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Could laparoscopic cystectomy improve intrauterine insemination with controlled ovarian hyperstimulation outcomes in women with endometrioma?

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ABSTRACT

Objectives: To clarify the effects of laparoscopic cystectomy of endometriomas on intrauterine insemination with controlled ovarian hyperstimulation (COH + IUI) success in women with the disease.

Material and methods: We performed a retrospective study with endometrioma patients having at least one patent fallopian tube. The study group consisted of 57 infertile patients with a history of laparoscopic cystectomy who underwent 83 COH + IUI cycles. The control group consisted of 88 patients with endometrioma who underwent 161 COH + IUI cycles without surgery.

Results: The total number of antral follicles was significantly lower in the study group than in the control group (10.1 ± 5.1 vs 11.9 ± 5.0; p = 0.008). No significant difference was observed in the clinical pregnancy and live birth rates per cycle [(9.6% vs 7.6%; p=0.7175 OR: 1.195% CI: 0.6–2.1) and (7.2% vs 6.2%; p = 0.9544 OR: 1.1 95% CI: 0.5–2.1], respectively) between the operated and non-operated groups.

Conclusions: The results of the study show that the presence of an endometrioma with at least one patent fallopian tube does not require any cystectomy before COH+IUI treatment because no improvement was observed in the treatment outcomes of the patients who underwent preceding surgery. We conclude that an operation may be taken into consideration when malignancy cannot be ruled out or severe pelvic pain related to endometrioma cannot be relieved.

Key words: endometrioma; ovulation induction; insemination; laparoscopic surgery; pregnancy rate; live birth

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INTRODUCTION

Endometrioma, defined as an ovarian cystic mass arising from ectopic endometrial tissue on the ovaries, also called ovarian endometriosis, is common in reproductive-aged women [1]. As a common form of endometriosis, endometrioma may be present in up to 20–40% of women with endometriosis [2]. Subfertility is a significant complication of endometrioma. One of the challenging areas in endometriosis-associated infertility is the presence of ovarian endometriomas.

Up to 10–25% of women with the disease require assisted reproductive treatment [1]. The presence of endometrioma does not alter ovarian function, but there is confusion on whether this affects fertility treatment outcomes. In addition to the publications claiming to reduce it [2], studies reporting that it does not affect it, have also been reported [3].

Ovarian cystectomy is the treatment of choice for endometriomas, given the low recurrence rate and associated high spontaneous pregnancy rate. On the other hand, surgical treatment of endometriomas is associated with the unintentional removal or destruction of ovarian follicles, which can cause a postoperative reduction in serum anti-Müllerian hormone (AMH) levels or antral follicle count (AFC) on ultrasound [4, 5].

In vitro fertilization (IVF) may be warranted in this setting as a primary intervention (where fertility is the only issue) since the documented loss of the ovarian cortex may further impair fertility. The problem arises when women do not want to have IVF.

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Controlled ovarian stimulation + intrauterine insemination (COH + IUI) is one of the treatment choices for patients with endometrioma who do not want to undergo IVF treatment. Optionally, COH + IUI treatment can follow a preceding surgery.

This surgery must be performed in a way that will provide the best results. However, the surgical management of endometriomas before COH + IUI treatment is still controversial.

In this study, COH + IUI cycles following surgery of infertile women treated with laparoscopic cystectomy for severe pelvic pain due to endometrioma were examined. The aim of the study was to evaluate the effects of laparoscopic endometrioma excision (with at least one patent fallopian tube) on COH + IUI cycles.

MATERIAL AND METHODS

In this retrospective study, the effect of surgery on COH+IUI cycles was evaluated in infertile women who underwent laparoscopic cystectomy for endometrioma and pelvic pain. The data were obtained from the hospital records of 1972 patients who were treated in the reproductive health clinic of the university hospital between July 1, 2015, and December 31, 2019. A total of 145 infertile women with endometrioma aged 18-40 years having at least one patent fallopian tube who participated in our program of COH + IUI were included in the study. Patients with unexplained infertility, bilateral tubal obstruction, advanced male factor infertility, (total motile sperm count less than 5×10^6) abnormal ovulatory function (oligo-anovulation due to polycystic ovary syndrome, hyperprolactinemia, thyroid dysfunction) were excluded from the study. Women who had deep infiltrating endometriosis, endometrial polyps, uterine fibroid, focal or diffuse adenomyosis, hydrosalpinx, and congenital uterine anomalies, also were excluded after clinical, pelvic ultrasound scan, and surgical observations.

The study group (operated group) consisted of 57 women who had a history of laparoscopic cystectomy for pelvic pain unresponsive to medical therapy and endometrioma larger than 3 cm and underwent 83 COH + IUI cycles in the following six months. In comparison, the control group comprised 88 women with endometrioma who were treated only with 161 COH + IUI cycles during the same period.

All patients with laparoscopic cystectomy were operated on by the same surgical team in our clinic, and in addition to cystectomy, removal of endometriotic lesions and adhesiolysis was performed when necessary.

Endometrioma was diagnosed by laparoscopy in the study group and by vaginal ultrasound in the control group. Laparoscopic cystectomy was performed in the study group. The diagnosis of tubal patency was confirmed via hysterosalpingography and laparoscopic methylene blue perturbation in control and study groups, respectively. This study was conducted followed by the approval of the University Ethics Committee.

All patients had undergone COH + IUI treatment. Ovulation induction was initiated on day 3 (D3) with recombinant follicle-stimulating hormone (r-FSH, GONAL-f®, Merck Global). The gonadotropin dose was determined as 50–100 IU daily according to the patient's age, total antral follicle count, and D3 basal hormonal levels. Ovarian response was monitored by transvaginal ultrasound. On day 5 of the stimulation, a transvaginal ultrasound (TVUS) examination was carried out. If the size of the dominant follicle did not reach the required size, the administration of r-FSH was continued, with daily TVUS examination. When leading follicles with an average diameter higher or equal to 17 mm were detected and endometrial thickness was measured at more than 7 mm, ovulation was induced with 250 international units of recombinant human chorionic gonadotropin (r-hCG, OVITRELLE®, Merck Global). Intrauterine insemination was scheduled 36 hours after the injection of r-hCG.

The double gradient method was used for semen preparation. Ejaculates, obtained by masturbation after 2–5 days of abstinence, were prepared for IUI. Semen was prepared on the day of insemination by centrifugation on a density gradient, as previously described [6]. The prepared sperm was gently inserted within 1 cm of the fundal extend of the uterine cavity using a soft catheter. Women remained supine for 20 minutes after the procedure. Micronized progesterone (200 mg/day) was used until the serum hCG test after IUI.

In patients with more than three follicles ≥ 14 mm in diameter, the cycles were aborted before triggering ovulation with r-hCG due to the risk of hyperstimulation syndrome.

A serum hCG test was performed to confirm pregnancy at the time of the first expected menstrual period. Clinical pregnancy was defined as the ultrasonographic demonstration of an intrauterine gestational sac two weeks after a positive test. Pregnancies over 22 weeks resulting in a live birth were included in the live birth rate.

For the statistical analyses presented in the following section, Statistical Package for the Social Sciences (SPSS) for Windows (version 26.0; SPSS Inc., Chicago, IL, USA) was used. A two-sample t-test for parametric variables and Fisher's exact test for nonparametric variables were performed to compare the two groups. A p-value < 0.05 was considered statistically significant.

RESULTS

The average age of the patients in the study and control groups were 32.19 ± 4.51 years and 31.98 ± 5.53 years, respectively. The characteristics of the patients in the operated and non-operated groups are shown in Table 1. There were

Table 1. Characteristics of the women in the operated and non-operated groups

	Operated group (n = 57)	Non-operated group (n = 88)	p-value
Age [years]	32.1 ± 4.5	31.9 ± 5.5	0.76
Duration of infertility [months]	85.1 ± 44.1	97.4 ± 54.9	0.07
Bilaterality of endometrioma, n (%)	14 (24.5%)	23 (26.1%)	0.99
Primary infertility	41 (71.9%)	67 (76.1%)	0.70

Data are presented as the mean ± standard deviation and n (percentage) where appropriate; P < 0.05 is statistically significant

Table 2. Characteristics of the operated and non-operated group cycles

	Operated group cycles (n = 83)	Non-operated group cycles (n = 161)	p-value
Total motile sperm count [10^6]	76.3 ± 83.9	61.1 ± 72.3	0.14
D3 E2 [pg/mL]	42.9 ± 28.9	44.8 ± 28.9	0.62
D3 FSH [IU/mL]	8.3 ± 3.1	7.8 ± 2.6	0.20
Total antral follicle count	10.1 ± 5.1	11.9 ± 5.0	0.00
Total gonadotrophin doses [IU]	971.4 ± 181.2	986.3 ± 170.5	0.53
Duration of stimulation [days]	12.4 ± 3.3	11.8 ± 4.1	0.21

Data are presented as the mean ± standard deviation; D3 — Day 3; E2 — estradiol; FSH — follicle stimulating hormone; IU — International Unit; mL — milliliter; pg — picogram; p < 0.05 is statistically significant

no significant differences in age, duration of infertility, type of infertility (primary/secondary), or bilaterality of disease between the two groups.

Total motile sperm count, D3 basal hormone levels [estradiol (E2), FSH], total gonadotropin dose, and duration of stimulation between the operated and non-operated group cycles were not significantly different, whereas the total antral follicle count was significantly lower in the operated group cycles than in the non-operated control group as shown in Table 2 (10.1 ± 5.1 vs 11.9 ± 5.0; p = 0.008).

The effect of endometrioma surgery before COH + IUI treatment on clinical pregnancy rate and pregnancy outcomes is evaluated in Table 3. Clinical pregnancy and live birth rates per cycle were not significantly different between the operated and non-operated group cycles [(9.6% vs 7.6%; p = 0.7175, OR = 1.1, 95% CI: 0.6–2.1) and (7.2% vs 6.2%; p = 0.9544, OR = 1.1, 95% CI: 0.5–2.1), respectively].

The cancellation rate was similar in both study and control groups (6.0% vs 8.0%; p = 0.7651, OR = 0.8, 95% CI: 0.3–1.7). The reason for two cycle cancellations in the control group was that patients had more than three follicles with a diameter greater than 14 mm before triggering ovulation with r-hCG. All five cycle cancellations in the operated group and eleven cycle cancellations in the non-operated group occurred due to no response to stimulus despite increasing the gonadotropin dose by 50%.

Only one patient with a twin pregnancy in the study group suffered from hyperstimulation syndrome at the sixth week of gestation. She was treated conservatively with close follow-up.

DISCUSSION

Although endometrioma is one of the causes of subfertility, there is no consensus on the management of these patients. According to the American Society for Reproductive Medicine (ASRM) guidelines, endometriomas that cause pain and mass effects can be removed to relieve patient complaints [5].

The European Society for Reproductive and Embryology (ESHRE) endometrioma treatment guidelines suggest that IVF is an appropriate treatment, especially if the tubal function is compromised, severe male factor infertility is present, or other treatments have failed [7]. In the absence of these conditions and in patients who do not prefer IVF, COH + IUI treatment should be kept in mind as an option for subfertility treatment. The effect of removal of endometriomas on pregnancy outcomes varies according to the type of treatment to be applied.

According to a Cochrane review, removal of endometriomas by laparoscopic cystectomy improves spontaneous pregnancy rates while not altering pregnancy outcomes in IVF treated patients [8]. In patients who are planning to

Table 3. Treatment outcomes of controlled ovarian stimulation + intrauterine insemination in operated and non-operated group cycles

	Operated group cycles (n = 83)	Non-operated group cycles (n = 161)	p-value	OR (95% CI)
Clinical pregnancy, n [%]	8 (9.6%)	12 (7.4%)	0.717	1.1 (0.6–2.1)
Live birth, n [%]	6 (7.2%)	10 (6.2%)	0.954	1.1 (0.5–2.1)
Cancellation, n [%]	5 (6.0%)	13 (8.0%)	0.765	0.8 (0.3–1.7)
Hyperstimulation, n	1	0	—	—
Multiple pregnancy, n	1	0	—	—

Data are presented as numbers (percentages) where appropriate; $p < 0.05$ is statistically significant; CI — confidence interval; COH + IUI — controlled ovarian stimulation + intrauterine insemination; OR — odds ratio

receive COH + IUI treatment, the effect of removal of endometriomas before treatment on pregnancy outcomes has not been clarified. Leone Roberti Maggiore et al. [9] reported that an endometrioma itself does not diminish ovarian function. In their study, ovulation rates of normal and endometriotic ovaries were similar. However, an endometrioma may reduce the number of follicles recruited in the ovary by exogenous FSH stimulation, there is no evidence that the cyst affects pregnancy or live birth rates after IVF [10].

On the other hand, ovarian surgery to remove the endometrioma could be associated with reduced ovarian reserve [11, 12]. Recently, laparoscopic cystectomy to remove endometrioma has caused concerns regarding damage to ovarian reserve [13]. Damage to the ovary becomes more severe as the diameter of the endometrioma increases [14]. Furthermore, Busacca et al. reported that patients who have undergone operations for bilateral endometrioma have a 2.4% risk of premature ovarian failure after surgery [15]. However, premature ovarian failure is associated with reduced ovarian reserve with a significant decrease in serum anti-Müllerian hormone (AMH) levels but not in antral follicle counts [11, 12].

However, in our study, we observed that the number of antral follicles decreased significantly in the operated group compared to the non-operated group, which was not in agreement with this study. A limitation of our study is that we did not measure serum AMH levels to assess ovarian reserve. Therefore, we did not know whether there is a change in AMH values. Nevertheless, when interpreting the decreased serum AMH levels after surgery, it should be kept in mind that the predictive value of AMH alone for ovarian reserve is not better than the total number of antral follicles in a clinically eligible patient for IUI [16].

Benaglia et al. reported that the presence of endometrioma in women selected for IVF did not significantly affect their response to ovarian stimulation [17]. Bongioanni et al. compared women with ovarian endometriosis and tubal factor-induced infertility and found that endometriomas did not impair IVF outcomes. In addition, the authors reported that laparoscopic removal of endometriomas has no beneficial effect on IVF outcomes but may have a negative effect on ovarian response to gonadotropins [18].

A recent meta-analysis showed that resection of endometriomas before IVF treatment does not improve pregnancy outcomes [19]. Decreased ovarian reserve is a potential risk factor for surgical resection of endometriomas, especially in women with bilateral disease [20]. Since endometriomas are associated with dense adhesions in most patients, standard surgical risks such as adjacent visceral injuries should be considered when deciding on the operation [5]. Surgery is not routinely recommended for patients with asymptomatic endometrioma due to subfertility in our clinic. However, many patients with endometrioma have had surgery for pelvic pain.

Gandhi et al. [21] showed that COH+IUI treatment did not improve pregnancy rates at any stage of endometriosis compared to spontaneous cycles. They recommended that patients who have been operated on for endometrioma should also receive IVF treatment. Conversely, Kereszturi et al. [22] reported that COH + IUI treatment following surgery was more effective than surgery alone. In our clinic, we recommend COH + IUI treatment instead of spontaneous follow-up to patients who have subfertility and have undergone surgery for endometrioma but do not want IVF treatment. In our study, clinical pregnancy and live birth rates per cycle were not different in the operated and non-operated groups after COH + IUI treatment. The cycle cancellation rate was similar in both groups.

CONCLUSIONS

According to the results of the study, laparoscopic cystectomy of endometriomas before COH + IUI treatment did not significantly improve the pregnancy outcomes in treated patients. Surgical removal of endometriomas in women suffering from subfertility should be considered if they are symptomatic or have malignancy potential. However, the risks of persistent endometriomas, such as the rupture of an endometrioma, infections, and future malignancy, should not be ignored. Further randomized controlled trials are needed to clarify the effect of endometrioma surgery on

treatment outcomes in COH + IUI cycles in women experiencing subfertility.

Conflict of interest

The authors declare that there are no conflicts of interest.

Authors' statement

All authors certify that they have no affiliations with or involvement in any organization or entity with any financial or nonfinancial interests in the subject matter or materials discussed in this manuscript.

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