Comparison of Ovulation Induction Protocols After Endometrioma Resection

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ABSTRACT

Background and Objectives: The aim of this study was to compare the in vitro fertilization (IVF) outcomes of long gonadotropin-releasing hormone agonist (GnRH-a) and GnRH-antagonist (GnRH-ant) protocols in endometriosis patients who have undergone laparoscopic endometrioma resection surgery. To our knowledge, there is no study in the current literature that compares the effectiveness of long GnRH-a and GnRH-ant protocols in management of IVF cycles in endometriosis patients who underwent laparoscopic endometrioma resection surgery.

Methods: Eighty-six patients with stage III to IV endometriosis who had undergone laparoscopic resection surgery for endometrioma were divided into 2 groups: those who had ovarian stimulation with a long GnRH-a protocol (n = 44), and those who had ovarian stimulation with a GnRH-ant protocol (n = 42).

Results: The number of follicles on human chorionic gonadotropin injection day, duration of hyperstimulation, number of retrieved metaphase II oocytes, and total number of grade 1 embryos were statically significantly higher in the long GnRH-a protocol. There were no significant differences in positive β-human chorionic gonadotropin pregnancy rates (25% vs 21.4%; $P = .269$) and ongoing pregnancy rates per patient (20.5% vs 19.1%; $P = .302$) between the 2 protocols.

Conclusions: Long GnRH-a and GnRH-ant protocols both present similar IVF outcomes in patients with endometriosis who have undergone laparoscopic endometrioma resection surgery. A long GnRH-a protocol may lead to a higher number of embryos that can be cryopreserved, providing the possibility of additional embryo transfers without having to go through the process of ovarian stimulation again.

Key Words: GnRH antagonist, GnRH agonist, Laparoscopic endometrioma resection, in vitro fertilization, intracytoplasmic sperm injection.

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INTRODUCTION

Endometriosis is a challenging disease observed in 20% to 40% of subfertile women.[1] Alterations of the immunologic milieu within the peritoneal cavity create a hostile environment in endometriosis that may impair gamete interaction and early embryo development. Endometriomas are a common form of endometriosis that may be present in 20% to 40% of women with endometriosis who undergo in vitro fertilization (IVF) treatment.[2] Both endometriomas and endometrioma resection surgery can have detrimental effects on the outcome of IVF due to the possible reduction in the number of developing follicles and subsequently on the retrieved number of follicles.[3–7]

Various protocols, which vary in duration, are used to achieve controlled ovarian hyperstimulation (COH) during IVF treatment. Long gonadotropin releasing hormone agonist (GnRH-a) and GnRH antagonist (GnRH-ant) protocols are the most commonly used protocols aiming to suppress the premature luteinizing hormone (LH) surge and to optimize IVF treatment outcomes. In the literature, mostly long and ultralong GnRH-a protocols have been evaluated in endometriosis patients, and ultralong GnRH-a protocol was associated with a better IVF outcome.[8–11] To our knowledge, there is no study in the current literature that compares the effectiveness of long GnRH-a and GnRH-ant protocols in the management of IVF cycles in endometriosis patients who have undergone laparoscopic endometrioma resection surgery.

The aim of this study was to compare the IVF outcome of long GnRH-a and GnRH-ant protocols in endometriosis

patients who have undergone laparoscopic endometrioma resection surgery.

MATERIALS AND METHODS

Subjects

A total of 86 patients who were undergoing IVF/intracytoplasmic sperm injection (ICSI) cycles, and who had undergone laparoscopic resection surgery for endometrioma in the infertility clinic of Istanbul University School of Medicine (Istanbul, Turkey) between January 1, 2002 and January 1, 2012, were included in this retrospective study. All the patients underwent IVF/ICSI cycles within 6 months following the resection surgery. The study protocol was approved by the Ethics Committee of Istanbul University School of Medicine, and informed consent was waived due to the retrospective nature of this study.

Inclusion criteria were age between 18 and 39 years, a larger unilateral or bilateral endometrioma (>4 cm) detected with vaginal ultrasonography, moderate to severe endometriosis as classified during surgery (stages III–IV), total antral follicle count (AFC) ≥5 prior to surgery, day-3 serum follicle-stimulating hormone (FSH) value of <10 IU/mc prior to surgery, normal hormone panel and regular menstrual cycles, couples undergoing the first IVF/ICSI cycle after the surgery, normal uterine documented by hysterosalpingography or hysteroscopy, no previous IVF attempts, and complete cyst excision.

Exclusion criteria were minimal to mild endometriosis (stages I–II), infertility due to male factor or a history of poor response, AFC of ≤5, day-3 serum FSH value of ≥10 IU/mc, thaw cycles, previous endometrioma resection surgery, endometrioma recurrence, detection of hydrosalpinx, no previous hormonal therapy in the last 3 months, and drainage and/or aspiration of a cyst.

The patients were divided into 2 groups according to the GnRH analogue that they received. Forty-four patients received the long GnRH-a protocol, whereas the remaining 42 patients received the GnRH-ant protocol.

Laparoscopic Endometrioma Resection Surgery

Laparoscopic endometrioma resection surgery was performed by 3 experienced surgeons. During the surgery, the ovary covering the endometrioma was separated from the pelvic sidewall and adhesions were lysed. After the cyst capsule was identified, 2 grasping forceps were used to gently strip the capsule from the ovary. The correct dissection plane was carefully maintained to avoid bleeding and potential damage to the primordial follicles. Bleeding sites were cauterized using a bipolar forceps. The ovarian cortex was left open and the pelvis was liberally irrigated at the end of the procedure. None of the patients received antiadhesion adjuvants.

Endometrioma was detected by vaginal ultrasonography and confirmed by the pathologic examination of the cyst wall extracted during laparoscopy. The stage of endometriosis was confirmed during laparoscopy for endometrioma resection according to the revised American Fertility Society classification.[12] After surgery, no patients received adjuvant treatments.

Controlled Ovarian Hyperstimulation

Vaginal ultrasonography was performed on all patients on the third day of the IVF cycle to evaluate follicular activity and the AFC. COH was started in patients if their ultrasonogram findings did not reveal a follicular cyst over 20 mm. Patients received GnRH-a or GnRH-, either Puregon (Schering-Plough, Merck & Co, Kenilworth, New Jersey) or Gonal-f (EMD Serono, Rockland, Massachusetts), in line with the preference of the clinician. The initial dose was determined according to patient's age, ovarian reserve, AFC, body mass index, and response to prior stimulation regime (if applicable). It was then adjusted according to the response of ovarian follicles, which were followed-up via vaginal ultrasonography.

COH treatment was started on the second or third day of menstrual bleeding with 225 to 300 IU of recombinant FSH (Gonal-f or Puregon).

Long GnRH-a Protocol

In the long GnRH-a protocol, pituitary desensitization was achieved in the luteal phase by the administration of 0.5 mg leuprolide acetate/day or 0.1 mg triptorelin acetate/day on day 21 of the previous cycle. Ovarian suppression criteria were an E_2 concentration <50 pg/mL in the serum and follicle size of ≤10 mm in the ovary. After starting COH treatment, the dose of agonist administered was decreased by half and continued until the human chorionic gonadotropin (hCG) injection day.

GnRH-ant Protocol

In the GnRH-ant protocol, multiple doses of the cetrorelix (Cetrotide, EMD Serono; 0.25 mg, subcutaneous) was injected daily, when the leading follicle was 12 to 13 mm in diameter and continued until the hCG injection day.

Ovarian Follicular Development and Oocyte Retrieval

Ovarian follicular development was observed via vaginal ultrasound at a 1- to 3-day frequency. When ≥3 follicles ≥17 mm in size were observed, 5000 to 10 000 IU hCG was injected to achieve follicular maturation.

Oocyte retrieval took place 35 to 36 hours after hCG injection. All follicles ≥ 14 mm in size were retrieved. The number of retrieved oocytes was recorded.

A 17-guage needle was utilized for oocyte retrieval, which was done under general anesthesia. After denudation and 2-hour incubation of the oocyte-corona complexes, ICSI was performed.

Embryo Transfer and Luteal Phase Support

On the day of the embryo transfer, the embryos with the best morphologic appearance were chosen. The selection of embryos was based on the number of blastomeres, absence of fragmentation, and the most advanced stage of development. Embryo morphology was graded between 1 and 4. Grade 1 embryos had to contain 6 to 8 blastomeres with no multinucleation and fragmentations.

Only fresh transfers were carried out in all cycles. The embryo transfer protocol was based on the age of the patient, the number and quality of embryos, and history of prior assisted conception attempts. Two or 3 high-quality embryos were transferred to each patient. In the present study, only grade 1 embryos were transferred. The transfer took place on either day 2 or 3.

The first morning after oocyte retrieval, all patients received 3 × 200 mg micronized progesterone as luteal phase support. If pregnancy occurred, vaginal progesterone support continued until the 12th week of gestation.

Evaluation of Assisted Reproductive Technique Results

On the fourth day after embryo transfer, the β-hCG level in the blood was measured and recorded. If the β-hCG level was >5 mIU/mL in either measurement, it was considered *positive β-hCG*, and patients with such levels were regarded as biochemically pregnant. At the sixth week of gestation, continuation of pregnancy was confirmed by vaginal ultrasonography via the presence of fetal heartbeat. Ongoing pregnancy was defined as pregnancy developing beyond 12 weeks.

Outcomes of the cycles with COH protocols including the antagonist and GnRH agonist were evaluated. Parameters included: day-3 FSH levels, day-3 and hCG injection day E_2 levels, number of antral follicles, number of follicles on hCG injection day, duration of COH, number of metaphase II (MII) oocytes, fertilization rate, number of grade 1 embryos, number of embryos transferred, and rates of biochemical (*positive β-hCG*) and ongoing pregnancies.

Statistical Analysis

All statistical calculations were performed using the Statistical Package for Social Sciences (version 20.0, SPSS Inc., Chicago, Illinois). The Student t test or Mann-Whitney U test was used to compare the mean values between the stimulation protocols. Differences in outcome rates were analyzed using a chi-square test or Fisher exact test. In all statistical analyses, $P < .05$ was considered statistically significant.

RESULTS

The characteristics of 86 patients who underwent surgery for endometrioma and stage III to IV endometriosis are presented in Table 1. Patients in the 2 groups (long GnRH-a and GnRH-ant) were matched in terms of age, AFC, basal FSH and estradiol levels, primary infertility ratio, body mass index, and period of infertility (Table 1). In addition, the number of unilateral and bilateral endometriomas was matched both within and between the groups (Table 1).

The comparison of IVF/ICSI cycle outcomes between the 2 different protocols used after endometrioma resection surgery is presented in Table 2. The total gonadotropin dose (3167.0 ± 1124.4 vs 3261.1 ± 1653.9; $P = .712$), duration of hyperstimulation 11.00 ± 2.13 vs 10.16 ± 1.98; 0.825), E_2 levels on hCG day (1645.2 ± 1156 vs 1779.3 ± 1241; $P = .654$), fertilization rate (75.75% ± 32.98 vs 71.32% ± 32.94; $P = .210$), the number of transferred embryos (2.24 ± 1.11 vs 1.98 ± 1.00; $P = .113$) were similar in long GnRH-a and GnRH-ant protocols.

The number of follicles on hCG day (11.68 ± 7.09 vs 8.44 ± 6.09; $P < .001$), number of retrieved MII oocytes (7.93 ± 5.43 vs 5.25 ± 5.51; $P < .001$), total number of grade 1/2 embryos (5.82 ± 3.00 vs 4.65 ± 2.14; NS) were similar for both protocols. There were no significant differences in *positive β-hCG* pregnancy rates (11 of 44 [25%] vs 9 of 42 [21.4%]; $P = .269$) and ongoing pregnancy rates (9 of 44 [20.5%] vs 8 of 42 [19.1%]; $P = .302$) between long GnRH-a and GnRH-ant protocols.

Table 1.
Characteristics of the Patients

Characteristics	Patients with stage III–IV endometriosis and endometrioma resection surgery		P value
	Long GnRH-a (n = 44)	GnRH-ant (n = 42)	
Age (y)	31.68 ± 4.37	32.25 ± 4.98	NS
Duration of infertility (mo)	54.36 ± 52.59	64.80 ± 53.38	NS
Primary infertility (n/n [%])	38/44 (86.6)	32/44 (72.0)	NS
Day-3 FSH (IU/mL)	7.20 ± 3.2	8.9 ± 6.1	NS
Day-3 estradiol (E_2)	41.85 ± 30.96	48.41 ± 43.10	NS
BMI (kg/m^2)	23.4 ± 3.2	24.4 ± 4.2	NS
Number of antral follicles	7.2 ± 0.5	6.2 ± 0.4	NS
Endometrioma location (n)			NS
Unilateral	26	23	
Bilateral	18	19	

Abbreviations: BMI, body mass index; FSH, follicle-stimulating hormone; GnRH-a, gonadotropin-releasing hormone agonist; GnRH-ant, gonadotropin-releasing hormone antagonist; NS, not significant.

Data are presented as mean ± SD, unless otherwise indicated.

$P < .05$ indicates statistically significant differences between long GnRH agonist and GnRH antagonist groups.

Table 2.
Comparison of the Long GnRH Agonist and GnRH Antagonist Protocols

	Long GnRH-a (n = 44)	GnRH-ant (n = 42)	P value
Total FSH/hMG (IU)	3167.0 ± 1124.4	3261.1 ± 1653.9	NS
Number of follicles on day of hCG	11.68 ± 7.09	8.44 ± 6.09	.001
hCG-day E_2 level (pg/mL)	1645.2 ± 1156	1779.3 ± 1241	NS
Duration of hyperstimulation	11.00 ± 2.13	10.16 ± 1.98	NS
Number of metaphase II oocytes retrieved	7.93 ± 5.43	5.25 ± 5.51	.001
Fertilization rate	75.75 ± 32.98	71.32 ± 32.94	NS
Total number of grade 1 embryos	5.82 ± 3.00	4.65 ± 2.14	.001
Mean number of transferred embryos	2.24 ± 1.11	1.98 ± 1.00	NS
Positive β-hCG pregnancy rate per patient (n/n [%])	11/44 (25)	9/42 (21.4)	NS
Ongoing pregnancy rate per patient (n/n [%])	9/44 (20.5)	8/42 (19.1)	NS

Abbreviations: hCG, human chorionic gonadotropin; hMG, human menopausal gonadotropin; other abbreviations as in Table 1.

Data are presented as mean ± SD, unless otherwise indicated.

$P < .05$ indicates statistically significant differences between long GnRH agonist and GnRH antagonist groups.

DISCUSSION

In IVF cycles, along with the adverse effects of endometriosis on growing follicles, oocytes, embryos, and endometrium, ovarian endometrioma itself and its surgical resection may have an additional negative impact on the outcome.[13] Choosing the appropriate ovarian stimulation protocol may prevent these adverse effects. In the present study, we tried to evaluate the efficacy of long GnRH-a and GnRH-ant protocols on patients that were specifically facing these detrimental factors due to prior laparoscopic endometrioma resection surgery.

To our knowledge, there are no studies in the literature that specifically compare long GnRH-a and GnRH-ant

protocols in patients with advanced endometriosis who have undergone laparoscopic endometrioma resection surgery. In the present study, the number of retrieved MII oocytes, grade 1 embryos, and aspirated follicles were higher in patients who received the GnRH-ant protocol, yet our findings did not reveal a statistically significant difference in pregnancy rates between the 2 protocols in which a similar number of embryos were transferred. Furthermore, a similar number of embryo transfers revealed comparable fertilization and pregnancy rates between the 2 protocols. Hence, the actual impact of GnRH analogues on IVF treatment may be on the ovarian response rather than on oocyte and embryo quality.

Ovarian response might also be affected by the chosen technique during laparoscopy. Coagulation with bipolar cautery is usually considered a safe and well-accepted approach in laparoscopic endometrioma resection surgery,[14] which was also the technique used in the present study. However, some studies in the literature indicated that this technique was associated with decreased ovarian reserve postoperatively.[15,16] Excessive use of bipolar coagulation during surgery may result in damage to ovarian function.[17,18] Recently, some studies investigated a vasopressin injection technique[19,20] that may help clearly define the boundary between the cyst and the ovarian stroma. Therefore, this technique may reduce the number of coagulations necessary for hemostasis.

There are multiple studies in the literature that evaluated the effects of endometriosis on IVF outcomes. A meta-analysis about stage III to IV endometriosis, which involved 22 studies, concluded that the fertilization, implantation and pregnancy rates, and the number of retrieved oocytes decreased in patients with endometriosis compared with the control subjects with tubal factor infertility.[21] It has been argued that women with severe endometriosis were 36% less likely to achieve pregnancy than those with mild endometriosis were.[5] The same researchers presented that women with stage III to IV endometriosis had fewer numbers of retrieved oocytes, lower E_2 levels, and lower fertilization and implantation rates in comparison with women with stage I to II endometriosis and women with infertility due to other causes.[22] Opoien et al.[23] documented that patients with stage I to II endometriosis had a lower fertilization rate, and patients with stage III to IV endometriosis had fewer oocytes retrieved. Furthermore, when the researchers split the stage III and IV patients with and without endometriomas, it was reported that the endometrioma group had significantly lower pregnancy, live birth, and ongoing pregnancy rates. Coccia et al.[24] showed the detrimental effects of severe

endometriosis on IVF outcome via significantly reduced pregnancy rates (clinical pregnancy rate per embryo transfer: 9.7% for stage III to IV, 25% for stage I to II, and 26.1% for tubal factor). In a very recent systematic review and meta-analysis, Harb et al.[25] concluded that the presence of severe endometriosis (stage III–IV) was associated with poor implantation and clinical pregnancy rates in women undergoing IVF treatment. In addition, Kitajima et al.[26] argued that presence of endometrioma is associated with diminished ovarian reserve.

Although there is no consensus on how to manage patients with advanced endometriosis and endometriomas, GnRH analogues have been used for the treatment of endometriosis for several years. The use of GnRH-a during IVF treatment in patients with advanced endometriosis has led to increased pregnancy rates in some studies.[27,28] GnRH-a may be suppressing endometriosis lesions in such patients. In support of this argument, patients who faced long-term suppression before the initiation of hyperstimulation with gonadotropins during IVF treatment had higher pregnancy rates.[29] The most efficient IVF/ICSI stimulation protocol in endometriosis patients is argued to be the "ultralong" (long-term pituitary down-regulation with a GnRH-a) protocol, studied by many researchers, including Surrey et al.[29] A Cochrane systematic review and meta-analysis performed by Sallam et al[30] established the advantages of this protocol with an odds ratio of 4.28 (in favor of long-term pituitary down-regulation with a GnRH-a). Alternatively, advantages of the antagonist (eg, easier and faster prevention of premature LH surge, flexibility of use, increased patient comfort due to shorter usage) make it an attractive choice for any IVF program. In a recent study by Rodriguez-Purata et al,[31] pregnancy rate after COH with either GnRH-a or GnRH-ant was found to be equally effective in patients with endometriosis (stage I to IV).

The number of retrieved oocytes might have an indirect effect on pregnancy rates, because higher-quality embryos can lead to more good-quality oocytes. In the literature, the results are varied when the protocols are compared with the number of retrieved oocytes. There was no statistical difference in some studies,[32,33] whereas a meta-analysis by Ludwig et al[34] suggested fewer retrieved oocytes in patients who received a GnRH-ant protocol. Albano et al[35] carried out a multicenter study and also documented that patients who received a GnRH-ant protocol revealed significantly fewer numbers of retrieved oocytes. In this study, the number of retrieved MII oocytes and follicles were higher in patients who received a GnRH-a protocol. It can be argued that higher gonadotro-

pin doses may lead to more aspirated follicles and retrieved oocytes. However, we used similar total doses of gonadotropin in the present study in both groups, yet significantly fewer numbers of aspirated follicles and retrieved oocytes were recorded in patients who received the GnRH-ant protocol.

When the protocols are compared for the pregnancy rates, there are contradicting results. Several studies and various meta-analyses have been carried out to compare pregnancy rates of GnRH-a versus GnRH-ant protocols. A meta-analysis of 14 randomized studies found no significant difference between the 2 GnRH analogues in the pregnancy rate.[36] Similarly, Ludwig et al[37] did not report a difference at the pregnancy rate between GnRH-a versus GnRH-ant protocols. In addition Pu et al[38] reported no statistical difference to the number of oocytes retrieved, the number of mature oocytes retrieved, the cycle cancellation and clinical pregnancy rates between GnRH-a versus GnRH-ant protocols in poor ovarian responders. On the other hand, a Cochrane meta-analysis by Al-Inany and Aboulghar,[39] which took into account 5 randomized studies, suggested that the usage of GnRH-ant protocol compared with GnRH-a provided lower pregnancy rates. However, the conclusions of this Cochrane meta-analysis cannot be generalized for the endometriosis patients. Merviel et al[40] also reported lower pregnancy rates in patients who used GnRH-ant protocols.

Because of the risks involved with multiple pregnancies, which is a common occurrence in IVF treatments, the standard practice in many countries became the transfer of 1 (elective single embryo transfer) or 2 embryos instead of 3. In Turkey, the Turkish Ministry of Health established a mandatory standard of single embryo transfer in March 2010 for all women under the age of 35 years, in their first 2 cycles. Hence, cryopreserved embryos became an appealing alternative for patients who were unable get pregnant during their IVF treatment or who want to have another pregnancy later in their lives. With cryopreserved embryos, patients have the chance of a frozen-thawed embryo transfer, which can alleviate the emotional, financial, and physical burdens of an additional IVF treatment. In the present study, the GnRH-a protocol revealed increased numbers of oocytes and embryos, so the patients who received this protocol had an opportunity to cryopreserve and transfer embryos later. Additionally, cryopreserved embryo transfer might have an advantage for women with endometriosis, because ovarian hyperstimulation is not required in frozen-thawed embryo transfer, which may potentially activate the endometriosis.[41]

Limitations of the present study were the involvement of >1 clinician and their preferences for different protocols (long GnRH-a versus GnRH-ant) and its retrospective design. In addition, differences in the skills of the surgeons, although in the present study all surgeons were experienced, might be considered as another limitation,[42] as the ability to preserve normal ovarian tissue after endometrioma resection surgery varies according to the skill of the surgeon and the technique used. In our clinic, patients with endometrioma who have a diminished ovarian reserve (AFC < 5, basal FSH ≥ 10 IU) do not undergo surgery solely because of infertility. Hence, another limitation was the fact that the subset of patients with poor response was omitted from the study. GnRH antagonists have been available commercially since the early 2000s, whereas GnRH agonists have been available for much longer. In our clinic, routine use of GnRH antagonists started around the mid-2000s. Therefore, there was a learning curve involved. Although the learning curve was not steep, it could still be regarded a limitation of this study.

CONCLUSIONS

Long GnRH-a and GnRH-ant protocols both present similar IVF outcomes in patients with endometriosis who have undergone laparoscopic endometrioma resection surgery. Long GnRH-a protocol may lead to a higher number of embryos, which can be cryopreserved, providing the possibility of additional embryo transfers without having to go through the process of ovarian stimulation again. However, further prospective research on larger sample sizes, in which live birth rates especially are evaluated, have to be carried out to compare the efficiency and success rates of the 2 protocols.

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