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The Impact of Tobacco Use on Preterm Premature Rupture of the Membranes

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Abstract

Objective—To determine if tobacco use increases the incidence of preterm premature rupture of the membranes (pPROM) or alters perinatal outcomes after pPROM.

Study Design—This is a secondary analysis of the databases of three completed *Eunice Kennedy Shriver* National Institute of Child Health and Human Development–supported Maternal Fetal Medicine Units Network studies. Self-reported tobacco exposure data was obtained. Its relationship with the incidence of pPROM and associated neonatal outcome measures were assessed.

Results—There was no difference in the incidence of pPROM when comparing non-smokers to those using tobacco. Although a trend was seen between the incidence of pPROM and the amount smoked, this did not reach statistical significance. Among the patients with pPROM, the use of tobacco was not associated with an increase in perinatal morbidity.

Conclusion—Our data do not support a significant relationship between tobacco use and pPROM.

Keywords

tobacco; premature rupture of the membranes

Preterm premature rupture of the membranes (pPROM) occurs in 0.7 to 3.0% of all pregnancies and has been implicated in 30% of preterm deliveries.^{1–3} The perinatal morbidity linked to this event is directly related to the gestational age at delivery. In addition to the risks inherent in prematurity (e.g., respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis), pregnancies complicated by pPROM are at an increased risk for intra-amniotic infection, neonatal sepsis, pulmonary hypoplasia, placental abruption, and cord compression.

The reported risk factors for pPROM include previous preterm delivery, previous pPROM, uterine overdistension, intrauterine infections, sexually transmitted diseases, cervical conization, vaginal bleeding, and drug use including tobacco.^{4,5} Although most studies have suggested an increase in the incidence of pPROM among patients who use tobacco,^{6–11} others, including data from the Collaborative Perinatal Project,¹² have demonstrated no such association. In addition, the data addressing the possibility that pregnancies complicated by pPROM and tobacco use may be at risk for shorter latent periods and an increase in overall perinatal morbidity are both limited and contradictory. The objectives of this study were (1) to determine whether tobacco use was associated with an increase in the incidence of pPROM and (2) to evaluate the possibility that tobacco use further worsened perinatal morbidity (shorter latent period, increased risk of infection) among pregnancies complicated by pPROM. If tobacco use is associated with pPROM, this would represent a potentially “modifiable” risk factor for this common perinatal complication.

Methods

This investigation represents a secondary analysis of data collected for three separate Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) supported Maternal–Fetal Medicine Unit (MFMU) Network Studies. These studies were Randomized Clinical Trials of Metronidazole to Improve Pregnancy Outcome in Women Infected with *T. vaginalis* [*Trichomonas vaginalis*] (TV) and in Women with Bacterial Vaginosis (BV)^{13,14} and Screening for Risk Factors for Spontaneous Preterm Delivery in Singletons and Twins.¹⁵

Otherwise healthy pregnant women with viable singleton pregnancies between 16⁰/₇ and 23⁶/₇ weeks’ gestation were screened for eligibility in the BV and TV trials. The BV trial required a Gram stain positive by Nugent criteria¹⁶ and a negative TV culture (Diamond’s media). The TV trial required a positive TV culture at less than 24 weeks’ gestation. Eligible and consenting women were randomized to four doses of either 2 g of metronidazole or matching placebo, with a primary outcome measure of preterm delivery (<37 weeks’ gestation).

The Preterm Prediction study was an observational cohort of 3000 women with singleton pregnancies and 150 women with twin pregnancies in whom psychosocial, medical, and cervical ultrasound data as well as serial biological samples were obtained biweekly from 24 to 30 weeks’ gestation and then analyzed for markers capable of predicting subsequent spontaneous preterm birth. This article only includes data on the singleton pregnancies.

Two hundred eighty-six women from the TV study, 956 women from the BV study, and 2963 women from the Preterm Prediction study constitute the patient population in this report. Institutional Review Board approvals for this secondary analysis were obtained at George Washington University (site of the Biostatistical Coordinating Center) and the University of Utah Health Science Center. Previous patient consent documents approved at all participating MFMU Network centers had specifically authorized permission for secondary analyses.

In the Preterm Prediction study, tobacco use was assessed by self-report at 23 to 24 weeks (initial visit) and again at 27 to 31 weeks of gestation. The BV and TV study participants were asked at the time they entered the study (8 to 22 weeks of gestation) whether or not they had smoked cigarettes since becoming pregnant (yes/no) and the average number of cigarettes smoked daily in the last week. For this analysis, patients were divided into two groups: those using tobacco and those denying tobacco use at study enrollment. Women who used tobacco were further categorized by the quantity of cigarettes smoked per day.

pPROM was defined as documented rupture of the membranes at <37 completed weeks of gestation. Additional outcome variables collected from the database included latency period (hours), estimated gestational age at delivery (weeks), birth weight (grams), positive neonatal cultures (blood, cerebrospinal fluid, or urine), suspected (defined as suspicious clinical findings of infection without positive cultures) or proven (defined as positive cultures *or* evidence of cardiovascular collapse or unequivocal X-ray findings in an infant who is believed to be clinically septic) neonatal sepsis, and neonatal length of stay (days). Assuming a background risk of pPROM of 3%, we calculated a sample size of ~2000 would be needed to detect a twofold increase (6%) in the incidence of pPROM among smokers with a power of 80% and an α error of 0.05, assuming that ~25% of our population were smokers. Categorical data were analyzed using chi-square and Fisher exact test, and ordinate data were analyzed with the Kruskal-Wallis test. Cochran-Armitage trend test and multivariate logistic regression were also performed to assess possible associations. A p value of <0.05 was considered significant.

Results

A total of 4205 patients with a singleton pregnancy and final delivery outcome were included in this study. Among those, 1129 patients reported the use of tobacco and 3076 denied using tobacco. Maternal characteristics are reported in Table 1 for both smokers and nonsmokers. There were more Caucasians (57.1% versus 18.5%, $p < 0.0001$) and significantly fewer nulliparous women (35.9% versus 44.0%, $p < 0.0001$) in the group of smokers. The mean age was greater (24.7 versus 23.1, $p < 0.0001$) among smokers and there was a lower rate of vaginal infections (37.0% versus 42.7%, $p = 0.0009$) when compared with nonsmokers. No significant difference was found in either previous spontaneous preterm birth ($p = 0.05$) or previous pPROM ($p = 0.21$).

Among all patients admitting to the use of tobacco during this pregnancy ($n = 1129$), 261 (23.1%) quit prior to study enrollment, 686 (60.8%) smoked less than one pack per day, and 182 (16.1%) smoked one pack or more per day. A trend of increasing incidence of pPROM from 4.1 to 5.5% was found with an increase in degree of tobacco exposure (nonsmokers = 4.1%, quit during pregnancy = 4.2%, continue to smoke less than one pack per day = 4.4%, continue to smoke one pack or more per day = 5.5%). However, this trend was not statistically significant ($p = 0.41$). Odds ratios and their 95% confidence intervals were calculated using nonsmokers as the reference group (Table 2). No significant association was found between the incidence of pPROM and smoking after adjusting for age, race, parity, vaginal infection, having one or more previous spontaneous preterm births, and

having one or more previous occurrences of pPROM (odds ratio = 1.36, 95% confidence interval 0.95 to 1.96).

Table 3 details the latency period, delivery within 48 hours after pPROM, delivery within a week after pPROM, gestational age at delivery, birth weight, neonatal length of stay, sepsis, and incidence of positive neonatal cultures in smokers and nonsmokers. There were no significant differences demonstrated in any of the outcome variables studied. There were no differences in either neonatal sepsis (24.5% versus 25.4%) or the incidence of positive neonatal cultures (4.1% versus 3.4%) when comparing smokers to nonsmokers.

Discussion

Our data suggest that there is no significant increase in the incidence of pPROM related to the use of tobacco. The results of this study contradict several other investigations that support an association between tobacco use and an increase in the incidence of pPROM.

Kyrklund-Blomberg and Cnattingius¹¹ reported on nearly 70,000 smokers from the Swedish Birth Registry between the years 1991 and 1993. pPROM was diagnosed in 2377 patients. The rate of pPROM among nonsmokers was 6.5/1000 compared with 9.3/1000 among those smoking one to nine cigarettes daily and 11.5/1000 among women smoking at least 10 cigarettes daily.

Whether the use of tobacco impacts the perinatal outcome in patients with a diagnosis of pPROM remains unclear. Our data do not support any significant difference in outcome among patients with pPROM with respect to tobacco use. Specifically, there was no difference in length of latency period, neonatal sepsis, positive neonatal cultures, or neonatal length of stay when comparing smokers to nonsmokers among those with pPROM. Several mechanisms have been suggested for ruptured membranes among tobacco users that have biological plausibility. Nutritional deficits, primarily attributed to smoking's effect on ascorbic acid levels, have been reported to increase the risk of pPROM.¹⁷ There is also evidence that reactive oxygen species generated by smoking can contribute to the development of pPROM.¹⁸

Adequate control for confounding variables that may contribute to pPROM, such as inadequate nutrition and intra-amniotic infection, was not possible given the retrospective design of the study. Both of these limitations are also found in the previously published studies that address the possible association of smoking and pPROM.

The association of tobacco use with pPROM has become generally accepted.^{4,5} Our data question the presence of this association. One possible explanation may be differences in the timing and amount of prenatal care from one study population to another. Inadequate prenatal care has been suggested as a marker for lifestyle variables that may lead to an increase in the incidence of pPROM.¹⁹ Likewise, it has been shown that women participating in clinical research may have different socioeconomic characteristics than women who decline participation.⁴ The women in this secondary analysis of three clinical studies had all received prenatal care in the first half of pregnancy and had all agreed to participate in clinical research, representing a potential sampling bias in comparison to the aforementioned cross-sectional studies.

Although the correlation between self-reported smoking and urinary cotinine levels is good,^{20,21} a prospective study, including the use of biochemical measures of tobacco exposure, would be helpful in establishing an unequivocal conclusion about the association between tobacco use and pPROM.

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Table 1**Maternal Characteristics by Smokers and Nonsmokers**

	Nonsmokers	Smokers	<i>p</i> Value
<i>n</i>	3076	1129	
Age (mean $\pm$ SD)	23.1 $\pm$ 5.3	24.7 $\pm$ 5.6	<0.0001
Race			
African-American	2319 (75.4%)	449 (39.8%)	<0.0001
Caucasian	568 (18.5%)	645 (57.1%)	
Hispanic	151 (4.9%)	21 (1.9%)	
Other	38 (1.2%)	14 (1.2%)	
Nulliparity	1353 (44.0%)	405 (35.9%)	<0.0001
Previous SPTB	157 (5.1%)	75 (6.6%)	0.05
Previous pPROM	130 (4.2%)	38 (3.4%)	0.21
Vaginal Infection	1313 (42.7%)	418 (37.0%)	0.0009

pPROM, preterm premature rupture of the membranes; SD, standard deviation; SPTB, spontaneous preterm birth.

Table 2

The Incidence of Preterm Premature Rupture of the Membranes Based upon Degree of Exposure to Tobacco

	<i>n</i>	Incidence of pPROM	OR	95% CI
Nonsmokers ^a	3076	125 (4.1%)		
Smokers	1129	51 (4.5%)	1.12	0.80–1.56
Quit during pregnancy	261	11 (4.2%)	1.04	0.55–1.95
Continued, <1 ppd	686	30 (4.4%)	1.08	0.72–1.62
Continued, 1 ppd	182	10 (5.5%)	1.37	0.71–2.66

CI, confidence interval; OR, odds ratio; ppd, packs per day; pPROM, preterm premature rupture of the membranes;.

^aNonsmokers were used as reference group to calculate the ORs and their 95% CIs.

Table 3

The Impact of Smoking on Perinatal Outcome Variables among Patients With Preterm Premature Rupture of the Membranes

	Nonsmokers (<i>n</i> = 125)	Smokers ^a (<i>n</i> = 51)	OR (95% CI)	<i>p</i> Value
Latent period (h), median (interquartiles)	15.7 (7.7–32.2)	17.3 (9.2–38.3)	—	0.51
Birth weight (g), median (interquartiles)	2415.5 (1917.5–2735.0)	2430.0 (1900.0–2680.0)	—	0.74
GA at delivery (wk), median (interquartiles)	35 (33–36)	35 (32–36)	—	0.42
Newborn length of stay (d), median (interquartiles)	4.0 (2.0–12.0)	3.5 (2.0–12.0)	—	1.00
Delivery within 48 h of rupture (%)	83.1	77.1	0.69 (0.30–1.57)	0.37
Delivery within 7 d of rupture (%)	91.5	95.8	2.13 (0.45–10.1)	0.51
Neonatal sepsis (%)	25.4	24.5	0.95 (0.44–2.06)	0.90
Positive neonatal culture (%)	3.4	4.1	1.21 (0.21–6.85)	1.00

CI, confidence interval; GA, gestational age; OR, odds ratio.

^aNonsmokers were used as reference group to calculate the ORs and their 95% CIs.