



## Risk Factors for Ectopic Pregnancy: A Comprehensive Analysis Based on a Large Case-Control, Population-based Study in France

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This case-control study was associated with a regional register of ectopic pregnancy between 1993 and 2000 in France. It included 803 cases of ectopic pregnancy and 1,683 deliveries and was powerful enough to investigate all ectopic pregnancy risk factors. The main risk factors were infectious history (adjusted attributable risk = 0.33; adjusted odds ratio for previous pelvic infectious disease = 3.4, 95% percent confidence interval (CI): 2.4, 5.0) and smoking (adjusted attributable risk = 0.35; adjusted odds ratio = 3.9, 95% CI: 2.6, 5.9 for >20 cigarettes/day vs. women who had never smoked). The other risk factors were age (associated per se with a risk of ectopic pregnancy), prior spontaneous abortions, history of infertility, and previous use of an intrauterine device. Prior medical induced abortion was associated with a risk of ectopic pregnancy (adjusted odds ratio = 2.8, 95% CI: 1.1, 7.2); no such association was observed for surgical abortion (adjusted odds ratio = 1.1, 95% CI: 0.8, 1.6). The total attributable risk of all the factors investigated was 0.76. As close associations were found between ectopic pregnancy and infertility and between ectopic pregnancy and spontaneous abortion, further research into ectopic pregnancy should focus on risk factors common to these conditions. In terms of public health, increasing awareness of the effects of smoking may be useful for ectopic pregnancy prevention.

abortion, induced; case-control studies; infertility, female; pregnancy, ectopic; registries; risk factors; sexually transmitted diseases; tobacco

Abbreviation: CI, confidence interval.

During the 1980s and 1990s, the incidence of ectopic pregnancy in developed countries increased by a factor of 3–4 (1–5), reaching 100–175 per 1,000,000 women aged 15–44 years.

Several risk factors for ectopic pregnancy have been identified (3, 6–8) including pelvic inflammatory disease, smoking, and, previous ectopic pregnancy. Other factors, such as age, surgical history, and obstetric history, are also thought to be involved. However, the role played by these factors remains unclear because of problems with the sample size or the design of previous studies. Published meta-analyses of ectopic pregnancy risk factors (9–11) only partly answered the questions addressed, mainly because their ability to adjust for confounders was limited (12, 13). This

problem is particularly severe in analyses of ectopic pregnancy, which has a large number of highly correlated risk factors. The selection of studies to be included in the meta-analysis and assessment of their quality may also cause difficulties. Strikingly, in the two most recent meta-analyses on this subject, two different sets of studies were selected (9, 10).

The ectopic pregnancy register of Auvergne (France) (14) and associated case-control studies provide an opportunity to analyze the risk factors for ectopic pregnancy in a large sample, representative of a geographically defined population. Results concerning women using contraception at the time of conception have already been published (15). This study focuses on women not using contraception at the time

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of conception. It aimed to provide a comprehensive analysis of the ectopic pregnancy risk factors in these women.

## MATERIALS AND METHODS

### Study population

The methodology of the register has been described elsewhere (14). The register was established in January 1992 in the Auvergne region in central France (around 1.1 million inhabitants). All the women between 15 and 44 years of age living in the target area who were treated for ectopic pregnancy were registered. At each center (15 maternity hospitals and 12 surgical units, either public or private), a trained investigator—a midwife or a physician—was responsible for case identification and data collection, and this investigator checked the completeness of case recording at the end of each year. The information collected for each woman (from interview and medical records) included sociodemographic characteristics; gynecologic, reproductive, and surgical history; conditions at conception (use of contraception, ovulation induction); smoking habits; results of serologic tests for *Chlamydia trachomatis*; characteristics of the ectopic pregnancy; and the treatment procedures used.

Each case of ectopic pregnancy in a woman not using contraception was associated with two controls: women who gave birth at the center at which the case was treated and women whose delivery occurred very shortly after treatment of the case. For some cases, only one control was interviewed, and no control was associated with cases retrieved at the end of the year when the completeness of the register was checked. The same questionnaire was used for cases and controls, except for items relating directly to the diagnosis and treatment of ectopic pregnancy. Between September 1993 (beginning of recruitment of controls) and December 2000, a total of 1,065 cases and 1,881 controls were collected.

Women who underwent induced abortion were not included in the control group because, in France, these women are referred to specialist centers not connected with maternity hospitals. However, a certain proportion of cases might have undergone induced abortion had their pregnancy been intrauterine. We attempted to take this into account by the method recommended by Weiss et al. (16), which involves restricting the analysis to women married (or living as a couple) and not using contraception at the time of conception (803 cases and 1,683 controls). As stated by Weiss et al., this restriction should make cases and controls more comparable, reducing the magnitude of the bias present when evaluating variables associated with induced abortion.

### Statistical analysis

We carried out a two-stage analysis as a large number of potential risk factors were investigated. We first assigned the risk factors to four groups: 1) sociodemographic characteristics, 2) surgical, gynecologic, and obstetric history, 3) potential exposure to infectious factors, and 4) contraceptive history and fertility markers. Univariate analyses were performed to generate crude odds ratios. Logistic regressions

were then performed within each group, including variables with  $p$  values of  $\leq 0.2$  in univariate analysis (17). Finally, variables with  $p$  values of  $\leq 0.2$  in these four partial analyses were included in a global logistic regression analysis. The assignment of a factor to a particular group was a matter of debate in some instances. We checked that the assignment of such factors to particular groups had no influence on the final logistic regression analysis.

For quantitative variables, such as age or time since the previous pregnancy, the association with ectopic pregnancy risk was plotted using fractional polynomials (18), a simple and powerful way of modeling nonlinear relations.

Finally, attributable risks were calculated for each risk factor. Attributable risks provide an additional dimension to risk factors that is useful for public health purposes. The odds ratio gives the individual increase in risk of ectopic pregnancy for a woman exposed to that risk, whereas the attributable risk indicates the burden of this risk factor at the population level. Attributable risks were adjusted for the other risk factors as described by Bruzzi et al. (19). For age, the category 25–29 years was taken as the reference because this corresponds to the mean age for delivery in France at the time of the study. Thus, the odds ratio and attributable risk were calculated with this category considered as “nonexposed.”

A woman experiencing several ectopic pregnancies during the study period generated multiple case entries, one for each ectopic pregnancy. In this study, 43 women experienced two ectopic pregnancies and four women experienced three ectopic pregnancies, that is, 12 percent of all ectopic pregnancies. Although this proportion was relatively small, the potential nonindependence of the data induced was taken into account using a random effects model (17) in the multivariate analysis; incidentally, we observed that the results were quite similar to those obtained with a usual logistic model.

Statistical analyses were performed with STATA software (20).

## RESULTS

The results of univariate analysis are shown in tables 1, 2, 3, and 4. Table 5 gives the results of multivariate analysis (final logistic regression), and table 6, the adjusted attributable risks.

### Sociodemographic characteristics and cigarette smoking

The crude risk of ectopic pregnancy increased with age (table 1). Although the trend was less marked after adjustment, it remained statistically significant (figure 1; table 5). The slope of the association appeared to be steeper after 35–40 years of age. There was no association between ectopic pregnancy and other sociodemographic characteristics (not shown).

The risk associated with smoking increased in a dose-dependent manner (table 5). Among past smokers, the time since smoking cessation was not associated with ectopic pregnancy risk (not shown). The prevalence of past or current smoking in our population was particularly high (41

**TABLE 1. Ectopic pregnancy and sociodemographic characteristics, register of the Auvergne region, France, 1993–2000**

Variables	Controls (n = 1,683)		Cases (n = 803)		Crude OR*	95% CI*	p value†
	No.	%	No.	%			
Woman's age (years)							
<20	19	1.1	5	0.6	0.7	0.3, 1.9	
20–24	288	17.2	91	11.3	0.9	0.6, 1.1	
25–29	686	40.9	253	31.5	1		<0.001
30–34	487	29.0	273	34.0	1.5	1.2, 1.9	
35–39	178	10.6	141	17.6	2.1	1.6, 2.8	
≥40	19	1.3	40	5.0	5.7	3.2, 10.2	
Smoking							
Never	990	59.1	299	38.9	1		<0.001
Past smoker	176	10.5	81	10.5	1.5	1.1, 2.0	
1–9 cigarettes/day	215	12.8	106	13.8	1.6	1.2, 2.1	
10–19 cigarettes/day	185	11.1	161	20.9	2.9	2.2, 3.7	
≥20 cigarettes/day	108	6.5	122	15.9	3.7	2.8, 5.0	
Educational level							
Primary	130	7.8	55	7.2	1		0.8
Secondary	1,125	67.5	530	69.5	1.1	0.9, 1.4	
Higher	411	24.7	178	23.3	1.0	0.7, 1.5	

\* OR, odds ratio; CI, confidence interval.

† p value (for variables with more than two categories, the p value of the test for trend is given).

percent among controls), resulting in an adjusted attributable risk of smoking as high as 35 percent (table 6).

### Surgical and obstetric history

Most of the items recorded in the patients' obstetric histories were associated with ectopic pregnancy (table 2). However, the age of the woman and previous intrauterine device use accounted for the crude association with prior delivery. We therefore did not include the variable "prior deliveries" in the final multivariate analysis to avoid overadjustment. Although the association with prior ectopic pregnancies was very strong, this variable was not included in the final multivariate analysis. Instead, we included a broader variable, "tubal surgery," which covered all indications for tubal surgery, not just ectopic pregnancy treatment.

Prior spontaneous abortions increased the risk of ectopic pregnancy, especially for women with three or more spontaneous abortions (tables 2 and 5).

The risk of ectopic pregnancy was higher in women with previous induced abortions. However, the odds ratio differed according to the method used for abortion (table 2). The results were similar after adjustment (table 5): With prior surgical abortion only, the odds ratio = 1.1 (95 percent confidence interval (CI): 0.8, 1.6), whereas the odds ratio in women with prior medical abortion only (mifepristone and misoprostol) was 2.8 (95 percent CI: 1.1, 7.2).

### Infectious history

Infectious history was studied through direct items, such as prior sexually transmitted diseases, or indirect items, such as the age at first intercourse and the number of sexual partners, which were considered to be markers of potential risk of sexually transmitted disease.

The indirect factors were associated with a risk of ectopic pregnancy in univariate analysis (table 3) but not in multivariate analysis. Prior sexually transmitted diseases were associated with a risk of ectopic pregnancy, with an adjusted odds ratio of 3.4 (95 percent CI: 2.4, 5.0) for prior confirmed pelvic infectious disease (table 5). If infectious history and prior tubal surgery (frequently performed because of infection) were considered together, their adjusted attributable risk was 0.33 (table 6).

### Contraceptive history and fertility markers

Previous use of oral contraception was associated with a decreased risk of ectopic pregnancy. In contrast, previous use of an intrauterine device was associated with an increased risk of ectopic pregnancy. The induction of ovulation with clomiphene citrate was associated with a risk of ectopic pregnancy in univariate analysis, but this association disappeared after adjustment for prior infertility. A history of infertility was strongly associated with the risk of ectopic pregnancy, with a dose-response relation and an adjusted odds ratio for more than 2 years of infertility of 2.7 (95 percent CI: 1.8, 4.2).

**TABLE 2. Ectopic pregnancy and surgical, gynecologic, and obstetric history, register of the Auvergne region, France, 1993–2000**

Variables	Controls (n = 1,683)		Cases (n = 803)		Crude OR*	95% CI*	p value†
	No.	%	No.	%			
Prior deliveries							
None	784	46.6	317	39.5	1		<0.001
1	616	36.6	286	35.6	1.1	0.9, 1.4	
2	214	12.7	136	16.9	1.6	1.2, 2.0	
≥3	69	4.1	64	8.0	2.3	1.6, 3.3	
Prior ectopic pregnancies							
None	1,661	98.8	672	84.1	1		<0.001
1	19	1.1	96	12.0	12.5	7.5, 20.9	
≥2	1	0.06	31	3.9	76.6	10.1, 580	
Prior spontaneous abortions							
None	1,365	81.1	566	70.5	1		<0.001
1	255	15.2	171	21.3	1.6	1.3, 2.0	
2	48	2.9	37	4.6	1.9	1.2, 2.9	
≥3	15	0.9	29	3.6	4.7	2.5, 8.8	
Prior induced abortions							
None	1,463	86.9	660	82.2	1		0.001
1	199	11.8	115	14.3	1.3	1.0, 1.6	
≥2	21	1.3	28	3.5	3.0	1.7, 5.3	
Type of prior induced abortion							
None	1,463	88.3	660	83.3	1		0.001
Surgical only	182	11.0	115	14.5	1.4	1.1, 1.8	
Medical only	11	0.7	13	1.6	2.6	1.2, 5.9	
Both	1	0.1	4	0.5	8.9	1.0, 79	
Appendectomy							
No, or unruptured appendix	1,630	96.9	756	94.6	1		0.006
Yes, ruptured appendix	52	3.1	43	5.4	1.8	1.2, 2.7	
Prior tubal surgery							
No	1,626	96.6	613	76.3	1		<0.001
Yes	57	3.4	190	23.7	8.8	6.4, 12.3	

\* OR, odds ratio; CI, confidence interval.

† p value (for variables with more than two categories, the p value of the test for trend is given).

The crude relation between time since previous pregnancy and risk of ectopic pregnancy gave a J-shaped curve (table 4). However, time since previous pregnancy was closely associated with the woman's age, infertility, and previous use of an intrauterine device. To avoid overadjustment, we did not include this variable in the multivariate analysis.

## DISCUSSION

This study was restricted to women without contraception at the time of conception because the epidemiology of ectopic pregnancy is different for these women and for women using contraception at the time of ectopic pregnancy. These two groups differ in the time trends of incidence (21),

risk factors (3, 15), subsequent fertility (22–24), and psychologic stress (25).

Almost all the women living in the Auvergne region who were treated for ectopic pregnancy during the study period were included in this study, with the completeness of the Auvergne ectopic pregnancy register estimated at about 90 percent (21, 26). Controls were selected from the same geographic population as cases.

Multicollinearity, due to the large number of highly correlated ectopic pregnancy risk factors, was dealt with in several ways including adjustment for confounders in multivariate analyses, the building of synthetic variables (for instance, prior sexually transmitted diseases), the removal of certain variables corresponding to possible intermediate factors from subsequent analysis (for instance, time since the

**TABLE 3. Ectopic pregnancy and sexual and infectious history, register of the Auvergne region, France, 1993–2000**

Variables	Controls (n = 1,683)		Cases (n = 803)		Crude OR*	95% CI*	p value†
	No.	%	No.	%			
Age at first intercourse (years)							
<14	109	6.8	70	9.6	1		0.002
15–17	621	38.4	302	41.5	0.8	0.5, 1.1	
18–20	756	46.8	311	42.7	0.6	0.5, 0.9	
>20	130	8.0	45	6.2	0.5	0.3, 0.9	
Lifelong no. of sexual partners							
1	433	27.4	176	25.0	1		0.003
2–5	935	59.1	386	54.9	1.0	0.8, 1.3	
>5	213	13.5	141	20.1	1.6	1.2, 2.1	
Prior sexually transmitted diseases							
None	1,154	69.0	411	52.7	1		<0.001
Yes, without salpingitis	407	24.3	157	20.1	1.1	0.9, 1.3	
Yes, with probable pelvic inflammatory disease‡	12	0.7	19	2.4	4.4	2.1, 9.3	
Yes, with confirmed pelvic inflammatory disease§	100	6.0	193	24.7	5.4	4.1, 7.2	

\* OR, odds ratio; CI, confidence interval.

† p value (for variables with more than two categories, the p value of the test for trend is given).

‡ Probable pelvic inflammatory disease, association of fever, abdominal pain, and vaginal discharge.

§ Pelvic inflammatory disease confirmed by laparoscopy and/or positive serologic tests for *Chlamydia trachomatis*.

last pregnancy), and the choice of variables closer to possible causal factors (for instance, age of the woman and previous intrauterine device use rather than prior delivery). This careful consideration of all potential factors and the large sample in this study resulted in a comprehensive study of the risk factors for ectopic pregnancy, whether previously known or only suspected.

#### Prior genital infections and tubal surgery

Tubal surgery may be a direct consequence of prior tubal infection and may therefore be considered with infectious factors. The importance of infectious factors in ectopic pregnancy is well documented (3, 6, 27, 28). There is probably a causal link. In Sweden, declining rates of chlamydial infections, attributed to preventive policies, have been accompanied by a fall in the risk of ectopic pregnancy (29). The other variables suggestive of a higher probability of exposure to sexually transmitted diseases (age at first intercourse and number of sexual partners) were associated with a risk of ectopic pregnancy in univariate analysis. However, this association was not significant after adjustment for diagnosed prior sexually transmitted diseases. This indicates both that these factors are not risk factors per se and that they are good markers of exposure to sexually transmitted diseases.

Finally, the adjusted attributable risk of ectopic pregnancy for both infectious factors and tubal surgery was 0.33 (table

6), making these the most important risk factors for ectopic pregnancy.

#### Smoking

A strong association between tobacco use and ectopic pregnancy has been demonstrated by several studies (3, 8, 28, 30, 31). Our study confirmed this association, demonstrating a dose-effect relation. This is probably a causal relation (32), and tobacco use may play a role at various stages in reproduction: ovulation, fertilization, viability, and implantation (33–36). Smoking cessation reduces the risk of ectopic pregnancy to a level intermediate between that of current smokers and that of women who have never smoked. However, no trend was observed for time since cessation.

Although the magnitude of the effect of smoking on ectopic pregnancy risk is sometimes poorly appreciated, it is striking to note the parallelism between smoking and infectious factors. The odds ratios, trends, and attributable risks are of similar magnitude (tables 5 and 6). Therefore, smoking is a risk factor for ectopic pregnancy that is almost as important as infectious factors.

#### Age

Age has long been suspected to play a role in ectopic pregnancy risk, but studies have provided conflicting results (1, 2, 6, 8, 29, 37, 38). In our study, after careful adjustment, we found a significant relation between age and ectopic preg-

**TABLE 4. Ectopic pregnancy, contraceptive history, and fertility markers, register of the Auvergne region, France, 1993–2000**

Variables	Controls ( <i>n</i> = 1,683)		Cases ( <i>n</i> = 803)		Crude OR*	95% CI*	<i>p</i> value†
	No.	%	No.	%			
Previous use of oral contraceptive							
No	298	17.8	209	26.5	1		<0.001
Yes	1,377	82.2	581	73.5	0.6	0.5, 0.7	
Previous use of intrauterine device							
No	1,460	87.2	637	80.6	1		<0.001
Yes	215	12.8	153	19.4	1.6	1.3, 2.0	
Ovulation induced with clomiphene citrate							
No	1,632	97.4	762	95.1	1		0.003
Yes	43	2.6	39	4.9	1.9	1.2, 3.0	
History of infertility							
No	1,475	89.0	543	69.2	1		<0.001
<1 year	47	2.8	35	4.5	2.0	1.3, 3.2	
1–2 years	58	3.5	64	8.2	3.0	2.1, 4.3	
>2 years	77	4.7	143	18.2	5.0	3.7, 6.8	
Time since previous pregnancy‡							
0–6 months	128	13.5	77	14.4	1.3	0.9, 1.9	0.11
7–12 months	96	10.1	54	10.1	1.2	0.8, 1.9	(0.02)§
13–24 months	165	17.3	82	15.4	1.1	0.8, 1.6	
25–36 months	201	21.1	92	17.2	1		
37–48 months	107	11.2	51	9.6	1.0	0.7, 1.6	
49–60 months	77	8.1	38	7.1	1.1	0.7, 1.7	
≥61 months	178	18.7	140	26.2	1.7	1.2, 2.4	

\* OR, odds ratio; CI, confidence interval.

† *p* value (for variables with more than two categories, the *p* value of the test for trend is given).

‡ Time from the end of the previous pregnancy to the beginning of the index pregnancy.

§ *p* value of the global test.

nancy. Therefore, unlike certain other authors (37, 38), we conclude that it is unlikely that the higher probability of exposure to most risk factors in older women accounts for the higher risk of ectopic pregnancy. The physiologic effect on ectopic pregnancy risk of an advanced maternal age at conception remains unclear. It is unlikely to involve an increase in chromosomal abnormalities in the trophoblastic tissue (39, 40). Age-related changes in tubal function may delay ovum transport and result in tubal implantation. However, these hypotheses remain to be tested (41).

#### Prior spontaneous abortions

The results concerning prior spontaneous abortion differ among studies (3, 11, 42, 43). We found a “dose”-response relation with prior spontaneous abortions, the adjusted risk of ectopic pregnancy being particularly high in women with three or more previous spontaneous abortions. Spontaneous abortions may have a causal effect, possibly mediated by infection (42). However, there may also be common risk factors for ectopic pregnancy and spontaneous abortions, such as chromosomal abnormalities (39, 44) or hormonal

factors (45, 46). The available evidence suggests that the chromosomal abnormalities may be ruled out (40), but hormonal factors require further study, together with other factors including immunologic factors.

#### Previous use of an intrauterine device

In previous studies, odds ratios greater than one were obtained for current intrauterine device use, but odds ratios were generally not significant for previous intrauterine device use (6, 47–49). A meta-analysis produced an odds ratio slightly greater than one, but adjustment for confounders is necessarily imperfect. In this study, the significant adjusted odds ratio for previous intrauterine device use (table 5) confirms that previous intrauterine device use has an etiologic role in ectopic pregnancy per se, not only through an association with infection as previously suggested (50, 51). We did not know the duration of past intrauterine device use, and we could not study the type of intrauterine device used because all but four of the women had used copper devices.

**TABLE 5. Main risk factors for ectopic pregnancy by final logistic regression analysis (random effects model), register of the Auvergne region, France, 1993–2000**

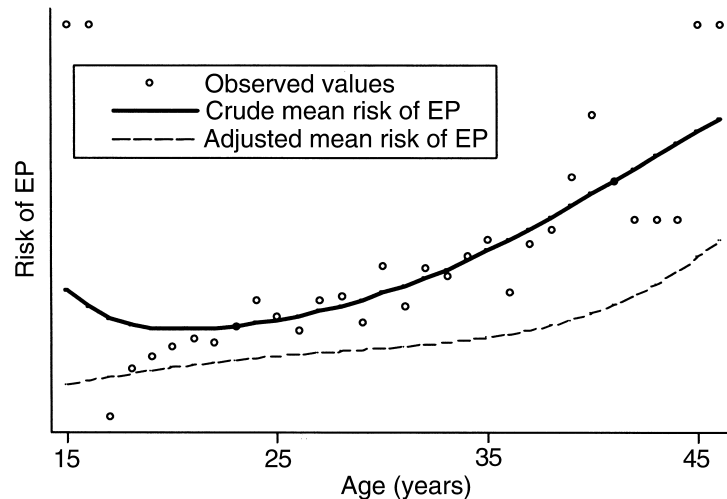
Variables	Adjusted OR*	95% CI*	<i>p</i> value†
Woman's age (years)			
<20	0.6	0.2, 2.1	
20–24	0.9	0.7, 1.3	
25–29	1		0.01
30–34	1.3	1.0, 1.7	
35–39	1.4	1.0, 2.0	
≥40	2.9	1.4, 6.1	
Smoking			
Never	1		<0.001
Past smoker	1.5	1.1, 2.2	
1–9 cigarettes/day	1.7	1.2, 2.4	
10–19 cigarettes/day	3.1	2.2, 4.3	
≥20 cigarettes/day	3.9	2.6, 5.9	
Prior spontaneous abortions			
None	1		0.02
1–2	1.2	0.9, 1.6	
≥3	3.0	1.3, 6.9	
Prior induced abortions			
None	1		0.05
Surgical only	1.1	0.8, 1.6	
Medical (or medical and surgical)	2.8	1.1, 7.2	
Appendectomy			
No, or unruptured appendix	1		0.20
Yes, ruptured appendix	1.4	0.8, 2.4	
Prior sexually transmitted diseases			
None	1		<0.001
Yes, without salpingitis	1.0	0.8, 1.3	
Yes, with probable pelvic inflammatory disease‡	2.1	0.8, 5.4	
Yes, with confirmed pelvic inflammatory disease§	3.4	2.4, 5.0	
Prior tubal surgery			
No	1		<0.001
Yes	4.0	2.6, 6.1	
Previous use of oral contraceptive			
No	1		0.03
Yes	0.7	0.5, 1.0	
Previous use of intrauterine device			
No	1		0.10
Yes	1.3	1.0, 1.8	
History of infertility			
No	1		<0.001
<1 year	2.1	1.2, 3.6	
1–2 years	2.6	1.6, 4.2	
>2 years	2.7	1.8, 4.2	

\* OR, odds ratio; CI, confidence interval.

† *p* value (for variables with more than two categories, the *p* value of the test for trend is given).

‡ Probable pelvic inflammatory disease, association of fever, abdominal pain, and vaginal discharge.

§ Pelvic inflammatory disease confirmed by laparoscopy and/or positive serologic tests for *Chlamydia trachomatis*.



**FIGURE 1.** Crude and adjusted association between age and ectopic pregnancy (EP) risk, register of the Auvergne region, France, 1993–2000. The figure provides the values of the risk of ectopic pregnancy. As this is a case-control study, these values cannot be interpreted directly and thus the y-axis is not scaled. However, the shape of the curves does correspond to the variation in ectopic pregnancy risk according to age. The observed values (circles) were calculated for 1 – age (years) classes.

### Infertility

We found that the adjusted risk of ectopic pregnancy increased with the duration of infertility, and this relation persisted if the analysis was restricted to women whose pregnancy was not induced. It is therefore likely that a history of infertility per se (independently of infertility drug use) is associated with ectopic pregnancy risk. However, as ectopic pregnancy is known to be a risk factor for subsequent infertility (24, 52, 53), the links between ectopic pregnancy and infertility, which seem to be mutual risk factors, are likely to be complex. Common risk factors for both conditions should be sought.

### Previous induced abortions

Conflicting results have been reported in previous studies on this issue (54). This study, including a larger number of cases and controls, found an association between previous induced abortions and ectopic pregnancy, with an adjusted odds ratio of 1.9 (95 percent CI: 1.0, 3.8) for women with two or more prior induced abortions. The main source of bias may derive from ascertainment of the number of previous induced abortions, which may be underreported by the subject herself (55). In France, estimates of the number of induced abortions for the year 1988 range from 22 to 30 per 100 births (56, 57). If we took into account the number of induced abortions for each woman, we note a slightly lower ratio in our control sample (15 declared induced abortions for 100 births). Similar results were obtained by Daling et al. (58) in the United States. Misclassification bias could account for the observed relation only if it were differential and concerned mainly controls but not cases (or to a lesser extent). Holt et al. (59) found such a differential bias but in the reverse direction. Although a differential misclassifica-

tion bias cannot be excluded, we think it unlikely that its magnitude or direction could account for our results.

In a previous study on another French population, we found an association between induced abortion and ectopic pregnancy (54). We interpreted the association as the consequence of uterine injuries or infections following abortion because most, if not all, of the abortions in this previous study were surgical. This interpretation was not confirmed by the study presented here: The risk of ectopic pregnancy was higher only for women who underwent medical abortions. However, the hypothesis that induced abortion leads to a higher risk of ectopic pregnancy as a result of infection cannot be rejected. The association with medical abortion may be accounted for by the absence of systematic antibiotic prophylaxis in this group of women, whereas such prophylaxis is more routinely given in cases of surgical abortion.

### Research perspectives

The total attributable risk of ectopic pregnancy for the known risk factors is around 70 percent. This figure should be interpreted with caution (60, 61), but there are clearly other factors that may cause ectopic pregnancy. The search has turned toward possible common risk factors for ectopic pregnancy and spontaneous abortion or infertility. It has been suggested that ectopic pregnancy is linked to chromosomal abnormalities (44, 62) or exposure to antineoplastic drugs (63). Specific studies were conducted, which did not support these hypotheses (39, 40, 64). Hormonal factors have also been suspected (45), and immunologic factors may be involved.

### Conclusion

Although several risk factors for ectopic pregnancy are known, the cause of a large proportion of ectopic pregnan-

**TABLE 6. Adjusted attributable risk of the main risk factors for ectopic pregnancy, register of the Auvergne region, France, 1993–2000**

Variables	Adjusted attributable risk	
Woman's age	0.14	
Past or current smoking	0.35	
Prior spontaneous abortions	0.07	
Prior induced abortions	0.03	
Appendectomy	0.02	
Prior sexually transmitted diseases	0.18	0.33*
Prior tubal surgery	0.18	
Previous use of oral contraceptive†	0.08	
Previous use of intrauterine device	0.05	
History of infertility	0.18	
Total	0.76	

\* The adjusted attributable risk of ectopic pregnancy if infectious history and prior tubal surgery are considered together.

† Attributable risk for not using oral contraceptive.

cies remains unknown. Our new findings on the association between previous medical induced abortion and ectopic pregnancy should be confirmed by further results. On the other hand, as ectopic pregnancy and infertility or spontaneous abortion have been found to be tightly linked, further research may concern both ectopic pregnancy epidemiology and the wider field of infertility. Increasing our knowledge of risk factors for ectopic pregnancy may improve our understanding of the causes of infertility.

In terms of public health, increasing awareness of the role of smoking may be useful in the formulation of ectopic pregnancy prevention policies. It would also be interesting to evaluate the effects on the incidence of ectopic pregnancy (and other infertility parameters) of the increase in sexually transmitted disease incidence observed in recent months or years (65, 66).

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