Ectopic Pregnancy and Prior Induced Abortion

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Abstract: We compared the prior pregnancy histories of 85 multigravid women with an ectopic pregnancy and 498 multigravid delivery comparison subjects. We found a relationship between the number of prior induced abortions and the risk of ectopic pregnancy: the crude relative risk of ectopic pregnancy was 1.6 for women with one prior induced abortion and 4.0 for women with two or more prior induced abortions; however, use of multivariate techniques to control confounding factors reduced the relative risks to 1.3 (95 per cent confidence interval, 0.6–2.7) and 2.6 (95 per cent confidence interval, 0.9–7.4), respectively. The analysis suggests that induced abortion may be one of several risk factors for ectopic pregnancy, particularly for women who have had abortions plus pelvic inflammatory disease or multiple abortions. (*Am J Public Health* 1982; 72:253–256.)

Introduction

An ectopic pregnancy can threaten a woman's life and future fertility. Three previous investigations of the relationship between induced abortion and subsequent ectopic pregnancy have yielded conflicting results: a study from Greece found that women with positive abortion histories were ten times more likely to have an ectopic pregnancy than women without this history,[1] while Yugoslavian[2] and Japanese[3] studies reported no excess risk for women with prior induced abortions. To investigate further this relationship among women in the United States, we performed a case-control study comparing the obstetrical histories of women having an ectopic pregnancy with women having a term delivery.

Methods

Between July 1976 and May 1978, we identified all cases at Boston Hospital for Women, Lying-In Division with a final post-operative diagnosis of ectopic pregnancy (176 women). Ninety-eight per cent of these pregnancies were located in the fallopian tubes; two were ovarian, one was abdominal, and one was cervical. We attempted to interview all cases using a standard questionnaire. Seven (4.0 per cent) refused to participate and four (2.3 per cent) were discharged before they could be reached for interview.

We also selected approximately five comparison subjects for each case. The comparison subjects were chosen randomly from the group of obstetrical patients who delivered on the day of the case's surgery. In all, we attempted to interview 866 delivery patients. Of these, 28 (3.2 per cent) refused to participate and 17 (2.0 per cent) were discharged before they could be interviewed.

The interview obtained information about past pregnancy outcomes, age, education, race, religion, payment method, smoking habits, prior pelvic infections, pelvic surgery, and contraceptive use. If the patient revealed a prior induced abortion, details of the procedure including any complications were elicited. After the interview the subject's current medical record and, whenever possible, the records of any admitted induced abortion were reviewed.

For the analysis, we included 171 cases who had pathological documentation of an ectopic pregnancy and five cases who met clinical criteria consistent with a tubal abortion. The latter had a positive test for the beta subunit of human chorionic gonadotropin plus evidence of blood and/or chorionic villi in the tube at surgery.

First, we eliminated uninterviewed subjects (11 cases and 45 comparison subjects) because we had no information regarding their obstetrical and medical history. Next we eliminated 19 comparison subjects whose delivery occurred prior to 37 weeks' gestation so that all comparison subjects had term deliveries. We also excluded primigravidas (61 cases and 299 comparison subjects), subjects who became pregnant with an intrauterine device in place (31 cases and five comparison subjects), subjects who had a prior sterilization (six cases and one comparison subject), and the three repeat ectopic pregnancies of subjects who had already been enrolled as a case and who became pregnant again during the study period. Because some subjects fell into more than one

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TABLE 1—Percentage of Subjects According to Prior Reproductive Outcomes*

Prior Outcome	Ectopic Cases (N = 85)	Comparison Subjects (N = 498)	Relative Odds of Ectopic Pregnancy
Ectopic Pregnancy	14.1	0.8	20.3[2]
Induced Abortion	34.1	20.5	2.0[1]
Spontaneous Abortion	34.1	27.3	1.4
Live Birth	67.1	79.1	0.5[1]

1) $p < 0.01$ (Chi-square test)
2) $p < 0.001$ (Chi-square test)
*The outcomes are not mutually exclusive; i.e., a subject may have had more than one prior outcome.

exclusion category, this left 85 cases and 498 comparison subjects for the final analysis. The relative risk, as approximated by the relative odds (odds ratio), was used to quantitate the association between the exposure (induced abortion) and the outcome (ectopic pregnancy).

The effect of confounding was assessed in two ways: we stratified the data by values of each potential confounder, calculated the Mantel-Haenszel summary relative risk,[4] and compared this risk to the crude relative risk; we used a multiple logistic regression model[5] including 15 variables to assess the simultaneous effect of potential confounders. Dichotomous variables included in the multivariate analysis were patient's race (Black, other), religion (Catholic, other), payment method (welfare and self-paying, other), parity (zero, one or more), prior spontaneous loss, prior ectopic pregnancy, prior use of oral contraceptives or intrauterine devices, prior pelvic surgery, dilatation and curettage (unrelated to an induced abortion), history of pelvic inflammatory disease, gonorrhea, and smoking. The regression analysis also included two dichotomous variables for prior induced abortion, one for one induced abortion and another for two or more induced abortions. We simultaneously entered all variables into the model and calculated the standardized relative risk for each variable while controlling for the other variables.

Results

Twenty-nine cases (34 per cent) and 102 comparison subjects (20 per cent) reported one or more induced abortions at interview or had a history of induced abortion in their medical records. For 76 per cent of these cases and 56 per cent of these comparison subjects, there was complete agreement between the interview and medical record. For 17 per cent of the cases and 26 per cent of the comparsion subjects, the medical records either contained no information regarding prior pregnancy outcome or did not specify whether a prior abortion was induced or spontaneous. For another 7 per cent of the cases and 10 per cent of the comparison subjects, the medical record omitted induced abortions revealed at interview. Finally, for 19 per cent of the comparison subjects, but for no cases, the medical record included a history of one or more induced abortions omitted during the interview. In the analysis, women were considered to have had an induced abortion if it was mentioned either at the interview or in the medical record.

An examination of the obstetrical histories (Table 1) indicated that greater percentages of cases than comparison subjects reported prior histories of ectopic pregnancy, induced abortion, and spontaneous abortion. Fewer cases reported one or more prior livebirths.

The relative risk of ectopic pregnancy was 20.3 for women with a prior ectopic pregnancy and 2.0 for women with one or more prior induced abortions. A history of prior spontaneous abortion had little association with ectopic pregnancy (relative odds = 1.4); and a history of one or more prior livebirths was associated with a reduced risk of subsequent ectopic pregnancy (relative odds = 0.5).

We reexamined these data omitting women with a prior ectopic pregnancy. Among the remaining subjects, the relative risk of an ectopic pregnancy following one or more induced abortions was 2.1, virtually the same as in the entire series. In addition, for each of the four women who had had both a prior ectopic pregnancy and induced abortion, the induced abortion preceded the ectopic pregnancy.

There appeared to be a direct relationship between the number of prior induced abortions and the relative risk of etopic pregnancy (Table 2). In comparison to women with no prior induced abortions, the crude relative risk of ectopic pregnancy was 1.6 for women with a history of one induced abortion and 4.0 for women with a history of two or more induced abortions.

We next took into account the possible combined effects of the difference in pregnancy duration between the cases and comparison subjects and the selection of comparison subjects on the basis of a similar date of hospitalization to the cases. In other words, the cases were "at risk" for having an induced abortion for several months longer than the comparison subjects. However, when we analyzed a subset of the data matching the subjects on the date of their last menstrual period, the increased risk for cases remained unchanged.

The distribution of induced abortion methods as reported by the women was similar among the cases and comparison subjects (Table 3). Almost twice as many of the prior induced abortions among the cases were performed in a foreign country or as an illegal procedure in the United States. When women with "foreign" or illegal abortions were excluded from the analysis, the relative risks of ectopic pregnancy given a history of one and two or more prior induced abortions were 1.3 and 3.3 respectively.

TABLE 2—Percentage of Subjects According to Number of Prior Induced Abortions

Prior Induced Abortion(s)	Ectopic Cases (N = 85)	Comparison Subjects (N = 498)	Crude Relative Odds
0	65.9	79.5	1.0
1	23.5	17.3	1.6
2+	10.6	3.2	4.0

TABLE 3—Percentage of Subjects with a Prior Induced Abortion According to Characteristics of (Last) Induced Abortion

Characteristics	Ectopic Cases (N = 29)	Comparison Subjects (N = 83)
Abortion Method		
Vacuum Aspiration	69.0	65.1
Dilatation and Curettage	20.7	28.9
Other (Intrauterine Injection, Hysterotomy)	10.3	6.0
Illegal or "Foreign" Procedure*	31.0	15.7
Post Abortal		
Curettage	10.3	4.9
Bleeding 1+ weeks	51.7	41.9
Pain 1+ weeks	10.3	4.9
Fever	17.2	6.2
Infection	17.2	3.6

*Induced abortion was performed in a foreign country or as an illegal procedure in the United States.

The ectopic cases reported post-abortal complications more frequently than did the comparison subjects. These complications included an additional post-abortal curettage, extended bleeding and pain, fever and infection. Post-abortal infections were reported four to five times more frequently by the cases. Moreover, 60 per cent (⅗) of the cases vs 33 per cent (⅓) of the comparison subjects experienced post-abortal infections after an illegal induced abortion. However, since only a small number of women (five cases and three comparison subjects) actually had post-abortal infections, their exclusion from the analysis did not alter the results.

A variety of gynecological problems, more common among the cases, included: prior pelvic and gonorrheal infection (excluding post-abortal infections), antibiotic therapy following pregnancy, a history of infertility and pelvic surgery. Pathological evidence of tubal infection (e.g., chronic salpingitis, follicular salpingitis or chronic follicular salpingitis) was found in 63.5 per cent of the cases. The crude relative risks of ectopic pregnancy for women with prior pelvic surgery, gonorrhea, and prior pelvic infection unrelated to induced abortion were 2.3, 5.7, and 11.1 respectively (Table 4).

We examined the extent to which these and other variables confounded the relationship between prior induced abortion and subsequent ectopic pregnancy. Standardization using the Mantel-Haenszel technique revealed that, individually, most variables including race, payment method, prior pill and IUD use, infertility, prior spontaneous loss, dilatation and curettage, history of pelvic infection (either omitting or including post-abortal infections), and gonorrhea explained little of the association between the exposure and outcome. Only when the data were standardized for parity or for smoking was the crude relative risk of ectopic pregnancy following one or two or more prior induced abortions reduced by at least 15 per cent.

Using the multiple logistic regression model including the 15 variables from Table 5, the adjusted relative risk of ectopic pregnancy was 1.3 for women with one prior induced abortion (95 per cent confidence interval 0.6–2.7) and 2.6 for women with two or more prior induced abortions (95 per cent confidence interval 0.9–7.4). The most important risk factors for ectopic pregnancy were prior ectopic pregnancy (RR = 7.7), prior pelvic infection (RR = 7.5), prior pelvic surgery (RR = 2.6), and payment method (RR = 3.0).

Excluding post-abortal infections, the crude relative risks of ectopic pregnancy for women having one or more prior induced abortions and for women having a prior history of pelvic infection were 1.5 and 9.1, respectively. There appeared to be a synergistic relationship between these two exposures and the occurrence of ectopic pregnancy: Eleven

TABLE 4—Percentage of Subjects According to Selected Gynecologic Characteristics

Characteristic	Ectopic Cases (N = 85)	Comparison Subjects (N = 498)
History of		
Pelvic infection*	29.4	3.6
Gonorrhea	16.5	3.2
Antibiotic therapy following a pregnancy	37.6	20.1
Medical assistance to become pregnant	22.4	13.9
Prior pelvic surgery	52.9	28.9
Prior endometriosis	3.5	3.4
Congenital abnormality of tubes or uterus	0.0	1.2
Clomiphene induced pregnancy (current)	2.4	1.2
>12 mos. to get pregnant (current)	38.7	7.8

*Excluding post-abortal infections

TABLE 5—Standardized* Relative Risks of Ectopic Pregnancy and 95 Per Cent Confidence Intervals According to Selected Characteristics

Characteristic	Relative Risk	95 Per Cent Confidence Interval
History of one induced abortion	1.3	0.6– 2.7
History of two or more induced abortions	2.6	0.9– 7.4
History of ectopic pregnancy	7.7	1.9–31.5
History of pelvic infection	7.5	3.5–16.0
Payment method	3.0	1.5– 6.0
History of pelvic surgery	2.6	1.4– 4.6
History of gonorrhea	2.5	0.9– 7.1
Prior dilatation and curettage	1.6	0.8– 3.3
Smoking	1.5	0.8– 2.8
Prior IUD use	1.4	0.7– 2.5
Race	1.4	0.6– 3.0
Prior spontaneous loss	0.9	0.4– 1.9
Religion	0.8	0.4– 1.5
Prior pill use	0.6	0.3– 1.2
Parity	0.5	0.2– 1.0

*Standardized using the multiple logistic regression model.

of the women having an ectopic pregnancy vs only four of the delivery patients had a prior history of both exposures, yielding a crude relative risk of 25.0, which greatly exceeds the sum of the risks for either factor alone (10.6). The increased risk remained after controlling for prior IUD use and age.

Discussion

There are many risk factors for ectopic pregnancy and several are indicated in the results of this study. When we used multivariate techniques to control the effects of these factors simultaneously, there was no detectable increase in the risk of ectopic pregnancy for women who had had one prior induced abortion. The risk for women who had had two or more prior abortions fell from an initial estimate of 4.0 to 2.6, and was no longer statistically significant. While we cannot eliminate chance as an explanation of our findings, a possible association of multiple prior induced abortions with subsequent ectopic pregnancy persists.

The Ljubljana Abortion Study found that neither one nor two or more induced abortions altered the crude relative risk of ectopic pregnancy.[2] Stratifying by age, the authors compared the obstetrical histories of incident cases of ectopic pregnancy and a control group designed to represent a population of intrauterine pregnancies. Delivery patients and women seeking induced abortions were pooled into the control group in a ratio reflecting the author's obstetrical practice. It is hard to justify the inclusion of controls who are seeking an induced abortion, since their frequency of prior abortion is comparatively high, or primigravidas, whose frequency of prior induced abortion is, by definition, zero. When we re-analyzed their data and compared multigravid cases and multigravid delivery controls, the crude relative risks of ectopic pregnancy for Yugoslavian women with one and two or more prior induced abortions were 1.7 ($p < 0.05$) and 2.4 ($p < 0.025$), respectively. These crude relative risks are similar in trend to our crude risk estimates. Furthermore, while the authors found that a history of pelvic inflammatory disease, sterility, and gynecological treatment also increased the risk of ectopic pregnancy, they did not perform a stratified or multivariate analysis to assess confounding and interaction by these variables.

A study from Greece[1] found a tenfold increase in the risk of ectopic pregnancy among women wtih prior induced abortions and the increased risk was present for both single and multiple aborters. The authors matched for hospital, educational level, age, and gravidity; however, they did not assess the data for confounding by prior gynecological infection or surgery. Induced abortion is illegal in Greece, and infection appears to be more common after illegal abortion. The effects of post abortal infection are too important to be ignored.

Finally, data from a Japanese study[3] indicate that one or more prior induced abortions were associated with a crude relative risk of 2.4 for subsequent ectopic pregnancy. Adjusting for hospital and year of ectopic pregnancy, the relative risk fell to 1.3. These data are similar to our results for persons who had one prior induced abortion.

There are several possible explanations for the fact that the existing studies are not in complete agreement; the most likely are the differences in study design and analytic methods just described. Differences in the populations, such as prior exposure to pelvic infections, or differences in abortion procedures, such as variations in the experience of the surgeons or in the type of instruments used, could account for some of the variation in results and would be extremely difficult factors to measure. The present study clearly indicates that there are several risk factors for ectopic pregnancy which are interrelated and it suggests that under certain circumstances prior induced abortion(s) may increase the risk of subsequent ectopic pregnancy. The existence of a large number of risk factors for ectopic pregnancy means that future studies directed at elucidating the precise role of induced abortion will have to be extremely large in order to control confounding.

REFERENCES

1. Panayotou PP, Kaskarelis DB, Miettinen OS, Trichopoulos DB, Kalandidi AK: Induced abortion and ectopic pregnancy. Am J Obstet Gynecol 1972; 114:507–510.
2. Hren M, Tomazevic T, Seigel D: Ectopic pregnancy. *In:* Andolsek L (ed): The Ljubjana Abortion Study, 1971–1973. Bethesda: National Institutes of Health, 1974; 34–38.
3. Sawazaki C, Tanaka S: The relationship between artificial abortion and extrauterine pregnancy. *In:* Harmful Effects of Induced Abortion. Tokyo: Family Planning Federation of Japan, 1966; 49–63.
4. Mantel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22:719–748.
5. Prentice RL: Use of the logistic model in retrospective studies. Biometrics 1976; 32:599–606.

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