Comparison of different endometrial preparation protocols in frozen-thawed embryo transfer cycles in women with polycystic ovary syndrome

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ABSTRACT

Aim: This study aimed to evaluate the most suitable endometrial preparation protocols such as hormone replacement therapy (HRT) with gonadotropin releasing hormone analogue (GnRH-a) suppression, HRT without GnRH-a suppression and mild ovarian stimulation (OS) for women with polycystic ovary syndrome (PCOS) undergoing frozen-thawed embryo transfer (FET).

Material and Method: We conducted a historical cohort analysis of 161 women with PCOS who underwent the "freeze-all" strategy between December 2018 and August 2020 because of their high risk for ovarian hyperstimulation syndrome. Three endometrial preparation protocols were used: HRT with GnRH-a suppression (n=43); HRT without GnRH-a suppression (n=86); mild-OS (n=32).

Results: The biochemical pregnancy results (55.8 % vs 54.65 % vs 53, p=0.900), ongoing pregnancy rates (44.2 % vs 43 % vs 40.62, p=0.572), and abort rates (20.8 % vs 21.3 % vs 23.52, p=0.900) were similar between the HRT with GnRH-a suppression, without GnRH-a suppression and mild-OS, respectively. This study showed no statistically significant difference between the three protocols in laboratory parameters (p>0.05).

Conclusion: There was no statistically difference between three groups in terms of pregnancy outcomes. Dependent on clinical experience and facility, one of these protocols could be deployed for FET in women with PCOS.

Keywords: Frozen-thawed embryo, GnRH-a, implantation, polycystic ovary syndrome

INTRODUCTION

Frozen embryo transfer (FET) is generally employed in assisted reproductive medicine due to its ability to lower the risk of ovarian hyperstimulation syndrome (OHSS) improving the reproductive outcomes (1). FET as an alternative to fresh cycle transfer has been suggested to be applied for women with polycystic ovary syndrome (PCOS) because of the significantly increasing risk of OHSS under this condition (2). In fact, there is much proof for a considerable advantage of this method for women with PCOS (1).

Depending on the diagnostic criteria, PCOS affects 5%-18% of reproductive-aged women worldwide (3). PCOS, as a common disorder, has a relationship with infertility (4,5). It is essential to identify the importance of the factors such as types of endometrial preparation protocols that affecting the success of assisted reproductive methods in women with PCOS.

The ideal endometrial preparation protocol should be considered for women with PCOS. Different strategies for endometrial preparation have been described, including a natural modified cycle (NMC) where hCG is administered to design embryo transfer (ET) rather than measuring luteinizing hormone (LH), a purely natural cycle (NC) with detection of LH in blood or urine, artificial cycle with progesterone (P4), and estradiol (E2), hormone replacement therapy (HRT) with or without gonadotropin-releasing hormone (GnRH) analogs and stimulated cycles with low doses.
of gonadotropins (6,7). In the latest meta-analysis, the use of one strategy over others is not supported, but using the pure NC over the NMC or a NC with progesterone over the NC have been supported by other authors to report better results (8,9). Several approaches in artificial or natural preparation has also been shown in surveys, including 179 centers in the world. One can find several different approaches in answers about preparation of FET and in questions such as if its timing in an artificial or a natural cycle shows various responses and if P4 is needed (6).

The comparison of the method of endometrial preparation in reproductive-aged women has been evaluated in many studies, and different results have been reported (10-13). Infertility is more prevalent in women with PCOS, and they need more assisted reproduction technology (14,15). However, the comparison of these methods in women with PCOS is less studied, and there is a need for serious research in this field.

The prominent importance of endometrial preparation protocols in the favorable pregnancy outcomes is known. However, the best protocol for women with PCOS who experience FET cycles is still uncertain. Women with PCOS do generally not have a regular menstrual cycle, so the NC or NMC protocol will not be the most suitable choice for women with PCOS (16). For this reason, this protocol was not examined in this research. This study aimed to evaluate the suitable endometrial preparation protocols such as HRT with GnRH-a suppression, HRT without GnRH-a suppression, and mild ovarian stimulation (OS) for women with PCOS undergoing FET.

MATERIAL AND METHOD
This study was carried out with the permission of Beykoz University Research and Project Development Ethics Committee (Date: 26.10.2020, Decision No:1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

One hundred sixty one women participated in this study between December 2018 and August 2020. In this period, 851 patients who underwent FET were examined, and 161 women with PCOS aged between 20 and 35 were included. In 43 patients, it was employed the HRT with GnRH-a suppression (Group:1), in 86 patients, it was employed the HRT without GnRH-a suppression (Group:2), and in 32 patients, it was employed the Mild ovarian stimulation (Group:3).

The exclusion criteria were as follows: 1) known chronic disease, 2) over 35 years of age, 3) body mass index (BMI)>30,4) Having additional infertility factors other than PCOS, and 5) 2 or more failed attempts. The inclusion criteria were as follows: 1) 20-35 years old, 2) Anti-mullerian hormone (AMH)>5 ng/ml, 3) Women with PCOS according to Rotterdam criteria, 4) Those who have no previous attempts or at most one attempt, and 5) Top-Good Quality (5AA-5AB-4AA-4AB) single blastocyst transfer.

Endometrium Preparation Protocols
The three primary endometrial priming protocols for FET were HRT, mild-OS, and NC. Among these protocols, mild-OS is employed less than the other two (7). HRT cycles can be used with or without GnRH-a for pituitary suppression (17).

Statistical Analysis
The Kolmogorov-Smirnov test performed to check the normality, and the nonparametric tests performed given the non-normality of the groups before the statistical analyses. Mean and standard deviations (SD) measured to check each continuous variable, including age, BMI, total oocytes, MII oocytes, , multi-pronuclei (PN), AMH, prolactin, Free T4 (FT4), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), E2, and endometrial thickness. The Kruskal Wallis-H test deployed to examine the difference between the three endometrial preparation protocols. Chi-square tests were applied to describe the relationship between proportions of categorical variables such as pregnancy results, ongoing pregnancy rate and abort rate. SPSS v24 used for statistical analyses. A value of p-value < 0.05 was accepted as statistically significant.

We utilized the G-Power 3.1 program to calculate the example size. The two groups' total mean was calculated based on the Mann-Whitney test with a power of 90%, an effect size of 50%, and a 0.05 type 1 error for at least 146 patients (18).

RESULTS
This study included One hundred sixty one age-matched (30.75±3.39) and BMI-matched (23.78±2.28) women. 43 patient in the first group with the mean age (30.34±3.90), 86 patient in the second group with the mean age (30.39±3.64), and 32 patient in the third group with the mean age (30.37±4.30) were compared with each other. Table 1 shown information about the descriptive statistics of maternal characteristics and laboratory parameters. We compared laboratory parameters between three groups and assessed the capability of those parameters to differentiate between groups.
As stated in Table 2, a Kruskal Wallis-H test did not find a statistically significant association between the three treatment groups in regard to age and BMI (p>0.05). AMH of first group (mean = 5.21) were comparable than the second group (mean = 5.17) and the third group (mean = 5.19). A Kruskal Wallis-H test indicated that this difference was not statistically significant (p>0.05). No significant difference was observed between the three groups regarding total oocytes, MII oocytes, PN, prolactin and FT4 (p>0.05). TSH, LH and FSH levels were similar between the three groups (p>0.05). There was no statistically significant difference between groups in terms of E2 and endometrial thickness (p>0.05).

As stated in Table 3, a chi square test found that there was not a statistically significant association between the pregnancy results (biochemical and ongoing) and the three treatment groups (HRT with GnRH-a suppression, HRT without GnRH-a suppression, and mild-OS) (p>0.05).

As stated in Table 4, a chi square test found that there was not a statistically significant association between the abort rate and the three treatment groups (p>0.05).

**DISCUSSION**

The present study investigated whether biochemical pregnancy results, ongoing pregnancy rates, and abort rates varied when three different endometrial preparation protocols were employed for FET in women with PCOS. Therefore, we retrospectively examined our data of FET cycles and included three endometrial preparation protocols in this study: HRT with GnRH-a suppression, without, and mild-OS. Our results indicate that overall, patients with programmed HRT with or without GnRH-a suppression did not have higher biochemical pregnancy results, ongoing pregnancy rates, and abort rates compared with patients with mild-OS.

In our study, biochemical pregnancy results (55.8 % vs 54.65 % vs 53, p=0.900), ongoing pregnancy rates (44.2 % vs 43 % vs 40.62, p=0.572), and abort rates (20.8 % vs 21.3 % vs 23.52, p=0.900) were similar between the HRT with GnRH-a suppression, without GnRH-a suppression, and mild-OS, respectively. The ongoing pregnancy rates and abort rates were relatively low in the mild-OS compared to the HRT protocols. This study showed no statistically significant difference between the three protocols in laboratory parameters.
By studying the literature, we found that many studies have been performed comparing women’s fertility outcomes of different endometrial preparation protocols. However, studies that have studied women with PCOS are limited. The comparison of endometrial preparation protocols in women with PCOS is a new topic, and a few existing studies have not reached a general conclusion about the ideal protocol. Some of the studies (19-22) have documented no significant differences between the different endometrial preparation protocols, and some studies (23-27) have indicated better pregnancy results for one protocol over the other. According to Li et al. (19), HRT protocols had pregnancy outcomes similar to stimulated cycles (STC) for endometrial preparation. The available evidence shows that HRT may be a reasonable choice for the PCOS young women prepared for FET, who do not accept injections. On the contrary, STC may lead to reduced operational costs and unnecessary anxiety, and increased flexibility for patients. Najarkolaei et al. (20) reported no difference in abort rates and pregnancy outcomes between the mild-OS and the HRT protocols. Peigne et al. (21) concluded that HRT and mild-OS groups showed comparable clinical pregnancy rates (20.8% vs. 24.4%). This study included women with PCOS i.e., about 20% of the patients.

The retrospective study by Yu et al. (22) showed similar endometrial thickness in the mildly stimulated cycle and HRT which resulted in non-statistically different rates of clinical and ongoing pregnancy and live birth. However, there was a significantly higher abortion rate in the mild-OS.

According to Man et al. (23), there is a significantly higher live birth rate in the PCOS women undergoing endometrial preparation during their initial FET cycle using the OS and NC methods using HRT. Nevertheless, there is a significantly higher rate of cycle cancelation in the NC group than in the other groups. the different groups do not show a significant difference in the rate of adverse events, such as preterm delivery, ectopic pregnancy, etc. This study has special significance since it is the first study on PCOS women.

Wang et al. (24) reported the better outcomes to HRT protocols. According to Niu et al. (25), both letrozole and Human Menopausal Gonadotropin (HMG) ovulation induction regimen had an association with more acceptable pregnancy results than the HRT regimen, such as a lower pregnancy loss rate, and a higher livebirth rate among the PCOS patients undergoing frozen single-blastocyst transfer.

Guan et al. (26) showed a higher live birth rate of the mild-OS and abort rates lower than the HRT in obese women with PCOS. This paper along with the available proof demonstrated superior pregnancy outcomes in the mild-OS than in the HRT. In a large retrospective study, Zhang et al. (27) reported significantly lower pregnancy loss rates of letrozole-stimulated cycles and higher live birth rates than the HRT protocol.

In this study, we acknowledge that we did not collect data about pregnancy difficulties, such as preeclampsia, gestational hypertension, and diabetes as the potential risk factors for adverse neonatal outcomes leading to a confounding effect on the results. The bias potential of medical records and the retrospective study design are the main limitations. The present study has the main strength which is the comparison of the most commonly used protocols for endometrial preparation in a large cohort of patients undergoing FET cycles, and the similarly increasing transferred good quality embryos in both HRT and mild-OS by the experienced clinicians and the verification method application in all embryos in a single center, affecting desirable outcomes of pregnancy.

**CONCLUSION**

This study revealed that pregnancy results, ongoing pregnancy rate and abort rate were similar among natural and artificial endometrial preparation protocols performed for FET cycles. Optimal endometrial preparation is necessary to receive successful pregnancy rates. Nevertheless, no statistical significance was found in the protocols. Dependent on clinical experience and facility, one of these protocols could be deployed for FET.

**ETHICAL DECLARATIONS**

**Ethics Committee Approval:** This study was carried out with the permission of Beykoz University Research and Project Development Ethics Committee (Date: 26.10.2020, Decision No:1).  
**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.  
**Referee Evaluation Process:** Externally peer-reviewed.  
**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.  
**Financial Disclosure:** The authors declared that this study has received no financial support.  
**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.
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