RESEARCH ARTICLE

Surgical treatment of endometriosis before gamete intrafallopian transfer (GIFT)

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Objective. To determine whether active pelvic endometriosis impairs the efficacy of GIFT (gamete intrafallopian transfer) and whether prior surgical treatment of endometriosis improves the efficacy of GIFT.

Design. Matched controlled retrospective study.

Setting. University-based assisted reproduction programme.

Patients. Patients who had GIFT between 1990 and 1997 were included in the study. Female patients were laparoscopically diagnosed as having endometriosis. Patients who did not have surgical treatment for endometriosis before GIFT were staged for endometriosis during the GIFT laparoscopy. Two patients, with no signs of endometriosis, were matched for every endometriosis case, and served as controls. Patients were matched for age, number of eggs transferred and percentage of normal sperm morphology.

Intervention. Patients in 80 cycles had surgical treatment for endometriosis and 128 patients had GIFT procedures as treatment for endometriosis-related infertility.

Main outcome measures. Ongoing pregnancies and deliveries.

Statistical analysis. A Mantel-Haenszel approach was used to estimate relative risk of pregnancy outcome in the endometriosis groups versus controls.

Results. There was a 22.9% pregnancy rate (11/48) among patients with active endometriosis who had GIFT procedures, versus a 37.0% pregnancy rate (37/100) for the controls, giving a relative risk of 0.62 (95% confidence interval (CI): 0.35 - 1.10, $p = 0.082$). There was a 36.3% pregnancy rate (29/80) among patients who had surgical treatment for endometriosis before GIFT, versus a 33.3% pregnancy rate (53/159) for the controls, giving a relative risk of 1.07 (95% CI: 0.75 - 1.54, $p = 0.647$).

Conclusion. There is an indication that GIFT pregnancy rates are impared in patients suffering from active endometriosis, while prior surgery may alleviate the impairment.

Various mechanisms have been proposed to explain endometriosis-related infertility, the most important being mechanical factors, hostile peritoneal environment, altered systemic immune response, ovulatory dysfunction, early pregnancy loss and altered sperm-oocyte interaction.

In the case of women with endometriosis little is known about the effect of peritoneal fluid on the functional aspects of spermatozoa leading to sperm-oocyte binding, fertilisation embryo development and implantation. It has been shown that laparoscopic resection or ablation of minimal and mild endometriosis enhances fecundity in infertile women.[1]

Gamete intrafallopian transfer (GIFT) has been suggested as a treatment modality for endometriosis where patients have patent tubes.[2] The aim of this retrospective matched control study was to compare pregnancy rate in patients treated with GIFT after endometriosis had been surgically removed, with the pregnancy rate in patients who had no surgical treatment for endometriosis before GIFT.

Material and methods

A retrospective analysis of patients with endometriosis was done from our computer database. All patients had an infertility history of more than 1 year. According to the data, 128 patients had GIFT procedures as treatment for endometriosis-related infertility. Their ages ranged from 21 to 40 years. The severity of endometriosis was staged according to the classification of the American

Society for Reproductive Medicine (ASRM) into mild endometriosis (ASRM stages I and II), or severe endometriosis (ASRM stages III and IV). Of the 128 GIFT cycles analysed, patients in 80 cycles had surgical treatment for endometriosis before GIFT was done. The endometriosis lesions were either removed surgically or cauterised using the argon beam coagulator. In 48 cycles, patients did not have surgical treatment for their endometriosis before GIFT treatment. The stage of endometriosis in these patients was determined and graded at GIFT laparoscopy. In order to accommodate for differences in the husbands' semen parameters, sperm morphology was evaluated according to the Tygerberg strict criteria[3-5] and subdivided into two groups: (*i*) normal sperm morphology of $\leq$ 4% (P-pattern – poor prognosis); and (*ii*) normal sperm morphology $\geq$ 5% (G-pattern – good prognosis). The number of cycles in the P-pattern sperm morphology group in all the categories was too small for statistical evaluation and were therefore not analysed separately. The post-preparation sperm count of all the men included in the study was $\geq 1 \times 10^6$/ml.[3,5] At the time of GIFT 500 000 sperm with good motility after preparation were placed in the fallopian tube, where possible with no more than 3 metaphase II (MII) oocytes.[6]

The group that had previous surgery for endometriosis and the group with no previous surgery were matched with patients who had a GIFT procedure performed during the same time period (within 3 months that patients in the study group were done), serving as controls for each test subject. These controls were carefully matched according to the woman's age, the number of oocytes transferred and also according to the husband's normal sperm morphology.

Patients were stimulated with clomiphene citrate (CC) and human menopausal gonadotropin (HMG), or GnRH agonist and HMG. The ongoing pregnancy rate (> 28 weeks' gestation) in each group was determined as an end point.

Statistical methods

A Mantel-Haenszel approach was used to estimate relative risk of pregnancy outcome in the comparison of the endometriosis groups versus the controls. The stratification used was either endometriosis stage or endometriosis stage by morphology. This choice was determined by the small number of patients in the P-pattern morphology group. The stratification used is indicated for each comparison.

Results

One hundred and twenty-eight endometriosis-related GIFT procedures were analysed. Eighty patients (80 cycles, Table I, group A) had had surgical treatment for endometriosis before the GIFT procedure. In 48 cycles (Table I, group B) a GIFT procedure was performed for patients who had no previous surgical treatment for endometriosis. The control group for group A included 159 GIFT cycles (Table II, group C), and the control group for group B included 100 GIFT cycles (Table II, group D).

In 72 GIFT treatment cycles all the women had prior surgical treatment for endometriosis, and in 46 cycles the women had no prior treatment, with their husbands' normal sperm morphology classified as G-pattern (Table I). The matched controls (Table II) for the surgically treated patients in the G-pattern morphology group consisted of 144 GIFT cycles (group C) and 96 GIFT cycles for the untreated group (group D).

The pregnancy rate in the active endometriosis group was 22.9% (Table I, group B) while the pregnancy rate in the respective control group was 37% (Table II, group D). The relative risk was estimated as 0.62 (95% confidence interval (CI): 0.35 - 1.10, $p = 0.082$) adjusting for endometriosis stage only.

The treated endometriosis group (group A) had a pregnancy rate of 36.3% compared with 33.3% for their respective controls (group C). The relative risk was estimated as 1.07 (95% CI: 0.75 - 1.54, $p = 0.647$) adjusting for endometriosis stage by morphology in three strata (stratum 1: stage I, II and G-pattern; stratum 2: stage III, IV and G-pattern; and stratum 3: stage I, II, III, IV and P-pattern).

There was no statistically significant difference between the 22.9% pregnancy rate obtained in the active endometriosis group (group B) compared with a combination of the selected control groups (33.3% and

Table I. Pregnancy rates in treated and untreated endometriosis patients by endometriosis stage and morphology category

Group A Endometriosis treated (*N* = 80)		Group B Active endometriosis (*N* = 48)	
Stage by morphology	**Ongoing pregnancy (*N* (%))**	**Stage by morphology**	**Ongoing pregnancy (*N* (%))**
G-pattern* (*N* = 72)		G-pattern (*N* = 46)	
Stage I, II† (*N* = 39)	16 (41)	Stage I, II (*N* = 26)	6 (23)
Stage III, IV (*N* = 33)	11 (33)	Stage III, IV (*N* = 20)	5 (25)
P-pattern (*N* = 8)		P-pattern (*N* = 2)	
Stage I, II (*N* = 4)	1 (25)	Stage I, II (*N* = 2)	0 (0)
Stage III, IV (*N* = 4)	1 (25)	Stage III, IV (*N* = 0)	
Total (*N* = 80)	29 (36.3)	Total (*N* = 48)	11 (22.9)

*Morphology category: G = good prognosis, P = poor prognosis.
†Grade of endometriosis: I, II = mild; III, IV = severe.

Table II. Pregnancy rates in the matched control patients for the treated and untreated endometriosis groups by endometriosis stage and morphology category.

Group C Matched controls for endometriosis treated patients (*N* = 159)		Group D Matched controls for active endometriosis patients (*N* = 100)	
Stage by morphology	**Ongoing pregnancy (*N* (%))**	**Stage by morphology**	**Ongoing pregnancy (*N* (%))**
G-pattern* (*N* = 144)		G-pattern (*N* = 96)	
Stage I, II† (*N* = 76)	30 (39)	Stage I, II (*N* = 54)	23 (42.6)
Stage III, IV (*N* = 68)	22 (32)	Stage III, IV (*N* = 42)	12 (28.6)
P-pattern (*N* = 15)		P-pattern (*N* = 4)	
Stage I, II (*N* = 10)	0 (0)	Stage I, II (*N* = 2)	2 (100)
Stage III, IV (*N* = 5)	1 (20)	Stage III, IV (*N* = 2)	0 (0)
Total (*N* = 159)	53 (33.3)	Total (*N* = 100)	37 (37)

*Morphology category: G = good prognosis, P = poor prognosis.
†Grade of endometriosis: I, II = mild; III, IV = severe.

37%) and the treated endometriosis group (36.3%). The relative risk was estimated as 0.64 (95% CI: 0.39 - 1.04, $p = 0.074$) adjusting for endometriosis stage by morphology in three strata (similar to the comparison of groups A and C). When performing a one-sided evaluation for the same data, testing the alternative hypothesis that the active endometriosis group would be negatively affected with regard to pregnancy outcome compared with the treated and control groups, a significant effect was detected ($p = 0.047$).

Of the 159 pregnancies in this study, 40 resulted in spontaneous abortions (25.2%), and 130 ongoing pregnancies were obtained, all of which resulted in live births. The abortion rate did not differ significantly among the different groups: group A 28.9%, group B 28.6%, control group C 21.2%, and control group D 27.1%.

Discussion

Evidence from the randomised controlled trial by Marcoux *et al.*,[1] supported by 5 cohort studies and 1 quasi-randomised trial, points to the effectiveness of surgical ablation of mild/minimal disease as a primary treatment option for improving infertility.[7] It is more difficult to recommend the correct approach to infertility in patients with more severe disease because of lack of randomised controlled studies. However, surgical approach to treatment seems to be the best option. The Canadian Consensus Conference on Endometriosis[8] was of the opinion that severe categories of endometriosis may be associated with a lower probability of pregnancy success. In women with milder disease, GIFT produced pregnancy rates that were similar to those in women with unexplained infertility.[8] The lower GIFT pregnancy rate in the active endometriosis group compared with the matched control groups correlated with the finding by Guzick *et al.*[9] In their matched case control GIFT study they reported a delivery rate of 23.7% per cycle compared with 22.9% (11/48) in our study. Furthermore, they reported a delivery rate of 35.5% in their control group compared with 36.3% (29/80) in our endometriosis-treated group, and 34.7% (90/259) in our combined control groups.

The absence of a relationship between the severity of endometriosis and pregnancy rates may be owing to an inadequate power in our sample. The higher pregnancy rate in the endometriosis group that had surgical treatment before GIFT may strengthen the view of Guzick *et al.*[9] that if the fallopian tubes are normal then the important parameter might simply be the presence or absence of endometriosis independent of severity.

Other factors that could have influenced pregnancy outcome in this study are the number and maturity of oocytes transferred[10] and semen parameters,[10,11] but these differences were carefully controlled for by the matching process. Also important is the observation that once patients were pregnant, the presence or absence of endometriosis did not seem to make any difference as the miscarriage rate among the groups was not significantly different.

The statistical estimates indicate a relative reduction of 36% in the pregnancy rate of women with active endometriosis versus selected and non-selected controls. However, based on this trend and the evidence obtained from the literature, we would argue that endometriosis-related infertility must be treated surgically before GIFT.

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