The Relationship of Smoking and Ectopic Pregnancy

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Abstract: A case-control study, using data abstracted between 1983 and 1987 from a large perinatal registry, was conducted to explore the relationship between smoking and ectopic pregnancy. Women with ectopic pregnancy (n = 634) seen at University of Illinois Perinatal Network Hospitals were compared to women who were delivered of a single live-born infant (n = 4287). Adjusted for age and race, women who reported smoking during pregnancy had a greater than twofold risk of ectopic pregnancy (Odds Ratio = 2.5, 95% confidence interval = 1.9, 3.2) compared to women who never smoked. The estimated relative risk rose from 1.4 (95% CI = 0.8, 2.5) for a woman smoking fewer than 10 cigarettes a day to 5.0 (95% CI = 2.9, 8.7) at one and a half or more packs of cigarettes per day (p-value for trend <0.001). Although further basic and epidemiologic research is necessary, the observed dose-response relation strengthens the argument that smoking may be a causal factor in the development of ectopic pregnancy. (*Am J Public Health* 1989; 79:1239–1242.)

Introduction

Although ectopic pregnancy is a relatively uncommon occurrence, its incidence has quadrupled from a rate of 5/1000 live births in 1970.[1] Simultaneously, maternal mortality rates from other causes have fallen, making ectopic pregnancy the primary cause of maternal mortality during the first trimester of pregnancy. Known risk factors for ectopic pregnancy include pelvic inflammatory disease, prior tubal surgery, contraceptive history, and a history of infertility.[2] As the rise in incidence of ectopic pregnancy has paralleled the increase in cigarette smoking among women, it is reasonable to examine smoking as a potential risk factor.

Most of the evidence for the positive association of smoking and ectopic pregnancy derives from studies in which smoking was not a primary hypothesis (Odds Ratios = 1.5 to 3.9).[3–6] Recently Chow, *et al*,[7] investigated the potential etiologic relationship between cigarette smoking at the time of conception and ectopic pregnancy, considering the effect of age at initiation, smoking duration, and intensity on this event. An overall association of smoking with ectopic pregnancy was evident (OR = 2.2), but a dose-response was not demonstrated, possibly due to an inadequate number of cases. To permit more stable estimates of the risk of ectopic pregnancy by level of smoking, a case-control study using data from a large perinatal registry was conducted.

Methods

The University of Illinois Hospital (UIH) Perinatal Network collects information on 425 variables for all maternal and neonatal events occurring at its 12 member hospitals. Data are abstracted daily from medical records by trained abstracters and entered into the UIH perinatal database.

Women with an ectopic pregnancy (n = 701) presenting at UIH Perinatal Network Hospitals from 1983–87 were identified. Cases with a prior ectopic pregnancy were excluded (n = 67), leaving 634 total cases for study. Controls were a 5 percent random sample of all women without a prior history of ectopic pregnancy delivered of a single live-born infant (n = 4287) at these same hospitals. Women with pregnancies resulting in spontaneous abortions or fetal deaths were excluded for use as controls in this study because of the known relationship between maternal smoking and these reproductive outcomes.[8,9]

Cigarette smoking data in the UIH perinatal database is a measure of smoking during the current pregnancy. It is recorded as a dichotomous variable (yes/no) and as a continuous variable (number of cigarettes smoked per day). Ascertainment of smoking history was similar between cases and controls. Information on smoking as a dichotomous variable was available for 93.4 percent of the cases and for 91.9 percent of the controls; information on cigarette dose was available for 87.9 percent of the cases and 87.6 percent of the controls. Five levels of cigarette smoking were considered: nonsmokers; less than 10 cigarettes/day; 10–19/day; 20–29/day; and 30 or more/day.

Other variables collected on the perinatal abstract form were examined as potential risk factors: maternal age, race, payment method (as an indicator of socioeconomic status), gravidity, parity, prior spontaneous abortion, and prior induced abortion. Past or present pelvic inflammatory disease, past and current contraceptive use, and detailed fertility history were not available for this analysis.

The odds ratio and 95% Taylor series confidence intervals were used to describe the association between ectopic pregnancy and smoking.[10,11] Adjusted odds ratios were calculated using the Mantel-Haenszel technique and 95% confidence intervals according to the method of Robins, Greenland, and Breslow.[12] Tests for trend were computed by the Mantel extension.[13] To adjust simultaneously for multiple factors, a multiple logistic regression model was fitted with smoking as a dichotomous independent variable (yes/no) and ectopic pregnancy as the dependent variable.[14] The model was restricted to women with no prior history of spontaneous abortion since spontaneous abortion history modified the smoking-ectopic relationship.

An adjusted dose-response relationship between smoking and ectopic pregnancy was tested in a second multivariable model, with cigarette smoking treated as a continuous variable. In a third multivariable model, smoking was treated as a series of dummy variables to estimate dose-specific odds ratios.

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Results

The rate of ectopic pregnancy at the University of Illinois Perinatal Network hospitals from 1983 to 1987 was 7.9 per 1000 live births. Increasing maternal age, Black race, increased gravidity, increased parity and prior spontaneous abortion are risk factors for ectopic pregnancy in this population (Table 1). Asians had a lower risk of ectopic pregnancy than other ethnic groups.

Women who reported smoking during pregnancy had a greater than twofold risk of ectopic pregnancy. Controlling for maternal age, race, payment method, gravidity, parity, and spontaneous abortion separately did not alter this crude estimate (range of estimates = 2.2–2.4). Smoking raised the risk of ectopic pregnancy less among women who had a prior spontaneous abortion (OR = 1.6, 95% CI = 1.1, 2.3) than among women who had not (OR = 2.5, 95% CI = 2.1, 3.1). This is due to the higher prevalence of smoking among women with ectopic pregnancy who have *not* had a prior spontaneous abortion (Table 1).

The smoking effect among women with no prior history of spontaneous abortion, adjusting for maternal age and race (Black versus other) was OR 2.5 (95% CI = 1.9, 3.2) (Table 2). A dose-gradient between cigarette smoking and ectopic pregnancy was evident when smoking was evaluated as a continuous variable (regression coefficient = 0.049, S.E. = 0.006) or as a categorical variable (Table 2 and Figure 1).

Discussion

In this study, women who reported smoking during pregnancy had a greater than twofold risk of ectopic pregnancy. This effect is similar to that seen in previous studies (Table 3).[4–7] The reported association is strengthened by the dose-response after adjusting for maternal age and race. Based on the estimates presented here, 60 percent of the ectopic pregnancies among smokers may be due to smoking.[11]

The significantly increased risk of ectopic pregnancy associated with increasing age and with Black race demonstrated in this report is consistent with other studies of ectopic pregnancy.[2] The gravidity and parity effect observed in the crude analysis disappeared when adjusting for prior spontaneous abortion. While in this population there was no increased risk of ectopic pregnancy associated with prior induced abortion, an increased risk with prior spontaneous abortion among multigravid women was observed. Previous

TABLE 1—Distribution of Cases and Controls by Selected Risk Factors and Smoking Status, Odds Ratios (OR), and 95% Confidence Intervals for Each Factor and Ectopic Pregnancy

	Cases (N = 634)		Controls (N = 4287)			
Risk Factors	n	% smoke[a]	n	% smoke[a]	OR	95% CI
Maternal age[b] (years)						
24 or Less	166	47	1618	27	1.0	
25–34	369	42	2268	22	1.6	1.3, 1.9
Over 35	99	32	400	19	2.4	1.8, 3.2
Missing	0		1			
Race						
White	317	47	2171	27	1.0	
Black	196	45	974	31	1.4	1.1, 1.7
Hispanic	103	26	849	13	0.8	0.7, 1.1
Asian	17	0	205	4	0.6	0.3, 0.9
Other/Missing	1		88			
Payment Method						
Private	349	38	2156	19	1.0	
Medicaid	140	52	1074	35	0.8	0.7, 1.0
Self	98	44	548	23	1.1	0.9, 1.4
Other	47	30	422	21	0.7	0.5, 0.9
Missing	0		87			
Gravidity[b]						
Primigravida	139	38	1298	19	1.0	
1 Prior	168	45	1237	21	1.3	1.0, 1.6
2 or More Prior	318	41	1667	29	1.8	1.4, 2.2
Missing	9		84			
Parity[b]						
Nulliparous	229	43	1730	22	1.0	
Primipara	188	41	1305	23	1.1	0.9, 1.3
2 or More Prior	208	41	1170	27	1.3	1.1, 1.6
Missing	9		82			
Prior Spontaneous Abortion[c]						
Yes	163	37	749	28	1.5	1.2, 1.8
No	323	45	2158	25	1.0	
Prior Induced Abortion[c]						
Yes	76	58	515	36	0.9	0.7, 1.1
No	410	40	2392	24	1.0	
Current Smoking						
Yes	246	39	932	22	2.3	1.9, 2.7
No	346		3008		1.0	
Missing	42		347			

[a]% Smokers in each category for cases and controls.
[b]Mantel Extension $p < 0.001$.
[c]For multigravid women only.

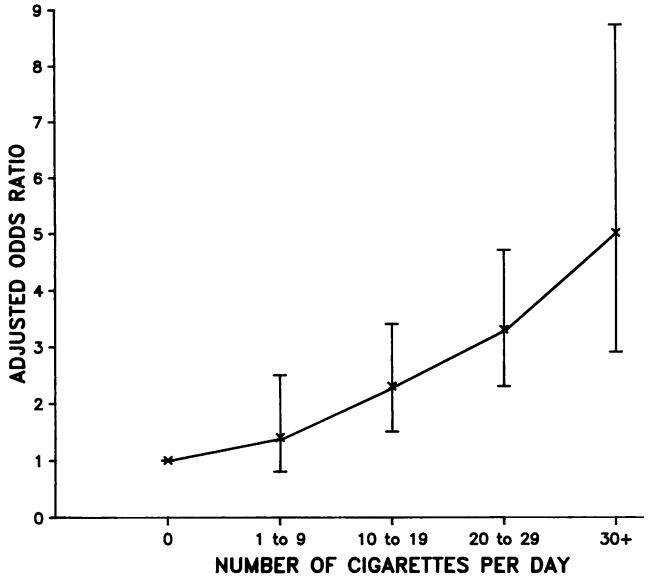

FIGURE 1—Dose Response Curve for Smoking and Ectopic Pregnancy among Women with no Prior Spontaneous Abortion, Adjusted for Maternal Age and Race.

TABLE 2—Frequency of Cases and Controls, Adjusted Odds Ratios (OR_{adj}), and 95% Confidence Intervals for Smoking and Ectopic Pregnancy among Women with no Prior Spontaneous Abortion

Smoking Status	Cases (N = 323) n	Controls (N = 2158) n	OR_{adj}[a]	95% CI
Current Smoking (Yes/No)	152	645	2.5	1.9, 3.2
Number of Cigarettes/Day[b]				
Nonsmoker	171	1513	1.0	
<10	16	94	1.4	0.8, 2.5
10–19	33	135	2.3	1.5, 3.4
20–29	53	146	3.2	2.3, 4.7
30+	22	41	5.0	2.9, 8.7
Missing	28	229		

[a]Adjusted for maternal age and race.
[b]p <0.001 for smoking as a continuous variable.

TABLE 3—Comparisons with Other Studies

Other Studies	Crude OR	95% CI
Matsunaga 1980[4]	2.3	1.0–5.5
Levin 1982[5]	1.5	0.8–2.8
WHO 1985[6]	2.1	1.7–2.6
Chow 1988[7]	2.2	1.4–3.4
Handler 1989	2.3	1.9–2.7

studies of the relationship between ectopic pregnancy and abortion of either type have been equivocal.[2,5,15–19*]

A major strength of this study is the large and ethnically diverse sample. Data collection was conducted without knowledge of the study's hypothesis, thereby preventing bias due to differential data collection for cases and controls. Despite the unexpected lower rate of ectopic pregnancy in this population, it is unlikely to affect the ascertainment of smoking data or the internal validity of the comparisons.

It is possible the exclusion of spontaneous abortions, antepartum and intrapartum fetal deaths in the control group led to an overestimate of the smoking effect since smoking increases the risk of spontaneous abortion and fetal deaths. A separate analysis including these outcomes in the control group did not alter the dose gradient observed.

The smoking data reported here refer to behavior during the current pregnancy as ascertained from medical records at the termination of pregnancy rather than interview or biochemical measures. For those identified as smoking during pregnancy, smoking behavior at conception and the duration of smoking prior to conception were unknown. Although these factors may be influential,[7] they seem unlikely to entirely explain the association with level of cigarette smoking. Additionally, women who stopped smoking just prior to pregnancy were not identifiable and their inclusion in the non-smoking group may lead to a conservative estimate of the relationship between smoking and ectopic pregnancy.

A weakness of this study is that three previously identified risk factors for ectopic pregnancy were not available in the University of Illinois Perinatal Network database and therefore could not be evaluated. These are prior or current contraceptive use, past or current history of pelvic inflammatory disease (PID), and past or current sexually transmitted diseases (STD). The World Health Organization's multinational study[6] of ectopic pregnancy found that adjustment for past history of PID or STD and for intrauterine device (IUD) use at the time of conception did not alter estimates of risk for current cigarette smokers when compared to pregnant (RR = 3.1) or nonpregnant (RR = 1.8) controls. Chow, *et al*, demonstrated an increased risk of tubal pregnancy associated with current smoking which was independent of past IUD use.

If the association between smoking and ectopic pregnancy is causal, the biologic mechanism might be one of several suggested by human and animal studies. In theory, any anatomic or physiologic factor impeding the transit of the ovum or blastocyst to the uterus may lead to an ectopic pregnancy.[20] Alterations in normal tubal architecture and tubo-ovarian relationships can mechanically delay ovum transport. This may explain the high incidence of ectopic pregnancy associated with tubal infection, pelvic surgery, and endometriosis which may cause partial tubal occlusions and/or pelvic adhesions.[21] However, up to 50 percent of the ectopic pregnancies are unexplained by any identifiable anatomical tubal factor.[22]

In humans, cigarette smoking can alter tubal motility by increasing muscular tone and the wave amplitude of tubal contractions as determined by uterotubal insufflation before and after smoking. Nicotine exposure leads to a short period of increased uterotubal activity followed by a longer period of tubal inactivity, providing increased opportunity for tubal implantation.[23]

Non-human primate and rodent studies have also demonstrated an alteration from baseline levels of tubal motility following injection of nicotine.[24–27] Nicotine treatment has been shown to delay ovum entry into the uterus, blastocyst formation, and blastocyst implantation as well as to alter spacing of implantation sites. These studies indicate cigarette smoking and nicotine are capable of affecting motility and could disrupt the complex sequence of coordinated tubal

*Holt V, Daling J, Voigt L: Induced abortion and the risk of subsequent ectopic pregnancy. Presented at the 21st Annual Meeting of the Society for Epidemiologic Research, Vancouver, Canada, June 1988.

contractions necessary for normal ovum transport.

Alternatively the effect of smoking on the occurrence of ectopic pregnancy may be due to the impairment of cellular and humoral immunity.[28–31] Smoking may be part of the causal chain linking pelvic inflammatory disease to ectopic pregnancy. It is possible that altered immunity in cigarette smokers may increase the incidence and prevalence of both tubal infection and pelvic inflammatory disease. However, the hypothesized association between smoking and pelvic inflammatory disease has not yet been explored.[7]

Basic research is needed to clarify the specific mechanism by which smoking may "cause" ectopic pregnancy. Epidemiologic studies controlling for all known risk factors are needed to confirm the dose-response relationship observed in this study between smoking and ectopic pregnancy.

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National Maternal and Child Oral Health Workshop

A national workshop entitled "Maternal and Child Oral Health" will be held September 10–12, 1989 in Washington, DC. The Workshop will solicit expert scientific and policy opinion from invited participants concerning mechanisms to optimize oral health for the maternal and child population.

The purpose of the National Workshop is to provide a set of recommendations and health policy proposals to the US Public Health Service which, when implemented, will improve the oral health of mothers and children. A report of the final recommendations will be disseminated for use by agencies, organizations, health care providers, and the public.

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