Published in final edited form as:

Pediatrics. 2009 May ; 123(5): e842–e848. doi:10.1542/peds.2008-2084.

Maternal Smoking during Pregnancy and Neonatal Behavior: A Large-Scale Community Study

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Abstract

Objective—To investigate the influence of prospectively-measured smoking during pregnancy on aspects of neonatal behavior in a large, community sample.

Patients and Methods—Participants were mothers and infants from the Providence Cohort of the National Collaborative Perinatal Project enrolled between 1960 and 1966. Mothers with pregnancy/medical complications and infants with medical complications and/or born premature or low birthweight were excluded. The final sample included 962 mother-infant pairs, of whom 23% were African-American. Maternal smoking was measured prospectively at each prenatal visit. Neonatal behavior was assessed using the Graham-Rosenblith Behavioral Examination of the Neonate. Items from the examination were reduced to three subscales: irritability, muscle tone, response to respiratory challenge.

Results—Sixty-two percent of the sample reported smoking during pregnancy with 24% of smokers reporting smoking a pack per day or more. We found a significant influence of maternal smoking exposure (none, moderate/less than a pack per day, heavy/pack a day or more) on irritability and muscle tone in the neonate (p 's<.005), with exposed infants showing greater irritability and hypertonicity. Effects remained significant after controlling for significant covariates: maternal socioeconomic status, age and race, and infant birthweight and age (p 's<.001). Post hoc tests suggested particular effects of heavy smoking on increased infant irritability, but both moderate and heavy smoking exposure on increased muscle tone.

Conclusions—In a large, community sample, exposure to maternal smoking was associated with increased irritability and hypertonicity in neonates. Exposure to maternal smoking did not influence neonatal response to respiratory challenge. This study is the largest-scale investigation to date of effects of maternal smoking (heavy and moderate) on examiner-assessed neonatal behavior. Given associations between both maternal smoking and infant irritability and later behavioral dysregulation, results have important implications for early identification and intervention with at-risk offspring.

Keywords

smoking; pregnancy; infant; neonate; behavior; irritability; muscle tone

Although rates of smoking have decreased over the last several decades, maternal smoking during pregnancy (MSDP) continues to be a major public health problem.¹⁻⁴ MSDP has been linked to numerous adverse health outcomes in infancy including low birthweight, admission to neonatal intensive care, and increased risk for sudden infant death syndrome.³⁻⁵ MSDP has also been linked to long-term adverse behavioral outcomes in offspring including conduct disorder, attentional and cognitive deficits, and substance use.⁶⁻⁹ However, relatively little is known about effects of maternal smoking on behavioral deficits in infancy.

Several small-scale, controlled studies investigating newborn response to structured, examiner-administered neurobehavioral examinations have revealed effects of maternal smoking on alterations in cry and soothability and increased muscle tone. In two studies in which MSDP was examined in the context of exposure to other drugs (alcohol, cocaine), exposed infants showed alterations in cry and increased muscle tone.^{10, 11} Law et al.¹² published the first study specifically designed to examine effects of MSDP on newborn neurobehavior. At 24-48 hours, smoking-exposed infants were more excitable, hypertonic, and more difficult to soothe compared to unexposed infants. An independent follow-up study also indicated persistent effects on soothability and excitability at 10-27 days.¹³ However, sample sizes were small and sampling frames not designed to be representative.

In addition to small, controlled studies of infant response to examiner-administered neurobehavioral examinations, several population-based epidemiological studies have suggested links between MSDP and maternal-report measures of excessive crying and infantile colic (IC).¹⁴⁻¹⁶ IC is a condition characterized by paroxysms of irritability, excessive crying and muscle tension during the first four months of life.^{17, 18} Sondergaard et al.¹⁶ showed a two-fold increased risk for colic in infants of mothers who smoked 15 or more cigarettes per day during pregnancy. Reijneveld et al.¹⁴ found nearly two-fold increased risk for “excessive crying” in infants of mothers who smoked 10 or more cigarettes per day throughout pregnancy, although effects for maternal smoking were not significant after adjustment for confounders. Most recently, in multivariate analyses, Canivet et al.¹⁹ found a 1.7-fold increased risk of colic related to maternal pre as opposed to postnatal smoking. However, maternal reports of infant crying and IC—particularly retrospective reports—may be confounded by factors linked with maternal smoking (e.g., increased distress/stress).²⁰

Thus, smaller, controlled studies examining effects of MSDP on response to examiner-administered neurobehavioral examination have shown effects on crying and hypertonicity, while large-scale population-based studies using maternal report have shown links between maternal smoking and crying/colic. However, samples in small, controlled studies may be unrepresentative, while maternal reports of infant behavior in larger-scale studies may be prone to subjective bias. In the present study, we conducted the first large-sample investigation of prospectively assessed MSDP on neonatal behavior assessed with an examiner-administered, structured behavioral examination. In light of burgeoning interest in offspring effects of MSDP, data collected through a substudy of the National Collaborative Perinatal Project (NCPP), was examined with respect to influences of heavy and moderate maternal smoking. Minimal social sanctions against smoking during the period of data collection (1960-1966) allow for a unique distribution of maternal smoking, with smokers comprising more than sixty percent of the sample.

PATIENTS AND METHODS

Participants

1256 mother-infant pairs from the Providence, RI site of the National Collaborative Perinatal Project (NCPP)²¹ completed the neonatal behavior substudy. The NCPP was a multi-site,

longitudinal, cohort study that involved prospective observation and examination of more than 50,000 pregnancies nationwide. Offspring were followed from birth through age seven. Mothers were recruited at the time of registration for prenatal care between 1960 and 1966. Enrollment for the Providence site was based on a sampling frame designed to yield a representative sample of women receiving prenatal care in Providence. Specifically, obstetric patients in a hospital clinic and private obstetric office were randomly selected, resulting in an average enrollment of one of three patients and a total of 4140 participants. Mothers and infants selected for the neonatal behavior study comprised approximately one-fourth of participants in the overall Providence Cohort; informed consent for the neonatal exam was obtained in the postpartum unit of the hospital. There were no significant differences in maternal (age, race, socio-economic status, gravida, parity) or infant (gestational age, birthweight, Apgar) characteristics between the sample selected for the neonatal behavior study and the overall Providence sample (all p 's=ns).

Excluded from current analyses were mothers with pregnancy/medical complications or who admitted to using other drugs or excessive alcohol during pregnancy ($n = 107$), and infants born prior to 37 weeks gestational age ($n = 127$), under 2500 grams ($n = 151$), and with medical complications. Gestational age was based on mothers' last menstrual period determined through medical records using the best obstetrical estimate. Also excluded were infants whose neurobehavioral examination was considered by the examiner to be invalid ($n=15$), and, in order to focus on the immediate neonatal period, infants over 3 days old ($n=77$). The final sample included 962 healthy mother-infant pairs. Infants born by both spontaneous vaginal and Cesarean section deliveries were included.

Procedures

Maternal Assessment—Demographic information including race/ethnicity, education, occupation, and income was assessed during the first prenatal visit. A composite index of socioeconomic status (range: 1= lowest SES through 10=highest SES) was derived from education (years) and occupation (manual, nonmanual, unemployed) of the head of household along with household income (based on US poverty threshold at the time) using methods developed by the US Census Bureau.²² MSDP was assessed at each prenatal visit up to time of delivery by study physicians. Mothers were asked whether they were currently smoking, and, if so, number of cigarettes smoked per day. Validity of NCPP maternal smoking reports through comparison with serum cotinine levels has been shown to be excellent (kappas = 83-87%).²³ Based on prior analyses in this cohort⁶, mothers were classified into three groups based on maximum number of cigarettes smoked per day over the course of pregnancy: (a) no smoking, (b) moderate smoking (less than one pack per day: >0 and <20 cigarettes per day), and (c) heavy smoking (one pack per day or more: 20+ cigarettes per day).

Newborn Assessment—Birthweight, gestational age, Apgar scores, and medical complications were determined by NCPP examiners present at delivery. The Graham-Rosenblith Behavioral Examination of the Neonate was administered to newborns prior to discharge from the hospital. The Graham-Rosenblith examination was developed by Graham²⁴,²⁵ and later adapted by Rosenblith²⁶,²⁷ to be administered by trained examiners. It is one of the earliest standardized assessments of infant behavioral responses to structured handling and a precursor to modern neurobehavioral assessments. The examination involves a standardized sequence of observations and manipulations of the infant. Rated on continuous Likert-type scales, items in the examination measure a variety of motor reflexes (e.g., crawl), responses to sensory stimuli (e.g., flashlight), active and passive muscle tone, responses to various types of respiratory challenge (e.g., cotton over nose; cellophane over nose and upper lip), soft signs of neurological damage (e.g., nystagmus, strabismus), and irritable behavior. The exam has demonstrated acceptable levels of test-retest reliability²⁶, inter-scorer

agreement²⁷ and has shown predictive validity with later psychological and physiologic outcomes.²⁸⁻³¹ Examiners included Dr. Rosenblith and her trained assistant, Rebecca Anderson Huntington.

Using an approach combining statistical and conceptual aggregation, items from the Graham-Rosenblith examination were reduced to three subscales: irritability, muscle tone, and response to respiratory challenge. An exploratory principal components analysis was conducted using half of the sample ($n=473$). Retained items were conceptually related to and loaded highly ($>.5$) on one of the three retained factors. The three-factor structure was replicated in a confirmatory principal components analysis in the other half of the sample ($n=489$). Subscale scores were created by taking the mean of items loading highly on each factor. The irritability subscale included two items (Cronbach's $\alpha=.88$): (a) amount of crying during the examination, and (b) subjective rating of infant irritability. The muscle tone scale included six items ($\alpha=.74$) measuring active and passive muscle tone, including (a) amount of resistance to arm displacement, (b) amount of resistance to leg displacement, (c) tension following a pull-to-sit manipulation, (d) supine tension, (e) tension in response to pushing of the infant's feet, and (f) subjective rating of muscle tension throughout the examination. The Response to Respiratory Challenge scale included four items ($\alpha=.79$) assessing response to respiratory challenge over three trials. Items were: (a) response to nasal respiratory challenge, (b) response to brief occlusion of nose and part of mouth, (c) vigor of response to respiratory challenge, and (d) persistence of response to respiratory challenge.

Statistical Analysis—Analysis of variance (ANOVA) was utilized to investigate differences between heavy, moderate, and non-smoking groups on maternal and infant characteristics and on the three Graham-Rosenblith subscale scores. Infant gender was initially included as an additional independent variable in all analyses; however, as no significant smoking group by gender interactions emerged, we collapsed across gender in all analyses. Analysis of covariance (ANCOVA) was also conducted to adjust for significant covariates. Potential covariates were selected from demographic and medical characteristics (see Table 1) and were included if they differed significantly ($p<.05$) between smoking groups, or were significantly correlated with Graham-Rosenblith subscale scores. Based on these criteria, included covariates were: maternal age, race and socio-economic status, infant birthweight, and infant age at time of the examination. Significant omnibus differences were followed by pair-wise least significant difference (LSD) tests--appropriate for groups with differing n 's using adjusted means.

RESULTS

Sample Description

Average age of mothers in the final sample was 24 years ($SD=6$). The sample was 76% Caucasian, 23% African-American, and 1% other races. Thirty-eight percent of participants were nonsmokers; 62% were smokers--divided into moderate (76%) and heavy (24%) smoking groups. Less than 1% of smokers quit during pregnancy. Mean smoking level was 13 cigarettes per day ($SD=7$) for the moderate smoking group and 35 cigarettes per day ($SD=8$) for the heavy smoking group. Forty-seven percent of the infants were female. Average gestational age was 40.5 weeks ($SD=1.9$). Average birthweight was 3340 grams ($SD=434$ grams), and average infant age at the time of the exam was 1 day old (range=0-3 days).

Demographic and Medical Characteristics by Smoking Group

Demographic and medical characteristics of the sample by maternal smoking group are shown in Table 1. Significant differences between groups emerged for maternal age, race and SES. Mothers in the smoking groups were younger, more likely to be Caucasian, and of lower SES.

There were no differences between groups in gravida or parity. Significant differences between maternal smoking groups emerged for infant birthweight. No significant differences in gestational age or Apgar scores were found.

Effects of Maternal Smoking on Graham-Rosenblith Summary Scales

Adjusted and unadjusted scores on the Graham-Rosenblith summary scales by maternal smoking group are shown in Table 2. Analyses of unadjusted and adjusted means revealed significant differences between groups in irritability ($F(2, 961)=7.7$ and $F(7, 916)=9.4$, unadjusted and adjusted for covariates, respectively, $p's<.001$) and muscle tone ($F(2, 961)=11.3$ and $F(7, 916)=7.9$, $p's<.005$). No significant effects of maternal smoking on response to respiratory challenge emerged. LSD tests conducted on adjusted means for irritability revealed a significant difference between the heavy and non-smoking groups ($p<.01$) and between the heavy and moderate smoking groups ($p<.01$) suggesting a threshold effect of heavy (pack-a-day) maternal smoking on infant irritability (See Figure 1a). LSD tests for infant muscle tone revealed significant differences between the moderate and non-smoking groups ($p<.05$) and between the heavy and non-smoking groups ($p<.05$), but no differences between moderate and heavy smoking groups. Results suggest an effect of any smoking on infant muscle tone (See Figure 1b).

DISCUSSION

Maternal smoking during pregnancy (MSDP) remains an enormous public health concern. However, despite robust links between MSDP and child behavior deficits (e.g., conduct disorder/ externalizing behavior), no large-scale studies have addressed unique effects of maternal smoking on neonatal behavior. We analyzed data from the National Collaborative Perinatal Project to provide the first *large-scale community* study to investigate effects of *prospectively measured* MSDP on a clinical neonatal behavior examination. To our knowledge, the present study represents the largest study of examiner-assessed neonatal behavior in smoking-exposed infants; sample size for the present study is nearly ten times larger than all prior studies. We found a significant influence of MSDP on infant irritability and muscle tone. Specifically, neonates exposed to heavy maternal smoking (one pack per day or more) showed greater irritability relative neonates exposed to moderate maternal smoking (less than a pack per day) or unexposed neonates. Neonates exposed to both heavy and moderate maternal smoking were also more hypertonic than unexposed neonates.

There are a number of notable strengths of this study. First, the large sample size, diversity of socio-economic status, and representative nature of the sample support the generalizability of results from the present study. Second, prospective assessment of maternal smoking (at each prenatal visit), prior verification of maternal reports with serum cotinine²³, and decreased social sanctions against smoking during the period of data collection support the validity of maternal smoking reports. Third the unique distribution of maternal smoking (62% smokers with one fourth smoking a pack a day or more) and decreased social sanctions against smoking at the time of data collection allowed for analyses of differential influence of moderate versus heavy smoking and examination of effects of maternal smoking less confounded by socio-economic status (SES) than in more recent samples. Fourth, strict maternal and infant exclusion criteria leading to a healthy sample of infants (no group differences in Apgar scores or gestational age) allowed us to examine effects of maternal smoking relatively unconfounded by health differences in infants. Finally, use of an examiner-administered behavioral examination (rather than maternal report) in this large-scale study allowed for increased validity and objectivity of behavioral outcome data.

Findings from the present study complement smaller-scale studies of MSDP and infant behavior but extend findings to a larger, more generalizable sample. Prior studies from our

group have shown unique effects of maternal smoking on arousal/ excitability, difficulty in soothing, hypertonicity, and signs of withdrawal in samples of healthy, full-term infants where smokers and non-smokers were matched on SES, maternal age, and alcohol use.^{12, 13} Additional studies examining effects of maternal smoking in the context of other drug use have shown effects on cry quality as well as hypertonicity.^{10, 11} Results from the present study highlight the influence of maternal smoking on infant irritability (confirming prior effects on cry, arousal/excitability and difficulty soothing¹¹⁻¹³) as well as hypertonicity^{10, 12} in a larger, more generalizable sample. We can articulate several possible mechanisms to explain consistent effects of MSDP on irritability and muscle tension. One possibility is that these outcomes represent acute effects/toxicity of nicotine. A second possibility is that irritability and muscle tension are part of a constellation of symptoms within a nicotine neonatal withdrawal syndrome. Effects on symptoms of abstinence in Law et al.¹², in neonates of smokeless tobacco users³², and in an intensive study of neonatal nicotine withdrawal over the first five days³³ substantiate this possibility across studies and withdrawal scales. Third, effects may represent the initial signs of persistent behavioral dysregulation, leading to long-term behavioral impairments seen in prior studies.⁶⁻⁹ Finally, effects of prenatal nicotine exposure have been shown to be mediated by nicotinic acetylcholine receptors, which may modulate release of numerous neurotransmitters (i.e., serotonin, norepinephrine), brain regions (brain stem, limbic, and cortical regions) and brain systems (arousal, stress systems) that may underlie early regulatory behaviors.³⁴⁻³⁹

Results are also consistent with prior studies of MSDP and infantile colic (IC)¹⁵, but extend findings to objective examiner-based infant behavioral assessment and to the early neonatal period. It has been theorized that IC and general infant fussiness may reflect more global and persistent difficulties with behavioral control and self-regulation⁴⁰⁻⁴¹. Suggestive of the global nature of the behavioral dysregulation, infants who cry excessively often also experience concurrent difficulties in other areas—e.g., feeding and sleep.^{42, 43} Parenting deficits may further exaggerate early behavioral differences. The combination of a fussy, tense infant with a smoking mother under higher stress with fewer resources could lead to strained mother-infant interactions during a critical period for maternal-infant bonding.^{13, 44} This combination could lead to a negative cycle increasing likelihood of further behavioral dysregulation in the infant/child.⁴⁵ Highlighting the persistence of behavioral dysregulation over development, Wolke⁴⁰ found that children who described as persistent criers in infancy were more frequently in the borderline clinical range for hyperactivity symptoms and showed more conduct problems and negative emotionality than controls. Thus, although increased irritability and muscle tension may acutely indicate withdrawal or neurotoxic effects, in combination with parenting deficits, may also represent early endophenotypic markers of risk for later behavioral dysregulation.

Although this study is large-scale and rigorous with important clinical and public health implications, we acknowledge two primary limitations. First, the original Graham-Rosenblith sub-study of the NCPP was not designed to examine the influence of maternal smoking; groups were not matched on additional maternal/infant factors that might influence behavioral outcome. However, strict maternal/infant inclusion criteria and statistical control for infant birthweight likely substantially reduced additional pre and perinatal influences on behavioral outcomes. Second, although the Graham-Rosenblith examination was state-of-the-art for its time and a precursor to modern neurobehavioral assessment, more recent neurobehavioral examinations allow for assessment of a broader range of subtle effects of drug exposure.⁴⁶ However, that we found significant effects of maternal smoking using an early behavioral exam not designed to reveal deficits due to drug exposure highlights the strength of effects.

Conclusion

The present study represents the largest study of examiner-assessed neonatal behavior in smoking-exposed infants. Maternal smoking was measured prospectively in a large community sample with a high proportion of smokers. Results reveal significant influences of maternal smoking on increased infant irritability and hypertonicity. No significant effects or differences were found in response to the respiratory occlusion challenge. That infants exposed to MSDP can be differentiated from their non-exposed counterparts at less than three days old highlights the possibility and importance of very early intervention and prevention efforts. Further research is needed not only to investigate whether these effects are acute or persistent but also to continue to examine trajectories to long-term outcomes.

Acknowledgments

We gratefully acknowledge Stephanie Paton and Kathy McGaffigan for administrative and programming assistance respectively. We also thank Rebecca Anderson Huntington, the principal Graham-Rosenblith examiner. Finally, we are grateful to mothers and infants who contributed to this study.

Preparation of this manuscript was supported by NIH grants R01 HD043844 to Dr. Stroud and P50 CA84719 to Dr. Niaura. There are no conflicts of interest.

ABBREVIATIONS

MSDP	maternal smoking during pregnancy
SES	socioeconomic status
NCPD	National Collaborative Perinatal Project

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Figure 1a.

Significant pair-wise differences between Maternal Smoking Groups on Infant Irritability

Figure 1b.

Significant pair-wise differences between Maternal Smoking Groups on Infant Muscle Tone

Table 1

Demographic and Medical Characteristics.

	Non- Smoking (<i>n</i> = 366)	Light-Moderate Smoking (<i>n</i> = 451)	Heavy Smoking (<i>n</i> = 145)	
Characteristics	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)	P
Maternal Demographics				
Maternal Age*	25.0 (6.4)	23.3 (5.6)	24.3 (5.4)	.001
Maternal Race				.001
% Caucasian	74.3	72.5	92.4	
% African American	24.6	26.2	7.6	
% Other	1.0	1.3	0	
Socioeconomic Status*	4.8 (2.1)	4.5 (2.0)	4.1 (1.9)	.001
Pregnancy History				
Gravida	2.5 (2.4)	2.2 (2.3)	2.6 (2.2)	.07
Parity	2.8 (1.9)	.8 (.5)	.89 (.6)	.25
Infant Medical Characteristics				
Gestational age (weeks)	39.8 (2.8)	39.9 (2.6)	40.1 (2.9)	.41
Birthweight (grams)	3347 (562)	3134 (522)	2990 (466)	.001
Apgar: 1 minute	8 (2)	8 (2)	8 (2)	.65
Apgar:5 minutes	9 (1)	9 (1)	9 (1)	.55

NOTE: *p* values denote statistical significance of differences between groups (non-smokers, moderate smokers, heavy smokers) by one-way analysis of variance. Asterisks highlight characteristics with statistically significant ($p < .05$) differences between groups.

Table 2

Unadjusted and Adjusted Graham-Rosenblith summary scores by smoking group. Adjusted for maternal age, race and SES, and infant birthweight and age at exam.

	Unadjusted			Adjusted			<i>p</i> =
	No Smoking <i>n</i> = 366	Moderate Smoking 1-19 cigs/day <i>n</i> = 451	Heavy Smoking 20+ cigs/day <i>n</i> = 145	No Smoking <i>n</i> = 349	Moderate Smoking 1-19 cigs/day <i>n</i> = 433	Heavy Smoking 20+ cigs/day <i>n</i> = 137	
Rosenblith Subscale (Range of Scores)	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)	Mean (<i>SD</i>)	<i>p</i> =
Irritability (0-4)	.87 (.76)	.91 (.84)	1.2 (1.0)	.85 (.73)	.91 (.83)	1.2 (1.0)	.001
Muscle Tone (1-6)	3.5 (.97)	3.8 (.98)	3.9 (.89)	3.5 (.98)	3.8 (.98)	3.9 (.89)	.004
Response to Respiratory Challenge (0-4)	2.7 (.55)	2.7 (.56)	2.6 (.61)	2.7 (.55)	2.7 (.56)	2.6 (.62)	.17