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Effect of Prolonged GnRH Agonist Therapy Prior to Frozen Embryo Transfer on IVF-ET Outcome in Patients with and without Endometrioma Surgery

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Abstract

Objective: It remains to be clarified whether prolonged Gonadotrophin-Releasing Hormone agonist (GnRHa) administration before frozen embryo transfer to patients with and without endometrioma resection improves reproductive outcome. This study was designed to investigate freeze-all cycles with subsequent prolonged GnRHa administration in patients with and without endometrioma surgery.

Method: A total of 164 patients with complaints of infertility and diagnosed with endometrioma were included in this case controlled study. Endometrioma resection was performed in 65 out of 164 women and then Controlled Ovarian Stimulation (COS) was performed (Group 1). Fresh embryos were transferred to 40 of 65 patients who underwent endometrioma surgery. Embryos were vitrified in 25 patients and administered leuprolide acetate 3.75 mg for 3 months. The remaining 99 patients were referred directly to the COS without any surgery for endometrioma (Group 2). While fresh-ET was applied to 49 of 99 cases, embryos were frozen in the remaining 50 cases. Subsequently they were administered leuprolide acetate 3.75 mg for 3 months. Primary outcome was Clinical Pregnacy Rates (CPR), Ongoing Pregnancy Rates (OPR), and Live Birth Rates (LBR).

Results: No significant difference was found between the operated and non- operated groups in terms of CPR, OPR and LBR between patients who received fresh-ET. While there was no significant difference in CPR and OPR in operated and non-operated groups who underwent frozen-ET, LBRs were found to be significantly higher in patients who were not operated ($p<0.01$). Making fresh-ET or frozen-ET in patients who underwent endometrioma surgery did not significantly affect CPR, OPR and LBR. Making frozen-ET in patients who did not undergo surgery significantly increased both CPR ($p <0.02$) and OPR ($p<0.03$).

Conclusion: Prolonged use of GnRH agonist treatment before frozen-ET in patients without endometrioma surgery resulted in significantly higher clinical and ongoing pregnancy rates than did patients with endometrioma surgery.

Keywords: Endometrioma; Endometrioma surgery; GnRH agonist; Reproductive outcome

Introduction

The hypothalamic Gonadotropin-Releasing Hormone (GnRH) is a decapeptide that plays an important role in the regulation of reproductive functions. In addition to pituitary expression GnRH/GnRH receptor (GnRHR) system was found to be expressed in extrapituitary regions such as endometrium and ovary [1,2]. GnRHR expressed in granulosa and luteal cells plays a role in follicle development and growth [2]. At the endometrium GnRH/GnRHR has been reported to regulates interaction between the embryo-endometrium in the early stage of implantation [3]. Antiproliferative activity of GnRH/GnRHR system has been suggested to be an effective direct molecular target for GnRH-analog-based therapeutic approaches to treat endometriozis. Continuous administration of GnRH analogs (GnRHa) induces a downregulation of GnRHR and suppresses the release of pituitary gonadotropins. In addition, GnRHa regulates the synthesis and release of peritoneal cytokines and endometrial integrin in endometriosis [4,5].

There is little evidence to support use of medical treatment in women with endometrioma who wish to improve fertility. In line with this, none of the hormonal drugs used in the medical

treatment of endometriosis patients cause an increase in spontaneous pregnancy rates [4,6]. On the other hand, long-term GnRHa suppression therapy has been reported to increase IVF-ET outcome during the time it is applied. Really, we have sufficient data to show that GnRHa application has both direct and indirect effects on folliculogenesis and endometrial receptivity in infertile patients with endometriosis. For this reason, prolonged GnRHa administration has started to be widely used either before initiation of controlled ovarian stimulation or before frozen-ET in order to increase the implantation and pregnancy rates in cases with endometriosis. Most of the studies reported that long-term GnRHa treatment performed before IVF-ET or frozen-ET in patients with stage III-IV endometriosis had a positive effect on pregnancy rates. A recent study reported that pregnancy rates increased in patients with endometriosis who received agonist suppression after vitrification [7]. However, there are also studies reporting results that it does not provide any benefit. A recent study reported that long-term GnRHa suppression given before IVF-ET did not cause a significant change in reproductive outcome compared to the untreated group [8].

To date, it remains to be clarified whether prolonged gonadotrophin-releasing hormone agonist administration before frozen embryo transfer to patients with and without endometrioma surgery improves reproductive outcome. When rewieving the literature there is no study comparing patients who underwent endometrioma surgery with patients who did not undergo surgery despite having endometrioma, giving GnRHa treatment before frozen-ET. This retrospective cohort pilot study evaluates freeze-all cycles with subsequent prolonged GnRHa administration in patients with and without endometrioma surgery.

Materials and Methods

164 patients who applied to the Department of Obstetrics and Gynecology & IVF Center, Memorail Kayseri Hospital between 2016 and 2020 with complaints of infertility and were diagnosed with endometrioma were included in the study. The diagnosis of ovarian endometrioma was made as a result of the detection of the following findings with USG (GE, Voluson 730 Pro.). The endometrioma was suspected when a diffuse, regular- margined cyst with a low level internal echo, indicating hemorrhagic cyst, was present for at least 2 cycles, to exclude the nonendometriotic hemorrhagic cyst. Endometrioma patients were divided into two groups according to whether surgical intervention was performed or not. Laparoscopic endometrioma resection was performed in 65 of 164 cases and then controlled ovarian stimulation (COS) was performed (Group 1). The remaining 99 patients were referred directly to the COS without any surgical procedure for endometrioma (Group 2). Fresh embryos were transferred to 40 of 65 patients who underwent endometrioma surgery. In the other 25 patients who underwent endometrioma surgery, all embryos were vitrified in Cryotops as described by previously [9]. Subsequently they were administered a long-lasting preparation of the GnRHa leuprolide acetate (Lucrin Depot®; Abbvie) 3.75 mg every 28 days for 3 months. 99 patients with endometrioma who did not undergo surgery in Group 2 were referred to COS. While fresh-ET was applied to 49 of 99 cases, embryos were frozen in the remaining 50 cases. Subsequently they were administered a long-lasting preparation of the GnRHa leuprolide acetate 3.75mg every 28 days for 3 months. Primary outcome was clinical pregnacy rates (CPR), ongoing pregnancy rates (OPR), and live birth rates (LBR).

All participants underwent a routine laboratory and radiological examination to diagnose the underlying factors of infertility. They had normal early follicular Follicle- Stimulating Hormone (FSH), Luteinizing Hormone (LH), Estradiol (E2), Thyroid-Stimulating Hormone (TSH), and Prolactine (PRL) levels, and normal midluteal progesterone levels indicating the presence of ovulation. To have information about over reserve Anti-Mullerian hormone (AMH) levels as well as antral follicle count determined at baseline transvaginal ultrasound examination performed in the early follicular phase. Participants in each group were noted to have a bilateral tubal patency, absence of intrauterine mass forming pathology in uterine cavity documented at Hysterosalpingography (HSG). Two semen analysis was performed in the male partners of the each woman at least 3 weeks' apart and upon 3 to 7 days of abstinence. Because of these detailed examinations, the only detectable cause of infertility was endometrioma in all participants. Participants found to have pathology in semen analysis or HSG were not included in the study. Patients who had received GnRH agonists, progestins or oral contraceptive for treatment of symptomatic endometriosis within 6 months of initiation of their IVF-ET treatment were excluded.

Statistical analysis

Descriptive statistics were presented as frequency, mean and standart deviation. Shapiro Wilks test was used for evaluation of normality of distribution. Pearson Chi- squared test was used in the analysis of relationships between categorical variables. For the comparison of continous variables, the Students t-test was used with normal distribution. Statistical analyses were performed by using the SPSS 21.0 packages program for Windows. $p<.05$ was accepted to show statistical significance.

Results

The data including the demographic and IVF-ET results of the cases are shown in Table 1 & 2. No significant difference was found between the two groups in terms of age, duration of infertility and BMI. The number of total oocyte and MII oocyte counts were found to be significantly higher in the non-surgical group compared to the surgical group. While 65 of 164 endometrioma patients were operated, 99 patients did not undergo any surgical procedure. While fresh-ET was applied to 40 of 65 patients who were operated, 25 of them were frozen-Et. While fresh-ET was applied to 49 of 99 patients to be operated, frozen-ET was applied to 50 patients. No significant difference was found between the

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operated and non- operated groups in terms of CPR, OPR and LBR between patients who received fresh-ET. On the other hand, while there was no significant difference in CPR and OPR in operated and non-operated groups who underwent frozen-ET, live birth rates were found to be significantly higher in patients who were not operated (p<0.01). When we evaluated the cases with subgroup analysis, performing fresh-ET or frozen-ET in patients who underwent endometrioma surgery did not significantly affect CPR, OPR and LBR (Table 1). On the other hand, performing frozen-ET in patients who did not undergo surgery significantly increased both CPR (p<0.02) and OPR (p<0.03). In terms of LBR, a statistically insignificant increase trend was detected (p<0.056). If we divide endometrioma patients into two groups as those who went to surgery and those who did not, regardless of the use of GnRHa, pregnancy rates were found to be similar in both groups following fresh-ET. If we do frozen-ET patients in these groups, CPR and OPR were found to be similar, while LBR was found to be significantly higher in the non-operated group.

Table 1: Demographic and clinical characteristics of each group of participants.

	Endometrioma Patients without Surgery (n=99)	Endometrioma Patients with Surgery (n=65)	*p*
Age (years)	31.70±4.94	32.65±4.83	0.226
Infertility duration (years)	5.97±3.42	5.65±3.64	0.564
BMI	26.00±3.49	25.42±2.63	0.253
Day 2 E2	38.07±14.16	34.72±10.72	0.106
Day 2 P4	0.40±0.22	0.32±0.16	0.328
IVF attempt	1.89±1.17	2.20±1.49	0.137
E2 on hCG day	1941.8±1279.3	1523.4±1195.7	0.037
P4 on hCG day	0.32±0.14	0.34±0.15	0.869
Total oocyte	12.36±7.57	9.72±8.25	0.037
MII oocyte	9.26±6.06	7.37±5.69	0.047
2PN	7.23±5.15	5.71±4.07	0.046

Table 2: Reproductive outcome of endometrioma patients taking prolonged course of GnRHa after freeze-all.

		N	Clinical PR	Ongoing PR	Live BR
Fresh-ET	Opere	40	17	14	11
	Non-opere	49	23	21	19
	p		0.675	0.45	0.263
Frozen-ET	Opere	25	15	12	7
	Non-opere	50	35	32	29
	p		0.386	0.185	0.014
Endometrıoma Surgery	Fres	40	17	14	11
	Frozen	25	15	12	7
	p		0.17	0.298	0.965
No-Surgery	Fresh	49	23	21	19
	Frozen	50	35	32	29
	p		0.02	0.035	0.056

Discussion

This retrospective cohort pilot study evaluated the impact of freeze-all cycles with subsequent prolonged GnRHa administration before embryo transfer on reproductive outcome in patients with and without endometrioma resection. In this trial, we found that administration of GnRHa therapy for 3 months before frozen-ET in patients with a history of previous endometrioma surgery resulted in significantly lower clinical and ongoing pregnancy rates compared to endometrioma patients who had not endometrioma surgery. With this study, it has been shown for the first time that performing fresh or frozen ET for patients with a history of endometrioma surgery does not significantly affect CPR, OPR and LBR. However, we do not know whether the similar pregnancy rates in patients who underwent fresh or frozen-ET after endometrioma surgery are a unique feature of

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the frozen cycle or a feature related to GnRHa suppression or the combined effect of both. In this study, GnRHa suppression was applied to all patients undergoing thaw cycle. In fact, patients who underwent thaw cycles should have been divided into two groups and frozen-ET should be performed only in one group and GnRHa plus frozen-ET should have been performed in one group. In this way, we could say more clearly whether the main effect on pregnancy rates was due to agonist administration or frozen-ET. However, as far as we know from the literature data, although it varies according to etiological factors and age, the reproductive outcome in frozen cycles is higher than fresh cycles. Similarly, it has been reported that GnRHa treatment before IVF-ET or before frozen-ET positively affects pregnancy rates. Surrey et al. showed that prolonged GnRHa therapy prior to initiation of COS in patients with endometriosis resulted in significantly higher ongoing pregnancy rates [4]. In a meta-analysis written by Sallam et al. it was reported that giving GnRHa treatment for 3-6 months before COS significantly increased both clinical pregnancy rates and live birth rates [10].

In our study, patients in surgery group who underwent endometrioma cystectomy received prolonged administration of GnRHa after vitrification of all embryos. Our expectation after this treatment was a significant increase in pregnancy rates. The main support behind this expectation was the studies of Celik et al. in which they reported a significant increase in endometrial receptivity genes after endometrioma surgery [11]. However, despite frozen-ET plus GnRHa treatment in patients with endometrioma surgery, the pregnancy rates were similar to those treated with fresh-ET suggesting that vitrification and long-term suppression are not beneficial in this patient group. When we evaluate our results and literature findings together performing frozen-ET plus GnRHa treatment in patients who underwent IVF-ET after endometrioma surgery does not provide any extra benefit in terms of reproductive outcome compared to fresh cycles.

The second most important result we obtained from this study is that combining freeze all-cyle with long-term GnRha treatment significantly increased both CPR and OPR in the patient without endometrioma surgery compared to fresh cycles. We can explain the possible reasons for the significant increase in pregnancy rates after frozen-ET in the non-surgical group in two ways. The first reason may be due to the gains arising from the nature of frozen cycles. With the help of frozen-ET, we can get rid of the negative effect of estrogen increase due to COS on endometrial receptivity. The second reason for the increase in pregnancy in patients without endometrioma surgery may be long-term GnRHa treatment. There are many studies showing that administration of GnRHa treatment before IVF-ET or before frozen-ET leads to an increase in pregnancy rates [12]. However, there are studies showing that long-term GnRHa treatment is useless. Pre-COS use of GnRHa has been replaced by pre-frozen-ET application due to the possibility of decreasing the number of eggs to be collected. Our results are consistent with the publications reporting that long-term suppressions performed before frozen-ET in patients with endometriosis increase reproductive outcome. Surrey et al. reported that prolonged GnRHa therapy following vitrification of all embryos in patients with endometriosis led to high implantation and ongoing pregnancy rates [7]. However, there are no studies investigating the effect of agonist suppression in patients with and without endometrioma surgery.

While applying GnRHa treatment before frozen-ET was useless in patients who underwent endometrioma surgery, it showed a positive effect on pregnancy rates in patients who did not undergo surgery. We can explain this paradox-like difference as follows. Since pertioneal cytokine and natural killer cell activity will be normalized in the group undergoing endometrioma resection, GnRHa administration may not provide extra benefit in these patients. Since the presence of endometriosis and/or endometrioma is required for the emergence of both the inflammation-blocking and cytokines regulating activities of GnRHa the use of this drug in a disease-free environment may prevent it from showing its normal effect [4,7,13]. On the other hand, in the patients without endometrioma surgery, the presence of endometrioma will trigger abnormal cytokine release and inflammation in the peritoneal microenvironment. Ferrero et al. showed that GnRHa therapy reduces inflammatory proteins in peritoneal fluid proteome of women with endometriosis [13].

Another possible reason for the increased pregnancy rates may be the increase in endometrial receptivity due to the administration of GnRHa. In line with this, Lessey et al. reported that endometrial integrin β3 expression was normalized in patients with superficial endometriosis who received agonist therapy for 3 months or more [5]. As it is known, the production and release of integrins, one of the basic endometrial receptivity molecules, has decreased in patients with endometriosis. In the light of the above data, we can summarize the reasons for the positive effects of long-term GnRHa treatment before frozen-ET on pregnancy rates in non- operated endometrioma cases as follows. GnRHa treatment before frozen-ET might increase the implantation rates by acting through the following mechanisms;

(i) regulates natural killer cell activity as well as cytokines such as interleukin-1 and tumor necrosis factor whose production and secretion are impaired in peritoneal fluids of patients with endometriosis,

(ii) neutralizes the embryotoxic effects of peritoneal fluid,

(iii) increases endometrial cell survival by decreasing apoptosis in endometrial cells,

(iv) enhances endometrial receptivity by increasing endometrial αvβ3 integrin expression,

(v) down-regulates peritoneal fluids inflammatory proteins [4,5,7,10,13].

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However, these possible mechanism of actions of GnRHa therapy need to be confirmed with more comprehensive studies.

The retrospective nature and the relative low number of cases are the main limitations of the study. Another limitation is that the absence of the frozen-ET group that is not given GnRHa treatment does not allow us to explain whether the positive results are GnRHa treatment or freezing of embryos or a combined effect. The strengths of our study include the fact that this is the first publication on the subject of use of prolonged GnRHa therapy in women with and without endometrioma surgery after vitrification of all embryos.

Conclusion

Performing endometrioma resection in the period before IVF does not provide any additional benefit to pregnancy rates. On the other hand, women with endometrioma who underwent IVF-ET without endometrioma surgery 3 months of GnRHa treatment before frozen-ET significantly increases CPR and OPR.

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