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Maternal Cigarette Smoking as a Risk Factor for Placental Abruption, Placenta Previa, and Uterine Bleeding in Pregnancy

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The authors carried out an epidemiologic study to evaluate the role of maternal cigarette smoking as a potential risk factor for placental abruption, placenta previa, and uterine bleeding of unknown etiology in pregnancy. Data for this prospective cohort study were obtained from women seeking prenatal care at any of the two tertiary, seven regional, or 17 community hospitals in the province of Nova Scotia, Canada, between January 1, 1986, and December 31, 1993. A total of 87,184 pregnancies (among 61,667 women) were registered in the database. Women who smoked during pregnancy (33%) were compared with nonsmokers, and all women were followed until the termination of pregnancy. Placental abruption was indicated in 9.9 per 1,000 pregnancies, while placenta previa and uterine bleeding of unknown etiology were indicated in 3.6 and 58.9 per 1,000 pregnancies, respectively. Women who smoked had a twofold increase in the risk of abruption (relative risk = 2.05, 95% confidence interval (CI) 1.75–2.40) in comparison with nonsmokers, while the relative risk for placenta previa was 1.36 (95% CI 1.04–1.79). However, cigarette smoking was not found to be associated with uterine bleeding of unknown etiology (relative risk = 1.01, 95% CI 0.94–1.08). There was no evidence for an increased risk of uteroplacental bleeding disorders with increasing numbers of cigarettes smoked. All analyses were adjusted for potentially confounding factors through logistic regression models based on the method of generalized estimating equations. The study confirms a positive association between cigarette smoking and placental abruption and a weak association with placenta previa but not with other uterine bleeding. The distinct pattern of results for placental abruption, placenta previa, and uterine bleeding of unknown origin suggests that these three uteroplacental bleeding disorders do not have a common etiology in relation to cigarette smoking. *Am J Epidemiol* 1996;144:881–9.

abruptio placentae; alcohol drinking; placenta praevia; pregnancy; smoking; uterine hemorrhage

Placental abruption, defined as the premature separation of a normally implanted placenta, and placenta previa, in which the maturing placenta obstructs or is situated close to the internal cervical os, are relatively rare but serious obstetric complications of pregnancy. They cause over one fifth of all perinatal deaths, and have been shown to result in excessively high rates of preterm delivery, low birth weight, stillbirth, and neonatal death (1, 2). Although the primary causes of placental abruption and placenta previa are not known with certainty (3), epidemiologic studies have identified several potential etiologic factors known to be associated with these conditions. These include advanced maternal age, grand multiparity, plural births, gestations with male fetuses, uterine tumors, uterine decompression, a short umbilical cord, a prior history of uterine scarring that resulted in endometrial and myometrial damage, trauma, prolonged rupture of the chorioamniotic membranes, and hypertensive disorders (1–9). Additionally, patients with a prior history of abruption or previa have also been shown to be at elevated risk of these complications in subsequent pregnancies (2, 7).

Previous studies have found placental abruption and placenta previa to be associated with cigarette smoking (10–17). However, some limitations of these studies justify further examination of the association between smoking and the risk of uteroplacental bleeding disorders. First, case-control studies using self-reported data on vaginal bleeding appear to suffer from underreporting (18). Moreover, data on cigarette smoking were based on recall at the time of delivery in

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Abbreviations: CI, confidence interval; RR, relative risk.

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most of these case-control studies, thereby introducing a potential for recall bias. Second, previous studies have been unable to assess dose-response relations between smoking and uteroplacental bleeding disorders because of small samples. Finally, the choice of patients in most earlier studies was restricted to referral hospitals, thereby limiting generalizibability.

The objective of this study was to evaluate the relations between cigarette smoking during pregnancy and the subsequent development of placental abruption, placenta previa, and uterine bleeding of unknown etiology in a large, population-based cohort, and to compare the impact of smoking across the different types of uteroplacental bleeding disorders.

MATERIALS AND METHODS

The Nova Scotia Atlee Perinatal Database

Data for this study were obtained from the computerized Atlee Perinatal Database during the period January 1, 1986, to December 31, 1993. Data collection was jointly initiated by the departments of Obstetrics and Gynecology and Neonatal Pediatrics at Dalhousie University in Halifax; the Grace Maternity Hospital; and the Nova Scotia Department of Health, Canada. The province of Nova Scotia has a long-standing system of regionalized reproductive health care. Data from the two tertiary care hospitals (6,000 pregnancies per year) and the seven regional care hospitals (4,000 pregnancies per year) were available from 1986 onwards, while the remaining 17 community hospitals (2,000–3,000 pregnancies per year) were initiated into the program in 1988. Estimated coverage in the province was 80 percent between 1986 and 1987, and it rose to 100 percent for the period 1988–1993 (Atlee Perinatal Database Committee, unpublished data, 1993).

The study's design is that of a population-based prospective cohort. Prenatal care forms and delivery records were standardized throughout the province of Nova Scotia to enable clinical variables for the database to be entered as part of the documentation of administered care. Provincial medical record technicians were trained to abstract data from the prenatal and delivery records. A detailed description of the database can be found elsewhere (19, 20). Information used in this analysis concerning placental abruption, placenta previa, uterine bleeding, cigarette smoking, and alcohol drinking has been found to have at least 90 percent agreement based on reabstraction of approximately 2 percent of the charts by two separate abstractors.

Starting with 94,189 pregnancies that ended between January 1, 1986, and December 31, 1993, we sequentially excluded multiple births (n = 2,859) and women with missing data on smoking during pregnancy (n = 4,146), which left us with 87,184 pregnancies among 61,667 women for analysis. Gestational age was estimated on the basis of an algorithm incorporating both the clinical estimate of gestational age at delivery and the last menstrual period. When the difference in gestational age between the clinical estimate and the date of the last menstrual period was greater than 3 weeks, the charts were reviewed to determine the source of the disparity. If the discrepancy could not be resolved, the clinical estimate was retained. When the disparity was less than 3 weeks, the estimate based on the last menstrual period was retained. If only the clinical estimate or the estimate based on the last menstrual period was available, that particular estimate was used in isolation. If neither of these estimates was available, gestational age was coded as missing.

Smoking during pregnancy

Information on cigarette smoking was collected both at the first prenatal visit and at the time of admission to the hospital for delivery. Women were asked whether they had ever smoked during the current pregnancy and, if they were smokers, the number of cigarettes smoked per day. Since the Atlee database contains only one smoking variable, changes in smoking behavior during the course of pregnancy were not recorded. If the average number of cigarettes smoked per day differed between the first prenatal visit and the time of delivery, the highest number was recorded in the database (19).

Classification of uteroplacental bleeding disorders

The diagnosis of placental abruption was based on the following criteria, confirmed upon clinical examination by the attending physician: complete or partial separation of a normally implanted placenta occurring prior to delivery and confirmed at delivery by evidence of retroplacental bleeding, usually accompanied by abdominal pain. Information on the severity of abruption was not recorded on the medical charts. The diagnosis of placenta previa was based on the following criteria: partial or complete coverage of the internal cervical os by the placenta, usually associated with uterine bleeding and usually warranting cesarean delivery. All instances of placenta previa were confirmed by a positive ultrasound diagnosis, although a diagnosis based solely on ultrasound was not considered sufficient.

Women who presented with bleeding beyond 20 weeks' gestation and for whom placental abruption, placenta previa, or bleeding due to genital tract lesions was ruled out as the cause of bleeding were categorized as having uterine bleeding of unknown etiology. Information on uterine bleeding was ascertained through two sources: women admitted to the obstetric wards with bleeding as the primary cause for hospital admission, and information on bleeding collected by patient recall during prenatal care visits. Details on the timing and severity of bleeding episodes were not available.

Statistical methods

We examined the risk of uteroplacental disorders in relation to cigarette smoking. Relative risks (with 95 percent confidence intervals) were computed as the measure of effect. All analyses related to smoking were performed by three methods. First, smoking was categorized as a dichotomous variable (yes/no). Second, the number of cigarettes smoked per day was treated as an ordinal variable to assess the dose-response relation between the number of cigarettes smoked and the risk of uteroplacental bleeding disorders. For this analysis, number of cigarettes smoked daily was categorized as none, 1–5, 6–10, 11–15, 16–20, 21–30, and 31 or more. Third, the number of cigarettes smoked per day was modeled as a continuous variable.

Adjusted odds ratios were derived from logistic regression models as estimates of adjusted relative risks. Potentially confounding factors assessed included maternal age, parity (nulliparous, primiparous, and parity ≥ 2), gravidity (primigravida, gravida 2, and gravida ≥ 3), alcohol consumption (yes/no), marital status (single vs. married), chronic hypertension, mild and severe preeclampsia, urinary tract infection, anemia, and premature rupture of the chorioamniotic membranes (yes/no). Variables were included in the final model for adjustment if their presence altered the crude relative risk for smoking by at least 10 percent or if they were of a priori interest—i.e., hospital type (tertiary, regional, and community hospitals) and year of delivery (1986–1987, 1988–1993).

Our analyses involved data collected over an 8-year period (1986–1993), allowing for the possibility of women having multiple pregnancies. Moreover, since placental abruption and placenta previa are known to recur in subsequent pregnancies with greater frequency, this violated the assumption of statistical independence. A violation of this assumption can lead to imprecise variance estimates, thereby affecting the confidence intervals of the odds ratios. Hence, all logistic regression models were fitted using the procedure of generalized estimating equations (21), which adjusts the variance estimates for the inherent correlation arising due to repeat pregnancies in the same woman. Odds ratios estimated from logistic regression models based on generalized estimating equations have the same interpretation as those from a simple logistic regression model.

We performed cubic spline transformations (22) on continuous variables (number of cigarettes smoked per day and maternal age) in the regression model. This method does not impose any restriction on the form of the relation between the continuous variable and the outcome (uteroplacental bleeding disorders). Since the shape of the distribution of number of cigarettes smoked was nonlinear, we conducted a four-piece spline regression analysis with nodes (connection points) assigned at 0, 5, 10, and 25 cigarettes per day. The fit of models with quadratic and cubic splines with three, four, five, and six nodes were compared on the basis of the likelihood ratio test (22); the restricted cubic spline model with four nodes provided the best fit. Similarly, a four-piece restricted cubic spline model with nodes at 18, 26, 30, and 36 years was assigned for maternal age. All statistical analyses were conducted using SAS (SAS Institute, Inc., Cary, North Carolina; version 6.11 for UNIX).

RESULTS

Placental abruption was present in 808 pregnancies, for an overall prevalence of 9.9 per 1,000 deliveries. Placenta previa was diagnosed in 290 pregnancies, for a prevalence of 3.6 per 1,000 pregnancies, while uterine bleeding of unknown etiology was indicated in 5,068 pregnancies, for a prevalence of 58.9 per 1,000 pregnancies. The distribution of uteroplacental disorders (table 1) indicates that tertiary hospitals recorded greater proportions of cases of placental abruption, placenta previa, and uterine bleeding than regional or community hospitals, which is consistent with the two tertiary hospitals' serving as referral centers for complicated and high risk pregnancies. The risk of placenta previa increased monotonically with increasing maternal age and parity, while the risks of placental abruption and uterine bleeding of unknown etiology were highest among teenagers and women over 35 years of age. Labor and delivery characteristics of women with placental abruption or placenta previa showed high rates of cesarean delivery, with increased risks of low birth weight, preterm delivery, neonatal and perinatal mortality, and low Apgar scores (table 2). There were more male fetuses in all three uteroplacental disorder groups, as noted in earlier studies (4, 23).

TABLE 1. Demographic and maternal characteristics of women in relation to uteroplacental bleeding disorders, Nova Scotia, Canada, 1986–1993

	Total no. of pregnancies (n = 87,184)	Uteroplacental bleeding disorder (%)			
		None (n = 81,018*)	Placental abruption (n = 808)	Placenta previa (n = 290)	Uterine bleeding (n = 5,068)
Hospital type					
Tertiary	49,425	91.3	1.1	0.4	7.2
Regional	28,203	94.9	0.8	0.2	4.1
Community	9,556	95.5	0.4	0.1	4.1
Year of delivery					
1986–1987	19,245	92.6	0.8	0.3	6.3
1988–1993	67,939	93.0	1.0	0.3	5.7
Maternal age (years)					
≤19	4,641	91.4	1.1	0.1	7.4
20–24	23,711	92.3	1.0	0.2	6.5
25–29	26,273	93.3	0.8	0.3	5.6
30–34	26,186	93.5	0.9	0.5	5.2
35–39	5,202	93.1	1.0	0.6	5.3
≥40	1,170	90.7	1.3	1.0	7.0
Parity					
0	38,341	92.7	0.9	0.2	6.3
1	30,995	93.4	0.9	0.4	5.3
≥2	17,836	92.8	1.1	0.6	5.6
Gravidity					
1	31,515	93.0	0.9	0.2	6.0
2	29,239	93.4	0.9	0.3	5.4
≥3	26,412	92.4	1.0	0.6	6.0
Marital status					
Married	63,889	93.5	0.9	0.4	5.2
Single	22,174	91.2	1.2	0.2	7.4
Unknown	1,121	91.6	0.7	0.5	7.1

* Numbers in parentheses, no. of pregnancies.

The overall prevalence of smoking during pregnancy was 32.7 percent in the province of Nova Scotia. Cigarette smoking was associated with a twofold increase in the risk of placental abruption (relative risk (RR) = 2.05, 95 percent confidence interval (CI) 1.75–2.40), with little gradient of increasing relative risk with increasing number of cigarettes smoked per day (table 3). Placental abruption was not associated with alcohol consumption during pregnancy (RR = 0.88, 95 percent CI 0.72–1.08). Adjustments for confounders had little influence on the pattern of associations.

Smoking was weakly associated with the risk of placenta previa (table 4). When adjusted for confounding due to marital status, maternal age, parity, chronic hypertension, preeclampsia, and alcohol use, the relative risk for placenta previa was 1.36 (95 percent CI 1.04–1.79). No dose-response gradient was observed in relation to the number of cigarettes smoked per day. Nevertheless, women who smoked 16–20 cigarettes per day were at 80 percent (95 percent CI 1.06–3.07) increased risk of placenta previa in comparison with nonsmokers. The risk of placenta previa was slightly elevated for women who drank alcohol during pregnancy (RR = 1.26, 95 percent CI 0.95–1.69), after adjustment for confounders.

Uterine bleeding of unknown etiology was not associated with cigarette smoking (RR = 1.01, 95 percent CI 0.94–1.08), except for a small increase in risk among the heaviest smokers (RR = 1.29, 95 percent CI 1.04–1.65) (table 5). Once again, no dose-response pattern between number of cigarettes smoked per day and the risk of bleeding was apparent. Alcohol was not found to be associated with bleeding.

When the number of cigarettes smoked daily was entered into the model as a continuous variable with a cubic spline transformation, the risk of abruption increased up to a level of 10 cigarettes per day, and thereafter remained constant at a relative risk of 2.1 (figure 1). However, the pattern was quite different for placenta previa and uterine bleeding of unknown etiology: Compared with nonsmoking, the adjusted relative risk for number of cigarettes smoked per day was almost flat around the null value.

TABLE 2. Women's labor and delivery characteristics and pregnancy outcomes in relation to uteroplacental bleeding disorders, Nova Scotia, Canada, 1986–1993

	Total no. of pregnancies (n = 87,184)	Uteroplacental bleeding disorder (%)			
		None (n = 81,018*)	Placental abruption (n = 808)	Placenta previa (n = 290)	Uterine bleeding (n = 5,068)
Mode of delivery					
Cesarean	16,564	18.4	42.8	92.1	19.4
Vaginal	70,620	81.6	57.2	7.9	80.6
Sex of infant					
Male	42,727	50.8	54.5	59.3	5.6
Female	44,454	49.1	45.5	40.7	6.0
Pregnancy outcome					
Live birth	86,450	99.3	86.1	97.2	98.2
Stillbirth	444	0.4	10.2	1.0	0.7
Neonatal death	290	0.3	3.8	1.7	1.1
Perinatal death	734	0.7	13.9	2.7	1.8
Birth weight (g)					
≤1,499	719	0.5	15.0	7.3	3.0
1,500–2,499	3,419	3.5	25.3	20.3	6.8
2,500–3,999	69,526	80.1	55.4	67.9	78.4
≥4,000	13,519	15.9	4.3	4.5	11.8
Gestational age (weeks)					
≤28	328	0.2	7.5	4.2	1.8
29–32	545	0.5	9.9	6.9	1.6
33–36	3,425	3.5	25.3	29.5	6.8
37–42	79,543	94.1	56.9	59.4	88.7
≥43	1,432	1.7	0.5	0.0	1.1
Apgar score, 1 minute, <8	14,565	16.4	44.2	32.6	19.2
Apgar score, 5 minutes, <8	2,121	2.2	16.5	10.2	3.6

* Numbers in parentheses, no. of pregnancies.

TABLE 3. Association between cigarette smoking and alcohol use in relation to placental abruption, Nova Scotia, Canada, 1986–1993

	Total no. of pregnancies	Placental abruption			
		No.	%	RR*,†	95% CI*
Smoking					
None	55,501	407	0.73	1.00‡	
Any	26,325	401	1.52	2.05	1.75–2.40
Cigarettes/day					
0	55,501	407	0.73	1.00‡	
1–5	3,281	43	1.31	1.79	1.27–2.52
6–10	6,234	95	1.52	1.94	1.50–2.50
11–15	7,522	117	1.56	2.20	1.75–2.75
16–20	3,068	46	1.50	2.07	1.49–2.88
≥21	6,220	100	1.61	2.18	1.81–2.69
Alcohol use					
None	66,324	625	0.94	1.00‡	
Any	12,793	114	0.89	0.88	0.72–1.08
Unknown	2,709	69	2.55		

* RR, relative risk; CI, confidence interval.

† Adjusted for hospital type, year of delivery, marital status, age, parity, chronic hypertension, and mild and severe preeclampsia through multivariable logistic regression based on generalized estimating equations. Alcohol was additionally adjusted for analysis related to smoking.

‡ Referent.

TABLE 4. Association between cigarette smoking and alcohol use in relation to placenta previa, Nova Scotia, Canada, 1986–1993

	Total no. of pregnancies	Placenta previa			
		No.	%	RR*,†	95% CI*
Smoking					
None	55,280	186	0.36	1.00‡	
Any	26,028	104	0.40	1.36	1.04–1.79
Cigarettes/day					
0	55,280	186	0.36	1.00‡	
1–5	3,249	11	0.34	1.45	0.79–2.67
6–10	6,160	21	0.34	1.27	0.78–2.06
11–15	7,432	27	0.36	1.27	0.81–2.00
16–20	3,038	16	0.53	1.80	1.06–3.07
≥21	6,149	29	0.47	1.29	0.83–2.02
Alcohol use					
None	65,912	213	0.32	1.00‡	
Any	12,742	63	0.49	1.26	0.95–1.69
Unknown	2,654	14	0.53		

* RR, relative risk; CI, confidence interval.
† Adjusted for hospital type, year of delivery, marital status, age, parity, chronic hypertension, and mild and severe preeclampsia through multivariable logistic regression based on generalized estimating equations. Alcohol was additionally adjusted for analysis related to smoking.
‡ Referent.

DISCUSSION

Placental abruption and placenta previa, although rare, are serious complications of pregnancy, with incidence rates varying from 0.5 percent to 2.5 percent for placental abruption and from 0.2 percent to 1.0 percent for placenta previa. This is consistent with our estimates of 1.0 percent for placental abruption and 0.4 percent for placenta previa. Our results corroborate the findings of several other earlier studies on the relation between placental abruption, placenta previa, and cigarette smoking. In previous reports, the odds ratio relating smoking to placental abruption has ranged between 1.4 and 1.7 (table 6), while we observed an

TABLE 5. Association between cigarette smoking and alcohol use in relation to uterine bleeding of unknown etiology, Nova Scotia, Canada, 1986–1993

	Total no. of pregnancies	Uterine bleeding			
		No.	%	RR*,†	95% CI*
Smoking					
None	58,417	3,323	5.69	1.00‡	
Any	27,669	1,745	6.31	1.01	0.94–1.08
Cigarettes/day					
0	58,417	3,323	5.69	1.00‡	
1–5	3,419	181	5.29	0.84	0.71–0.98
6–10	6,534	395	6.05	0.96	0.86–1.08
11–15	7,939	534	6.73	1.08	0.98–1.20
16–20	3,217	195	6.06	0.91	0.78–1.08
≥21	6,560	440	6.70	1.29	1.04–1.65
Alcohol use					
None	69,768	4,069	5.83	1.00‡	
Any	13,481	802	5.95	0.96	0.89–1.04
Unknown	2,837	197	6.94		

* RR, relative risk; CI, confidence interval.
† Adjusted for hospital type, year of delivery, marital status, age, parity, chronic hypertension, and mild and severe preeclampsia through multivariable logistic regression based on generalized estimating equations. Alcohol was additionally adjusted for analysis related to smoking.
‡ Referent.

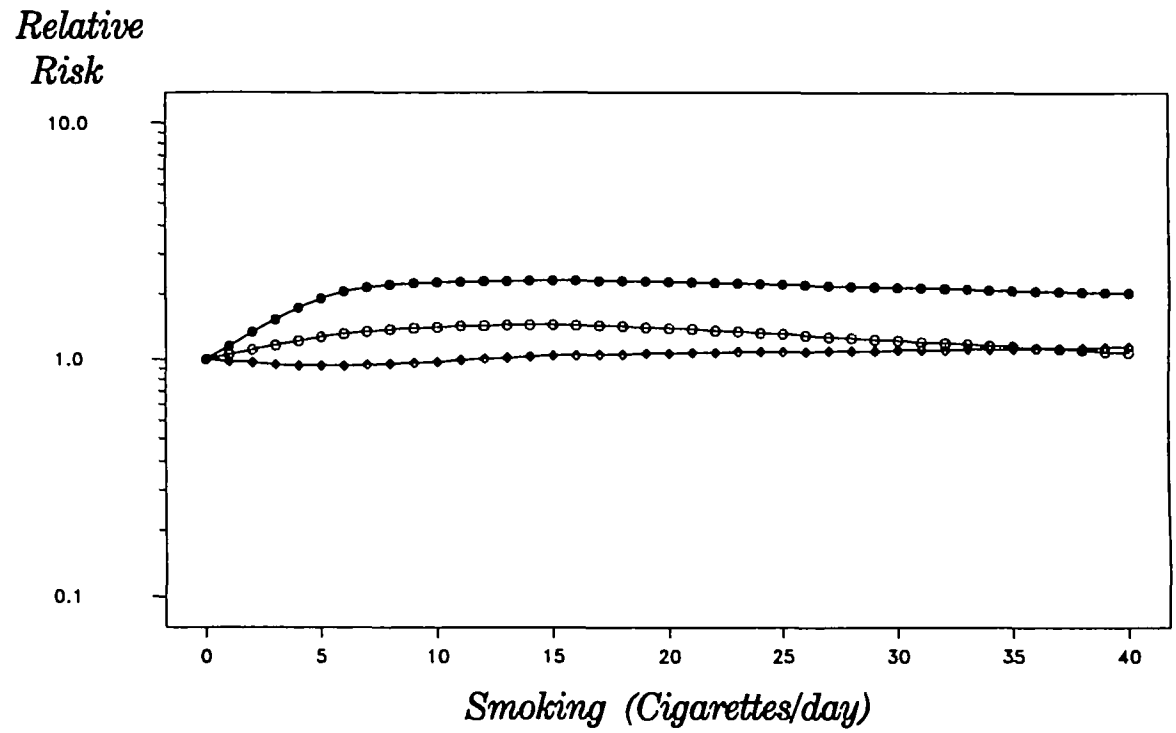

FIGURE 1. Associations between placental abruption (●), placenta previa (○), and uterine bleeding of unknown etiology (◇) and cigarette smoking during pregnancy, Nova Scotia, Canada, 1986–1993.

odds ratio of 2.1. However, Eriksen et al. (24) observed smoking to be associated with a 2.5-fold increase in the odds of placental abruption in comparison with nonsmoking. The elevated odds ratio in their study was possibly a result of their missing smoking data for 58 percent of cases of abruption and 27 percent of controls (24). Cigarette smoking also appears to be an independent risk factor for placenta previa (table 6), with odds ratios ranging from 1.3 to 2.6 in previous studies, while we observed a relative risk of 1.4.

There is less evidence to support an association between smoking and uterine bleeding of unknown etiology (25–27). Because of the variation in the time periods used to define vaginal bleeding during gestation (refer to table 6), comparison of results across studies is difficult. Uterine bleeding of unknown etiology is usually small to moderate in amount, and may

TABLE 6. Association between cigarette smoking and uteroplacental bleeding disorders in selected studies

Authors (ref. no.(s))	Placental abruption		Placenta previa		Uterine bleeding	
	OR*	95% CI*	OR	95% CI	OR	95% CI
Williams et al. (4, 14, 25)	1.5	1.0–2.2	2.6	1.3–5.5	0.8	0.7–0.9
Raymond and Mills (6)	1.4	1.1–1.8				
Voigt et al. (11)	1.6	1.3–1.8				
Meyer et al. (10)	1.4					
Naeye et al. (12)	1.4					
Zhang and Fried (13)			1.3	1.1–1.6		
Williams et al. (15)	1.7	1.5–2.0				
Kramer et al. (16)			1.9	1.5–2.8		
Handler et al. (17)			1.7	1.3–2.2		
Eriksen et al. (24)	2.5	1.2–5.1				
Berkowitz et al. (26)					1.1	1.0–1.3†
Strobino et al. (27)					0.9	0.7–1.1
Ananth et al. (present study)	2.1	1.8–2.4	1.4	1.0–1.8	1.0	0.9–1.1

* OR, odds ratio; CI, confidence interval.
† Vaginal bleeding up to the seventh month in pregnancy (unadjusted odds ratio).

or may not be associated with abdominal pain and uterine irritability. This condition has been attributed to "peripheral placental separation," which suggests that it is a probable variant of placental abruption (28). While we do not yet fully understand the pathophysiology relating smoking and uterine bleeding of unknown etiology, our data clearly suggest that placental abruption and uterine bleeding of unknown origin are etiologically distinct complications with regard to cigarette smoking, and that bleeding is not simply a mild form of placental abruption or a failure to properly diagnose placental abruption.

The lack of a dose-response relation between number of cigarettes smoked daily and uteroplacental bleeding disorders in our study is striking. Results from earlier studies evaluating a dose-response relation for both placental abruption and placenta previa are, at best, inconclusive. Monica and Lilja (7) observed odds ratios of 1.4 (95 percent CI 1.3–1.6) among women who smoked fewer than 10 cigarettes per day and 1.7 (95 percent CI 1.5–1.9) among women who smoked 10 or more cigarettes per day for placenta previa. Other studies (13, 17) reported similar observations, while Williams et al. (14) did not observe any dose-response pattern. Similarly, in an analyses of placental abruption, Williams et al. (4) observed an odds ratio of 1.4 (95 percent CI 0.8–2.2) for smoking 1–9 cigarettes per day and 1.5 (95 percent CI 0.8–2.8) for 10–19 cigarettes per day. In comparable analyses, we observed relative risks of 1.3 (95 percent CI 0.9–2.0) and 1.4 (95 percent CI 1.0–1.8) for placenta previa and 1.9 (95 percent CI 1.5–2.4) and 2.2 (95 percent CI 1.9–2.6) for placental abruption among women who smoked 1–10 and >10 cigarettes per day, respectively. Both analyses indicate the presence of a modest dose-response gradient, although this pattern vanishes when number of cigarettes smoked per day is stratified more finely.

Several potential mechanisms relating cigarette smoking during pregnancy to the development of placental abruption or placenta previa have been proposed. The placentas of smokers have been shown to be enlarged, with an increased surface area, and to have lesions characteristic of underperfusion of the uterus (29), while Spira et al. (30) observed an increased frequency of hypoxia among smokers compared with nonsmokers. Suzuki et al. (31) speculated that smoking may cause endothelial cell changes which subsequently cause vasoconstriction and rigidity of the arteriolar walls, with placental underperfusion. This, in turn, may lead to ischemia of the decidua basalis, with eventual decidual necrosis and hemorrhage. Any of these mechanisms could be responsible for the increased incidence of uteroplacental disorders attributable to cigarette smoking.

Some lesser degrees and milder forms of placental abruption or marginal or low-lying placenta previa could have been overlooked in our study. Assuming that there was slight misclassification of abruption or previa, the misclassification would probably have been nondifferential with regard to smoking, thereby biasing the associations toward the null value. Since the incidence rates of these disorders in our study are consistent with those reported in other studies, it is very unlikely that our results were grossly biased due to misclassification. On the other hand, the results pertaining to uterine bleeding of unknown etiology must be interpreted with caution. Although most instances of uterine bleeding that required hospital admission would have been due to heavy bleeding, some women with lesser degrees of bleeding may have been missed from this group. Finally, the possibility of variation in the classification and diagnosis of uteroplacental bleeding disorders, especially placental abruption, due to different physicians' using different diagnostic criteria cannot be overlooked.

Information on cigarette smoking and alcohol use was collected through maternal self-report, which could have resulted in underestimation, since there is some stigma associated with these lifestyle factors. However, since patients were unaware of the future occurrence of uteroplacental bleeding disorders, the underestimation, if any, would have been nondifferential, resulting in a weaker association. Given the high overall prevalence of smoking in Nova Scotia, however, we do not believe that there was substantial underreporting. It has been reported that approximately 18 percent of women who smoke quit smoking by their first prenatal visit (32), which may also have resulted in underestimation of the association between smoking and uteroplacental bleeding disorders in our study. Women who use cocaine are also more likely to be smokers, and cocaine use has been shown to result in placental abruption (17). Unfortunately, we could not control for cocaine use during pregnancy, since this information was not available in our database. This could perhaps account for some of the excess risk found in our study. It should also be noted that since our patient population consisted of predominantly white women (over 95 percent), our results may not be generalizable to other patient populations.

Our population-based study corroborates and strengthens earlier findings on the positive association between smoking and placental abruption and the presence of a weak association with placenta previa. In future studies, careful assessment of past and current history of smoking, with reliable information on co-

caine and "crack" use during pregnancy, in relation to these uteroplacental bleeding disorders may help in furthering our understanding of the etiology of these complications. The distinct pattern of results observed in our study for placental abruption, placenta previa, and uterine bleeding of unknown origin suggests that the three uteroplacental bleeding disorders do not share a common etiology in relation to cigarette smoking. Although smoking is largely avoidable, one of every three women in Nova Scotia smokes during pregnancy, yielding attributable risks of 27 percent for placental abruption and 12 percent for placenta previa. Hence, if women stopped smoking during pregnancy, 27 percent and 12 percent of abruption and previa cases, respectively, could be avoided. The increased risk of uteroplacental bleeding disorders attributable to smoking is yet another reason to encourage women to quit smoking during pregnancy.

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REFERENCES

1. Naeye RL, Harkness WL, Utts J. Abruptio placentae and perinatal death: a prospective study. Am J Obstet Gynecol 1977;128:740–6.
2. Karegard M, Gennser G. Incidence and recurrence rate of abruptio placentae in Sweden. Obstet Gynecol 1986;67: 523–8.
3. Iyasu S, Saftlas AK, Rowley DL, et al. The epidemiology of placenta previa in the United States, 1979 through 1987. Am J Obstet Gynecol 1993;168:1424–9.
4. Williams MA, Lieberman E, Mittendorf R, et al. Risk factors for abruptio placentae. Am J Epidemiol 1991;134:965–72.
5. Krohn M, Voigt L, McKnight B, et al. Correlates of placental abruption. Br J Obstet Gynecol 1987;94:333–40.
6. Raymond EG, Mills JL. Placental abruption: maternal risk factors and associated fetal conditions. Acta Obstet Gynecol Scand 1993;72:633–9.
7. Monica G, Lilja C. Placenta previa, maternal smoking and recurrence risk. Acta Obstet Gynecol Scand 1995;74:341–5.
8. Abdella TN, Sibai BM, Hays JM Jr, et al. Relationship of hypertensive disease to abruptio placentae. Obstet Gynecol 1984;63:365–70.
9. Nelson DM, Stempel LE, Zuspan FP. Association of prolonged, preterm premature rupture of the membranes and abruptio placentae. J Reprod Med 1986;31:249–53.
10. Meyer MB, Jonas BS, Tonascia JA. Perinatal events associated with maternal smoking during pregnancy. Am J Epidemiol 1976;103:464–76.
11. Voigt LF, Hollenbach KA, Krohn MA, et al. The relationship of abruptio placentae with maternal smoking and small for gestational age infants. Obstet Gynecol 1990;75:771–4.
12. Naeye RL. Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. Obstet Gynecol 1980;55:701–4.
13. Zhang J, Fried DB. Relationship of maternal smoking during pregnancy to placenta previa. Am J Prev Med 1992;8:278–82.
14. Williams MA, Mittendorf R, Lieberman E, et al. Cigarette smoking during pregnancy in relation to placenta previa. Am J Obstet Gynecol 1991;165:28–32.
15. Williams MA, Mittendorf R, Monson RR. Chronic hypertension, cigarette smoking, and abruptio placentae. Epidemiology 1991;2:450–3.
16. Kramer MD, Taylor V, Hickok DE, et al. Maternal smoking and placenta previa. Epidemiology 1991;2:221–3.
17. Handler AS, Mason ED, Rosenberg DL, et al. The relationship between exposure during pregnancy to cigarette smoking and cocaine use and placenta previa. Am J Obstet Gynecol 1994; 170:884–9.
18. Ananth CV, Savitz DA. Vaginal bleeding and adverse reproductive outcomes: a meta-analysis. Paediatr Perinat Epidemiol 1994;8:62–78.
19. Dodds L. Prevalence of smoking among pregnant women in Nova Scotia from 1988 to 1992. Can Med Assoc J 1995;152: 185–90.
20. Ananth CV, Savitz DA, Luther ER, et al. Pre-eclampsia and preterm birth subtypes in Nova Scotia, 1986 to 1992. Am J Perinatol 1996 (in press).
21. Zeger SL, Liang K-Y. Longitudinal data analysis for discrete and continuous outcomes. Biometrics 1986;42:121–30.
22. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551–61.
23. MacGillivray I, Davey D, Isaacs S. Placenta praevia and sex ratio at birth. Br Med J 1986;292:371–2.
24. Eriksen G, Wohlert M, Ersbak V, et al. Placental abruption: a case-control investigation. Br J Obstet Gynecol 1991;98: 448–52.
25. Williams MA, Mittendorf R, Lieberman E, et al. Adverse infant outcomes associated with first-trimester vaginal bleeding. Obstet Gynecol 1991;78:14–18.
26. Berkowitz GS, Harlap S, Beck GJ, et al. Early gestational bleeding and pregnancy outcome: a multivariable analysis. Int J Epidemiol 1983;12:165–73.
27. Strobino B, Pantel-Silverman J. Gestational vaginal bleeding and pregnancy outcome. Am J Epidemiol 1989;129:806–15.
28. Harris BA Jr. Peripherial placental separation: a review. Obstet Gynecol Surv 1988;43:577–81.
29. Christianson RE. Gross differences observed in the placentas of smokers and nonsmokers. Am J Epidemiol 1979;110: 178–87.
30. Spira A, Philippe E, Spira N, et al. Smoking during pregnancy and placental pathology. Biomedicine 1977;27:266–70.
31. Suzuki K, Minei LJ, Johnson EE. Effect of nicotine upon uterine blood flow in the pregnant rhesus monkey. Am J Obstet Gynecol 1980;136:1009–13.
32. Lumley J. Stopping smoking. Br J Obstet Gynaecol 1987;94: 289–92.