Article

Effect of endometrioma cystectomy on IVF outcome: a prospective randomized study

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Abstract

The study was conducted to investigate the effect of conservative surgery of ovarian endometriomas before an ICSI cycle. Ninety-nine patients with endometriomas who were referred to an intracytoplasmic sperm injection (ICSI) cycle were enrolled in the study. The patients were prospectively randomized into two groups; group I (49 patients) underwent conservative ovarian surgery before the ICSI cycle and group II (50 patients) underwent the ICSI cycle directly. The stimulation was started 3 months after the operation in group I and directly in group II. In the ovarian surgery group, stimulation was significantly longer (14.0 days in group I and 10.8 days in group II; $P = 0.001$), total recombinant FSH dose was significantly higher (4575 IU in group I and 3675 IU in group II; $P = 0.001$), and mean number of mature oocytes was significantly lower (7.8 in group I and 8.6 in group II; $P = 0.032$). There was no difference in terms of fertilization (86% in group I and 88% in group II), implantation (16.5% in group I and 18.5% in group II) and pregnancy rates (34% in group I and 38% in group II). Ovarian surgery resulted in longer stimulation, higher FSH requirement and lower oocyte number, but fertilization, pregnancy and implantation rates did not differ between the groups.

Keywords: *endometrioma cystectomy, ICSI, IVF, outcome*

Introduction

Endometriosis affects 2.5–3% of women of reproductive age and is diagnosed in 20–68% of the women with infertility (Houston *et al*., 1987; Koninckx *et al*., 1991; Mahmood and Templeton, 1991). Extensive endometriosis may simply impair fertility by mechanical means. However, the main visible features of the minimal and mild stages of endometriosis are peritoneal or ovarian endometriotic implants and filmy adhesions on the Fallopian tubes or ovaries and the causal link between these cases and infertility is much debated (Olive and Schwartz, 1993; Davies, 1994; Thomas, 1995; Babu *et al*., 2004).

There are a variety of treatment options for women with endometriosis. These include expectant management, medical and surgical therapy (Fatemi *et al*., 2005). It is generally agreed that women with moderate to severe endometriosis who desire pregnancy benefit from surgical therapy (Evers, 2001; Garcia-Velasco *et al*., 2004).The impact of ovarian endometriomas on assisted reproduction outcomes is controversial (Loh *et al*., 1999; Tinkanen and Kujansuu, 2000; Canis *et al*., 2001; Ho *et al*., 2002; Marconi *et al*., 2002). It has been suggested that the presence of an ovarian endometriotic cyst might impair oocyte quality in the ipsilateral ovary and the response to ovarian stimulation, as well as fertilization and implantation rates, might be decreased (Barnhart *et al*., 2002; Mahutte and Arici, 2002; Nisolle, 2002).

There is controversy concerning the effect of surgery in patients with endometriosis on future response and IVF outcome. Following ovarian endometrioma cystectomy, some studies have shown conflicting results on ovarian response, with some patients showing a detrimental effect (Tinkanen

and Kujansuu, 2000; Ho *et al.*, 2002) and others showing no adverse effect (Loh *et al.*, 1999; Canis *et al.*, 2001; Marconi *et al.*, 2002). All studies concerning the effect of ovarian endometrioma cystectomy on assisted reproduction outcome are either retrospective or case-control studies. There is a lack of randomized controlled studies to report definitively the impact of conservative surgery of ovarian endometriomas prior to IVF/ICSI cycles.

The aim of the present study was to investigate whether ovarian endometrioma cystectomy before ovarian stimulation improved the outcome of ICSI cycles

Materials and methods

At the Clinic Women Health, Infertility and IVF Centre, Ankara, Turkey, between January 2001 and March 2005, 99 patients with endometriomas with a diameter of ≥3 cm and <6 cm who were referred to an ICSI cycle were prospectively randomized into two groups; patients in group I (49 patients) underwent conservative ovarian surgery before the ICSI cycle and patients in group II (50 patients) underwent the ICSI cycle directly. Only patients with single or multiple unilateral ovarian endometriomas with diameter between 3 and 6 cm were included. Patients with multiple bilateral endometriomas with diameter between 3 and 6 cm were excluded from the study. None of the patients had had ovarian surgery before the study. In all, 54.5% of patients had had diagnostic laparoscopy and 64% had a diagnosis of minimal endometriosis in their medical history. There was no significant difference between group I and II with regard to body mass index (BMI). The rate of male factor infertility was similar in groups I and II (59.18 versus 62.00%). Since most couples in this study were affected by male infertility and in order to provide homogeneity in the study groups, all patients were treated with ICSI as a clinical policy.

The diagnosis of endometrioma was made by transvaginal ultrasonography for all patients in their current admission. An ovarian endometrioma was diagnosed when an adnexal mass with diffuse, low-level internal echoes and absence of particular neoplastic features was visualized, and if no features of acute haemorrhage, multilocularity or hyperechoic wall foci were present (Patel *et al.*, 1999). The diagnosis was also histologically confirmed in the surgery group (49 patients). For patients in group II, endometrioma was aspirated at the time of oocyte retrieval and cytological diagnosis was performed. No malignancy was found in all cases.

The laparoscopic surgery, which was performed by the same surgical team for group I, consisted of drainage of the endometrioma cyst and dissection of the pseudocapsule of the endometrioma from the underlying stroma by gentle traction and counter traction in the right plane. Gentle bipolar coagulation was performed to the ovarian stroma when necessary. Patients in whom sutures were used for any reason during laparoscopy were excluded from the study.

All patients were stimulated with luteal long protocol. The stimulation was started 3 months after the operation in group I and immediately in group II. Leuprolide acetate (1.0 mg Lucrin; Abbott, Istanbul, Turkey) was started at the luteal phase. Recombinant FSH (Gonal-F; Serono, Istanbul, Turkey) was administered in a step-down fashion, starting with 300 IU/day by the documentation of suppression during menses; after 5 days the dose was adjusted according to the ovarian response.

Human chorionic gonadotrophin (HCG, 10,000 IU i.m., Profasi 5000 IU; Serono) was administered when at least two or three follicles reached a mean diameter of 17 mm and the serum oestradiol concentration was >500 pg/ml. Transvaginal oocyte retrieval was scheduled 36 h after HCG injection. ICSI was performed for all metaphase II oocytes and embryo transfers were performed on day 3 for all patients under ultrasound guidance. Stimulation parameters, fertilization, implantation and pregnancy rates were compared between the groups.

Institutional review board approval was obtained for this prospective randomized controlled study.

Statistical analysis

Data are expressed as the mean ± SD or percentages. Computer assisted randomization was used. The Yates corrected chi-squared test, Student's *t*-test and Fisher's exact test were used for statistical analysis with Statistics Package for Social Sciences software, version 10.0 for windows. Statistical significance was set at $P < 0.05$.

Results

Patient characteristics (age, basal FSH) and ovarian stimulation parameters (total FSH, stimulation days, peak oestradiol concentrations) are given in **Table 1**. There were no significant differences between groups I and II with regard to age and basal FSH. However, total FSH dosage consumed per cycle and days of stimulation were significantly higher and peak oestradiol concentrations were significantly lower ($P = 0.001$) in the endometrioma-removed compared with the endometrioma-present group.

Comparisons of ICSI cycle outcome parameters between group I and II are shown in **Table 2**. The number of mature oocytes retrieved was significantly lower in the surgery group ($P = 0.032$). There were no significant differences in fertilization rates, number of embryos transferred, implantation rates and clinical pregnancy rates between the two groups.

Table 1. Patient characteristics and ovarian stimulation parameters for those who underwent ovarian endometrioma cystectomy (group I) and those who did not (group II).

Characteristics	*Group I* (n = *49*)	*Group II* (n = *50*)	P-*value*
Age (years)	35.2 ± 0.3	34.9 ± 0.2	NS
Basal FSH (mIU/ml)	8.2 ± 0.38	7.9 ± 0.36	NS
Total FSH dose (IU)	4575 ± 530.54	3675 ± 792.58	0.001
Stimulation days (day)	14.0 ± 2.5	10.8 ± 2.6	0.001
Peak oestradiol (pg/ml)	1170 ± 417.14	1680 ± 428.69	0.001

Data are presented as mean ± SD. NS = not statistically significant.
The Student *t*-test was used for statistical analysis.

Table 2. Comparison of intracytoplasmic sperm injection cycle outcome parameters between patients who underwent ovarian endometrioma cystectomy (group I) and those who did not (group II).

Characteristics	*Group I* (n = *49*)	*Group II* (n = *50*)	P-*value*
Number of mature oocytes retrieved	7.8 ± 3.07	8.6 ± 2.82	0.032[a]
Fertilization rate (%)	86.2	88.3	NS[b]
Number of embryos transferred	3.2 ± 0.84	3.4 ± 0.67	NS[a]
Implantation rate (%)	16.5	18.5	NS[c]
Clinical pregnancy rate (%)	34.4	38.2	NS[c]

Data are presented as mean ± SD or percentages. NS = not statistically significant.
[a]Student *t*-test, [b]Yates corrected chi-squared test, and [c]Fisher's exact test were used for statistical analysis.

Discussion

Endometriosis may be present in 40% of patients with unexplained infertility (Tanahatoe *et al.*, 2003). The possible mechanism for impaired fertility may involve both anatomic distortion from pelvic adhesions and endometriomas, and the production of substances (e.g. prostanoids, cytokines, growth factors) that disrupt normal ovulation, fertilization and implantation.

In patients with early stage endometriosis, some functional mechanisms and peritoneal factors may be responsible for impaired infertility (Schenken *et al.*, 1984; Fakih *et al.*, 1987; Halme *et al.*, 1987; Oral *et al.*, 1996; Lyons *et al.*, 2002; Babu *et al.*, 2004; Urman *et al.*, 2005).

IVF offers the highest pregnancy rates for endometriosis patients, but there are conflicting data regarding the effect of endometriosis on IVF outcome. Numerous studies have compared IVF outcome (in terms of number of oocytes retrieved, fertilization rate, embryo development, implantation and pregnancy rates). In some studies, no effect of endometriosis has been shown (Harlow *et al.*, 1996; Evers, 2001). On the other hand, some investigators have reported a reduction in the number of oocytes and fertilization rate (Bergendal *et al.*, 1998). Moreover, lower pregnancy rates have been reported in patients with endometriosis (Garrido *et al.*, 2000; Evers, 2001; Aboulghar *et al.*, 2003).

The impact of ovarian endometrioma on infertility, and oocyte and pregnancy outcome in IVF cycle remains controversial. Comparisons of surgically treated endometriosis on IVF outcome are scarce in the literature. Published studies are almost exclusively retrospective and observational. In a recent retrospective study, it was suggested that endometriosis did not affect embryo quality and the related parameters of pregnancy (fertilization, implantation, pregnancy and live birth rates). However, their results also demonstrated that endometriosis, even after diagnostic laparoscopy with treatment when necessary, clearly affected the number of oocytes, irrespective of the presence of an ovarian endometrioma (Suzuki *et al.*, 2005).

One clinical dilemma is how to approach a woman with an ovarian endometrioma who is planning to undergo IVF. A major concern is that resection of endometriomas results in the loss of small follicles adjacent to the cyst wall and a reduced oocyte pool, which itself is associated with infertility (Exacoustos *et al.*, 2004). In fact, several retrospective studies have reported reduced responses to gonadotrophins after cystectomy for

ovarian endometriomas in young women (Pagidas *et al.*, 1996; Loh *et al.*, 1999; Al-Azemi *et al.*, 2000; Tinkanen and Kujansuu, 2000). Such findings suggest that at least some of the adverse effects of endometriomas on fertility outcomes might derive from prior surgical interventions rather than the endometriosis itself. For example, in one study (Tinkanen and Kujansuu, 2000) the effect of operative treatment of recurrent ovarian endometriosis on the pregnancy rate in IVF was evaluated. In that study during IVF treatment, 45 patients with ovarian endometriomas (36 of the cases had recurrent endometriosis after previous operation) were compared with the control group (55 patients with a history of endometrioma cystectomy without recurrence). Patients with endometriomas had significantly more embryos for transfer than women without endometriomas. The clinical pregnancy rate was 38% in the endometrioma group and 22% in the control group. This was probably because of the more extensive radical surgery in the control group. Radical surgery resulted in no recurrence, but at the same time it caused diminished ovarian response (Tinkanen and Kujansuu, 2000). In the present study, the number of oocytes retrieved in the endometrioma cystectomy group was also lower. It is acknowledged, however, that although the difference was statistically significant and accompanied a significantly decreased oestradiol concentration in group I, the difference represents only a fraction of an oocyte so may not have biological significance. It is thought that ovarian damage may have been the cause of this result in the endometrioma cystectomy group.

Several retrospective studies have reported reduced responses to gonadotrophin after cystectomy (Pagidas *et al.*, 1996; Al-Azemi *et al.*, 2000; Tinkanen and Kujansuu, 2000). In one retrospective study (Geber *et al.*, 2002), a higher dosage of gonadotrophin was needed in the advanced age group. Pregnancy rate was apparently higher in the control group, although this was not statistically significant. In another study (Garcia-Velasco *et al.*, 2004), effect of conservative surgery on ovarian endometriomas before IVF cycle was evaluated. They compared assisted reproduction cycle outcome of 133 women treated by laparoscopic cystectomy for an endometrioma >3 cm with 56 women with an ovarian endometriotic cyst of similar size who had not previously undergone conservative ovarian surgery. IVF cycles were started within 12 months of surgery. There was no difference in terms of number of oocytes retrieved, fertilization rate, number of embryos transferred, implantation and clinical pregnancy rates between the groups.

In contrast, some retrospective studies did not show adverse outcomes after ovarian endometrioma cystectomy compared with the control group (tubal infertility) (Donnez *et al.*, 1996; Canis *et al.*, 2001; Marconi *et al.*, 2002). In one study (Marconi *et al.*, 2002), it was reported that laparoscopic cystectomy of ovarian endometriomas did not affect the ovarian response to gonadotrophin stimulation, although the gonadotrophin dose was higher in the endometrioma-removed group.

As far as is known, no randomized trials have been performed to evaluate the effect of removing endometriomas prior to IVF. In the present prospective randomized controlled study, in the ovarian surgery group stimulation was significantly longer ($P = 0.001$), total recombinant FSH dose was significantly higher ($P = 0.001$) and mean number of mature oocytes were significantly lower ($P = 0.032$), and there were no significant differences in terms of fertilization, implantation and pregnancy rates.

In conclusion, ovarian endometrioma cystectomy before starting ovulation induction in assisted reproduction cycles does not seem to improve the cycle outcome in asymptomatic and uncomplicated patients with certain diameters. In this study, surgery also resulted in decreased ovarian response in ICSI cycle and decreased ovarian response may be related to ovarian damage by operation and thermal coagulation. Moreover; surgery may be time consuming and expensive.

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Received 5 December 2005; refereed 20 December 2005; accepted 13 February 2006.