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Fetal Neurobehavioral Effects of Exposure to Methadone or Buprenorphine

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Abstract

As part of a double-blind study of medication treatment for opioid dependence during pregnancy, 17 opioid-dependent pregnant women maintained on either buprenorphine or methadone underwent fetal monitoring at 24, 28, 32, and 36 weeks gestation. Maternal demographic information and infant outcomes did not significantly differ by medication group. Earlier in gestation (24 and 28 weeks), buprenorphine-exposed fetuses had higher levels of fetal heart rate variability, more accelerations in fetal heart rate and greater coupling between fetal heart rate and fetal movement than the methadone-exposed group (all *p*'s <.05). Later in gestation (32 and 36 weeks), buprenorphine-exposed fetuses displayed less suppression of motor activity and longer duration of movements than the methadone-exposed group (all *p*'s <.05). These results may have implications for the optimal treatment of the opioid-dependent pregnant woman.

Keywords

buprenorphine; drug dependency; fetal heart rate; fetus; methadone; opioids; pregnancy

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INRODUCTION

Opioid dependency, both use of illicit opioids and misuse of licit opioids, during pregnancy remains a public health dilemma internationally. Opioid dependent pregnant women comprise a special population due to the multiple considerations of the mother, the pregnancy, and the fetus. Maintenance treatment with methadone, a full mu-agonist, is the current recommended standard of care for the opioid dependent pregnant woman [16], offering many well-known benefits for the mother-infant dyad [6]. However, research from animal and human studies has raised concerns regarding short- and long-term adverse effects. Animal literature has shown that prenatal methadone exposure predicates a disruption to neural maturation in exposed fetuses [21,22], and there is evidence of similar disruption in human neurodevelopment. When compared to non-exposed fetuses, methadone-exposed fetuses have reduced baseline heart rate, proportion of accelerations [17,20], and heart rate variability [20]. At times of maternal peak methadone levels, methadone-exposed fetuses have less motor activity [24,10] slower and less variable heart rates, and attenuated integration between fetal heart rate and fetal movement [10] compared to the same fetuses at times of trough maternal methadone levels. Additionally, prenatal exposure to methadone predisposes the infant to develop symptoms of neonatal abstinence syndrome (NAS) in most cases [19,23]. However, the benefits provided by methadone maintenance delivered within a comprehensive care setting to this patient population, which include prevention of relapse to substance use, reduced fetal exposure to illicit drug use and other maternal risk behaviors, improved adherence with obstetrical care and enhanced neonatal outcomes, outweigh the potential risks of treatment [13].

Although buprenorphine, a partial mu opioid agonist medication, is only approved by the Food and Drug Administration (FDA) for opioid-dependence treatment in non-pregnant patients, there is gathering interest in the use of this medication during pregnancy. Prenatal exposure to buprenorphine has resulted in similar or reduced levels of NAS severity than methadone [5,14,8,11,4] without greater risk to the mother or pregnancy [8,11,15]. Current recommendations state that buprenorphine should only be prescribed for pregnant opioid dependent patients when the benefits outweigh the risks and the patient has refused methadone [2].

The purpose of the present study was to provide preliminary data comparing fetal neurobehaviors in methadone- and buprenorphine-exposed fetuses during the second half of pregnancy. Based on literature that supports a lower incidence of neurobehavioral dysregulation (NAS) in buprenorphine-exposed as compared to methadone-exposed infants [7], we expected that buprenorphine-exposed fetuses would display less depression of fetal parameters, including heart rate, heart rate variability and motor activity, than methadone-exposed fetuses.

MATERIALS AND METHODS

Participants

Participants were drawn from a sample of pregnant women who received care at the Center for Addiction and Pregnancy (CAP), at Johns Hopkins Bayview Medical Center, a multidisciplinary, comprehensive care treatment facility for pregnant drug-dependent women and their children [9] and consented to participate in a multi-site, double-blind, double-dummy protocol evaluating the safety/efficacy of methadone and buprenorphine maintenance during pregnancy (Maternal Opioid Treatment; Human Experimental Research; Jones, H., PI [13]). Thirty women consented to participate in a sub-study, conducted only at the CAP site, focused on evaluating the differential effects of maternal methadone vs. buprenorphine treatment on fetal neurobehaviors. The research was approved

by the Johns Hopkins University School of Medicine Institutional Review Board and all participants provided informed consent. Participants were screened for recent drug use at the time of each fetal assessment using a five-panel onsite drug test card, testing for marijuana, opiates (excluding methadone), cocaine, amphetamines and benzodiazepines (CLIAwaived ©, Inc.) and recent alcohol use via breathalyzer screening (Lifeloc Technologies, Wheat Ridge, CO) which measures blood alcohol content to 0.02%, or the equivalent of one drink; women screening positive for use of illicit or misuse of licit drugs or alcohol did not undergo fetal monitoring at that time. Maternal demographic and infant medical data were collected at the times of fetal testing and birth, respectively. All fetal tracings were evaluated immediately after study procedures by a maternal-fetal medicine specialist with expertise in the evaluation of drug-exposed fetuses (LM). No fetal tracing was interpreted as non-reassuring or requiring further obstetrical evaluation or immediate intervention.

Recruitment for the fetal study took place between 23 and 35 weeks gestation. Before randomization, all participants received a brief period of inpatient rapid-release morphine sulfate for medical stabilization and to ease the transition onto double-blind medication [12]. Of the original 30 participants, 13 became ineligible for this analysis: 9 participants declined to continue with the parent treatment protocol prior to scheduled fetal monitoring, 2 became ineligible due to a positive urine toxicology at the time of fetal testing (one of these subsequently dropped out of the parent study prior to rescheduled fetal monitoring, and the other one delivered a preterm infant prior to rescheduled monitoring), 1 was disenrolled due to insulin dependence for gestational diabetes, and 1 participant was tested before buprenorphine therapy had begun as a result of blinding. Of the remaining 17 women, 11 were treated with methadone and 6 with buprenorphine.

Maternal characteristics are presented in Table 1. There were no significant differences between the methadone-exposed and buprenorphine-exposed groups in terms of race, parity or age between the two groups. No participant screened positive for recent alcohol use at any point although virtually all (94%) smoked cigarettes daily; there were no significant differences in the number of cigarettes smoked daily between groups. Maternal use of illicit substances or misuse of licit substances were measured by thrice weekly (MWF) urine toxicology screens which were tested on-site for the presence of PCP, barbiturates, opiates (including oxycodone and excluding methadone and buprenorphine), cocaine, benzodiazepines, marijuana, amphetamine and methamphetamines throughout the period of enrollment in the fetal study. Given the variety of substances and small numbers of users of specific combinations, it was not possible to analyze these separately by substance. Instead, the percent of total number of urine toxicology screens collected during the period of study enrollment that was positive for substance use or misuse was calculated for each subject. There were no significant differences in percent positive urine toxicology screening results by medication condition.

Procedure

Fetal assessments took place at 24, 28, 32 or 36 weeks gestation, as determined by second trimester ultrasound, 2 ½ hours after single daily maternal medication dose. Some participants were tested more than once while others received only a single recording. Given the small sample size and to avoid an excessive number of statistical comparisons, data collection sessions were grouped into the two lowest (24 and 28 weeks) and two highest (32 and 36 weeks) gestational age groups. If a participant was monitored at both intervals (e.g., at 24 *and* 28 weeks), the earlier assessment was selected for the analysis.

Fetal monitoring occurred with women in a semi-recumbent position and proceeded for 60 minutes. Fetal heart rate and motor activity data were collected using a Toitu (MT325) fetal actocardiograph which detects fetal movement (FM) and fetal heart rate (FHR) using a

single wide array transabdominal Doppler transducer. The actograph detects fetal movement by bandpassing the frequency components of the Doppler signal that are associated with FHR and maternal somatic activity. Fetal data were collected from the output port of the monitor and digitized through an internal A/D board and streaming software. Data were analyzed off-line using customized software (James Long Company, Caroga Lake NY). Digitized heart rate data underwent error rejection procedures based on moving averages of acceptable values as needed. A total of six fetal measures were derived. Three cardiac variables were extracted: fetal heart rate and fetal heart rate variability (root mean squared), both computed in 1 minute epochs and averaged over the recording period; and episodic accelerations of fetal heart rate (count), identified when FHR values attained 10 bpm above baseline for greater than or equal to 15 seconds. Fetal motor activity was based on the actograph signal and also averaged over the entire 60 minute session to yield a measure of the total amount of fetal movement. In addition, the duration of individual fetal movements was computed. The relation between changes in fetal movement and fetal heart rate (i.e., FM-FHR coupling) was calculated as the percent of fetal movements associated with excursions in FHR ≥ 5 bpm over baseline within 5 sec before the start of a movement or within 15 sec after the start of a movement. This definition is based on prior work that suggests that this measure provides an indicator of the developing fetal nervous system [1,3].

RESULTS

Eight of the 11 methadone-exposed and 4 of the 6 buprenorphine-exposed participants received fetal monitoring at 24 or 28 weeks gestation; at 32 to 36 weeks there were 6 methadone-exposed and 5 buprenorphine-exposed assessments. Six participants (3 from each group) provided data at both gestational age periods.

Infant outcomes are presented in Table 2. There were no differences in infant sex, birth weight, Apgar scores, gestational age at delivery, or the percent of infants treated pharmacologically for NAS by medication condition. Note that one infant in the methadone group was delivered at a different hospital; since NAS scoring and therefore number of days treated for NAS is a subjective measure and can vary significantly between hospitals, this infant's NAS data were excluded. Although more than twice as many infants in the methadone group were treated for NAS in the neonatal period and for more than double the amount of time, there was insufficient power to detect these outcome differences. Also, there was wider variation in the range of treatment days for the methadone-exposed condition than the buprenorphine-exposed condition (4 to 75 days vs. 5 to 19 days, respectively).

Fetal assessment comparisons

Non-parametric statistics (Mann-Whitney U test) were used to evaluate group differences by medication due to the small sample sizes at each of the two gestational age periods. Summary statistics are presented in Table 3. Earlier in gestation, buprenorphine exposure was associated with higher levels of fetal heart rate variability, more accelerations (in fact, no accelerations were observed in the 8 methadone-exposed fetuses prior to 28 weeks gestation), and greater FM-FHR coupling, as well as a trend towards longer movement duration. At the later gestational period, no significant associations were detected with cardiac measures, but overall motor activity was significantly depressed along with shorter movements in the methadone-exposed group.

In addition to the quantitative cardiac and motor activity analyses, a clinician highly experienced in evaluation of fetal monitor tracings and blinded to medication group was asked to provide an overall impression of the tracings based on her impression of fetal well-

being. When informed that all participants were maintained on either methadone (a full mu opioid agonist) or buprenorphine (a partial mu opioid agonist theoretically having less effect on fetal neurobehaviors), the expert correctly identified maternal medication category in 12 (71%) of 17 cases: 5/6 buprenorphine-exposed fetuses, and 7/11 methadone-exposed fetuses [Cohen's κ =.42 (*SE*=.20), *p*=.06].

DISCUSSION

This preliminary report on the effects of buprenorphine as an alternative agent for the treatment of opioid dependent pregnant women provides encouraging results. When compared to the standard methadone therapy, buprenorphine-exposed fetuses have better indications of fetal well-being than methadone-exposed fetuses, including greater variability in fetal heart rate, more accelerations, and better coupling between fetal movements and heart rate. These differences were significant earlier in gestation but not later, suggesting that the developing fetal nervous system is more vulnerable to threats earlier in the second half of gestation than later. In contrast, fetal motor activity was most consistently suppressed in methadone-exposed fetuses at the later gestational period. The effects on the electronic fetal monitoring records were substantial enough that a blinded clinician correctly identified 83% of the buprenorphine exposed cases.

CONCLUSIONS

These results may have implications for the optimal treatment of the opioid dependent pregnant woman. Fetal neurobehavior serves as a window to the developing nervous system, and its disruption implies threat to the neural development of the fetus [18]. A medication that provides less depression of fetal neurobehaviors and equal efficacy for the treatment of maternal opioid dependency during pregnancy, such as buprenorphine [8,11] may be a more optimal choice for the treatment of opioid addiction during pregnancy. Although these promising but preliminary results should be interpreted with caution due to the small sample sizes, they support the need for a larger comparison on a greater number of opioid-dependent pregnant women.

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Table 1

Maternal characteristics by medication condition

	Methadone (n = 11) ***M* (*SD*) [range]**	**Buprenorphine (n = 6)** ***M* (*SD*) [range]**
Age (years)	31.8(6.1) [23–40]	33.8(5.1) [25–40]
Race		
Caucasian	5 (45.5%)	3 (50%)
African American	6 (54.5%)	3 (50%)
Parity	2.6 (1.6)	2.8 (1.6)
GA at enrollment into parent study (weeks)	18.9 (5.4)	19.0 (5.0)
Smokers	10 (90.9%)	6 (100%)
Mean number cigarettes smoked daily	14.5 (4.9)	10.3 (4.8)
Urine toxicology screens positive† for substances (%)	23.4 (20.2)	37.0 (27.7)

†Urine toxicology screens were performed thrice weekly and screened for PCP, barbiturates, opiates (including oxycodone and excluding methadone and buprenorphine), cocaine, benzodiazepines, marijuana, amphetamine and methamphetamines

Table 2

Infant characteristics by medication condition

	Methadone (*n* = 11) *M* (*SD*)	**Buprenorphine (*n* = 6) *M* (*SD*)**
Sex (male)	4 (36.4%)	3 (50.0%)
Birth weight (g)	2826.8 (538.0)	2936.7(571.4)
Apgar score at 1 minute	7.4 (1.8)	7.7(1.0)
5 minutes	8.0 (1.6)	8.7 (0.8)
Gestational age at birth (weeks)	37.5(2.56)	38.9 (2.0)
Pharmacotherapy for NAS	7 (63.6%)	2 (33.3%)
Days treated for NAS	28.7 (24.7)	12.0 (9.9)

Table 3

Fetal cardiac and movement parameter comparisons by treatment group

	Methadone M(*SD*)	**Buprenorphine M(*SD*)**	***z***
24/28 weeks	*n* = 8	*n* = 4	
Fetal heart rate (bpm)	139.11(5.51)	136.10(7.77)	−0.85
Fetal heart rate variability	3.69(1.01)	5.05(1.04)	−2.06*
Accelerations	0(0)	1.25(1.89)	−2.09*
Motor activity	4.80(1.45)	5.95(.79)	−1.36
Movement duration	16.07(4.72)	27.46(14.91)	−1.87^
FHR-FM coupling(%)	7.64(6.49)	18.78(9.26)	−2.04*
32/36 weeks	*n* = 6	*n*=5	
Fetal heart rate (bpm)	133.42(7.89)	134.58(7.12)	−0.18
Fetal heart rate variability	4.43(0.78)	5.30(2.16)	−0.37
Accelerations	1.17(1.17)	2.80(3.83)	0
Motor activity	3.58(1.18)	5.92(2.95)	−2.01*
Movement duration	8.74 (2.71)	21.53 (13.22)	−2.01*
FHR-FM coupling(%)	27.42(13.97)	18.88(6.90)	−1.10

^ $p < .10$.

* $p < .05$.