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ORIGINAL RESEARCH

Comparing methadone and buprenorphine maintenance with methadone-assisted withdrawal for the treatment of opioid dependence during pregnancy: maternal and neonatal outcomes

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Abstract: Pregnancy can motivate opioid-dependent women to seek substance abuse treatment. Research has demonstrated that although prenatal exposure to buprenorphine results in less severe neonatal abstinence syndrome (NAS) relative to prenatal methadone exposure, the maternal and other neonatal outcomes are similar for the two medications. Maternal and neonatal outcomes for opioid-dependent pregnant women receiving these medications have not been systematically compared with methadone-assisted withdrawal. The present study provides an initial assessment of the relative efficacy of both methadone and buprenorphine maintenance versus methadone-assisted withdrawal in terms of neonatal and maternal delivery outcomes. Data were derived from (1) the MOTHER (Maternal Opioid Treatment: Human Experimental Research) study at the Johns Hopkins University Bayview Medical Center (JHBMC), or (2) retrospective records review of women who underwent methadone-assisted withdrawal at the JHBMC during the time period in which participants were enrolled in the MOTHER study. Compared with the methadone maintenance group, the methadone-assisted withdrawal group had a significantly lower mean NAS peak score (Means = 13.7 vs 7.0; $P = 0.002$), required a significantly lower mean amount of morphine to treat NAS (Means = 82.8 vs 0.2; $P < 0.001$), had significantly fewer days medicated for NAS (Means = 31.5 vs 3.9; $P < 0.001$), and remained in the hospital for a significantly fewer number of days, on average (Means = 24.2 vs 7.0; $P < 0.019$). Compared with the buprenorphine maintenance group, the methadone-assisted withdrawal group required a significantly lower mean amount of morphine to treat NAS (Means = 8.2 vs 0.2; $P < 0.001$) and significantly fewer days medicated for NAS (Means = 12.0 vs 3.9; $P = 0.008$). Findings suggest that it is possible for some opioid-dependent pregnant women to succeed with methadone-assisted withdrawal. Future research needs to more fully evaluate the potential benefits and risks of methadone-assisted withdrawal for the maternal-fetal dyad.

Keywords: pregnancy, methadone, buprenorphine, detoxification, women, neonates

Introduction

Opioid dependence during pregnancy is associated with multiple adverse consequences for the maternal-infant dyad, including high rates of infection, premature delivery, and low birth weight.[1–4] These adverse events can be important risk factors for later developmental delay of the child.[1,4,5] Given these risks, it is critically important to provide opioid-addicted women with every opportunity to receive effective treatment. Several different treatment options are available, including either maintenance on opioid-agonist medications, such as methadone[5–9] and buprenorphine,[10] or medication-assisted withdrawal.[11]

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Methadone maintenance has been the 'gold standard' for treating pregnant women with opioid addiction. It is the oldest and most established medication prescribed during pregnancy for opioid addiction.[9] Recent research suggests that buprenorphine does not differ from methadone in terms of maternal outcomes and may prove superior to methadone in terms of fetal and neonatal outcomes, including neonatal abstinence syndrome (NAS).[10,12–16]

Both methadone and buprenorphine are long-acting opioids. The duration of action of these opioids is longer than for short-acting opioids such as heroin. Consequently, long-acting opioids do not need to be administered as frequently as heroin to avoid withdrawal symptoms.[17] Like heroin, methadone and buprenorphine act by binding to opioid receptors in the central nervous system.[18] Methadone elicits its pharmacodynamic properties through binding to the μ-, κ-, and δ-opioid receptors.[19] Methadone may cause analgesia, respiratory difficulty, depression, physical dependence, and tolerance.[19] The elimination half-life of methadone is about 12–36 hours; therefore, it is sufficient to administer once daily to prevent withdrawal symptoms.[20] Buprenorphine differs somewhat from methadone in that is a partial agonist at the μ-opioid receptors and an antagonist at the κ-opioid receptors.[21] As a partial agonist at the μ-receptors, buprenorphine does not typically activate the receptors to the same degree as methadone. Therefore, increasing the buprenorphine dose beyond a maximum level will not increase its euphoric effect. The strong binding to the μ-receptors enables buprenorphine to block the effects of opioids with a weaker binding, such as heroin.[22] The half-life of buprenorphine is about twice that of methadone and has been reported to cause less intense withdrawal symptoms when abruptly discontinued.[21]

Fetal vulnerability to teratogenic agents may be greater during the stages of rapid cell differentiation, tissue specialization, and organogenesis.[23] Within these stages, the period most critical for developing functional abilities occurs between 24 weeks and 34 weeks of gestation.[24] It has been suggested that disruption in normal development during this period may cause attention deficit and learning disorders later in childhood.[23] However, a recently published review of the potential effects on cognitive development following prenatal exposure to methadone and buprenorphine reported an absence of studies addressing the issue of whether children's cognitive development is affected by the timing of prenatal opioid agonist exposure.[17]

Opioid-addicted nonpregnant patients who receive maintenance treatment with methadone or buprenorphine are less likely to relapse to illicit drug use or nonmedical use of prescription drugs compared with opioid-addicted nonpregnant patients who receive methadone-assisted withdrawal. Among both pregnant and nonpregnant patients in treatment for opioid dependence, a reduction in use of illegal substances is often followed by a reduction in other problem areas as well.[25–27] Methadone and buprenorphine maintenance therapies facilitate treatment retention and increase the use of other treatment options, including medical and psychiatric treatment and social service care.[10,28] Thus, agonist treatment provides an opportunity for improved health and well-being in both mothers and children.[28]

There are several reasons why an opioid-addicted pregnant woman might choose methadone-assisted withdrawal over methadone or buprenorphine maintenance. First, she may refuse methadone or buprenorphine maintenance treatment due to either self-imposed or external pressure from friends, family, and/or health care providers. Indeed, health care providers may recommend that the pregnant woman avoid opioid agonist medication during pregnancy to reduce exposure of her fetus to opioids and to avoid the risk of withdrawal for her neonate. Second, agonist medication may not be available in the woman's community. Third, she may be one of a minority of women who uses medications that are incompatible with opioid-agonist medications.[29] Although these circumstances do exist, it must be stressed that methadone-assisted withdrawal during pregnancy is not the recommended approach for the treatment of opioid dependence during pregnancy, given the significantly lower treatment retention and participation rates among pregnant women in methadone-assisted withdrawal relative to their counterparts in agonist maintenance treatment.[30] To reduce the risks of miscarriage, opioid agonist withdrawal-induced fetal stress, and premature labor, all of which are associated with methadone-assisted withdrawal, the current recommendation is to withdraw opioid-dependent pregnant patients between Weeks 14 and 32 of gestation.[31] Poorer maternal outcomes may place the mother-child dyad at risk for negative longer-term consequences.[28] Jones et al[28] found that pregnant women in methadone-assisted withdrawal showed shorter duration of treatment retention than pregnant women in methadone maintenance. With longer treatment retention, women are more likely to receive adjunctive medical treatment and social service care. Thus, longer retention can create an opportunity for improved health and well-being for mothers, their newborn children, and possibly the family unit as a whole.

Studies have shown that opioid agonist treatment during pregnancy with either methadone or buprenorphine results in

generally similar maternal and neonatal outcomes (excepting NAS). Studies have also shown that methadone-assisted withdrawal is associated with high rates of attrition and opioid use relapse.[32,33] However, no single study has yet compared methadone and buprenorphine maintenance treatment outcomes to methadone-assisted withdrawal outcomes.[14]

Purpose of the present study

The goal of the present study was to conduct an initial assessment of the relative efficacy of both methadone and buprenorphine maintenance versus methadone-assisted withdrawal in terms of neonatal and maternal delivery outcomes. There were two hypotheses of primary interest: (1) buprenorphine maintenance treatment and (2) methadone maintenance treatment would prove superior to methadone-assisted withdrawal in terms of both maternal and neonatal outcomes.

Methods

Data were derived from two sources: (1) publicly available data (http://www.jefferson.edu/jmc/pediatrics/mother/databases.cfm) from participants in the MOTHER (Maternal Opioid Treatment: Human Experimental Research) study[14] at the Johns Hopkins University Bayview Medical Center (JHBMC) site, or (2) retrospective records review of women who underwent methadone-assisted withdrawal at the JHBMC during the time period in which participants were enrolled in the MOTHER study.

The present study was approved as exempt by the Johns Hopkins School of Medicine Institutional Review Board.

MOTHER study

The MOTHER study was a multisite, double-blind, double-dummy, flexible-dosing, randomized controlled trial that compared the relative safety and efficacy of buprenorphine and methadone in pregnant opioid-dependent women and their neonates enrolled between May 4, 2005 and October 31, 2008. A detailed description of site selection, study coordination, participant selection, and protocol details for the MOTHER study has been published.[34] MOTHER findings indicated that, on average, neonates exposed in utero to buprenorphine needed significantly less morphine to treat NAS, spent fewer days in the hospital, and spent less time being medicated for NAS compared with neonates exposed in utero to methadone. There were no significant differences between the two medications on any maternal treatment efficacy outcome.[14]

Seven sites (six in the US and one in Austria) recruited a total of 175 MOTHER participants, of whom 131 completed participation and delivered. Inclusion criteria required participants to be between the ages of 18 years and 41 years, between 6 weeks' and 30 weeks' estimated gestational age as confirmed by ultrasound, and carrying a singleton pregnancy. Exclusion criteria included current benzodiazepine or alcohol abuse or dependence as defined by the Structured Clinical Interview of the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, module E; HIV seropositivity; current or impending legal complications; non-English speaking (non-German speaking at the Austrian site); and/or a medical or psychiatric condition determined by the medically responsible investigator to contraindicate participation.

The JHBMC contributed data on 17 of the 131 maternal and neonatal participants, 12 participants in the methadone condition, and five in the buprenorphine condition. Data from these 17 MOTHER participants are included in the present paper. Data from the participants at the remaining sites were not included in the present analyses in order to eliminate any effects of site heterogeneity due to differences in the populations sampled and/or slight differences in the MOTHER protocol that existed.

JHBMC MOTHER procedures

All participants signed informed consent for study participation. An extensive baseline assessment was performed to determine study eligibility. Potential participants provided demographic information; completed medical, obstetrical, and psychiatric examinations; provided a blood sample for a complete blood chemistry; and completed a nicotine dependence assessment. This information was collected during the first 3–5 days following entrance into the study, during which time maternal participants who were not already admitted to the Center for Addiction and Pregnancy (CAP) (see Setting) were stabilized on medication for opioid maintenance, or, in the case of participants who were already admitted to CAP, prior to stabilization on double-blind study medication.

Neonatal abstinence syndrome assessment

Neonates in the MOTHER study were assessed for NAS signs for a minimum of 10 days. Neonates not enrolled in the MOTHER study were assessed for NAS signs for a minimum of 4 days, which is the usual care at the JHBMC hospital. All hospitalized neonates were examined for NAS every 4 hours by trained staff.

A modified Finnegan scale[35] composed of 28 items was used to measure NAS. Modifications to the Finnegan measure included reductions in the weights of some individual item scores and the addition of failure to thrive (weight loss of

10% or more of birth weight) and excessive irritability. Of the 28 MOTHER NAS scale items, 19 were used for scoring and medication decisions: crying, sleeping, Moro reflex, disturbed tremors, undisturbed tremors, increased muscle tone, excoriation, generalized seizure, fever, frequent yawning, sweating, nasal stuffiness, sneezing, tachypnea, poor feeding, vomiting (regurgitation), loose stools, failure to thrive, and excessive irritability. A total MOTHER NAS score was calculated by adding the score assigned to each individual sign, resulting in a possible range of scores between 0 (minimal withdrawal) and 42 (maximal withdrawal).

A neonate severity-based treatment protocol was followed based on the MOTHER NAS scale, with an oral solution of morphine sulfate of 0.04 mg for a score of 9–12, 0.08 mg for a score of 13–16, 0.12 mg for a score of 17–20, 0.16 mg for a score of 21–24, and 0.20 mg for a score of 25 or above every 3–4 hours.

MOTHER outcome measures

There were five primary neonatal outcome measures: number of neonates requiring NAS treatment, peak score on the MOTHER NAS scale during the assessment period, total amount of morphine sulfate needed to treat NAS, neonatal length of hospital stay in days, and head circumference at birth. There were also seven secondary neonatal outcomes: number of days during which medication was given for NAS, length and weight at birth, preterm birth (defined as birth at <37 weeks of gestation), gestational age at delivery (as determined by delivery obstetrician), and 1-minute and 5-minute Apgar scores. In addition, there were nine secondary maternal outcomes: cesarean section delivery (yes vs no), maternal weight gain during the course of pregnancy (measured from entry into the study to last prenatal exam prior to birth), normal fetal presentation at delivery (vertex vs otherwise), anesthesia during delivery (yes vs no), urine drug screening results at delivery (positive for opiates [morphine, codeine] other than methadone or buprenorphine, cocaine, PCP, amphetamines, benzodiazepines, marijuana, and barbiturates vs negative), medical complications at delivery (yes [eg, pre-eclampsia, arrest of dilation – as determined by the delivery obstetrician] vs no), number of prenatal obstetrical visits, amount of voucher money earned for drug-negative tests, and study discontinuation.

Retrospective JHBMC sample

Setting

Charts for this retrospective record review were selected from patients admitted to CAP, a comprehensive care setting located on the JHBMC campus in Baltimore, MD.[36,37] CAP care includes addiction treatment (group and individual therapy), methadone maintenance for opioid dependence, methadone-assisted withdrawal for opioid-dependent patients declining methadone maintenance or those not meeting current opioid dependence criteria, case management, obstetrical care, psychiatric evaluation and treatment, general medical management, and on-site child care and pediatric care. Maternal treatment includes a 7-night stay on an assisted living unit followed by intensive outpatient treatment. All patients, methadone- or buprenorphine-maintained women and women receiving methadone-assisted withdrawal, received the same elements of comprehensive care.

For CAP patients using opioids, the initial determination of methadone maintenance or methadone-assisted withdrawal was made by the patient in consultation with the CAP staff on the day of admission. The presence or absence of current opioid dependence was determined by clinical staff assessing the patient using Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, criteria.

Patients who elected methadone-assisted withdrawal and who were admitted to CAP during the time MOTHER participants were enrolled received a 7-day methadone-assisted withdrawal that began with methadone 40 mg (all patients received 30 mg, and an additional 10 mg was available on the first day), 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, and 5 mg per consecutive day from Days 1–7, respectively.

Participants and sampling for the methadone-assisted withdrawal condition

Inclusion criteria for the methadone-assisted withdrawal condition included (1) meeting methadone-maintenance criteria and refusing it, (2) receiving a prescription for methadone-assisted withdrawal, (3) having no other concurrently medication-assisted tapers from alcohol or benzodiazepines, (4) having an available maternal medical chart and complete delivery outcome information accessed through the JHBMC, and (5) singleton pregnancy. (Medical records of patients delivering outside the JHBMC are routinely ordered by CAP staff and added to the patients' JHBMC records.)

A total of 51 women entered the CAP during this period who met criteria for current opioid dependence and elected methadone-assisted withdrawal at treatment admission. A total of 43 potential participants were excluded due to either entering methadone maintenance during the course of treatment (n = 39) or missing the majority of their outcome data (n = 4). Thus, eight patients were included in the sample who received only methadone-assisted withdrawal followed

by medication-free aftercare. These eight patients were not significantly different from the remainder of the cohort in terms of demographic characteristics (maternal age, race, employment status, marital status, and years of completed education). In addition, the same proportion of women in both samples were currently smoking cigarettes.

Measures and data sources

All data were abstracted from the respective maternal and neonatal hospital charts of the patients.

Present study outcome measures

Outcomes for the present study were the same as those outcomes described previously for the MOTHER study, with the exception of two measures: patients who did not participate in the MOTHER study did not earn voucher money for drug-negative tests, and study discontinuation could not be considered an outcome for the retrospective chart review participants who had not participated in the MOTHER study. Finally, in the present study no distinction was made between primary and secondary outcome measures.

Statistical analysis

Statistical methods

The statistical method chosen was dependent on the assumptions regarding the distribution of the outcome measure in the population. Peak score on the MOTHER NAS scale during the assessment period and neonatal head circumference, birth weight, and length were each assumed to be normally distributed, so least-squares regression was utilized. Treated for NAS, preterm birth status, cesarean section, non-normal presentation at delivery, analgesia during delivery, drug screen status at delivery, and medical complications at delivery were each assumed to follow a binomial distribution, so logistic regression was utilized. Neonatal length of stay in the hospital in days, estimated gestational age at delivery, number of prenatal obstetrical visits, and Apgar scores at 1 minute and 5 minutes were assumed to follow a Poisson distribution, so Poisson regression was employed. Because of the preponderance of zero values possible in their theoretical distributions, the total amount of morphine administered to alleviate NAS severity and the number of days medicated for NAS were both assumed to follow a zero-inflated Poisson distribution, and thus zero-inflated Poisson regression was utilized for these two variables. In the case of both logistic and Poisson regression analyses, a scale parameter was permitted in the model to allow for overdispersion due to the possible failure to meet the assumptions of the respective model regarding variance homogeneity. The single explanatory variable in the model was a three-level fixed-effect factor representing the three treatment groups: methadone-assisted withdrawal, methadone, or buprenorphine maintenance. For both the least-squares and Poisson analyses, interpretation focused on model-derived least-squares means and exponentiated means, respectively, and their standard errors. In the case of the zero-inflated Poisson models, the means are only for those neonates who were treated for NAS, because a zero-inflated Poisson regression estimates the parameters for the zero and the non-zero values separately. For the logistic regression analyses, interpretation was based on odds ratios and their standard errors.

Planned comparisons

In order to answer the two primary questions of interest, two single-degree-of-freedom, nonorthogonal planned contrasts were created. The two planned contrasts compared the methadone-assisted withdrawal group with the (1) methadone maintenance group and (2) buprenorphine maintenance group, respectively. The methadone and buprenorphine maintenance conditions were not compared with each other, as that comparison had previously been reported for the entire MOTHER sample.[14] Thus, these two contrasts address the question of whether or not (1) methadone and/or (2) buprenorphine maintenance produces superior neonatal and maternal birth outcomes relative to methadone-assisted withdrawal.

Results

Participant characteristics

Table 1 presents summary statistics for various demographic and background characteristics for the three treatment groups. The patients at treatment entry were, on average, in their early 30s (seven were in there 20s, and three were in their 40s), either black or white with approximately the same frequency of occurrence, often with less than a high school education (15 had graduated from high school, and none had graduated from college), universally unmarried, universally unemployed, and generally legally unencumbered. Of note, estimated gestational age at treatment entry ranged from 11 weeks to 36 weeks with a mean of 22.2 weeks in the total sample.

Overall, there were no statistically significant differences among the three treatment groups on any demographic and background characteristic examined.

Differences in treatment outcome

Table 2 summarizes the results of the inferential statistical analyses. As can be seen in the table, significant differences

Table 1 Descriptive statistics for demographic and background characteristics in the three treatment groups (N = 25)

Background characteristic	Methadone-assisted withdrawal (n = 8)	Methadone (n = 12)	Buprenorphine (n = 5)	*P*
Maternal age in years	33.3 (7.6)	31.4 (5.3)	33 (6.1)	0.79
Race				0.88
White	4 (50%)	5 (42%)	3 (60%)	
Black	4 (50%)	7 (58%)	2 (40%)	
Years of education	11.4 (1.2)	10.8 (2.0)	11.8 (0.4)	0.50
Employed	0	0	0	–
Legal status uninvolved	6 (75%)	12 (100%)	3 (60%)	0.10
Married	0	0	0	–
Current cigarette smoker	7 (88%)	12 (100%)	5 (100%)	0.52
Estimated weeks of gestational age at study entry	22.8 (8.3)	21.8 (6.0)	22.0 (6.9)	0.96

Note: Estimates in cells are either *f* (%) or mean (SD). Percentages are within the respective treatment group. All tests of significance for binary variables are likelihood ratio tests of independence, and all associated probability values are exact, while all tests for continuous variables are one way analyses of variance, – indicates it was not possible to conduct inferential tests due to lack of variability for that variable.

between methadone-assisted withdrawal and methadone maintenance occurred for four outcomes, whereas significant differences between methadone-assisted withdrawal and buprenorphine maintenance occurred for two of these four outcomes. Surprisingly, differences in all six cases favored methadone-assisted withdrawal.

Neonates in the methadone-assisted withdrawal group, in comparison with neonates in the methadone maintenance group, had significantly lower mean NAS peak score (Means = 7.0 vs 13.7), required a significantly lower mean amount of morphine to treat NAS (Means = 0.2 vs 82.8), had significantly fewer days medicated for NAS (Means = 3.9 vs 31.5), and,

Table 2 Frequencies (%) or means (standard errors) and *P* values for the two planned contrasts for the outcome measures in the three treatment groups (N = 25)

Outcome measure	Methadone-assisted withdrawal (n = 8)	Methadone (n = 12)	Buprenorphine (n = 5)	Methadone-assisted withdrawal vs	
				Methadone *P*	Buprenorphine *P*
Neonatal outcomes					
Treated for NAS [yes]	2 (25%)	8 (66.7%)	2 (40%)	0.079	0.571
NAS peak score	7.0 (1.4)	13.7 (1.2)	10.2 (1.8)	**0.002**	0.182
Total amount of morphine for NAS (mg)	0.2 (0.1)	82.8 (3.2)	8.2 (2.0)	<**0.001**	<**0.001**
Days of infant hospital stay	7.0 (3.4)	24.2 (5.1)	9.0 (4.8)	**0.019**	0.727
Head circumference (cm)	33.1 (0.7)	32.8 (0.6)	33.0 (0.9)	0.701	0.901
Days medicated for NAS	3.9 (1.4)	31.5 (2.0)	12.0 (2.4)	<**0.001**	**0.008**
Birth weight (gm)	3023.0 (220.9)	2849.6 (180.4)	2911.0 (279.4)	0.549	0.756
Infant length (cm)	48.7 (1.1)	48.0 (0.9)	48.8 (1.3)	0.633	0.948
Pre-term (<37 weeks) birth [yes]	3 (37.5%)	4 (25%)	1 (20%)	0.848	0.512
Gestational age at delivery (weeks)	38.1 (0.9)	37.2 (0.8)	39.0 (1.2)	0.414	0.575
Apgar score at 1 minute	8.4 (0.6)	7.2 (0.5)	7.6 (0.8)	0.127	0.445
Apgar score at 5 minutes	9.0 (0.4)	8.1 (0.3)	8.6 (0.5)	0.092	0.565
Maternal outcomes					
Cesarean section [yes]	1 (12.5%)	3 (25%)	1 (20%)	0.501	0.718
Maternal weight gain (kg)	5.5 (3.0)	7.4 (2.1)	10.7 (3.2)	0.606	0.248
Non-normal presentation [yes]	1 (12.5%)	1 (8.3%)	0 (0%)	0.762	0.947
Analgesia during delivery [yes]	6 (75%)	10 (83.3%)	3 (60%)	0.650	0.571
Drug screen at delivery [positive]	1 (14.3%)	2 (16.7%)	0 (0%)	0.891	0.958
Medical complications at delivery [yes]	4 (50%)	9 (75%)	1 (20%)	0.258	0.295
Number of prenatal obstetrical visits	10 (1.5)	10.1 (1.2)	10.2 (1.9)	0.966	0.935

Notes: Estimates in the table are *f* (%) or mean (SE). Means for total amount of morphine for NAS and days medicated for NAS were estimated only for those neonates treated for NAS, based on the use of a zero-inflated Poisson regression model (see text for details). One case from the methadone-assisted withdrawal group was missing a value for drug screen at delivery. Significant effects are noted with *P* values in bold.
Abbreviation: NAS, Neonatal Abstinence Syndrome.

on average, remained in the hospital for a significantly lower number of days (Means = 7.0 vs 24.2). In contrast, neonates in the methadone-assisted withdrawal group, in comparison with neonates in the buprenorphine maintenance group, required a significantly lower mean amount of morphine required to treat NAS (Means = 0.2 vs 8.2) and significantly fewer days medicated for NAS (Means = 3.9 vs 12.0).

Discussion

This discussion summarizes the extent to which this study's sample is representative of the larger drug-addicted pregnant population, how these results fit into the wider literature, the limitations of the present study, and the opportunities for future research.

This sample of current opioid-dependent pregnant patients has characteristics that are, on average, similar to other published samples of pregnant drug-addicted participants. For example, similar to this study, past studies show that average patient characteristics include a majority being unemployed, unmarried, and cigarette smokers.[32,37–40]

Several findings deserve comment. First, 77% of the 51 eligible methadone-assisted withdrawal participants switched to methadone maintenance during their pregnancy, which underscores the acceptability of methadone maintenance among opioid-dependent pregnant patients. The fact that 77% of patients switch from methadone-assisted withdrawal to methadone maintenance represents an increase from 48%[28] over the last decade and is likely due to staff, provider, and patient education about the value and importance of methadone maintenance for improving maternal and neonatal outcomes. Opioid-addicted pregnant women who receive methadone-assisted withdrawal are more likely to experience relapse than pregnant women maintained on methadone or buprenorphine; with relapse there is greater fetal exposure to illicit drugs.[28] A study comparing the effect of in utero exposure with methadone or cocaine on mouse brain development[41] suggested that exposure to cocaine had negative effects on brain development but did not seem to cause growth retardation in mouse offspring. In contrast, exposure to methadone resulted in offspring being somewhat smaller but did not seem to adversely affect normal brain development.[41] Second, it is noteworthy that there were no significant differences between either opioid-agonist treatment group when compared with the methadone-assisted withdrawal group on any of the seven maternal outcomes examined. All groups showed relatively low rates of cesarean section deliveries and relatively high proportions of urines samples negative for illicit drugs at delivery. Third, given the modest sample size, the differences between the methadone-assisted withdrawal group and the opioid-agonist groups in terms of neonatal results are striking. Interestingly, the proportion of neonates treated for NAS was not significantly different between the groups. This finding is important in that it is commonly assumed that prenatal exposure to either methadone or buprenorphine maintenance will result in an increased likelihood of the neonate being treated for NAS. Fourth, the methadone-assisted withdrawal group showed improved neonatal outcomes compared with both opioid-agonist treatment groups in terms of the total amount of morphine used to treat NAS and the total number of days of medication for NAS. Neonates in the methadone-assisted withdrawal group were also found to have a significantly lower NAS peak score and shorter length of hospital stay compared with neonates in the methadone maintenance group but not neonates in the buprenorphine maintenance group. It is important to note that the sample in the present study is a very small and select sample, so appropriate regard should be taken in inferring clinical significance in the study results. Health care professionals especially should exert caution in taking any patient-related actions based on the results. Previous research has found that, compared with methadone-assisted withdrawal, opioid maintenance treatment provides superior relapse prevention, reduces fetal exposure to illicit drugs, enhances compliance with obstetrical care, and enhances neonatal outcome.[28]

As with any other medications given during pregnancy, methadone and buprenorphine have associated risks and benefits. However, for pregnant women and their fetuses, the consequences of not receiving these medications may be life-threatening. Moreover, drug abuse rarely occurs in the absence of confounding biopsychosocial issues, and the effects of any drug (including methadone and buprenorphine) are best understood in the context of the complex life challenges experienced by many opioid-dependent individuals.[42]

To our knowledge, this is the first study that compares outcomes from buprenorphine maintenance treatment with methadone-assisted withdrawal. Thus, the present study provides new knowledge on treatment outcomes for pregnant women with opioid addiction.

Limitations

First, the methadone-assisted withdrawal group is clearly a highly motivated set of patients, and a very different pattern of results may have been observed with a different comparison

group, such as one that included only those patients who received methadone-assisted withdrawal and were also opioid-positive at delivery. Second, the sample sizes for all three medication groups were relatively small, which likely limited our ability to detect differences between the three groups. Third, the small sample size excluded the possibility of using covariates to adjust for group differences. Fourth, the relatively large number of tests each at $\alpha = 0.05$ has likely led to an increase in the cumulative error rate. However, a more conservative rate would run the risk of failing to detect a small but potentially important difference between methadone-assisted withdrawal and either of the two medication conditions, an important goal of an initial investigation of this issue as occurred in the present study. Nonetheless, we were able to detect differences on four outcome variables – three of which (excluding peak NAS score) were found to significantly discriminate between buprenorphine and methadone maintenance in the MOTHER study, strongly suggesting that our results are unlikely to be spurious.

Conclusion

Findings from this study could, at first reading, be taken to suggest that methadone-assisted withdrawal could be a successful approach in the treatment of opioid dependence in pregnancy. However, despite our findings, which are certainly surprising, we would argue that such a conclusion would be decidedly at variance with the literature on methadone-assisted withdrawal, which has shown that such an approach to treatment has an extremely high rate of relapse to opioid use.[28]

It is important to underscore that the methadone-assisted withdrawal group in this study was a select group (16% of the total potential sample) in the sense that it comprised mothers who had chosen methadone-assisted withdrawal and had not subsequently either left the treatment program or chosen to enter methadone maintenance treatment. This group represents an appropriate comparison group with the methadone and buprenorphine maintenance groups, because the women in these latter two groups had also maintained their respective treatment status throughout their pregnancy. Participants in all three groups remained in their respective medication or nonmedication status throughout their pregnancy and at delivery. Nonetheless, the analyses could best be constructed as a "completers analysis" rather than an "intent-to-treat" analysis.

Finally, we do note that there are occasions where methadone-assisted withdrawal is necessary, such as when a patient declines to participate in any substance abuse treatment unless she is medication-free at delivery, when she is unable to receive agonist maintenance in her community (due to lack of clinic space or the lack of a clinic), when she is prescribed a medication that is incompatible with methadone, or when she has a medical condition for which a medication such as methadone is contraindicated (eg, sleep apnea, asthma, or extreme obesity). Our results suggest that it is possible for opioid-dependent pregnant women to be successful with methadone-assisted withdrawal. However, more research needs to be conducted on the impact of methadone-assisted withdrawal on the fetus in order for us to understand the potential consequences of this treatment approach.

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