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ORIGINAL ARTICLE

Comparison of natural versus artificial cycles for endometrial preparation prior to frozen embryo transfer

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ABSTRACT

BACKGROUND

The endometrial preparation phase preceding embryo transfer assumes pivotal significance in achieving optimal endometrial receptivity and ensuring the success of pregnancy. The natural cycle (NC) and artificial cycle (AC) are the preferred methods for many in vitro fertilization (IVF) specialists. The objective of this study was to compare the difference between NC and AC in women undergoing frozen-thawed embryo transfer (FET) after IVF.

METHODS

A cross-sectional study was conducted involving 150 adult women who underwent FET with a single autologous blastocyst stage embryo in a 5-year period (2014-2019). Bivariate analysis was conducted to discern implantation and pregnancy rates associated with NC and AC for endometrial preparation. Multiple logistic regression was used to assess the association between endometrial preparation and clinical outcomes while adjusting for potential confounders.

RESULTS

Of the 150 subjects meeting study criteria, 19 underwent NC, while 131 underwent AC for endometrial preparation. Natural cycle exhibited a higher biochemical pregnancy rates compared to AC (89.5% vs. 53.4%; p=0.003). Artificial cycle is a significant determinant for biochemical pregnancy rates compared to NC (aOR: 0.132;95% CI: 0.028 – 0.623; p=0.010)

CONCLUSION
In women undergoing FET, NC resulted in higher biochemical pregnancy rates compared to AC. However, clinical pregnancy rates and ongoing pregnancies rates did not exhibit significant disparities between NC and AC. Future studies will hopefully further illuminate which protocol is most suitable for the individual patient. Further multi-center randomized clinical trials are needed to confirm the relationship between biochemical pregnancy rates and NC.

Keywords: Infertility, IVF, frozen embryo transfer, natural, hormone replacement, biochemical pregnancy rates

INTRODUCTION

Infertility afflicts a substantial proportion of couples globally, with prevalence estimates ranging from 3.5% to 16.7% in developing countries and 6.9% to 9.3% in developed nations.[1,2] Approximately one in six people have experienced infertility at some stage in their lives, globally.[1,2] In Indonesia, approximately 10–15% of couples, constituting 6–9 million persons, are affected by infertility.[3,4] The Indonesian In Vitro Fertilization Association (PERFITRI) reported 8033 cases undergoing in vitro fertilization (IVF) procedures in 2022.[5] Embryo transfer is one of the final and most important procedures in IVF. Of note, about 80% of IVF patients undergo the embryo transfer procedure, with only 30-40% achieving pregnancy.[2] The embryos transferred may either be fresh or frozen, the latter increasingly practiced due to more efficient cryopreservation methods, apart from indications such as elevated progesterone level, preimplantation genetic testing, and concerns of ovarian hyperstimulation syndrome (OHSS) especially in hyper-responder patients.[6] A meta-analysis conducted by Roque et al.[7] highlighted that a significant increase in live birth rate (LBR) was noted with elective frozen embryo transfer (eFET) compared with fresh embryo transfer in the overall IVF population [risk ratio (RR) = 1.12; 95% CI: 1.01-1.24]. Despite its increasing prevalence, the most effective protocol for endometrial preparation in FET remains unclear.[6] Endometrial preparation, a pivotal step preceding embryo transfer, significantly influences endometrial receptivity for accepting implantation and subsequently enhancing pregnancy rates.[8] Natural cycle (NC) and artificial cycle (AC) using hormonal replacement treatment (HRT) constitute the primary approaches to endometrial preparation for FET.[8,9] The NC can be used in women with regular menstrual cycles and does not require administration of exogenous hormones. This method is often seen as a more physiologic approach, therefore may result in higher pregnancy rates. Meanwhile, the HRT cycle utilizes exogenous hormones, namely estrogen and progesterone, to obtain an endometrial surface thickness suitable for implantation, achieving endometrial receptivity and successful pregnancy. This method gives more flexibility to the physician as it requires minimal monitoring, permits easy scheduling, and produces lower cancellation rates.[10]

Numerous studies have sought to determine the most effective endometrial preparation method, yielding conflicting findings. Previous studies found that there was no significant difference in the occurrence of pregnancy in patients who underwent FET procedures using NC or AC cycle.[6,11] In contrast, Elsayed et al.[12] observed significantly higher pregnancy rates with the AC (62.25% vs 37.5%). Meanwhile, another study by Holder et al.[13] stated that the NC approach to preparing the endometrium before FET resulted in a higher pregnancy rate (36.76% vs 22.99%; p=0.029).[13] The NC approach is more patient-friendly, requiring less medical treatment and fewer injection procedures. However, the NC presents challenges in predictability, necessitating frequent clinical monitoring to assess endometrial thickness, follicle development, and ovulation, compared to the AC [11] In view of these conflicting data, we compared biochemical pregnancy rates following FET conducted using NC and AC in women who were undergoing endometrial preparation for upcoming FET.

METHODS

A cross-sectional study was conducted between 2014 – 2019 at Yasmin IVF Clinic, Dr. Cipto Mangunkusumo Kencana Hospital, Jakarta, Indonesia.

Research subjects

A total of 536 subjects from the medical records who underwent FET with a single autologous embryo vitrified at the blastocyst stage in the period of 2014–2019 were included.

The subjects included women who were undergoing endometrial preparation for upcoming FET procedures, using both NC and AC. The subjects were excluded if their data was not complete, if they were without good grade embryos or had endometriosis as the cause of infertility. The inclusion criteria for this study were women of reproductive age who underwent endometrial preparation for frozen embryo transfer and had primary or secondary infertility. The exclusion criteria included patients with non-gynecological predisposing factors, such as autoimmune diseases, cancer, and medication side effects, patients who were not willing to participate in the research, and those with incomplete data.

Data collection

Background and risk factors were acquired by anamnesis. Endometrial thickness was determined by ultrasound. Sperm quality was analyzed. After follow up, biochemical pregnancy, clinical pregnancy, and ongoing pregnancy rates were observed.

Endometrial preparation protocols

Two types of endometrial preparation methods were used prior to performing frozen embryo transfer.

Natural cycle for FET

The NC was used when a surge in serum luteinizing hormone (LH) for ovulation could be detected, such that the clinician could define the timing of the transfer. Follicle monitoring began on days 8-10 of the menstrual cycle. When the leading follicle reached a mean diameter of >17mm and serum LH was <20 IU/L, an amount of 10000 IU human chorionic gonadotropin (hCG) was administered to trigger oocyte release (ovulation). Ovulation was confirmed by transvaginal ultrasound the day after hCG and the next day. When LH was >20 IU/L, transvaginal ultrasound was performed every day until ovulation occurred. [11-13]

Artificial cycle for FET

The AC was used when ovulation was to be triggered using hormonal administration. In women treated with AC, endometrial priming started on the fifth day of the menstrual cycle with estradiol valerate (Progynova; Bayer Schering Pharma AG, Berlin, Germany) orally administered at a dose of 6mg daily. After 10-12 days of endometrial preparation, transvaginal ultrasound and progesterone level determination were performed. In women with endometrial thickness >8mm and serum progesterone (P) level <1.5ng/mL, intramuscular progesterone at a dose of 60mg daily was administered. The timing of FET was based on the day of embryo freezing and the day of ovulation (i.e. 3 days after ovulation for cleavage stage embryos and 5 days after ovulation for blastocyst stage embryos). Triple-line endometrial patterns were classed as pattern A (a triple-line pattern consisting of a central hyperechoic line surrounded by two hypoechoic layers), pattern B (an intermediate iso-echogenic pattern with the same reflectivity as the surrounding myometrium and a poorly defined central echogenic line), and pattern C (homogenous, hyperechogenic endometrium).[14]

Cycle outcome measures

The outcome measures for this research were biochemical pregnancy, clinical pregnancy, and ongoing pregnancy rates. Biochemical pregnancy rates was defined as pregnancy that was detected using laboratory tests such as hCG, but not progressing into clinical pregnancy. Clinical pregnancy rates was defined as pregnancy that was diagnosed using imaging and the presence of a gestational sac. Ongoing pregnancy rates was defined as pregnancy that was developing and was not a miscarriage.

Statistical analysis

Bivariate analysis was performed on the collected data using the chi-square test to determine implantation and pregnancy rates in FET using SPSS for Windows ver. 26. We conducted bivariate analysis for numeric variables. If the distribution of the variable was normal, the t test was performed. However, if the distribution was not normal, the Mann-Whitney test was performed. Chi-square tests were performed to compare the categorical variables. For multivariate analyses, logistic regression was utilized. Odds ratios (OR) with 95% confidence interval (CI) were calculated to assess the association between covariates and clinical outcomes.

Ethical clearance

This research was submitted to the Ethics Committee and carried out after obtaining written approval in the form of Ethical Clearance letter No. KET – 191/ U2. F1/ ETIK/ PPM.00.02/2019 from the Permanent Committee for Medical Research Ethics, Faculty of Medicine, Universitas Indonesia, Jakarta.

RESULTS

The patients were admitted to the IVF program and planned into the FET procedure, receiving either NC or AC for endometrial preparation. Nineteen out of 150 patients that participated in the study were included into the group with NC, the other 131 subjects underwent AC. The recruitment protocol can be seen in Figure 1.

The results of the analysis are shown in Table 1. Biochemical, clinical, and ongoing pregnancy rates were 58.0%, 35.33%, and 30.67%, respectively. When divided into NC and AC endometrial preparation groups, the duration of infertility was the only significant difference between the groups (p=0.025) (Table 2).

Table 3 demonstrates the comparison of biochemical, clinical, and ongoing pregnancy rates between NC and AC endometrial preparation groups. Biochemical pregnancy rate (89.47% vs 53.43%; p<0.05) were significantly higher in NC compared to AC for endometrial preparation. Clinical and ongoing pregnancy rates were also higher in the NC group. However, there were no statistically significant differences between both groups.

We conducted logistic regression to discover the relationship of determinants with biochemical, clinical, and ongoing pregnancies. We have discovered that AC is a significant protective factor (decreased likelihood) for biochemical pregnancy (aOR: 0.132;95% C.I.0.028–0.623; p=0.01). However, AC is not a significant determinant for clinical pregnancy (aOR: 0.846;95% C.I.:0.300–2.381; p=0.751) and ongoing pregnancy (aOR: 0.786;95 % C.I.: 0.271–2.279;p= 0.658) (Table 4).

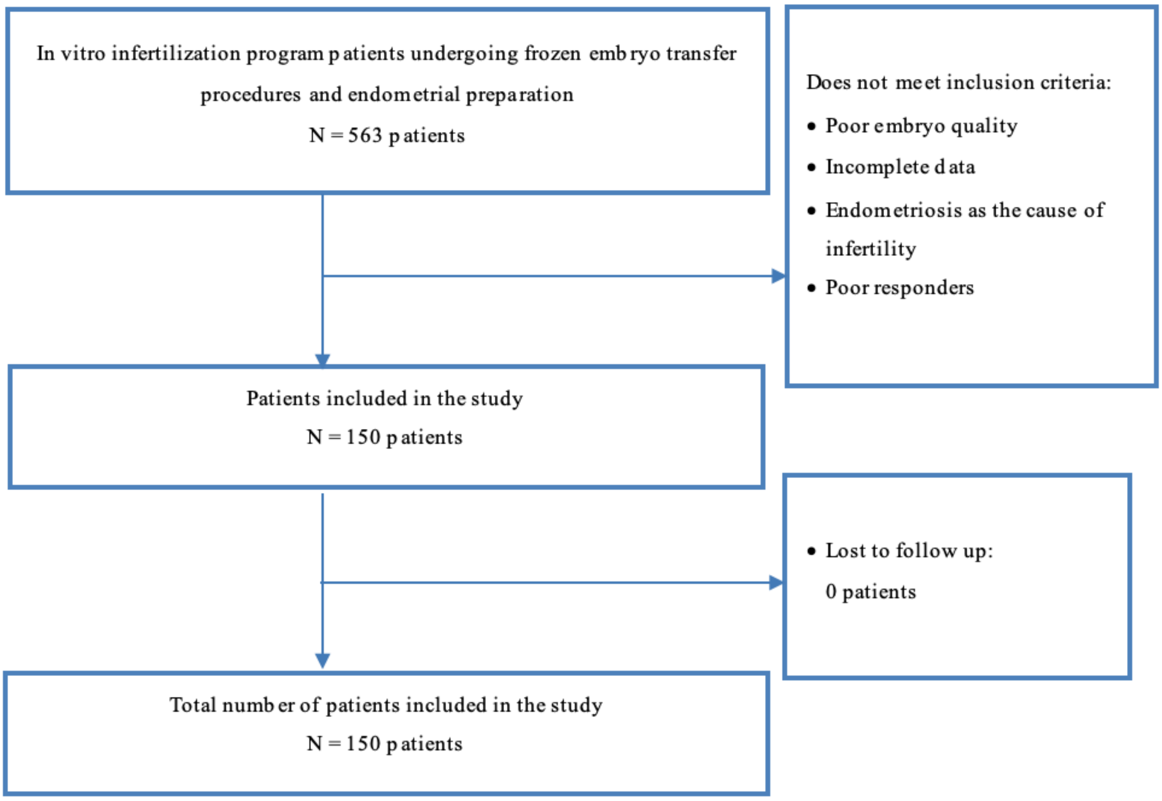

Figure 1. Subjects' recruitment flow

Table 1. Baseline characteristics of the subjects (n=150)

Characteristics	n (%)
Age (years)	34.55 ± 4.55
< 35	73 (48.70)
≥ 35	77 (51.30)
Infertility duration (years)	5 (1-18)
Endometrium thickness (mm)	11.15 (7.4-20)
< 8	16 (10.67)
≥ 8	134 (89.33)
Numbers of embryo transferred	2 (1-4)
Embryo quality	
Good-excellent	69 (39.43)
Moderate	106 (60.57)
Infertility causes	
Male factor	45 (30.00)
Mixed factors	37 (24.67)
Tubal factor	22 (14.67)
Polycystic ovary syndrome	19 (12.67)
Endometrial factor	15 (10.00)
Unexplained infertility	9 (6.00)
Hypothalamic amenorrhea	3 (2.00)
Sperm quality	
Normal	67 (44.67)
Abnormal	83 (55.33)
Endometrial preparation	
method	19 (12.67)
Natural	131 (87.33)
Artificial	
Biochemical pregnancy	
Yes	87 (58.0)
No	63 (42.0)
Clinical pregnancy	
Yes	53 (35.33)
No	97 (64.67)
Ongoing pregnancy	
Yes	46 (30.67)
No	104 (69.33)

Data are presented as mean ± SD; n (%) or median (minimum value-maximum value)

DISCUSSION

The findings of this study indicate that NC for endometrial preparation exhibits significantly increased biochemical pregnancy rates compared to AC. Interestingly, this study also found higher clinical and ongoing pregnancy rates in the NC group, although the results were not statistically significant. This result is in line with a study conducted in Iran, involving 170 participants, which observed higher biochemical pregnancy rates in NC compared to AC for endometrial preparation (48.2% vs. 45.9%), along with increased clinical pregnancy (38.9% vs. 35.3%) and ongoing pregnancy rates (37.6% vs. 34.1%) without significant differences between the two groups.[15] A randomized controlled study involving 1032 patients showed no inferiority in the clinical pregnancy rates (23.3% vs. 22.1%) and ongoing pregnancy rates (14.5% vs. 13.2%) in AC compared to NC prior to FET.[16] Another research study found a significant difference in implantation, clinical pregnancy, and ongoing pregnancy rates between the two methods.[17] However, a comprehensive review and meta-analysis by Groenewoud et al.[18] revealed no discernible differences in clinical pregnancy, ongoing pregnancy, and live birth rates between NC and AC for endometrial preparation. In contrast, conflicting results from other studies suggested lower clinical pregnancy (49.4% vs. 58.6%) and live birth rates (42.2% vs. 50.8%) in NC compared to AC.[19] The discrepancies in these findings may stem from variations in sample size and study design across different investigations. Importantly, the study indicated no significant difference in frozen embryo preparation, whether NC or AC.[15]

Natural endometrial preparation involves the intricate processes of folliculogenesis and ovulation, necessitating follicle observation and ovulation evaluation through ultrasonography. Challenges may arise due to irregular folliculogenesis and difficulties in accurately determining the timing of ovulation, potentially leading to the cancellation of frozen embryo transfer. [20] In contrast, artificial endometrial preparation relies on the administration of exogenous estrogen and progesterone, simulating the proliferative and secretory phases of the menstrual cycle and ensuring optimal endometrial receptivity. This method offers greater flexibility and procedural efficiency for clinicians conducting frozen embryo transfers.[20] However, AC also has some disadvantages such as increased costs, and discomfort and increased risk of thrombosis when using exogenous estrogen.[20] In the present study, subjects aged 35 years and older constituted 51.3% of the cohort, surpassing subjects below 35 years (48.7%). Existing research underscores a significant association between age and pregnancy rates following frozen embryo transfer procedures. In contrast to comparable studies where both NC and AC groups spanned an age range of 30 years, no statistically significant difference was discerned in the age distribution concerning the chosen FET method.[15]

Table 2. Endometrial preparation methods and pregnancy outcomes in NC and AC

Variable	Study groups		p value
	NC (n = 19)	AC (n = 131)	
Age (years)			
<35	10 (52.60)	63 (48.1)	0.711
≥35	9 (47.400)	68 (51.90)	
Infertility duration (year)	4.68 ± 3.056	6.77 ± 4.00	0.025*
Endometrial thickness (mm)			0.064
<8	5 (26.32)	11 (8.40)	
≥8	14 (73.68)	120 (91.60)	
Embryo quality			
Good-excellent	14 (20.30)	55 (79.70)	0.647
Moderate	11 (10.40)	95 (89.60)	
Sperm quality			0.484
Normal	7 (36.80)	60 (45.40)	
Abnormal	12 (63.20)	71 (54.60)	

Data are presented as mean ± SD; n (%) or median (minimum value-maximum value);NC : natural cycle;AC: artificial cycle;*p<0.05

Table 3. IVF outcomes of different endometrial preparation methods

Variable	Study groups		p value
	NC (n = 19)	AC (n = 131)	
Biochemical pregnancy			
Yes	17 (89.47)	70 (53.43)	0.003*
No	2 (10.52)	61 (46.56)	
Clinical pregnancy			
Yes	8 (42.11)	45 (34.35)	0.509
No	11 (57.89)	86 (65.65)	
Ongoing pregnancy			
Yes	8 (52.65)	39 (29.77)	0.500
No	12 (63.15)	92 (70.23)	

Data are presented as mean ± SD; n (%) or median (minimum value-maximum value); NC: natural cycle; AC: artificial cycle;*p<0.05

Table 4. Relationship between endometrial preparation and clinical outcomes in different models (NC and AC)

Outcome	OR (95% CI)	p value	aOR (95% CI)	p value
Biochemical pregnancy				
NC	Ref.	0.010	Ref.	0.010
AC	0.135 (0.03 – 0.608)			
Clinical pregnancy				
NC	Ref.	0.510	Ref.	0.751
AC	0.719 (0.270 – 1.916)			
Ongoing pregnancy				
NC	Ref.	0.488	Ref.	0.658
AC	0.700 (0.256 – 1.915)			

OR: odds ratio; aOR: adjusted odds ratio; NC: natural cycle; AC: artificial cycle

Advanced maternal age is known to correlate with diminished fertility, with younger women exhibiting significantly higher implantation rates than their older counterparts. The observed decline in endometrial fertility among older women may be attributed to decreased numbers of progesterone receptors concomitant with declining estrogen receptors as posted by Chen et al.,(21) who found that being 38–40 years of age was a risk factor for non-live birth (OR=2.121, 95% CI: 1.233–3.647) and adverse pregnancy outcomes (OR=1.630, 95% CI: 1.010–2.633).

Analysis of endometrial thickness revealed a lower occurrence of thickness ≥8 mm in the NC group compared to the AC group (78.9% vs. 92.2%) although not statistically significant. While previous studies have not identified a significant correlation between endometrial thickness and pregnancy rates post-FET, various findings from other investigations suggest a substantial association between endometrial thickness and FET endometrial preparation methods.(17,22,23) Endometrial thickness has long served as a pivotal marker for uterine receptivity and an influential prognostic factor in embryo transfer outcomes. Further high-quality research is warranted to unravel the multifaceted factors influencing endometrial thickness and its nuanced relationship with clinical efficacy.

Importantly, a meta-analysis conducted by Zaat et al.(24) showed that preparation of the endometrium by NC will reduce the risk of obstetric morbidity and adverse neonatal outcomes. The natural cycle for endometrial preparation showed lower birth weight than the HRT cycle. Moreover, NC might also reduce the risk for gestational age, low birth weight, early miscarriage, preterm birth, very preterm birth, hypertension in pregnancy, pre-eclampsia, placenta previa, and postpartum hemorrhage. These conditions are hypothesized to be related to disturbances in placentation, invasion of extra villous trophoblast, and absence of the corpus luteum in the natural cycle. Vasoactives produced by the corpus luteum such as relaxin, renin, and prorenin are found in lower amounts in the NC than in the HRT cycle and may probably cause disturbances, such as hypertension in pregnancy or pre-eclampsia.(24)

The current study presents some limitations, specifically the notable discrepancy in sample sizes between the two methods, with the smaller sample being in the natural endometrial preparation group. This disparity is reflective of the infrequent utilization of natural endometrial preparation methods at Yasmin Clinic RSCM Kencana, possibly influenced by its intricacies and a heightened risk of procedural delays or cancellations. Moreover, ovulatory dysfunction due to conditions such as polycystic ovarian syndrome (PCOS) and hyperprolactinemia, constitute major causes of infertility at Yasmin Clinic RSCM Kencana. Therefore, AC for endometrial preparation emerges as a more feasible approach, such that this study must be continued by involving more women with NC.

This study led us to discover that NC demonstrated higher implantation and biochemical pregnancy rates, thereby allowing the clinician to prioritize NC instead of AC during frozen embryo transfer. More high-quality studies with proper analysis should be conducted to elucidate the role of NC during frozen embryo transfer.

CONCLUSIONS

This study demonstrated that NC for endometrial preparation in FET achieved higher biochemical pregnancy rates compared to AC. Therefore, both methods of endometrial preparation might be used before performing FET in an IVF program. Further studies should be carried out especially to determine the effect of these two endometrial preparation methods on pregnancy and neonate outcomes.

Conflict of Interest

The authors have no conflict of interest.

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Author Contributions

GAT, KHN, and GP conceptualized the background and draft for the study, GAT, MM, and AKH reviewed the methods and outcomes of the study. Sampling was done by GAT, GP, KHN, and MM, KS, and SWL reviewed the outcomes, data collection, and analysis, while revision was done by GAT, NT, IAHA, and AMY. All authors have read and approved the final manuscript.

Data Availability Statement

The data of the analysis is available. Requests for the original data presented in this study can be directed to the corresponding author.

Declaration of Use of AI in Scientific Writing

We did not use artificial intelligence to create this article. The data analysis and the manuscript creation were conducted by the authors.

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