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Original Article

The effect of GnRH Agonist use in Frozen Cycles on pregnancy results

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Abstract

Aim: The aim of this study was to investigate the effect of GnRH agonist use on pregnancy and abortion in the preparation of the endometrium in autologous frozen embryo transfers performed with hormone replacement therapy.

Material and Methods: All autologous artificial Frozen – thawed embryo transfer (FET) between 1/2016 and 1/2018 were evaluated retrospectively in order to investigate the effect of GnRH agonist use on pregnancy and abortion rates in frozen embryo FET cycles.

Results: 226 patients were included in the study. The mean age of the patients included in the study was 30.76 ± 4.72 years. Of the patients, 144 (63.7%) were diagnosed with unexplained infertility, 20 (8.8) with low ovarian reserve, and 62 (27.4) with male factor. No significant difference was found in terms of pregnancy result and abortion in patients using (N: 22) and not using GnRH agonist (p = 0.212, 1,000).

Conclusion: No significant effect of GnRH agonist use on pregnancy rate or abortion was detected in autologous frozen embryo transfers performed with HRT. The prospective studies involving larger patient populations are needed to clarify this subject.

Keywords: GnRH agonist; frozen embryo transfer; pregnancy rate

INTRODUCTION

The embryo transfer is the most important step of IVF treatment. Synchronization between the embryo and the endometrium is necessary for pregnancy to occur. Therefore, the preparation of endometrium in frozen cycles is very important.

Nowadays, endometrial preparation before frozen embryo transfer is mainly performed in two ways: Natural or artifical cycles. In the natural cycle, spontaneous ovulation is followed and then embryo transfer is performed. In the artificial cycle, the endometrium is prepared by performing external steroid hormone replacement (1,2).

The natural cycles should be followed-up closely. The ovulation may be missed during this follow-up. The artificial cycles are more suitable for patients with irregular cycles. It is a great advantage that we can adjust the transfer time for ourselves in the artificial cycle.

The pituitary down regulation can be performed by using GnRH Agonists before cycles performed with HRT. The aim is to prevent spontaneous ovulation. In this method, the preparation takes longer and the cost increases and hypoestrogenic effects are seen. In the literature, there are studies showing that it does not change pregnancy results (3-6), while there are studies indicating that it increases pregnancy rate and implantation (7).

The aim of this study was to investigate the effect of GnRH agonist on pregnancy and abortion in Frozen – thawed embryo transfer (FET) transfers performed in our center retrospectively.

MATERIAL and METHODS

Our study was designed as a retrospective cohort study. All frozen autologous embryo transfers performed between 1/2016 and 1/2018 at Ondokuz Mayıs University IVF center were retrospectively reviewed. The ethical committee approval was obtained from Ondokuz Mayıs University. Subjects have given their written informed consent.

Inclusion criteria

Only embryo transfers whose endometrium was prepared with HRT were included in the study. Only patients who

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received embryo transfer on the 5th day were included in the study. All patients had frozen embryos from a previous IVF cycle. 226 patients between the ages of 18-40 were included in the study.

Exclusion criteria
Patients with a history of more than 3 failed transfer histories were excluded from the study. Patients with endometrial thickness less than 7 mm on the 11th day were excluded.

Patients were evaluated according to whether GnRH agonist was used in the preparation of endometrium.

Patients using GnRH agonist: In the midluteal phase of the previous cycle, 0.1 mg of the leuprolide acetate (Lucrin) was initiated and the dose of GnRH agonist was reduced to 0.05 mg on the second day of menstruation, estrofem 4 mg / day on days 1–4, 6 mg / day estrofem on days 5–8, and 8 mg / day estrofem from day 9 onward were administered

Patients not using GnRH agonist
Endometrial preparation was initiated on day 2–3 of the cycle with oral estradiol hemihydrate (estrofem 2 mg; Novo Nordisk, Denmark). The endometrium preparation protocol began with 4 mg/day estrofem on days 1–4, 6 mg/day estrofem on days 5–8, and 8 mg/day estrofem from day 9 onward.

In both groups
A second transvaginal ultrasound was performed after 10 days of estrogen treatment. The embryo transfer was scheduled if the endometrial thickness was at least 7 mm. Progesterone was administered intramuscularly (progestan 50 mg; Koçak, Turkey) at a dose of 100 mg for 5 days prior to embryo transfer. One or two embryos were transferred depending on the patient's age and the quality and number of embryos. All of the embryos were 5 day embryos.

All transfers were performed by the same experienced reproductive endocrinologist (D.G). As luteal support, 8 mg estradiol (estrofem 2 mg; Novo Nordisk, Denmark) and progesterone (progestan 50 mg; Koçak, Turkey) were administered until 12 weeks of gestation.

The bhcg positivity 14 days after the transfer was evaluated as biochemical pregnancy. Abortion is defined as termination of pregnancy before 20th gestational week.

Statistical Analysis
The data were analyzed with IBM SPSS V23. Compliance with normal distribution was examined with Komogorov Smirnov test. The Mann Whitney U test was used to compare quantitative data, which did not show normal distribution, according to the presence of lucrin. Chi-square test was used to compare categorical data with lucrin. Analysis results were presented as median (min-max) for quantitative data and as frequency (percentage) for categorical data. Significance level was considered as $p<0.05$.

RESULTS

The median age values did not show any difference according to the groups ($p = 0.719$). The median value was 30 in Group 1 and was obtained as 31 in those with Lucrin. There was also a significant difference between the groups regarding the FSH median values ($p<0.001$). The median value was 7 in group 1, whereas it was obtained as 4.45 in group 2. The E1 median values did not show any difference according to the groups ($p = 0.239$). The

Table 1. Descriptive Statistics

	Group 1 (n = 204) (GnRH Agonist not used)	With Lucrine (n = 22) (GnRH Agonist used)	Total (n = 226)	p
Age	30 (21 - 39)	31 (25 - 40)	30 (21 - 40)	0.719
FSH (FSH at the beginning of the cycle)	7 (3 - 14)	4.45 (1 - 11)	7 (1 - 14)	**<0.001**
E1 (estradiol at the beginning of the cycle)	37 (5 - 153)	31.5 (5 - 63)	36 (5 - 153)	0.239
L1 (LH at the beginning of the cycle)	4.7 (0.1 - 42)	2.35 (0.1 - 11)	4.3 (0.1 - 42)	**<0.001**
P1 (Progesterone at the beginning of the cycle)	0.2 (0.05 - 5.7)	0.2 (0.05 - 1)	0.2 (0.05 - 5.7)	0.124
Endometrium	10 (6 - 17)	9 (5 - 12)	10 (5 - 17)	**<0.001**
E2 (Estradiol before transfer)	205 (45 - 638)	231 (100-459)	208 (45 - 638)	0.464
P2 (Progesterone before transfer)	0.2 (0.02 - 7.4)	0.2 (0.03 - 0.8)	0.2 (0.02 - 7.4)	0.176
L2 (LH before transfer)	9 (0.1 - 78)	2.65 (0.3 - 7.1)	8 (0.1 - 78)	**<0.001**
Number of antral follicles	17 (4-26)	15 (7 - 18)	16.5 (4 - 26)	**0.029**
Duration of infertility	3.5 (2 - 4)	2 (2 - 4)	3.5 (2 - 4)	0.089

median value was 37 in group 1, whereas it was obtained as 31.5 in group 2. There was also a significant difference between the groups regarding the L1 median values (p<0.001). The median value was 4.7 in group 1, whereas it was obtained as 2.35 in group 2. The P1 median values did not show any difference according to the groups (p = 0.124). The median value was 0.2 in group 1, whereas it was obtained as 0.2 in group 2. There was also a significant difference between the groups regarding the endometrium median values (p<0.001). The median value was 10 in group 1, whereas it was obtained as 9 in group 2. The E2 median values did not show any difference according to the groups (p = 0.464). The median value was 205 in group 1, whereas it was obtained as 231 in group 2. The P2 median values did not show any difference according to the groups (p = 0.176). The median value was 0.2 in group 1, whereas it was obtained as 0.2 in group 2. There was also a significant difference between the groups regarding the L2 median values (p<0.001). The median value was 9 in group 1, whereas it was obtained as 2.65 in group 2. There was also a significant difference between the groups regarding the median value of antral follicle number (p=0.029). The median value was 17 in group 1, whereas it was obtained as 15 in group 2. The median values of infertility time did not differ between the groups (p = 0.089). The median value was 3 in group 1, whereas it was obtained as 2 in group 2 (Table 1).

There was no difference between the groups in terms of causes of infertility, number of embryos, pregnancy and abortion (p values 0.239, 0.588, 0.212 and 1.000, respectively). Embryo Grade was significantly different between the groups (p<0.001). In Group 1, 88.2% were blast, while 9.8% were G1 and 2% were G2. When group 2 was examined, 59.1% were Blast and 40.9% were G1(Table 2).

There was no difference between the groups in terms of causes of infertility, number of embryos, pregnancy and abortion (p values 0.239, 0.588, 0.212 and 1.000, respectively). Embryo Grade was significantly different between the groups (p <0.001). In Group 1, 88.2% were blast, while 9.8% were G1 and 2% were G2. When group 2 was examined, 59.1% were Blast and 40.9% were G1.

Table 2. Comparison of categorical data between groups

	Group 1 (n = 204)	Group 2 (n = 22)	Total (n = 226)	p
Causes of Infertility				
Unexplained	130 (63.7)	14 (63.6)	144 (63.7)	
Low ovary	20 (98)	-	20 (8.8)	0.239
Male	54 (26.5)	8 (36.4)	62 (27.4)	
Number of embryos transferred				
1	151 (74)	18 (81.8)	169 (74.8)	0.588
2	53 (26)	4 (18.2)	57 (25.2)	
Embryo Grade				
Blast	180 (88.2)	13 (59.1)	193 (85.4)	
G1	20 (9.8)	9 (40.9)	29 (12.8)	**<0.001**
G2	4 (2.0)	-	4 (1.8)	
Pregnancy result				
Negative	115 (56.4)	16 (72.7)	131 (58)	0.212
Positive	89 (43.6)	6 (27.3)	95 (42.0)	
Abortus				
None	198 (97.1)	22 (100)	220 (97.3)	1.000
Yes	6 (2.9)	-	6 (2.7)	

DISCUSSION

FET is currently used quite frequently in IVF practice. It has many advantages such as storing and transferring embryos obtained in a single IVF cycle, reducing the risk of OHSS.

The most important issue in FET success is providing the synchronization of the endometrium with the embryo. For this reason, it is very important that the preparation of the endometrium is done correctly (8).

In the preparation of endometrium, natural cycles and artifical cycles are applied. In the artificial cycles, suppression can be performed with GnRH Agonist.

There are previous randomized controlled studies on this subject. In one of these, a fixed dose of micronized estradiol was given orally. The group receiving GnRH agonist was given 6 mg and the group not receiving was given 4 mg. There was no difference between pregnancy results (6).

In the other, transdermal estrogen was given as step up and it was found that the use of GnRH agonist did not affect pregnancy results (5).

Hebsiha et al. have used estrogen in an oral fixed dose in their prospective study and showed that GnRH agonist use increased pregnancy rate and implantation rate unlike the other studies.

In our study, when evaluated retrospectively, no significant effect of GnRH agonist use on pregnancy results was found.

Simon et al. (6) have found no difference between the two groups in terms of cycle cancellation rate (4.3%). In our study, no patient had cycle cancellation in either group.

Studies have shown that estrogen replacement prevents spontaneous ovulation if started within the first 3 days. If deferred to the day after the 3rd day, spontaneous LH may cause surge and luteinization of the endometrium. In addition, it was determined that the presence of a dominant follicle in the cyclus prepared by HRT did not have an effect on pregnancy results (9). And it was stated that step up protocols mimic normal physiology better and may lead to better implantation (10). One of the shortcomings of our study is being retrospective and a low number of patients.

CONCLUSION

In our study, we found that GnRH Agonist use did not change pregnancy rates in accordance with the literature. The use of GnRH Agonist does not seem to be advantageous given the prolongation of time and increased cost.

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