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IS PROGESTERONE SUPPLEMENTATION NECESSARY FOR LUTEAL PHASE SUPPORT IN MODIFIED NATURAL CYCLE FROZEN EMBRYO TRANSFERS?

MODIFIYE DOĞAL SIKLUS DONDURULMUŞ EMBRIYO TRANSFERLERINDE LUTEAL FAZ DESTEĞI IÇIN PROGESTERON TAKVIYESI GEREKLI MIDIR?

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ABSTRACT

Introduction: This study aimed to evaluate the effect of progesterone supplementation as luteal phase support on pregnancy outcomes in women under thirty-eight years of age undergoing modified natural cycle frozen embryo transfer.

Methods: A retrospective analysis was conducted on 2216 modified natural cycle frozen embryo transfers performed at Sisli Memorial Hospital, Assisted Reproductive Technology (ART), and Reproductive Genetics Centre between 2011 and 2023. The study included women under thirty-eight who transferred a single embryo, classified as top quality or good quality. Cycles involving medium-quality or poor-quality embryos, double embryo transfers, and preimplantation genetic testing for aneuploidy were excluded. Participants were categorised into three groups: Group A (n=493) with no luteal phase support, Group B (n=1327) receiving 200 mg of vaginal micronised progesterone twice daily, and Group C (n=396) receiving 200 mg of vaginal micronised progesterone plus 25 mg of subcutaneous progestin daily. Statistical analysis was performed using SPSS 22.

Results: Demographic and fresh cycle characteristics were similar among groups. There were no statistically significant differences in pregnancy outcomes: live birth rates were 58.4% (A), 60.8% (B), and 60.1% (C) (p=0.650); clinical pregnancy rates were 65.9% (A), 69.1% (B), and 68.2% (C) (p=0.432); biochemical abortion rates were 4.5% (A), 6.6% (B), and 5.3% (C) (p=0.186); and clinical abortion rates were 6.3% (A), 6.7% (B), and 5.3% (C) (p=0.828).

Conclusions: Modified natural cycle frozen embryo transfers in women under 38 years of age showed similar pregnancy outcomes regardless of using progesterone for luteal phase support.

Keywords: Modified natural cycle frozen embryo transfer (mNC-FET), Luteal phase support, Progesterone supplementation

ÖZET

Giriş: Bu çalışmanın amacı, modifiye doğal siklusta dondurulmuş embriyo transferi yapılan otuz sekiz yaş altı kadınlarda luteal faz desteği olarak progesteron takviyesinin gebelik sonuçları üzerindeki etkisini değerlendirmektir.

Yöntemler: Şişli Memorial Hastanesi, Üremeye Yardımcı Teknoloji (ÜYTE) ve Üreme Genetiği Merkezinde 2011-2023 yılları arasında gerçekleştirilen 2216 modifiye doğal siklusta yapılmış dondurulmuş embriyo transfer siklusu retrospektif olarak analiz edildi. Çalışmaya, otuz sekiz yaşın altında, en iyi kalite veya iyi kalite olarak sınıflandırılan tek embriyo transferi yapılan kadınlar dahil edildi. Orta kaliteli veya düşük kaliteli embriyoları içeren sikluslar, çift embriyo transferleri ve anöploidi için preimplantasyon genetik testi yapılan sikluslar hariç tutuldu. Vakalar üç gruba ayrılarak incelendi. Luteal faz desteği almayan Grup A (n=493), günde iki kez 200 mg vajinal mikronize progesteron alan Grup B (n=1327) ve günde 200 mg vajinal mikronize progesteron artı 25 mg subkutan progesteron alan Grup C (n=396). İstatistiksel analiz SPSS 22 kullanılarak gerçekleştirilmiştir.

Bulgular: Demografik ve siklus özellikleri gruplar arasında benzerdi. Gebelik sonuçlarında istatistiksel olarak anlamlı bir fark yoktu: canlı doğum oranları %58,4 (A), %60,8 (B) ve %60,1 (C) (p=0,650); klinik gebelik oranları %65,9 (A), %69,1 (B) ve %68,2 (C) (p=0,432); biyokimyasal düşük oranları %4,5 (A), %6,6 (B) ve %5,3 (C) (p=0,186); ve klinik düşük oranları %6,3 (A), %6,7 (B) ve %5,3 (C) (p=0,828).

Sonuç: Modifiye edilmiş doğal siklusta dondurulmuş embriyo transferi yapılan 38 yaşın altındaki kadınlarda luteal faz desteği için progesteron kullanılmasına bakılmaksızın benzer gebelik sonuçları olduğu görülmüştür.

Anahtar Kelimeler: Modifiye doğal siklusta dondurulmuş embriyo transferi, luteal faz desteği, progesteron takviyesi.

INTRODUCTION

Progesterone is a crucial hormone in regulating the female reproductive system, significantly contributing to maintaining the luteal phase and the early stages of pregnancy (1). Progesterone, predominantly synthesised by the corpus luteum after ovulation, is crucial for conditioning the endometrium and embryo implantation (2). Inadequate progesterone levels during the luteal phase can lead to implantation failure or early miscarriage (3-5). In an artificial or hormone replacement cycle, which is one of the endometrial preparation protocols for frozen embryo transfer

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cycles, exogenous progesterone is routinely administered because there is no endogenous progesterone production. However, progesterone-secreting corpus luteum supports the luteal phase in a natural or modified natural cycle frozen embryo transfer (mNC-FET). Therefore, the need for additional progesterone supplementation in these cases is unclear. Numerous studies suggest that exogenous progesterone supplementation may be unnecessary in women undergoing mNC-FET cycles, as the corpus luteum is expected to produce adequate endogenous progesterone (6-9). Nonetheless, some clinicians persist in prescribing progesterone throughout the luteal phase due to concerns about luteal phase insufficiency, believed to be a possible contributor to embryo implantation failure and early pregnancy loss (10,11). Different methods in clinical practice perform progesterone administration as luteal phase support. One method typically involves the use of vaginal progesterone, which is preferred because of its simple administration and the high local concentrations achieved in the endometrium. However, alternative procedures combine vaginal progesterone with subcutaneous progestins to improve systemic progesterone concentrations. In some cases, especially in patients who do not respond adequately to vaginal therapy, intramuscular progesterone is preferred because of its reliable absorption and prolonged release into the bloodstream.

We aimed to assess whether progesterone supplementation is essential for luteal phase support (LPS) in patients undergoing mNC-FET cycles. This research has important clinical implications. In mNC-FET cycles, if the corpus luteum produces sufficient endogenous progesterone to sustain the luteal phase, it may be possible to streamline treatment protocols by eliminating unnecessary progesterone supplementation. It may be possible to simplify treatment protocols by eliminating unnecessary progesterone supplementation. Such an approach could improve patient comfort, reduce healthcare costs, and facilitate ART procedures without compromising pregnancy outcomes. Furthermore, determining whether progesterone supplementation is necessary for mNC-FET cycles may contribute to improving clinical guidelines and developing individualised treatment strategies for women undergoing FET.

METHODS

Ethical approval: The Institutional Review Board of Istanbul Memorial Sisli Hospital, Istanbul, Turkey, accepted this study. (Approval number: 28.06.2024/003).

This retrospective study examines 2216 mNC-FET cycles between 2011 and 2023. It was conducted at Sisli Memorial Hospital, Assisted Reproductive Technology (ART), and Reproductive Genetics Centre. This investigation aimed to ascertain whether progesterone supplementation is essential to the luteal phase in mNC-FET cycles. For analysis purposes, the mNC-FET cycles were categorised into three distinct groups: The luteal phase was not supported for participants in Group A, which consisted of 493 cycles. In Group B, consisting of 1327 cycles, a vaginal dose of 200 mg micronised progesterone was administered two times a day. Group C, consisting of 396 participants, received 25 mg progesterone subcutaneous injection in addition to progesterone vaginal capsules two times daily. The cycle characteristics and pregnancy outcomes of the groups were compared. The study focused on women under the age of 38 who underwent single embryo transfer (SET) in mNC-FET cycles, specifically involving embryos of top quality (TQ) or good quality (GQ). Embryo transfers involving medium-quality (MQ) or poor-quality (PQ) embryos were excluded from the analysis. The study excluded cases of double embryo transfer, cycles employing preimplantation genetic testing, and women with Müllerian abnormalities. Furthermore, patients with untreated endocrine disorders or with endometrial thickness below 7 mm on the day ovulation was triggered were excluded from the study.

Controlled ovarian hyperstimulation was initiated on the second day of the cases' menstrual cycle. Starting dosages were based on patient characteristics. Ovarian stimulation was performed as described in our previous study (12). 250 mcg of recombinant human chorionic gonadotropin (r-hCG) (Ovitrelle; Merck, Switzerland) or GnRH analog (Gonapeptyl®, lucrin®) was administered to trigger ovulation. Thirty-six hours after administering the trigger medication, the oocyte collection procedure was performed using transvaginal ultrasound (TVUSG) guidance.

mNC/ FET cycle

Patients were checked with TVUSG on the 2nd day of menstruation for mNC-FET cycle preparation. In cases with normal ultrasound findings, i.e., no hormone-secreting cyst or any pathology was found to affect the endometrial cavity, follicle follow-up was started to determine the time of ovulation. E2 and LH levels were analysed when the follicle size reached when LH reached 15 IU/L and above a specific level, a single subcutaneous dose of r-hCG was administered to trigger it. In cases where LPS was recommended, progesterone treatment was started 2 days after triggering. Blastocyst transfer was performed 6 days after trigger. Following blastocyst transfer, a pregnancy test was administered after 9 days. For patients who tested positive, LPS was maintained through the 10th week of gestation.

Embriyo grading

Embryo morphological evaluation was performed using the classification protocol established by Gardner et al. Embryos with 3AA-4AA-5AA-6AA were classified as TQ, and embryos with 3AB-4AB-5AB-6AB-3BA-4BA-4BA-5BA,6BA were classified as GQ. This study excluded low or medium-

quality embryos. Freezing followed the manufacturer's guidelines utilising Kitazato Vitrification Medium (Kitazato, Japan). Kitazato Warming Medium was used to thaw the blastocysts. Any thawed embryos that exhibited a decrease in grade were excluded from the study.

Pregnancy outcomes

Beta-human chorionic gonadotropin (β-hCG) level equal to or exceeding 20 IU/L was utilised as the threshold for defining a biochemical pregnancy. The occurrence of a biochemical pregnancy loss was characterised by the detection of serum β-hCG levels that did not progress to a clinically recognisable pregnancy. Ultrasonography was used to detect a fetal heartbeat, which indicated a clinical pregnancy. The absence of a fetal heartbeat in a pregnancy that had been previously confirmed as clinical was considered a clinical pregnancy loss. The live birth rate (LBR) was calculated as the number of live births per embryo transfer cycle.

Statistical Analysis

SPSS 22 was used for statistical analysis. Results were provided as mean ± standard deviation for variables with a normal distribution. However, numerical variables without a normal distribution were reported as medians with minimum and maximum values. Categorical variables were shown as frequencies and percentages to simplify the statistical presentation. The descriptive statistical methods were evaluated using the Shapiro-Wilk test and boxplot diagrams. Non-normally distributed metric variables were analysed using the Kruskal-Wallis test. Categorical data were evaluated among groups utilising the chi-square test and a post hoc Bonferroni adjustment. Statistical significance was determined as a p-value of < 0.05.

RESULTS

The study comprised three groups based on the type of luteal phase support: group A without progesterone (n = 493, 22.2%), group B receiving vaginal progesterone tablets (n = 1327, 59.9%), and group C administered a combination of vaginal progesterone tablets and subcutaneous progesterone (n = 396, 17.9%) Figure 1. Patient demographics and clinical features are shown in Table 1. No substantial difference was observed among the three groups regarding, male age, female age, body mass index (BMI), duration of infertility, anti-Müllerian hormone levels, number of frozen embryos, number of collected oocytes, number of Metaphase II (MII) oocytes, and number of fertilised oocytes (PN2) (p > 0.05). When the groups were compared in terms of endometrial thickness, the mean endometrial thickness in the vaginal progesterone group was 10.77 ± 3.24 mm. In the subcutaneous progesterone group, the mean endometrial thickness was 10.72 ± 1.88 mm, and a statistically significant difference was found (p = 0.047). The study did not identify any significant differences in the rate of biochemical pregnancy, clinical pregnancy, biochemical pregnancy loss, clinical pregnancy loss, ongoing pregnancy, and live births among the three groups (p values>0.05).

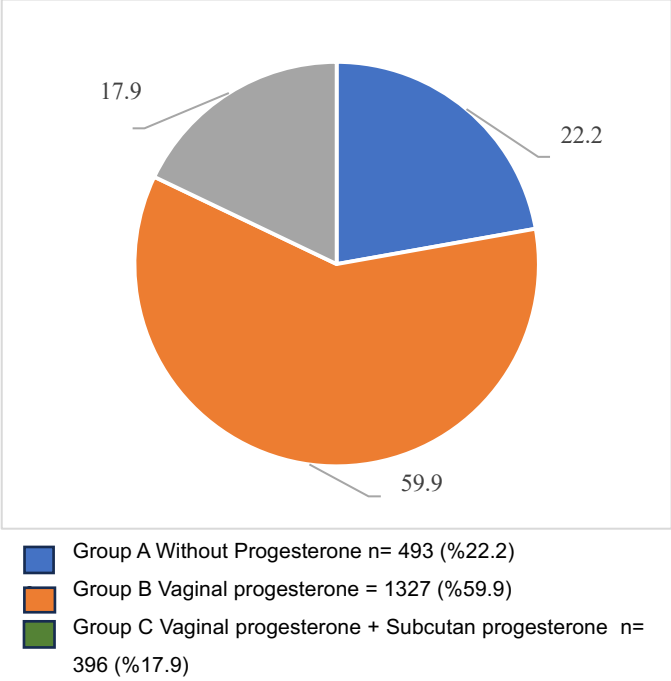

Figure 1. Cycle distribution based on luteal phase support

DISCUSSION

This study assessed the necessity of LPS with progesterone in mNC-FET cycles and its effect on pregnancy outcomes. Our findings suggest that progesterone supplementation, whether administered vaginally or in combination with subcutaneous progestin, does not significantly improve clinical outcomes compared to cycles without progesterone support. Notably, live birth rates and clinical pregnancy rates remained statistically similar across all groups, indicating that LPS with progesterone may not be essential in mNC-FET cycles.

The evidence for the need for progesterone supplementation for LPS in-modified natural cycle frozen embryo transfer is mixed. Some studies support its use to improve live birth rates, while others have shown that progesterone production by the corpus luteum is sufficient, and progesterone supplementation is not required. A randomised controlled trial by Horowitz et al. showed that vaginal progesterone supplementation did not significantly enhance clinical pregnancy rates compared to no supplementation in mNC-FET cycles, suggesting that the need for exogenous progesterone may be less critical in these particular conditions(6). In a systematic review and meta-analysis based on randomised controlled trials, the authors showed that moderate-quality evidence indicated that progesterone supplementation for LPS was associated with increased live birth rates and clinical pregnancy rates in

Table 1. Comparison of demographics and cycle characteristics of patients

	Group A		Group B		Group C		p
	Mean ± SD	Med.	Mean± SD	Med.	Mean± SD	Med.	
Female age (years)	30.93 ± 3.73	31	30.91 ± 3.72	31	30.96 ± 3.88	31	0.884
Male age (years)	30.93 ± 3.73	34	34.44 ± 4.68	34	34.54 ± 4.47	34	0.697
BMI (kg/m^2)	24.38 ± 4.23	23.6	24.29 ± 4.34	23.6	24.72 ± 4.89	23.9	0.490
Duration of infertility (years)	3.84 ± 3.08	3	3.53 ± 2.80	3	3.90 ± 3.10	3	0.080
AMH (ng/ml)	3.26 ± 2.41	2.80	3.26 ± 2.37	2.70	3.26 ± 2.28	2.68	0.929
Endometrial thickness (mm)	10.49 ± 1.83	10	10.77 ± 3.24	10.50	10.72 ± 1.88	10.65	0.047
Number of embryos frozen	5.54 ± 3.64	5	5.85 ± 3.72	5	6.09 ± 4.13	5	0.102
Number of retrieved oocytes	14.93 ± 8.22	13	14.71 ± 8.05	13	14.74 ± 7.92	13	0.847
Number of Metaphase II oocytes (MII)	12.58 ± 6.82	11	12.56 ± 6.79	12	12.64 ± 6.89	11	0.991
Number of Fertilized oocytes (PN2)	10.40 ± 5.80	9	10.31 ± 5.81	9	10.46 ± 5.91	9	0.886

AMH= anti Mullerian hormone, BMI=body mass index, SD: Standard Deviation, Med.: Median.

true NC-FET cycles. However, they noted that the efficacy of progesterone supplementation in mNC-FET cycles needs to be further validated by conducting large, randomised controlled trials (10). Recent studies suggest that LPS via additional progesterone supplementation may be unnecessary even in natural cycles where ovulation occurs without exogenous r-hCG administration. Li et al. showed that the pregnancy outcomes of NC FET with or without LPS were similar. The authors stated that the women's age was the most critical factor affecting the clinical pregnancy rates (13). Waldman et al. also found that using progesterone to support the luteal phase in cryopreserved blastocyst transfers for true natural cycles did not significantly affect the number of ongoing pregnancies. This suggests that natural cycles may not necessitate additional progesterone support (14).

Some studies contradict our results. In a retrospective study of 231 cases, Schwartz et al. compared the groups with and without progesterone as LPS in mNC/FET cycles. They reported higher live birth rates in the progesterone group. However, in this study, both cleavage periods and blastocyst transfers were performed and without any information about embryo quality. Since the existing literature shows the effect of embryo quality on pregnancy outcomes (12,15,16), this may have affected the results. Our study compared only the 2216 TQ/GQ blastocyst transfer results to avoid bias and evaluate progesterone supplementation's effectiveness.

Most studies recommending progesterone support as LPS are true natural cycles, not mNC/FET cycles (4,8,17). In a mNC/FET cycle, the administration of human chorionic gonadotropin (hCG) serves a dual purpose: it not only triggers ovulation but also enhances serum progesterone (P4) production during the early and mid-luteal phases. support (18). Therefore, progesterone support in mNC/FET cycles is unnecessary, especially in cases under the age of thirty-eight. Luteal phase defects may occur at older age (19). Therefore, we compared the groups by including younger patients in our study.

One of the study's strengths is the large sample size and well-defined inclusion criteria, particularly the inclusion of only TQ and GQ embryos under the age of 38. Nonetheless, the study’s retrospective design limits the ability to establish causal relationships definitively.

CONCLUSION

In conclusion, our study suggests that in mNC-FET cycles among women under 38, the natural luteal support provided by hCG-triggered ovulation and corpus luteum activity may suffice, making additional progesterone supplementation unnecessary. Additionally, progesterone supplementation can cause physical discomfort. Therefore, the decision to use progesterone should be individualised based on patient-

Table 2. Comparison of pregnancy outcomes

Outcomes of FET cycles	Group A	Group B	Group C	Test	P value
Biochemical Pregnancy	347 (70.4)	1005 (75.7)	291 (73.5)	5.474	0.065
Clinical Pregnancy	325 (65.9)	917 (69.1)	270 (68.2)	1.678	0.432
Biochemical Pregnancy Loss	22 (4.5)	88 (6.6)	21 (5.3)	3.361	0.186
Clinical Pregnancy Loss	31 (6.3)	89 (6.7)	29 (7.3)	0.377	0.828
Ongoing Pregnancy	294 (59.6)	828 (62.4)	241 (60.9)	1.243	0.537
Live Birth	288 (58.4)	807 (60.8)	238 (60.1)	0.861	0.650

specific factors and clinical judgment. To support these findings further, prospective randomised controlled trials are essential, as they would provide more evidence on the necessity of progesterone LPS in mNC-FET cycles. Future studies might also investigate potential subgroups that could benefit from LPS or explore different LPS regimens in modified natural cycle protocols.

Ethics Committee Approval: The Institutional Review Board of Istanbul Memorial Sisli Hospital, Istanbul, Turkey, accepted this study. (Approval number: 28.06.2024/003).

Informed Consent: No need.

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