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The Effect of Prenatal Alcohol Co-Exposure on Neonatal Abstinence Syndrome in Infants Born to Mothers in Opioid Maintenance Treatment

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Abstract

Objective—This study examined the effects of prenatal alcohol exposure (PAE) on the incidence and severity of neonatal abstinence syndrome (NAS).

Study design—For this pilot study, 70 pregnant women on opioid maintenance therapy (OMT) were recruited from a perinatal substance abuse clinic. Subjects were categorized into three study groups based on the timing of alcohol use during pregnancy as assessed by repeated self-reported measures and a comprehensive panel of ethanol biomarkers. NAS outcomes included: duration of hospital stay, the need for pharmacological treatment of NAS, newborn age at the initiation of NAS treatment, duration of treatment, and cumulative methadone dose administered.

Results—The study included a large proportion of ethnic minorities (81.4% Hispanic, 5.7% American Indian), women with less than a high school education (52.2%) and unplanned pregnancy (82.9%). In multivariate analysis, PAE was not associated with NAS outcomes; however, one newborn diagnosed with Fetal Alcohol Syndrome demonstrated much more severe NAS compared to other PAE infants. Interestingly, 3rd trimester PAE was associated with a higher prevalence of microcephaly (62.5%) compared to the PAE abstaining group (36.8%; $p=0.08$).

Conclusion—In this study, PAE was not associated with NAS severity; however, further examination in a larger study is needed.

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Keywords

pregnancy; alcohol; neonatal abstinence syndrome; opioids; methadone

Background

The incidence of pregnant women who exhibit opioid dependency at delivery has more than quadrupled between 2000 and 2009 [1]. The pharmacological treatment of opioid dependency in pregnant women is opioid maintenance therapy (OMT) with methadone or buprenorphine [2]. While OMT treatment in pregnancy has numerous benefits, including reduced pregnancy complications and lower neonatal morbidity and mortality [3,4], the primary drawback is the potential for neonatal abstinence syndrome (NAS) due to opiate withdrawal [5]. To alleviate withdrawal symptoms, the newborn often requires opioid replacement with morphine or methadone followed by a slow wean of the medication resulting in lengthy treatment and greater healthcare expenditures [1,6].

Alcohol use among pregnant women in substance abuse facilities has been reported in the range of 5-28% [6-8]. Prenatal alcohol exposure (PAE) is known to be associated with devastating effects on the developing fetus, collectively known as Fetal Alcohol Spectrum Disorder (FASD) [9]. However, the contributing effect of PAE on fetal/newborn outcomes has not been studied in opioid-dependent pregnant women. Both OMT agents and alcohol can produce withdrawal effects in newborns [10]; therefore, it is important to understand the relationship between these substances and newborn health outcomes. The primary objective of this study was to examine the contributing effect of PAE on the incidence and severity of NAS. We hypothesized that third trimester PAE in opioid-dependent women might potentiate withdrawal symptoms in the newborn leading to more severe NAS.

Methodology

Study design

This study was a secondary analysis of a prospective cohort study [11,12], which focused on the validity of novel ethanol biomarkers in pregnant women and their newborns. Patients were recruited from a comprehensive perinatal substance abuse program at the University of New Mexico (UNM). Eligible women were at least 18 years old, less than 35 gestational weeks, and had no prenatal diagnosis of a major structural anomaly. Patients were enrolled during one of their first prenatal care visits and followed to delivery. Overall, 102 patients were recruited into the parent study. For the purposes of this analysis, the sample size was restricted to 70 patients who received OMT during pregnancy. This study was approved by the UNM Human Research Review Committee.

Treatment

Pregnant women were titrated on their OMT dose based on serial Clinical Opiate Withdrawal Scale scores and clinician evaluation [13]. Urine drug screens (UDS) were performed randomly or if changes in substance use were suspected. OMT outpatient dosing

was continued through delivery as weaning of OMT is discouraged due to concerns for the effect of withdrawal on the fetus and the high likelihood of maternal relapse.

Based on the newborn's gestational age at delivery and overall health, the newborn was admitted to one of three interrelated neonatal units at the UNM hospital. All providers received the same education and standardized protocols regarding NAS treatment. All infants were observed until at least 96 hours of life for evidence of opioid withdrawal. If a newborn exhibited signs of withdrawal, the Modified Finnegan Neonatal Abstinence Scoring System was performed every four hours to determine if pharmacologic treatment was needed [14,15]. Treatment was initiated if the newborn scored ≥ 8 three times in a row, if the mean of three scores was ≥ 8 , or if two consecutive scores were ≥ 12 . Methadone was the predominant medication used for treatment of NAS; however, morphine was also used for infants born to women on buprenorphine. Newborns were titrated and weaned using structured protocols based on Finnegan scores.

Assessment of PAE and covariates—At enrollment, a structured in-person baseline interview was conducted at the clinic by a study coordinator. The interview captured socio-demographic characteristics, medical and reproductive history, and frequency of substance abuse. Substances evaluated included tobacco, marijuana, cocaine, benzodiazepines, amphetamines, heroin, and prescription opioids. Patients were categorized as 'exposed' to a particular substance if they tested positive for that substance at least once on a UDS or self-reported use after the last menstrual period (LMP). Substance abuse was further categorized into 1st/2nd trimester versus 3rd trimester use since we hypothesized that 3rd trimester use would more likely affect NAS. A patient was categorized as a 3rd trimester user if she tested positive for the substance on a UDS at least once during the 3rd trimester.

Frequency and quantity of alcohol consumption during the two weeks prior to the baseline and delivery interviews were determined using the Timeline Follow-back Procedure (TLFB) [17]. Following the interview, maternal blood and urine samples were collected for analysis of ethanol biomarkers. The following biomarkers were analyzed in maternal blood: γ -glutamyltransferase (GGT), carbohydrate-deficient transferrin (%dCDT), and phosphatidylethanol (PEth). Urine samples were tested for ethyl glucuronide (UeG) and ethyl sulfate (UeS).

A follow-up interview was conducted during the hospital stay after delivery. The interview captured alcohol consumption later in pregnancy and any changes in substance use after the baseline interview. Maternal blood and urine samples were collected at admission and tested for the same battery of biomarkers. In the newborn, an additional dry blood spot (DBS) card was collected and analyzed for PEth (PEth-DBS) as previously described [12]. The chosen biomarkers had different detection windows; thus, could capture different patterns of alcohol use in the study population [18]. In addition, PEth-DBS was chosen as the biomarker of choice in the newborn given recent reports of its high sensitivity and specificity [19] and limitations of meconium biomarkers [20].

Patients were categorized into three PAE groups based on the timing of exposure: no PAE during pregnancy, 1st/2nd trimester PAE, and 3rd trimester PAE. To be categorized into the

no PAE group, patients had to report abstinence from alcohol after LMP and be negative on all biomarkers both at baseline and at delivery. The 1st/2nd trimester PAE group included patients who self-reported alcohol use after LMP and/or were positive on any of the baseline biomarkers. The 3rd trimester PAE group included patients who tested positive on any of the maternal or newborn biomarkers at delivery.

Information on the OMT agent used during pregnancy (methadone, buprenorphine, both), the last OMT dose before delivery, the duration of OMT therapy (gestational weeks), and whether or not the mother was established on OMT prior to pregnancy were recorded in maternal electronic medical records (EMR) and abstracted to the research database. Results from UDS results were also abstracted from the patients' EMR.

Newborn outcomes

Presence and severity of NAS was assessed through the newborns' inpatient pharmacy records. Measures of NAS severity included the need for pharmacologic treatment for NAS (yes/no), duration of hospital stay (days), cumulative methadone or morphine dose used to treat NAS (mg), duration of NAS treatment (days), and length of time from birth to NAS treatment initiation (hours). Additional newborn outcomes included anthropometric measures (birth weight, height, occipital frontal circumference [OFC]) and gestational age at delivery (weeks). Sex-specific percentiles for birth weight, length, and OFC were determined by using the 2000 CDC growth chart and adjusted growth chart for full term and preterm infants, respectively [16].

Statistical analyses

Anticipated effect size (difference in the outcomes between the groups) could not be used from prior literature for power calculations as there are no prior studies evaluating the effect of PAE on NAS severity. Power calculations were carried out to estimate the minimal detectable differences between the study groups based on estimated sample size prior to initiation of statistical analysis. With the given group sample sizes of 16 (PAE) and 32 (no alcohol), the study had 80% power to detect a 38 % difference in the need for initiation of pharmacological treatment of NAS. The proportion in the PAE group was assumed to be 0.50 under the null hypothesis and 0.88 under the alternative hypothesis; the proportion in the no PAE group was assumed to be 0.50. With respect to the mean duration of hospital stay, with sample sizes of 16 and 32 subjects the study had 80% power to detect a 2.6 day difference between the null hypothesis that both group means are 15.0 days and the alternative hypothesis that the mean of PAE group is 17.6 days (SD=3.0). All power calculations were two-sided with a significance level (alpha) of 0.05.

Univariate associations between each NAS outcome and potential predictors were evaluated by chi-square or t-test analysis for categorical (alcohol use, smoking, marijuana use, cocaine use, benzodiazepine use, amphetamine use, heroin or opiate use, use of OMT prior to pregnancy, opiate used for OMT, breastfeeding, and maternal age) and continuous (maternal methadone dose, maternal buprenorphine dose, OMT duration, and gestational age) predictors, respectively. Pearson correlation coefficients determined the associations

between continuous variables (e.g. between maternal OMT dose and duration of infant's hospital stay).

Multiple logistic and linear regression were performed to determine the effect of alcohol on NAS outcomes and delivery outcomes after controlling for other variables. Predictors which were associated with NAS outcomes at a $p < 0.2$ in univariate analysis (i.e., maternal OMT agent used, breastfeeding, gestational age at delivery, smoking status, and amphetamine use) were included in the final multivariate models. All analyses were performed in SAS® 9.2 (SAS Institute, Cary, NC, USA).

Results

The study population consisted of 70 maternal-newborn pairs. The mean maternal age at recruitment was 25.9 ± 4.6 years. The sample included a high proportion of ethnic minorities (81.4% Hispanic, 5.7% American Indian), Medicaid recipients (90%), and patients with low education level (52.2% < high school). The vast majority reported an unplanned pregnancy (87.1%), and approximately half were serum positive for Hepatitis C (53.5%). The average number of UDS during the third trimester was 4.9 ± 3.2 . There were no significant differences in demographic characteristics among the study groups ($p > 0.05$) except for gravidity ($P = 0.02$; Table I).

The predominant OMT agent was methadone (72.9%), followed by buprenorphine (21.4%). The remaining patients were started on buprenorphine and were later switched to methadone (5.7%). Approximately one third (30.0%) of the sample had been initiated on OMT prior to the index pregnancy. In this sample, 91.4% of patients used two or more non-OMT substances. The most frequently used substances were heroin and/or non-OMT opiates (80%) followed by marijuana (54.3%), cocaine (47.1%), benzodiazepines (31.4%), and amphetamines (25.7%). Tobacco use near delivery was also common in this study population with 54.3% of patients reporting use of 1-9 cigarettes per day and 15.7% reporting use of 10 or more cigarettes per day.

Half (50%) of the study population used alcohol sometime during pregnancy. Alcohol use was prevalent during the periconceptional period but declined later in pregnancy either due to under-reporting or the actual cessation of alcohol use after pregnancy recognition (Table II). Among patients classified as 3rd trimester users, 6.3% admitted alcohol use in the two weeks before delivery, but 100% tested positive for at least one ethanol biomarkers at delivery. PEth in dried blood spot was the most frequent positive biomarker in this group (43.8%) followed by %CDT (31.3%) and GGT (25%).

In univariate analysis, PAE was not associated with fetal growth measures or gestational age at delivery (Table III). Microcephaly (OFC $< 10^{\text{th}}$ percentile) was more prevalent among 3rd trimester alcohol users (62.5%) compared to abstainers (37.1%), and this relationship trended towards significance ($p = 0.08$). In addition, 3rd trimester alcohol use appeared to worsen NAS outcomes; however, differences were not statistically significant. One infant in the 3rd trimester PAE was diagnosed with fetal alcohol syndrome (FAS). This infant had a much longer than average duration of NAS treatment (63 days) and a higher than average

cumulative methadone dose (62.4 mg). In multivariate analyses, the effects of PAE remained nonsignificant after adjusting for the type of OMT agent, amphetamine use, breastfeeding, gestational age at delivery, and tobacco use. Maternal use of methadone compared to buprenorphine was associated with earlier treatment initiation of NAS in a newborn ($\beta = -36.75$; $p < 0.01$). In addition, 3rd trimester amphetamine use was also associated with earlier treatment initiation of NAS ($\beta = -41.67$; $p < 0.01$), while 1st/2nd trimester use of amphetamines was associated with less need for pharmacological treatment of NAS (OR=0.08; 95% CI:0.01;0.57).

Discussion

In this pilot prospective cohort study, no clear contributing effect of PAE on NAS severity was observed. One infant with a much higher level of PAE (positive for 3 ethanol biomarkers) and full FAS demonstrated much more severe NAS than other less exposed infants. While no definitive conclusions can be made with only one FAS case, this finding suggests that the contributing effect of PAE, if any, could be dose dependent. There are several possible explanations for why a relationship between alcohol exposure and NAS was not found in this study. First, while some studies show synergistic central nervous system depressant effects between alcohol and opiates, others have demonstrated that opiates can decrease maximum blood alcohol levels up to 20% due to decreased gastric motility [21]. Due to this pharmacokinetic interaction, there could be decreased alcohol exposure to the fetuses with mothers on OMT.

Second, the level of alcohol consumption in this cohort may not have been sufficiently high to significantly affect NAS incidence and severity. While the majority of patients reported very high alcohol use in the periconceptional period, alcohol use decreased upon pregnancy recognition in many participants. In this case, the battery of alcohol biomarkers used in the study was extremely valuable as it provided information on the timing and intensity of alcohol use. Urine EtG and EtS are sensitive biomarkers (potentially elevated with less than one drink per day) with a short detection window of 5 days [18]. GGT and %CDT are typically elevated after chronic heavy alcohol use within the past 8 weeks. Among the 16 patients in the 3rd trimester PAE group, only three were positive for EtG/EtS, whereas nine were positive for %CDT or GGT. Given that GGT and %CDT have relatively broad detection windows, these patients could have been abstinent from alcohol within the last couple of weeks prior to delivery, which could have diluted the effects, if any, on NAS. Unfortunately, the sample size did not allow for additional stratification beyond grouping PAE by trimester of use.

Poly-drug use (2 substances used) was found in the majority of the sample (91.4%) and is often a reality when treating opioid-dependent populations. Methadone maintenance was correlated with earlier initiation of therapy for opioid withdrawal in a newborn suggesting earlier and more severe NAS withdrawal compared to buprenorphine. Patients who used amphetamines earlier in pregnancy (1st/2nd trimester) had nearly half the incidence of NAS compared to women who had no amphetamine use (45% vs. 81%) – a finding which requires further investigation. However, patients who used amphetamines during the third trimester had increased NAS incidence (86% vs. 81%) and earlier initiation of NAS therapy

(14.2 vs. 42.0 hours). It should be noted that none of the subjects were prescribed amphetamines during pregnancy, so a positive UDS was indicative of illicit amphetamine use.

Strengths of this study include prospective determination of PAE by repeated self-reported measures and a comprehensive battery of maternal ethanol biomarkers measured at mid-gestation and at admission for labor and delivery as well as a confirmation of PAE in a newborn child by PETH-DBS test. The inclusion of multiple NAS outcome measures is a strength of the study given the multi-factorial and complex nature of NAS. Finally, our study population was comprised of mostly Hispanic/Latina and Native American patients – ethnic groups which are rarely included in other clinical studies.

Several limitations should be acknowledged. Due to the study's small sample size and larger than expected standard deviations in NAS outcomes, it is likely that this study did not have sufficient power to rule out a relationship between PAE and NAS. For these reasons, the results should be considered to be hypothesis-generating rather than definitive. Another potential limitation is polydrug use in our study population. Polysubstance abuse is common among OMT patients, making it difficult to disentangle the effect of PAE from other substances. To address this issue, polysubstance abuse was identified through UDS and repeated maternal interviews and controlled for in multivariate analyses. Finnegan scores were not utilized as a NAS outcome by design due to their known inter-rater variability [22]. The NAS outcomes selected for this study have been used in previous studies and were chosen as they are less subjective and more clinically relevant [6,23].

In summary, this pilot study did not identify a statistically significant relationship between PAE and NAS; however, several important trends were identified warranting additional investigation. Future studies examining the possibility of a dose-related effect of PAE on NAS are recommended.

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Table I
Description of the Study Population (n = 70)

Maternal Characteristics	No PAE (n=35)	1 st /2 nd Trimester PAE (n=19)	3 rd Trimester PAE (n=16)	P-value
Maternal Age (years)	24.8±4.1	26.4±5.6	27.6±3.9	0.11
Gestational age at recruitment (weeks):	21.2±7.0	22.6±10.2	20.6±7.1	0.72
Gestational age at delivery (weeks):	38.6±2.7	38.3±1.8	38.9±1.4	0.76
Marital Status				
Single	51.4%	52.6%	50.0%	1.0
Married/cohabiting	42.9%	42.1%	43.8%	
Separated/divorced/widowed	5.7%	5.3%	6.3%	
Education				
Less than high school	50.0%	52.6%	56.3%	0.82
High School or equivalent	32.4%	21.1%	18.8%	
Some college/vocational school or higher	17.7%	26.3%	25.0%	
Race				
White	91.4%	84.2%	93.8%	0.82
American Indian	5.7%	5.3%	6.3%	
Black or African American	2.9%	0%	0%	
Asian/Asian American Islander	0%	5.3%	0%	
Ethnicity: Hispanic	80.0%	89.5%	75%	0.48
Gravidity: Primigravida	31.4%	10.5%	0%	0.02
Parity: Nulliparous	40.0%	21.1%	18.8%	0.19
Health insurance: Medicaid	94.3%	89.5%	81.3%	0.06
Other public insurance	5.7%	0%	12.5%	
History of adverse outcomes *	51.4%	57.9%	50.0%	0.87
Presence of at least one chronic condition **	68.6%	68.4%	56.3%	0.66
Unplanned pregnancy	82.9%	89.5%	93.8%	0.65

Mean±SD or %; PAE, prenatal alcohol exposure;

* Includes miscarriages, stillbirths, and ectopic pregnancies;

** The most common conditions were hepatitis C (53.45%), anxiety (17.8%), and depression (13.7%)

Table II
Quantity and Frequency of Alcohol Use by Study Group

Alcohol Use Measures	No PAE (N=35)	1st/2nd Trimester PAE (N=19)	3rd Trimester PAE (N=16)	p-value
<i>Past 12 months</i>				
AUDIT (Mean±s.d.)	3.5 ± 6.1	11.0 ± 7.4	9.1 ± 10.4	0.002
AUDIT 8 (%)	8.6%	63.2%	31.3%	<0.001
<i>Alcohol use in periconceptional period</i>				
Frequency of binge (4 drinks)				
No binge episodes (%)	100%	10.5%	50%	<0.001
Once/week or less (%)	0	52.6%	18.8%	
2-4 times a week (%)	0	26.3%	12.5%	
5 times/week (%)	0	10.5%	18.75%	
Average number of drinks/week	0.14± 0.32	13.6 ± 18.3	21.7±40.1	0.003
<i>Alcohol use at enrollment visit</i>				
1binge drinking episode (%)	0%	89.5%	60.0%	<0.001
Admitted alcohol use 2 weeks before enrollment (%)	0%	10.5%	6.3%	0.12
Positive for 1maternal biomarkers(%)	0%	42.10%	20%	<0.001
GGT >55 IU/L	0%	5.3%	0%	
%CDT >2.0%	0%	0%	6.3%	
PEth >8 ng/mL	0%	15.8%	12.5%	
UEtG 25 ng/mL	0%	15.8%	12.5%	
UEtS 7 ng/mL	0%	21.1%	12.5%	
<i>Alcohol use at delivery visit</i>				
Admitted alcohol use 2 weeks before delivery (%)	0%	0%	6.3%	0.25
Number of drinks reported per week between enrollment and delivery	0.00±0.00	0.02±0.11	0.04 ±0.13	0.20
Positive for 1maternal or newborn biomarkers(%)	0%	0%	100%	<0.001
GGT >55 IU/L	0%	0%	25.0%	
%CDT >2.0%	0%	0%	31.3%	
PEth >8 ng/mL	0%	0%	12.5%	
UEtG 25 ng/mL	0%	0%	12.5%	
UEtS 7 ng/mL	0%	0%	18.8%	
PEth-DBS of a newborn >8 ng/mL	0%	0%	43.8%	

AUDIT, alcohol use disorders identification test; PAE, prenatal alcohol exposure; GGT, γ -glutamyltransferase; %CDT, carbohydrate-deficient transferrin; PEth, phosphatidylethanol; UEtG, urine ethyl glucuronide; UEtS, urine ethyl sulfate; PEth-DBS, phosphatidylethanol measured in dry blood spots

Table III
Association between PAE and Adverse Perinatal Outcomes among Women on OMT
(n=70)

Outcomes	No PAE (n=35)	1 st /2 nd Trimester PAE (n=19)	3 rd Trimester PAE (n=16)	p-value
Delivery/newborn outcomes				
Gestational age at delivery (weeks)	38.6 ± 2.7	38.3 ± 1.8	38.9 ± 1.4	0.76
Birth weight (g)	2804 ± 511	2788 ± 408	2852 ± 415	0.91
Birth weight 10%	37.1%	36.8%	37.5%	1.00
Birth length(cm)	47.9 ± 3.7	47.0 ± 3.6	47.2 ± 3.9	0.62
Birth length 10%	14.3%	26.3%	25%	0.50
OFC (cm)	33.0 ± 2.5	33.4 ± 3.9	34.0 ± 4.3	0.61
OFC 10%	37.1%	47.4%	62.5%	0.24
Breastfeeding	57.1%	63.2%	43.8%	0.50
NAS outcomes				
Need for pharmacologic treatment for NAS	74.3%	70.7%	81.3%	0.87
Duration of hospital stay (days)	17.3 ± 10.4	14.7 ± 8.6	19.5 ± 15.7	0.47
Age at treatment initiation (hours) (n=55)	39.8 ± 33.7	37.3 ± 20.6	36.7 ± 21.8	0.94
Duration of treatment (days) (n=55)	17.9 ± 9.0	14.1 ± 7.1	19.1 ± 14.6	0.40
Cumulative methadone dose (mg) (n=46)	10.4 ± 7.8	8.3 ± 2.5	14.2 ± 16.2	0.35

PAE, prenatal alcohol exposure