Drug and Alcohol Dependence 201 (2019) 38–44

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Maternal buprenorphine treatment during pregnancy and maternal physiology

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ARTICLE INFO

Keywords:
Buprenorphine
Maternal physiology
Heart rate variability
Skin conductance
Nicotine
Neonatal abstinence syndrome

ABSTRACT

Background: Buprenorphine, used for opioid use disorder (OUD) treatment during pregnancy, provides unknown effects on maternal physiological activity. The primary aim of this report is to document acute effects of buprenorphine administration on indicators of maternal autonomic functioning. Effects of maternal buprenorphine dose and other substance exposures on maternal measures were examined, as were neonatal abstinence syndrome (NAS) outcomes.

Methods: Forty-nine pregnant, buprenorphine-maintained women yielded maternal physiologic information (heart rate and variability, electrodermal activity, and respiratory rate) at 24, 28, 32 and 36 weeks gestation. Monitoring at trough and peak maternal medication levels was implemented to ascertain acute physiologic effects of buprenorphine administration.

Results: Buprenorphine administration accelerated maternal heart rate and reduced variability at two gestational ages (24 and 36 weeks) and suppressed sympathetic (electrodermal) activation at 24, 28 and 32 weeks at times of peak maternal medication levels. Maternal autonomic parameters were unrelated to polysubstance exposure with the exception of cigarette smoking. Heavier smoking dampened maternal heart rate variability across gestation and potentiated reactivity to buprenorphine at 24 and 36 weeks. Heavier smoking was also associated with reduced electrodermal activity at 36 weeks. Buprenorphine dose was unrelated to observed effects. Larger degree of maternal heart rate reactivity to buprenorphine administration was related to more severe NAS expression.

Conclusions: These findings detail the maternal autonomic response to buprenorphine administration but also illustrate the significant effect of concurrent cigarette use on maternal autonomic regulation. This suggests the importance of smoking-reduction strategies in the comprehensive, medication-assisted treatment of women with OUD.

1. Introduction

The opioid crisis continues to be a major public health concern in the US, with increasing numbers of opioid-exposed infants experiencing neonatal abstinence syndrome (NAS) with attendant escalation of costs principally borne by Medicaid (Winkelman et al., 2018). Therefore, efforts to optimize maternal treatment for opioid use disorder (OUD) have become increasingly important. Buprenorphine is increasingly used in the US since publication of research within the past decade indicating less deleterious effects for the fetus and infant (Jones et al., 2010; Jansson et al., 2011; Salisbury et al., 2012) as compared to methadone. In contrast to effects on the developing fetus, little is known about how substance exposures in general, and buprenorphine administration in particular, affects physiological functioning of pregnant

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https://doi.org/10.1016/j.drugalcdep.2019.03.018
Received 21 November 2018; Received in revised form 23 March 2019; Accepted 26 March 2019
Available online 31 May 2019

women.

Prior work on methadone administration comparing maternal autonomic indicators at times of pharmacologic peak (2 h after daily oral administration) versus trough (just prior to daily administration) in a sample of 40 pregnant women revealed temporary suppression of maternal parasympathetic regulation, indexed by lower respiratory sinus arrhythmia, along with slower respiration at 36 weeks gestation (Jansson et al., 2005). A second sample of comparable size explicitly compared the effects of delivery of split (every 12 h) versus single (once daily) dosing in adjacent weeks and, in contrast to the earlier study, noted significantly depressed sympathetic activity (i.e., electrodermal) at peak under both dosing schedules (Jansson et al., 2009a). Neither study detected correspondence between maternal methadone dose and physiological responsiveness. However, the degree to which methadone administration elicited vagal reactivity in women at 36 weeks gestation was significantly predictive of the severity of NAS in offspring (Jansson et al., 2007).

To our knowledge, no corresponding information regarding the physiological effects of buprenorphine on pregnant women is available. Buprenorphine is a partial μ-agonist, with lower activity at the μ receptors as compared to the full agonist capacity of methadone. As such, buprenorphine has maximal subjective and physiologic effects that are less than full mu agonist maximal effects, i.e., a plateau or ceiling effect at a maximal value (Ariens, 1983; Walsh et al., 1994). In non-pregnant adults, buprenorphine produces little or no autonomic signs and symptoms of opioid withdrawal following abrupt determination, in contrast to reports for methadone and heroin (Johnson et al., 2003).

The current report is part of a larger investigation of the effects of maternal buprenorphine treatment during pregnancy; consequences for the fetus and infant have been previously reported (Jansson et al., 2017a, b). Here we focus on whether buprenorphine confers acute or cumulative effects on indicators of maternal autonomic functioning. These include heart rate and respiratory period as general indicators of baseline physiological functioning, along with heart rate variability as representative of parasympathetic inputs and electrodermal activity as an indicator of sympathetic control. Electrodermal activity, in this case skin conductance, reflects changes in conductivity of the skin mediated by eccrine glands and is singly innervated by the sympathetic branch of the nervous system. In pregnant women without OUD, measures of autonomic functioning are extremely stable during the second half of pregnancy such that the rank ordering of women on all of these indicators remains relatively the same over time, even though mean values may change (DiPietro et al., 2005). This suggests that autonomic regulation has trait-like characteristics that may provide a foundation for responsiveness to medication-assisted treatment and longer-term infant outcomes. As such, and given the findings regarding responsivity to methadone administration (Jansson et al., 2007), the predictive utility of maternal reactivity to buprenorphine administration as a marker of autonomic liability in relation to neonatal abstinence syndrome was also evaluated.

Polysubstance use is common in this population, and prior research with women with OUD detected deleterious confounding and contributory influences of non-prescribed substances, including cigarette smoking and illicit substance use, on fetal, neonatal and maternal parameters (Jansson et al., 2017a,b; Jones et al., 2013; Winklbaur et al., 2009). Of all competing exposures, cigarette smoking is the most ubiquitous in pregnant women receiving medication-assisted treatment, with estimates as high as 90% (Chisolm et al., 2013). As a result, smoking and polysubstance use will be evaluated as potential moderating or confounding exposures.

2. Methods

2.1. Study overview

A prospective, longitudinal study to document the neurobehavioral development of the buprenorphine-exposed fetus and acute effects of buprenorphine administration on fetal neurobehaviors and maternal physiology over the second half of gestation (24, 28, 32 and 36 weeks gestation) was undertaken between 2012 and 2016. Eligibility was restricted to pregnant women with OUD and singleton, otherwise uncomplicated pregnancies absent of chronic maternal illness or pregnancy-induced conditions. Significant maternal conditions that could independently affect fetal functioning, including HIV infection, hypertension, and diabetes mellitus, were exclusionary. Because of population norms, use of other licit (e.g., cigarettes) and illicit (e.g., heroin) substances was not exclusionary, with the exception of current alcohol dependence to avoid potential teratogenic effects and/or heavy benzodiazepine use when the potential for withdrawal during the inpatient buprenorphine induction period was considered unsafe. The protocol was reviewed by the overseeing Institutional Review Board, and all participants provided written consent.

2.2. Protocol

2.2.1. Maternal medication induction and treatment

Participants included women enrolled into the study while stable on buprenorphine (n = 12) and those who underwent a 3-day induction on an inpatient clinical research unit (n = 37). The induction protocol included a period of opioid washout and attendant withdrawal due to the pharmacologic characteristics of buprenorphine. Stable methadone-maintained women were not offered study participation. Because participants were pregnant women at up to 34 weeks of gestation, no more than mild withdrawal (i.e., score of 8, indicating mild withdrawal) based on frequent scoring using the Clinical Opioid Withdrawal Scale (Tompkins et al., 2009) was tolerated before initial buprenorphine dosing. A maximal dose of 24 mg could be achieved by the third day of the induction protocol, after which participants returned to the treatment program as outpatients. Participants who entered the study as stable, buprenorphine-maintained patients were dosed with their maintenance dose and entered the treatment program as outpatients. Participants received a single, daily, observed (through tablet dissolving) sublingual dose of mono-buprenorphine at approximately the same time each morning, with take-home dosing only when necessary and approved. All women received substance use disorder and obstetric care at the treatment program from intake through delivery; psychiatric care was provided to women as necessary for the same time period.

2.2.2. Maternal monitoring

During treatment, women participated in up to four monitoring sessions during one day at each of the following gestational ages: 24, 28, 32 and 36 weeks. The monitoring protocol was implemented only after at least 7 days of continuous dosing with buprenorphine at the same dose. The first session took place at time of medication trough (i.e., just prior to oral dosing) and the second at peak (2.5 h after dosing) later that day. Women were asked to refrain from eating, drinking caffeinated beverages, and smoking for two hours prior to monitoring. Monitoring proceeded for 60 undisturbed minutes during each session with women lying in a semi-recumbent left lateral position.

In an effort to distinguish medication effects from acute other substance exposures, urine toxicology testing (Alere™ point of care drug screen urine test panel) for substance (cut off value): opiates (300 ng/mL), tetrahydrocannabinol (50 ng/mL), benzodiazepines (300 ng/mL), cocaine (300 ng/mL), opioid-containing pain relievers (100 ng/mL), methadone (300 ng/mL), methamphetamine (500 ng/mL), amphetamines (1000 ng/mL), barbiturates (300 ng/mL), and buprenorphine (10 ng/mL) and breathalyzer testing for alcohol was done just prior to each monitoring session. Women with positive results indicating recent substance use/misuse except THC were excluded from monitoring on that day and, if possible, rescheduled for fetal testing at a date later within that gestational week when toxicology results were negative.

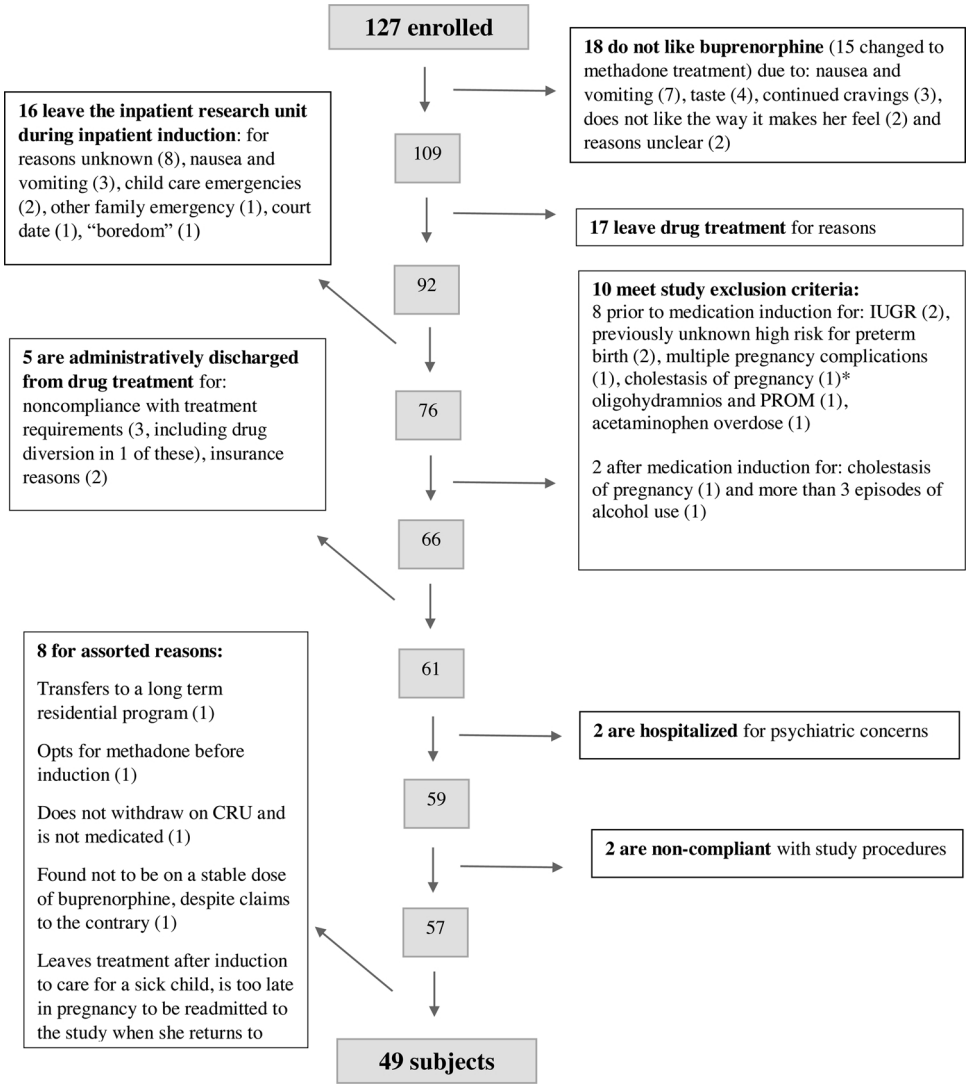

Fig. 1. Study enrollment flow chart.

2.2.3. Maternal physiological data collection

The maternal electrocardiogram was recorded from three carbon fiber disposable electrodes in triangulated placement (right mid subclavicle, left mid axillary thorax, and upper left thigh for ground lead). Electrodermal activity was monitored from two silver-silver chloride electrodes with a gelled skin contact area placed on the distal phalanxes of the first and index fingers of the non-dominant hand. Electrodes were affixed with adhesive collars to limit gel contact to a 1 cm diameter circle and secured with velcro. Respiration was measured from a bellows apparatus stretched across the ribcage below the breasts. Maternal physiological signals were amplified using a multi-channel, electrically isolated bioamplifier (Model JAD; James Long Company, Caroga Lake, NY). Data were digitized at 1000 Hz via an internal analog to digital board using Snapstream data acquisition system (HEM Data Corporation, Southfield, MI).

Data quantification proceeded off-line using the PHY General Physiology System and IBI Analysis Systems (James Long Company). ECG data underwent R-wave detection, manual editing for artifact, and interbeat interval computation in msec. Variability (i.e., standard deviation) in heart period was computed from those values. Skin conductance level (SCL) was measured by administering a constant 0.5 V root-mean-square 30 Hz AC excitation signal and detecting the current flow (μS). Respirations were measured by quantifying inspiration to inspiration and expiration to expiration periods based on the detected peaks and troughs of the respiratory waveform. All values were averaged over the 60-minute monitoring period.

2.2.4. Additional treatment and exposure information

Maternal dose (mg) at each gestational age was recorded as the amount of buprenorphine participants received in a single sublingual daily dose on the day of each scheduled data collection session. Cumulative maternal dose was ascertained by compiling all administered doses until that time. As expected in populations of this nature, poly-substance use (both licit and illicit) during treatment was common. Weekly urine testing, M = 17.8 (7.8) tests, during treatment revealed illicit substance use/licit substance misuse by over half of the women by delivery (n = 29, 59.2%) as indicated by at least one positive toxicology finding. Of those with positive findings, the percent of positive toxicology screens ranged from 4% to 100%, M (SD) = 27.2 (27.4). Substances detected by urine toxicology testing indicating recent substance use (n = 145) included: opiates 22.1%; THC 42.1%; benzodiazepines 22.1%; cocaine 11.7%, methadone 4.8%; oxycodone 4.8%, and less than 2% were for methamphetamine and/or amphetamine.

Infants resided with their mothers after delivery and throughout their time after delivery in a rooming-in care paradigm, and all were provided non-pharmacologic care (Velez and Jansson, 2008) beginning at delivery. Infants were assessed for indicators of NAS using a modified

version of the Finnegan scoring system (Jansson et al., 2009b) conducted every 3–4 h for a minimum of four days post-birth. When indicated, pharmacotherapy included oral morphine sulfate with a secondary medication (clonidine, orally) added for infants reaching maximal morphine doses. NAS was quantified by severity of expression on day 4 postpartum, which coincided with the peak expression of symptoms (i.e., highest modified Finnegan score) in this sample and the number of days during hospitalization requiring pharmacotherapeutic treatment for NAS. All NAS pharmacologic treatment occurred during the inpatient stay; no infants were discharged on medication.

2.3. Data analysis

Participation by visit was as follows: n = 20 (24 weeks), n = 30 (28 weeks), n = 41 (32 weeks) and n = 40 (36 weeks). Most participants provided data at two or more visits (n = 41; 83.6%). Initial exploratory analyses evaluated whether maternal substance use was associated with maternal peak and trough values at each gestation using correlational analyses for continuous values and T-tests for group comparisons. Preliminary analyses indicated significant patterns of associations with maternal smoking. Analyses to detect acute buprenorphine effects relied on repeated measures analysis of variance comparing maternal values at peak versus trough, stratified by two levels of cigarette use (light v heavy); linear analyses to confirm stratified results were based on the number of cigarettes reported smoked per day. Correlations were also used to evaluate associations between buprenorphine dose, both specific to each gestational age and cumulative to that time, thereby accounting for differing lengths of time in treatment. Change scores from peak to trough were computed to analyze individual differences in responsivity in relation to dosing and to NAS outcomes.

3. Results

3.1. Participants

A total of 127 women consented to participate. As seen in Fig. 1, 78 women left the protocol for a variety of reasons. Of those, 39 women (50%) remained in treatment but either switched to methadone or chose not to receive medication assisted treatment, and 39 women (50%) left the treatment program altogether. The final sample was comprised of 49 women who attended comprehensive substance use disorder treatment and obstetric care in an urban treatment center, previously described (Jansson et al., 1996). Participating women were M (SD) = 27.6 (4.4) years of age with 11.5 (1.9) years of education, primarily Caucasian (87.8%; 12.2% African American), 100% Medicaid recipients, and multigravid (83.7%). Of all participants, 12 (24.5%) were stable buprenorphine patients at the time of enrollment, with the remaining participants inducted onto buprenorphine during pregnancy as follows: 3 (6.1%) first trimester, 26 (53.1%) second trimester, and 8 (16.3%) third trimester. The predominance of second trimester induction is a result of the fact that women most commonly seek OUD treatment in mid-pregnancy. On average, participants entered the study at M (SD/range) 21.3(7.0/5.3–32.5) weeks of gestation. Eight maternal participants left the protocol prior to delivery after providing some fetal data. Infant outcome data, available for n = 41 infants, indicated normally grown infants delivered at term: gestational age at delivery = 39.4 (1.3) weeks, birth weight = 3317 g (411).

3.2. Maternal autonomic measures

Table 1 provides descriptive values for trough and peak per gestational age for the four maternal measures. Maternal heart rate was originally collected as inter-beat interval (i.e., ms between each R-wave) but converted to beats per minute (bpm) for ease of interpretation. The relation between each parameter was assessed using correlations based on mean trough values computed across the four gestational periods. As expected, women with faster heart rates had lower levels of heart rate variability, $r(47) = -.41$, $p < .01$, and higher electrodermal activity (skin conductance), $r(47) = .29$, $p < .05$; associations at peak were comparable. Respiratory period was unrelated to any other parameter, although there was a trend toward higher skin conductance at peak only, $r(47) = .26$, $p < .08$.

3.3. Poly-substance use and maternal autonomic measures

Both continuous (i.e., percent of positive toxicology findings) and group analyses (i.e., comparisons between abstainers and non-abstainers) failed to detect significant associations between illicit maternal substance use and maternal measures at any gestational age. In contrast, both the amount of cigarettes women smoked per day and/or group comparisons between heavier versus lighter smokers revealed consistent patterns of associations with a number of the maternal measures. As a result, and given the constrained sample size, subsequent analyses were conducted using smoking status as the only substance covariate.

3.4. Effects of buprenorphine on maternal autonomic measures

As shown in Table 1, based on repeated measures analysis of variance, buprenorphine administration significantly accelerated maternal heart rate and dampened maternal heart rate variability at 24 and 36 weeks; maternal cardiac measures were unaffected by buprenorphine during the intermediary periods. Skin conductance level was significantly dampened by buprenorphine exposure at each gestational age with the exception of 36 weeks. Maternal respiratory period was unaffected by buprenorphine administration.

3.5. The effect of maternal dose on maternal autonomic measures

The mean buprenorphine dose was 12 mg during the study period, with a range from 2 to 28 mg. Dosing levels remained highly stable for individuals from the start to end of treatment (between gestational correlations rs = .88 to .97). No significant correlations were detected between maternal dose per gestational age or cumulative dose over time with any trough, peak, or change scores from trough to peak for any maternal measure.

3.6. Cigarette use and moderation of response to buprenorphine

Only three women reported not smoking at all during the gestational periods assessed. Of the remaining, there was no change over time in reported cigarette use during this period of pregnancy [M cigarettes per day = 10.3 (24 weeks), 11.1 (28 weeks), 10.0 (28 weeks) and 10.1 (36 weeks)]. Almost all (n = 46, 93.9%) women smoked cigarettes; M (SD) cigarettes per day averaged during gestation = 10.2(6.5). Within participants, there was strong consistency in the number of cigarettes women smoked per day between gestational periods (rs range from .74 to .91) which is consistent with previous reports in similar populations (Chisolm et al., 2013). Mean cigarette values were used to stratify participants into two groups: 0 to 9 cigarettes, (i.e., < ½ ppd), n = 20 vs > 10 cigarettes, (i.e., > ½ ppd), n = 29. Only 1 participant reported smoking more than 20 cigarettes per day at any gestational age. Consistently significant associations in CO levels assessed by breathalyzer (range 2 to 55 ppm) with the number of cigarettes reported (range 0–30 cigarettes per day) and between the stratified groups (ps < .001) serve as validation for self-reported usage.

As indicated by the ANOVA results presented in Table 1, smoking was significantly associated with MHRV at each gestational age. Examination of means (not shown) indicates a reduction in MHRV in the heavier (> 10 cigarettes/day) smoking group. Furthermore, at 24 and 36 weeks, smoking moderated the buprenorphine response as noted by the significant interactions. Fig. 2 illustrates these findings at these two

Table 1
Maternal physiologic measures at trough and peak buprenorphine levels analyzed by buprenorphine administration, level of daily cigarette use, and their interaction.

Maternal measure	*n*	Trough M (SD)	Peak M (SD)	Buprenorphine (Peak v trough) *F* value	Cigarettes < 10 v ≥10 *F* value	Interaction *F* value
Maternal heart rate (bpm)						
24 weeks	20	78.0 (8.5)	81.5 (9.8)	4.86*	0.02	0.01
28 weeks	30	82.0 (12.8)	82.3 (11.1)	0.01	0.29	0.61
32 weeks	39	84.2 (11.3)	85.0 (12.5)	0.32	0.01	2.61
36 weeks	38	82.8 (11.3)	85.8 (10.1)	10.06*	0.26	0.64
Maternal heart rate variability (*ms*)						
24 weeks	20	57.5 (28.9)	44.4 (15.5)	12.64**	12.41**	6.79*
28 weeks	29	47.9 (19.2)	52.0 (23.2)	2.47	4.75*	2.68
32 weeks	41	51.0 (17.4)	52.0 (18.1)	0.29	7.88*	0.36
36 weeks	38	55.1 (22.7)	50.7 (16.7)	8.70**	6.87*	13.34**
Skin conductance (μS)						
24 weeks	18	4.7 (4.8)	3.1 (3.6)	5.86*	0.26	1.27
28 weeks	29	4.1 (3.1)	2.9 (2.8)	7.54**	0.33	1.61
32 weeks	37	4.5 (4.0)	2.8 (2.5)	8.74**	0.37	0.00
36 weeks	37	4.1 (3.7)	3.3 (3.2)	2.04	4.37*	1.35
Respiratory period (s)						
24 weeks	14	3.8 (0.8)	3.7 (0.7)	0.56	0.54	2.67
28 weeks	21	4.0 (0.7)	4.3 (1.2)	0.40	0.39	1.77
32 weeks	29	4.1 (1.0)	3.9 (1.0)	0.16	1.17	0.06
36 weeks	30	3.9 (0.9)	3.9 (1.0)	0.01	3.75	0.16

Note: Minor variation in *ns* for the first 3 measures reflects occasional technical problems with signal quality; the more substantial loss of data for respiratory period is the result of challenges in collecting data via respiratory bellows in pregnant women.
*p < .05.**p < .01.

gestational periods. Suppression of MHRV to buprenorphine exposure was present only in the group that smoked less, given the already depressed levels in the heavier smoking group at trough. The association with smoking was also confirmed by linear analysis using the number of daily cigarettes such that the more cigarettes smoked per day, the lesser the change in MHRV from trough to peak was (r (20) = −.48, p < .05 and r (38) = −.41, p < .01 at 24 and 36 weeks, respectively). Smoking more than ½ ppd was also associated with lower electrodermal activity at 36 weeks (M = 2.9 v 5.0), but smoking did not moderate the SCL response to buprenorphine.

3.7. Maternal Autonomic Responsivity and Infant NAS Outcome

Forty-one of the 49 fetuses were retained in the study at the time of delivery. Urine toxicology indicated recent substance use/misuse in 3 women [opiates (2) and THC (1)] at delivery. More than half (n = 24; 58.5%) of infants required pharmacotherapy for NAS; the mean (SD) number of hospitalization days was 14.7(9.0). To reduce the number of analyses and increase the sample size available for correlations, mean change scores from trough to peak were averaged across gestation. Partial correlations controlling for buprenorphine dose, which was previously found to be associated with NAS in this sample (Jansson et al., 2017b), were computed with each of the four maternal measures and the two measures of NAS severity. The degree of change in MHR to buprenorphine administration across gestation was significantly associated with total hospitalization, r (36) = .33, p < .05, and there was a trend level toward more severe NAS expression on day 4, r (36) = .29, p = .08. Analysis of the direction of the change revealed that greater activation in MHR to buprenorphine was associated with greater NAS severity; of those infants that did express NAS requiring pharmacotherapy, MHR was increased by 2.8 as compared to 0.9 bpm for those whose infants did not exhibit NAS requiring pharmacotherapy. Maternal SCL responsivity was also associated with day 4 symptomatology, r (37) = .32, p < .05. Other associations between maternal variables and NAS indicators did not attain significance.

4. Discussion

Maternal buprenorphine administration generated a number of acute effects on maternal autonomic functioning, although no cumulative effects were detected. At peak pharmacologic concentration, MHR was significantly faster at 24 and 36 weeks gestation, while MHRV was reduced. These cardiac effects are suggestive of a withdrawal of parasympathetic tone at times of highest buprenorphine

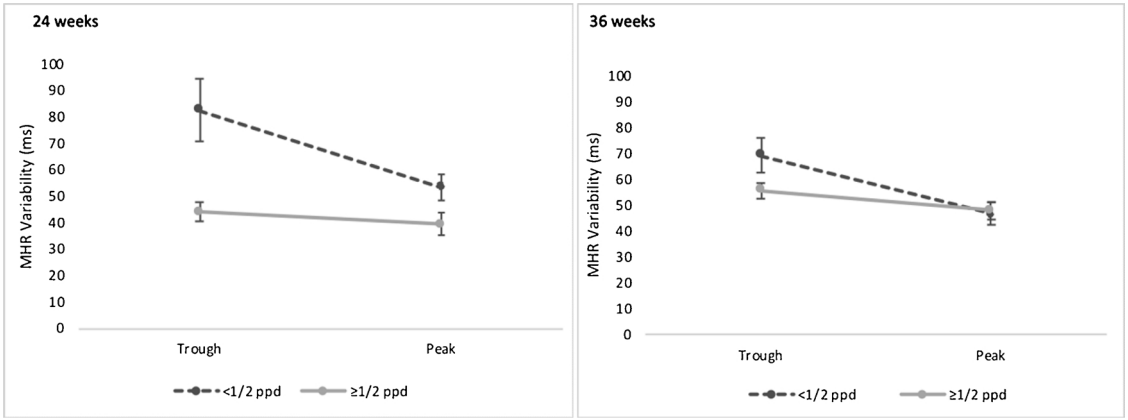

Fig. 2. Effect of buprenorphine administration on maternal heart rate variability at 24 and 36 weeks gestation stratified by maternal cigarette use. PPD = pack per day based on 20 cigarettes per pack. Both interaction values are significant (see Table 1).

plasma concentrations. In addition, buprenorphine administration was followed by dampened electrodermal activity at all gestational ages, significantly so at 24, 28, and 32 weeks. As electrodermal activity is singly innervated by the sympathetic nervous system (Venables, 1991), this suggests buprenorphine also suppresses sympathetic activation. In contrast to earlier findings regarding methadone administration (mean dose 78.4 mg, range 40–115 mg/day; Jansson et al., 2005), buprenorphine was not associated with decreased respiratory rate at 36 weeks or at any other gestational period. This finding is in keeping with those of less respiratory depression for buprenorphine as compared to methadone due to partial agonist effects of the medication (Coe et al., 2018) and is also consistent with a previous report on a buprenorphine-maintained non-gravid female study population (Tantucci et al., 1992). The observed effects were unrelated to maternal dose of buprenorphine and similarly unrelated to cumulative maternal dose of buprenorphine, which is consistent with our previous studies in methadone-maintained women (Jansson et al., 2005).

Here, reported maternal cigarette exposure, confirmed by CO analysis, had as profound an effect on maternal heart rate variability as did acute buprenorphine exposure. With the exception of a single association at 36 weeks for SCL, other maternal variables were not associated with maternal smoking, suggesting a unique effect on parasympathetic control. Buprenorphine dose is not associated with variations in the rate of nicotine metabolism (Gubner et al., 2017).

The moderating effect of cigarette smoking on maternal heart rate variability depicted in Fig. 2 is reminiscent of a prior finding in this sample related to fetal neurobehavior. Fetuses of women who smoked more exhibited depressed levels of fetal motor activity at trough, and as a result buprenorphine administration generated less reduction in fetal motor activity given the already low levels (Jansson et al., 2017b). Others have reported deleterious effects of smoking during pregnancy on the fetus (Holbrook, 2016), including on fetal heart rate (Kutlu et al., 2017; Zeskind and Gingras, 2006) in non-opioid-exposed pregnancies.

As noted, there are few studies of maternal autonomic functioning in pregnancy, and those that exist often exclude smokers (DiPietro et al., 2005) so less is known about maternal effects. Nonetheless, the combined evidence reinforces the importance of smoking reduction within treatment programs offering medication assisted treatment to women with OUD (Choo et al., 2004; Jones et al., 2013; Winklbaur et al., 2009).

Modest associations with the degree to which women responded physiologically to buprenorphine administration and features of NAS in their offspring were primarily restricted to maternal heart rate and skin conductance. We did not replicate a prior finding that related maternal vagal tone reactivity to similar markers of NAS severity (Jansson et al., 2007), although the measure of variability used in this study is a less robust measure of vagal tone. The implications of these associations are unclear and likely lack clinical relevance but suggest that buprenorphine may exert indirect effects on NAS mediated through repetitive patterns of maternal responsivity as well as direct pharmaceutical ones.

The maternal physiological response to buprenorphine administration was not the same at each gestational period studied, and this variation is difficult to interpret. Detection of significant effects at some gestational ages but not others, when multiple data points are used, is a common problem in prenatal research (DiPietro et al., 2018). Pregnancy is not a monolithic period, and maternal physiology continues to change during the twelve-week span of this study (DiPietro, 2005). However, it is uncertain whether significant associations are truly unique to the specific gestational age(s) at which they were detected as a result of an underlying physiological mechanism or simply a manifestation of the difficulties inherent in the vagaries of small samples. Individual variation in other licit and illicit exposures provides a further complication that belies appropriate control in samples of this size.

Limitations of this study might include the open-label nature of the design, which could introduce some bias into the population of study as women opting for buprenorphine treatment as part of a research study, and relatively small numbers of participants – a limitation common to this research field. Additionally, weekly urine toxicology testing may have failed to detect some incidences of substance use in our subjects.

5. Conclusion

As buprenorphine has become a more commonly used OUD treatment during pregnancy, its benefits have begun to emerge and become better documented. These include less severe maternal withdrawal, lower risk of opioid overdose death, increased availability as an outpatient medication and less severe NAS in buprenorphine-exposed infants (ACOG Committee on Health Care for Underserved Women, American Society of Addiction Medicine, 2012; Jones et al., 2010). Using this sample of buprenorphine-treated women and fetuses/infants, we have documented that maternal buprenorphine administration affects fetal heart rate and movement with increasing magnitude over the course of gestation (Jansson et al., 2017a) and that maternal polysubstance use was the most potent predictor of NAS severity (Jansson et al., 2017b). Here we have extended this body of knowledge to include autonomic effects on pregnant women, which revealed buprenorphine-related effects on autonomic balance. This study finds that buprenorphine administration acutely affects maternal heart rate, maternal heart rate variability, and skin conductance with no relationship to dose. More frequent than daily dosing may be a more optimal treatment strategy in buprenorphine-treated pregnant women (Caritis et al., 2017), and future work should include measures of maternal autonomic functioning in women in the split-dosed condition; however, maternal physiologic parameters were unaffected by dosing condition in methadone-maintained women (Jansson et al., 2009). Additionally, previous work (Bastian et al., 2016) has demonstrated alterations in buprenorphine dose-normalized plasma concentrations across gestation, indicating an apparent increase in buprenorphine clearance during pregnancy; future work might include investigations earlier in gestation. Further, recognition of the relatively potent effects of cigarette smoking, particularly on parasympathetic control and its potentiation of buprenorphine effects, reinforce the need to incorporate cigarette-reduction programs into comprehensive, medication-assisted treatment for women with OUD. Prediction of which infants will develop NAS remains an elusive goal, and it is likely that a complex interplay of genetic and epigenetic factors, as well as gestational dependent functional teratology, may all contribute. The current findings of a small association between maternal autonomic responsivity to buprenorphine administration and some indicators of NAS expression suggests the subtle role of maternal factors and highlights the complexity of attaining this ultimate goal.

Role of funding source

This research was funded by NIH/NIDARO1DA031689. Indivior, Inc. provided medication for this research.

Medication for this study was provided by Indivior, who had no role in study design, collection, analysis and interpretation of the data, in the writing of this manuscript, or the decision to submit the manuscript for publication.

Contributors

All authors contributed to the material presented, and all have reviewed and approved the final draft.

Conflict of interest

The authors report no conflicts of interest.

Acknowledgements

The authors thank the staff and women of the Center for Addiction and Pregnancy, without whose support this work could not be possible.

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