Laparoscopic resection or sonography-guided vaginal aspiration of endometriomas prior to ICSI-ET does not worsen treatment outcomes

T. Cirpan[1], *Assist. Prof.*; **F. Akercan**[1], *Assoc. Prof.*; **E.N. Tavmergen Goker**[1,2], *Prof.*
E. Ozyurek[3], *Specialist*; **R. Levi**[2], *Assoc. Prof.*; **E. Tavmergen**[1,2], *Prof.*

[1]*Department of Obstetrics and Gynecology, Ege University Faculty of Medicine, Izmir;*
[2]*Infertility-Family Planning Research and Treatment Center, Ege University, Izmir;*
[3]*Department of Obstetrics and Gynecology, Uludag University Faculty of Medicine, Bursa (Turkey)*

Summary

Objective: To evaluate the effect of the management modality of ovarian endometriomas on ovarian response to COH (controlled ovarian hyperstimulation) and ART (assisted reproductive technology) treatment outcome. *Design:* Retrospective case control study. *Setting:* Ege University Infertility-Family Planning Research and Treatment Center. *Patients:* 115 cycles of 84 patients who underwent ICSI-ET (intracytoplasmic sperm injection-embryo transfer) with ejaculated sperm were enrolled in the study. The endometrioma resection group (Group I) was comprised of 36 cycles in 29 patients who were treated with laparoscopic endometrioma cyst resection prior to treatment; endometrioma aspiration (Group II) was comprised of 26 cycles in 15 patients whose endometriomas were aspirated prior to treatment; and the control group (Group III) was comprised of 53 cycles in 40 patients for whom the only infertility cause was the tubal factor. *Interventions:* ICSI-ET treatment, laparascopic ovarian endometrioma cyst resection, transvaginal ultrasonography-guided endometrioma cyst aspiration. *Main Outcome Measures*: COH results and ICSI-ET treatment outcomes. *Results:* The groups were similar in all characteristics except for the mean age of the patients in group II being older than those in group I. Gonadotropin consumption was higher, peak estradiol level lower, and the number of oocytes less in the laparascopic resection group (Group I) with respect to the control group. The number of follicles was lower in the cyst aspiration group (Group II) with respect to the control group. The number of follicles larger than 15 mm, number of metaphase II oocytes, the fertilization, pregnancy and implantation rates were similar in all three groups. *Conclusion:* Interventions (laparascopic endometrioma resection, transvaginal ultrasound-guided endometrioma cyst aspiration) performed on endometriomas prior to ART treatment do not worsen the treatment outcome.

Key words: Endometrioma; Resection; Aspiration; ART.

Introduction

Endometriosis remains as one of the most common and puzzling gynecologic disorders in women [1]. Endometriosis is associated with infertility in 30-50% of infertile women and affects 7-50% of reproductive-aged women [2, 3]. It has been suggested that endometriosis could affect the ovarian response to gonadotropins, oocyte recovery rates, fertilization and implantation rates [4-6].

Because medical therapy is not an effective treatment, ovarian endometriomas should be managed surgically in infertile women [7]. Various surgical treatment modalities have been proposed for ovarian endometriomas. These modalities include laparoscopic stripping, laparoscopic simple drainage and/or coagulation, laparoscopic fenestration and coagulation, laparoscopic vaporization of the internal layers of the endometrioma wall with the CO2 laser, cystectomy via laparotomy and ultrasound-guided aspiration via transabdominal or transvaginal routes [8-12].

Residual ovarian function and follicle development after such surgery is an important consideration. Of particular concern is the amount of ovarian tissue that may be removed inadvertently during cystectomy and the damage that may be caused on the ovarian stroma by electrosurgical coagulation during hemostasis [10, 13].

The aim of the present study was to compare controlled ovarian hyperstimulation (COH) and intracytoplasmic sperm injection-embryo transfer (ICSI-ET) outcomes of ovarian laparascopic endometrioma resection, transvaginal ultrasound-guided aspiration with patients unaffected by endometriosis to determine if surgical intervention has any negative influence from the perspective of assisted reproductive technology (ART).

Materials and Method

We reviewed the medical records of infertile patients undergoing ICSI procedures in our program at Ege University Infertility and Family Planning Research and Treatment Center from December 2000 to December 2004. Eighty-four couples within the first three ART cycles with no apparent male factor (sperm count > 20X10^6/ml, mobility > 50%, normal forms according to Kruger's [14] criteria > 13%), endometrial pathologies, with normal endocrinological profiles (day 3: FSH < 8 mIU/ml, estradiol < 50 pg/ml, sonographic ovarian antral follicle count 4-10) and within the third to sixth year of marriage. The design of the groups was as follows:

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Group I consisted of 36 cycles in 29 patients with ovarian endometriomas of ≥ 3 cm in diameter who were treated with ovarian cystectomy with laparoscopy no earlier than five years before the treatment cycles. In the Ege University IVF and Family Planning Center laparascopic endometrioma resection operations are carried out by a single experienced laparascopist. Endometriomas larger than 3 cm are resected in infertile patients with normal ovarian reserve. Endometriomas are resected by stripping, and in the presence of excessive ovarian bleeding hemostasis is carried out with ovarian suturing or thermocoagulation. In endometriosis cases where it is feasible to improve the tubo-ovarian relation, salpingo-ovariolysis is performed; and if at least additionally, uni-lateral tubal patency is confirmed, conventional treatment is planned, otherwise ART treatment is in order. In cases where cysts persist despite follow-up, with diameters 15-30 mm, including endometriomas in the presence of blood estradiol levels lower than 50 pg/ml and progesterone levels less than 0.6 ng/ml at the beginning of ovulation induction or when recurrent endometriomas are detected, cysts are aspirated under transvaginal sonographic guidance. *Group II* consisted of 26 cycles in 15 patients with ovarian endometriomas of < 3 cm in diameter who underwent ultrasound-guided transvaginal puncture and aspiration on day 3 of the menstrual cycle (first day ovulation induction). After vaginal cleansing with povidone-iodine solution and paracervical block with anesthetic injection, aspirations of ovarian endometriomas were performed transvaginally with ultrasound guidance. Aspirated material was sent for cytopathologic examination. *Group III* (the control group) included 55 cycles in 40 patients who laparoscopically evaluated, and for whom the only apparent cause of infertility was the tubal factor.

The diagnosis of an ovarian endometrioma in group I was confirmed by histopathologic examination of the operation specimen. The definition of ovarian endometrioma in group II was based on a combination of clinical signs, macroscopic characteristics of the aspirated fluid and cytologic examination, when possible.

Controlled ovarian hyperstimulation (COH) was performed using a GnRH analogue (long protocol; 0.1 mg of Decapeptyl; Ferring, Kiel) for down-regulation and r-FSH (Gonal F 75U Amp-Serono Switzerland) for induction. The GnRH analogue was administered from day 21 of the preceding cycle. Sonography and blood hormone level determinations were carried out on the tenth day of treatment or following menstrual bleeding (at the earliest on the 7th day of treatment) after the beginning of GnRH analogue administration to confirm down-regulation. Down-regulation was confirmed (with blood levels of estradiol < 50 pg/ml, progesterone < 0.5 ng/ml, LH < 5 m IU/ml). When down-regulation was confirmed, r-FSH was started. Cycle monitoring was done with blood estradiol levels and transvaginal sonography.

When E_2 levels reached a level of ≥ 500 pg/ml (± 200 pg/ml per follicle of > 16 mm in diameter) and at least two follicles of ≥ 18 mm in diameter were present, hCG (Profasi 5,000 IU, Serono, Switzerland) was administered (10,000 IU). Oocyte retrieval was performed at approximately 36 hours after hCG administration under transvaginal ultrasound guidance. ICSI was the fertilization method for all the oocytes of all patients. Embryo-transfer (ET) was performed on the third or fifth day of fertilization depending on individual factors. A maximum of three embryos were transferred.

Results

The groups were similar in all aspects except for the mean age of the patients in Group II being older than that in Group I. Due to this, a control group (Group III) was used as a reference group. ANOVA post-hoc tests were used for the analysis. Statistical significance was determined when $p < 0.05$.

The groups were similar in all characteristics except for the mean age of the patients in groups I and II differing. Gonadotropin consumption was higher, peak estradiol level lower, and the number of oocytes less in the laparascopic resection group (Group II) with respect to the control group. The number of follicles was lower in the cyst aspiration group with respect to the control group. The number of follicles larger than 15 mm, number of metaphase II oocytes, fertilization, pregnancy and implantation rates were similar in all three groups. Patient characteristics and controlled ovarian hyperstimulation parameters in groups I, II and III are shown in Table 1. ICSI outcomes of all groups are shown in Table 2.

Table 1. — *Patient characteristics and controlled ovarian hyperstimulation parameters in Groups I, II and III.*

	Group I	Group II	Group III
	Cystectomy of ovarian endometrioma by laparoscopy	Ultrasound-guided aspiration of ovarian endometrioma	Tubal factor infertility
No. of patients	29	15	40
No. of cycles	36	26	53
Age of patients	31.05 ± 3.81[1]	34.88 ± 4.05[1]	3.54 + 4.37[1]
BMI (kg/m^2)	26.3 + 4.2[2]	25.8 + 3.1[2]	25.5 + 2.9[2]
Basal FSH (IU/ml)	5.31 + 2.11[2]	4.80 + 1.82[2]	4.68 + 1.58[2]
Basal E2 (pg/ml)	64.32 + 8.53[2]	45.1 + 7.3[2]	61.8 + 9.8[2]
E2 peak level (pg/ml)	1328.25 ± 841.20[3]	1554.69 + 1194.43	2216.73 + 2186.90[3]
No. of units of gonadotropins	2502.77 ± 1017.01[4]	3351.92 ± 1523.71[4]	2944.62 ± 1386.51
No. of follicles	9.19 + 7.31	8.42 + 7.235	13.75 + 10.15[5]
No. of follicles > 15 mm	4.58 ± 2.54[2]	7.07 ± 7.132	5.19 ± 2.92[2]

Data are number or mean ± SD, [1]significantly different $p < 0.05$, [2]NS = not significant, [3]significantly different $p = 0.05$, [4]significantly different $p = 0.047$, [5]significantly different $p = 0.042$.

Table 2. — *ICSI outcomes in groups I, II and III.*

	Group I	Group II	Group III
	Cystectomy of ovarian endometrioma by laparoscopy	Ultrasound-guided aspiration of ovarian endometrioma	Tubal factor infertility
No. of retrieved oocytes	6.58 ± 3.71[1]	7.15 ± 7.61	10.52 ± 9.20[1]
No. of M II oocytes	5.80 ± 3.19[2]	5.11 ± 4.17[2]	5.88 ± 3.76[2]
Fertilization rate (%)	66[2]	70[2]	84[2]
Pregnancy rate (%)	35[2]	17[2]	35[2]

Data are number or mean ± SD, [1]significantly different $p = 0.05$, [2]NS = not significant.

Discussion

Endometriosis is present in 30-60% of all infertile patients [14, 15]. Endometriomas are observed in 25-50% of these patients and are very often coincidentally detected in infertile patients prior to ART [16]. The sonographic diagnosis of endometriomas is 80-100% sensitive and requires verification with histopathology or by other means [17]. Surgery for accompanying endometriosis has the potential to enhance fertility [18]. Moreover, the presence of an endometrioma has been suggested by Wong *et al.* to be the dominant determining factor for infertility in contrast to those individuals without an endometrioma or

those who have been operated on [19]. Though at a low rate, endometriomas have been shown to be precursors for malignant transformation [20]. Hence, for an infertile patient, with a suspected ovarian endometrioma, especially larger than 3 cm, laparascopy or ART are sensible intervention options.

Endometriosis and endometriomas are associated with limited ovarian reserve; however, it has not yet been well defined whether operating on these cysts helps the ovarian response to get any better or worse. While many studies suggest that operating on endometriomas does not do any harm to the ovarian reserve, many others suggest that it does or that the presence of an endometrioma has already deformed the ovary to a low responding one [21-26].

Monolateral endometriomas have not been shown to decrease the overall number of oocytes, mature oocytes, grade 1 embryos and the number of embryos transferred as well as the cumulative pregnancy rates in contrast to bilateral endometriomas [27]. Yet, in this former study, the operated ovary produced a lower number of oocytes in contrast to the contralateral one. Sonographically guided cyst aspiration for endometriomas does not provide any data to define the cyst as an endometrioma or any benefit on the treatment outcome; it is also associated with a high recurrence rate and a cause of infection [28, 29]. The severity of peritoneal endometriosis can not be defined without laparascopy.

IVF-ET treatment for an infertile woman with an endometrioma or endometriosis has been shown to be associated with low fertilization, cleavage and implantation rates resulting in low pregnancy rates [31, 32]. The ART success with different degrees of severity of endometriosis is controversial and has been stated to be lower in milder stages of endometriosis by some authors, most probably due either to the presence of unidentified contributing male factors influencing the outcome or peritoneal factors acting to harm the gametes and embryo development [32]. Miscarriage rates have not been proved to be higher in endometriosis [33].

In this study, the patients in the endometrioma aspiration group (Group II) were older than those in the laparascopic resection group (Group I). Despite the age difference between these two groups, peak estradiol levels, number of follicles, follicles larger than 15 mm obtained with ovulation induction, retrieved oocytes, metaphase II oocytes, the fertilization and the pregnancy rates were similar. However, this is not enough to compare these two approaches because the patient number in Group II was 15, so histopathological confirmation of these aspirated cysts as endometriomas was not done; and even if it had been, the extent of endometriosis was not defined with laparascopy.

Oocyte donation-ICSI/ET cycles have been analyzed: both in case groups when only the donors had endometriosis, the fertilization, cleavage and implantation rates were lower. However, endometriosis in the recipient did not seem to have a negative effect on endometrial receptivity [34, 35]. Hence, endometriosis-associated infertility considered apart from peritoneal effects distorting the tubo-ovarian relation mainly stems from intrinsically malfunctioning or negatively influenced gametes. Hence, if IVF-ET cycles are not successful, ICSI-ET may be the next best alternative [31].

Rather than expecting a beneficial effect on the treatment outcome, it needs to be determined whether endometrioma resection is harmful to the outcome. Our findings are unique in the sense that almost all the patients treated with laparascopic resection had unilateral endometriomas and the laparoscopically defined endometriosis cases were at least Stage III. Male factors were ruled out in all couples. In all cycles, fertilization was carried out with ICSI and laparascopic resections were carried out by one senior laparoscopist. The patients in the control group were examined by laparoscopy and endometriosis was ruled out in this group. The variety in the experience of the surgeons, the operation techniques as well as if and how hemostasis has been carried out have most probably contributed to the variation in the answers given to the question about whether operating on endometriomas will do any harm to the ovarian reserve, in addition to the derangement endometriosis has already caused [22-24].

In those patients diagnosed with endometriomas larger than 3 cm, laparascopic resection with an appropriate technique as well as ovariolysis to free the ovary into the vaginal sonographic range, to make the ovum pick-up procedure easier, to rule out an occult malignancy or to prevent an infectious oophoritis, torsion or abdominal pain due to cyst rupture or leakage following the procedure is feasible and does not worsen the treatment outcome.

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Address reprint requests to:
T. CIRPAN, M.D.
Department of Obstetrics and Gynecology
Ege University Faculty of Medicine
Bornova, Izmir (Turkey)