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Poor Response of Ovaries with Endometrioma Previously Treated with Cystectomy to Controlled Ovarian Hyperstimulation

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***Purpose*:** To compare ovarian response to controlled ovarian hyperstimulation (COH) between normal ovaries and ovaries previously treated surgically for unilateral ovarian endometrioma.

***Methods*:** From January 1996 to December 2001, 32 patients with unilateral ovarian endometrioma previously treated surgically underwent 38 cycles of COH. Their records were reviewed retrospectively. The number of dominant follicles observed on the day of hCG injection and the number of eggs retrieved from the diseased and the normal ovaries in each patient were compared.

***Results*:** The numbers of dominant follicles from diseased and normal ovaries were 1.9 ± 1.5 and 3.3 ± 2.1, respectively ($P < 0.001$). During ovum pick up, the numbers of eggs retrieved from diseased and normal ovaries were 2.9 ± 2.6 and 6.1 ± 4.1, respectively ($P < 0.0001$). For diseased ovaries, 21.1% (8/38) had no dominant follicles, while only 7.9% (3/38) of normal ovaries lacked dominant follicles. The clinical pregnancy rate and the implantation rate per embryo transfer were 33.3 and 17.6%.

***Conclusions*:** Surgery for ovarian endometrioma may damage ovarian reserve. It potentially results in poor ovarian response to COH, compared to the response of the contralateral normal ovary in the same individual.

KEY WORDS: Endometrioma; ovarian cystectomy; ovarian reserve.

INTRODUCTION

Endometriosis is a common cause of infertility. Surgical intervention has traditionally been the mainstay of treatment for patients with endometrioma-associated infertility. However, there have been questions as to whether such surgery may damage ovarian reserve. Many studies have evaluated surgical outcome by using pregnancy rates (1–3), and have not evaluated the effect of surgery per se on ovarian reserve. However, many other factors associated with ovarian endometriomas affect pregnancy rates as well. In addition to ovarian reserve, severe pelvic adhesions, endometriosis outside the ovaries, uterine adenomyosis, or inflammatory substances in the peritoneal fluid may all influence pregnancy rates in patients who have had ovarian endometriomas treated surgically. The best way to evaluate ovarian reserve itself is to perform controlled ovarian hyperstimulation (COH) and monitor the ovarian response.

The focus of our study was ovarian response after cystectomy of ovarian endometriomas, comparing

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the response of a unilateral operated ovary with the contralateral normal ovary during COH.

MATERIALS AND METHODS

Patients treated with in vitro fertilization (IVF) between January 1996 and December 2001 were retrospectively selected from our database. We included patients who had previously undergone enucleation of a unilateral ovarian endometrioma. Patients older than 40 years of age and those whose COH cycles were canceled due to poor response were excluded from the study, in order to exclude patients with other possible reasons for poor ovarian reserve. The study was approved by our local institutional review board.

Enucleation of a unilateral ovarian endometrioma had been done by laparotomy or laparoscopy. The inner lining of the cysts was stripped slowly from the normal ovarian tissue. When conception did not occur within 12 months after the operation, the patients were referred to our IVF program.

All patients received the long protocol with a GnRH analogue, leuprolide acetate (Lupron; Abbott laboratories, Illinois), for pituitary desensitization from the midluteal phase of the previous cycle to the day of hCG injection. COH was achieved by combination of three to four vials of human menopausal gonadotropin (hMG, Pergonal; Serono, Rome, Italy) and follicle stimulating hormone (FSH, Metrodin; Serono, Rome, Italy), starting from Day 3 of the menstrual cycle. The dose was modified based on monitoring of serum estradiol (E2) and ultrasound evaluation.

When the level of serum estradiol was >600 pg/mL and two or more leading follicles had mean diameters of >18 mm in two dimensions, 10,000 units of human chorionic gonadotropin (hCG, Pregnyl; Organon, Oss, The Netherlands) were given. Transvaginal-sonographically guided ovum retrieval was performed under general anesthesia 34 h following hCG administration. The number of dominant follicles on the day of hCG injection and the number of oocytes retrieved from ovaries of diseased site and normal sites was recorded. The definition of dominant follicle was a greatest diameter of >16 mm, or a mean diameter of >14 mm for all follicles. Each patient's contralateral ovary, which had been confirmed as normal at surgery, was used as a control.

Transcervical or transfallopian embryo transfer (ET/TET) was carried out 48–72 h after oocyte retrieval. The luteal phase was supported by three injections of 2500 units of hCG every 3rd day, beginning 48 h after oocyte retrieval, or 50 mg of progesterone (progesteron, Tai Yu Chemical Pharmaceutical Co., Shing Ju, Taiwan) administered intramuscularly daily, beginning the day of ovum pick up. Clinical pregnancy was documented by the presence of an intrauterine gestational sac on transvaginal ultrasound 4 weeks after embryo transfer.

A paired comparison was made between the treated and normal ovaries of each patient. A P value of <0.05 was considered statistically significant.

Table I. Patients Characteristics

Number	32
COH cycles	38
Age (years)	31.5 ± 4.3 (21–39)
Duration of infertility (years)	3.8 ± 3.3 (2–14)
Interval between operation and COH (months)	31.5 ± 27.2 (12–97)
Days of stimulation	10.1 ± 2.2 (6–16)
Gonadotropin used (ampoules)	36.2 ± 8.3 (23–54)
Maximal estradiol value (pg/mL)	2002.6 ± 1465.7 (646–7258)
No. of total embryos	4.7 ± 3.6
No. of embryo transferred	3.2 ± 1.5
Pregnancy rate/ET or TET	33.3%
Implantation rate/ET or TET	17.6%

RESULTS

A total of 32 patients fulfilled the inclusion criteria (Table I). They had undergone 38 cycles of COH. Their average age was 31.5 years (range 21–39 years). Eighteen patients (21 cycles of COH) had had left ovarian endometriomas removed, and the remaining 14 (17 cycles) had had right-sided disease.

The mean numbers of dominant follicles on the day of hCG injection in diseased and normal ovaries were 1.9 ± 1.5 and 3.3 ± 2.1, respectively ($P < 0.001$) (Table II). During ovum pick up, the mean numbers of eggs retrieved from diseased and normal ovaries were 2.9 ± 2.6 and 6.1 ± 4.1, respectively ($P < 0.0001$). The follicular response in postcystectomy ovaries was thus reduced significantly compared with normal ovaries in the same patients.

Table II. Ovarian Response Between Normal Ovary and Diseased Ovary Previously Treated Surgically for Unilateral Endometrioma

	Diseased site	Normal site	P
No. of dominant follicles[a]	1.9 ± 1.5	3.3 ± 2.1	<0.001
No. of eggs retrieved	2.9 ± 2.6	6.1 ± 4.1	<0.0001

[a] Dominant follicles observed on the day of hCG injection.

Of the diseased ovaries, 21.1% (8/38) had no dominant follicles at all, compared with only 7.9% (3/38) of normal ovaries failing to produce any follicles.

The mean number of embryos per transfer was 3.2 ± 1.5. The clinical pregnancy rate and the implantation rate per embryo transfer were 33.3 and 17.6%, respectively.

DISCUSSION

Endometriosis is a frequent cause of infertility. Patients with ovarian endometriomas are usually classified as having advanced endometriosis and have a poorer fertility potential. The mechanisms of endometrioma-associated infertility include severe pelvic adhesions, cytotoxic inflammatory substances in pelvic ascites, and poor ovarian reserve, especially after surgery for endometriomas. Proposed causes of the poor ovarian reserve in patients with ovarian endometriomas include mechanical stress on ovarian tissue, impaired vascular networks, alternation of cortical stroma and functional potential (4), inflammatory reaction, distortion of ovaries, and severe periovarian adhesions (5). However, data from Isaacs *et al.* and Williams *et al.* showed that ovarian endometriomas themselves did not adversely affect pregnancy success in IVF programs (6,7). Ovarian surgery for endometriomas therefore might be the cause of poor ovarian response to COH. There is considerable controversy with respect to the most appropriate treatment for this disorder (2,7–16).

Al-Azemi *et al.* found that patients with ovarian endometriomas had a decreased ovarian response to gonadotropins, but they did not have clear data regarding whether or not their patients had been treated surgically (17). Isaacs *et al.* found that patients with aspiration of ovarian endometriomas had the same ovarian response as patients without endometriomas (6). However, they did not state whether the patients had unilateral or bilateral ovarian disease. Williams *et al.* found that previous bilateral ovarian cystectomy for endometriomas had a deleterious effect on ovarian response to COH (7), but they compared patients who had had surgery with a control group of normal individuals, which again did not avoid individual variation to show how surgery had an effect on an operated ovary.

Stripping off the cyst walls may remove viable ovarian tissue, since the endometrioma is usually surrounded by fibrosis, which makes separation of endometriotic tissue from normal ovarian cortex difficult (3). Hachisuga *et al.* found primordial follicles in 68.9% of capsules that were easily removed laparoscopically from ovarian endometriomas (18). Therefore, cystectomy may damage the ovarian reserve. However, Saleh and Tulandi rejected this argument, since follicles were absent from all histopathologic specimens of excised tissue in their series (11,19). Loh *et al.* suggested that the postcystectomy ovarian response to gonadotropins was comparable to the contralateral normal ovary, but the follicular responses of postcystectomy ovaries were significantly reduced in natural and clomiphene citrate stimulated cycles compared with contralateral normal ovaries in women <35 years of age (20). Donnez *et al.* used laparoscopic vaporization instead of cystectomy for unilateral endometrioma and concluded that their procedure did not impair postsurgical ovarian response to gonadotropins (3,12).

Previous studies have concluded that there were no statistical differences between right and left ovarian response in IVF patients with healthy ovaries (21,22), even though the different degrees of response to COH between both side ovaries were noted in some patients occasionally. In our study, each patient's own contralateral normal ovary served as the control. In any one individual, the ovaries were of the same age, had been subject to the same endometriosis-affected pelvic environment, and underwent precisely the same COH regimen. In the treated ovaries, fewer dominant follicles developed, fewer eggs were picked up, and there was a greater chance of the ovary being silent, i.e., no dominant follicles developing at all. Given the conclusion of Isaac *et al.* noted above that endometrioma per se does not affect ovarian reserve (6), our results suggest that cystectomy itself impairs ovarian production of mature follicles, even under gonadotropin stimulation.

An important advantage of cystectomy is the ability to make an accurate tissue diagnosis and completely eradicate the ovarian lesion. In histopathologic studies, 75–88% of clinically suspected endometriomas have had endometrial epithelial lining (18,23,24). Drainage and coagulation or vaporization of endometriomas is associated with an increased chance that the true diagnosis will be missed. Also, Hachisuga's demonstration that the depth from the surface of the deepest penetrating endometrial glands ranged from 1.0 to 3.0 mm calls into question the ability of coagulation or vaporization to completely eradicate these penetrating endometrial glands (18). Saleh and Tulandi reported a higher recurrence rate in patients who underwent drainage and coagulation (11).

Therefore, cystectomy is still recommended by many authors (2,8,11,19).

From our point of view, cystectomy damages ovarian reserve. Some follicles in the normal ovarian cortex may be removed together with the cyst wall. Suturing the ovary after cystectomy results in an inflammatory reaction and may impair local ovarian circulation. Damage may be inflicted on the ovarian stroma or follicles by electrosurgical coagulation during destruction of the cyst wall or during hemostasis. Although the exact mechanism of recruitment of ovarian follicles is still under investigation, ovarian reserve will undoubtedly be impaired by the aforementioned surgical procedures.

In spite of the decreased response in the diseased ovaries, patients in the current study also had a 33.3% pregnancy rate and a 17.6% implantation rate. In Al-Azemi's series, patients with endometriomas treated with surgery achieved cumulative pregnancy and live birth rates similar to those of control subjects, despite decreased ovarian response to gonadotropins in IVF cycles (17). Surgical removal of ovarian endometriomas restores normal pelvic anatomy and ovarian structure, and removes inflammatory or cytotoxic substances. The only problem is that the surgery itself may to some extent damage ovarian reserve. However, eggs that actually are produced by the damaged ovary seem to be capable of producing successful pregnancy at an acceptable rate.

Controversy still exists as to whether to perform surgery to patients with bilateral ovarian endometriomas. Williams' group and ours have found significantly increased cancellation rates and poor ovarian response to COH in patients who had had bilateral cystectomy (7,25). However, for patients with unilateral ovarian endometrioma, surgical treatment may still be appropriate. Although the diseased ovaries may lose a certain degree of ovarian reserve, surgical treatment does correct other problems such as pelvic adhesions and anatomic distortion. These patients who subsequently undergo IVF may have acceptable pregnancy and implantation rates (2,17). In our study, although fewer dominant follicles developed and fewer oocytes were retrieved from cystectomized unilateral ovaries, the pregnancy (33.3%) and implantation rates (17.6%) were acceptable.

CONCLUSION

Ovarian surgery for unilateral ovarian endometrioma appears to damage ovarian reserve, potentially resulting in a poorer response of the operated ovary to COH than that of the contralateral normal ovary. However, this does not seem to adversely affect the chance for success of subsequent IVF.

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