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The Influence of Maternal Cigarette Smoking on Placental Pathology in Pregnancies Complicated by Abruption

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Abstract

Objective—To evaluate the effect of maternal cigarette smoking on placental histology in women with abruption.

Study design—Data were derived from the New Jersey-Placental Abruption Study (NJ-PAS)—an ongoing, case-control study, conducted since August 2002 in two large hospitals in NJ. Abruption cases were identified based on a clinical diagnosis. Histological evaluations were performed by two perinatal pathologists who were blinded to the abruption status. Maternal smoking during pregnancy was determined based on patient's self report. Among abruption cases, histological findings were compared between smokers and non-smokers, and the association expressed as odds ratio (OR) with 95% confidence interval (CI). All analyses were adjusted for potential confounders.

Results—A total of 189 abruption cases were available for analysis, of which 10.6% (n=20) were smokers. Intervillous thrombus was more common in women who smoked (20%) than in non-smokers (3.0%) (OR 17.5, 95% CI 3.1, 99.4). However, placental infarcts were seen less frequently among smokers than non-smokers (10.0% vs 32.5%; OR 0.2, 95% CI 0.1, 0.8).

Conclusion—These findings suggest that different pathologic mechanisms may be responsible for the histologic findings between smokers and non-smokers diagnosed with placental abruption.

Keywords

Placental abruption; smoking; villous fibrosis; intervillous thrombus; microinfarcts; trophoblast knotting

Placental abruption complicates approximately 1% of all pregnancies,[1, 2] with an increase in its incidence over time.[3] This condition is associated with significant maternal morbidity and

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Condensation Increased intervillous thrombi and decreased placental infarcts were observed among women with abruption who smoked versus non-smokers.

perinatal morbidity and mortality.[1, 4] Although the etiology of abruption remains unclear, a number of risk factors have been identified. These include advanced maternal age, poor socioeconomic and single marital status, hypertension, preeclampsia, cigarette and cocaine use, grand multiparity, multifetal gestation, premature rupture of membranes and prior abruption.[2, 4-8]

The association of maternal smoking with placental abruption has been well documented with studies reporting relative risks of 1.4 to 2.5.[9-11] Cigarette use is associated with a 2.5 fold increase in severe abruption resulting in fetal death.[9] The risk of abruption increases with the number of cigarettes smoked per day,[11] with a threshold effect at approximately 10 cigarettes per day after which the risk remains constant.[12]

Studies focusing on smoking-related placental abruption pathology are sparse. These studies allude to the mechanism of abruption in smokers that is initiated by decidual necrosis at the margin of the placenta.[13, 14] Maternal smoking has been shown to decrease placental blood flow.[15] This effect may be mediated through changes in production of vasoactive substances, such as prostacyclin and nitric oxide,[16] or endothelial cell damage.[17]

The sequence of events in the placentas of smokers leading to placental abruption is poorly understood. The direct effect of smoking may be mediated through vasoconstrictive effects of nicotine on uterine and umbilical arteries as well as increased carboxyhemoglobin concentrations that interfere with oxygenation. We believe that that such hypoxic change can cause microinfarctions occurring at the periphery of the placenta leading to necrotic foci, separation at the necrotic foci, and eventually, an abruption.

Although the biologic mechanisms through which maternal smoking increases the risk for abruption remains unclear, we hypothesized that abruption associated with smoking may have placental abnormalities that would suggest a distinct pathophysiologic pathway. Therefore, we carried out a secondary analysis of a case-control study of abruption to compare, among abruption cases, histologic lesions between the placentas of smokers versus those that remained non-smokers throughout their pregnancy.

Materials and Methods

This study is part of the ongoing “New Jersey-Placental Abruption Study,” a multicenter, case-control study of placental abruption. It has been conducted since August 2002 at Robert Wood Johnson University Hospital and Saint Peter’s University Hospital, New Brunswick, NJ. Placental abruption cases for this study were identified in the antepartum or intrapartum period by an attending physician based on any one (or more) of the following clinical criteria: (i) vaginal bleeding accompanied by fetal distress or uterine hypertonicity/contractions, (ii) ultrasound-based diagnosis, (iii) evidence of retroplacental clot(s) or hemorrhage on the placental surface. Data pertaining to maternal smoking, defined as smoking consistently at least one cigarette per day during a pregnancy, was ascertained through in-person interview of women following their delivery and prior to discharge from the hospital. Further details of the NJ-PAS have been published elsewhere.[18]

Histopathologic lesions

All placentas that were examined were immersed in 10% buffered formalin. After a detailed gross examination, representative sections were submitted including one each from the fetal and maternal surfaces, one from the membranes and one from the umbilical cord. Any unusual areas and areas of infarcts and intervillous thrombus were sampled. These blocks were embedded in paraffin and cut at 4-6 micron thickness. The slides were put into a stainer which put the slides through several stages including deparaffinization, rehydration through alcohols

and water, and finally stained with hematoxylin and eosin. Histological evaluation of placentas was performed by one of the two perinatal pathologists who were blinded to the patients' abruption status.

Microscopic examination was performed on all the cases. Fetal membranes were examined for presence of pigment (meconium or hemosiderin staining), related pigment-laden macrophages, and hemosiderin granules. The presence of chorioamnionitis was noted, and graded as mild, moderate or severe. The umbilical cord was examined for the presence of funisitis. Placental sections were carefully studied during microscopic examination for foci of infarction (areas of ischemic villous necrosis) and microinfarctions, segmental villous fibrosis, villous morphology (edema, stromal hemorrhage, and vascularity), degree of maturation, presence of villous maldevelopment. The presence of vascular lesions such as chorangioma and features suggestive of hypoxia such as chorangiomatosis were noted. Evidence of hypoxic change in the form of increased perivillous fibrin, intervillous fibrinoid, intervillous thrombus was noted. Decidual pathology such as acute or chronic deciduitis, decidual hemosiderosis, decidual vasculopathy (decidual vessel exhibiting muscular hypertrophy, decidual thrombosis, fibrinoid necrosis) were also recorded when present.

Statistical analysis

We compared the distributions of maternal socio-demographic and pregnancy characteristics between women that did and did not smoke throughout their pregnancy among all abruption cases. The Fisher's exact probability test or the Chi-square test was applied for categorical data, or the students t-test for continuous variables. The associations between histological lesions and smoking status among women diagnosed with placental abruption were based on fitting multivariable logistic regression model, from which odds ratio (OR) and 95% confidence interval (CI) were derived. A variety of confounders were used in the model for adjustment, including maternal race/ethnicity (Caucasian, African-American, Hispanic and others), parity (0, 1, 2 or more), maternal education (high school or more), and marital status (single or married). If inclusion of confounders in the regression model changed the crude odds ratio by at least 10%, we retained the confounder for adjustment. In addition, we adjusted all analyses for parity and maternal race/ethnicity. Statistical analysis was performed using SAS software (SAS institute, Cary, NC). All statistical tests were two-tailed, and a P-value <0.05 was considered to denote statistical significance.

Results

There were 189 women diagnosed with placental abruption for whom complete histological analysis was available. Of these abruption cases, 10.6% (n=20) women smoked during the pregnancy. The distributions of sociodemographic and pregnancy characteristics of women that did and did not smoke are shown in Table 1. There were no statistically significant differences for any of these characteristics between the groups. However, there was a tendency for smokers with abruption to be less educated and non-married.

Table 2 shows the comparison of histologic lesions between the two groups of women with placental abruption analyzed by smoking status. Intervillous thrombus was more common in women who smoked as compared to those that remained non-smokers throughout the pregnancy (20.0% vs 3.0%, respectively; OR 17.5, 95% CI 3.1, 99.4). Placental infarcts and microinfarcts were seen less frequently among smokers compared to non-smokers (10.0% vs 32.5%, respectively; OR 0.2, 95% CI 0.1, 0.8). There was a trend toward higher rate of villous fibrosis (25.0% vs 11.8%) in women who smoked compared to non-smokers, although this association did not reach statistical significance (P=0.10). Adjustment for confounding factors did not alter these associations.

Comment

Smoking during pregnancy is one of the most important and preventable risk factors for an array of adverse pregnancy outcomes, including placental abruption.[4, 19-21] Despite widely known risks and large educational campaigns, up to 25% of reproductive age women continue to smoke, and an increasing percentage of them smoke heavily.[22]

Although smoking is a well known risk factor for placental abruption, the etiology of this association continues to be unknown. Several hypotheses linking maternal smoking with abruption have been proposed. It has been previously reported that smoking is associated with increased frequency of placental calcifications and subchorionic fibrin deposits.[23] There is higher frequency of hyperplastic cytotrophoblasts and obliterative endarteritis[4] and nuclear clumps in the perivillous syncyotrophoblasts[24] in placentas of smokers. It is likely that the prominent syncyotrophoblast knotting is due to an abortive attempt by the villi to increase surface area by angiogenesis and neovascularization. This would increase oxygenating capacity in order to compensate for possible chronic ischemia caused by smoking. Several researchers focused on structural changes in placentas of women who smoked and showed increased villous membrane thickness as well as decreased capillary volume.[25, 26] It has been speculated that placental hypoperfusion resulting from vasoconstrictive effects of smoking on maternal placental vasculature could cause decidual ischemia with subsequent necrosis and hemorrhage leading to placental separation.[15]

Our results are consistent with previous studies[23, 24] that have shown increased rates of lesions that are essentially reflective of chronic hypoxic change in the placentas of smokers. We demonstrated higher frequency of intervillous thrombi in the placentas of smokers who had placental abruption versus nonsmokers with abruption. Intervillous thrombosis is thought to result from intraplacental hemorrhage from villous capillaries and is associated with chorionic villous hemorrhage.[27] This may alter uteroplacental/fetal blood flow leading to chronic underperfusion. This chronic hypoxia is manifested by increased rate of villous fibrosis, decrease in villous capillaries and increased trophoblast knotting.

One of the interesting but unexpected findings was the increased frequency of placental infarcts and microinfarcts among non-smoking women with abruption. The biologic underpinnings for this association remain unclear. Perhaps the etiology of abruption in non-smokers may be related to intrinsic maternal conditions, such as thrombophilia, which is more likely to cause ischemic villous necrosis.

The possibility of our findings being affected by type II error (i.e., lack of statistical power) is likely. The NJ-PAS was not primarily designed to compare histologic lesions between smokers and non-smokers in the setting of placental abruption. A *post-hoc* power analysis for many of the lesions evaluated in this study reveal that the lack of association might be driven by low statistical power. Furthermore, some of the associations may be imprecise due to fairly wide confidence intervals. Another potential limitation is that data on cigarette smoking was collected through maternal self-report, possibly resulting in an underestimation of its prevalence. Moreover, since most women would have been informed of their abruption status prior to the interviews, the possibility of a smoking misclassification may have been differential. If present, the non-differential misclassification would have likely biased the effect measures (i.e., odds ratio) away from the null. Studies using biochemical markers, such as urinary cotinine, have demonstrated that women consistently underreport smoking behavior.[28, 29]

In summary, it appears that there might be different pathologic mechanisms responsible for the placental findings in abruption of smokers versus non-smokers. Placental abruption due to cigarette smoking may be associated with chorionic villous hemorrhage and intervillous

thrombosis. However, the ischemic villous damage, as evidenced by the number of infarcts, is higher in the absence of smoking suggesting a distinct underlying pathophysiologic pathway.

APPENDIX

Investigators currently participating or who have been involved in the New Jersey— Placental Abruption Study include Cande V. Ananth, PhD, MPH (Principal investigator), Darios Getahun, MD, MPH, Neela Srinivas, MD, MPH, Celeste DeMarco, RN, BSN, Denise Elsasser, MPH, Yu-Ling Lai, RN and Shelby Pitts, RN (Division of Epidemiology and Biostatistics), John C. Smulian, MD, MPH, Wendy L. Kinzler, MD, Morgan R. Peltier, PhD, and Marian Lake, RN, MPH (Division of Maternal-Fetal Medicine), Department of Obstetrics, Gynecology, and Reproductive Sciences; Claire Philipp, MD (Department of Medicine), all at UMDNJ-Robert Wood Johnson Medical School, New Brunswick, NJ; and George G. Rhoads, MD, MPH (Department of Epidemiology) and Dirk F. Moore, PhD (Department of Biostatistics), UMDNJ-School of Public Health, Piscataway, NJ.

Other investigators that were involved with the study included Rima R. Rozen, PhD and Jacques Genest, MD (McGill University, Montreal, Canada); Susan Shen-Schwarz, MD (Department of Pathology, Saint Peter's University Hospital, New Brunswick, NJ); and Vinay Prasad, MD (Department of Pediatric Pathology, Arkansas Children's Hospital, University of Arkansas Medical Sciences, Little Rock, AR)

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Table 1

Distribution of maternal and pregnancy characteristics of women with placental abruption based on their smoking status

Maternal characteristics	Smokers		Non-smokers		P-value
	No.	%	No.	%	
Maternal age (years)					0.18
< 20	7	35.0	30	17.8	
20-34	8	40.0	91	53.9	
≥35	5	25.0	48	28.4	
Maternal race/ethnicity					0.12
Caucasian	5	25.0	28	16.6	
African-American	9	45.0	54	32.0	
Hispanic	6	30.0	58	34.3	
Other	0	0	29	17.1	
Parity					0.30
Nulliparous	4	20.0	63	37.3	
Primiparous	9	45.0	60	35.5	
Parity ≥ 2	7	35.0	46	27.2	
High school education or higher	8	40.0	104	61.5	0.09
Single marital status	10	50.0	50	29.6	0.07
Chronic hypertension	2	10.0	10	5.9	0.37
Preeclampsia	2	10.0	22	13.0	1.00
Diabetes (IDDM)	0	0	4	2.4	1.00
Preterm PROM	2	15.4	28	23.9	0.73
BMI (mean ± SD)		22.7±6.5		24.0 ±6.1	0.51
Gestational age (mean±SD)		31.9 ±4.0		32.0 ±5.1	0.34
Birthweight (mean±SD)		2280.2±701.7		2090.7±887.2	0.48
Placental weight (mean±SD)		411.6±79.3		391.5±137.6	0.46

IDDM, insulin-dependent diabetes mellitus; PROM, premature rupture of membranes; BMI, body-mass index; SD, standard deviation.

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Table 2

Comparison of histologic lesions between smokers and non-smokers among pregnancies complicated by placental abruption

Histologic lesions	Smokers % (n)	Non-smokers % (n)	P value	Odds ratio* (95% CI)
Chorioamnionitis	45.0 (9/20)	33.3 (56/168)	0.30	1.8 (0.5, 6.9)
Chorioangioma	5.6 (1/18)	4.1 (7/169)	0.78	3.1 (0.3, 33.6)
Deciduitis	35.0 (7/20)	32.3 (53/164)	0.81	0.6 (0.1, 2.2)
Decidual vasculopathy	10.5 (2/19)	7.7 (13/168)	0.67	4.4 (0.6, 30.6)
Fetal vessel thrombosis	5.3 (1/19)	3.0 (5/166)	0.48	5.8 (0.4, 95.3)
Membrane histology	10.3 (2/19)	15.2 (25/164)	0.74	0.7 (0.2, 3.0)
Funisitis	25.0 (5/20)	15.1 (25/166)	0.25	1.1 (0.3, 5.0)
Infarctions/microinfarctions	10.0 (2/20)	32.5 (55/169)	0.04	0.2 (0.1, 0.8)
Intervillous thrombus	20.0 (4/20)	3.0 (5/169)	0.0007	17.5 (3.1, 99.4)
Villous fibrosis	25.0 (5/20)	11.8 (20/169)	0.10	2.2 (0.5, 9.0)
Perivillous fibrin	5.0 (1/20)	3.6 (6/169)	0.75	2.2 (0.2, 23.9)
Villitis	5.0 (1/20)	3.0 (5/166)	0.63	0.4 (0.03, 7.4)
Villous histology	15.0 (3/20)	18.3 (31/169)	0.98	0.6 (0.1, 2.5)

CI, confidence interval

* Odds ratios were adjusted for maternal race, parity, education, and marital status through multivariable logistic regression