Maternal Smoking and Infantile Gastrointestinal Dysregulation: The Case of Colic

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ABSTRACT. *Background.* **Infants' healthy growth and development are predicated, in part, on regular functioning of the gastrointestinal (GI) tract. In the first 6 months of life, infants typically double their birth weights. During this period of intense growth, the GI tract needs to be highly active and to function optimally. Identifying modifiable causes of GI tract dysregulation is important for understanding the pathophysiologic processes of such dysregulation, for identifying effective and efficient interventions, and for developing early prevention and health promotion strategies. One such modifiable cause seems to be maternal smoking, both during and after pregnancy.**

Purpose. **This article brings together information that strongly suggests that infants' exposure to tobacco smoke is linked to elevated blood motilin levels, which in turn are linked to an increased risk of GI dysregulation, including colic and acid reflux. We base this hypothesis on evidence supporting a link between maternal smoking and infantile colic (IC) and on additional evidence proposing increased motilin release, attributable to exposure to tobacco smoke and its metabolites, as a physiologic mechanism linking maternal smoking with infantile GI dysregulation.**

Methods. **We critically review and synthesize epidemiologic, physiologic, and biological evidence pertaining to smoking and colic, smoking and motilin levels, and motilin and colic.**

Results. **Six studies have investigated the link between maternal smoking and IC, but IC was defined according to Wessel's rule of threes (crying for ≥3 hours per day, ≥3 days per week, for ≥3 weeks) in only 1 of these studies. The remaining studies used definitions that ranged from less-stringent variations of Wessel's criteria to definitions that would suggest excessive crying but not necessarily colic. Results from 5 of these studies suggest that there is an independent association between maternal smoking and excessive crying, as well as IC. Recent studies of the GI system provide strong, but indirect, corroborating evidence suggesting physiologic pathways through which maternal smoking can be linked to IC. This physiologic evidence can be outlined as follows: (1) smoking is linked to increased plasma and intestinal motilin levels and (2) higher-than-average levels of motilin are linked to elevated risks of IC. Although these findings from disparate fields suggest a physiologic mechanism linking maternal smoking with IC, the entire chain of events has not been examined in a single cohort. A prospective study, begun in pregnancy and continuing through the first 4 months of life, could provide definitive evidence linking these disparate lines of research. Key points for such a study are considered.**

Conclusions. **New epidemiologic evidence suggests that exposure to cigarette smoke and its metabolites may be linked to IC. Moreover, studies of the GI system provide corroborating evidence that suggests that (1) smoking is linked to increased plasma and intestinal motilin levels and (2) higher-than-average intestinal motilin levels are linked to elevated risks of IC. In the United States, nearly one-half of all women smokers continue to smoke during their pregnancies. This amounts to ~12% of all women who give birth. Moreover, it is estimated that 50% to 80% of employed adults have regular exposure to environmental tobacco smoke and that >30% of nonsmokers live with smokers. If, as we suspect, exposure to cigarette smoke increases the risk of colic, then this would provide additional incentives to parents to abstain from smoking. Decreased exposure to tobacco smoke can be expected to provide widespread and long-term health benefits to maternal and child populations.** *Pediatrics* **2004;114:e497–e505. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1036;** ***colic, smoking, smoking during pregnancy, motilin, GI dysfunction, maternal and child health.***

ABBREVIATIONS. GI, gastrointestinal; IC, infantile colic; ETS, environmental tobacco smoke; RR, risk ratio; CI, confidence interval; MMC, migrating motor complex.

Infants' healthy growth and development are predicated, in part, on regular functioning of the gastrointestinal (GI) tract. In the first 6 months of life, infants typically double their birth weights.[1] During this period of intense growth, the GI tract needs to be highly active and to function optimally. Identifying modifiable precursors of GI tract dysregulation is important for understanding the pathophysiologic processes of such dysregulation, for identifying effective and efficient interventions, and, most importantly, for developing early prevention and health promotion strategies.[2] One such modifiable precursor seems to be maternal smoking, both during and after pregnancy.

Our aims for this article are twofold. First, we present evidence supporting a link between maternal smoking and infantile GI tract dysregulation. Second, we present evidence to propose motilin release

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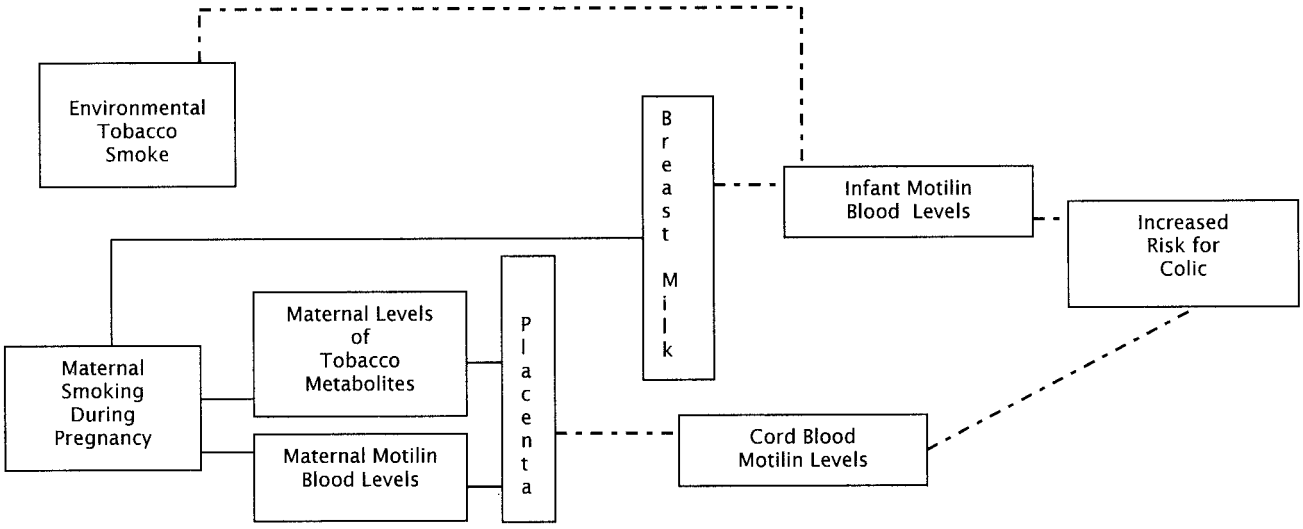

Fig 1. Proposed mechanisms for effect of maternal smoking on infant risk for colic.

as a physiologic mechanism linking maternal smoking and infantile GI dysregulation (Fig 1). There is evidence linking exposure to tobacco smoke with a number of GI dysfunctions, including gastroesophageal reflux, esophagitis, and infantile colic (IC).[3–8] This evidence is most well developed for IC; therefore, we focus on the link between maternal smoking and IC and on the evidence suggesting physiologic plausibility of the proposed link between maternal smoking and IC.

MATERNAL SMOKING AND IC

IC

IC is a syndrome characterized by paroxysms of irritability, inconsolable crying, and screaming accompanied by clenched fists, drawn-up legs, and a red face.[9] The most commonly accepted, but not necessarily most commonly used, diagnostic criteria are based on the "rule of threes" proposed by Wessel,[10] which requires the syndrome to persist for (1) ≥3 hours per day, (2) ≥3 days per week, and (3) ≥3 weeks. IC presents a few weeks after birth and peaks at 5 to 8 weeks of age; it usually resolves spontaneously by 4 months of age. Among newborns in Western countries, the prevalence of colic is estimated to be between 5% and 28%.[11]

The available evidence suggests that IC has multiple independent causes. IC has been attributed variously to infants' difficulty self-regulating, type of feeding, exposure to cow's milk proteins (especially α-lactalbumin) in formula or breast milk, exposure to tobacco smoke, and maternal depression or anxiety.[9] In cases of maternal depression or anxiety,[12] any association may be attributable to the effect of the colicky infant on the mother, rather than the converse. In his classic study, Illingworth[13] found the incidence of colic to be independent of maternal factors such as age, parity, and pregnancy history, as well as infant factors such as gender, weight, feeding habits, allergies, and weight gain. In self-reported studies of colic or colicky behavior, the odds of reported IC were slightly higher for infants with older, better educated, and more affluent parents.[14] Reporting bias cannot be ruled out in those studies, because less affluent women with limited education may be reluctant to report problems for fear of appearing incompetent. The type of feeding (ie, breastfeeding versus bottle-feeding) has been reported to be correlated with colic, but the evidence regarding which type of feeding is positively associated with IC is contradictory.[13–15] Despite at least 3 reports to the contrary,[16–18] it is reasonable to suggest that cow's milk allergies are linked with colic for some infants. The positive evidence was collected from a series of studies that used the double-blind, crossover design to assess the association between exposure to cow's milk and IC.[19–21] In those studies, symptoms of IC were reduced for both formula-fed infants and breastfed infants when cow's milk was eliminated from the infants' or mothers' diets, and symptoms reappeared when infants were orally challenged with bovine whey protein. In all studies in that series, IC was defined on the basis of Wessel's rule of threes. In contrast, in 2 of the studies with null findings, the diagnosis of colic was based on a history of persistent crying for no apparent reason[17] or IC was defined as unexplained crying and restlessness (in a population-based survey).[16] Because the diagnosis of IC was not based on Wessel's rule of threes, excessive crying might have been misclassified as IC. In a third study with null findings, a double-blind crossover design was used and the diagnosis of IC corresponded to Wessel's rule of threes. However, intolerance to cow's milk protein was evaluated with serum immunoglobulin E measurements and radioallergosorbent tests.[18] It is difficult to detect specific immunoglobulin E among infants <1 year of age, and the secondary development of tolerance is usually not established among young infants.[22] Therefore, the presence of cow's milk allergies cannot be ruled out completely in that study.

Evidence of a Link Between Maternal Smoking and IC

We searched Medline for original research articles, review articles, commentaries, and letters on maternal smoking and colic published between January 1, 1966, and March 10, 2004. This search was conducted in 3 steps. First, using the keywords "colic" and "infantile colic," we produced a list of ~4900 references. Next, using the keywords "maternal smoking," "cigarette smoking," and "tobacco," we produced a list of ~116 000 references. Finally, we identified 25 articles that appeared in both lists. We reviewed those articles to identify those that specifically addressed maternal smoking and colic and to identify additional studies that we might have missed. This review led to a list of 7 references for 6 studies, including non-English reports that were not cited in Medline (Table 1). Two of the references were for the English abstract[23] and the Danish report[24] of the same study; our review of this study was based on the English report and our e-mail communication with the first author (March 2004). Another study[25] had only an abstract available in English; our review of this study was based on e-mail communication with the study's first author (March 2004).

Of the 6 studies, only 1[4] used Wessel's criteria to define IC (Table 1). The remaining studies used definitions that ranged from less-stringent variations of Wessel's criteria[26] to definitions that would suggest excessive crying and not necessarily colic.[27,28] These distinctions are noteworthy, because relatively small differences in definitions can result in considerable variability in the estimated prevalence of IC and can also result in the identification of different subsets of infants and corresponding risk groups.[29,30]

Studies of Excessive Crying

In a cross-sectional study of 253 infants examined at routine health surveillance visits at 3 months of age, Said et al[27] investigated the associations between smoking of ≥1 cigarette per day by either parent and regular crying with apparent pain after feeding and crying for ≥2 hours in the early evening. Mothers were interviewed, and information on socioeconomic status, parity, birth weight, delivery conditions, feeding method, education, and parents' smoking habits was collected. In bivariate analyses, smoking of ≥1 cigarette per day by either parent, socioeconomic status, and feeding method were all associated with apparently painful crying after feeding (clinical indices were not reported) ($P < .001$, χ^2 test). The association between parental smoking and crying after feeding remained significant after controlling for socioeconomic status and feeding method; however, the analytic strategy in the study was not well described. There was no association between parental smoking and crying in the early evening. This study also found that, among infants of mothers who did not smoke, there was a positive association between the extent of paternal smoking and the likelihood of colic. Although these findings are suggestive, this study over-relied on exploratory statistical methods, to the exclusion of more-appropriate multivariate methods. Moreover, the lack of relative measures of risk makes it difficult to determine the public health significance of the reported association between parental smoking and regular crying in the early evening.

In a second cross-sectional study, the link between colic-like behaviors and parental smoking was examined among a convenience sample of 80 infants.[28] Visiting nurses in Stockport, England, recruited parents of 2 infants from their caseload, 1 who exhibited "nonspecific colic-like" behavior and 1 who did not. These nurses judged infants to be colicky or to have been colicky during the preceding few months on the basis of a list of colic symptoms provided by the investigators, which apparently included crying despite all basic needs being met, continuous crying for extended periods, and not being particularly pacified by handling and cuddling (the symptoms included in the questionnaire were not specified in the article; however, the introduction to the study suggested that these were the queried symptoms). The parents of the infants reported the number of cigarettes smoked in the home. In bivariate analyses, no association was found between the number of cigarettes smoked at home and colic-like behavior; multivariate analyses were not conducted. However, the small sample size and poor assessment of symptoms make these findings suspect.

In a third cross-sectional study, a random sample of 16% of women who gave birth in Norway in 1985 reported at 4 months after the birth, via mailed questionnaire, their demographic characteristics, postpartum smoking habits, breastfeeding, and infant disorders.[23] Among mothers who smoked ≥5 cigarettes per day, 40% of breastfed infants exhibited excessive crying for more than 2 to 3 hours per day at least 4 days per week, compared with 26% of infants' of nonsmokers ($P < .05$). This association was independent of maternal education and socioeconomic status. This association was not observed among bottle-fed infants. In this study, the combination of smoking and breastfeeding was associated with a 50% increase in the incidence of excessive crying, whereas no association was found with the 2 factors separately. This was a well-designed, population-based study; however, the lack of relative measures of risk makes it difficult to draw inferences regarding the public health significance of the findings.

The fourth study was a retrospective investigation of a randomly selected sample of Danish children born in the autumn of 1995.[25] Personal interviews were conducted with mothers at their homes when the infants were either 8 or 36 weeks of age. Eighty-seven percent of the mothers in the sample answered an extensive battery of questions, including questions on pregnancy complications, type of feeding, emotional health, and current number of cigarettes smoked per day. Mothers were also asked if their infants had had an "attack" of colic. Mothers who smoked ≥15 cigarettes per day were more likely than others to report that the infant had had an attack of colic (risk ratio [RR]: 1.30; 95% confidence interval [CI]: 1.05-1.61). This was a well-designed, population-based study. Although the study was retrospec-

TABLE 1. Existing Studies of Maternal Smoking and IC

Study	Study Design	Case Definition	Covariates	Exposure	Reported Results, RR* (95% CI)
Studies of excessive crying					
Said et al, 1984[27]	Cross-sectional study of 253 infants examined at routine pediatric consultation at 3 mo of age	"Postprandial colic" defined as crying after meals and appearing to be in pain or agitated; "evening colic" defined as crying for ≥2 h in early evening	Parity, birth weight, method of delivery, feeding method; demographic and socioeconomic background	Either parent smoked ≥1 cigarettes/d	Association with postprandial colic but not with evening colic
Haggart and Giblin, 1988[28]	Cross-sectional study of 80 infants visited by health visitors in Stockport, England	"Nonspecific colic-like behavior," as reported by parents	No covariates were included in analyses	Either parent smoked ≥1 cigarettes; time unit not specified	No association
Matheson and Rivrud, 1989[23]†	Cross-sectional survey of random sample of 885 women who gave birth in Oslo, Norway, in 1985	Excessive crying by normal babies for ≥2 h/d for ≥4 d/wk	Feeding type, coffee intake, infant disorders, demographic characteristics	Maternal smoking (postpartum), ≥5 cigarettes/d; 2 estimates: 1) bottle-fed babies, 2) breast-fed babies	1) No association,‡ 2) 1.54 (significant)§
Christoffersen 1998[25]‖	Cross-sectional survey of 5998 children drawn at random among all Danish children born between September 15 and October 31, 1995	Mothers' affirmative response to the question, "Did the child have daily attacks of colic?"	Marital status, age at first birth, delivery complications, current age of >35 y, maternal stress, muscular rheumatism, type of feeding, socioeconomic background	≥15 cigarettes/d	1.30 (1.05–1.62)
Studies of IC					
Reijneveld et al, 2000[26]	Cross-sectional survey of national sample of 3345 infants (1–6 mo of age) in the Netherlands	≥3 h of crying/d for ≥3 d during the previous week	Obstetric history, type of feeding, demographic and socioeconomic background	Maternal smoking (postpartum), 1) <15 cigarettes/d, 15–50 cigarettes/d	1) 1.50 (0.97–2.29), 2) 2.21 (1.24–3.92)
Sondergaard et al, 2001[4]	Prospective follow-up study of 1820 singleton infants delivered by Danish mothers between May 1991 and February 1992	Cases were identified by mothers (86%) or health visitors (14%); case definition for mothers: several hours of crying per day for several days; case definition for health workers: ≥3 h of crying/d on ≥3 d/wk for ≥3 wk or ≥1.5 h of crying/d on 6–7 d	Medical and obstetric history, alcohol and caffeine intake, psychologic distress during pregnancy, type of feeding, marital status, education	≥15 cigarettes/d, 1) during pregnancy, 2) after the birth, 3) during pregnancy and after the birth	1) 2.5 (1.4–3.2), 2) 2.0 (1.3–3.1), 3) 1.5 (1.1–2.0)

* RR comparing infants exposed to smoking with nonexposed infants.
† Also appears as Nylander and Matheson, 1989[24] (only the abstract is available in English).
‡ RR estimated on the basis of the report of no association between maternal smoking and colic among bottle-fed babies. Information for estimating CIs was not available.
§ RR estimated on the basis of the following report: among breast-fed babies, 40% of exposed infants vs 26% of nonexposed infants had colic ($P = .05$). Information for estimating CIs was not available.
‖ Only the abstract is available in English. Reported information is based on personal communication.

tive in design, recall bias was an unlikely source of bias, because questions regarding smoking were included among many other health-related questions.

The studies reviewed thus far relied on the parents' perceptions of the severity of their infants' crying. Parents' perceptions of their children's crying has important practical implications, because such perceptions, independent of a medical diagnosis, often motivate concerned calls to the pediatrician and even visits to the emergency department. However, to establish links between potential antecedents and an outcome such as IC, it is important to have uniform definitions among studies. This can be achieved by using a widely accepted definition, such as Wessel's. To date, only 2 studies have used this definition, both of which were well-designed, population-based studies.

Studies of Colic

In a population-based, retrospective study conducted in the Netherlands between 1997 and 1998,[26] physicians and nurses interviewed mothers of a nationally selected sample of infants, 1 to 6 months of age, regarding smoking, colic, and a host of related variables. IC was defined, on the basis of a modification of Wessel's criteria, as crying for ≥3 hours per day on >3 days in the week preceding the interview. Among completely formula-fed infants, maternal smoking of ≥15 cigarettes was associated with colic (RR: 1.8; 95% CI: 1.2–2.7), independent of socioeconomic status, obstetric history, and age of the infant.

Finally, in a population-based prospective study,[4] mothers who delivered a singleton infant between May 1991 and February 1992 at a regional Danish hospital and who still resided in the region 8 months after the birth answered either self-administered or health visitor-administered questionnaires on sociodemographic factors, their pregnancy, and postpartum health-related behaviors, including smoking. In the self-administered questionnaires, colic was defined as several hours of crying per day for several days with legs drawn up toward the abdomen, distended abdomen, and excessive flatus. For health visitors, colic was defined as at least 3 hours of crying per day for at least 3 days per week for >3 weeks or >1.5 hours of crying per day in 6 out of 7 days and included the characteristic behaviors of drawn-up legs, abdominal distention, and excessive flatus. Compared with infants of nonsmokers, infants of mothers who smoked at least 15 cigarettes during pregnancy had a twofold increase in their risk of IC (RR: 2.1; 95% CI: 1.4–3.2). Infants of mothers who smoked after the birth but not during pregnancy were also twice as likely to have colic (RR: 2.0; 95% CI: 1.3–3.0). Surprisingly, infants of mothers who smoked both during pregnancy and after the birth were only 50% more likely to have colic, compared with infants of nonsmokers (RR: 1.5; 95% CI: 1.1–2.0).

In sum, there seems to be a link between maternal smoking and excessive crying as well as IC. With 1 exception, these studies suggest this link to be independent of feeding type. To date, only 1 study has considered both prenatal and postnatal exposure to tobacco smoke. There are currently no studies in which exposure to environmental tobacco smoke (ETS) has been directly measured and quantified.

PHYSIOLOGIC LINK BETWEEN MATERNAL SMOKING AND IC

Recent studies of the GI system provide strong but indirect corroborating evidence suggesting physiologic pathways through which maternal smoking can be linked to IC. This physiologic evidence can be outlined as follows: (1) smoking is linked to increased plasma and intestinal motilin levels and (2) higher-than-average levels of motilin are linked to elevated risks of IC.

GI Activity Among Humans and Motilin

GI activity among humans consists of 2 major contractile states, ie, the digestive and interdigestive states.[31,32] In the digestive state, repetitive contractions occurring simultaneously at all levels of the intestine mix and churn the nutrients with secretions and repeatedly present nutrients to the GI mucosa. The interdigestive or fasting state is characterized by the migrating motor complex (MMC), which consists of 3 phases. Phase I is a 15- to 60-minute period with little or no contractile activity, which is followed by a 15- to 60-minute period of intermittent and irregular contractions (phase II). Phase II is followed by a series of intense phasic contractions lasting ~5 minutes (phase III), which completes the MMC cycle.

Motilin, a 22-amino acid hormone, is produced in the duodenal and jejunal mucosa and is present throughout the GI tract of humans and other species.[33] Experimental evidence shows that intravenous infusion of the GI hormone motilin induces phase III activity.[31] In particular, motilin stimulates gastric and intestinal motility by inducing interdigestive phase III antral and duodenal MMC.[34] The only known function of motilin is initiation of the MMC.[35]

Motilin is released cyclically every 90 minutes in the fasting state. The highest plasma motilin levels are seen during fasting, when the average adult level is 72 ± 6 pmol/L, although individual levels vary over a wide range.[36] Gut hormones are present early in fetal development, and adult patterns of motilin distribution in the GI tract are evident by 20 weeks of gestation. Fetal plasma motilin levels are ~60% of maternal levels by 18 to 22 weeks of gestation. However, MMC is seldom seen before 32 weeks of gestation, suggesting that motilin receptor cells do not mature until late in the third trimester. Motilin levels in infancy are much higher than adult levels, with average preprandial levels of 172 ± 33 pmol/L and an average postprandial trough of 68 ± 12 pmol/L by day 13, and decrease with age.[37] Serum levels also differ according to feeding type. Average basal serum motilin levels are higher for formula-fed infants than for breastfed infants (65 ± 44 pmol/L vs 32 ± 8 pmol/L).[15]

Recently, motilin receptor cells were isolated from the human stomach, duodenum, and colon. This suggests that motilin acts directly on smooth muscle cells. In addition to motilin's direct effects on smooth muscle, changes in motilin levels are partly under the control of the vagus nerve.[38,39] Motilin receptors

have been found in the postrema area and on the vagus nerve. Animal studies suggest both local and vagally mediated control of motilin concentrations.[40] It is also known that vagus nerve stimulation increases both the number and force of MMC contractions. Therefore, vagal stimulation of motility may be mediated by motilin. This suggests that the difficulty of comforting colicky infants may be partly the result of a self-perpetuating cycle of increased GI motility, continued crying, and, as a result of vagal stimulation, even higher plasma motilin levels.

It is also noteworthy that input from the vagal complex (cranial nerves IX–XII) and the phrenic and thoracic nerves to the intrinsic muscles of the larynx determine acoustic characteristics of the cry.[41] Several studies have shown alterations in acoustic cry characteristics among infants with colic.[42,43] It has been suggested that the vagal complex may provide the neurophysiologic link between spasms in the GI tract and changes in acoustic cry characteristics associated with colic.[44]

Overall, the role of motilin in the central nervous system remains speculative, and there are conflicting reports of vagal stimulation both inhibiting and stimulating the release of motilin.[45,46] It is quite possible that several mechanisms are responsible and that motilin release is dependent on the equilibrium between stimulating and inhibiting factors.[47]

Linkage of Exposure to Tobacco Smoke With Elevated Plasma Motilin Levels

Two studies have examined the effects of smoking on serum motilin levels; both found a positive association between smoking and plasma motilin levels. In a study by Bell et al,[48] heavy smokers, during the course of 1 hour, smoked either 4 high-nicotine cigarettes or 4 low-nicotine cigarettes. Smoking high-nicotine cigarettes, compared with low-nicotine cigarettes, resulted in significantly higher motilin levels and also in shortening of phase I and II of MMC. Beyond its acute effects, smoking seems to have chronic effects on motilin levels. In a second study designed to determine whether high motilin levels are related to smoking habits or only to acute nicotine exposure, serum motilin concentrations of fasting smokers who abstained from smoking for at least 10 hours were compared with serum motilin levels of fasting nonsmokers. Smokers had significantly higher motilin levels than did nonsmokers.[49] These studies provide strong but preliminary evidence that smoking is linked to increased plasma motilin levels.

Linkage of High Intestinal Motilin Levels With Higher Risk of Colic

Motilin is known to reduce the small-intestinal transit time in humans and animals. Motilin is actively involved in the change in motility in rabbits with induced colitis.[39] Plasma motilin levels are also significantly elevated among human patients with inflammatory bowel disease or Crohn's disease.[31,50] These findings are consistent with evidence that implicates motilin in diarrheal diseases.[51,52]

Among humans, there is evidence that colicky infants have higher serum motilin levels than do infants without colic. In a hospital-based, case-control study, Lothe et al[51] examined serum levels of 3 gut hormones, ie, motilin, gastrin, and vasoactive intestinal peptide. Case subjects were 40 infants with colic (age: 2–22 weeks), and control subjects were 42 healthy, age-matched infants (age: 3–36 weeks). The following important findings emerged from this study: (1) formula-fed infants, irrespective of colic status, had higher serum motilin levels than did breastfed infants; (2) infants with colic had significantly higher serum motilin levels than did similarly fed control subjects; and (3) vasoactive intestinal peptide and gastrin levels were not elevated, suggesting some specificity with respect to the role of motilin.

In a prospective study of 78 infants born during 1 month in 1986 at a Swedish hospital,[15] motilin levels for 1-day-old neonates who later developed colic were higher than those for infants who did not develop colic. This is particularly noteworthy because elevated motilin levels occurred before the onset of any colic symptoms. In this study, formula-fed infants had higher basal motilin levels than did breastfed infants, irrespective of colic status, and there were no differences between motilin levels of mothers of colicky infants and those of mothers of infants without colic. The authors speculated that the increased motilin levels were "caused by an affectation of the gut present already at birth."[15(p414)]

In sum, evidence suggests that infants with colic have higher motilin levels independent of feeding type, an association that is consistent with evidence that motilin levels are increased in disorders associated with GI dysregulation. Although these findings from disparate fields provide a cohesive model (Fig 1) for the physiologic pathway linking maternal smoking with IC, the entire chain of events has not yet been examined among a single cohort, nor has the link between maternal smoking and IC been replicated in a study that simultaneously considers all sources of prenatal and perinatal exposure to tobacco smoke.

CONSIDERATIONS FOR FUTURE STUDIES

Ideal Study Design

A prospective study begun in pregnancy and continuing through the first 4 months of life could provide definitive evidence linking these disparate lines of research. Assessment of all sources of tobacco exposure would require 2 interviews. Ideally, the first interview to assess maternal smoking during pregnancy would occur at the hospital (before the onset of colic), where it would also be possible to collect cord blood for the measurement of motilin levels. A more in-depth interview conducted 4 to 8 weeks later at home would allow diagnosis of colic and collection of information on maternal smoking, feeding patterns, and other confounding variables.

Comprehensive Assessment of Tobacco Exposure

Infants can be exposed to tobacco smoke and its metabolites while in utero, through breastfeeding,

and through exposure to ETS after birth. Accurate estimation of infants' exposure to cigarette smoke and its metabolites is contingent on consideration of all 3 sources of exposure. The first source is in utero exposure. Throughout pregnancy, nicotine is readily transferred across the placenta; consequently, fetuses of mothers who smoke are exposed to relatively higher nicotine concentrations than are their mothers.[53–55] Exposure can be assessed with standard questionnaires on smoking, and results can be validated with measurements of serum cotinine levels for a randomly selected group of participants.[56] The second source is breastfeeding. Because of its lipophilic nature, nicotine is readily found in human milk, at concentrations that can be 3 times as high as those in the blood; because nicotine is absorbed orally, the infant of a smoking mother is exposed to significant amounts of nicotine if breastfed.[57–60] When the infant is formula fed, it is important to note the formula type. The third source is ETS exposure after birth. There is a significant positive association between passive smoking during pregnancy and neonates' nicotine and cotinine levels, which can be as high as those found among infants of mothers who are light smokers.[61–64] ETS exposure can be assessed with standard questionnaires.[65] Ideally, a randomly selected subsample of participants could receive an additional visit ~1 week before the home visit, for the purpose of placing an ETS monitor next to the newborn's crib. Data collected from the air monitors could be used to validate data from the questionnaires.

Measurement of Motilin

Serum motilin levels vary according to the volume, type, and acid and fat contents of oral intake and the time of measurement in relation to the last meal. Therefore, it would be ideal to extract motilin from cord blood, which is readily available from umbilical cord stumps routinely collected in the delivery suite. In addition, some women who refrain from smoking during pregnancy may begin to smoke after the birth. For this reason, and because of the possibility of ETS exposure, it would be necessary also to measure infants' motilin levels after birth. It would be preferable to assess infants' motilin levels at 4 to 8 weeks of age, to coincide with the time of peak incidence of colic. For this measurement, whole blood could be collected via heelstick. To account for the covariation between amount and time of feeding and serum motilin levels, the time and amount of each infant's last feeding must also be ascertained.

Diagnosis of Colic

It is important to diagnose colic on the basis of objective standards and continuous units of measurement. By asking for objective information, such as the number of hours the child cries on any given day, without reference to colic, researchers can minimize problems pertaining to the social desirability of the mother's responses. The Colic Symptom Checklist, a useful instrument that has been used in related work,[42–44] allows quantitative measurement of the severity of colic symptoms and provides an overall score for the number of colic symptoms. The accuracy of a diagnosis of colic would be enhanced with information on competing diagnoses, the most prevalent of which is probably reflux; this is both because some reflux symptoms overlap with those of colic and because the incidence of reflux is linked to exposure to tobacco smoke.[4–6] Reflux can be diagnosed with a readily available instrument.[66]

Confounding Variables

Because the hypothesis is that colic is at least partly a physiologic disorder, it would be useful to rule out related problems (in particular, a maternal history of GI problems). The mother's and infant's use of erythromycin, a motilin agonist that can influence motilin levels, must also be assessed. Maternal stress and mood would be useful to assess, preferably with structured instruments.[67,68] Sociodemographic variables must also be assessed. Key among these variables are those related to parenting skills and resources, such as parity and mother's age.

CONCLUSIONS

In the United States, nearly one-half of all women smokers continue to smoke during their pregnancies.[69] This amounts to ~12% of all women who give birth.[70] More than 500 000 infants each year are exposed to cigarette smoke in utero. Moreover, it is estimated that 50% to 80% of employed adults have regular exposure to ETS and that >30% of nonsmokers live with smokers.[71] This is an important source of exposure, because breast milk of nonsmoking women can contain nicotine if the women are exposed to ETS.[60] Although cotinine levels are lower among infants nursed by passive smokers, compared with active smokers, neither nicotine nor cotinine is found in the plasma of infants nursed by nonsmokers without ETS exposure, indicating that ETS exposure alone results in exposure of infants to nicotine through breast milk.[72] The home is an important source of ETS. It is conservatively estimated that 40% of all US children <5 years of age are regularly exposed to tobacco smoke after birth, through someone in the household.[73]

Tobacco exposure, and its physiologic consequences outlined above, could have important effects on child growth and development. Colic in infancy has potentially long-lasting effects on both the mother-child dyad and the entire family. For example, in at least 1 study, children identified as having crying and feeding problems during infancy were more likely to be perceived as vulnerable and having behavior problems at 3 1/2 years of age. In this study, there was some indication that those who were more severely affected were also more likely to experience later adverse effects.[74] Infants with colic may also have more sleep problems, both during the colic period and after the colic has resolved,[75] as well as more feeding difficulties.[9] A longitudinal follow-up study showed that infants who had colic at 3 months displayed more sleep difficulties and temper tantrums at 3 years of age, compared with children who did not have colic.[76,77]

As distressing as IC may be for the infant, colic is also quite distressing for the caretaker. Caretakers of infants with colic have been reported as exhausted,[78] depressed, and angry.[79] These feelings can be expected to influence the strength of the mother-child bond during a critical period of development. To the extent that mothers of colicky infants provide fewer positive responses to their infants, relative to the mothers of noncolicky infants,[80–82] colic may hinder mother-child attachment, with serious long-term consequences for the mother-infant dyad[44] and the entire family unit.[83] Preventing colic can improve caregiver's feelings of self-assurance. If, as we suspect, exposure to cigarette smoke increases the risk of colic, then this would provide additional incentives to parents to abstain from smoking. Decreased exposure to tobacco smoke can be expected to provide widespread, long-term, health benefits to maternal and child populations.[84,85]

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REFERENCES

1. Uvnas-Moberg K. The gastrointestinal tract in growth and reproduction. *Sci Am.* 1989;261:78–83
2. Shenassa E. Delivering the goods: the relevance of classification accuracy to the design of community intervention and prevention programs. *J Community Psychol.* 2002;30:197–210
3. Kadakia SC, Kikendall JW, Maydonovitch C, Johnson LF. Effect of cigarette smoking on gastroesophageal reflux measured by 24-h ambulatory esophageal pH monitoring. *Am J Gastroenterol.* 1995;90:1785–1790
4. Sondergaard CH, Henriksen TB, Obel C, Wisborg K. Smoking during pregnancy and infantile colic. *Pediatrics.* 2001;108:342–346
5. Shabib SM, Cutz E, Sherman PM. Passive smoking is a risk factor for esophagitis in children. *J Pediatr.* 1995;127:435–437
6. Smit CF, Copper MP, van Leeuwen JA, Schoots IG, Stanojcic LD. Effect of cigarette smoking on gastropharyngeal and gastroesophageal reflux. *Ann Otol Rhinol Laryngol.* 2001;110:190–193
7. Martin AJ, Pratt N, Kennedy JD, et al. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics.* 2002;109:1061–1067
8. Rahal PS, Wright RA. Transdermal nicotine and gastroesophageal reflux. *Am J Gastroenterol.* 1995;90:919–921
9. Barr RG. Colic. In: Walker WA, Durie P, Hamilton J, Walker-Smith J, Watkins J, eds. *Pediatric Gastrointestinal Disease: Pathophysiology, Diagnosis, and Management*. 2nd ed. St. Louis, MO: Mosby-Year Book; 1996:241–250
10. Wessel M. Paroxysmal fussing in infants, sometimes called "colic." *J Pediatr.* 1954;14:421–423
11. Lucassen PL, Assendelft WJ, van Eijk JT, Gubbels JW, Douwes AC, van Geldrop WJ. Systematic review of the occurrence of infantile colic in the community. *Arch Dis Child.* 2001;84:398–403
12. Carey WB. "Colic": primary excessive crying as an infant-environment interaction. *Pediatr Clin North Am.* 1984;31:993–1005
13. Illingworth R. Three months colic. *Arch Dis Child.* 1954;29:165–174
14. Crowcroft NS, Strachan DP. The social origins of infantile colic: questionnaire study covering 76,747 infants. *BMJ.* 1997;314:1325–1328
15. Lothe LI, Ivarson S-A, Ekman R, Lindberg T. Motilin and infantile colic. *Acta Paediatr Scand.* 1990;79:410–416
16. Stahlberg MR. Infantile colic: occurrence and risk factors. *Eur J Pediatr.* 1984;143:108–111
17. Evans RW, Fergusson DM, Allardyce RA, Taylor B. Maternal diet and infantile colic in breast-fed infants. *Lancet.* 1981;1:1340–1342
18. Liebman WM. Infantile colic: association with lactose and milk intolerance. *JAMA.* 1981;245:732–733
19. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics.* 1982;70:7–10
20. Lothe L, Lindberg T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double blind crossover study. *Pediatrics.* 1989;83:262–266
21. Jakobsson I, Lindberg T. Cow's milk as a cause of infantile colic in breast-fed infants. *Lancet.* 1978;2:437–439
22. Bock SA, Sampson HA. Food allergy in infancy. *Pediatr Clin North Am.* 1994;41:1047–1067
23. Matheson I, Rivrud GN. The effect of smoking on lactation and infantile colic. *JAMA.* 1989;261:42–43
24. Nylander G, Matheson I. Breast feeding: effects of smoking and education [in Norwegian]. *Tidsskr Nor Laegeforen.* 1989;109:970–973
25. Christoffersen M. *Spaedbarnsfamilien*. Copenhagen, Denmark: The Danish National Institute of Social Research; 1998
26. Reijneveld SA, Brugman E, Hirasing RA. Infantile colic: maternal smoking as potential risk factor. *Arch Dis Child.* 2000;83:302–303
27. Said GP, Patois E, Lellouch J. Infantile colic and parental smoking. *Br Med J.* 1984;289:660
28. Haggart M, Giblin MJ. Passive smoking and colic-like behavior in babies. *Health Visit.* 1988;61:81–82
29. Reijneveld SA, Brugman E, Hirasing RA. Excessive infant crying: the impact of varying definitions. *Pediatrics.* 2001;108:893–897
30. Reijneveld SA, Brugman E, Hirasing RA. Excessive infant crying: definitions determine risk goups. *Arch Dis Child.* 2002;87:43–44
31. Depoortere I. Motilin and motilin receptors: characterization and functional significance. *Verh K Acad Geneeskd Belg.* 1999;29:511–529
32. Johnson LR, ed. *Gastrointestinal Physiology*. 5th ed. St. Louis, MO: Mosby-Year Book; 1997
33. Jadcherla SR, Klee G, Berseth CL. Regulation of migrating motor complexes by motilin and pancreatic polypeptide in human infants. *Pediatr Res.* 1997;42:365–369
34. Milla P. Effects of regulatory gut peptides on basic function of the normal GI tract. In: Heinz-Erain P, Deutsch J, Granditsch G, eds. *Regulatory Gut Peptides in Pediatric Gastroenterology and Nutrition*. Basel, Switzerland: Karger; 1992:70–83
35. Christofides ND, Bloom SR, Besterman HS, Adrian TE, Ghatei MA. Release of motilin by oral and intravenous nutrients in man. *Gut.* 1979;20:102–106
36. Mitznegg P, Bloom SR, Christofides N, Besterman H, Domschke W, Domschke S, Wunsch E, et al. Release of motilin in man. *Scand J Gastroenterol.* 1976;11(suppl):53–56
37. Lucas A, Adrian TE, Christofides N, Bloom SR, Aynsley-Green A. Plasma motilin, gastrin, and enteroglucagon and feeding in the human newborn. *Arch Dis Child.* 1980;55:673–677
38. Feighner SD, Tan CP, McKee KK, et al. Receptor for motlin identified in the human gastrointestinal system. *Science.* 1999;284:2184–2188
39. Depoortere I, van Assch G, Thijs T, Geboes K, Peeters TL. Differential changes in ACh-, motilin-, substance P-, and K^+-induced contractility in rabbit colitis. *Am J Physiol.* 1999;277:G61–G68
40. Chung SA, Greenberg GR, Diamant NE. Relationship of postprandial motilin, gastrin, and pancreatic polypeptide release to intestinal motility during vagal interruption. *Can J Physiol Pharmacol.* 1992;70:1148–1153
41. Lester BM. Developmental outcome prediction from acoustic cry analysis in term and preterm infants. *Pediatrics.* 1987;80:529–534
42. Lester BM. Infantile colic: acoustic cry characteristics, maternal perception of cry and temperament. *Infant Behav Dev.* 1992;15:15–26
43. Zeskind PS, Barr RG. Acoustic characteristics of naturally occurring cries of infants with "colic." *Child Dev.* 1997;68:394–403
44. Lester B, Boukydis C, Garcia-Coll C, Hole W. Colic for developmentalists. *Infant Ment Health J.* 1990;11:321–333
45. Heinz-Erain P. Regulatory gut peptides in normal children. In: Heinz-Erain P, Deutsch J, Granditsch G, eds. *Regulatory Gut Peptides in Pediatric Gastroenterology and Nutrition*. Basel, Switzerland: Karger; 1992;103–114
46. Kitazawa T, Ishii A, Taniyama K. The Leu13-motilin (KW-5139)-evoked release of acetylcholine from enteric neurones in the rabbit duodenum. *Br J Pharmacol.* 1993;109:94–99
47. Goll R, Nielsen SH, Holst JJ. Regulation of motilin release from isolated perfused pig duodenum. *Digestion.* 1996;57:341–348
48. Bell JS, DiMagno EP, Go VLW. Cigarette smoking alters the human interdigestive migrating motor complex. *Clin Res.* 1981;39:303A
49. Hanson M, Almer L-O, Ekman R, Janzon I, Trell E. Motilin response to a glucose load aberrant in smokers. *Scand J Gastroenterol.* 1987;22:809–812
50. Annese V, Bassotti G, Napoliatna G, Usai P, Andriulli A, Vantrappen G. Gastrointestinal motility disorders in patients with inactive Crohn's disease. *Scand J Gastroenterol.* 1997;32:1107–1117

51. Lothe L, Ivarsson SA, Lindberg T. Motilin, vasoactive intestinal peptide and gastrin in infantile colic. *Acta Paediatr Scand.* 1987;76:316–320
52. Besterman HS, Christofides ND, Welsby PD, Adrian TE, Sarson DL, Bloom SR. Gut hormones in acute diarrhoea. *Gut.* 1983;24:665–671
53. Levin E, Slotkin T. Developmental neurotoxicity of nicotine. In: Slikker W Jr, Chang W, eds. *Handbook of Developmental Neurotoxicology*. San Diego, CA: Academic Press; 1998;587–615
54. Navarro HA, Seidler FJ, Eylers JP, et al. Effects of prenatal nicotine exposure on development of central and peripheral cholinergic neurotransmitter systems: evidence for cholinergic trophic influences in developing brain. *J Pharmacol Exp Ther.* 1989;251:894–900
55. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. *J Am Acad Child Adolesc Psychiatry.* 2001;40:630–641
56. Lindqvist R, Lendhals L, Tollbom O, Aberg H, Hakansson A. Smoking during pregnancy: comparison of self reports and cotinine levels in 496 women. *Acta Obstet Scand.* 2002;81:240–244
57. Centers for Disease Control and Prevention. *Women and Smoking: A Report of the Surgeon General*. Atlanta, GA: Centers for Disease Control and Prevention; 2001
58. American Academy of Pediatrics, Work Group on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics.* 1997;100:1035–1039
59. Luck W, Nau H. Nicotine and cotinine concentrations in serum and urine of infants exposed via passive smoking or milk from smoking mothers. *J Pediatr.* 1985;107:816–820
60. Dahlstrom A, Lundell B, Curvall M, Thapper L. Nicotine and cotinine concentrations in the nursing mother and her infant. *Acta Paediatr Scand.* 1990;79:142–147
61. Koren G. Fetal toxicology of environmental tobacco smoke. *Curr Opin Pediatr.* 1995;7:128–131
62. Eliopoulos C, Klein J, Phan MK, et al. Hair concentrations of nicotine and cotinine in women and their newborn infants. *JAMA.* 1994;271:621–623
63. Ostrea EM Jr, Knapp DK, Romero A, Montes M, Ostrea AR. Meconium analysis to assess fetal exposure to nicotine by active and passive maternal smoking. *J Pediatr.* 1994;124:471–476
64. Makin J, Fried PA, Watkinson B. A comparison of active and passive smoking during pregnancy: long-term effects. *Neurotoxicol Teratol.* 1991; 13:5–12
65. Matt GE, Hovell MF, Zakarian JM, Bernert JT, Pirkle JL, Hammond SK. Measuring secondhand smoke exposure in babies: the reliability and validity of mothe reports in a sample of low-income families. *Health Psychol.* 2000;19:232–241
66. Orenstein SR, Shalaby TM, Cohn JF. Reflux symptoms in 100 normal infants: diagnostic validity of the infant gastroesophageal reflux questionnaire. *Clin Pediatr (Phila).* 1996;35:607–614
67. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987;150:782–786
68. Berry J, Warren J. The parental stress scale: initial psychometric evidence. *J Soc Pers Relat.* 1995;12:463–472
69. Ebrahim SH, Floyd RL, Merritt RK II, Decoufle P, Holtzman D. Trends in pregnancy-related smoking rates in the United States, 1987–1996. *JAMA.* 2000;283:361–366
70. Mathews TJ. Smoking during pregnancy in the 1990s. *Natl Vital Stat Rep.* 2001;49:1–14
71. Emmons KM, Abrams DB, Marshall RJ, et al. Exposure to environmental tobacco smoke in naturalistic settings. *Am J Public Health.* 1992;82: 24–28
72. Haustein KO. Cigarette smoking, nicotine and pregnancy. *Int J Clin Pharmacol Ther.* 1999;32:417–427
73. Overpeck M, Moss A. Children's exposure to environmental cigarette smoke before and after birth: health of our nation's children: US, 1988. *Adv Data.* 1991;18:1–11
74. Forsyth BW, Canny PF. Perceptions of vulnerability 3 1/2 years after problems of feeding and crying behavior in early infancy. *Pediatrics.* 1991;88:757–763
75. Weissbluth M. Sleep and the colicky infant. In: Guilleminault C, ed. *Sleep and Its Disorders in Children*. New York, NY: Lippincott Williams & Wilkins; 1987:129–140
76. Pinyerd B. Mother-infant interaction and temperament when the infant has colic. In: *Colic and Excessive Crying: Report of the 105th Ross Conference on Pediatric Research.* Columbus, OH: Ross Products Division, Abbott Laboratories; 1997:101–114
77. Rautava P, Lehtonen L, Helenius H, Sillanpaa M. Infantile colic: child and family three years later. *Pediatrics.* 1995;96:43–47
78. Jones JA. Can fussy babies be spoiled? *Pediatrics.* 1985;76:854–855
79. Brazelton TB. Crying in infancy. *Pediatrics.* 1962;29:579–588
80. Waldman W, Sarsgaard E. Helping parents to cope with colic. *Pediatr Basics.* 1983;33:12–14
81. Shaver B. Maternal personality and early adaptation as related to infantile colic. In: Shereslefsky P, Yarrow L, eds. *Psychological Aspects of a First Pregnancy and Early Postnatal Adaptation*. New York, NY: Raven Press; 1979:209–215
82. Shaw C. A comparison of the patterns of mother-baby interaction for a group of crying, irritable babies and a group of more amenable babies. *Child Care Health Dev.* 1977;3:1–12
83. Raiha H, Lehtonen L, Korhonen T, Korveranta H. Family life 1 year after infantile colic. *Arch Pediatr Adolesc Med.* 1996;150:1032–1036
84. Shenassa E, McCaffery J, Swan G, Khroyan T, Lyons M, Lerman C. Intergenerational transmission of tobacco use and dependence: a transdisiplinary perspective. *Nicotine Tob Res.* 2003;5(suppl 1):S55–S69
85. Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry.* 2003;160:1978–1984

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