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Comparison of pregnancy outcomes of frozen embryo transfers in women undergoing artificial endometrial preparation with and without short and long-acting gonadotropin releasing hormone agonists

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ABSTRACT

Background & aim: There are conflicting results regarding the benefit of gonadotropin releasing hormone (GnRH) agonist treatment on frozen embryo transfer (FET) outcome. No study was found to compare pregnancy outcome between patients undergoing short and long acting types of GnRH agonist for FET cycles. This study aimed to assess the effectiveness of short and long acting GnRH agonist on FET cycle outcomes.

Methods: The present retrospective study was conducted on 296 patients who underwent FET cycles between 2016 and 2017 at Mehr Medical Institute, Rasht, Iran. Pregnancy outcome were compared among three groups: Group A (n=103) received artificial hormone-mediated cycles without GnRH agonists, Group B (n=100) and C (n=93) received artificial hormone-mediated cycles with short and long-acting GnRH agonists, respectively. Also 16, 26, 12 polycystic ovarian syndrome (PCOS) patients (in group A, B and C respectively) were also assessed for ongoing pregnancy rate among three groups. Data were analyzed using analysis of variance, Kruskal-Wallis, Chi-square goodness of fit test and multivariate logistic regression.

Results: No statistically significant differences were observed in terms of endometrial thickness (p=0.053), implantation (p=0.94), biochemical (p=0.67), clinical (p=0.82) and ongoing (p=0.96) pregnancy rates in three groups. Also, PCOS patients did not show significant differences in ongoing pregnancy rate among three groups (p=0.72).

Conclusion: The findings revealed that neither non- PCOS nor PCOS patients undergoing artificial hormone-mediated endometrial preparation benefit from the addition of short or long-acting GnRH agonist to FET cycles.

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Introduction

Supraphysiological estradiol and progesterone levels during controlled ovarian stimulation impair endometrial receptivity by shortening the duration of implantation window

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during fresh embryo transfer cycles (1). According to the evidence, it is suggested that cryopreserved/thawed embryo transfer (FET) may improve assisted reproductive technology outcome rather than fresh embryo transfer (2, 3).

Endometrial preparation is a curial step in FET cycles, which should be synchronized with the developmental stage of embryos. Several FET protocols have been introduced; however, a consensus related to the optimal protocol for frozen-thawed embryo transfer is still lacking. The FET strategies include natural cycles following spontaneous ovulation and hormone-mediated cycles with or without gonadotropin-releasing hormone (GnRH) agonist (4-7).

The natural cycle is an effective method of contraception, which is more preferable due to no requirement for hormone therapy, patient convenience, and cost-effectiveness. Nonetheless, timing and monitoring of spontaneous ovulation is very critical and can increase the cancelation rate of FET cycle (8). Artificial hormone-mediated cycles without GnRH agonist enable physicians to choose the day of embryo transfer; however, this method has lower advantages in women with irregular cycles. Pituitary suppression using GnRH agonist before hormone-replacement therapy is a convenient method for the inhibition of spontaneous ovulation (9); nonetheless, it is less patient-friendly and more expensive.

To the best of our knowledge, there has been no study that compares pregnancy outcomes among the patients undergoing short- and long-acting types of GnRH agonist in FET cycles. The present study aimed to compare pregnancy outcomes among the patients undergoing artificial hormone-mediated cycles with and without short- and long-acting GnRH agonist.

Materials and Methods

The present retrospective study was conducted on patients who underwent FET cycles during April 2016 and May 2017 at Mehr medical institute in Rasht, Iran. In this study, all FET cycles were included, and outcomes were compared among the three groups, including group A (n=103) that received artificial hormone-mediated cycles without GnRH agonist, as well as groups B (n=100) and C (n=93) that received artificial hormone-mediated cycles with short- and half-dose long-acting GnRH agonist, respectively. Patients with thin endometrium or homogenous hyperechogenic endometrium were excluded from the study. The eligibility of subjects for each group was decided by physicians. Written informed consent was obtained from all the participants.

Artificial hormone-mediated cycles without gonadotropin-releasing hormone agonist protocol

All the patients were given oral contraceptives in the preceding cycle of FET. In artificial hormone-mediated cycles (i.e., group A), estradiol valerate (2 mg, Aburaihan, Iran) was commenced at 6 mg/day since days 2 to 9 and continued at 8 mg/day up to clinical pregnancy approval. First transvaginal ultrasound monitoring of endometrial development was performed on day 13 and continued every other day. When endometrial thickness (EnT) reached approximately 7 mm, vaginal (400 mg, Fertigest, Aburaihan, Iran) and intramuscular (IM) 100 mg (50 mg, Fertigest, Aburaihan, Iran) progesterone supplementation was administrated for 3 to 5 days with respect to the cleavage stage of embryos.

Artificial hormone-mediated cycles with short-acting gonadotropin-releasing hormone agonist

In short-acting GnRH agonist cycles (i.e., group B), buserelin acetate (Cinnafact, Cinnagen, Iran) was administrated at a dose of 0.3 mg/day since day 21 of the preceding cycle to day 2 of FET cycle and continued with a dose of 0.2 mg/day up to day 6. Endometrial preparation was started with estradiol valerate and followed by progesterone supplementation in the same pattern as in group A.

Artificial hormone-mediated cycles with long-acting gonadotropin-releasing hormone agonist

In long-acting GnRH agonist cycles (i.e., group C), a single half-dose of depot GnRH agonist (Decapeptyl 1.875 mg, Ferring, Germany) was administrated on day 21 of the preceding cycle. Endometrial preparation was started with estradiol valerate and followed by progesterone supplementation in the same pattern as in group A. The embryo transfer was canceled, if EnT had no response to further

estradiol treatment (10 mg, IM estradiol valerate, Aburaihan, Iran) and remained<7 mm. The embryos were transferred on day 3 or 5. All embryo transfer procedures were carried out by the same surgeon.

The rates of ongoing pregnancy, clinical pregnancy, biochemical pregnancy, implantation, fertilization, and EnT, as well as the number of embryos and blastocyst transfer, were recorded in this study. The ratio of the number of gestational sacs to the total number of transferred embryos was considered as implantation rate. Patients with the polycystic ovarian syndrome (PCOS) were assessed for ongoing pregnancy rate in the groups. Biochemical pregnancy was approved by positive β human chorionic gonadotropin hormone test 2 weeks after embryo transfer. Clinical pregnancy was approved after the assessment of fetal heartbeat at 7 weeks of gestation. Ongoing pregnancy was distinguished as a viable pregnancy at 12 weeks of gestation.

Statistical analysis was performed using SPSS software (version 21). Normally distributed variables were analyzed using the analysis of variance, and the Kruskal-Wallis test was utilized for the analysis of non-normal variables. Categorical variables were assessed by the Chi-square goodness of fit test. According to univariate logistic regression, variables with P-value less than 0.2 were considered as confounding factors and evaluated by multivariate logistic regression. P-value less than 0.05 was considered statistically significant.

Results

The three groups were comparable in the baseline characteristics, such as body mass index, age, antimullerian hormone (AMH), types and etiologies of infertility, and duration of infertility (Table 1).

Table 1. Basal characteristics of patients

Variable	Group A (n=103)	Group B (n=100)	Group C (n=93)	P-value
Age (years)	30.39±5.43	31.36±5.42	30.88±5.81	0.46*
Body mass index (kg/m^2)	25.83±3.81	25.36±3.28	26.67±4.05	0.11*
Antimullerian hormone (ng/ml)	3.86±2.58	4.19±2.8	3.35±2.24	0.2**
Type of infertility				
Primary (years)	6.6±5.7	6.7±4.9	6.1±5	0.61**
Secondary (years)	3.7±3.4	4.2±5.1	2.8±3.9	0.21**
Infertility etiologies (%)				
Male factor	23 (22.3)	21 (21)	27 (29)	
Tubal factor	4 (4)	7 (7)	10 (10.7)	
Polycystic ovarian syndrome	16 (15.5)	26 (26)	12 (13)	0.061***
Endometriosis	6 (5.8)	1 (1)	2 (2.1)	
Others	54 (52.4)	45 (45)	42 (45.2)	

Results are presented as mean±standard deviation and percentage

*: Analysis of variance test

**: Kruskal-Wallis test

***: Chi-square test

Clinical results of patients are summarized in Table 2. Differences in EnT (P=0.053), fertilization rate (P=0.88), total number of transferred embryos (P=0.77), embryo transfer day (P=0.09), blastocyst (P=0.49), and grade A transferred embryos (P=0.8) were not statistically significant among the groups. There were no significant differences in the rates of implantation (P=0.94), biochemical (P=0.67), clinical (P=0.82), and ongoing (P=0.96) pregnancy (Table 2).

Table 2. Clinical outcome of frozen embryo transfer cycles

Variable	Group A (n=103)	Group B (n=100)	Group C (n=93)	P-value
Endometrial thickness (mm)	8.36±1.1	8.80±1.3	8.38±1.2	0.053*
Fertilization rate (%)	990/1345 (74)	937/1261 (74)	747/1016 (74)	0.88*
Number of transferred embryos	2.5±0.94	2.45±0.82	2.53±0.86	0.77*
Number of transferred blastocyst	0.61±0.95	0.52±0.8	0.69±0.93	0.49*
Number of grade A transferred embryos	1.31±1.02	1.31±0.91	1.25±0.96	0.8*
Embryo transfer day	3.76±1.01	3.80±1.02	4.07±1.03	0.09*
Implantation rate (%)	37/258 (14)	34/245 (14)	35/235 (15)	0.94**
Biochemical pregnancy (%)	35/103 (34)	40/100 (40)	34/93 (36.6)	0.67**
Clinical pregnancy (%)	31/103 (30.1)	33/100 (33)	27/93 (29)	0.82**
Ongoing pregnancy (%)	23/103 (22.3)	24/100 (24)	21/93 (22.5)	0.96**

Results are presented as mean±standard deviation and percentage
*: Kruskal-Wallis test
**: Chi-square test

The patients with PCOS did not show any significant differences in clinical pregnancy rate among the three groups (A: 31.57%, B: 41.66%, and C: 30.76%; P=0.72).

The crude odds ratios for clinical pregnancy rate were 0.874 (95% confidence interval [CI]; 0 .483-1.581) and 1.052 (95% CI; 0.569-1.946) for groups B and C, when compared to the group A. The results of univariate logistic regression indicated that AMH, as well as number of blastocysts and grade A transferred embryos, were reported with a significance level less than 0.2. After adjustment to these variables, the odds ratio for groups B and C were 0.940 (95% CI, 0.527-2.067) and 1.043 (95% CI, 0.527-2.067), respectively. The obtained aforementioned results are summarized in Table 3.

Table 3. Multivariate regression analysis with clinical pregnancy rate

	Crude odds ratio	P-value	95% Confidence interval	Adjusted odds ratio	P-value	95% Confidence interval
Group A						
Group B	0.874	0.656	0.483-1.581	0.940	.854	0.487-1.814
Group C	1.052	0.870	0.569-1.946	1.043	.903	0.527-2.067
Antimullerian hormone	0.863	0.003	0.783-0.951	0.867	.008	0.780-0.963
Number of blastocyst transferred	0.699	0.008	0.535-0.913	0.686	.014	0.508-0.926
Number of grade A transferred embryos	0.497	<0.001	0.375-0.660	0.493	<0.001	0.367-0.664
Constant				13.931	<0.001	

Discussion

The results of this study demonstrated that the short- and long-acting types of GnRH agonist were comparable in their efficacy, and the addition of GnRH agonist to FET cycles could not improve pregnancy outcomes in patients undergoing artificial hormone-mediated endometrial preparation. There are conflicting results about the benefit of GnRH agonist treatment in terms of pregnancy outcomes; however, some studies used short-acting GnRH agonists and others used long-acting GnRH agonists.

Toukhy et al. (10) randomized patients into two groups, including group A who received daily buserelin acetate, starting from the 21th day of previous cycle and group B without pituitary suppression. Monitoring of spontaneous ovulation was not performed in the two groups. They significantly indicated a higher rate of chemical, clinical, and live birth in group A than that in group B. These results are not consistent with the findings of the present study. There was no improvement in the rates of clinical and ongoing pregnancy in patients undergoing short-acting GnRH agonist, compared to those in the control group. It is possible that the difference between the two studies arises from the ultrasound monitoring of ovarian activity in the present study.

In a retrospective cohort study conducted by Hill et al. (5), patients undergoing natural frozen blastocyst transfer cycles were compared with those undergoing artificial hormone-mediated blastocyst transfer cycles with short-acting GnRH agonist pretreatment. The results indicated that artificial cycles were associated with a higher pregnancy rate in frozen blastocyst transfer cycles. However, the results of the present study indicated an association between ongoing pregnancy rate and number of blastocysts. In addition, in the study performed by Hill et al., no association was observed in this regard.

The results of another study performed by Vijver et al. (11) indicated the efficacy of artificial endometrial preparation without GnRH agonist when the endocrine monitoring of ovarian function was conducted. The results of the present study are in accordance with the findings of the aforementioned study; however, ovarian monitoring was performed using an ultrasound scan. In contrast to the results of the present study, multiple regression analysis indicated the relation between pregnancy outcome and number of transferred embryos (i.e., two embryos versus one embryo).

Dal Prato et al. (4) evaluated the clinical results of FET with and without pituitary suppression by long-acting GnRH agonist, and no significant difference was observed in EnT and pregnancy outcome between the two groups. They concluded that endometrial preparation without GnRH agonist pretreatment is as effective as preliminary pituitary desensitization. One strength of the present study is that in this study, half-dose depot GnRH agonist was used for maintaining pituitary suppression that imposed less cost on the patients.

In addition, in two recent systematic reviews (6, 12), no superiority of any natural or artificial procedures with or without GnRH agonist was indicated in patients undergoing FET. To the best of our knowledge, there was no study comparing the impact of GnRH agonist types on endometrial preparation. The impact of GnRH agonist on endometrial preparation via the suppression of spontaneous ovulation was mentioned above. Moreover, it was revealed that exogenous or endogenous GnRH agonist had the ability to affect the proliferation of endometrial tissues (13). The results of the present study indicated that endometrial preparation with GnRH agonist regardless of short- and long-acting types cannot affect the FET outcomes even after adjustment to confounding variables.

In a study carried out by Xie et al. (14), pregnancy outcomes were compared between artificial FET cycles with or without long-acting GnRH agonist pretreatment. They also classified FET outcomes into the subgroups of patients with different infertility etiologies and concluded the superiority of artificial endometrial preparation with GnRH agonist pretreatment in various types of infertility mainly in PCOS patients.

In another study performed by Gong et al. (15), it was indicated that pituitary down-regulation with GnRH agonist before FET can

affect endometrial receptivity by decreasing androgens in patients with PCOS. In the present study, the subjects suffering from PCOS did not show significant differences in ongoing pregnancy rate among the three groups. Considering the importance of GnRH agonist treatment in endometriosis and adenomyosis patients (16), it seems that FET endometrial preparation with GnRH agonist pretreatment is beneficial for these groups of women; however, in the present study, it was not assessed for a low number of patients with endometriosis.

Conclusion

In this study, all three procedures revealed similar ongoing pregnancy rates. This result suggests that the accurate monitoring of ovarian activity without using GnRH agonist is an effective method for hormone-mediated endometrial preparation related to lower costs and higher patient comfort. It also seems that GnRH agonist treatment could not improve the ongoing pregnancy rate in PCOS patients.

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Conflicts of interest

The authors declare no conflicts of interest**.**

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