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Endometriosis and infertility: a laparoscopic study of endometriosis among fertile and infertile women

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To test the widely accepted—but not well-supported—impression that endometriosis and infertility are associated, we compared the prevalence of endometriosis visualized at laparoscopy in 100 patients being evaluated for infertility and in 200 fertile control subjects (two age-matched to each patient) undergoing tubal ligation. The extent of endometriosis and adhesions noted in the operative reports was classified according to the system proposed by The American Fertility Society. Endometriosis was found in 21 of the 100 infertile patients—mild in 11, moderate in 8, severe in 2. It was found in 4 (2%) of the 200 controls and was mild in all 4. Thus, endometriosis is more often present, and more often severe, among infertile patients. The risk of infertility was estimated to be almost 20 times greater with endometriosis than without. These data support the clinical impression that an association exists. Fertil Steril 38:667, 1982

Clinical data indicate that the prevalence of infertility is about 15% in the general population but approaches 30% to 40% in patients with endometriosis.[1] Moreover, among women in this latter group who have no other apparent cause for the infertility, conservative surgical procedures for endometriosis are followed by subsequent pregnancies in half or more of the cases, depending on the severity of the disease.[2, 3]

Conversely, a substantial proportion of infertile women—reportedly between 30% and 40%[4]—have evidence of endometriosis. This has been considered high, even though the prevalence of endometriosis in the general population remains unknown.

In a prospective study of 968 consecutive cases in which abdominal celiotomy was performed at the Mayo Clinic from 1964 to 1969,[5] ectopic endometrium was found in 50% of the patients. Of 130 women who underwent a conservative surgical procedure (thus preserving childbearing potential), 33 declared infertility as their chief complaint, and endometriosis was found in 52%. However, it was found also in 48% of the 97 women who did not complain of infertility (and so were presumed fertile). This suggested that endometriosis might actually be equally prevalent among fertile and infertile women. If true, some doubt would be cast on the importance of endometriosis as a cause of infertility.

To further assess the relationship between endometriosis and infertility, we compared the clinical histories and operative descriptions of 100 patients who underwent laparoscopy for evaluation of unexplained infertility with the findings

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from 200 patients of known fertility who desired permanent sterilization and underwent laparoscopy for tubal ligation.

MATERIALS AND METHODS

From January 1970 to December 1979, 101 women underwent diagnostic laparoscopy at the Mayo Clinic for evaluation of infertility. In one case the procedure was aborted because of extensive omental adhesions, and the pelvis could not be visualized. The remaining 100 patients constituted the infertile study group, for which 200 fertile control subjects were chosen from among the 1905 patients who underwent laparoscopy for tubal ligation during the same period. Each of the infertile women had been unsuccessful for 1 year or more in trying to conceive, whereas the control women had completed their families. Two control subjects were matched to each infertile patient by age (± 2 years) at the time of laparoscopy (index date) and by closest clinic registration number. Because the clinic number is based on the date of first registration at a Mayo Clinic facility, the periods covered in the medical records of patients and control subjects are also roughly equivalent.

The original medical records of each infertile patient and control subject were retrieved and reviewed by one of us (J. H. S.). This was done in a randomly mixed order, to eliminate any bias or drift that might arise from repetitively analyzing one group, then the other. Although the review could not be conducted in a blind fashion, the data of interest typically were recorded unequivocally in the charts. Data obtained for analysis included patient age, race, prior clinical diagnosis of endometriosis, signs and symptoms referable to the female reproductive tract prior to the index date, presence of other factors affecting fertility (i.e., ovulatory, tubal, or male factors), prior and subsequent treatment for endometriosis, and prior and subsequent obstetric history. The extent of endometriosis and adhesions noted at laparoscopy was abstracted from the operative reports and classified according to the system proposed by The American Fertility Society[6] in 1979. The presence of other pelvic disease, i.e., uterine myomata, paratubal cysts, etc., was also noted.

Differences in the frequency of various characteristics among patients and control subjects were evaluated by use of chi-square tests within the matched infertile-and-control triplets. We estimated the relative risk of infertility after endometriosis from the odds ratio, using the matched triplet method of Miettinen.[7]

RESULTS

PATIENT CHARACTERISTICS

The characteristics of the first and second control subjects were practically identical; so the two subgroups were combined in the tables and in comparisons with the infertile group. The mean age of the study patients was 28.7 ± 3.7 years (range 20 to 39), and the mean age of the control subjects was 29.5 ± 3.7 years (range 20 to 40). Both groups were predominantly Caucasian: one infertile patient was of Oriental extraction, and there was one black patient each in the study group and the control group.

CLINICAL HISTORY PRIOR TO INDEX DATE

Of the 100 infertile patients, 60% presented with primary infertility and 40% with secondary infertility. Among the 21 infertile patients later found to have endometriosis, 16 had primary infertility and 5 had been pregnant previously. One of the five had had a spontaneous abortion. Among the 79 infertile patients without endometriosis, the frequency of primary and secondary infertility was more even, being 44 and 35, respectively.

Other features of the obstetric histories of the fertile and infertile women are presented in Table 1. The numbers of ectopic pregnancies and spontaneous and induced abortions were quite similar in the two groups. A history of stillbirth (after more than 20 weeks' gestation) was found only in the fertile control group, but it must be noted that the control subjects had many more pregnancies. Thus, any one of these four adverse outcomes occurred in 30 of 67 pregnancies (45%) of the infertile women and in only 79 of 531 pregnancies (15%) among the fertile women. The control subjects thus had a generally more favorable experience.

The infertile women, however, were much more likely to have had one or more of the signs and symptoms listed in Table 2 ($P < 0.001$). In fact, every problem except metrorrhagia was more common among infertile women. Before the index date, clinical endometriosis had not been detected in any control case, but it had been diagnosed clinically in 12 of the 100 cases of infertility. Among these 12, 10 had multiple signs and symp-

Table 1. *Obstetric History: Frequency of Events Prior to Laparoscopy Among 100 Women Evaluated for Infertility and 200 Matched Control Subjects Undergoing Tubal Ligation (Mayo Clinic, 1970–1979)*

Obstetric event	Group	% Frequency, by no. of occurrences						
		0	1	2	3	4	5	6+
Pregnancy	Infertile	60	25	5	8	2	—	—
	Fertile	—	10	44.5	29	9.5	3.5	3.5
Birth	Infertile	70	24	5	1	—	—	—
	Fertile	—	12.5	54	25.5	7	1	—
Intrauterine death	Infertile	79	16	1	4	—	—	—
	Fertile	76	16	5	1.5	0.5	0.5	0.5
Ectopic pregnancy	Infertile	98	1	1	—	—	—	—
	Fertile	99.5	0.5	—	—	—	—	—
Spontaneous abortion[a]	Infertile	84	12	—	4	—	—	—
	Fertile	82.5	12.5	3	0.5	0.5	0.5	0.5
Induced abortion	Infertile	97	3	—	—	—	—	—
	Fertile	95.5	3.5	0.5	0.5	—	—	—
Stillbirth[b]	Infertile	100	—	—	—	—	—	—
	Fertile	95.5	4.5	—	—	—	—	—

[a]Gestation ≤ 20 weeks or fetus < 500 gm.
[b]Gestation ≥ 20 weeks or fetus > 500 gm.

toms. However, only 5 of the 12 clinical diagnoses of endometriosis were confirmed at laparoscopy. Treatment for endometriosis prior to laparoscopy included oral estrogen and progesterone in two cases, danazol in one, conservative surgery in three, and oophorectomy for an endometrioma in one.

The presence of other factors affecting fertility is summarized in Table 3. Of the infertile patients, approximately one-third had evidence of ovulatory dysfunction (oligomenorrhea, Stein-Leventhal syndrome, anovulation, etc.), and one-third had tubal abnormalities noted on the hysterosalpingogram; but as might be expected, not nearly so many had congenital uterine anomalies, cervical and male factors, a clinical history of pelvic inflammatory disease, and other conditions. All of these factors were uncommon among the fertile control subjects. In sum, one or more factors were noted in 69% of the infertile patients but in only 3% of the control subjects, a highly significant difference ($P < 0.001$).

Also of interest is that 101 of the 200 fertile control subjects were using oral contraceptives (OCs) at the time they requested permanent sterilization. Previously, one of the control subjects had had the problem of infertility, formally diagnosed; but it had since resolved.

RESULTS OF LAPAROSCOPY

Laparoscopy revealed evidence of endometriosis in 25 subjects: 21 of the infertile patients (21%) and 4 of the fertile controls (2%)—a highly significant difference ($P < 0.001$). Among the infertile group, the location of endometriosis was peritoneal in 18 and ovarian in 11, with direct tubal endometriosis in 2. (In many of this group more than one site was involved.) Among the four fertile patients with endometriosis, involvement was peritoneal in two and ovarian in two. It should be noted that in two infertile patients where laparoscopy disclosed pelvic adhesions without evidence of endometriosis, subsequent laparotomy for lysis of the adhesions did reveal endometriosis. These 2 are not included among the 21 infertile patients noted to have endometriosis at laparoscopy. Within that subgroup of 21, the disease was mild in 11, moderate in 8, and severe in 2 by the standards of The American Fertility Society. All four of the fertile patients with endometriosis had mild disease.

Other pathologic findings at laparoscopy are presented in Table 4. Pelvic adhesions, uterine

Table 2. *Obstetric Signs and Symptoms: Frequency Prior to Laparoscopy Among 100 Women Evaluated for Infertility and 200 Matched Control Subjects Undergoing Tubal Ligation (Mayo Clinic, 1970–1979)*

	Infertile	Fertile
	% of 100	*% of 200*
Dysmenorrhea	50	5
Dyspareunia	16	2.5
Chronic pelvic pain[a]	19	2
Menorrhagia	5	1
Metrorrhagia	7	9.5
Amenorrhea	5	1
Adnexal mass	9	0
Cul-de-sac nodularity	9	0.5
Any combination	68	18

[a]Excluding dysmenorrhea and dyspareunia.

Table 3. *Other Factors Affecting Fertility Among 100 Women Evaluated for Infertility and 200 Matched Control Subjects Undergoing Tubal Ligation (Mayo Clinic, 1970–1979)*

	Infertile	Fertile
	% of 100	*% of 200*
Ovulatory dysfunction	30	2.5
Tubal factor (hysterosalpingogram)	36	—[a]
Congenital uterine anomaly	2	0.5
Cervical factor	4	0.5
Male factor	7	—[a]
Clinical history of pelvic inflammatory disease	7	0
Other[b]	9	0
Any combination of factors	69	3

[a]Hysterosalpingogram and semen analysis were not obtained in the fertile control population.

[b]Prior pelvic surgery (correction of bicornuate uterus, salpingectomy for ectopic pregnancy), congenital absence of left ovary, inadequate coital technique, previous tubal ligation, etc.

myomata, clubbed tubes (noted with instillation of dye in the infertile patients), and other miscellaneous findings all were more common in the infertile patients. The most frequent cause for pelvic adhesions, other than previous pelvic inflammatory disease or endometriosis, was prior pelvic or abdominal surgery. Pelvic adhesions of varying severity were noted in 10 of the 21 infertile patients with endometriosis, but not in any of the 4 control subjects with endometriosis.

OUTCOME FOLLOWING LAPAROSCOPY

After laparoscopy, 13 of the 21 infertile patients with endometriosis underwent therapy for the condition. Two received estrogen and progesterone orally, two received danazol, one received conjugated estrogens (for 4 months), and eight underwent conservative surgery.

Eight of the 21 became pregnant (and 1 had two spontaneous abortions). Six of the eight had received some form of therapy for endometriosis at some time prior to conception: OCs in one case and danazol in another, both of mild disease, and surgical therapy in the remaining four, where the disease was moderate in two and severe in two. Five patients with endometriosis have not yet become pregnant, and eight have been lost to follow-up. Of the 79 infertile patients without endometriosis, 22 have conceived, 27 have not, and 30 have been lost to follow-up.

The rates of subsequent pregnancy among the infertile women with and without endometriosis cannot be compared directly, because the duration of follow-up was quite different. About 50% of each group was followed for at least 1 year; but 38% of those with endometriosis were followed for more than 2 years, versus only 15% of those without endometriosis.

Not to be ignored is the obstetric history of the fertile population after tubal ligation. One patient delivered a full-term infant 8 months after the ligation, and one had an ectopic pregnancy several months after the procedure.

INFLUENCE OF ORAL CONTRACEPTIVES

To investigate the extent to which use of OCs may be a confounding factor with respect to the presence of endometriosis in our data, we stratified the fertile and infertile women on the basis of contraceptive use. As shown in Table 5, the proportion of women with endometriosis was less among those taking OCs, whether they were fertile or infertile. However, the numbers involved were quite small. Only 1% of the fertile control subjects taking OCs had endometriosis; but even if the frequency of endometriosis in this group was the same as in the fertile control subjects not taking contraceptives (3%), it is apparent that endometriosis among the infertile women (21%) would still be significantly more common.

EFFECT OF ENDOMETRIOSIS ON FERTILITY

The analysis to this point has compared the relative frequency of endometriosis and various other characteristics in the traditional manner, given that the patient was either infertile (cases) or fertile (control subjects). However, it is also possible to calculate an epidemiologic "odds ratio" that estimates the risk of infertility, given that

Table 4. *Findings at Laparoscopy Among 100 Women Evaluated for Infertility and 200 Matched Control Subjects Undergoing Tubal Ligation (Mayo Clinic, 1970–1979)*

	Infertile		Fertile	
	% of 100		*% of 200*	
Endometriosis		21		2
Pelvic adhesions		42		7.5
Pelvic inflammatory disease	19		0.5	
Other	23		7	
Uterine myomata		15		6
Clubbed tubes		32		1.5
Other[a]		28		9

[a]Paratubal cysts, ovarian fibromas, surgically or congenitally absent ovaries, enlarged or multicystic ovaries, hemorrhagic corpus luteum, etc.

Table 5. *Oral Contraceptive (OC) Use and Endometriosis Among 100 Women Evaluated for Infertility and 200 Matched Fertile Control Subjects*

		Endometriosis		Total
		Yes	No	
Infertile women	OC	0	2	2
	No	21	77	98
Fertile control subjects	OC	1	100	101
	No	3	96	99

one has endometriosis or does not. From these data, we estimate that the risk of infertility is 19.5 times greater with endometriosis than without, a highly significant ($P < 0.001$) increase (95% confidence interval 4.6 to 154.2).

DISCUSSION

In contrast to previous studies relating endometriosis and infertility, which were concerned with conception after treatment for endometriosis, the investigation reported here substantiates these observations by comparing groups of fertile and infertile women with respect to the presence of endometriosis documented by laparoscopy. Endometriosis was significantly more common among the infertile women and, when present, was more often severe. Although an association between endometriosis and infertility is thus demonstrated, the cause-and-effect relationship is uncertain. Actions of steroid hormones and prostaglandins and consequences of luteal-phase defects have been postulated.[8-14] Our observations bring forth a very pertinent question: Did the fertile control subjects become pregnant because they did not have endometriosis, or was endometriosis not apparent because they had been pregnant in the past? One can gain insight into this by considering the type of infertility present in patients with endometriosis. Among the 21 instances of endometriosis in our infertile group, the infertility was primary in 16 (76%). Buttram,[3] reviewing 206 cases of infertility in patients with endometriosis, found that the infertility was primary in 146 (71%). One might speculate that when endometriosis is present, it is more likely that the patient has never been pregnant. Consequently, it appears that the fertile women were unlikely to have had significant endometriosis prior to pregnancy.

Clinical signs and symptoms referable to the female reproductive tract were noted more frequently among the infertile women, except for metrorrhagia. The higher proportion of fertile patients with metrorrhagia may be a result of patient selection—patients facing anesthesia for a dilatation and curettage for evaluation of a menstrual irregularity may have chosen to undergo tubal ligation at the same time.

The frequencies of other factors affecting fertility in our infertile group approximate the frequencies in the usual infertile groups, with a few exceptions. Speroff and associates[14] stated that the male factor is implicated in 40% of infertility problems, ovulatory failure in 10% to 15%, tubal pathology in 20% to 30%, and the cervical factor in 5%, with the remaining 10% to 25% of couples having no identifiable cause for their infertility. The 30% of patients with ovulatory dysfunction in our series include those with oligoovulation as well as anovulation. Frequency of the male factor is decreased in our series, probably because of patient selection, for a male factor alone should not occasion laparoscopy.

The diagnosis of endometriosis can only be suspected clinically and must be confirmed by direct visualization, usually at laparoscopy or laparotomy. In two women of the infertile group, however, after laparoscopy had demonstrated pelvic adhesions but not endometriosis, laparotomy within the following year did reveal endometriosis. This serves to point out possible limitations in the use of laparoscopy to diagnose or exclude endometriosis in the presence of pelvic adhesions.

Two features of the control group warrant further discussion. In a study comparing infertile and fertile women with respect to the presence of endometriosis, one must deal with the presumed therapeutic effects of pregnancy and OC use on endometriosis. The historical fact of pregnancy was a necessary element for a control group designed to be fertile and would only have influenced our main results if pregnancy prevented endometriosis or caused the lesions to be invisible at laparoscopy. The same is true of OCs. Although Kistner[1] indicated that pregnancy might ameliorate the symptoms of endometriosis in certain patients, the literature indicates that the effect of pregnancy on the ectopic endometrium is variable, from complete regression of disease to fatal hemorrhage from stimulated endometriomas.[15] Persistent disease is the more common finding. Further, although the lesions of endometriosis may regress during pregnancy, it is uncertain how long this effect lasts. All of the fertile patients in our control group were at least 3 months postpartum.

The other potentially confounding factor in the control group is the fact that 101 of the fertile patients had been taking OCs. Kistner[1] discussed evidence suggesting that women ingesting OCs have a diminished chance of developing endometriosis secondary to endometrial atrophy and decreased reflux tubal menstruation. OCs have been used in treatment of existing endometriosis. Success has varied,[1] usually according to the extent of disease. Although complete obliteration of vaginal endometriosis has been histologically documented following estrogen and progesterone therapy,[16] it appears to be the exception rather than the rule. In fact, recent animal studies support the contrary. diZerega and associates,[17] in their study of monkeys, found that estrogen or progesterone, or both, were not necessary for the initiation of the growth of endometrial plaques that were transplanted to the peritoneal cavity. Beyond 4 weeks, however, either estradiol or progesterone, alone or in combination, was required for maintenance. The conflicting results raise some question as to the exact effect of OCs on existing endometriosis.

To further assess the extent to which use of OCs may be a confounding factor with respect to the presence of endometriosis in the fertile and infertile groups in our study, the data were stratified according to OC use. Although endometriosis was found somewhat less frequently among the contraceptive users, this could not have accounted for the large difference observed between the fertile and infertile patients.

We also used the data in our study to estimate the risk of infertility, given the presence of endometriosis; and a significantly increased risk was found. However, this estimate is based on several assumptions: namely, that the patients are representative of infertile women, that the control subjects are representative of fertile women, and that the disease in question (infertility) is uncommon. Since there are no adequate population-based data on the prevalence of endometriosis in the community, it is difficult to assess the extent to which our study subjects conform to these assumptions. However, if the control subjects in our study had less endometriosis than fertile women in the population, our estimate of the risk of infertility after endometriosis may be somewhat too high.

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