larger than most other studies in this area, was still modest and limited our power to detect weak associations between maternal buprenorphine dose and NAS. A number of factors affect potential generalizability to all pregnant women being treated with buprenorphine. There was a difference in numbers of patients from earlier in the study period versus later in the study period. Although we included all patients starting January 1, 2000 and going to April 1, 2016, buprenorphine was not widely prescribed initially, and the majority of study patients entered into care in the latter half of the study period. Prenatal care has changed some over the 16-year period of the study, and this may have some effect on results. We did not exclude mothers with positive marijuana screens at the time of delivery because marijuana can persist in the urine for weeks after last use and is legal in the state of Washington. However, only 4 of the 89 patients tested positive for marijuana, with 2 infants requiring morphine and 2 not, so it is unlikely to have affected our results dramatically. Nine infants requiring morphine for NAS were started on morphine doses lower than the normal 0.05 mg/kg due to provider concern for other medical issues or infant sedation. These infants, when compared with the other infants who received protocol-based initial doses of morphine, had no difference in sex, maternal age, maternal buprenorphine dose, time to start morphine, or peak NAS scores, but did have fewer prenatal visits (mean visits 4 for lower-dose morphine vs 7.4; $P = 0.038$), and lower peak morphine doses. Although they were started on lower than normal morphine doses, the 9 infants did receive NAS scoring per protocol, and morphine was increased per protocol. It may be these 9 infants represent a subset of infants with complex presentations due to medical issues. In addition, 2 of the infants treated for NAS also received clonidine to help symptoms. This may well have affected peak morphine dose and days of treatment,

but we have no way to model that in our analyses. Finally, as an observational study, our findings are potentially subject to effects of unmeasured confounders and associations in observational studies may not be causal. Successful breastfeeding probably reflects a combination of mother–infant factors. Our regression analyses predicting breastfeeding indicated that breastfed infants were slightly more mature, in terms of gestational age, and more likely to be female (80% vs 57%). We also saw that exclusively breastfeeding mothers had more prenatal visits, smoked fewer cigarettes, and had less SSRI use. It may be that successful breastfeeding results from a combination of more motivated mothers and more capable infants, and infants with more severe NAS may be less able to breastfeed.

CONCLUSIONS

Overall, our findings suggest there is no association between maternal buprenorphine dose and incidence and severity of NAS, adding to the limited literature on the outcomes of buprenorphine in pregnancy. Providers should feel comfortable going to higher doses of buprenorphine if needed to keep women engaged in care, minimize cravings/withdrawal, and reduce risk of relapse. Our findings also support present literature encouraging breastfeeding for infants with NAS, though future study is needed. Particularly in the setting of America's current epidemic of opioid dependence, our data provide more support for the safety of buprenorphine treatment of pregnant women with opioid use disorder.

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