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Maternal smoking during pregnancy and newborn neurobehavior: A pilot study of effects at 10–27 days

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Abstract

Objective—To examine effects of maternal smoking during pregnancy on newborn neurobehavior at 10–27 days.

Study design—Participants were 56 healthy infants (28 smoking-exposed, 28 unexposed) matched on maternal social class, age, and alcohol use. Maternal smoking during pregnancy was determined by maternal interview and maternal saliva cotinine. Postnatal smoke exposure was quantified by infant saliva cotinine. Infant neurobehavior was assessed through the NICU Network Neurobehavioral Scale.

Results—Smoking-exposed infants showed greater need for handling and worse self-regulation ($p < .05$) and trended toward greater excitability and arousal ($p < .10$) relative to matched, unexposed infants (all moderate effect sizes). In contrast to prior studies of days 0–5, no effects of smoking-exposure on signs of stress/abstinence or muscle tone emerged. In stratified, adjusted analyses, only effects on need for handling remained significant ($p < .05$, large effect size).

Conclusions—Effects of maternal smoking during pregnancy at 10–27 days are subtle and consistent with increased need for external intervention and poorer self-regulation. Along with parenting deficits, these effects may represent early precursors for long-term adverse outcomes from maternal smoking during pregnancy. That signs of abstinence shown in prior studies of 0–5 day-old newborns did not emerge in older newborns provides further evidence for the possibility of a withdrawal process in exposed infants.

Keywords

maternal smoking; newborn; infant; behavior; NNNS; cotinine; pregnancy

Prenatal nicotine exposure via maternal smoking during pregnancy has been described as “the most widespread prenatal drug insult in the world”.¹ Despite pervasive medical and societal sanctions against maternal smoking, between 11 and 30% of women continue to smoke during pregnancy.^{2–4} Rates are as high as 50% in high-risk samples, including

young, poor, and urban populations.^{3, 4} Compared with other pregnant substance users, pregnant smokers are less likely to quit during pregnancy,⁵ and use cigarettes more frequently.³ Maternal smoking during pregnancy has been linked to low birthweight, admission to neonatal intensive care units, increased risk for sudden infant death syndrome,^{2, 3, 6} and long-term adverse neurobehavioral outcomes in offspring including attention deficits, hyperactivity, conduct disorder, and substance/nicotine use.^{7–10}

Relatively less attention has been focused on neurobehavioral outcomes of maternal smoking during the newborn period. Documenting early effects of maternal smoking is critical for identifying vulnerability markers for intervention and prevention efforts, examining unfolding developmental pathways, and educating parents of exposed infants. Our group published the first study specifically designed to examine effects of maternal smoking on newborn neurobehavior controlling for likely confounds and involving biochemical verification of smoking.¹¹ We utilized a neurobehavioral examination designed for examining effects of prenatal drug exposure in infants: the NICU Network Neurobehavioral Scale; NNNS.¹² After adjustment for significant covariates, tobacco-exposed infants were more excitable, hypertonic, and required more handling compared with unexposed infants. Exposed infants also showed higher scores on the NNNS stress-scale—a scale demonstrated to reveal signs of neonatal abstinence following exposure to other drugs of abuse.

Effects of maternal smoking/nicotine exposure on offspring neurobehavior and signs of abstinence in the immediate newborn period (up to postnatal day 5) have been corroborated by two additional studies. Both examined specific effects of maternal tobacco exposure and involved biochemical verification of exposure.^{13, 14} What remains unknown, however, is whether behavioral effects in the newborn period signify acute effects of nicotine, a withdrawal process, or more persistent dysregulation representing early vulnerability for later neurobehavioral deficits. This pilot study represents the first examination of specific effects of maternal smoking during on infant neurobehavior at 10–27 days. The half-life of nicotine is approximately 2.5 hours in adults¹⁵ and 9–11 hours in newborns,¹⁶—one of the shortest half-lives of drugs used during pregnancy¹⁷. Most nicotine withdrawal symptoms in adults peak at one week.¹⁸ Further, neonatal withdrawal from drugs with longer half-lives (e.g., caffeine) typically last less than 10 days¹⁷. Thus, examining infants at 10–27 days is less likely to indicate acute effects of nicotine or nicotine withdrawal and may represent a neurobehavioral profile more consistent with early vulnerability to long-term behavioral deficits. As in our prior study,¹¹ we utilized the NNNS to measure infant neurobehavior and cotinine as a bioassay for nicotine exposure. By design, smokers and non-smokers were matched for common confounders as in prior studies: socioeconomic status, alcohol use, and age. Exposed and unexposed infants were selected to be healthy, full-term, and normal birthweight.

METHODS

Participants were 56 mothers, age 17–36 years ($M = 25$, $SD = 5$), and their 10–27-day-old infants ($M = 17$, $SD = 4$) recruited at Women and Infants' Hospital of Rhode Island. Racial/ethnic breakdown was: 73% Caucasian, 4% Asian, 5% African-American, 18% Hispanic. Mothers were recruited between 1 and 4 days ($M = 1.3$) postpartum. The protocol was approved by all relevant Institutional Review Boards; written informed consent was obtained from all enrolled mothers. Eligibility was determined through maternal self-report and medical record review. Exclusion criteria included illicit drug use, consumption of >3 alcoholic drinks per month, use of psychotropic, steroid, or thyroid medications, and psychiatric or physical complications during pregnancy. Infants were singletons born at 38–

42 weeks gestation, of appropriate weight for gestational age, 50% female. Infants with congenital anomalies, jaundice, or serious medical complications were excluded.

Both maternal self-report and a bioassay were used to identify smoking exposure during pregnancy. Participants were assigned to the smoking or non-smoking group based on self-report of cigarette use during the maternal interview or a positive cotinine bioassay (> 10 ng/mL) of maternal saliva. (See below.) Cotinine assays were obtained for all participants. Twenty-eight mothers reported smoking at any point during pregnancy and were categorized as smokers. Thirty-seven mothers denied use and were categorized as non-smokers. All had levels of cotinine that were not detectable or below the limit of quantification (< 10 ng/mL), consistent with no smoking around the time of the assay. Following exposure status classification, controls were matched to smokers on socioeconomic status (SES), maternal age, and pregnancy alcohol use. Nine controls did not meet matching criteria and were excluded, leaving 28 matched controls.

Measures

Salivary Cotinine—Nicotine exposure was measured using a saliva bioassay for cotinine, the primary metabolite of nicotine. Cotinine is a reliable biomarker for nicotine levels (sensitivity of 96–97%, specificity of 99–100%)¹⁹, and is readily passed from mother to infant, with fetal concentrations reaching approximately 90% of maternal values.²⁰ Saliva for maternal cotinine determination was obtained from the mother in her hospital room during the initial interview. No smoking was permitted on the postpartum unit or anywhere indoors at the hospital. Thus, second-hand smoke exposure for mother during the hospital stay was unlikely. Infant saliva samples were obtained at the time of the NNNS exam. Maternal and infant saliva samples were collected, sealed, and stored at -80°C following collection. Maternal samples were assayed using gas chromatography-mass spectrometry techniques at Clinical Pharmacology Laboratories (University of California, San Francisco). Infant saliva samples were assayed using high-sensitivity enzyme immunoassay (designed for assessing cotinine in small volumes of saliva obtained from infants) at Salimetrics Laboratories (State College, PA).

NICU Network Neurobehavioral Scale (NNNS)—The NNNS was developed for the National Institutes of Health to assess effects of prenatal drug exposure in infants.^{12, 21} The exam is sensitive to effects of intrauterine drug exposure^{22, 23} but also captures the normative range of behaviors. NNNS assessment includes 3 components: 1) classical neurological items to assess active and passive tone, primitive reflexes, central nervous system integrity, and infant maturity; 2) behavioral items including state, sensory and interactive responses derived from the Neonatal Behavioral Assessment Scale²⁴; and 3) stress/abstinence items based on the Finnegan scale²⁵ and signs of stress observed in high-risk infants. Administration includes a standard sequence of procedures: a) pre-examination observation, b) neurologic components, c) behavioral components. NNNS items are scored and combined into summary scales (Tables I and II) with coefficient alphas ranging from 0.56–0.85.²⁶

Procedures

Maternal Interview—Maternal interviews were completed in the hospital post-partum unit. After completing a brief medical history questionnaire, mothers completed the Timeline Follow Back (TLFB) interview regarding smoking and alcohol use during pregnancy. The calendar-based TLFB is a reliable, valid structured clinical interview designed to gather detailed information on substance use using anchor points to facilitate recall.^{27, 28} Mean number of cigarettes and alcoholic drinks per day during each trimester of pregnancy and three months prior was determined. Mothers also completed an SES

interview from which the Hollingshead four-factor index of SES was derived²⁹. Hollingshead scores of 4 or 5 (1–5 scale; 1=highest SES) were utilized to categorize low SES participants. Maternal caffeine consumption (i.e., coffee, tea, cola, caffeine-containing food) and hours of second-hand smoke exposure (home, work/school, other) over pregnancy were also assessed using detailed interviews covering each trimester.

The NNNS was administered to infants at post-birth days 10 – 27 ($M = 17$) by a certified examiner blind to infant exposure status. Exams took place either at the infant's home ($n = 54$) or at the hospital's Infant Development Center ($n = 2$). Examiner blind for home visits was assured through requests to mother (e.g., hide smoking paraphernalia, no discussion of smoking status with examiner, return of second-hand smoke questionnaire in sealed envelope) and examiner training focused on multiple sources for signs/smells of smoke—e.g., other smokers in the home or mother. Infant postnatal exposure to second-hand smoke was assessed at this visit using a detailed questionnaire assessing total hours of exposure since birth, and an infant saliva sample assayed for cotinine. Saliva was collected with a braided cotton dental roll swabbed along the infant's mouth. Feeding method (breast-feeding, bottle-feeding, both), and maternal depressive symptoms (Center for Epidemiological Studies-Depression (CES-D) scale)³⁰ were also assessed.

Statistical Analysis—Unadjusted mean differences between exposed and unexposed groups were determined for maternal/infant demographics and NNNS summary scores using 2-sample *t*-tests, χ^2 –tests, and ordinary logistic regression. Standard deviations (SD) for continuous NNNS scales were calculated separately by exposure group; when there was no evidence of between-group heteroscedasticity, SDs were pooled across exposure groups to provide an appropriate scale for calibrating between-group differences using Cohen³¹ effect size measures. We also conducted a conservative set of analyses adjusting for confounding variables in prior studies of maternal smoking during pregnancy: 1) maternal second-hand smoke exposure during pregnancy (average hours of exposure per day); 2) infant second-hand smoke exposure in the immediate postnatal period (infant saliva cotinine); 3) breast feeding status (some breast-feeding versus all bottle-feeding); and 4) maternal postnatal depressive symptoms (CES-D score). For these adjusted analyses, a conditional normal regression model³² was estimated within strata defined by maternal SES (High (Hollingshead 1–3) versus Low (Hollingshead 4–5)) and maternal age (17–22, 23–27, >27) categories; pre and postnatal second-hand smoke exposure, breast-feeding, and maternal depression were included as covariates in the regression model. Both unadjusted and regression-adjusted between-group differences are presented in Tables I.

Additionally, two of the NNNS subscales (Hypertonicity and Hypotonicity) had essentially binary response patterns and were dichotomized at zero, with odds ratios combined across strata defined by maternal age and SES using the Mantel-Haenszel procedure.³³ Unadjusted and adjusted odds ratios pertaining to these subscales are presented separately in Tables II. Due to the small sample size, emphasis was placed upon effect size estimation, rather than hypothesis testing, so that potentially clinically significant findings could be highlighted for replication in future studies.

RESULTS

Demographic and Medical Characteristics

Maternal characteristics did not differ between smokers and controls, with the exception of maternal second-hand smoke exposure during pregnancy ($p < .001$) (Table III). Notably, no significant differences emerged between groups for infant characteristics including Apgar scores, gestational age, birthweight (< 50 gram difference between groups), breast-feeding,

second-hand smoke exposure, and maternal depression, providing further evidence of successful matching between exposure groups.

Patterns of Maternal Smoking

Average number of cigarettes smoked during each trimester and number of smokers per trimester is shown in Table IV. Mean cigarettes smoked over the pregnancy, including three months prior was 8.6 ($SD = 6.0$). Self-report cigarette use was significantly associated with maternal saliva cotinine ($r = .60, p < .0001$).

NNNS Outcomes: Unadjusted

Analysis of unadjusted mean scores for continuous NNNs subscales are shown in Table I with estimates of between-group differences and standard errors (SE). Unadjusted hypertonicity and hypotonicity rates are accompanied by point estimates and 95% confidence intervals (CI) for corresponding odds ratios between exposed and unexposed groups calculated using ordinary logistic regression (Table II). Smoking-exposed infants show significantly worse self-regulation and greater need for handling and trended toward greater arousal and excitability than unexposed infants (Cohen's d s = .54, .57, .45, and .52, respectively). Unlike results from the immediate newborn period,¹¹ no significant group differences emerged for stress/abstinence or hypertonicity scales.

NNNS Outcomes: Adjusted

We also report regression coefficients of maternal smoking during pregnancy obtained for each continuous NNNs subscale from conditional normal regression models with covariates described above, estimated within strata defined by maternal SES and age (Table I). Handling was the only continuous NNNs scale to remain significant in the adjusted analyses; maternal smoking during pregnancy was associated with a 0.18 unit increase in need for handling (95% CI = .04–.32). In addition to large effects on handling (Cohen's $d = .76$), moderate effects of MDSP were observed for both excitability and arousal (Cohen's d s = .55 and .41, respectively). We report Mantel-Haenszel stratified odds ratios for effects of maternal smoking during pregnancy on hypertonicity and hypotonicity, with associated 95% CIs (Table II). Neither scale was significantly associated with maternal smoking during pregnancy.

DISCUSSION

We previously found unique effects of maternal smoking on infant neurobehavior including signs of abstinence in the immediate newborn period (24–48 hours).¹¹ In this study, we investigated effects of maternal smoking during pregnancy on infant neurobehavior measured at 10–27 days - well past the half-life of nicotine. Our goal was to conduct an initial examination of differences between acute and persistent effects of maternal smoking during pregnancy using the NNNs, a neurobehavioral examination designed to reveal deficits in high-risk and drug-exposed infants. We found evidence for greater need for handling and poorer self-regulation in exposed compared with unexposed infants at 10–27 days. Although effect sizes were moderate, exposed infants trended toward greater excitability and arousal. In contrast to results from the immediate newborn period,¹¹ we found no differences between exposed and unexposed groups in signs of stress/abstinence and hypertonicity.

This pilot study examines unique effects of maternal smoking during pregnancy on infant neurobehavior. A notable strength of the present study was the care taken to achieve strict comparability between exposed and unexposed groups by matching on covariates identified in prior studies. Smoking mothers were of comparable gravida, parity, social class, and

employment to non-smoking mothers, and displayed similarly low levels of alcohol use and similar caffeine consumption. Infant medical characteristics were nearly identical across exposed and unexposed groups. Notably, smoking-exposed infants, on average, weighed only 49 grams less than unexposed infants at birth, a difference much smaller than the 200-grams typically found in prior studies.³⁴ In addition to comparability between groups, further strengths of this study include model-based adjustment for potential confounds in the pre and postnatal periods (breast-feeding, maternal and infant second-hand smoke exposure, maternal depressive symptoms), and use of biomarkers for maternal and infant nicotine. Maternal cotinine was included to confirm maternal self-report of smoking; infant cotinine provided a biomarker for postnatal nicotine exposure via second-hand smoke and/or breast milk.

The profile of a smoking-exposed infant in the later neonatal period includes greater need for external intervention to maintain a quiet alert state (either to arouse infant from a sleeping state or calm infant from a crying state), greater difficulty in self-regulation, and a tendency toward increased arousal and excitability. The pattern of results suggests that smoking-exposed infants were more irritable and less able to self-soothe than unexposed infants. The combination of an excitable infant requiring more external regulation with a smoking mother who may have fewer resources and parenting skills could lead to strained mother-infant interactions during a critical period for development of mutual regulation processes.³⁴ From a maternal and infant health perspective, this has important implications for trajectories toward positive versus adverse outcomes. Even subtle differences in newborn behavior and self-regulation skills in the context of a mother with greater stress and fewer resources may set the stage for further behavioral dysregulation in the infant and, potentially, a trajectory toward long-term behavioral deficits.^{7–10}

Patterns of effects of maternal smoking during pregnancy on infant neurobehavior at 10–27 days in the present study differed from those shown at 1–2 days in the previous study from our group. Effects of maternal smoking during pregnancy on poorer self-regulation and increased arousal were evident at 10–27 but not 1–2 days. In contrast, effects of maternal smoking during pregnancy on signs of stress/withdrawal, and increased muscle tension were evident 1–2 but not 10–27 days. Effects on excitability and need for handling were evident in both the early and later neonatal period, suggesting persistent neurotoxic effects. That effects of smoking exposure on signs of stress/abstinence were no longer evident past the half-life of nicotine/cotinine in the present study, but were strong at 24–48 hours in our previous study, points to a possibility of a withdrawal process in infants exposed to maternal smoking during pregnancy. Results from our group are complemented by Godding et al,¹³ who also found evidence for withdrawal symptoms and neurological deficits in newborns exposed to maternal smoking during pregnancy. Taken together, convergent findings from these studies suggests a need for increased monitoring and education, and, potentially, non-pharmacological intervention for infants exposed to maternal smoking during pregnancy in the first days of life.

We acknowledge a number of limitations with this study. First, it is important to note that because definitive evidence for a neonatal nicotine withdrawal syndrome and its time course have not been established, we cannot rule out the possibility that effects shown at 10–27 days in this study represent prolonged symptoms of withdrawal rather than persistent neurotoxic effects. Future studies are needed to examine more definitively the possibility and time course of withdrawal in smoking-exposed infants. Second, although inclusion of maternal saliva cotinine to verify self-report of smoking is a strength of the study, cotinine was assessed in the immediate postpartum (days 1–4, mean= day 1) period rather than during pregnancy, leading to greater likelihood of false-negative (smokers with negative cotinine) results. Finally, greater levels of depressive symptoms in the unexposed versus

smoking-exposed group is puzzling and inconsistent with prior research.³⁵ However, the difference was not statistically significant, and effects of depressive symptoms were controlled in adjusted analyses. Differing results from prior studies may be related to our use of a control group matched on socio-economic status.

Several adjusted effect sizes in the current study were of large-to-moderate level according to Cohen's³¹ nomenclature (Handling=.73, Excitability=.55, Arousal=.41), although only the effects of handling attained statistical significance. These effect sizes are comparable or stronger than those seen following exposure to other drugs of abuse including cocaine and heroin,²² which have typically been considered more detrimental to the developing fetus than nicotine.³⁶ Further, effect sizes represent differences between infants exposed to relatively low levels of cigarette smoking and unexposed infants *after matching* for numerous critical confounds (e.g., SES, maternal age) and selecting for healthy infants. Given that these moderate-to-large neurobehavioral effects from maternal smoking during pregnancy emerged in infants exposed to low levels of smoking *and* selected as healthy and normal birthweight, even greater effects may be evident in infants exposed to higher levels of smoking, low birthweight infants, and/or infants who show additional complications related to maternal smoking.

In summary, exposure to maternal smoking during pregnancy was associated with increased need for external handling to maintain a quiet alert state, greater difficulties in self-regulation, and increased arousal and excitability at 10–27 days, past the half-life of nicotine/cotinine. That these effects are evident in the first month suggests the possibility of early identification of offspring who may, in combination with exposure to poor parenting and other postnatal factors, be at greater risk for later adverse neurobehavioral outcomes. Early identification and targeted intervention efforts for both infants and parents may help to prevent disruptions in early maternal-infant bonding, and, ultimately, long-term adverse outcomes.

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ABBREVIATIONS

NNNS	NICU Network Neurobehavioral Scale
SES	socio-economic status
TLFB	Timeline Follow Back
CES-D	Center for Epidemiological Studies—Depression

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Table 1**Maternal and Infant Characteristics by Smoking Group.**

	Exposed (n = 28)	Unexposed (n = 28)	
	Mean (SD) or %	Mean (SD) or %	p
<i>Maternal Characteristics/Demographics</i>			
Maternal age group (% 17–22 years) ¹	57%	32%	.20
Race (% Caucasian)	82%	64%	.13
Delivery mode (% vaginal delivery)	61%	71 %	.41
Gravida	2 (1)	2 (1)	.81
Parity	2 (1)	2 (1)	.94
Employed	61%	64%	.79
Low socio-economic status ² (%)	54%	39%	.28
<1 drink/mo during pregnancy (%)	96%	89%	.30
≤200mg caffeine/day ³ (%)	57%	68%	.41
>1 hr ETS exposure/day ⁴ (%)	18%	54%	.01
<i>Newborn Characteristics</i>			
Gestational Age, weeks	39.6 (1.2)	39.6 (1.0)	.95
Birthweight, grams	3365 (385)	3416 (396)	.63
Apgar, 1 minute	8 (1)	8 (1)	.83
Apgar, 5 minutes	9 (0)	9 (0)	1.0
Age at exam (in days)	17 (4)	18 (4)	.26
Exposed to second-hand smoke (%)	43%	25%	.16
Exposed to maternal depression ⁵ (%)	14%	25%	.31
Any breast-feeding ⁶ (%)	64%	50%	.28

¹ Age intervals included: 17–22, 23–27, and 27+.

² Based on a score of 4 or 5 on the Hollingshead Index

³ Equivalent of 2 cups of coffee per day.

⁴ ETS=Environmental Tobacco Smoke

⁵ Based on cut-off score of 16 on Center for Epidemiological Studies Depression (CES-D) scale.

⁶ Percentage of infants who were breast-fed only or who were breast and bottle-fed at the time of the neurobehavioral assessment.

Table 2

Patterns of maternal smoking

	Smokers <i>n</i>	Cigarettes per day Mean (SD)
3 months prior	28	12 (6)
1 st Trimester	28	15 (1)
2 nd Trimester	21	6 (6)
3 rd Trimester	22	5 (5)

Table 3

NNNS Summary Scores by Maternal Smoking Exposure: Continuous Scales

NNNS Subscale	Maternal Smoking Group		Between-Group Differences			
	Exposed		Unexposed		Adjusted	
	Mean (SD)	Mean (SD)	Mean (SE)	p	Mean (SE)	p
Attention	5.31 (1.62)	5.56 (1.44)	-0.25 (0.42)	0.554	-0.07 (0.48)	0.879
Arousal	4.24 (0.78)	3.85 (.93)	0.39 (0.23)	0.091	0.36 (0.28)	0.217
Self-Regulation	5.60 (0.71)	5.99 (.74)	-0.39 (0.20)	0.049	-0.28 (0.22)	0.221
Handling	0.44 (0.23)	0.31 (0.23)	0.13 (0.06)	0.038	0.18 (0.07)	0.017
Quality of Movement	4.88 (0.71)	5.05 (0.59)	-0.17 (0.18)	0.354	-0.15 (0.20)	0.462
Excitability	3.43 (2.49)	2.18 (2.34)	1.25 (0.66)	0.058	1.36 (0.80)	0.098
Lethargy	4.04 (1.86)	4.21 (2.11)	-0.17 (0.54)	0.738	-0.29 (0.60)	0.629
Asymmetric Reflexes	1.36 (1.25)	1.07 (0.98)	0.29 (0.31)	0.346	0.12 (0.36)	0.732
Non-Optimal Reflexes	3.79 (2.23)	3.79 (2.11)	0.00 (0.59)	1.000	-0.69 (0.67)	0.314
Habituation	6.02 (2.13)	6.74 (1.10)	-0.72 (0.65)	0.253	-1.30 (0.85)	0.139
Total Stress/ Abstinence	0.08 (0.05)	0.07 (0.05)	0.01 (0.01)	0.616	0.01 (0.02)	0.455

Table 4

NNNS Summary Scores by Maternal Smoking Exposure: Binary Scales.

	Maternal Smoking Group		Odds Ratio			
	Exposed		Unexposed		Adjusted	
	Rate	Rate	Estimate	95% CI	Estimate	95% CI
<i>NNNS Subscale</i>						
Hypertonicity	0.07	0.11	1.56	0.24–10.14	1.57	0.28–8.95
Hypotonicity	0.29	0.18	0.54	0.15–1.93	0.56	0.15–2.07