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Does Depot Analog Suppression Have Positive Effects on All Other Frozen-thawed Embryo Transfer Cycles in Addition to Endometriosis?

Nur Dokuzeylül Güngör[1] · **Tuğba Gürbüz**[2] · **Arzu Yurci**[3]
[1]*Gyneacology and IVF Clinic, Bahçeşehir University, Medical Park Hospital, Istanbul, Turkey*
[2]*Gynaecology and Obstetrics Clinic, Istanbul Medistate Hospital, Istanbul, Turkey*
[3]*Gynaecology, IVF Clinic, Kayseri Memorial Hospital, Kayseri, Turkey*

Introduction: The study investigated whether Gonadotropin-releasing hormone analogue (GnRH-a) suppression before elective frozen-thawed embryo transfer (FET) allows better ongoing pregnancy rates (OPR) in women without endometriosis.
Material and methods: Retrospective cohort study including FET cycles performed in one academic fertility center from 2014 October to 2019 December. In the analog suppression group (ASG), depot analog was given at day 2 or 3, and estradiol (E_2) treatment was started at 21th day of analog usage. Intramuscular progesterone (100 mg/d) was added to E_2 till the fetal heartbeat was seen. Then vaginal progesterone (600 mg/d) was continued until the 12th week of gestation.
Results: Among 523 FET, 22.4% underwent analog suppression, 77.6% had not undergone analog suppression before FET. There was no difference between groups concerning endometrial thickness, the number of embryos transferred, development of embryo stage at FET cycle, and cryopreservation technique. Implantation rate and ongoing pregnancy rates were significantly higher in the ASG than in the non-analog suppression group (NASG).
Conclusion: The use of GnRH-a before FET increases implantation rate and ongoing pregnancy rate not only in endometriosis cases but also in other patients with different infertility causes.
Keywords: Analog suppression, Assisted reproductive technology, frozen-thawed embryo transfer

Introduction

Gonadotropin-releasing hormone (GnRH) is the major hypothalamic regulatory hormone for reproduction. Roger Guillemin and Andrew Schally in 1971, were the first persons who isolated, characterized, and synthesized GnRH, leading to the grant of the Nobel Prize. Gonadotropin-releasing hormone analogue (GnRH-a) is similar to GnRH but changed at sites where GnRH was enzymatically degraded to resist peptidases increasingly and increase receptor binding affinity (1). The next step to develop agonists was to substitute many amino acids from the primary composition, to enhance their affinity for receptors, to reduce renal elimination, and their resistance to proteolytic degradation.

The first live birth following the thawed cryopreserved embryos was transferred was

Corresponding Author: Tuğba Gürbüz, MD; Gynecology & Obstetric Clinic, Istanbul Medistate Hospital, Istanbul, Turkey
ORCID: 0000-0003-3555-3767
E-mail: drtgurbuz@hotmail.com
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reported in Australia in 1983 based on a slow freezing protocol (2). There was a significant improvement in cryopreservation of human embryos in the last decade, once vitrification protocols were introduced (3-6). There has been the routine application of the embryo vitrification for the "freeze-all" (FA) strategy, based on the ovulation triggering, ovarian stimulation segmentation, vitrified-warmed embryo transfer in subsequent artificial or natural cycles, and the elective cryopreservation of all viable embryos and (7). FA policies have become popular in recent years. According to some authors, FA strategy increased outcomes of pregnancy and decreases risks of Ovarian hyperstimulation syndrome (OHSS) (8, 9). Also, the physiological milieu of the uterus in frozen-thawed embryo transfer (FET) cycles may positively affect not only implantation and endometrial receptivity and but also fetal growth and placentation (10). On the other hand, the workload of the laboratory is increased when FA is preferred in routine practice, which brings some risks. However, some questions remain unanswered regarding ideal method of endometrial preparation (11).

Endometriosis is the cause of pelvic pain and infertility in more than 35% of women at reproductive ages (12). As a fact, GnRH-a treatment before intracytoplasmic sperm injection (ICSI) in infertile women with adeno myosis or endometriosis remarkably improved pregnancy results in both fresh and frozen FET cycles (13). The present study hypothesized that administration of GnRH-a might also help improve the results of other groups of patients undergoing FET cycles.

Material and Methods

The population in this retrospective study was composed of 523 women undergoing FET from October 2014 to December 2019 in an academic fertility center. We extracted all data of the study from the electronic medical record of the hospital system.

Ethical Statement

The ethics committee of the Beykoz University (2020/002) approved the study. All procedures were conducted according to the 1975 Helsinki declaration of and its further modifications. The inclusion criteria were as follows: [1] those with previous in vitro fertilization (IVF) cycles with cryopreservation of embryo, [2] between 20-39 years of age, and [3] first three cycles. The exclusion criteria were [1] uterine congenital abnormalities [2] cycles of preimplantation genetic diagnosis [3] recurrent pregnancy loss, [4] presence of endometriosis [5] ≥40 years of age, and [6] using ICSI testicular sperm.

Endometrial Preparation Protocols

The two protocols were used before the FET:

1. GnRH analog suppression group (ASG): In the group of 3.75 mg depot GnRH-a, leuprolide acetate was administered subcutaneously at day 2 or 3 of the previous cycle. First hormonal and ultrasound (estradiol and progesterone) testing were done 21 days following the injection. Then, endometrial preparation was initiated. Endometrial preparation started with oral estradiol (E_2) (Estrofem; Novo Nordisk, Denmark) 2mg x 2/day for 3 days then continued as 2mg x 3/day. If the endometrial thickness was below 7 mm after 10 days of E_2 treatment, the dose of E_2 was raised to 8 mg/day. Then, hormonal and ultrasound (progesterone and estradiol) testing were conducted at 10-12th day of E_2 treatment and repeated if necessary. Once the thickness of the endometrium reached minimally 8 mm and the level of the serum progesterone was below 1.5 ng/ml,

progesterone supplementation was started with progesterone (IM) (Progestan ampule 50 mg/ml; Koçak Farma, Turkey) 100 mg daily starting four days before the FET for cleavage-stage embryos or six days before FET for blastocysts. We continued supplementation until we performed the βhCG test. For a positive test, the patients continued estradiol treatment until the 7th-week gestation and progesterone treatment until the 12th of gestation respectively.

2. Non-Analogue Suppression Cycle (NASG): Endometrial preparation started with estradiol (E_2) and continued as in the ASG group.

Embryos

The vitrification protocol was applied to freeze all embryos. We mainly froze Embryos at the stage of cleavage until May 2015 and then at the blastocyst stage afterward. They were transferred on the same day as thawing for blastocysts and thawed two days before transfer for D_3 embryos. Embryo morphology was assessed according to the symmetry, compaction degree, number, multinucleated blastomeres and fragmentation percentage(18). Gardner's classification was applied to score blastocysts. Grade 3AA and higher blastocysts were vitrified in turn on a cryotop (Kitazato; Japan) using a commercially available kit (Vitrolife; Sweden) using the following the manufacturer's instructions.

Pregnancies

Pregnancy was defined as a positive βhCG test performed 12 days after FET. First vaginal ultrasonography was performed 10 days after a positive pregnancy test to confirm the presence of gestational sac (clinical pregnancy) and then 2 weeks later to check fetal heart-beat at 7th weeks of gestation. Furthermore, at the 12th week, we perform transabdominal ultrasonography to confirm that there was a continual pregnancy. An early pregnancy loss was defined as the spontaneous cessation of a clinical pregnancy before the 12th week of gestation.

Clinical Outcomes Definition

ASRM 2017 consensus definitions were used (14) for the clinical outcomes. We defined implantation as the number of observed gestational sacs divided by the number of the transferred embryos. Biochemical pregnancy was a pregnancy diagnosed only by detecting the βhCG in urine or serum. Clinical pregnancy was defined as a pregnancy diagnosed by definitive clinical signs of pregnancy or ultrasonographic visualization of one or more gestational sacs. We defined miscarriage as the unplanned loss of a clinical pregnancy before 22 weeks of gestational age completed, where the fetuses or embryos are nonviable and are not spontaneously expelled or absorbed from the uterus. We defined preterm birth as a birth occurring before 37 completed weeks and after 22 weeks of gestational age. We defined live-birth as the delivery of at least one baby with live birth beyond 22 weeks of gestation. We defined the rate of live birth as live deliveries (at least one live birth) for women after the transfer of the embryo.

Statistical Analysis

The mean and standard deviation were used to show the baseline characteristics for continuous variables or proportions and counts for categorical variables. The groups were compared using or ANOVA (continuous variables with normal distribution), a Kruskal-Wallis test (continuous variables with abnormal distribution), or chi-square tests (for categorical variable). The relationship between endometrial preparation type and live birth was assessed

using the logistic regression analysis. OR and adjusted OR with 95% CI were calculated. The continuous variables included age of the woman at oocyte retrieval (years), age during embryo transfer (years), infertility duration (in years), AFC, Body mass index (BMI) (kg/m^2), number of retrieved oocytes, and endometrial thickness during the administration of progesterone (mm). The categorical variables included the fresh cycle protocol (antagonist or agonist), transferred embryos number, number of transferred high-quality embryos, type of infertility (secondary or primary infertility), triple-line endometrial pattern (B, A, or C), transferred embryo type (blastocyst stage or cleavage stage), and type of fertilization (IVF or ICSI). The statistical data analysis was conducted through SPSS 23.0 package program. We summarized the categorical measurements as percentages and numbers. On the other hand, Continuous measurements as standard deviation and mean (minimum-maximum and median when needed). Fischer's Precision Test and Chi-square test were used in a comparison of categorical variables, and the logistic regression method was used for multivariance evaluations. Analytical methods (Shapiro Wilk Tests/Kolmogorov-Smirnov) and Visual (probability and histogram graphs) were used to investigate conformity of the variables to normal distribution. In the comparison of continuous measurements between the groups, we used independent student t-test for parameters that were showing normal distribution, and Mann Whitney U tests for parameters that were not showing normal distribution. All tests used 0.05 as the statistical significance level.

Table 1. Baseline characteristics of the patients undergoing FET cycles

Characteristics		ASC (n=117)	NASG (n=406)	*P value*
Age at oocyte retrieval *(year)*		32,67±4,19	32,33±4,70	0,603
Age at embryo transfer *(year)*		32,70±4,18	32,35±4,69	0,631
Paternal age (*year)*		36,25±5,02	36,13±,15	0,871
BMI *(kg/m²)*		24,86±2,96	24,93±2,74	0,731
Infertility duration *(year)*		5,03±2,06	4,95±1,98	0,847
Ongoing smoking women	*Yes*	13 (11,1)	43 (10,6)	0,494
	No	104 (88,9)	363 (89,4)	
AMH *(ng/ml)*		1,97±1,04	2,07±1,03	0,3
No. of oocyte retrieved *(n)*		9,15±3,68	9,53±3,35	0,261
Infertility type *(%)*	*Primary* *Secondary*	76,9 (90/117) 23,07 (27/117)	79,1 (321/406) 20,9(85/406)	0,352
Number of ART trial		1,71±1,77	1,52±1,64	0,221
Protocol in fresh cycles *(%)*	*Antagonist* *Agonist*	97,4 (114/117) 2,5 (3/117)	97,7(397/406) 2,2(9/406)	0,825
Endometrial thickness *(mm) at the beginning of progesterone supplementation		10,9±0,45	10,8±0,73	0,172
Duration of cryopreservation *(days)*	*<90 day* *90-180 day* *180-365 day* *>365 day*	61,5 (72/117) 35,9 (42/117) 1,7 (2/117) 0,9 (1/117)	57,6 (234/406) 40,6 (165/406) 1,7 (7/406) 0 (0/406)	0,238

Abbreviations: AMH:Anti-mullerian hormone; BMI: Body Mass Index; ASG: Analog Supression Group; NASG: Non-Analog Supression Group;

Results

From October 2014 to December 2019, we included 523 FET cycles in this retrospective analysis. 117 (22.4%) patients received analog suppression, and 406 (77.6%) not before FET. Table 1 shows the baseline characteristics. No cycle cancellation was observed.

Both groups were compared in terms of age at transfer, BMI, smoking, oocyte retrieval age (y), embryo transfer age (y), paternal age (y), infertility duration (y), Anti-Mullerian hormone (AMH) (ng/ml), no of the retrieved oocyte, fresh cycles protocol (%) and endometrial thickness (mm) at the beginning of progesterone supplementation habits (Table 1). Although it is not significant, male factor infertility is more common in NASG than ASG (35.5% vs 29.1%; p=0,119). The differences of tubal infertility (p=0,07), unexplained infertility (UEI) (p=0,494) and anovulatory (p=0,527) were also non-significant between the two groups (Table 2).

Table 2. Causes of infertility

Infertility Cause *(%)*	ASG *(n=117)*	NASG *(n=406)*	*P value*
Male infertility	29,1 (34/117)	35,5 (144/406)	0,119
Tubal infertility	13,7 (16/117)	8,1 (33/406)	0,07
Anovulatory	17,1 (20/117)	19,7 (80/406)	0,527
Unexplained infertility	40,2 (47/117)	36,7 (149/406)	0,494

No significant difference was found in embryos characteristics or final endometrial thickness between groups (Table 1). The mean duration between fresh and frozen cycle was <90 day (61% vs 57.6%), 90-180 day (35.9% vs 40,6%), 180-365 day (1,7% vs 1,7%) and >365 days (0,9% vs 0%) respectively (p=0,238).

Pregnancy outcomes per FET are shown in Tables 3. According to the findings in Table 3, no statistically significant difference was found between the patients' findings of type of embryo transferred (%), transferred embryos number, βhCG after 14 days of ET, βhCG after 16 days of HCG and βhCG (+) (%) and the patients in which AS was used and was not used (p>0,05) (Table 3). It was found that D_3-D_5 positiveness (88.2% vs 64.8%; p=0,0001), D5 frozen positiveness (51.85% vs 51.04%, p=0,0001) and the implantation rate (%) (33.6% vs 30.0%, p=0,0001) in patients in which AS was used were higher than the patients in which AS was not used. Besides, the rates of ongoing pregnancy (%)/ET (35.04% vs 33.4%), live birth rate (46.1% vs. 41.3%), delivery rate (35% vs. 33.4%), and multiple pregnancies/ongoing pregnancy (%) (31.7% vs 24.2%) in patients in which AS was used were found as statistically and significantly higher than the rates of the patients in which AS was not used.

In the multiple regression analysis in Table 4, the variables of the model cryopreservation day, the day on which ET was implemented, duration of infertility, the age on the day of ET, the age on the day of oocyte pick up (OPU), BMI, infertility type, total trial number, the reason of infertility, duration of cryopreservation and endometrial thickness on HCG day were added and it was determined the day of cryopreservation was 1.39 times effective on live birth (OR=1,397) and the total trial number was 0.86 times effective on live birth (OR=0,865).

Discussion

GnRH-a suppresses ovarian steroidogenesis by a downregulation of pituitary GnRH receptors that affects gonadotropin secretion. GnRH -a can be administered by different routes but the sc way is preferred because of its ease of use. GnRH-a has been successfully used for the

Table 3. Outcomes of analog supression therapy and non-analog supression therapy in FET cycles

Variables	ASG [used] *(n=117)*	ASG [not used] *(n=406)*	*P value*
Type of embryo transferred (%) ▪ Cleavage stage ▪ Blastocyst stage	 %15,4 (18/117) %84,6 (99/117)	 %15,3 (62/406) %84,7 (344/406)	0,539
No. of embryos transferred ▪ 1 ▪ 2	 n=14 (%11,9) n=103 (%88)	 n=61 (%15) n=345 (%84,9)	0,251
Thawed D_3-ET D_5 ▪ Positive ▪ Negative	N=51 %88,2(45/51) %11,7 (6/51)	N=202 %64,8 (131/202) %35,1 (71/202)	**0,0001**
Thaw D_5-ET D_5 ▪ Positive ▪ Negative	N=27 %51,85 (14/27) %48,1 (13/27)	N=143 %51,04 (74/143) %48,9 (69/143)	**0,0001**
βhCG after 14 day of ET	76,34±95,37	66,51±80,74	0,53
βhCG after 16 day of HCG	153,88±195,96	135,68±176,31	0,532
Implantation rate (%)	%33,6 (74/220)	%30 (225/749)	**0,0001**
βhCG (+) (%)	%53,8 (63/117)	%53,4 (217/406)	0,512
Ongoing pregnancy rate (%)	%35,04 (41/117)	%33,4 (136/406)	**0,0001**
Live-birth rate (%)	%46,1 (54/117)	%41,3 (168/406)	
Delivery rate (%)	%35 (41/117)	%33,4 (136/406)	
Miscarriage rate (%)	22,2	20,4	
Preterm birth rate (%)	4,8	14,7	
Ectopic pregnancy rate (%)	%0,85 (1/117)	%0 (0/406)	
Multiple pregnancy/ET (%)	%11,1(13/117)	%8,1(33/406)	
Multiple pregnancy/Ongoing pregnancy (%)	%31,7(13/41)	%24,2(33/136)	

Table 4. Univariate analysis for live-birth rate

Variables	Odd Ratio	95% C.I. for Odd Ratio		*P value*
		Lower	*Upper*	
The day of cryopreservation	1,397	1,080	1,805	**0,011**
The day on which ET was implemented	0,895	0,647	1,238	0,502
Duration of infertility	0,982	0,884	1,09	0,729
Age at ET	0,544	0,192	1,54	0,251
Age at EPU	1,831	0,649	5,165	0,253
BMI	0,996	0,920	1,079	0,921
Infertility type	0,864	0,503	1,483	0,595
Total trial number	0,865	0,767	0,976	**0,018**
The reason of infertility	1	-	-	0,288
The reason of infertility (1)	1,331	0,696	2,547	0,388
The reason of infertility (2)	0,649	0,279	1,51	0,315
The reason of infertility (3)	0,947	0,495	1,809	0,868
Duration of cryopreservation day	0,998	0,993	1,003	0,399
Endometrial thickness on the day of HCG	0,79	0,554	1,127	0,194

* $p<0.05$: Multivariate logistics regression test

medical management of endometriosis for many years. Lower estrogen (E) production or counteract E action at a peripheral level are thought to have beneficial effects on endometrial implants. Luteinizing hormone is deeply suppressed, whereas FSH levels show a significant decrease only at the 1st month of therapy, followed by a constant rise. The pituitary gonadotropin secretion was suppressed in COH to prevent premature Luteinizing hormone (LH) luteinization and surge reducing the rate of cancellation (15) and improving the routine organization of assisted reproduction (16). Clinicians' and patients' convenience increased using the formulations of GnRH-a. A single administration has a remarkable advantage in terms of compliance and simplicity. When the studies in the literature were taken into consideration, it was observed that the clinical results were contradictory. Mackens et al (11) reported that the endometrial preparation type did not significantly affect the FET clinical outcome, while El-Toukhy showed an association between the medicated frozen embryo replacement cycles timed based on the measurement of endometrial thickness alone without controlling/suppressing ovarian activity and decreased outcome (17). Our study aimed to evaluate the value of using GnRH agonist before exogenous steroid supplementation for endometrial preparation in FET cycles other than cases of endometriosis as the study by El-Toukhy showed. Also, it was determined that the rate of ongoing pregnancy(%) / ET, Multiple Pregnancy(%)/ET, Multiple Pregnancy/Ongoing pregnancy (%), rate of live-birth (%) / ET were higher in those using the AS than patients who did not use AS as in El- Toukhy's study(17). But, pituitary suppression was done by using 400 mcg buserelin acetate every day in El-Toukhy's study whereas depot leuprolide acetate was used in our study. It appears that the results are not consistent with Dal Prato's study, concluding that endometrial preparation for the transfer of frozen-thawed embryos using only steroid supplementation has the same as that with initial pituitary desensitization (18). Nevertheless, the two studies cannot be compared easily due to the different dosages and formulation of the used medication. In contrast to our study, it was indicated that endometrial preparation with exogenous steroids does not reduce the FET success rate without GnRH agonist pretreatment. There is a similarity between the success rate and that reached with the more traditional protocol with initial desensitization with a GnRH agonist (19-21). Despite inhibition of ovulation through estradiol treatment in the early follicular phase (22), effective cycle control and full pituitary suppression may not occur and there can be some follicular activity. Because we started the optimal dose (6 mg/dL) of E_2 on day 2, we had no cycle cancellation in both groups. Especially in those with ovaries function, there can be an association between the supplementation of exogenous estrogen from the early follicular stage with no pituitary suppression and increasing LH level (22). Increased levels of LH during hormonal supplementation can disrupt the receptive window, leading to implantation defects. Also, Lelaidier et al. (22), reported that steroid supplementation caused an early pregnancy loss rate of 50% without pituitary suppression preventing endometrial development and predisposition to pregnancy loss during the first trimester. In our study, although it is non-significant, the miscarriage rate was also lower in patients who underwent analog suppression before the FET cycle. There

is a close relationship between a successful FET and exact synchronization between embryo development and endometrial maturation (23). There may be such synchronization during the natural cycle after preparing the endometrium with exogenous steroids artificially (24, 25) or after spontaneous ovulation (23, 24). A competent embryo interacting synchronously with a receptive endometrium is a complex molecular process that is necessary for successful implantation (26). Receptivity is caused by decidualization due to its effect on the active choice of embryos with implantation (27). In a recent study, it was shown that patients with idiopathic repeated implantation failure can benefit from pituitary suppression before the transfer of frozen embryos (28). The endometrium receptivity may be enhanced through treatment in these patients. Also in our study, the implantation rate was higher in the analog used group.

Conclusion

According to the results, endometrial preparation controlled hormonally with the previous suppression of GnRHa during FET cycles can help patients and even those not endometriosis. The main advantages of pretreatment with GnRH agonist are that the implantation rates and ongoing pregnancy rates are increased, avoiding the cycle cancellation risk due to spontaneous ovulation. Also, we can easily schedule the embryo transfer or thaw date. Nevertheless, it is expensive to treat with a GnRH agonist; the treatment takes longer and there may be hypoestrogenic side effects.

Conflicts of Interest

The authors declared no conflict of interest for the present article.

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Contact Details

Nur Dokuzeylul Güngör, MD
Gynecology and IVF Clinic, Bahçeşehir University, Goztepe Medical Park Hospital, Istanbul, Turkey
ORCID: 0000-0002-7234-3876
E-mail: drnur9eylul@hotmail.com

Tuğba Gürbüz, MD
Gynecology and Obstetric Clinic, Istanbul Medistate Hospital, Istanbul, Turkey
ORCID: 0000-0003-3555-3767
E-mail: drtgurbuz@hotmail.com

Arzu Yurci, MD
Gynecology, IVF Unit, Kayseri Memorial Hospital, Kayseri, Turkey
ORCID:0000-0003-4808-9019
E-mail: arzuyurci@yahoo.com

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