Nicotine Replacement Therapy During Pregnancy and Infantile Colic in the Offspring

WHAT’S KNOWN ON THIS SUBJECT: Infantile colic affects almost 10% of all infants and is characterized by crying and fussing in an otherwise healthy and well-fed infant. Prenatal exposure to tobacco smoking is a risk factor, but it is unclear whether nicotine causes the association.

WHAT THIS STUDY ADDS: Infants exposed to nicotine replacement therapy during pregnancy had elevated infantile colic risk of the same magnitude as infants exposed to tobacco smoking. Intrauterine exposure to nicotine may play a causal role in the pathogenesis of infantile colic.

abstract

OBJECTIVE: To investigate the associations between use of nicotine replacement therapy (NRT) and smoking during pregnancy and infantile colic in the offspring.

METHODS: We used data from maternal interviews (from pregnancy and at 6 months post partum) from the Danish National Birth Cohort (1996–2002). We included 63 128 live-born singletons with complete information on nicotine exposure during pregnancy and infantile colic symptoms as recorded at 6 months of age.

RESULTS: A total of 46 660 infants (73.9%) were unexposed to nicotine during pregnancy, 207 (0.3%) were exposed to NRT, 15 016 (23.8%) smoked and used NRT had OR = 1.6 (1.0–2.5), smokers had OR = 1.3 (1.2–1.4), and women who both smoked and used NRT had OR = 1.6 (1.3–1.9). Partners’ smoking was not associated with infantile colic after adjustment for maternal smoking.

CONCLUSIONS: We corroborated the association between smoking and infantile colic after adjustment for several possible confounders in a large cohort study. Moreover, we found that infants exposed to NRT prenatally had an increased risk for infantile colic of the same magnitude as those exposed to tobacco smoke. Thus, nicotine may play a role in the pathogenesis of infantile colic.
Wessel defined infantile colic as paroxysms of crying and fussing for more than 3 hours per day for more than 3 days per week for more than 3 weeks in an otherwise healthy and well-fed infant.1 In Western countries up to 8% to 10% of infants fulfill this definition in the first 3 months of life. Infantile colic is generally considered a benign and self-resolving condition, yet it poses a burden on the affected families and may even trigger violent behavior toward the child.3 Causal hypotheses relate to a gastrointestinal or a neurodevelopmental origin, such as altered gut microflora,4,5 altered gastrointestinal motility,6 lactose intolerance,7,8 or a disorder in behavior regulation mechanisms.1,9 Some consider infantile colic as an outlier in the developmental variation.10−12 Maternal smoking has repeatedly been shown to increase the risk of infantile colic by a factor of almost 2,13−16 and this association does not seem to be confounded by maternal education, socioeconomic status, obstetric history, gestational age (GA), or birth weight (BW).13,17 Smoking cessation has become a priority in recent years for many Western countries, and the use of nicotine replacement therapy (NRT) has proven effective.18 U.S. Food and Drug Administration approved the first NRT (nicotine gum) in 1984, and the same year it became available over the counter in Denmark. An increasing number of pregnant women use NRTs19 because NRT is generally considered to be a better alternative than continued smoking. However, NRTs are characterized as drugs that may pose a risk to the fetus, and some studies question their use in pregnancy.19−21 Nicotine may be involved in the pathogenesis of infantile colic because it affects the gastrointestinal function6 as well as the development of the fetal central nervous system.22,23 Because NRTs release only nicotine, studying NRT users may be useful for examining whether the association between smoking and infantile colic is due to nicotine.

We therefore compare the association between intrauterine exposure to tobacco smoke and infantile colic with the possible association between NRT and infantile colic, on the basis of the hypothesis that any nicotine exposure would increase the risk of infantile colic.

METHODS

The Danish National Birth Cohort: Study Population

Our study was based on data from the Danish National Birth Cohort (DNBC), a nationwide population-based cohort of pregnant women recruited from 1996 to 2002.24 Approximately 50% of the pregnant population was invited by their general practitioner to join the cohort at the first antenatal visit, and nearly 60% of those consented.25 The original cohort included 101 042 pregnancies. The establishment of the original cohort was approved by the Danish Science Ethical Committee system (j.nr. [KF] 01-471/94). The current study was approved by the Danish Data Protection Agency (j.nr. 2009-41-3755).

Exposures during pregnancy, the mother’s health status, medical and obstetric history, lifestyle and diet, working and living conditions, psychological stress, and socioeconomic status were assessed in 2 computer-assisted telephone interviews at ∼17 and 32 gestational weeks (designated second- and third-trimester interviews, respectively). A similar interview concerning the last part of pregnancy and the infant’s behavior, development, nutrition, and frequency and duration of cry episodes was conducted when the child was 6 months old (postpartum interview).

Outcome Assessment

Infantile colic was reported by the mothers in the interview 6 months post partum, and identification of cases was based on the modified Wessel’s criteria: crying or fussing for more than 3 hours...
a day for more than 3 days a week. Because some infants had more than 1 period with crying and fussing, their first crying period had to start before the age of 3 months. The reported un-

Statistical Analysis

Infantile colic was modeled as a binary outcome using logistic regression, with prenatal exposure to smoking and NRT as the independent variables. We calculated odds ratio (OR) (with 95% confidence interval [CI]) for infantile colic in the offspring for the different exposures to nicotine. Statistical signifi-
cance was defined as 2-sided P value of <0.05.

We first estimated the risk of infantile colic among infants exposed prenatally to NRT, tobacco smoke, or both, using unexposed infants as a reference. We also identified a subgroup of NRT users who reported no smoking in both prenatal interviews and compared the risk of infantile colic in their offspring with the risk among unexposed infants. Because of the small number of exclusive NRT users we could not further stratify by type of NRT. Subsequently, we ana-

RESULTS

From the 101 042 pregnancies regist-
ered in the DNBC, a total of 92 676 resulted in singleton live births. Among those, 66 823 completed both the second-trimester and postnatal interviews with an assessment of nicotine use in pregnancy and symptoms of infantile colic in the offspring. The main analysis was based on first child in the cohort, ex-

Low BW has been associated with in-

fantine colic27 and is closely linked to GA. Because nicotine exposure is a risk factor for low BW and early delivery, these were considered potential in-

termediate variables and were not in-

cluded in the main analysis. To explore this further, we repeated all analyses restricted to infants born between 37 and 41 completed gestational weeks with a BW above 2500 g. Moreover, we performed regression analyses, adding BW and GA as a linear, as a poly-

nomial, and as a categorical variable.
and many of them (n = 255) combined smoking with a slow-release NRT (patch).

Mothers who smoked, exclusively or in combination with NRT, tended to be less educated, slightly younger, and more concerned about the current pregnancy and the health of their child (Table 1). Their infants were smaller at birth, more often exposed to environmental tobacco smoking and less often exclusively breastfed. All types of nicotine exposure were associated with higher coffee consumption. NRT users who did not smoke were similar to the nonsmokers on many characteristics.

A total of 4974 (7.9%) infants fulfilled the criteria for infantile colic. All 3 types of prenatal nicotine exposure were associated with elevated risk for infantile colic compared with unexposed (Table 2). Notably, the OR for infantile colic among infants exposed to NRT was comparable to that of infants exposed to tobacco smoke. Adjustment for the potential confounders had negligible impact on the point estimates, and including the socioeconomic status in the model left results unchanged. Similar associations between prenatal exposure to nicotine and infantile colic were found across strata of socioeconomic status (data not shown). The risk for offspring infantile colic among NRT users compared with nonsmokers remained elevated (OR = 1.5 [0.9–2.4]), when we restricted the analysis to the subgroup of NRT users who reported no smoking in both prenatal interviews (n = 176), but was nonsignificant.

An increasing number of cigarettes smoked per day was associated with an increasing risk for infantile colic (Table 3). For the combination variable, the highest OR was observed in women who smoked 5 to 9 cigarettes, alone (OR = 1.5 [1.3–1.6]) or in combination with NRT (OR = 1.8 [1.4–2.3]) (Fig 1).

In a subpopulation of 3658 pairs of siblings, 349 pairs were discordant for smoking exposure in pregnancy and 444 for infantile colic. However, only 46 pairs were informative, and this small number did not allow for meaningful comparisons.

Partners’ smoking was not associated with offspring infantile colic after adjustment for maternal exposure to nicotine (OR = 1.1 [1.0–1.1]; P = .10). Moreover, the positive association between maternal smoking and infantile colic was not modified by partners’ smoking habits (Table 3).

We observed results similar to those already presented in a secondary analysis restricted to children born between 37 and 41 completed gestational weeks with a BW above 2500 g (n = 53906). None of the reported results changed when BW was added to the model as a linear, a quadratic, or as a categorical term. The ORs for offspring infantile colic in mutually exclusive
groups of smokers (smoking in pregnancy and not during lactation, smoking only during lactation, continuous smoking during both pregnancy and lactation) were all higher than in non-smokers, with continuous smokers having a slightly higher OR for offspring infantile colic (data not shown).

**DISCUSSION**

Exposure to nicotine exclusively from NRT during pregnancy was associated with an increased risk of infantile colic in the infant of the same magnitude as cigarette smoking. This finding indicates that nicotine may be the component in tobacco smoke responsible for the increased risk for infantile colic.

Although this is 1 of the largest studies of NRT use in pregnancy, the number of exclusive NRT users was still limited, and some estimates have large CIs. The results are based on a large population-based follow-up study after adjusting for several covariates, and the exposure assessment was carried out prospectively during pregnancy, which precludes differential reporting in relation to the outcome.

Maternal smoking at any time during pregnancy was associated with increased risk for infantile colic in the offspring, as seen in most but not all studies. Some authors argue that the association between smoking and infantile colic is entirely attributable to uncontrolled confounding by factors related to smoking behavior, such as social class. In our study the 2 models, adjusted and unadjusted for socioeconomic status, yielded similar results. The magnitude of association between nicotine exposure and infantile colic was similar across strata of socioeconomic status categories. Furthermore, if the observed association is indeed confounded by lifestyle or any other unknown factors associated with smoking, we would expect maternal and partners’ smoking during pregnancy to be equally good proxy measures of these factors, which was not seen. The dose-response like association seen between level of nicotine exposure and risk for infantile colic might indicate a causal link. In addition, NRT users in our sample were quite similar to the unexposed population with respect to other characteristics, which reduces the risk of confounding. Even so, we cannot rule out unmeasured or residual confounding due to our observational study design.

Data did not allow us to distinguish between early, late gestational, and postnatal exposure to nicotine because most exposed women were exposed to some

**TABLE 2** Crude and Adjusted OR With 95% CIs for Infantile Colic According to Maternal Use of NRT and Tobacco Smoking During the First and Second Trimester of Pregnancy

<table>
<thead>
<tr>
<th>Nicotine Exposure</th>
<th>Infantile Colic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td>Unexposed</td>
<td>46 660</td>
</tr>
<tr>
<td>NRT users</td>
<td>207</td>
</tr>
<tr>
<td>Smokers</td>
<td>15 016</td>
</tr>
<tr>
<td>Smoking and NRT</td>
<td>1245</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reference group.

N, number; OR, adjusted for maternal age, first parity, daily coffee consumption, weekly consumption, and binge-drinking episodes; OR, further adjusted for couple’s combined educational and occupational status.

**TABLE 3** Crude and Adjusted OR With 95% CIs for Infantile Colic According to Level of Maternal Smoking and Partners’ Smoking Habits

<table>
<thead>
<tr>
<th>Level of Maternal Smoking&lt;sup&gt;c&lt;/sup&gt; (Cigarettes Per D)</th>
<th>Infantile Colic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
</tr>
<tr>
<td></td>
<td>Partner Nonsmoker</td>
</tr>
<tr>
<td>Unexposed</td>
<td>46 660</td>
</tr>
<tr>
<td>&lt;1</td>
<td>1066</td>
</tr>
<tr>
<td>1–4</td>
<td>2727</td>
</tr>
<tr>
<td>5–9</td>
<td>4616</td>
</tr>
<tr>
<td>10–14</td>
<td>3757</td>
</tr>
<tr>
<td>≥15</td>
<td>2707</td>
</tr>
</tbody>
</table>

Adjusted for maternal age, first parity, daily coffee consumption, weekly alcohol consumption, binge-drinking episodes, and couple’s educational and occupational status.

<sup>c</sup> Among non-NRT users.

<sup>b</sup> Reference group.
extent throughout and after the pregnancy. The association between smoking during the first and second trimester and infantile colic was weaker compared with smoking throughout pregnancy. The limited numbers and the lack of postnatal assessment did not allow for such a comparison among NRT users.

Women tend to change their smoking habits during pregnancy, and many have several attempts to quit and relapses, especially light smokers. By assessing nicotine exposure twice during pregnancy and by asking about the entire pregnancy up to the interview and not only the current status we expect to identify the majority of exposed infants. Indeed, very few nonsmokers changed their smoking status (n = 360) or NRT use (n = 3) after the second-trimester interview, and our results were similar regardless of whether their infants were coded as exposed or not. Some women may have discontinued their exposure late in pregnancy, but this would most likely lead to bias toward no association. Some of the observed association between NRT and infantile colic could be due to nonreported tobacco exposure among NRT users. However, when we restricted our analysis to women who reported to have remained tobacco-free during pregnancy, point estimates were unchanged for the association between NRT and infantile colic. Underreported smoking during pregnancy is possible, but women would probably disclose their NRT use because there is no public awareness of negative effects of NRT use to the fetus in Denmark. Nonjudgmental attitude of the interviewer combined with several questions addressing smoking as in the DNBC should facilitate a rather accurate disclosure.

Infantile colic was assessed after resolution of the symptoms, and the prevalence of infantile colic in our study was comparable to that reported by a prospective assessment in the same source population. We adjusted for relevant covariates that may affect perceptions of abnormal cry behavior, such as parity and social status. We furthermore attempted to use siblings as controls in the sibling subpopulation analysis, but the number of siblings discordant for exposure was insufficient.

CONCLUSIONS

The mechanisms responsible for the association between prenatal exposure to tobacco smoking and infantile colic are unknown, but our data indicate that nicotine may play a role. A causal role of nicotine in the pathogenesis of infantile colic is biologically plausible. Nicotine acts as a neurotransmitter to the nicotinic acetylcholine receptors and up-regulates them. It also modifies the function of serotonin receptors in the fetus and thus interferes with the actions of critical neurotransmitter signals in the developing brain. Similar receptors exist in the adult intestinal epithelial cells, and they were recently found to be involved in inflammatory conditions and diseases such as ulcerative colitis. Furthermore, nicotine causes vasoconstriction in the gastrointestinal system and increases serotonin secretion from the intestinal chromaffinic cells, stimulating gastrointestinal motility and secretion. Our study does not warrant a contraindication for using NRT for women who cannot stop smoking while pregnant but calls for more studies on the safety of NRT use in pregnancy.

REFERENCES

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