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Induced abortions, miscarriages, and tobacco smoking as risk factors for secondary infertility

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Abstract

***Study objective*—The aim was to determine whether induced abortions could increase the risk of secondary infertility.**

***Design*—This was a case-control study; cases were women with secondary infertility, individually matched to two controls who were currently pregnant. Each participant was interviewed by one of two medical doctors using a questionnaire that sought information on their demographic, socioeconomic, medical, and reproductive status. The data were analysed by conditional logistic regression.**

***Setting*—The study took place in the Alexandra Maternity Hospital in Athens, Greece, in 1987–88.**

***Participants*—84 women consecutively admitted with secondary infertility and 168 pregnant controls took part.**

***Main results*—Eight cases and no controls reported a previous ectopic pregnancy, confirming that the occurrence of a pregnancy of this type dramatically increases the risk of secondary infertility. Furthermore, the occurrence of either induced abortions or spontaneous abortions independently and significantly increased the risk of subsequent development of secondary infertility. The logistic regression adjusted relative risks (and 95% confidence intervals) for secondary infertility were 2·1 (1·1–4·0) when there was one previous induced abortion and 2·3 (1·0–5·3) when there were two previous induced abortions. Tobacco smoking significantly increased the risk of secondary infertility, the adjusted relative risk being 3·0 (1·3–6·8).**

***Conclusions*—Legalised induced abortions, as currently practised in Greece, appear to increase slightly the relative risk of secondary infertility.**

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The epidemiology of secondary infertility has been extensively studied but is not adequately understood.[1 2] In earlier reports (quoted in[3 4]) there was a widespread opinion, frequently based on clinical impressions or on uncontrolled clinical series, that induced abortion was an important cause of secondary infertility. By contrast, most recent studies[5–8] do not support this hypothesis. However, epidemiological studies exploring the role, if any, of induced abortions in the aetiology of secondary infertility are inherently complex, because women who develop secondary infertility are likely to be subfertile and, therefore, to have fewer pregnancies "at risk" for artificial termination. In a study undertaken in the early 1970s in Athens, an effort was made to control for this important confounding factor by matching cases and controls for the total number of preceeding pregnancies, and the results indicated that women with at least one induced abortion and no miscarriages were 3·4 times more likely to develop secondary infertility than women without any miscarriage or induced abortion. Nevertheless, this finding has been considered as an outlier by most investigators, who were inclined to attribute it to chance or to the fact that induced abortions were, at that time, illegal in Greece.[4 5] To address these issues, a case-control study was undertaken in Greece in the same geographical and institutional setting as the previous one.[3] Fifteen years after the earlier study, induced abortions have been legalised in Greece and socioeconomic and medical conditions have substantially improved. Furthermore, the study design was modified to accommodate the observation of Weiss *et al*[9] that case-control studies using as controls women *completing* full term pregnancies (rather than being simply diagnosed as pregnant, without prejudice as to potential outcome) may overestimate the relative risk associated with induced abortion. This is because women willing to allow a pregnancy to proceed are likely to have a lower than average frequency of induced abortions in their reproductive histories. An additional objective of the present study was to examine the role, if any, of tobacco smoking in the development of secondary infertility. This issue has been studied by several investigators,[10–12] but the collective evidence is not yet conclusive.

Methods

During an 11 month period between 1987 and 1988, some 150 women residents of Athens complaining of secondary infertility (cases) were consecutively admitted to the Alexandra teaching hospital in which the First Department of Obstetrics and Gynaecology of the University of Athens Medical School is based. The Alexandra hospital is the major of two state maternity hospitals in the Athens area, also served by five private maternity hospitals. For the purpose of the present study, a diagnosis of secondary infertility was accepted if there had been a previous conception, if the patient was married and the husband had a normal semen analysis, and if the patient had been trying to become pregnant for at least 18 months; 103 patients fulfilled these diagnostic criteria and 95 were included in the study (the remaining eight left the hospital before an interview could be arranged).

For every patient with secondary infertility, an attempt was made to select two controls from the maternity clinics of the same hospital, matched for age, gravidity, and level of education. During the study period, about 2500 women visited these clinics at an early stage of their pregnancy or were diagnosed as pregnant in these clinics (many of these women had their pregnancies terminated or were delivered subsequently in one of the private maternity hospitals in Athens). Controls had to be residents of Athens; to be of about the same age (±3 years) and of the same educational status (−5, 6–11, 12+ schooling years—years of schooling have repeatedly been found[13] to represent the best socioeconomic indicator in Greece); and to have had before their current pregnancy the same total number of pregnancies as the corresponding patient with secondary infertility. Thus if a 30 year old woman complained of secondary infertility after her third pregnancy (including abortions and miscarriages), her matched controls, in addition to having the same age and level of education, should previously have been pregnant three times and should have remained fertile (the last, ie, the "current", pregnancy of control women was an indication of their fertility and was not taken into account in the analysis). Two control women were found for 84 of the women with secondary infertility, whereas only one control was found for seven cases and no matching controls were available for the remaining four cases. For simplicity of presentation the analysis was based on the 84 matched triplets. Individual matching was introduced in order to maximise efficiency in the analysis,[14] since age, socioeconomic status, and number of preceeding pregnancies are possible confounding variables.

Cases and controls were interviewed in person, and in symmetry, by two of us. Because the interviewers were medical doctors associated with the hospital, there were no refusals. Questionnaires covered demographic, socioeconomic, and medical data, as well as contraceptive practices and detailed reproductive histories by order of pregnancy. The data were analysed by conditional logistic regression.[15 16] This procedure allows control for any number of confounding variables, in addition to those matched for in the design.

Table I Demographic and biometric characteristics of 84 women with secondary infertility and 168 matched control women.

	Cases (%)	Controls (%)
Age (years)		
–24	22·6	28·0
25–29	32·1	30·9
30–34	28·6	28·6
35+	16·7	12·5
Years of schooling		
1–11	35·4	35·9
12+	64·6	64·1
Occupation		
Manual	8·4	2·4
Non-manual	25·3	24·0
Housewife	66·3	73·6
Height (cm), mean (SEM)	161·1 (0·9)	163·4 (0·9)
Weight (kg), mean (SEM)	60·2 (0·9)	62·3 (0·8)
Age at menarche (years)		
−12	39·7	40·3
13	29·5	32·9
14	24·4	18·3
15+	6·4	8·5
Menstrual regularity		
Regular	90·5	95·8
Irregular	9·5	4·2
Tobacco smoking		
Never	65·5	81·5
Past	5·9	10·1
Present	28·6	8·4

For several of the variables there are a few missing values.

Table II Contraceptive practices by 84 women with secondary infertility and 168 matched control women.

Contraceptive practice	Cases (%)	Controls (%)
Oral contraceptives		
Never	95·5	88·4
Ever	4·5	11·6
Diaphragm		
Never	100·0	100·0
Ever	0·0	0·0
Vaginal creams or suppositories		
Never	100·0	98·8
Ever	0·0	1·2
Coitus interruptus		
Rarely	32·8	9·7
Frequently	67·2	90·3
Condom		
Rarely	62·7	41·8
Frequently	37·3	58·2
Rhythm		
Rarely	83·6	71·8
Frequently	16·4	28·2
Surgical sterilisation		
No	100·0	100·0
Yes	0·0	0·0
Intrauterine device		
Never	98·5	91·3
Ever	1·5	8·7

Results

In table I demographic and biometric characteristics of cases and controls are given. The two groups were similar with respect to age and years of schooling (matching variables), and fairly similar with respect to occupation, height, weight, age at menarche, and menstrual regularity (none of the respective differences was substantial or statistically significant). However, the proportion who had ever smoked was significantly ($p < 0·01$) higher among cases (34·5%) than among controls (18·5%). It should be pointed out that since controls were pregnant whereas cases were not, some of the former may have changed smoking status because of their pregnancy, and this indicates that only the contrast between women who had ever smoked and those who had never smoked is aetiologically meaningful.

Table II summarises the reported patterns of contraceptive practices by women in the two groups. As expected, use of various methods of birth control was substantially more common among control women than among women with secondary infertility.

Cases and controls had an average of 1·607 previous pregnancies. Table III shows the outcomes of these pregnancies, expressed as mean values for woman in each group. Cases had higher mean values of all outcomes except livebirths, whereas controls of the same average gravidity had substantially higher mean value of livebirths.

Table III Outcome of preceeding pregnancies of 84 women with secondary infertility and 168 matched controls.

	Cases		Controls	
	Total	Mean	Total	Mean
Livebirth	32	0·381	147	0·875
Stillbirth	3	0·036	3	0·018
Miscarriage	31	0·369	24	0·143
Induced abortion	61	0·726	96	0·571
Previous ectopic pregnancy	8	0·095	0	0·000
All outcomes	135	1·607	270	1·607

Table IV Frequency distribution of 84 cases with secondary infertility and 168 matched controls by tobacco smoking and outcome of their preceeding pregnancies, and conditional logistic regression derived adjusted relative risk estimates.

Outcome of preceeding pregnancies	Cases (n)	Controls (n)	Relative Risk	95% Confidence interval	p value (two tailed)
Livebirth(s) only	17	79	Baseline	—	—
Livebirth(s) and miscarriage(s)[a]	3	13	1·0	(0·2–4·3)	0·95
Livebirth(s) and induced abortion(s)	6	24	1·0	(0·3–3·9)	0·99
Livebirth(s) and miscarriage(s) and induced abortion(s)	2	6	2·2	(0·2–30·1)	0·54
Miscarriage(s) only	15	6	8·9	(3·1–26·1)	<0·001
Induced abortion(s) only	28	40	3·0	(1·4–6·5)	0·006
Miscarriage(s) and induced abortion(s)	5	0	Infinitely large relative risk estimate		
Ectopic pregnancy and any other	8	0	Infinitely large relative risk estimate		
Never smoked	55	137	Baseline	—	—
Ever smoked	29	31	3·0	(1·3–6·8)	0·01

[a] Miscarriage(s) include also stillbirth(s)

Table IV shows frequency distributions of cases and controls by type of outcome of their preceeding pregnancies and by tobacco smoking habit, ie, the variables that, on the basis of tables I to III, appear to be associated with secondary infertility and may be aetiologically important. Since these variables are interrelated and may have mutually confounding effects, the relative risks, estimated by odds ratios, for secondary infertility were adjusted through conditional logistic regression. Adjusted relative risk estimates and 95% confidence intervals (CI) are presented in table IV. As expected, the relative risk for secondary infertility increased dramatically after an ectopic pregnancy. Furthermore women who have had only miscarriages, only induced abortions, or only miscarriages and induced abortions (but not livebirths) were at an increased risk for secondary infertility.

Table V examines the same issues but focuses on the outcome of the last pregnancy. Again, the risk of secondary infertility was substantially higher when the last pregnancy was ectopic or ended in miscarriage or through an induced abortion, compared to the risk following a pregnancy that led to a livebirth.

In Table VI an attempt was made to assess whether an increasing number of miscarriages or induced abortions is associated with an increasing risk for secondary infertility, controlling for mutual confounding effects. Both linear trends were statistically significant ($p < 0.05$), although a pattern of increasing relative risk was more evident in association with an increasing number of miscarriages.

Women without a previous ectopic pregnancy were also classified irrespective of their number of livebirths but according to whether they had neither induced abortions nor miscarriages, had miscarriages (one or more), had induced abortions (one or more), or had both miscarriages and induced abortions (one or more of each type). Compared to women with only livebirths (baseline), women who had only miscarriages (with or without livebirths) had a relative risk of 4·6; women who had only induced abortions (with or without livebirths) had a relative risk of 2·8; and women who had both miscarriages and induced abortions (with or without livebirths) had a relative risk of 14·8. It appears, therefore, that there is an interaction between miscarriages and induced abortions with respect to the risk of secondary infertility. Women with both types of exposures had a relative risk (14·8) substantially higher than that predicted from an additive model (6·4) and very close to that predicted from a multiplicative model (12·9). It should be pointed out that a dichotomous classification does not allow complete control of the confounding introduced by the frequent coexistence of miscarriages and induced abortions, and this explains why the relative risk for women with one or more induced abortions is higher than the corresponding estimates for women with either one or two or more induced abortions (table VI).

In the models used for tables IV, V, and VI, women who had ever smoked always had a significantly increased risk for secondary infertility ($p < 0.05$); the point estimate of the corresponding relative risk was as low as 2·6 (table V) or as high as 3·2 (table VI). It appears, therefore, that the association of tobacco smoking with secondary infertility is largely unconfounded by pregnancy outcome. Tobacco smoking was also associated with secondary infertility when the analysis was restricted to cases and controls who had only had livebirths, although the relative risk was in this instance slightly smaller (2·3) and statistically not significant (there were only 17 cases and 79 controls in an unconditional logistic regression analysis adjusting for age, level of education, and gravidity).

Table V Frequency distribution of 84 cases with secondary infertility and 168 matched controls by tobacco smoking and outcome of their last pregnancy (for controls, the pregnancy preceeding their "current") and conditional logistic regression derived adjusted relative risk estimates.

Last pregnancy outcome	Cases (n)	Controls (n)	Relative risk	95% Confidence interval	p value (two tailed)
Livebirth	21	110	Baseline	—	—
Miscarriage or stillbirth	22	11	9·1	(3·7–22·7)	<0·001
Induced abortion	33	47	4·0	(1·9–8·2)	<0·001
Ectopic pregnancy	8	0	Infinitely large relative risk estimate		
Never smoked	55	137	Baseline	—	—
Ever smoked	29	31	2·6	(1·2–6·0)	0·020

Table VI Classification of women with secondary infertility and control women by number of preceeding miscarriages and induced abortions, and mutually adjusted relative risk estimates (CI).

Miscarriages + stillbirths	Induced abortions 0	1	2+	Total	RR (CI)
0	17/79	25/48	9/16	51/43	1·0
1	14/17	2/4	2/2	18/23	2·7 (1·3–5·4)
2+	4/2	3/0	0/0	7/2	15·0 (3·5–63·6)
Total	35/98	30/52	11/18	76[a]/168	
RR (CI)	1·0	2·1 (1·1–4·0)	2·3 (1·0–5·3)		

[a] Cases with ectopic pregnancy excluded

Discussion

The present study has two strengths. (1) It was based on individual matching that was preserved in most analyses, which were carried out by modelling through conditional logistic regression; this made the study sufficiently powerful in the statistical sense. (2) It was designed to address effectively the possible negative confounding introduced by the likely subfertility of the cases and the possible bias that would have been introduced if the controls were selected among women in an advanced stage of their last pregnancy.[9] Occasionally, case-control studies are susceptible to selection and information bias,[4] but there was no evidence of lack of comparability of cases and controls in the present investigation, and it is not likely that women interviewed by their own doctors in a medical setting would have

given misleading or erroneous information about major events of their reproductive lives. Furthermore, we used the same design in a separate study of induced abortion as a risk factor for ectopic pregnancy.[17] Induced abortion did not appear to increase the risk of ectopic pregnancy significantly and the relative risk estimate was comparable to the overall estimate derived from a variety of studies. It is unlikely that recall bias can account for the present findings, although this theoretical possibility cannot be completely eliminated in memory dependent case-control studies.

Another concern is that the likelihood of a woman seeking medical help for infertility may depend on the number of her living children. However conditional logistic regression allows analytic control of confounding variables that were not matched for.[15 16] In the present study controlling for number of livebirths effectively controls for parity and number of living children, since there were only three stillbirths among cases and three among controls, and the number of livebirths is approximately equal to the number of living children when infant and childhood mortality are as low as they are in Greece.[13] Results were virtually identical, whether livebirths were individually (1, 2+) or collectively (table IV) considered.

If the results of the present study are valid, it would still be possible that they are not generalisable, because they were influenced by interacting local conditions in Greece. However, abortions have de facto been legalised in Greece for more than two decades; medical conditions are no worse in Greece than in most other countries of the world; and most Greek obstetricians perform so many abortions that their collective experience is indisputable. It appears more likely that the induced abortion related excess risk for secondary infertility is too small to be detected in all but the most powerful studies—and then only if the negative confounding generated by the subfertility of women who eventually develop secondary infertility is effectively addressed and the analysis is adequately performed. There have been very few studies that meet all these criteria.

In this context, it is of some interest to re-examine the results of an influential major cohort study undertaken under the auspices of the World Health Organization[5] and reported as negative. Table VII is taken from this report, and according to the authors "... there is no evidence of a reduced ability to conceive following an induced abortion ..." Yet, even if there were only 100 women in every group (and there were up to *four times* as many in every group) the results, if appropriately analysed with a log-rank test, would indicate a significant difference in time to conception (and therefore ability to conceive) between women in the abortion and the comparison group.

Table VII Cumulative pregnancy rates per 100 recruited women.

	Debrecen (Hungary)		*Seoul (South Korea)*	
Months after recruitment	*Abortion group*	*Comparison group*	*Abortion group*	*Comparison group*
6	21·4	14·0	32·4	33·8
12	47·3	49·3	51·0	64·1
18	65·2	76·1	70·8	77·5
24	83·7	93·7	79·5	87·3
30	96·9	98·7	90·2	93·7

Source: World Health Organization Task Force on Sequelae of Abortion (1984)

The results of the present study provide additional support for the notion that women who develop secondary infertility are in general subfertile since, in comparison to control women with the same average number of total pregnancies, they report lower frequency of use of virtually every contraceptive method. Furthermore, women who developed secondary infertility had a substantially higher frequency of miscarriages, and there was evidence of interaction between miscarriages and induced abortions in the development of secondary infertility. Finally, the present study confirmed that an ectopic pregnancy dramatically increases the risk of secondary infertility.[8]

Most of the studies that examined the relation between tobacco smoking and secondary infertility (or delayed conception) have found an effect, but this was usually weak and occasionally non-significant.[1 10–12 18] The results of the present investigation strengthen the collective evidence that implicates tobacco smoking in the development of secondary infertility.

In conclusion, this investigation indicates that induced abortions may increase the risk of secondary infertility, particularly in women with subfertility reflected in the occurrence of repeated miscarriages. This finding cannot in itself influence a more general abortion policy, but should be taken into account in the decision making process by the interested woman.

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