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Infections and obstetrical outcomes in opioid-dependent pregnant women maintained on methadone or buprenorphine

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Abstract

Aims—To characterize infections and compare obstetrical outcomes in opioid-dependent pregnant women who participated in a randomized controlled trial comparing agonist medications, methadone and buprenorphine.

Design—Incidence of infections was identified as part of the screening medical assessment. As part of a planned secondary analysis, ANOVA and polytomous logistic regressions were conducted on obstetrical outcome variables using treatment randomization condition (maternal maintenance with either methadone or buprenorphine) as the predictor variable, controlling for differences between study sites.

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Declaration of interests:
The clinical trial was registered with *ClinicalTrials.gov* (Identifier: NCT00271219; Title: RCT Comparing Methadone and Buprenorphine in Pregnant Women).
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Setting—Six United States sites and one European site that provided comprehensive treatment to opioid-dependent pregnant women.

Participants—Pregnant opioid-dependent women (*n* = 131) who delivered while participating in the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study.

Measurements—Obstetrical, infectious, and other maternal medical complications captured by medical records, physical exam, blood tests, and self-report. Neonatal medical complications captured by medical records.

Findings—Hepatitis C (HCV) was the most common infection (32.3%), followed by hepatitis B (7.6%) and Chlamydia (6.1%) among participants at study enrollment. Maternal methadone versus buprenorphine maintenance was associated with a higher incidence of preterm labor (P = 0.04) and a significantly higher percentage of signs of respiratory distress in neonates at delivery (P = 0.05). Other medical and obstetrical complications were infrequent in the total sample, as well as in both methadone and buprenorphine conditions.

Conclusions—Buprenorphine appears to have an acceptable safety profile for use during pregnancy.

Keywords

tbc

Introduction

The medical and obstetrical complications associated with opioid substance use disorders may be exacerbated by a number of biopsychosocial factors, making effective management difficult. The majority of studies that examine substance abuse during pregnancy focus on the effects of the drug on pregnancy, i.e., teratology or perinatal factors, the status of the mother at delivery, and the outcome of the newborn. However, a number of infectious medical and obstetrical complications have historically been identified with heroin use.

The association of opioid dependence with an increased risk of infectious medical complications stems from a number of studies that focused on the prevalence and incidence of specific infections such as hepatitis [1–3], bacterial endocarditis [4–7], tetanus [8–9], cellulitis [10–11] and syphilis [12–13] among heroin-dependent individuals. However, few of these studies included pregnant women and we are aware of no contemporary studies that examine the prevalence of infectious medical complications among opioid-dependent pregnant women.

Obstetrical complications in opioid-dependent women appear to be similar to non –drug using pregnant women who do not receive prenatal care. These complications include an increased risk of spontaneous abortion, placental insufficiency, intrauterine growth restriction, premature labor/delivery, premature rupture of membranes, anemia, preeclampsia, and abruptio placentae [14]. Contemporary studies have identified a number of antenatal complications associated with prenatal methadone exposure, including prematurity, low birth weight, and growth restriction [15–20]. However, these studies reflect multiple drug exposures, including heroin, methadone, tobacco and/or other drugs. In fact, in

two prospective studies that controlled for covariates, methadone exposure was not associated with increased rates of prematurity, low birth weight or small for gestational age [20–21].

Several studies have also compared obstetrical outcomes for methadone and buprenorphine maintenance [21–25]. Most of these studies have suggested that outcomes are comparable with the two agonist medications [21, 23–25] although Kakko *et al*. (2008) found lower birth weight and gestational age in infants exposed in utero to methadone versus buprenorphine [22]. However, only two of these studies were randomized controlled trials [24–25], and both had small sample sizes.

Recently, the Maternal Opioid Treatment Human Experimental Research (MOTHER) study, a double-blind, double-dummy, flexible dosing, randomized clinical trial designed to compare the relative effectiveness of methadone versus buprenorphine for treatment of opioid dependence during pregnancy [26] was completed. Analyses examined the effects of methadone and buprenorphine on a number of obstetrical and neonatal variables, including maternal weight gain, medical complications at delivery, non-vertex presentation, cesarean section, preterm birth, and infant birth weight, head circumference, gestational age at delivery and Apgar scores and found no difference between methadone and buprenorphine in these obstetrical and neonatal outcomes [26].

This study has two primary aims. The first aim is to characterize the infectious medical complications in opioid-dependent pregnant women enrolled in the MOTHER study. The second aim is to compare obstetrical and neonatal outcomes in opioid-dependent pregnant women maintained on methadone and buprenorphine, not previously examined in the MOTHER Study.

Method

This study is a secondary analysis of the MOTHER study's medical and peripartum data that were not included in the primary outcome study. The primary and key secondary outcomes analyses from the MOTHER study have been reported elsewhere [26].

Participants

Data were obtained from the 131 opioid-dependent pregnant women and their infants who completed the MOTHER study. Completers were participants who gave birth while receiving double blind study medication; methadone $n = 73$, buprenorphine $n = 58$. Participants were between the ages of 18 and 41years old, carried a singleton pregnancy and were randomized between 6 and 30 weeks estimated gestational age (EGA) as confirmed by ultrasound. Exclusion criteria included current benzodiazepine or alcohol abuse or dependence as defined by the Structured Clinical Interview of the DSM-IV (SCID) module E, HIV seropositivity, impending incarceration, non-English speaking (non-German-speaking at the Vienna site), or a medical or psychiatric condition contraindicating study participation as determined by the medically responsible investigator.

Procedures

All participants signed a local IRB approved informed consent form for study participation. An extensive screening assessment was conducted to determine eligibility for the study, including demographic information, medical history, psychiatric assessment, nicotine dependence, obstetrical assessment, and a complete blood chemistry. These data were collected during the first 3 to 5 days of maternal stabilization on medication for opioid maintenance, or prior to stabilization on double-blind study medication for women who were already methadone-maintained.

Measures

Maternal medical complications—A complete medical history was obtained as part of the study screening. A physical exam was conducted by study physicians and included assessment of cardiovascular, respiratory, gastrointestinal, genitourinary, musculoskeletal, neurological, endocrine, hematopoietic, and lymphatic systems. Complete blood chemistry, along with tests for syphilis and hepatitis B (HBV) and hepatitis C (HCV), were conducted. Adverse event data were collected weekly throughout the pregnancy and postpartum.

Nicotine use—Typical number of cigarettes smoked daily was aggregated from screening data and monthly administration of the Addiction Severity Index [27] and Fagerstrom Test for Nicotine Dependence.

Obstetrical [28] and neonatal complications—Participants received an initial obstetrical exam as part of the screening process which included an ultrasound and Pap test. Subsequently, obstetrical data from prenatal visits and blood chemistry were collected monthly during pregnancy and once postpartum. Additional data pertaining to the intrapartum period were obtained from maternal delivery and neonatal medical records. Adverse event data for mothers and neonates were collected weekly through patient self-report and medical records. Please refer to Jones et al. [26,29] for a complete description of serious and non-serious maternal and neonatal adverse events by medication condition.

Data Analyses

Percentages of infectious medical complications and percentages of obstetrical and neonatal complications were calculated. Data on infectious medical complications were collected prior to randomization and were not expected to differ statistically by medication groups. However, due to differing percentages between the methadone and buprenorphine groups, odds ratios were calculated to detect differences in the rate of HBV, HCV and Chlamydia. An analysis of variance (ANOVA) and multiple (polytomous) logistic regressions were conducted on three obstetrical outcomes variables using treatment randomization condition (maternal maintenance with either methadone or buprenorphine) as the predictor variable, controlling for differences between study sites (see [26] for study site definition). The dependent variable in the ANOVA was pH of the arterial cord blood. Arterial cord blood pH was examined because of its importance as an indicator of fetal metabolism and as an adjunctive diagnostic tool to rule out birth asphyxia in infants with low Apgar scores. Nominal dependent variables in logistic regressions were presence of preterm labor and signs of respiratory distress at delivery. Typical daily number of cigarettes smoked was

included as a control variable in both analyses, and estimated gestational age (EGA) was included as a control variable in the model predicting respiratory distress signs at delivery. All analyses were performed using STATA 8.2 software (StataCorp LP, College Station, TX).

Results

Maternal characteristics

The mean gestational age at study entry was 18.7 weeks. One of every five mothers reported a prior preterm birth. Average typical daily cigarettes smoked was 12.0 (SD = 6.4). There was a low incidence of illicit drug use in the sample with only small percentages testing positive during the two weeks prior to delivery for benzodiazepines (3%, *n* = 4), cocaine (7%, *n* = 9), or opiates (8%, *n* = 10). A majority of the sample were prescribed medication during their pregnancy for co-occurring psychiatric disorders, with 31.8% (*n* = 32) reporting use of selective serotonin reuptake inhibitors (SSRIs), antidepressants, or antipsychotics, and 34.1% (*n* = 43) taking anxiolytics (Table 1).

Characterization of infectious medical and obstetrical complications

Although 53.1% of the sample reported injection drug use during the 30 days prior to study enrollment, infections were generally infrequent (Table 2), with less than 2% of the sample diagnosed with cellulitis (*n* = 2) or syphilis *(n* = 2), and no incidence of bacterial endocarditis or tetanus. The most common medical complication was HCV with infection present in 32.3% (*n* = 42) of the sample (see McNicholas *et al*. [30], in this supplement for more information on HCV in this sample). Incidence of HBV was 7.6% (*n* = 10) and Chlamydia was 6.1% (*n* = 8). Overall, there was a low incidence of obstetrical complications as well (Table 3).

To provide context to the present study, the primary analyses [26] reported that the Apgar scores assessed the majority of the infants to be relatively vigorous at birth, with the average 1 minute Apgar score being 8.0 for the methadone and 8.1 for the buprenorphine-exposed neonates, respectively. At 5 minutes, average Apgar scores were 9.0 for both groups. The majority of infants in the sample were born at term, with a mean EGA of 37.9 weeks for methadone-exposed infants and 39.0 weeks for buprenorphine-exposed infants. Birth weight, head circumference, and length were similar for infants in both medication conditions. Maternal weight gain (measured from entry into the study to last prenatal exam prior to birth) averaged 8.6 kg for the methadone-maintained women and 8.3 kg for buprenorphine-maintained women. Delivery via cesarean section was 37.0% *(n* = 27) in the methadone condition and 29.3% (*n* = 17) in the buprenorphine condition. No differences were found between medication groups on any of the above variables.

The three most common obstetrical/neonatal complications were preterm premature rupture of the membranes (PPROM), gestational diabetes, and placental abruption, occurring in 3.0% (*n* = 4), 2.3% (*n* = 3), and 2.3% (*n* = 3), respectively, of the sample. Although there was not adequate power to examine the association of PPROM and medication condition, it is of interest that the 4 cases were all in the methadone medication group and led to

premature delivery. As the majority of obstetrical and neonatal complications examined (i.e. gestational diabetes, meconium aspiration, placental abruption, placenta previa, premature rupture of membranes, preeclampsia, sepsis, and small for gestational age) did not occur, or were very infrequent (less than 3.5%) in the overall sample, they were not compared statistically by medication condition.

Associations between maternal medication condition and infectious medical and obstetrical complications

There was no difference between groups in the prevalence of HBV (buprenorphine 12.5%, methadone 4.2%) (OR = 0.3; CI = 0.8 – 1.2; P = 0.09) or HCV (buprenorphine 26.3%, methadone 36.6%) (OR = 1.6; CI = 0.8 – 3.5; P = 0.22). There were no differences in rates of Chlamydia infection (buprenorphine 10.3%, methadone 2.7%) (OR = 0.2; CI = 0.04–1.2; P = 0.08). Average arterial cord blood pH for methadone-exposed infants was 7.3 (0.08 SD) versus 7.3 (0.07 SD) for buprenorphine-exposed infants. ANOVA revealed no differences between groups for arterial cord blood pH (F (3) = 0.89; P = 0.45). Multiple logistic regression showed that mothers maintained on methadone were more likely than those maintained on buprenorphine to present with preterm labor (methadone 14.9%, buprenorphine 1.8%) (b= 2.3; CI = 0.2 – 4.4; P = 0.04), controlling for maternal cigarette smoking. Respiratory distress signs were also much more frequent at delivery among neonates born to methadone-maintained versus buprenorphine-maintained women (methadone 18.9%, buprenorphine 5.3%) (b = 1.75; CI = 0.12–3.3;P = 0.05), controlling for EGA (P = 0.004) and maternal cigarette smoking (P = 0.71).

Discussion

These data provide an overview of the current incidence of infectious medical complications and obstetrical outcomes in a sample of opioid-dependent pregnant women maintained on agonist medication. The incidence of infectious medical complications in our sample was low compared to the reported rates for heroin users in the literature. There was no incidence of tetanus or bacterial endocarditis, both of which have been associated with heroin use [4, 9, 31]. Less than 2% of the sample exhibited cellulitis or syphilis. Rates of cellulitis in community samples of IV heroin users have been reported as high as 27% [11]. More information is needed on the current incidence of syphilis in opioid-dependent populations. A review by Semaan *et al*. (2007) reports seropositivity rates for syphilis ranging from 2–6% for individuals in substance abuse treatment, although these are not restricted to opioid-dependent populations [32]. However, our results suggest that syphilis infection is infrequent in opioid-dependent pregnant women. The prevalence of HCV was considerably lower in this sample than the rates for heroin-using and methadone-maintained populations reported in the current literature (as high as 70–90% for injecting drug users) [1–2]. Studies focusing on opioid-dependent pregnant women in treatment report rates of HCV from 11–93% [17–18, 22, 24–25, 33]. Our results may be in part because of the higher proportion of prescription opioid drug abusers at some of the study sites versus intravenous heroin users. None of our participants were HIV positive as this was an exclusionary criterion for the study.

Obstetrical complications were also infrequent, suggesting that the comprehensive care received by the participants helped to reduce obstetrical and neonatal morbidity, consistent with the findings of Jones *et al*. [25] in a much smaller sample. As reported in Jones *et al.* [26] there were no differences between methadone and buprenorphine in serious maternal or neonatal adverse events. The obstetrical complications noted in the early literature on narcotic-dependent mothers, such as premature rupture of membranes, preeclampsia, small for gestational age, and abruption placentae [14] were infrequent or absent in this sample. As reported in Jones *et al.* [26], mean birth weight for both methadone-exposed infants and buprenorphine-exposed infants in this sample was consistent with the methadone literature [16, 20] and contemporary studies comparing methadone and buprenorphine-exposed infants [21–25, 34]. In addition, one- and five-minute Apgar scores of 8 and 9, respectively, were similar to those reported in the current literature for methadone- and buprenorphine-exposed neonates [21–25].

Differences were found between the methadone and buprenorphine condition with preterm labor and signs of neonatal respiratory distress higher in the methadone medication condition. There are little data available examining preterm labor in opioid-dependent pregnant women. However, the percent of women who developed preterm labor in our sample was comparable to the rates of preterm birth reported by Jones *et al*.[25], Lejeune *et al*. [23], and Bakstad *et al*. [21] (9.1–12.3%), but considerably lower than the preterm rates generally reported in the published literature (approximately 30%) for opioid-dependent women [17,19, 30–31]. However, these studies also included pregnancies with ongoing exposure to multiple drug use. Gestational age at delivery is a surrogate marker for neonatal outcomes and respiratory distress syndrome (RDS) is the most common morbidity associated with prematurity. As such, a higher incidence of respiratory distress signs in one medication group might reflect a higher rate of prematurity, although no significant differences were reported in prematurity (e.g. <37 weeks) or gestational age in the primary analyses [26]. The high percentage of neonates exhibiting signs of respiratory distress may also be due to the prevalence of heavy maternal nicotine use in the sample, but there were no significant between-group differences in cigarette smoking that would account for the association found between signs of neonatal respiratory distress at delivery and maternal methadone maintenance. Although significant differences were not found between medication conditions in occurrence of cesarean section, abnormal presentation, and medical complications at delivery, a higher incidence of each occurred in the methadone group. In aggregate, this may have contributed to the greater likelihood of respiratory distress signs observed in the methadone-exposed neonates.

There was also a high percentage of cesarean sections for both medication conditions, with a third of the sample delivering via this route. The incidence of cesarean sections varied widely by study site, ranging from 18–66%, and may in part be due to different regional obstetrical practices. However, the overall rate is within the range reported for other opioid-dependent samples (21.2–39%) [21–22, 24] although Jones *et al*. [25] reported lower rates of 9–11%.

Our findings are limited by a sample size that is relatively small to examine phenomena that occur infrequently. The study may be underpowered to assess some of the outcomes or to

provide a full picture of the prevalence and incidence of these infectious and medical complications in the population of opioid-dependent women. Additionally, the current report is a secondary analysis of data from a study that was not primarily designed to examine these outcomes. Finally, while the minimal illicit drug use achieved through use of contingency management allowed for more precise assessment of the MOTHER study primary outcomes, it may have minimized the incidence of obstetrical complications that are commonly seen in this population.

Nevertheless, our study represents an important addition to the literature in that it reports on a relatively large treatment sample of opioid-dependent pregnant women receiving opioid-agonist maintenance and comprehensive care with minimal concomitant drug abuse. These data suggest that the incidence of infectious medical complications for opioid-dependent pregnant women may be notably lower than in the general population of opioid-dependent individuals, with the exception of HCV infection which remains a significant concern. Many of the obstetrical complications noted in the early literature appear to be infrequent in our sample. This difference may be due to the inclusion of women with ongoing polydrug abuse in previous samples, the current availability of comprehensive care for pregnant opioid-dependent women; and/or the proportion of prescription versus intravenous drug users enrolled in the MOTHER study. However, the elevated rates of preterm labor and signs of respiratory distress that appear to occur with greater frequency in methadone versus buprenorphine- maintained mothers is an area of concern that requires further research. Our study represents one of only a few randomized studies that compare methadone and buprenorphine maintenance during pregnancy and is the only study to date with a large sample size. Additional research in samples that have a high incidence of illicit or non-prescribed drug abuse is needed in order to provide a fuller picture of the obstetrical complications and treatment issues involved in the management of care for this especially vulnerable population.

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Table 1

Maternal characteristics of opioid-dependent pregnant women maintained on methadone or buprenorphine

Variable	Buprenorphine (*n* = 58) Mean (SD); % (n)	Methadone (*n* = 73) Mean (SD);% (n)
EGA at study entry (weeks)	18.7 (0.7)	18.7 (0.8)
Prior preterm birth	15.5% (*n*=9)	24.7% (*n*=18)
Typical daily cigarettes (#)	11.1 (6.2)	12.8 (6.6)
Positive UDS 2 weeks prior to delivery		
Benzodiazepines	5.6% (*n*=3)	1.4% (*n*=1)
Cocaine	9.3% (*n*=5)	5.6% (*n*=4)
Opiates	11.1% (*n*=6)	5.6% (*n*=4)
SSRIs	27.8% (*n*=16)	21.9% (*n*=16)
Anxiolytics	40.4% (*n*=23)	27.8 % (*n*=20)

Note. EGA: estimated gestational age; UDS: urine drug screen; SSRIs: maternal receipt of selective serotonin reuptake inhibitors, antidepressants, or antipsychotics

Table 2

Prevalence of infectious medical complications in pregnant opioid-dependent women at study enrollment

	Total sample (*N* = 131	Buprenorphine (*n* = 58)	Methadone (*n* = 73)
Variable	**Percent**	**Percent**	**Percent**
Cellulitis	1.5%	0% (*n* = 0)	2.7% (*n* = 2)
Chlamydia	6.1%	10.3% (*n* = 6)	2.7% (*n* = 2)
Endocarditis	0%	0% (*n* = 0)	0% (*n* = 0)
Gonorrhea	3.8%	3.4% (*n* = 2)	4.1% (*n* = 3)
Hepatitis B	7.6%	12.1% (*n* = 7)	4.1% (*n* = 3)
Hepatitis C	32.3%	25.9% (*n* = 15)	37.0% (*n* = 27)
Syphilis	1.5%	0% (*n* = 0)	2.7% (*n* = 2)
Tetanus	0%	0% (*n* = 0)	0% (*n* =0)

Note: Descriptive data on infectious medical complications was collected prior to randomization and, as expected, did not differ by medication group.

Table 3

Incidence of obstetrical/neonatal complications among opioid-dependent women maintained on methadone or buprenorphine

	Buprenorphine (*n* = 58)	**Methadone (*n* = 73)**
	Percent	**Percent**
Gestational diabetes	1.8% (*n* = 1)	2.7% (*n* = 2)
Meconium aspiration	1.8% (*n* = 1)	0% (*n* = 0)
Placental abruption	0% (*n* = 0)	4.1% (*n* = 3)
Placenta previa	0% (*n* = 0)	1.4% (*n* = 1)
PROM	3.5% (*n* = 2)	0% (*n* = 0)
PPROM	0% (*n* = 0)	5.4% (*n* = 4)
Preeclampsia	0% (*n* = 0)	0% (*n* = 0)
Sepsis (Infant)	0% *(n* =0)	0% (*n* = 0)
Small for gestational age:		
Head sparing	1.8% (*n*=1)	1.4% (*n*=1)
Non-head sparing	0% (*n*=0)	1.4% (n=1)

Note. PROM: premature rupture of membranes ≥37 weeks EGA; PPROM: preterm premature rupture of membranes <37weeks EGA