Substance Abuse: Research and Treatment

ORIGINAL RESEARCH

A Comparison of Buprenorphine + Naloxone to Buprenorphine and Methadone in the Treatment of Opioid Dependence during Pregnancy: Maternal and Neonatal Outcomes

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Abstract: Given that buprenorphine + naloxone is prescribed for opioid-dependent pregnant women, it is important to examine the extent to which it differs from buprenorphine alone, methadone, or methadone-assisted withdrawal on neonatal and maternal outcomes. Summary statistics on maternal and neonatal outcomes were collected from 7 previously published studies examining treatment for opioid-dependent pregnant women that represented a range of research methodologies. Outcomes from these studies were compared to the same outcomes for 10 women treated with the combined buprenorphine + naloxone product. There were no significant differences in maternal outcomes for buprenorphine + naloxone compared to buprenorphine, methadone, or methadone-assisted withdrawal. Preliminary findings suggest no significant adverse maternal or neonatal outcomes related to the use of buprenorphine + naloxone for the treatment of opioid dependence during pregnancy. However, further research should examine possible differences between buprenorphine + naloxone and buprenorphine alone or methadone in fetal physical development.

Keywords: buprenorphine, methadone, opioid dependence, pregnancy, neonates

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Background

Since the late 1960s, methadone has been prescribed to pregnant women to treat opioid dependence.[1] Research conducted during the last decade indicates that maternal outcomes following use of buprenorphine during pregnancy are similar to maternal outcomes following use of methadone during pregnancy.[2–7] However, buprenorphine seems to be superior to methadone in regard to some neonatal outcomes, including yielding a shorter duration of neonatal abstinence syndrome (NAS) and a shorter length of hospital stay.[3,5,8–13]

To date, research on the use of buprenorphine during pregnancy has focused almost exclusively on buprenorphine alone rather than the most commonly prescribed form of buprenorphine in the United States, buprenorphine + naloxone. Buprenorphine + naloxone has been the preferred form of prescribed buprenorphine due to its reduced abuse liability relative to buprenorphine alone.[14,15] This research emphasis on buprenorphine alone is largely due to two reasons. First, pregnant women are advised to limit fetal exposure to exogenous compounds; thus, prescribing buprenorphine alone avoids fetal exposure to naloxone. Second, data from animal studies suggest that prenatal exposure to naloxone may produce maternal and subsequently fetal hormonal changes, such as increased corticotrophin releasing hormone and the adrenocorticotropic hormone.[16,17]

Little is known about buprenorphine + naloxone relative to either buprenorphine alone, methadone, or methadone-assisted withdrawal in the treatment of opioid dependence during pregnancy. Buprenorphine + naloxone is now being prescribed to opioid-dependent pregnant women. It is therefore important to examine whether neonatal and maternal treatment outcomes for pregnant women being treated for opioid dependence with buprenorphine + naloxone differ from pregnant women in treatment for opioid dependence with buprenorphine, methadone, or methadone-assisted withdrawal on these same outcomes.

The current study had 3 objectives. Neonatal and maternal outcomes from a group of opioid-dependent women who were prescribed buprenorphine + naloxone during their pregnancy were compared to (1) groups of opioid-dependent pregnant women prescribed buprenorphine alone, (2) groups of opioid-dependent pregnant women prescribed methadone, and (3) a group of opioid-dependent pregnant women who completed a 7-day methadone-assisted withdrawal.

Methods

All data presented in this review come from previously published studies that represent a wide range of studies on buprenorphine and/or methadone pharmacotherapy during pregnancy.[2–4,18–21] We reviewed the literature on buprenorphine treatment of pregnant women, as summarized by Jones et al,[22] and selected what we considered to be representative high-quality studies that reported a common subset of outcome measures and provided data that could be easily subjected to re-analysis. We also took care in choosing studies that represented a range of study methodologies; both randomized controlled trials and retrospective studies were examined, increasing generalizability of the findings. Several authors of these papers provided additional data (eg, standard deviations) that were not available in their published papers.

Studies

Buprenorphine + naloxone: an initial study of maternal and neonatal safety

Debelak et al[19] conducted a retrospective chart review in a community health setting. There were 10 women who had received buprenorphine + naloxone during the course of their pregnancies. Maternal outcomes reported in this study included cesarean section, days of maternal hospital stay, maternal weight gain, non-normal presentation, analgesia during delivery, drug-screen at delivery, medical complications at delivery, number of prenatal obstetrical visits, fetal presentation at delivery and breastfeeding following delivery. Neonatal outcomes included were: treated for NAS, total amount of morphine for NAS, days treated for NAS, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, and Apgar scores at 1 and 5 minutes. They reported neonatal growth parameters to be within normal limits, with only 40% of the neonates treated for NAS. Mean number of days with NAS treatment was 6.9 (SD = 10.1). Findings indicated that there were no obvious adverse maternal or neonatal outcomes related to the use of combination buprenorphine + naloxone product for treatment of opioid-dependence in pregnant women.

Maternal outcomes were similar to what has been found for women using buprenorphine alone. This study has several limitations: the sample size is small, it is retrospective, and it does not control for potential confounding variables.

Comparing maternal and/or neonatal outcomes: methadone versus buprenorphine

Czerkes et al[18] conducted a retrospective chart review from 2004–2008 that examined differences in outcomes in neonates born to women who had been prescribed methadone (n = 101) or buprenorphine (n = 68) during pregnancy. Participants were excluded if the delivery was not performed at Maine Medical Center or if there was preterm delivery (before 37 weeks of gestation). The following neonatal outcomes were measured: treated for NAS, length of hospital stay, mean neonatal abstinence score, neonates requiring treatment, birth weight, Cord pH, 1 and 5 minute Apgar scores. The Finnegan scale was used to evaluate NAS scores. Neonates in the buprenorphine group had a lower mean NAS score than neonates in the methadone group. Number of neonates (48.8% versus 73.3%, $P < 0.001$) treated for NAS and mean length of hospital stay (8.4 versus 15.7 days, $P < 0.0001$) of those neonates treated were also significantly lower in the buprenorphine group. Analyses also revealed no significant differences in maternal characteristics between the two groups. As a retrospective chart review, this study does not control for potential confounding variables that might have been related to outcome.

Fischer et al[2] conducted a randomized, double-dummy, double-blind, flexible-dosing trial comparing buprenorphine to methadone in opioid-addicted pregnant women to evaluate safety and efficacy of the two medications in pregnant women. Included participants provided informed consent, and were willing to follow the protocol and cease use of illegal drugs. Women with high-risk pregnancies, or additional severe psychiatric or somatic diseases were excluded. The maternal outcome reported, separately for buprenorphine and methadone conditions, was cesarean section. Neonatal outcomes reported were: treated for NAS, total amount of morphine for NAS, days treated for NAS, birth weight, preterm birth, gestational age at delivery, and Apgar scores at 1 and 5 minutes. The Finnegan scale was used to assess NAS. Eighteen women were randomly assigned to either buprenorphine or methadone. There were 6 women in the methadone and 8 women in the buprenorphine condition at delivery. Methadone dose ranges were 40–100 mg while buprenorphine dose ranges were 8–24 mg. Retention was higher in the buprenorphine condition, whereas methadone was more effective than buprenorphine for preventing the use of additional opioids ($P < 0.05$). Although this study is a tightly controlled randomized trial, its sample size is small.

Metz et al[21] examined maternal and neonatal outcomes in pregnant opioid-agonist-maintained women in a randomized clinical trial compared to a group of women undergoing a structured standard pharmacotherapy protocol with either buprenorphine or methadone at the Medical University of Vienna. The women included in the randomized controlled trial portion were part of Jones et al.[4] Therefore, only data from the women that underwent the structured standard pharmacotherapy protocol with either buprenorphine or methadone were included in the present paper. Included participants were 18 to 41 years of age, had a single fetus pregnancy, and were not dropouts from the clinical trial in the same study. Women were excluded from the study if they had an abortion or miscarriage, or decided to deliver at another clinic. The maternal outcomes reported were cesarean section and urine toxicology during the third trimester. The neonatal outcomes reported were treatment for NAS, total amount of morphine for NAS, days treated for NAS, days of hospital stay, head circumference, birth weight, infant length, gestational age at delivery, and Apgar scores at 1 and 5 minutes. NAS was assessed using a modified version of the Finnegan scale. Opioid maintenance medication was determined on an individualized basis and chosen according to patient preference for buprenorphine or methadone, as well as according to medical criteria. Maternal outcomes were fairly similar in the buprenorphine and methadone groups, apart from more positive urine toxicologies overall in the methadone than the buprenorphine group. Neonatal outcomes were superior in the buprenorphine than in the methadone group in terms of gestational age at delivery and the following physical characteristics: body length, body weight, and head circumference. Fewer neonates in

the buprenorphine group needed NAS treatment and among neonates who did need treatment, total morphine dose was lower and days of morphine treatment were fewer compared to neonates in the methadone group. Potential limitations with this study are that the women in the structured standard protocol condition were probably more severely addicted women than the women in the clinical trial. Moreover, many participants used benzodiazepines, whereas this was an exclusion criteria in the clinical trial.

Jones et al[3] conducted a randomized, double-blind, double-dummy, flexible-dosing parallel-group controlled trial that compared NAS in neonates born to women maintained on buprenorphine or methadone. Included participants were aged 21–40 years, had an estimated gestational age of 16–30 weeks, currently met DSM-IV criteria for opioid dependence, requested maintenance therapy, reported using opioids on >4 days during the past 7 days, and had a positive urine sample at intake. Excluded participants had a positive urine sample for undocumented methadone at intake, alcohol abuse or dependence according to DSM-IV criteria, used benzodiazepines > 7 days per month or >1 day per week. Women who received co-medication for another Axis I disorder or who had a serious medical illness that might compromise study participation were also excluded. Thirty women who met all of the eligibility criteria were randomized to either the buprenorphine or methadone condition. At delivery, 11 women in the methadone and 9 in the buprenorphine group had completed the study. Maternal outcomes reported were: cesarean section, days of hospital stay, non-normal presentation, analgesia during delivery, drug screen at delivery and maternal medical complications. Neonatal outcomes included were: treated for NAS, total amount of morphine for NAS, NAS peak score, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, and Apgar scores at 1 and 5 minutes. A modified 19-item Finnegan Scale was used to assess NAS. Morphine sulfate was the pharmacotherapy treatment for NAS. 2 of 10 (one woman gave birth to twins) neonates (20%) exposed to buprenorphine and 5 of 11 (45.5%) exposed to methadone were treated for NAS. The total amount of morphine solution to treat NAS was three times higher in the methadone condition than in the buprenorphine condition, although this difference was not significant (93.1 versus 23.6; $P = 0.3$). Length of hospitalization was significantly shorter for buprenorphine- than for methadone-exposed neonates ($P = 0.02$). As with Fischer et al,[2] this study is a tightly controlled clinical trial with a small sample size.

Jones et al[4] conducted a double-blind, double-dummy, flexible-dosing, randomized study comparing the use of buprenorphine and methadone in 175 pregnant women in comprehensive care at seven international sites. Of the 131 neonates born to the mothers followed to the end of their pregnancies, 73 were exposed in utero to methadone and 58 to buprenorphine. Excluded participants had medical or other condition that may compromise participation in the study, were pending legal action that may contradict participation, or had disorders related to use of alcohol or benzodiazepines. The following maternal outcomes were reported: cesarean section, days of maternal hospital stay, maternal weight gain, non-normal presentation, analgesia during delivery, drug-screen at delivery, medical complications at delivery, number of prenatal obstetrical visits. Neonatal outcomes reported included whether they were treated for NAS, total amount of morphine for NAS, days treated for NAS, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, and Apgar scores at 1 and 5 minutes. NAS was assessed using a modified Finnegan Scale. Dose adjustments were based on medication adherence, urine toxicology results, participant request, and self-reported symptoms of craving or withdrawal. Hospitalized neonates were examined every 4 hours by trained staff, while NAS scores were obtained twice a day for neonates already released to their homes. The mean morphine sulfate dose required to treat the buprenorphine-exposed neonates were significantly lower (1.1 mg versus 10.4 mg, $P < 0.01$) than the dose for methadone-exposed neonates. Buprenorphine-exposed neonates also required a significantly shorter hospital stay (10 days versus 17.5 days, $P < 0.01$) and duration of treatment for NAS (4.1 days versus 9.9 days, $P < 0.01$). A potential limitation with the study is that the numerous exclusion criteria used limits the generalizability of the findings. However, these exclusion criteria ensured a sample where the effects of methadone and

buprenorphine could be studied without the presence of confounding variables.[23]

Maternal and neonatal outcomes: methadone maintenance versus methadone taper

Jones et al[20] conducted a retrospective record review that compared neonatal and maternal outcomes in pregnant women in treatment for opioid dependence. The women received either continuous methadone maintenance (n = 52) or 7-day (n = 28) methadone-assisted withdrawal. The women were not randomized to these treatment options. Methadone-assisted withdrawal inclusion criteria included meeting and refusing methadone maintenance criteria, receiving a prescription for 7 days of methadone assisted withdrawal, and no receipt of medication-assisted tapering for benzodiazepines or alcohol. Medical charts and complete information on delivery outcome had to be available at Johns Hopkins Bayview Medical Center. The maternal outcome reported was a positive drug screen at delivery. Neonatal outcomes included treatment for NAS, days of infant hospital stay, head circumference, birth weight, infant length, pre-term birth, gestational age at delivery, and Apgar score at 1 and 5 minutes. The proportion of women with positive urine toxicology tests for illegal drugs at delivery was more than twice as high (57%) among women in 7-day detoxification compared to women in methadone maintenance (23%). Women in methadone maintenance attended more obstetrical visits and remained in treatment longer than the women with 7-day methadone-assisted withdrawal. There are several limitations with this study, including the fact that its sample size is modest, and it is a retrospective chart review without systematic data collection and information about routine urine testing.

Outcome Measures

Neonatal outcomes

Summary descriptive statistics (frequencies or means and standard deviations) for 10 neonatal outcomes were extracted from the above articles: treated for NAS (yes versus no), total amount of morphine used to treat NAS (mg), number of days treated for NAS, infant length of hospital stay, pre-term (<37 weeks) birth, estimated gestational age at delivery (weeks), Apgar scores at 1 and 5 minutes, infant head circumference (cm), birth weight (gm), and length (cm).

Maternal outcomes

Summary descriptive statistics (frequencies or means and standard deviations) for 8 maternal outcomes were extracted from the above articles: whether the women gave birth through cesarean section (yes versus no), days of maternal hospital stay, maternal weight gain (kg), non-normal presentation of fetus at delivery (yes versus no), used analgesia during delivery (yes versus no), positive drug screening (for opioids [other than their study medication], cocaine, barbiturates, benzodiazepines) at delivery (yes versus no), medical complications at delivery (yes versus no), and number of prenatal obstetrical visits.

Statistical analysis

Two different types of summary statistics were collected from articles that provided comparison data: frequencies for binary variables (eg, treated for NAS: yes versus no) and means and standard deviations for continuous variables (eg, total amount of morphine for NAS). Data were not available for all outcome variables in every article. However, because frequencies were available for the binary outcomes and means and standard deviations were available for the continuous outcomes for the respective groups in each comparison article for which data were available, it was possible to utilize logistic regression to analyze the binary data using an events/trials approach, or analysis of variance to analyze the continuous outcome measures. Because some of the cells for studies that did yield data had zero or very small frequencies, Firth's penalized maximum likelihood approach was utilized to conduct tests of significance for the logistic regression analyses.[24] One-way analysis of variance was employed to analyze the continuous outcome measures, making use of the summary statistics.[25]

In order to address the three questions posed in this study, three single-degree-of-freedom, non-orthogonal planned contrasts were created for each outcome measure. The first planned contrast compared the buprenorphine + naloxone group to the available buprenorphine groups, pooled, which addressed the question of whether or not buprenorphine + naloxone produces superior neonatal and/or maternal outcomes relative to buprenorphine. The second planned contrast

compared the buprenorphine + naloxone group to the available methadone groups, pooled, which addressed the question of whether or not buprenorphine + naloxone produces superior neonatal and/or maternal outcomes relative to methadone. The third planned contrast compares buprenorphine + naloxone to 7-day methadone-assisted withdrawal, which addressed the question of whether or not buprenorphine + naloxone produces superior neonatal and/or maternal birth outcomes relative to methadone-assisted withdrawal. The error term for all contrasts in the one-way ANOVAs was the within-cells term (as in 'standard' one-way ANOVA).

Due to the relative complexity of the proposed contrasts, the last row of Table 1 illustrates the set of coefficients that would be used for the outcome variable total amount of morphine for NAS in order to compare the mean of the buprenorphine + naloxone group to the pooled means of the Fisher et al,[2] Jones et al,[3] and Jones et al[4] comparison samples. In this case, x indicates data were missing for the respective comparison group, zero indicates data were available for that comparison sample, but were not included in the contrast—in this case because the data in question were for methadone—while the non-zero values indicate that the buprenorphine + naloxone mean is being compared to the unweighted average of the means of the three comparison samples with buprenorphine data. Thus, this comparison is the 'standard' one-way ANOVA contrast among means, which would likewise use the unweighted average of the means for a planned contrast.

Results

In general, the samples were similar in maternal age (mean age range was 23.9–30.3 years). [Demographic data other than age that might allow presentation of a general summary of each sample were not consistently available in the studies.] Only two studies reported opioid-agonist medication dose at delivery: Metz et al[21] reported a mean methadone dose of 74.2 and buprenorphine dose of 9.9, while Jones et al[4] reported means of 79.1 and 18.7, respectively.

Table 1 contains the frequencies (percentages) or means (standard deviations) of the outcome measures available in each study. Table 2 contains results of the analyses for maternal and neonatal outcomes.

Maternal outcomes

There were no significant differences in maternal outcomes for women exposed to buprenorphine + naloxone compared to women exposed to buprenorphine, methadone, or methadone-assisted withdrawal.

Neonatal outcomes

Head circumference was significantly higher on average among neonates exposed in utero to buprenorphine + naloxone compared to neonates exposed to methadone-assisted withdrawal; Ms = 32.8 (SE = 0.60) versus 31.2 (SE = 0.36), $F(1, 307) = 5.24$, $P < 0.03$, while neonates exposed in utero to buprenorphine + naloxone were shorter on average than neonates exposed to buprenorphine alone; Ms = 46.3 (SE = 1.08) versus 50.56 (SE = 0.51), $F(1, 307) = 12.74$, $P < 0.001$, although both groups were within the normal range according to the World Health Organization (WHO) international standards of child growth.[26] Mean Apgar scores at 5 minutes were significantly lower in the buprenorphine + naloxone group compared to the buprenorphine alone group; Ms = 8.6 (SE = 0.29) versus 9.6 (SE = 0.12), $F(1, 499) = 4.88$, $P < 0.03$.

Discussion

The present evaluation of buprenorphine + naloxone suggests that maternal and most neonatal outcomes from exposure to buprenorphine + naloxone are not dissimilar to the same outcomes found in women and their neonates exposed to buprenorphine alone and methadone.

Findings suggest that rates of cesarean section, non-normal presentation, analgesia during delivery, screening positive for illicit substances, and medical complications at delivery, together with length of maternal hospital stay, maternal weight gain, and number of prenatal visits for women using buprenorphine + naloxone during pregnancy do not differ significantly from women using either buprenorphine or methadone. These findings are not surprising, given that previous research has indicated that maternal outcomes are comparable across buprenorphine and methadone treatment.[2–5,7]

There were three significant differences in neonatal outcomes when neonates exposed to buprenorphine + naloxone were compared to neonates exposed to buprenorphine alone, methadone,

Table 1. Neonatal and maternal outcomes in 7 published studies: comparing buprenorphine + naloxone (B + N) to buprenorphine (B), methadone (M), and methadone-assisted withdrawal.

Outcome measure	Debelak et al[19]	Czerkes et al[18]	Fischer et al[2]		Metz et al[21]		Jones et al[3]		Jones et al[4]			Jones et al[20]	
	B + N (n = 10)	M (n = 101)	B (n = 68)	M (n = 6)	B (n = 8)	M (n = 51)	B (n = 26)	M (n = 11)	B (n = 9)	M (n = 73)	B (n = 58)	M (n = 52)	7-day detox (n = 28)
Neonatal													
Treated for NAS [yes]	4 (40%)	74 (73.3%)	33 (48.5%)			31 (65%)	15 (58%)	5 (45.4%)	2 (22.2%)	41 (57%)	27 (47%)	14 (27%)	10 (36%)
Total amount of morphine for NAS (mg): all neonates*	1.4 (2.38)			1.4 (1.82)	1.3 (1.83)	13.1 (23.22)	2.5 (5.88)	0.85 (1.16)†	0.10 (0.21)†	19.2 (51.47)	1.7 (2.99)		
Total amount of morphine for NAS (mg): neonates treated for NAS*	3.5 (2.64) [n = 4]			2.7 (1.68) [n = 3]	2.0 (2.00) [n = 5]	21.6 (26.64) [n = 31]	4.3 (7.30) [n = 15]	1.9 (0.99) [n = 5]	0.5 (0.13) [n = 2]	33.7 (64.82) [n = 41]	3.5 (3.54) [n = 27]		
Days treated for NAS: all neonates‡	5.2 (8.51)			2.7 (3.06)	3.0 (3.30)	13.0 (19.51)	3.81 (6.89)			12.3 (17.23)	4.6 (6.22)		
Days treated for NAS: neonates treated for NAS‡	13.0 (9.06) [n = 4]			5.3 (1.53) [n = 3]	4.8 (2.87) [n = 5]	21.3 (21.22) [n = 31]	6.6 (8.07) [n = 15]			21.7 (17.89) [n = 41]	9.8 (5.33) [n = 27]		
Days of infant hospital stay: all neonates€	10.1 (9.84)	15.7 (11.02)	8.4 (4.85)			29.4 (17.94)	13.9 (17.33)	8.3 (4.05)	5.8 (2.57)	18.3 (17.2)	10.1 (7.03)	12.8 (16.7)	8.9 (4.8)
Head circumference (cm)	32.8 (1.24)					32.9 (1.72)	33.6 (1.75)	33.2 (0.98)	34.5 (2.20) [n = 7]	33.0 (2.12)	33.8 (1.89)	31.8 (2.1)	31.2 (1.7)
Birth weight (gm)	2816.1 (368.28)	2990.0 (560.0)	3130 (480.0)	2688.7 (570.51)	2922.9 (786.96)	2729 (510.48)	3151.1 (541.64)	2973.9 (502.6)	3376.3 (455.7) [n = 7]	2880.0 (546.07)	3096.9 (561.2)	2819.1 (577.8)	2823.9 (478.1)
Infant length (cm)	46.3 (2.15)					48.3 (3.30)	50.2 (3.28)	49.6 (2.73)	51.7 (3.20) [n = 7]	47.8 (4.62)	49.8 (2.75)	48.2 (2.8)	47.5 (3.0)
Pre-term (<37 weeks) birth [yes]	2 (20%)			3 (50%)	2 (25%)			1 (9.1%)	0	14 (19%)	4 (7%)	10 (19.2%)	10 (35.7%)

(*Continued*)

Table 1. (*Continued*)

Outcome measure	Debelak et al[19]	Czerkes et al[18]	Fischer et al[2]		Metz et al[21]		Jones et al[3]		Jones et al[4]			Jones et al[20]	
	B + N (n = 10)	M (n = 101)	B (n = 68)	M (n = 6)	B (n = 8)	M (n = 51)	B (n = 26)	M (n = 11)	B (n = 9)	M (n = 73)	B (n = 58)	M (n = 52)	7-day detox (n = 28)
Gestational age at delivery (weeks)	37.5 (3.49)	38.7 (1.36)	38.5 (4.71)	37.5 (2.51)	38.5 (2.14)	38.6 (1.92)	39.7 (1.62)	38.7 (2.05)	39 (1.51) [n = 7]	38.0 (2.29)	39.1 (2.23)	38.2 (2.8)	37.3 (2.3)
Apgar score at 1 minute	8.0 (2.49)	7.7 (1.36)	7.8 (1.11)	9.0 (0)	8.88 (0.35)	8.6 (0.93)	9.0 (0.20)	8.3 (0.79)	8.1 (0.57)	8.0 (1.49)	8.1 (1.55)	7.9 (1.8)	7.9 (0.8)
Apgar score at 5 minutes	8.6 (1.26)	8.7 (0.75)	8.8 (0.46)	10.0 (0)	9.88 (0.35)	9.4 (1.0)	10.0 (0.20)	8.9 (0.30)	8.7 (0.48)	8.9 (0.99)	9.0 (1.12)	8.6 (1.1)	8.5 (0.6)
Maternal													
Cesarean section [yes]	1 (10%)			0§	2 (25%)¤	17 (33%)	9 (35%)	1 (90.1%)	0	27 (37.0%)	17 (29.3%)		
Days of maternal hospital stay	4.1 (4.54)							2.2 (0.60)	2.2 (0.63)	6.6 (6.96)	6.6 (5.67)		
Maternal weight gain (kg)	7.8 (3.89)									8.7 (7.83)	8.8 (6.33)		
Non-normal presentation [yes]	2 (20%)							0	0	10 (14.1%)	3 (5.2%)		
Analgesia during delivery [yes]	6 (60%)							7 (63.6%)¬	7 (77.8%)¬	60 (82.2%)	49 (84.5%)		
Drug screen at delivery [positive]	0							1 (9.1%)	0	11 (15.3%)	5 (8.8%)	12 (23.1)	16 (57.1%)
Medical complications at delivery [yes]	0 [n = 5]							0	0	37 (51%)	18 (31%)		
Number of prenatal obstetrical visits	9.0 (6.38)									8.7 (3.57)	8.8 (3.05)		

Sample contrast	1	x	x	0	−1/4	0	−1/4	0	−1/4	x	x

Notes: B + N = buprenorphine + naloxone; **B** = buprenorphine; **M** = methadone. Values are frequencies (percentages) or means (standard deviations). Standard deviations for the Czerkes et al (2010) means were not reported in their article. We thank Dr. Czerkes for his kindness in providing this information. The subsample means and standard deviations for Czerkes et al reported their birth weights in kilograms. The means and their respective standard deviations reported in this table have been transformed to grams to allow for comparison among the groups. The subsample means (standard deviations) for total amount of morphine required to treat NAS, birth weight, estimated gestational age at delivery, 1- and 5-minute Apgar scores, and maternal weight gain for Fischer et al (2006) were not reported in their article. We thank Drs. Fischer and Jagsch for their kindness in providing this information. We thank Dr. Metz for providing the means and standard deviations for apgar scores at 1 and 5 minutes as for Metz et al (2011). As noted in Table 2 of Jones et al (2005), twin data from the set of buprenorphine-exposed neonates whose mother was part of the trial were removed from the analyses of: gestational age at delivery, birth weight, head circumference, and length, reducing the sample to n = 7 in the buprenorphine group for these four variables. These same data were omitted from the respective analyses in the present study, given findings that suggest that these four variables are altered by twin status. The means (standard deviations) for the Jones et al (2005) and Jones et al (2010) studies do not agree with the values in Table 2 of their respective articles, because model-derived means (standard errors) are reported in Table 2 of the respective tables, while simple means and standard deviations are reported in the present table. The means (standard deviations) for the total amount of morphine drops for Jones et al (2005) are based on the 2 and 5 neonates, respectively, who were treated for NAS. The sample contrast in the last row of the table illustrates the coefficients that would used for the outcome variable total amount of morphine for NAS in order to compare the mean of the buprenorphine + naloxone group to the pooled means of the Fisher et al (2006), Jones et al (2005), and Jones et al (2010) buprenorphine comparison samples. *There are two rows for the variable "total amount of morphine" because Fischer et al (2006) reported their data only for the neonates treated for NAS in mg. Jones et al (2005) reported their data only for neonates treated for NAS in "Total number of morphine drops administered", while Jones et al (2010) reported their data for all infants (including those neonates not treated with values of zero) in total amount of morphine in mg. The mean and standard deviation provided by Fischer (2006) were used to calculate the mean and standard deviation for total amount of morphine for the total sample of 6 and 8 neonates, respectively. The mean and standard deviation provided by Fischer (2006) were used to calculate the mean and standard deviation for total amount of morphine for the total sample of 11 and 9 neonates, respectively (see next footnote); ‡the total number of drops of medication in Jones et al (2005) was transformed into mg based on the fact that the drops were "equivalent to morphine 0.02 mg/drop"; ¢day of hospital stay is not included for Fischer et al (2006) since there was an obligatory 10 day stay in inpatient treatment independent of symptoms of NAS; §vacuum extraction due to "prolonged delivery"; ¶both were planned cesarean sections; ¯article says anesthesia.

or 7-day methadone-assisted withdrawal. Head circumference in the buprenorphine + naloxone group was significantly greater than in the 7-day methadone-assisted withdrawal group. Previous studies have shown that opioid maintenance treatment is superior to medication-assisted withdrawal with regard to compliance with obstetrical care, superior relapse prevention, reduced fetal exposure to illicit drugs and improved neonatal outcomes, including birth parameters.[27] Therefore, it is not surprising that the neonates in the buprenorphine + naloxone group had greater head circumference than the neonates in the methadone-assisted-withdrawal group. Neonates in the buprenorphine + naloxone group were significantly shorter at birth compared to the buprenorphine alone group. We are unable to speculate why infants in the buprenorphine + naloxone group were shorter than infants in the buprenorphine alone group, but it does suggest an area for future research. However, it should be noted that the birth parameters of the buprenorphine + naloxone group were within the normal range.[19] Apgar scores at 5 minutes were significantly lower in neonates in the buprenorphine + naloxone group compared to neonates exposed to buprenorphine alone; however, the mean Apgar scores for both groups are considered normal and not clinically concerning. Moreover, the American Academy of Pediatrics[28] has noted that 1- and 5-minute Apgar scores are not predictive of an infant's future outcome, although 5-minute Apgar scores are predictive of neonatal mortality. There were no significant differences between the groups on any other neonatal outcome measures, including whether they were treated for NAS, total amount of morphine used in treatment of NAS, days treated for NAS, days of infant hospital stay, preterm birth, gestational age at delivery, and Apgar scores at 1 minute. The fact that the methadone-assisted withdrawal group did not differ from the buprenorphine + naloxone group, with the exception of having a significantly smaller head circumference, should not be interpreted as indicating the relative efficacy of medication-assisted withdrawal as a treatment modality. Considerable previous research has shown that maintenance on opioid agonist medication is superior to methadone-assisted withdrawal in regard to relapse prevention, fetal exposure to illicit drugs, compliance with obstetrical care, and neonatal outcome.[20] The non-significant

Table 2. Results for tests of significance for planned contrasts.

Outcome measure	Planned contrast	Test statistic	*P*
Neonatal			
Treated for NAS	Buprenorphine + naloxone *v.* Buprenorphine	$\chi^2(1) = 0.03$	0.86
	Buprenorphine + naloxone *v.* Methadone	$\chi^2(1) = 1.36$	0.24
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$\chi^2(1) = 0.06$	0.81
Total amount of morphine for NAS: all neonates*	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 168) = 0.00$	0.99
	Buprenorphine + naloxone *v.* Methadone	$F(1, 168) = 0.20$	0.66
Total amount of morphine for NAS: neonates treated for NAS*	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 80) = 0.00$	0.95
	Buprenorphine + naloxone *v.* Methadone	$F(1, 80) = 0.13$	0.72
Days treated for NAS: all neonates‡	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 150) = 0.09$	0.77
	Buprenorphine + naloxone *v.* Methadone	$F(1, 150) = 0.22$	0.64
Days treated for NAS: neonates treated for NAS‡	Buprenorphine + naloxone v. Buprenorphine	$F(1, 119) = 0.52$	0.47
	Buprenorphine + naloxone v. Methadone	$F(1, 119) = 0.14$	0.71
Days of infant hospital stay	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 476) = 0.02$	0.90
	Buprenorphine + naloxone *v.* Methadone	$F(1, 476) = 3.46$	0.06
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$F(1, 476) = 0.07$	0.80
Head circumference	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 307) = 3.10$	0.08
	Buprenorphine + naloxone *v.* Methadone	$F(1, 307) = 0.13$	0.72
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$F(1, 307) = 5.24$	0.02
Birthweight	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 486) = 2.99$	0.08
	Buprenorphine + naloxone *v.* Methadone	$F(1, 486) = 0.03$	0.87
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$F(1, 486) = 0.00$	0.97
Length	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 307) = 12.74$	<0.001
	Buprenorphine + naloxone *v.* Methadone	$F(1, 307) = 3.84$	0.051
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$F(1, 307) = 0.90$	0.33
Pre-term birth	Buprenorphine + naloxone *v.* Buprenorphine	$\chi^2(1) = 0.89$	0.34
	Buprenorphine + naloxone *v.* Methadone	$\chi^2(1) = 0.01$	0.91
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$\chi^2(1) = 0.60$	0.44
Gestational age at delivery	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 486) = 2.72$	0.10
	Buprenorphine + naloxone *v.* Methadone	$F(1, 486) = 0.83$	0.36
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$F(1, 486) = 0.04$	0.84
Apgar 1 minute	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 488) = 0.72$	0.40
	Buprenorphine + naloxone *v.* Methadone	$F(1, 488) = 0.52$	0.47
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$F(1, 488) = 0.04$	0.84
Apgar 5 minutes	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 499) = 4.88$	0.03
	Buprenorphine + naloxone *v.* Methadone	$F(1, 499) = 3.61$	0.06
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$F(1, 499) = 0.09$	0.77
Maternal			
Cesarean section	Buprenorphine + naloxone *v.* Buprenorphine	$\chi^2(1) = 0.24$	0.62
	Buprenorphine + naloxone *v.* Methadone	$\chi^2(1) = 0.16$	0.69

Days of maternal hospital stay	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 156) = 0.02$	0.89
	Buprenorphine + naloxone *v.* Methadone	$F(1, 156) = 0.02$	0.89
Maternal weight gain	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 138) = 0.18$	0.68
	Buprenorphine + naloxone *v.* Methadone	$F(1, 138) = 0.14$	0.70
Non-normal presentation	Buprenorphine + naloxone *v.* Buprenorphine	$\chi^2(1) = 2.16$	0.14
	Buprenorphine + naloxone *v.* Methadone	$\chi^2(1) = 1.33$	0.25
Analgesia during delivery	Buprenorphine + naloxone *v.* Buprenorphine	$\chi^2(1) = 1.87$	0.17
	Buprenorphine + naloxone *v.* Methadone	$\chi^2(1) = 0.76$	0.38
Drug screen at delivery	Buprenorphine + naloxone *v.* Buprenorphine	$\chi^2(1) = 0.02$	0.90
	Buprenorphine + naloxone *v.* Methadone	$\chi^2(1) = 0.39$	0.53
	Buprenorphine + naloxone *v.* 7-day methadone-assisted withdrawal	$\chi^2(1) = 3.8$	0.051
Medical complications at delivery	Buprenorphine + naloxone *v.* Buprenorphine	$\chi^2(1) = 0.09$	0.77
	Buprenorphine + naloxone *v.* Methadone	$\chi^2(1) = 0.22$	0.64
Number of prenatal obstetrical visits	Buprenorphine + naloxone *v.* Buprenorphine	$F(1, 138) = 0.03$	0.87
	Buprenorphine + naloxone *v.* Methadone	$F(1, 138) = 0.06$	0.81

Note: *‡See Table 1 for an explanation for why there are two outcome measures for total amount of morphine for NAS and days treated for NAS.

differences in birth length between the neonates in the buprenorphine + naloxone group and the neonates in the buprenorphine alone group may be related to non-significant differences between the groups in gestational age. Although these birth parameters are within the normal range, future studies should consider investigating these potential differences further.

Limitations

The strength of any inferences from the present findings must be tempered by the fact that the sample size for buprenorphine + naloxone was small. Moreover, the use of summary descriptive statistics to conduct inferential analyses does not allow examination of the extent to which violation of the statistical assumptions might have impacted the findings. Data were only collected for neonates and mothers where pregnancy ended in live births. Therefore, information about abortion frequency and miscarriage, which is potentially important information when comparing medications for opioid dependence in pregnant women, is lacking. Finally, the studies under examination used various forms of the Finnegan scale to assess neonatal abstinence syndrome.

It is also true that some factors were uncontrolled in several studies included in the present article. For example, there is no available information on use of illicit substances, depression, exposure to sexual victimization, physical violence, or inadequate nutrition in the studies by Czerkes et al[18] and Debelak et al.[19] Thus, analyses in the present study cannot control for such factors that may account for some degree of the differences between medications in neonatal outcomes.[27] Assessment of the benefits and risks for opioid-dependent pregnant women associated with buprenorphine + naloxone, buprenorphine alone, methadone, and methadone-assisted withdrawal can best be undertaken when such factors are taken into consideration.[29]

Pooling data from randomized controlled trials with data from retrospective chart reviews offers challenges. For example, information regarding factors such as exclusion of preterm births is not included in all the studies. There is a lack of background information on the women, such as information on what kind(s) of treatment in addition to their medication, when they started their medication and medication dose. Hence, it is uncertain how

comparable the women in these studies are to the women in the randomized controlled trials where information regarding inclusion and exclusion criteria was available. These same challenges are present in the conduct of meta-analyses, which must attempt to aggregate data across research studies. Many meta-analyses focus on the characteristics of the studies under evaluation—such as whether or not a study is a randomized controlled trial—with little attention to these same issues of patient, treatment, and outcome measure similarities. Rather than focus on such a narrow bandwidth in the choice of our studies, in the present paper we determined to choose representatively among studies that would provide us with similarity of outcome information. Such an effort at breadth was done at the cost of choosing studies whose patient populations and treatment characteristics were potentially substantially different. However, our strategy of choosing a representative sample of studies across the spectrum of designs yields the potential gain of greater generalizability of the findings, and allows for an examination of the extent to which there is enough signal in the medication differences to overcome the heterogeneity of study and patient characteristics.

There are still unanswered questions about the maternal and neonatal safety of buprenorphine + naloxone. The neonatal outcomes in Debelak et al[19] presented in the present study would benefit from confirmation from other and larger samples of women.

It is important to note that in most US locations, buprenorphine + naloxone may be the only buprenorphine treatment available to pregnant women. In other nations, such as Norway for example, buprenorphine alone is the recommended opioid medication for pregnant women with opioid dependence[30]. Pregnant women already in buprenorphine + naloxone treatment are encouraged to transfer to buprenorphine alone. This recommendation is based on the existing research on maternal and neonatal safety of buprenorphine alone and the lack of research investigating the safety of buprenorphine + naloxone during pregnancy.

Strengths

This is the first comparison of neonatal and maternal outcomes from exposure to buprenorphine + naloxone to the other available treatment options for opioid-dependent pregnant women: buprenorphine, methadone, and methadone-assisted withdrawal.

Conclusions

Findings from the present study suggest no obvious significant adverse maternal outcomes related to the use of buprenorphine + naloxone for the treatment of opioid dependence in pregnancy. The birth parameters for the neonates in the buprenorphine + naloxone group were within the normal range. However, the potential for lower physical birth parameters in this group compared to neonates exposed to buprenorphine alone merit further research on neonatal physical development, and suggests caution in the use of buprenorphine + naloxone. Larger samples, in controlled clinical trials, and in prospective studies that control for confounding factors, are necessary to further examine the relative neonatal safety of buprenorphine + naloxone for the treatment of opioid-dependent pregnant women.

Clinical Implications

The advent of buprenorphine + naloxone has brought a new treatment option for opioid-dependent pregnant women and new challenges to health care providers regarding rational decision-making about which treatment option is the most appropriate for their opioid-dependent pregnant patients. Providers who choose to treat their opioid-dependent pregnant patients with buprenorphine + naloxone may need to closely monitor the neonates of their patients in terms of their fetal and neonatal outcomes, until further research has addressed this issue. The data on the safety of buprenorphine + naloxone is not sufficient for the medication to be recommended to pregnant women. Buprenorphine alone should be made available for opioid-dependent pregnant women, because the maternal and neonatal safety of this medication has been investigated and the collective results suggest that, when taken as a part of a treatment program, it has an acceptable safety profile for both mother and child.[2–4,21] Patient preference, side effects, and retention in treatment should be evaluated carefully.

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Competing Interests

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Author Contributions

Conceived and designed the experiments: IOL, KEO'G, HEJ. Analyzed the data: KEO'G, IOL. Wrote the first draft of the manuscript: IOL. Contributed to the writing of the manuscript: IOL, GF, GKW, KEO'G, KD, WRM, HEJ. Agree with manuscript results and conclusions: IOL, GF, GKW, KEO'G, KD, WRM, HEJ. Jointly developed the structure and arguments for the paper: IOL, GF, GKW, KEO'G, KD, WRM, HEJ. Made critical revisions and approved final version: IOL, GF, GKW, KEO'G, KD, WRM, HEJ. All authors reviewed and approved of the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. The external blind peer reviewers report no conflicts of interest.

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