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Cigarette Smoking and Neonatal Outcomes in Depressed and Non-Depressed Opioid-Dependent Agonist-Maintained Pregnant Patients

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Abstract

Aims—To investigate whether cigarette smoking and/or depression contribute to neonatal abstinence syndrome (NAS) severity.

Design—Cohort study analyzing data from a randomized, controlled trial of methadone versus buprenorphine.

Setting—Seven study sites that randomized patients to study conditions and provided comprehensive addiction treatment to pregnant patients.

Participants—119 of 131 opioid-dependent pregnant patients who completed the MOTHER study.

Measurements—Smoking data and depression status were obtained from the Addiction Severity Index and Mini International Neuropsychiatric Interview, respectively. Neonatal outcomes (birth weight, preterm delivery and NAS pharmacologic treatment) were collected from the medical charts. Study site was a fixed-effect factor in all analyses.

Findings—Cigarette smoking was reported by 94% of participants and depression identified in 35%. Smoking was associated with low birth weight, preterm delivery, and NAS pharmacologic treatment in both depressed and non-depressed participants. The association between smoking and NAS treatment differed significantly between depressed and non-depressed participants. Among

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Declaration of Interest

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non-depressed participants, adjusting for site and illicit drug use, each additional average cigarette per day (CPD) increased the odds of NAS treatment by 12% [95% CI: (1.02-1.23), $p=0.02$]. Among depressed participants, each additional average CPD did not statistically increase the odds of NAS treatment [OR: 0.94, 95% CI: (0.84-1.04), $p=0.23$].

Conclusions—These results are consistent with the hypothesis that NAS expression is influenced by many factors. The relationship between CPD and NAS pharmacologic treatment is attenuated among depressed women in this study for reasons currently unknown. Further investigations are needed to clarify the complex relationships among maternal smoking, depression, and NAS.

Keywords

Cigarettes; depression; neonatal; pregnancy; opioids

Introduction

In an effort to improve the maternal and infant health outcomes of opioid-dependent pregnant women, stabilization on therapeutic doses of methadone in the context of prenatal care and ancillary services has been the accepted standard of care (1). More recently, buprenorphine has been evaluated in randomized clinical trials for the treatment of opioid dependence during pregnancy (2-4).

Prenatal exposure to methadone, as well as other opioids including buprenorphine, often leads to neonatal abstinence syndrome (NAS) in the newborn. NAS in prenatally opioid-exposed newborns is a constellation of signs and symptoms representing central nervous, autonomic, respiratory, and gastrointestinal dysregulation (5) such as hypertonicity, tachypnea, feeding problems, and irritability (6). Although nearly all opioid-exposed infants express some signs of NAS, the presentation varies widely and only a subset of these infants develop signs severe enough to require pharmacologic treatment (7). The reason for this variability in NAS expression is not well understood. Most studies suggest that the severity of NAS expression is unrelated to maternal methadone dose (7-11). Numerous other factors, such as placenta efflux transporters, antidepressant medication exposure and infant vagal tone, may modulate NAS expression exist and require further study (4,12-19).

Maternal cigarette smoking is one of the many variables postulated to affect NAS expression. There have been several reports that indicate an association between heavy maternal nicotine exposure and severity of NAS expression (4,14-18). However, because at least 90% of opioid-dependent pregnant patients smoke cigarettes (14,16,18,20-23), it has been challenging to disentangle this variable from the other potential risk factors for NAS severity.

Another variable frequently found in opioid-dependent pregnant smokers (24), which may also play a role in NAS expression, is maternal depression. Up to 50% of opioid-dependent pregnant women who smoke are also depressed (25), and depression is causally linked to numerous other adverse neonatal outcomes (26,27). However, the contribution of maternal depression in opioid-dependent women to NAS expression has not been previously examined. Nor have studies of maternal cigarette smoking and NAS concurrently examined the impact of the presence of co-occurring maternal depression on NAS.

In this study we aim to expand on the previous literature by examining whether maternal cigarette smoking and/or depression contribute significantly to the severity of NAS expression in the infant. This study will explore the possibility that maternal cigarette

smoking and depression may have additive or synergistic effects on NAS severity in the infant.

Methods

Sites

This is a secondary analysis of data from the multi-site MOTHER study, which examined the comparative safety and efficacy of methadone and buprenorphine in the treatment of opioid-dependence among pregnant women and their neonates (28).

Participants

Participants in this cohort study were selected from 131 opioid-dependent agonist-maintained pregnant patients who completed a multi-site randomized controlled, double-blind, double-dummy intervention trial of methadone versus buprenorphine.

Eligibility and categorization of participants into groups—Of the 131 completers of the randomized controlled trial, 12 were excluded due to missing data on key variables: 7 lacked information on cigarette smoking, 3 lacked maternal urine toxicology screens within two weeks of delivery, and 2 lacked data on infant NAS treatment. 119 women had complete data for the outcomes and covariates of interest and so were eligible for inclusion in the subsequent cohort analyses. Both smokers ($n = 112$) and non-smokers ($n=7$) were included in the study cohort. Smoking status was identified based on self-report, and their cigarette smoking quantified using the Addiction Severity Index (29-31) at study entry and during study period. Both depressed participants ($n = 42$) and non-depressed ($n=77$) participants were included in the study cohort. Depression status was identified based on Mini International Neuropsychiatric Interview (MINI) (32) screening at study entry.

Measures

Addiction Severity Index (ASI)—All participants completed a modified ASI 5.0 (30), a semi-structured interview assessing lifetime (study entry only) and past month pre-treatment psychosocial functioning (study entry and monthly follow-up prior to delivery). For this study, number of cigarettes per day (CPD) smoked by the participant over study period was averaged and comparisons were made between average CPD and neonatal outcomes.

Mini International Neuropsychiatric Interview (MINI)—All participants completed at study entry the MINI, a brief structured diagnostic psychiatric interview designed for multicenter clinical trials and epidemiology studies (32). Endorsement of one or both of two items (“Have you been consistently depressed or down, most of the day, nearly every day, for the past two weeks?”; “In the past two weeks, have you been less interested in most things or less able to enjoy the things you used to enjoy most of the time?”) has been demonstrated to be a reliable and valid indicator of the presence of a current episode of major depressive disorder (MDD) (32). For this study, patients were categorized as depressed or non-depressed based on response to these two items on the MINI.

Neonatal medical documentation—Neonatal outcomes were collected from the medical charts and included birth weight, preterm delivery (<37 weeks) (yes v. no), and administration of NAS pharmacologic treatment (yes v. no).

Analyses—Baseline demographics and rates of maternal cigarette smoking, substance use, and antidepressant treatment were tabulated. Rates of adverse neonatal outcomes (low birth rate, preterm delivery, and NAS pharmacologic treatment) were tabulated for the total

sample, and separately, for depressed and non-depressed mothers. Univariate and bivariate logistic regression was used to assess potential risk factors (and their interactions) for NAS pharmacologic treatment. Linear combinations of parameter estimates were used to calculate the point estimates and confidence intervals for the increase in odds of NAS treatment associated with each additional cigarette, separately for depressed and non-depressed individuals. Site was a fixed-effect factor in all analyses: urban US (Baltimore, MD; Philadelphia, PA; Detroit MI; Providence, RI) *v.* rural US (Burlington, VT; Nashville, TN) *v.* urban European (Vienna), the latter of which was the control site for the parametric analyses. Pooling the sites minimized the possibility that site heterogeneity might adversely impact the analyses. Maternal illicit drug use is a well known risk factor for adverse neonatal outcomes and so adjusting for maternal urine toxicology screens positive for illicit drugs minimized the possibility that this factor might adversely impact the analyses. All analyses were performed with the randomized controlled intervention trial blind intact.

Results

Participant Characteristics: Study Entry

Maternal demographic, substance use, cigarette smoking, and depression data at study entry are presented in Table 1. All participants were opioid-dependent, but 29% and 13% at study entry were also using cocaine and marijuana, respectively. Over 90% reported smoking cigarettes and 35% of women screened positive for MDD.

Participant Characteristics: During Treatment

Cigarette smoking, depression, antidepressant medication and illicit drug use during study period are found in Table 2. Most (94%) of participants reported smoking cigarettes, with an average number of cigarettes per day (CPD) of 11.3 ($SD = 6.5$). Twenty nine percent of participants used antidepressant medication. At least once during the study period, 25% of participants tested positive for illicit opioids, 17% for cocaine, 14% for cannabis, and 8% for sedatives. However, only 9% tested positive for any illicit drug within 2 weeks of delivery.

Total Sample Neonatal Outcomes: Low Birth Weight and Preterm Delivery

Maternal cigarette smoking, adjusting for site and illicit drug use, was associated with lower birth weight [β :-20.49, 95% CI: (-35.42,-5.55), $p<0.01$] but not with lower gestational age at delivery [β :-0.03, 95% CI: (-0.09,0.03), $p=0.33$] among both depressed and non-depressed patients. The association between maternal smoking and low birth weight was attenuated, but still persisted after adjusting for estimated gestational age [β :-15.44, 95% CI: (-26.54,-4.35), $p<0.01$].

Total Sample Neonatal Outcomes: Administration of NAS Pharmacologic

Treatment—A significant site effect was seen in administration of NAS pharmacologic treatment: neonates of both urban and rural US mothers were statistically significantly less likely to require NAS pharmacologic treatment as compared to infants of urban European mothers [urban US OR: 0.31, 95% CI: (0.12,0.79), $p=0.01$; rural US OR: 0.15, 95% CI: (0.05,0.43), $p<0.01$].

Neonatal Outcomes by Maternal Depression and Smoking Status—Neonatal outcomes by maternal depression status are presented in Table 3. About half of the total sample's offspring were administered NAS pharmacologic treatment. Table 4 contains results of the univariate analyses, which show that infants born to depressed women were significantly less likely to need NAS treatment. Although CPD was not associated with NAS treatment in the univariate analyses, because this variable has been implicated in NAS development and severity in past studies (4,14-18) it was included in the multivariate

analyses, which are shown in Table 5. These analyses, as well as the linear combinations in Table 6, reveal that the association between smoking and administration of NAS pharmacologic treatment differed between depressed and non-depressed patients. Among non-depressed mothers, adjusting for site and illicit drug use, each additional average cigarette per day (CPD) increased the odds of administration of NAS pharmacologic treatment by 12% [95% CI: (1.02,1.23), $p=0.02$]. The odds ratio (OR) for the association between maternal depression and NAS pharmacologic treatment, adjusting for average CPD, site and illicit drug use, was 3.81 [95% CI: (0.66-21.92), $p=0.13$]. There was a statistically significant interaction between maternal depression and average CPD [ratio of ORs: 0.84, 95% CI: (0.72,0.97), $p=0.02$], such that among depressed mothers, adjusting for site and illicit drug use, each additional average CPD did not statistically increase the odds of NAS pharmacologic treatment [OR: 0.94, 95% CI: 0.84-1.04), $p=0.23$].

Additional analyses revealed no significant association between selective serotonin reuptake inhibitor antidepressant treatment and NAS pharmacologic treatment, adjusting for CPD, illicit drug use, depression and cigarette smoking/ depression interaction [OR: 1.66, 95% CI: (0.64,4.29), $p=0.30$].

No significant association between maternal illicit drug use within two weeks of delivery and NAS pharmacologic treatment, adjusting for CPD, depression, and cigarette smoking/ depression interaction, was found [OR: 0.63, 95% CI: (0.14, 2.79), $p=0.54$].

Discussion

The finding that the average number of cigarettes per day smoked by a non-depressed opioid-agonist-maintained pregnant woman is a factor that predicts her offspring's subsequent need for NAS pharmacologic treatment is not surprising. Although the finding that the same relationship is not true for the offspring of depressed women was unexpected, both are compatible with the well-recognized association of smoking with poor neonatal outcome (33) and the hypothesis that NAS expression is influenced by multiple factors (13,17,19). Alterations in maternal (34) and infant ((13) autonomic functioning have been found to be associated with NAS severity in opioid-exposed pregnancies, and the role of fetal programming has been implicated in underlying deficits present in alcohol exposed children (35,36). Epigenetic alterations and fetal programming have also been implicated in NAS expression (37,38). Further studies regarding the relationship between adult autonomic function and depression in both children and adults (39-42) suggest that depressed psychiatric patients have elevated levels of plasma catecholamines and other markers of altered autonomic function compared with non-depressed controls. The relationship between CPD and NAS pharmacologic treatment is attenuated among depressed women in this cohort of mother-infant dyads for reasons currently unknown. However, the suggestion that maternal depression results in altered maternal autonomic functioning and, through fetal programming, may affect the infant's autonomic functioning, which may be expressed ex-utero as more severe NAS expression, warrants further study. Possible mechanisms for the attenuated relationship between smoking and NAS among depressed women in this study may include maternal smoking being a stronger determinant of adverse neonatal outcomes compared to maternal depression. Thus, maternal smoking may eclipse the effect of depression on NAS expression and antidepressant medication treatment, which may mitigate the effect of maternal smoking on NAS expression in infants born to opioid-dependent depressed mothers. These findings are provocative and clearly highlight the need for further research regarding the interaction of cigarette smoking, depression and NAS in opioid-dependent pregnant patients.

There are several limitations of this study. First, data were collected as part of a larger randomized controlled trial. As a result, this study was not optimally designed to examine the variables of maternal cigarette smoking and depression. Although, it used a broadly-defined self-report measure of both smoking and depression, a prospective trial on this topic could include more comprehensive and sensitive measures (e.g., biological measurement of smoking via carbon monoxide and/or cotinine; diagnosis of depression via clinical examination and/or lengthier structured clinical interview). The sample sizes of the examined groups are small and variable, which may limit the power and ability to detect all differences of interest. Ongoing measures of depression in the participants were not conducted limiting the interpretation of the role of antidepressant medication treatment in these women. Addressing these limitations would yield results supporting stronger conclusions. However, this study represents a first step in understanding the possible interaction between maternal cigarette smoking and depression in the expression of NAS.

The present study provides some of the first data examining the complex relationship among concomitant prenatal exposure to opioid-agonist medication, cigarette smoke, and maternal depression on NAS. While the health risks of maternal opioid medication treatment, cigarette smoking, and depression during pregnancy are independently well known for both mother and neonate, as a constellation these factors have received less attention. The present study is a first attempt at exploring some of these complex relationships. In addition, this study measured CPD as a continuous variable, in contrast to past studies of maternal cigarette smoking and NAS, which measured CPD as a dichotomous variable. Measurement of CPD as a continuous variable may improve the ability to detect maternal smoking effects on NAS expression.

Thus, future research must focus on several important issues. First, examining whether the type of opioid-agonist medication (i.e., methadone *v.* buprenorphine) to which the fetus is exposed alters the interaction among cigarette smoking, depression and NAS is indicated given previous differential findings between methadone and buprenorphine regarding the relationship between smoking and NAS (18). Second, characterizing how other combinations of the specific risk factors (i.e., type of opioid-agonist medication, presence or absence of cigarette smoking, cigarette smoking profiles, and/or depression during various stages of pregnancy) exacerbate or mitigate negative maternal and neonatal outcomes is needed. Third, how opioid-dependence, which is the focus of treatment, in combination with cigarette smoking and depression, fuels negative bio-behavioral outcomes in these women and their offspring is of interest. Fourth, identifying and implementing safe and effective treatments to reduce and eliminate smoking over the course of pregnancy to improve maternal and child health is imperative, especially in opioid-dependent patients who are at great risk for compromised maternal and neonatal outcomes.

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Table 1

Participant demographic, depression and drug use characteristics at study entry

Characteristics	Percent or Mean (SD)
Demographics	
Race, white	89
Marital status, never married	72
Age (years)	26 (.5)
Education (years)	11 (.2)
Estimated gestational age (weeks)	17 (.6)
Depression	
Probable major depressive disorder	35
Drug abuse or dependence	
Opioids	100 ^I
Cocaine	29
Cannabis	13
Alcohol	3
Sedatives	3
Stimulants	3

^I 3% no illicit opioid use but agonist-maintained on entry

Table 2

Cigarette smoking, antidepressant medication use and drug use during study duration

Characteristics	Percent Or Mean (SD)
Cigarette smoking	94
Cigarettes per day	11.3 (6.5)
Antidepressant use	29
Drug use	
Opioids	25
Cocaine	17
Cannabis	14
Sedatives	8
Any drug use within 2 weeks prior to delivery	9

Table 3

Maternal depression and neonatal outcomes

Group	Neonatal outcomes (%)		
	Low birth weight ¹ (n = 20)	Pre-term delivery ² (n = 13)	NAS pharmacologic treatment (n = 61)
Total sample (N = 119)	17	10	51
Depressed	45	38	25
Non-depressed	55	62	75

¹<2500 grams

²<37 weeks (estimated gestational age)

Table 4

Univariate analyses of NAS pharmacologic treatment

Maternal characteristics	NAS pharmacologic treatment					
	Unadjusted			Adjusted for site and drug use		
	OR	95% CI	p-value	OR	95% CI	p-value
Depression	0.37	0.17, 0.82	0.01	0.58	0.24, 1.39	0.22
Cigarettes per day (CPD)	1.04	0.98, 1.10	0.18	1.03	0.97, 1.09	0.40
Illicit drug use near delivery	0.51	0.14, 1.85	0.31	0.72	0.19, 2.76	0.63

Table 5

Multivariate analyses of NAS pharmacologic treatment, adjusted for site and drug use

Maternal characteristics	<u>NAS pharmacologic treatment</u>		
	OR	95% CI	<i>p</i> -value
Depression	3.81	0.66 , 21.92	0.13
Cigarettes per day (CPD)	1.12	1.02, 1.23	0.02
Illicit drug use near delivery	0.63	0.14, 2.79	0.54
CPD/depression interaction	0.84	0.72, 0.97	0.02
Site			
Rural US	0.44	0.15, 1.31	0.14
Urban US	0.29	0.09, 0.94	0.04

Table 6

Linear combinations, adjusted for site and drug use

Maternal characteristics	<u>NAS pharmacologic treatment</u>		
	OR	95% CI	<i>p</i> -value
CPD & no depression	1.12	1.02, 1.23	0.02
CPD & depression	0.93	0.84, 1.05	0.23