Maternal Cigarette Smoking and the Development of Necrotizing Enterocolitis

WHAT’S KNOWN ON THIS SUBJECT: Fetal factors that predispose infants to necrotizing enterocolitis (NEC) have been extensively studied. Maternal factors that may affect future risk for NEC are less clear.

WHAT THIS STUDY ADDS: We hypothesized that maternal factors were the primary cause of NEC. Through a case-control design we determined that maternal smoking predisposes infants to the development of NEC. Our results highlight the importance of smoking cessation in pregnancy.

abstract

BACKGROUND: The maternal variables that affect fetal development and correlate with necrotizing enterocolitis (NEC), the most common gastrointestinal emergency in premature infants, are not well defined. We hypothesized that maternal risk factors were the primary determinant of future development of NEC.

METHODS: Patients with NEC were identified from an established NICU database and were control-matched with 2 neonates treated at the same institution. The medical records of each patient during the NICU admission as well as the prenatal and delivery record of the patient’s mother were reviewed. Perinatal data, including maternal smoking, maternal hypertension, maternal BMI, maternal gestational diabetes, conduct of labor and type of delivery, Apgar scores, types of feedings, and placental pathology, were examined, with $P < .05$ deemed significant.

RESULTS: A total of 73 neonates diagnosed with NEC and 146 matched controls were identified. Medical records for each subject and their mothers were reviewed (438 records total). Maternal cigarette smoking was significantly associated with the future development of NEC ($P = .02$). Maternal gestational diabetes, maternal hypertension, formula feeding, and pathologic chorioamnionitis or uteroplacental insufficiency did not correlate with NEC.

CONCLUSIONS: These data identified maternal cigarette smoking as the only risk factor that is associated with the development of NEC in premature infants. Our data imply that smoking delivers toxins and nicotine to the uterine microenvironment that can affect microvascular development and may predispose the fetus to future NEC. Pediatrics 2012;130:78–82

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KEY WORDS smoking, pregnancy, necrotizing enterocolitis

ABBREVIATION

NEC—necrotizing enterocolitis

All authors listed have met criteria as authors of this final article. Each has made substantial contributions to the concept and design, acquisition of data and analysis, interpretation of the data, and the drafting and revising of the final content of the following article.

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Necrotizing enterocolitis (NEC) is the most common gastrointestinal emergency in neonates and is poised to become the leading cause of death in this population.² The search for risk factors for development of NEC has focused largely on postnatal events such as infection, hypothermia, and hypoxia. To this end, it has been determined that NEC occurs almost uniformly in premature infants, but other factors such as formula feedings, infection with certain bacterial pathogens, prolonged ventilation, and prenatal glucocorticoid exposure have been variably associated with NEC.³⁴ Although several well-designed prospective studies have not definitively determined which premature infants will develop NEC, few have evaluated the role of prenatal events in the ultimate outcome of the infant.³⁵⁶ We hypothesized that maternal variables are the primary factor that affect fetal development and that these correlate with future development of NEC. We specifically thought that maternal risk factors such as smoking, age, hypertension, high BMI, and gestational diabetes might predispose infants to develop NEC. We also wanted to evaluate the idea that placental insults such as chorioamnionitis or uteroplacental insufficiency may be present in infants who ultimately develop NEC. We correlated prenatal maternal variables and postnatal data in neonates with and without NEC by using a retrospective, paired-control design to assess the potential role of maternal factors in the development of NEC.

METHODS

After institutional review board approval (09.0337) was obtained, a preexisting database containing prospectively collected information of all infants hospitalized in the NICU at a single institution from 2004 to 2009 was queried. Patients were identified as cases (NEC) if they were classified in the database as having NEC and subsequent review of their medical record confirmed clinical or radiographic signs of NEC (ie, bloody stools, abdominal distension, thrombocytopenia, pneumatositis intestinalis, portal venous air, pneumoperitoneum).

Two control patients were selected from the database for each case patient and were matched for date of birth (<6 month difference), estimated gestational age (<1 week apart), and birth weight (<100 g difference). Maternal records for each case and control were obtained and reviewed, with particular attention given to known and suspected risk factors for later development of NEC (ie, smoking status, age, hypertension, BMI, and gestational diabetes).

Placental specimens of a selected group of NEC and control patients were reviewed by a blinded pathologist. Particular attention was paid to irregularities in vascular development, chorioamnionitis, and uteroplacental insufficiency. Chorioamnionitis was deemed “severe” if it included funisitis (neutrophils in the cord) or purulence. Uteroplacental insufficiency was defined as severe if it was described as having multiple infarcts, retroplacental hematomas >10% of surface area, or atherosis.

Univariate statistical analyses were performed by using unpaired t test for continuous variables and χ² analysis for categorical variables (Jandel SigmaPlot Version 11.1.0.102, Systat Software, Inc, San Jose, CA). The significance level was set at P < .05 a priori. The findings from the univariate analysis were confirmed with the multivariate general linear model (SPSS Version 19.0.0, IBM, Armonk, NY).

RESULTS

Seventy-three infants were identified with NEC, and 146 controls were selected after controlling for date of birth, estimated gestational age, and birth weight. Maternal records for all cases and controls were reviewed as well. Demographic information of the NEC and control patients is depicted in Table 1.

Table 2 shows the maternal and fetal factors thought likely to be associated with development of NEC based on our literature review. Of note, maternal smoking is the only risk factor significantly associated with future development of NEC (P = .02). Other commonly held risk factors, such as formula feeding, transfusions, low Apgar scores, gestational diabetes, and maternal hypertension, were not statistically significantly different among the 2 groups.

Table 3 shows our evaluation of the placental specimens of a select group of case NEC patients (n = 48) and control patients (n = 46). It is noteworthy that there were no differences in placental

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Demographic of Studied Patients With Associated Statistical Analyses</th>
</tr>
</thead>
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<tr>
<td>Neonatal Demographics</td>
<td>Control (n = 146)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>85</td>
</tr>
<tr>
<td>Female</td>
<td>61</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>78</td>
</tr>
<tr>
<td>Black</td>
<td>64</td>
</tr>
<tr>
<td>American Indian/Alaskan</td>
<td>0</td>
</tr>
<tr>
<td>Hispanic</td>
<td>2</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
</tr>
<tr>
<td>Fetal weight</td>
<td>1283.4 ± 52.1</td>
</tr>
<tr>
<td>Fetal height</td>
<td>36.7 ± 0.4</td>
</tr>
</tbody>
</table>

There were no significant differences between the Control and NEC groups. Numbers represent patients in each group, and variables are denoted by mean ± standard error of the mean (SEM).
demonstration of pathologic chorioamnionitis or uteroplacental insufficiency, regardless of severity, between the NEC and control groups.

DISCUSSION

This study is the first to definitively determine the association of maternal smoking with future development of NEC. By the design of this study, several factors that have previously been associated with future development of NEC, such as birth weight and gestational age, have been controlled for. In addition, we selected controls based on the approximate “era” of birth, such that, if significant changes in clinical care occurred over time, these changes should be inconsequential.

This study represents a novel evaluation of risk factors for NEC in that maternal factors are the primary determinants of outcome in this study. We used a case-control study design to maximize the likelihood that the maternal factors are the only different variables in the patients and therefore should be the critical determinants by which infants go on to develop NEC.

In addition, factors such as younger maternal age (<20 years of age, \( P = 0.08 \)) and formula feeding (\( P = 0.07 \)) near statistical significance. We limited our study population to those infants in a single NICU to facilitate acquisition of accurate records, but both of these factors might become statistically significant if we had a larger population.

Potential downsfalls in this study are that, although the information in the database is prospectively collected, it does require retrospective review to identify cases and controls. We tried to validate diagnoses of NEC and ensure that cases actually had NEC by evaluating their medical records and ensuring that they had clinical symptoms and objective signs of NEC, but retrospective determination of this information is certainly limited by the data that are available. Another potential downfall is that we did not investigate whether mothers were using a nicotine replacement program during pregnancy.

Placentas and the pathologic conditions associated with them have been an area of interest in neonatology. Chorioamnionitis has been studied as a potential correlate for the development of NEC. A recent study in 2009 examined placentas and patients who had clinically evident chorioamnionitis either limited to the placenta or extending to the fetus at delivery. They found that evidence of chorioamnionitis in the fetus increased the rate of NEC from 2% to 8%.

Of note, chorioamnionitis seemed to increase the risk of NEC only when it had invaded the fetal tissues. We did not specifically evaluate this in our review of the placentas.

There has been a strong interest in the vascular flow patterns to the placenta and the possible development of NEC or growth retardation. One study of 404 severely growth-retarded infants found no meaningful predictive value of prenatal Doppler studies of placental function for NEC.

The effects of nicotine and smoking on the developing placenta have long been of clinical interest. In 1985, Luck and colleagues described the transport of nicotine and 1 of its active metabolites, cotinine, across the placenta. They found that the human fetus is exposed to higher levels of nicotine than the mother, determining amniotic fluid and maternal serum nicotine levels and expressing this as a ratio. They described the level increase as a ratio of 1.54 (amniotic fluid/maternal vein serum levels) at 16 to 24 weeks’ gestation, meaning that the amniotic fluid had a nicotine concentration 1 ½ times that of the mother’s serum. The reason this is important is that the human fetus lacks keratinization during the second trimester; therefore, nicotine can easily be absorbed from the amniotic fluid into the fetus; in fact, nicotine is easily absorbed by adult human skin. This study overall showed that nicotine is concentrated in the amniotic

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**TABLE 2** Comparison of NEC-Affected and Control Patients, Maternal and Fetal Factors

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 48)</th>
<th>NEC (n = 75)</th>
<th>Test (( \chi^2 ))</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>46 (32%)</td>
<td>35 (48%)</td>
<td>( \chi^2 = 4.959 )</td>
<td>.026</td>
</tr>
<tr>
<td>Age, y</td>
<td>26.1 ± 0.5</td>
<td>24.7 ± 0.6</td>
<td>( t = -1.752 )</td>
<td>.081</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>12 (8.2%)</td>
<td>2 (2.7%)</td>
<td>( \chi^2 = 1.612 )</td>
<td>.204</td>
</tr>
<tr>
<td>Hypertension</td>
<td>42 (29%)</td>
<td>14 (19%)</td>
<td>( \chi^2 = 1.874 )</td>
<td>.171</td>
</tr>
<tr>
<td>Neonatal factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formula feeding</td>
<td>80 (55%)</td>
<td>50 (68%)</td>
<td>( \chi^2 = 3.239 )</td>
<td>.072</td>
</tr>
<tr>
<td>Apgar 1 min</td>
<td>5.7 ± 0.2</td>
<td>6.0 ± 0.3</td>
<td>( t = 0.940 )</td>
<td>.348</td>
</tr>
<tr>
<td>Apgar 5 min</td>
<td>7.6 ± 0.1</td>
<td>7.7 ± 0.2</td>
<td>( t = 0.233 )</td>
<td>.816</td>
</tr>
</tbody>
</table>

The only factor significantly different in the 2 groups is maternal smoking. It is noteworthy that formula feeding did not influence the future development of NEC. These factors have previously been associated with the development of NEC. Depicted values are \( n (% of group) \) and variables are means ± standard error of the mean (SEM). A \( P \) value of .05 is considered significant.

**TABLE 3** Placental Comparison Between NEC and Control Patients

<table>
<thead>
<tr>
<th></th>
<th>NEC (n = 48)</th>
<th>Control (n = 48)</th>
<th>Statistical Analysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>All chorioamnionitis</td>
<td>22</td>
<td>14</td>
<td>( \chi^2 )</td>
<td>.186</td>
</tr>
<tr>
<td>Severe chorioamnionitis</td>
<td>12</td>
<td>8</td>
<td>( \chi^2 )</td>
<td>.959</td>
</tr>
<tr>
<td>All uteroplacental insufficiency</td>
<td>13</td>
<td>16</td>
<td>( \chi^2 )</td>
<td>.559</td>
</tr>
<tr>
<td>Severe uteroplacental insufficiency</td>
<td>6</td>
<td>6</td>
<td>( \chi^2 )</td>
<td>.956</td>
</tr>
</tbody>
</table>

A select group of 94 patients was evaluated here. Numbers represent \( n \) in each group. Note that some patients had both uteroplacental insufficiency and chorioamnionitis so that columns will not total to sample size. A \( P \) value of <.05 is considered significant.
fluid exposing the fetus to a higher level of nicotine than the mother.

More recently, nicotine has been under additional investigation because of the widespread availability of nicotine replacements that are presumed to be a better alternative to smoking. With this change in clinical recommendations, recent animal studies on prenatal nicotine exposure have shown fetal programming of vascular oxidative stress in the adult offspring of these nicotine-exposed dams. Nicotine, itself, stress in the adult offspring of these programming of vascular oxidative stress, recent animal studies on prenatal nicotine exposure have shown fetal

CONCLUSIONS

Although care of the infant with NEC is primarily provided by neonatologists and pediatric surgeons, the findings of the current study are relevant to a much broader audience. Physicians in the outpatient setting have a major role in identifying potential at-risk infants and providing earlier, primary prevention of this devastating disease. Obstetricians and gynecologists typically provide counseling and smoking cessation programs to their pregnant patients, and these techniques can be successful. However, not all women seek prenatal care in a timely fashion, or even at all, after discovering their pregnancy. A novel approach at preventing this costly disease can start with the general pediatrician.

Most women come in contact with a pediatrician at some point during their pregnancy. Either they are trying to find a new health care provider for the infant, or they are visiting their established pediatrician with 1 of their other children while they are pregnant. These interactions between pediatrician and future mother can be a critical point of intervention for the smoking woman. The role of the pediatrician is to be an advocate for his/her patient. This can be done by asking the mother about her tobacco use; counseling her on the negative effects smoking can have on her developing baby, including the possibility of future development of NEC, and providing resources to help her with smoking cessation. Obviously, in addition to improved prevention and treatment strategies, more research is necessary to further elucidate the risk factors and pathogenesis of NEC. With the current study linking maternal cigarette smoking to development of NEC, and the knowledge we have of the effects of tobacco and nicotine on placental vascularization, in the future it would be worthwhile to evaluate blood vessel development in the gastrointestinal tract of affected infants. Our hope is that this study urges stronger counseling and more aggressive programs to stop smoking in pregnant women and in the antenatal period, because the delicate vascular development of the placenta and the fetus occurs in the first weeks of gestation.

REFERENCES

HOW HIGH?: My wife and I have lived in Vermont for almost 20 years. In that time, we have raised four kids and a host of farm animals, seen a million soccer and lacrosse games, and been to countless dinners and functions. Whether on the “farm,” at a game, or at work in Montpelier, I think the largest heel I saw on a pair of shoes was about an inch on a pair of muck boots. So, I was pretty surprised when, during a recent trip to Milan, I saw droves of women walking the streets perched on immensely high high-heeled shoes. The windows of the upscale fashion houses and department stores were stuffed with women’s shoes that had heels measuring anywhere from two to six inches. According to an article in The Wall Street Journal (On Style: April 5, 2012), creating a stable, comfortable high-heeled shoe takes talent and is big business. Last year, women in the U.S. spent more than $20 billion on shoes with heels of at least three inches. High-heeled shoes are popular because they are thought to project sexiness and power.

Designing high-heeled shoes is similar to an architectural project. The elements consist of: a toe box into which the toes must fit comfortably, a platform or area beneath the balls of the feet, a shank for the base of the foot, a heel bed on which the heel rests, and finally the shoe heel, which needs to be carefully centered beneath the heel of the foot. The heel and shank need to be very rigid and stable, and in expensive shoes are usually made of high-quality steel. Because the height of the heels tends to force the weight forward to the balls of the feet, leading to leg and foot fatigue, designs that distribute the weight under the arch and heel are more comfortable. The maximum heel height that most women can tolerate is approximately four inches. To create shoes that incorporate heels that can be up to six inches high, designers build platforms that may be two inches in height. In this way, the foot still is not bent over a distance greater than four inches. While I am sure that my wife would look great in some tall “Manolos,” she is pretty fast chasing kids and soccer balls. I suspect I won’t be seeing her in anything over an inch anytime soon — and I don’t have to worry much about her breaking an ankle.

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