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Ablation of lesions or no treatment in minimal–mild endometriosis in infertile women: a randomized trial

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In order to analyse the efficacy of resection/ablation of minimal/mild endometriotic lesions for improving fertility, we conducted a randomized clinical trial. Eligible patients were women aged ⩽36 years who were trying to conceive and had a laparoscopically confirmed diagnosis of minimal/mild endometriosis (stage I or II of the revised American Fertility Society classification) and otherwise unexplained infertility for ⩾2 years. Eligible women were randomly assigned to resection or ablation of visible endometriosis (54 patients) or diagnostic laparoscopy only (47 patients). After laparoscopy women tried to conceive spontaneously for 1 year (follow-up period). A total of five women withdrew from the study: three for personal reasons, and two were lost to follow-up. Considering 51 women in the resection/ablation and 45 in the no-treatment group who ended the follow-up period, 12 (24%) in the resection/ablation group and 13 (29%) in the no treatment group conceived; the difference was not significant. Two spontaneous abortions were observed in the resection/ablation group and three in the no-treatment one. Thus the 1 year birth rate was 10 out of 51 women (19.6%) in the resection/ablation group and 10 out of 45 women (22.2%) in the no-treatment group. In conclusion, the results of this study do not support the hypothesis that ablation of endometriotic lesions markedly improves fertility rates.

Key words: clinical trial/endometriosis/infertility/laparoscopy

Introduction

The role of resection or ablation of minimal–mild endometriotic lesions and filmy adhesions from Fallopian tube or ovaries in order to improve fertility is not well defined. Studies comparing laparoscopic laser/cautery or no treatment or danazol for the treatment of endometriosis-associated infertility have given controversial results: two cohort studies (Fayez *et al.*, 1988; Paulson *et al.*, 1991) and one quasi-randomized study (Nowroozi *et al.*, 1987) including as a whole ~750 patients, suggested that surgery is superior to no treatment or medical treatment with danazol, but other studies, comprising ~300 patients (Seiler *et al.*, 1986; Levinson, 1989; Chong *et al.*, 1990), did not confirm these findings.

More convincing evidence emerged from a recent randomized clinical trial comparing diagnostic laparoscopy alone or resection or ablation of visible lesions that included 341 infertile patients with minimal or mild endometriosis (Marcoux *et al.*, 1997), in whom surgery enhanced fertility. However, the 36 weeks cumulative probability of pregnancy in untreated women was about 20%, and only fecundity rates and not delivery rates were considered.

In this paper, we present the results of a randomized clinical trial comparing diagnostic laparoscopy or resection or ablation of visible endometriosis in order to improve the reproductive prognosis in infertile women with minimal–mild endometriosis (Struzziero *et al.*, 1998).

Materials and methods

Eligible patients were women aged ⩽36 years who were trying to conceive and had a laparoscopically confirmed diagnosis of minimal or mild endometriosis [stage I or II of the revised American Fertility Society classification (American Fertility Society, 1985)] and otherwise unexplained infertility lasting ⩾2 years. Women were eligible if they had normal results on standard medical and gynaecological examination and hysterosalpingogram, luteal phase endometrial biopsy, hormone profile (two follicle stimulating hormone, luteinizing hormone, and oestradiol assays in the follicular phase and three progesterone and prolactin assays in the luteal phase) and post-coital test. All partners had two semen analyses to exclude severe dyspermia ($>10\times10^6$ spermatozoa per ml, volume >1.5 ml, >30% progressive motility, >30% morphologically normal spermatozoa, absence of agglutination). Women with a previous clinical or laparoscopic–laparotomic diagnosis of endometriosis or with any other disease that might affect fertility (e.g., uterine malformation or uterine myomas) were specifically excluded. No women had had therapy for endometriosis or infertility.

The investigators obtained approval of the protocol from their institutional review board which established the procedures for obtaining informed consent.

A total of 101 women observed between 1994 and 1995 at seven participating centres entered the study. The average number at each centre was 14. The diagnosis of endometriosis before randomization was made under the supervision of a senior physician in each centre.

Eligible women were assigned by computer-generated randomization to either resection or ablation of visible endometriosis (54

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patients), or diagnostic laparoscopy only (47 patients). Adhesiolysis was allowed in women allocated to resection or ablation of visible endometriosis, but not in those allocated to diagnostic laparoscopy only. Histological confirmation of diagnosis of endometriosis was not requested.

Treatment was allocated during laparoscopy by telephone calls to the randomization centre (1st Obstetrics and Gynaecology Clinic, University of Milan). Separate randomization lists were used for each centre. Treatment allocation was respected in all cases.

After laparoscopy women tried to conceive spontaneously for 1 year (follow-up period). The protocol allowed after surgery the use of a medical treatment (tryptorelin 3.75 mg slow release every 28 days for 3 months) according to the physician's judgement. Treatment for ovulation induction was allowed only after the end of the follow-up period, i.e. when women were out of the study.

With our sample size, the probability (1–β) of detecting, at $\alpha = 0.05$ (two-tailed test), an increase of ~2.5 times in pregnancies in the treated group, with a baseline pregnancy rate of ~25% in the untreated one, is ~80%. The potential benefit of ablation/resection of lesion in comparison with no surgical treatment was estimated from the results of a meta-analysis published before this study began, which showed an odds ratio (OR) of 2.7 of becoming pregnant in treated versus untreated women (Hughes *et al.*, 1993).

The usual χ^2 test was used to established the statistical significance of differences in baseline characteristics of the patients and in the frequency of pregnancy, spontaneous abortions, and delivery on the total of observed pregnancies, in relation to treatment. To allow for potential confounding effect of stage and medical treatment on the fertility rate, the Mantel–Haenszel procedure was used (Mantel and Haenszel, 1959).

Results

Five women withdrew from the study, three of them for personal reasons (two received treatment for infertility and one decided not to try for pregnancy) and two were lost to follow-up.

Table I shows the main characteristics of women randomized to resection/ablation or no treatment. The two groups were similar in terms of baseline characteristics: for example mean age and mean duration of infertility in years were respectively 30.6 and 3.9 and 30.3 and 3.8 in the resection/ablation or no-treatment group. In the resection/ablation group, 20 women (39%) were stage I and 31 (61%) stage II; the corresponding figures were 20 (44%) and 25 (56%) women in the no-treatment group. No subject underwent ovulation induction treatment during the follow-up period.

Considering the 51 women in the resection/ablation and the 45 in the no-treatment group who completed the follow-up period, 12 (24%) in the resection/ablation and 13 (29%) in the no-treatment group conceived (difference not significant). Two spontaneous abortions were observed in the resection/ablation group and three in the no-treatment one (not significant). Thus the 1 year birth rate was 10 out of 51 women (20%) in the resection/ablation group and 10 out of 45 (22%) in the no-treatment group (Table II).

Considering the women who received medical treatment after surgery the pregnancy rates were 39% (seven out of 18 women) in women allocated to ablation/resection of lesions and 30% (seven out of 23 women) in those allocated to laparoscopy alone. The corresponding figures for women who did not receive medical treatment were 18% (five out of 28 women) for women allocated to ablation/resection of lesions and 30% (six out of 20) for those allocated to laparoscopy alone. These differences were not statistically significant.

Table I. Distribution of patients according to selected characteristics and treatment allocation

	Resection or ablation of visible endometriosis			
	Yes		No	
	No.	(%)	No.	(%)
Age (years)				
Mean (SD)*	30.6*	(3.6)	30.3	(3.8)
Disease stage				
I	20	(39.2)	20	(44.4)
II	31	(60.8)	25	(55.6)
History of spontaneous abortion				
No	48	(94.1)	42	(93.3)
Yes	3	(5.8)	3	(6.7)
Years of infertility				
Mean (SD)*	3.9*	(2.7)	3.8	(2.3)
Body mass index (kg m^{-2})				
Mean (SD)*	21.3*	(3.3)	21.4	(2.3)
Education (years)				
Mean (SD)*	11.3*	(4.2)	11.4	(3.7)
Pain (dysmenorrhoea and/or pelvic pain)				
No	18	(34.6)	18	(40.0)
Yes	33	(64.7)	27	(60.0)
Medical treatment after surgery				
No	29	(56.9)	21	(46.7)
Yes	22	(42.3)	24	(53.3)

*Patients who withdrew from the study are excluded.
SD = standard deviation.

Table II. Pregnancies and births according to treatment allocation. Italy

	Resection or ablation of visible endometriosis			
	Yes		No	
	No.	(%)	No.	(%)
Pregnancy				
No	39	(76.5)	32	(71.1)
Yes	12	(23.5)	13	(28.9)
Outcome of pregnancy				
Abortion	2	(16.7)	3	(23.1)
Term delivery	10	(83.3)	10	(76.9)

Discussion

The limitations of this study should be considered. The main drawback is its power: the trial was able to identify a difference in pregnancy rate between the two groups of ~2.5 times. Although this difference may be marked, a review of the literature reported that laparoscopic ablation of endometriotic lesions versus no treatment had a similar effect in improving fertility rates (Hughes *et al.*, 1993). With regard to other

sources of bias, most randomized patients were regularly observed, compliance with the study protocol was generally complete, and the two groups were comparable in terms of age, reproductive history, disease stage and particularly medical treatment after laparoscopy. Women who received medical treatment after laparoscopy actually tried to conceive for 9 months only (because they were under treatment for 3 months). No marked differences emerged, however, when the analysis was conducted separately for women who received and those who did not receive medical treatment after laparoscopy.

The physicians in the various centres were specifically trained to pay the same care to the diagnosis of endometriosis and to the ablation/resection of endometriotic lesions. They were instructed to perform complete resection or ablation of the lesions of visible endometriosis. However, no data are available on depth of ablation or on treatments of margins around areas of resection. The diagnosis of endometriosis was not histologically confirmed. However, though some misdiagnosis cannot be excluded, this potential bias should be similar in both groups.

The results do not confirm previous indications that resection or ablation of minimal and mild endometriosis increases the short-term likelihood of pregnancy in infertile women as compared with diagnostic laparoscopy alone (Nowroozi *et al.*, 1987; Fayez *et al.*, 1988; Paulson *et al.*, 1991; Hughes *et al.*, 1993). Part of this discrepancy may be explained by different criteria for selecting patients. For example, a meta-analysis (Hughes *et al.*, 1993) suggested that laparoscopic surgery increases the probability of becoming pregnant ~2.7 times compared to no surgery or medical treatment in infertile women with endometriosis. Re-analysis and updating of this review, however, suggested a significant, but less strong beneficial effect of laparoscopic surgery (OR 1.5) (Adamson and Pasta, 1994). The meta-analysis included some non-randomized studies, some including both minimal/mild and severe conditions, and some comparing no surgery or medical treatment with laparoscopic surgery.

A recent study (Marcoux *et al.*, 1997; Berube *et al.* 1998), not considered in the previous meta-analysis, comprising ~350 infertile women with stage I–II endometriosis, showed that the 36-week cumulative proportion of pregnant women was 31% in the laparoscopic surgery group and 18% in the diagnostic laparoscopy one. The study, however included women with a median duration of infertility of ~2 years, much less than the median infertility period reported in women included in the present study. Another difference between the populations in the Canadian study and in the present one, is the different stage I–II ratio. In the Canadian study ~30% of women had stage II endometriosis, compared with ~60% in the present study. The distribution of stages of endometriosis we observed is consistent with the findings of a large epidemiological survey conducted in Italy (Gruppo Italiano per lo Studio dell'Endometriosi, 1994). Other published studies (Pouly *et al.*, 1987; Levinson 1989; Chong *et al.*, 1990; Arumugam and Urquhart, 1991; Adamson *et al.*, 1993; Seiler *et al.*, 1996) did not show any effect of ablation/resection of endometriotic lesions in enhancing fertility prognosis.

A secondary finding of this study is that seven out of the 18 patients treated with resection/ablation who received postoperative medical treatment achieved pregnancy versus the pregnancy rate of 18% (five out of 28) for patients who did not receive a medical therapy postoperatively; this finding was, however, not statistically significant.

In conclusion, the results of this study do not confirm that ablation of endometriotic lesions in an early stage markedly improves fertility rates compared with no treatment.

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