

Can Laparoscopic Cystectomy Improve Pregnancy Outcomes in Endometrioma? A Prospective Clinical Trial Study

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Abstract

Background: The purpose of this prospective study was to compare the ovarian response and pregnancy outcomes in the infertile women with endometrioma undergoing assisted reproductive technologies (ART) in two groups, who were underwent laparoscopic cystectomy and received gonadotropin releasing hormone-agonist (GnRH-agonist) and who only received GnRH-agonist without any surgery.

Materials and Methods: In this prospective clinical trial study, 79 infertile women with asymptomatic endometriomas cyst (2-6 cm) were enrolled and randomly assigned to two groups. First group underwent laparoscopic cystectomy and received GnRH-agonist. Second group only received GnRH-agonist without any surgery. Following ovulation induction, all patients underwent intracytoplasmic sperm injection (ICSI). Different parameters such as the number of retrieved oocytes and embryos; were made our outcomes that analyzed using SPSS.

Results: The pregnancy rate, chemical and clinical, and live birth rate were higher in the combined group, although these differences were not statistically significant (48.48% vs. 30.8%, $P=0.12$, 36.36% vs. 25.6%, $P=0.32$, 36.36% vs. 23.1%, $P=0.29$). The number of injections, antral follicles, retrieved oocytes, mature oocytes, total embryos, transferred embryos and duration of stimulation were similar in two groups.

Conclusion: Laparoscopic cystectomy followed by receiving GnRH-agonist improves pregnancy outcomes in endometrioma prior to treatment with ART (registration number: IRCT201106116689N2).

Keywords: Cystectomy, Endometrioma, Infertility, GnRH-Agonist

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Introduction

Endometriosis is defined as endometrial glands and stroma that occur outside of the uterine cavity. Evidence suggests that peritoneal microenvironment is altered by immune cells, extracellular matrix metalloproteinase and pro-inflammatory cytokines, creating the conditions for abnormal endometrial cell proliferation and survival (1, 2). Infertility is the most important complaints in patients with endometrioma (ovarian endometriotic cyst). Endometriomas reduces the number of follicles and oocytes quality (3-5). *In vitro* fertilization (IVF) is considered as an effective method for treatment of infertility in patients with endometrioma (6). In the presence of endometrial cyst lower embryo quality, lower implantation rate and higher pregnancy complications were seen compared to the absence of endometrial cyst during IVF cycles (7). There are different treatment options for women with ovarian endometriotic cysts before IVF, including surgical treatment, medical treatment, and

a combination of surgical and medical treatments and expectant management among infertile women (8-12)

The gonadotropin releasing hormone-agonist (GnRH-agonist) is one of the medical options. Since the endometrioma is an estrogen-dependent disorder, GnRH agonist can produce a hypo-estrogenic environment by suppression of the hypothalamus and improve pregnancy rates at IVF (12, 13).

The purpose of the present prospective study was to investigate the ovarian response and pregnancy outcomes after laparoscopic cystectomy plus GnRH- agonist versus GnRH- agonist alone among infertile women suffering from endometrioma.

Materials and Methods

Obtaining the formal approvals from the Ethics Committee of Tehran University of Medical Sciences, Tehran, Iran (90-02-30-14261-40996) this prospective

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clinical trial study was conducted in the Shariati Hospital of Tehran University of Medical Sciences, Tehran, Iran. Also, this study was restarted at the Iranian Registry of Clinical Trials (IRCT201106116689N2). All participants signed an informed consent before entering the study.

All women less than 40 years old with endometriosis and asymptomatic (without pain, torsion or rupture) endometrioma (2 to 6 cm diameter) who were candidate to intracytoplasmic sperm injection (ICSI) were invited to this study. Who suffered of endometrioma cyst smaller than 2 cm or larger than 6 cm and who have history of surgery for endometrioma or other ovarian cysts were excluded. Also, women that their husbands suffered of azoospermia were omitted of this study.

In this prospective study, all infertile women who met the inclusion criteria were randomly assigned to two groups by a nurse from 2015 to 2019. This study was blinded for the nurse who randomized the participants and the statistician who analyzed the results. Randomization was done with an allocation sequence generated by block randomization by the trial statistician. All participants signed an informed consent before entering the study.

During this period, ninety-one of the women were assessed. Twelve of them did not have inclusion criteria. Six patients did not agree to be in a group and were excluded from the study. Finally, 73 participants were divided into 2 almost equal groups given a block size of 40.

Endometriosis was diagnosed in all patients previously by laparoscopy and sonography. Ultrasound diagnosis of endometrioma was present of round shaped homogeneous hypoechoic tissue. All transvaginal ultrasound examinations underwent by an expert physician gynecologist. The non-surgical diagnosis of endometrioma with transvaginal ultrasound is a valid method (14, 15). The combined group (laparoscopic cystectomy plus GnRH-agonist) underwent the laparoscopic cystectomy by a single experienced surgeon and the surgical technique consisted of resection of the endometriotic cyst wall. Then patients received 3 doses of Diphereline 3.75 mg (Beaufouipfen, France, IM) in 3 consecutive months. The GnRH-a alone group received three doses of Diphereline 3.75 mg (Beaufouipfen, France, IM) during three consecutive months.

Ovarian stimulation was conducted in two groups by Gonal F (Serono, Switzerland, 300-450 IU daily), ten days after the third injection of Diphereline. Seven days later, Gonal F was replaced by human menopausal gonadotropin (hMG, Ferring, Germany, 300-450 IU daily) until the observation of 18 mm follicles in the transvaginal ultrasound. With observation of at least two 18-mm follicles, human Chorionic Gonadotropin (hCG, Ferring Co, Germany, 10000 IU, IM) was injected and trans-vaginal oocyte retrieval was performed under general anesthesia after 36 hours. Fertilization was performed through ICSI. For blinding the study, counting the number of retrieved oocytes; determining the quality of oocytes and embryos and

fertilization were performed by an embryologist who was not aware of the treatment groups. Transcervical embryo transfer was carried-out after three days. The chemical pregnancy was diagnosed based on the rising concentration of serum hCG levels. This measurement was performed in the Shariati hospital Laboratory service based on the standard serology method 14 days after embryo transfer. The clinical pregnancy was detected by observation of the pregnancy sac in transvaginal ultrasound, two weeks later of the hCG level rising.

Finally, the number of retrieved oocytes and embryos; quality of retrieved oocytes and embryos; fertilization rate, chemical and clinical pregnancy rates, abortion and live birth rates were compared between two groups by a statistician.

Statistical analysis

This study was blinded for the statistician who analyzed the results. All data were analyzed by SPSS software (Version 25, Armonk, New York, USA). The groups were initially compared on baseline variables with chi-square tests and independent samples t tests. Also, multiple logistic regression was used to examine the variables. Data were expressed as the mean \pm standard deviation (mean \pm SD) or percent (number). Statistical significance was defined as $P < 0.05$.

Results

There were 79 patients who were divided into two groups randomly based on Bernoulli distribution and all of them underwent ovulation induction (Fig.1).

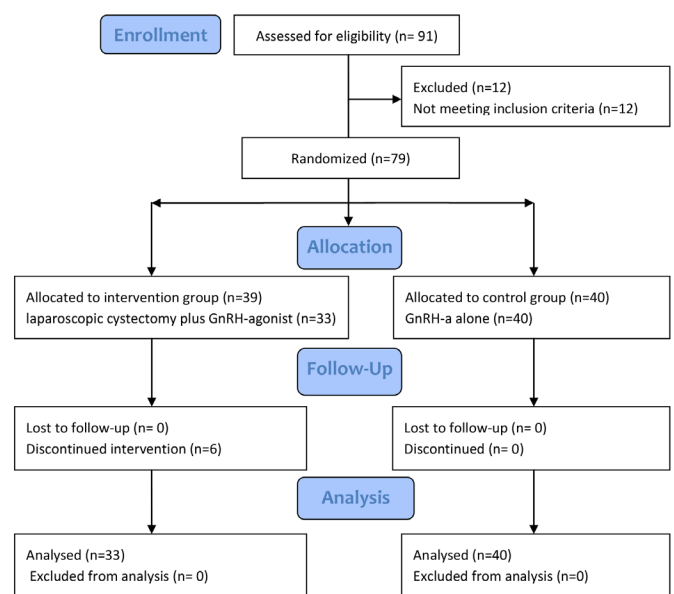


Fig.1: Study flowchart.

The demographic characteristics of two groups are shown in Table 1.

Table 1: Demographic characteristic of our study groups

Characteristic	Combined group (n=33)	GnRH-a alone group (n=40)	P value
Mean age (years \pm SD)	30.3 \pm 4.61	31.44 \pm 4.49	0.125
BMI (kg/m ²)	23.91 \pm 3.24	26.90 \pm 3.78	0.004
Cyst diameter (mm)	49.18 \pm 11.99	31.87 \pm 10.63	<0.001
Duration of infertility (years \pm SD)	6.21 \pm 3.89	6.71 \pm 4.30	0.309
Bilateral cyst (%)	18	8	0.108
Day 3 FSH (m IU/ml)	4.75 \pm 2.22	6.58 \pm 3.61	0.041
Day 3 LH (m IU/ml)	5.14 \pm 3	5.30 \pm 5.25	0.872
Day 3 estradiol (pg./ml)	56.24 \pm 22.97	48.63 \pm 37.34	0.435
Day 21 progesterone (pg./ml)	10.88 \pm 9.20	8.13 \pm 9.02	0.215
CA125 (m IU/ml)	51.9 \pm 37.25	22.98 \pm 15.37	0.004
AMH (ng/ml)	1.45 \pm 0.95	1.70 \pm 0.99	0.201

Crude and adjusted odds ratio for the association between the variables were reported as a confidence interval (CI) of 95%. Values are presented as mean \pm SD. P<0.05 is defined for statistical significance. BMI; Body mass index, FSH; Follicle-stimulating hormone, LH; Luteinizing Hormone, GnRH; Gonadotropin-releasing hormone, and AMH; Anti mullerian hormone.

The IVF outcomes of two groups are shown in Table 2.

After laparoscopic cystectomy and receiving 3 doses of Diphereline, there were 16 chemical pregnancies in 33 patients. All of chemical pregnancies lead to live births (n=12, 3 twins /12); there were three abortions and one ectopic pregnancy (EP). Among 40 patients who received 3 doses of Diphereline before ART, there were 12 chemical pregnancies who lead to nine live births (3 twins); there

were two abortions and one EP. Pregnancy outcomes of two groups are compared in Table 3.

Based on Table 1 Cyst size and CA125 level in combined group were higher; BMI and baseline FSH were lower than another group. Therefore, two groups were adjusted for BMI, Cyst diameter, FSH and CA125 levels in Table 4. There was no statistically significant difference between two groups regarding the live birth rate (Table 4).

Table 2: Comparison of IVF outcomes in our study groups

Characteristic	Combined group (n=33)	GnRH-a alone group (n=40)	P value
Duration of stimulation, day	10.07 \pm 2.67	10.42 \pm 1.55	0.529
Gonadotropin dose (IU)	3565.50 \pm 1936.50	3578.25 \pm 1593.75	0.797
No. of antral follicles	10.78 \pm 5.97	11.92 \pm 5.38	0.173
No. of retrieved oocytes	8.47 \pm 6.52	9.55 \pm 7.06	0.442
No. of mature oocytes	4.62 \pm 3.62	5.30 \pm 3.93	0.380
No. of total embryos	3.46 \pm 2.77	3.62 \pm 2.51	0.797
No. of grade 1 embryos	2.34 \pm 1.82	2.15 \pm 1.62	0.682
No. of transferred embryos	2.62 \pm 1.59	2.38 \pm 1.11	0.588
Cancellation rate, n (%)	2 (6.06)	1 (2.5)	0.398
Fertilization rate (%)	79	68	0.471

Crude and adjusted odds ratio for the association between the variables were reported as a confidence interval (CI) of 95%. Values are presented as mean \pm SD. P<0.05 is defined for statistical significance. IVF; *in vitro* fertilization and GnRH; Gonadotropin-releasing hormone.

Table 3: Pregnancy outcomes in our study groups

Characteristic	Combined group (n=33)	GnRH-a alone group (n=40)	P value
Chemical pregnancy rate	16 (48.48)	12 (30.8)	0.124
Clinical pregnancy rate	12 (36.36)	10 (25.6)	0.325
Live birth rate	12 (36.36)	9 (23.1)	0.292
Abortion rate	3 (9.09)	2 (5)	0.740

Values are presented as n (%). P<0.05 is defined for statistical significance.

Table 4: Crude and adjusted OR for the association between type of intervention and live birth rate

Intervention	Crude OR (95% CI)	P value	Adjusted odds ratio* (95% CI)	P value
Combined/GnRH-a alone	1.91 (0.68-5.32)	0.220	1.08 (0.51-22.77)	0.961

BMI; Body mass index, FSH; Follicle-stimulating hormone, OR; Odds ratio, CI; Confidence interval, GnRH; Gonadotropin-releasing hormone, and *; Adjusted for: BMI, Cyst diameter, FSH, CA125.

No adverse effect or harm related to the drug and/or operation was observed in these groups.

Discussion

Endometriosis is a chronic inflammatory estrogen-dependent disease in which the endometrial glands and stroma grow outside the uterus. Infertility is the most important complaints in the patients with endometrioma (ovarian endometriotic cyst). IVF is considered as an effective method for treatment of infertility in patients with endometriomas (6).

Removal of endometriomas before IVF in infertile women is controversial. Since oocyte retrieval is difficult in the presence of endometrioma and because of the risk of follicular fluid contamination many clinicians consider cystectomy prior to the ART. Furthermore, bloody component of endometriomas is an excellent cultural environment and following the puncture of the cyst during the oocytes retrieving procedure, there are some risks for infection and pelvic abscess formation (16).

On the other hand, because of pseudo cyst nature of endometrioma without any capsule, it invades the ovarian cortex and its resection will be accompanied with the resection of natural ovarian tissues. It was shown that primordial follicles were found in more than 50% of resected endometrial cysts (17). Additionally, the ischemic injury resulted from the electro-coagulation and the related local inflammation will injure ovaries. Through the evaluation of the numbers of antral follicles and oocytes and anti-Mullerian hormones, many studies have reported ovarian reserve reduction after cystectomy (18-20).

Based on the European Society of Human Reproduction and Embryology (ESHRE) guideline (12), GnRH agonists for a period of 3-6 months prior to treatment with ART is one of the medical options used for improvement of clinical pregnancy rates in the infertile women with endometriosis. Sallam et al. (21) study showed that 3-6 months of treatment with GnRH agonists before the start of IVF associated with 4 times increase in the pregnancy rate of endometriosis patients. The theory for improvement of pregnancy rates at IVF with GnRH agonist pre-treatment is normalization of inflammation. Postoperative medical therapy with GnRH agonist can produce a hypo-estrogenic environment for treating microscopic foci which were not surgically removed (22).

In our study, although the rates of chemical and clinical pregnancy and live birth rate were higher in the combined group than GnRH-agonist alone group but

these differences were not statistically significant.

Decleer et al. (23) divided patients with mild peritoneal endometriosis in the two groups. A group received GnRH agonist post-surgical for a 3-month period and the other group treated immediately after laparoscopy with stimulation for IVF. They detected no differences in the number of MII oocytes, embryos and pregnancy rate between their groups.

In the Dong et al. (24) study, 153 women underwent laparoscopic cystectomy then IVF and 68 women with an endometrioma cyst directly received IVF procedure. They found no significant difference regarding the numbers of retrieved oocytes, embryos; chemical and clinical pregnancy rates and live birth rate, that their results were consistent with our results.

Zhao et al. (13) concluded that prolonged GnRH-a protocol after ovarian endometrioma cystectomy may be an optimal choice in patients with Diminished ovarian reserve.

In Lee's study (25), patients with endometrioma were divided into three groups (surgery, aspiration of endometriomas and control) before ICSI, although the numbers of retrieved oocytes, were similar to our study. The clinical pregnancy rate was similar in all groups.

Alborzi et al. (26) enrolled patients with endometriosis in 3 groups: Letrozole group (2.5 mg/day, Femara, Novartis Pharma AG, Basel, Switzerland), GnRH-agonist group (Amp Diepherelin 3.75 mg, Beaufour Ipsen Pharma Paris, France) and control group. The chemical pregnancy rate in stages III and IV of endometriosis in the all groups were similar to our GnRH-agonist alone group.

Yang et al. (27) reported that GnRH-a for six months after laparoscopic surgery can improve pregnancy rate in endometriosis. The pregnancy rate in this group was significantly higher than laparoscopic surgery group (30.77% vs. 9.23%, P=0.002).

In the Barra et al. (28) and Laganà et al. (29) study, IVF outcomes improved in patients with endometriosis who received Dienogest (progestin) for 3 months.

In the present study, the rates of chemical and clinical pregnancy and live birth were higher in the combined group than GnRH-agonist alone group but these differences were not statistically significant.

Our study had some limitations that should be mentioned. The sample size of this study was relatively small. Therefore, further randomized controlled trials are required to confirm the results of this study.

Conclusion

This study suggests that in the infertile women with endometriomal cyst Laparoscopic cystectomy followed by receiving GnRH-agonist prior to treatment with assisted reproductive technologies (ART) improve the rates of chemical and clinical pregnancy and live birth.

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Authors' Contributions

S.H., L.S.; Conceived and designed the experiments. A.A., M.A., S.H.; Performed the experiments. S.H., M.T.; Recorded the results. S.H.; Wrote the manuscript. All authors performed editing and approving the final version of this manuscript for submission.

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