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Bilaterality of ovarian endometriomas does not affect the outcome of in vitro fertilization/ intracytoplasmic sperm injection in infertile women after laparoscopic cystectomyHsing-Tse Yu ^{a,b}, Hong-Yuan Huang ^{a,b}, Hsiao-Jung Tseng ^{a,c,d},
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ABSTRACT

Background: To assess whether the unilateral or bilateral lesions can affect ovarian reserve and pregnancy outcome in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) in infertility patients underwent laparoscopic cystectomy.

Methods: A total of 148 IVF/ICSI cycle in patients who had undergone laparoscopic cystectomy for unilateral or bilateral endometriomas were reviewed retrospectively. There were 103 cycles where laparoscopic cystectomy had been carried out for unilateral endometriomas and 45 cycles after bilateral-side surgery. Primary outcome measures were ovarian reserve and ovarian response. Secondary outcome measures were the implantation rate, clinical pregnancy rate, and live birth rate.

Results: The number of dominant follicle on the day of human chorionic gonadotropin (hCG) administration (5.2 ± 3.1 vs. 4.2 ± 2.7 ; $p = 0.048$), and oocytes retrieved (10.0 ± 6.9 vs. 7.6 ± 6.6 ; $p = 0.047$) were significantly lower in the bilateral-side group compare with the unilateral-side group. However, the mean number of antral follicle count, metaphase II oocytes, the doses of gonadotropin used, fertilization rate, the rate of good quality embryos transferred, implantation rate and clinical pregnancy, live-birth rate and miscarriage rate were similar between the two groups.

Conclusion: There were no associations among the bilaterality of ovarian endometriomas, ovarian reserve and pregnancy outcomes in IVF/ICSI cycles. However, bilateral ovarian endometriomas after laparoscopic cystectomy may impair ovarian response as compared to unilateral ovarian endometrioma.

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At a glance commentary

Scientific background on the subject

The incidence of endometriosis was reported 25–40% in infertile women. Laparoscopic surgery has traditionally been the standard treatment for patients with ovarian endometrioma. Bilateral lesions occur in 19–28% of patients with ovarian endometriomas. We previously reported the experience of the laparoscopist may play a crucial factor for ovarian reserve and live-born rate after treating ovarian endometrioma in infertile women with IVF/ICSI. The aim of our study is to assess whether the unilateral or bilateral lesions can affect ovarian reserve and pregnancy outcome of IVF/ICSI in infertility patients underwent laparoscopic cystectomy.

What this study adds to the field

Previous studies conducted laparoscopic cystectomy for bilateral ovarian endometriomas may impair ovarian reserve. However, our study showed that bilateral cystectomy for ovarian endometriomas may not affect implantation rate and potentially not influence the clinical pregnancy and live-born rate. Even so, laparoscopists should perform conservative surgery for ovarian endometriomas delicately, particularly dealing with bilateral side lesions.

Endometriosis is a common disease that is generally thought to contribute to infertility. Endometriosis occurs in 10–15% of all women of reproductive age while it has been reported that one-third of women with endometriosis have ovarian endometriomas [1,2]. The pathogenesis of endometriosis is poorly understood; however, there is an inflammatory process for ectopic endometrial fragments to adhere, invade, and develop that result in dense adhesion between normal tissue and endometriotic lesions.

Laparoscopy is the most widely accepted modality for removal of ovarian endometrioma. For most patients, laparoscopic cystectomy provides a minimally invasive way to accomplish the removal of tumors with a lower cost to employers on the basis of lost work hours than traditional abdominal approach. However, it needs greater skill and experience on the part of the surgeon and training. An inexperienced surgeon is detrimental to a reduction of ovarian function for inadvertent removal a consistent amount of normal ovarian tissue during cystectomy, especially for bilateral ovarian lesions.

Bilateral lesions occur in 19–28% of patients with ovarian endometriomas [3]. In theory, there will be poor ovarian response on controlled ovarian stimulation (COH) and impaired implantation rate after laparoscopic surgery for bilateral ovarian endometriomas rather than unilateral ovarian endometriomas. Esinler et al. reported that laparoscopic cystectomy for bilateral ovarian endometriomas had a negative impact on ovarian reserve comparing to unilateral

ovarian endometrioma [4]. Very recently, Yu et al. showed that the experience of the surgeon impaired the ovarian reserve and pregnancy outcome after treating ovarian endometrioma in infertile women with *in vitro* fertilization/intracytoplasmic sperm injection (IVF/ICSI) [5]. The aim of our study is to assess whether the unilateral or bilateral lesions can affect ovarian reserve and pregnancy outcome of IVF/ICSI in infertility patients underwent laparoscopic cystectomy.

Methods

This retrospective cohort study was conducted from January 2005 through December 2009 in Chang Gung Memorial hospital at Linkou. IVF/ICSI cycles in infertile women who had undergone laparoscopic conservative surgery for ovarian endometriomas were recruited. Patients with unilateral ovarian endometriomas, concomitant uterine diseases (ex. fibroids and adenomyosis) or other endocrine diseases (ex. thyroid disease, hyperprolactinemia, or adrenal disorders), evidence of premature ovarian failure, or proven ovarian malignancy were excluded. This study was based on review of both electronic and paper medical records. A total of 148 cycles were recruited in patients who previously underwent laparoscopic surgery for ovarian endometrioma(s). To clarify the impact of the severity of endometrioma on the outcome of IVF/ICSI, we divided the lesions into unilateral and bilateral. This study was approved by Institutional Review Board of Chang Gung Memorial Hospital for chart review.

Operative technique

All surgeries were performed with a similar technique which is described elsewhere [5,6]. All operations were performed under general endotracheal anesthesia with patient in the dorsolithotomy Trendelenburg position. Both legs were protected by elastic bandages, and a Foley catheter was inserted for constant urinary drainage. Laparoscopic examination of the pelvis and lower abdomen was performed to determine the accessibility of the surgical field. Three or four trocars were used according to complexity of pelvis. A disposable laparoscopic grasper, scissors, and suction-irrigator were used to perform various procedures such as holding, cutting, exploring, and dissecting. A sharp cortical incision was made by unipolar scissors and a cleavage plane was identified. The capsule of the endometrioma was then enucleated and stripped from the normal ovarian tissue. Large bleeders were coagulated by using bipolar forceps with an electro-surgical bipolar unit (Elmed, Addison, IL). Complete hemostasis and approximation of ovarian defect were achieved by using a 3-0 monofilament polyglactone 25 suture (Monocryl; Ethicon Inc, Somerville, NJ, USA.) on a large curved needle following the principles of laparotomy. The specimens were removed from the abdomen using a disposable endobag for the purpose of avoiding contaminating the abdominal wall. The peritoneal cavity was then irrigated and lavaged until a bloodless condition was achieved. All port sites were sutured with 3-0 polyglycolic acid suture at the level of the fascia to

prevent herniation. The skin was approximated by sterile adhesive tape.

Parameters including patient's demographics, operation records, ovarian reserve (day 2 or day 3 serum follicle stimulating hormone [FSH] and antral follicle count) after surgery, number of ampoules of gonadotropin used for controlled ovarian hyperstimulation (COH), number of follicles greater than 14 mm in mean size, serum estradiol (E_2) levels and endometrial thickness on the day of human chorionic gonadotropin (hCG) administration, number of oocytes aspirated, the proportion of mature (MII) oocytes, number of embryos transferred, good-quality embryo for transfer, clinical pregnancy rate, implantation rate and live-born rate were analyzed. Operative findings were scored according to the revised classification of the American Fertility Society (rAFS) [7]. In this study, we defined embryos of grade 1 or 2 as good quality. Clinical pregnancy was determined by the presence of at least one gestational sac, documented with transvaginal ultrasonography two weeks after a positive pregnancy test. Implantation rate was calculated as number of gestational sacs, divided by number of transferred embryos and multiplied by 100.

All cases were compared by age, body mass index (BMI), infertility duration to a matched control group of unilateral ovarian lesions. The primary outcome measures of this study were ovarian reserve and ovarian response. Secondary outcome measures were the implantation rate, clinical pregnancy rate, and live-birth rate. Parametric continuous variables were compared with Student's *t* test and categorical values were compared with Pearson χ^2 analysis. All probability values were two-sided. Significance level was accepted at $p < 0.05$. SPSS for Windows version 15.0 (SPSS Inc., Chicago, IL) was used for the statistical calculations.

Results

Histologic examination of the resected tissue showed endometriotic tissue in all patients. During the study period, 148

IVF/ICSI cycles were included in this analysis. There were 103 cycles where laparoscopic cystectomy had been carried out for unilateral endometrioma (age, range 25–43 years; median, 34 years) and 45 cycles for bilateral-side surgery (age, range 25–47 years; median, 33 years). Patient characteristics and operative information are summarized in Table 1. Both groups were similar in mean age, BMI, duration of infertility and serum cancer antigen 125 (CA-125) levels before operation. Comparing with unilateral-side group, there were significantly longer operating time (116.5 ± 29.7 min vs. 98.7 ± 46.6 min, respectively; $p = 0.034$) and higher rAFS scores (64.8 ± 27.9 vs. 41.0 ± 23.8 , respectively; $p < 0.001$) in bilateral-side group.

Table 2 summarizes the baseline ovarian reserve after surgery and the response of subsequent COH. There were no differences in day 2 or day 3 serums FSH and E_2 level, the hCG day, dosage of recombinant FSH, number of antral follicles, number of stimulating days, endometrial thickness and peak E_2 level in both groups. The mean number of dominant follicles was significantly fewer in the bilateral-side group (4.2 ± 2.7 vs. 5.2 ± 3.1 , respectively; $p = 0.048$).

Table 3 shows the fertility and reproductive outcomes after IVF/ICSI. The number of retrieved oocytes (10.0 ± 6.9 vs. 7.6 ± 6.6 , respectively; $p = 0.047$) and number of embryos transferred (2.9 ± 1.4 vs. 2.4 ± 1.4 , respectively; $p = 0.02$) were significantly more in the unilateral-side group. Nevertheless, the proportion of MII oocytes, fertilization rate, and implantation rate were not statistically different. The rates of good-quality embryos for transfer per cycle (64.7% vs. 65.1%, respectively; $p = 0.49$), clinical pregnancy rate per cycle (33.3% vs. 33.3%, respectively; $p = 1.0$), and live-born rate per cycle (19.4% vs. 22.2%, respectively; $p = 0.696$) were also similar between the two groups.

Discussion

Laparoscopic stripping technique is a standard method for removal of ovarian endometrioma. Owing to difficulty to identify pseudocapsule between endometrioma and normal ovarian tissue, it is associated with excision of normal ovarian tissue, causing follicular loss. Muzii et al. reported that 54% of cases who underwent laparoscopic cystectomy for removal of endometrioma had involuntarily excision of normal ovarian tissue in the same place [8]. Meanwhile, recent studies stressed the negative impact of stripping technique for excision of endometrioma together with normal ovarian tissue [8–10]. With regard to loss of follicle, Ragni et al. observed the reduction of dominant follicle and high-quality embryos in the operated gonad among women with endometriomas [11]. Benaglia et al. also showed that the incidence of severe ovarian damage after laparoscopic surgery for ovarian endometriomas was as high as 13% [12].

Laparoscopic cystectomy owns the advantages of minimal invasion; nevertheless, it involves electrosurgery to dissect tissue and control bleeding. Therefore, laparoscopists should pay much attention when dealing with women with ovarian endometrioma(s). Our earlier study supported the importance of surgical impact on IVF/ICSI outcome, that is, the experience of surgeons who performed laparoscopic surgery for endometriosis would affect the ovarian reserve and subsequent

Table 1 Patient characteristics.

	Unilateral side	Bilateral sides	<i>p</i> value
Cycles	103	45	
Age (years)	34.2 ± 3.9	33.3 ± 4.3	NS
BMI (kg/m^2)	21.4 ± 3.2	20.5 ± 2.2	NS
Infertility duration (years)	4.5 ± 2.7	4.0 ± 2.9	NS
CA125 before operation (U/mL)	97.6 ± 193.3	119.7 ± 121.3	NS
Size of dominant endometrioma during operation (cm)	5.0 ± 2.0	5.3 ± 1.4	NS
Operation time (min)	98.7 ± 46.6	116.5 ± 29.7	0.034
rAFS score	41.0 ± 23.8	64.8 ± 27.9	<0.001

Abbreviations: BMI: body mass index; CA125: cancer antigen 125; rAFS: revised classification of the American Fertility Society; NS: non-significant.
Significant at $p < 0.05$. values are given as mean \pm SD or number.

Table 2 Baseline characteristics and responses after controlled ovarian hyperstimulation of study participants.

	Unilateral side	Bilateral sides	p value
Day 2 or day 3 FSH (mIU/mL)	7.9 ± 2.9 (7.9; 1.6–15.4)	10.1 ± 7.2 (8.4; 2.5–32.1)	NS
Day 2 or day 3 E ₂ (pg/mL)	40.1 ± 37.9 (27; 10–188)	29.1 ± 25.2 (23.5; 2.1–100)	NS
Antral follicle count	7.3 ± 4.4 (6; 0–21)	7.0 ± 4.2 (6; 2–23)	NS
FSH dosage (IU)	2387.9 ± 1054.6 (2175; 800–9090)	2130.5 ± 1035.6 (1900; 700–5400)	NS
Number of days of stimulation	10.0 ± 1.5 (10; 7–14)	10.0 ± 2.0 (10; 7–17)	NS
No. of follicles >1.4 cm on hCG day	5.2 ± 3.1 (5; 1–15)	4.2 ± 2.7 (4; 0–12)	0.048
Endometrium thickness on hCG day (cm)	1.1 ± 0.2 (1.0; 0.6–1.9)	1.1 ± 0.3 (1.1; 0.6–1.55)	NS
Peak E ₂ level (pg/mL)	1692.8 ± 1199.5 (1305; 259–5008)	1473.4 ± 1532.1 (1241; 95–9998)	NS

Abbreviations: FSH: follicle-stimulating hormone; E₂: estradiol; hCG: human chorionic gonadotrophin; NS: non-significant. Significant at $p < 0.05$. values are given as mean ± SD or number (median; range).

Table 3 Fertility and reproductive outcomes after in vitro fertilization/intracytoplasmic sperm injection.

	Unilateral side	Bilateral sides	p value
No. of oocytes retrieved	10.0 ± 6.9 (8; 1–33)	7.6 ± 6.6 (5; 0–39)	0.047
MII oocytes	7.2 ± 5.1	6.1 ± 4.6	NS
Proportion of MII oocytes (%)	75.2 ± 24.3	78.3 ± 21.9	NS
Normal fertilization rate (%)	64.9 ± 23.6	65.9 ± 22.6	NS
No. of embryos transferred	2.9 ± 1.4	2.4 ± 1.4	0.020
Cryopreservation for surplus embryos (%)	20.4	17.8	NS
No. of cleavage stage embryo transfer (%)	93 (90.3)	45 (100)	0.032
Good-quality embryos for transfer (%) ^a	64.7	65.1	NS
Implantation rate (%)	13.6	20.8	NS
Clinical pregnancy rate per cycle (%)	33.3	33.3	NS
Live-born rate per cycle (%)	19.4	22.2	NS

Abbreviations: MII: mature; NS: non-significant. Significant at $p < 0.05$. values are given as mean ± SD or % (median; range).
^a Good-quality embryos are defined as grade 1 or 2 embryos.

live birth rate on IVF/ICSI [5]. Surgeons should realize the principles of electrosurgery and use the bipolar diathermy with care. It is crucial to perform ovarian hemostasis mainly with suture rather than electrocautery. This manner can decrease the thermal injury and preserve the ovarian reserve theoretically.

In the present study, basal ovarian reserve does not differ between patients who underwent laparoscopic cystectomy for unilateral ovarian endometrioma and those who underwent surgery for bilateral ovarian lesions. Despite the more operation time and less dominant follicles on hCG day in the bilateral-side group, the severity of ovarian endometrioma does not have negative impact on good embryos for transfer, implantation rate, clinical pregnancy rate and live-born rate. Conversely, our findings are not in agreement with other studies in the literature [4,13,14]. Esinler et al. studied 34 IVF cycles in women with unilateral cystectomies and compared their outcomes with those in 23 cycles of women with bilateral cystectomies and in 99 cycles of women with tubal factor [4].

Bilateral cystectomies may impair ovarian reserve and need more requirement of FSH dosage compared to unilateral cystectomies and the group with tubal factor. However, clinical pregnancy, implantation and miscarriage rate did not differ among the three groups.

Serum anti-Müllerian hormone (AMH) has shown its value to represent the ovarian reserve and its level was lower in older patients theoretically [14,15]. Alborzi et al. performed a longer term follow-up periods to observe the impact of laparoscopic cystectomy on the serum AMH levels. Those patients with bilateral lesions had significantly lower levels of AMH, 1 week, 3 and 9 months after surgery and similar findings also were observed in those older than 38 years [14]. Hirokawa et al. reported the rate of decline of the serum AMH level was significantly higher in the bilateral group than the unilateral group at 1 month post-surgery, but no significant correlation with patients' age [13]. Even the inconsistent results were reported, surgeon should not ignore the impact of operation on ovarian reserve, especially in older patients and those with bilateral endometriomas.

We note some weaknesses to the present study. First, its retrospective cohort design inevitably included a heterogeneous population of patients (operative procedure was not uniform because different surgeons were involved in this study and various stimulation protocols were used). Second, the information of interval from operation dates to IVF date was lacking, which probably had an influence on the ovarian reserve. The recovery of the ovarian reserve impaired by surgery has been reported by sequential evaluation of the serum AMH levels [16,17]. Third, the baseline and post-operative AMH levels were not measured in the study, for patients with longer interval from operation to IVF, the serum AMH levels may gradually increase by time. However, we measured the antral follicle count (AFC), dosage of recombinant FSH for COH, and number of stimulating days, the rationalization of these together could bring us to a better comprehension of the surgical impact on the outcome of IVF/ICSI for infertile women with endometriomas. Finally, it is difficult to know which side of the ovaries contributed to the majority of AFC and formation of each embryo and fetus. A larger prospective study on this topic is warranted to further confirm the present results, specifically with studies powered to evaluate implantation and live-born rate.

In conclusion, the present study showed that the bilaterality of ovarian surgery for endometrioma before IVF may have minor effects on ovarian response but did not affect

ovarian reserve. Bilateral cystectomy for ovarian endometriomas may not affect implantation rate and potentially not influence the clinical pregnancy and live-born rate. Even so, laparoscopists should perform conservative surgery for ovarian endometriomas delicately, particularly dealing with bilateral side lesions.

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Conflicts of interest

There are no conflicts of interest.

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