

ORIGINAL STUDY

Natural cycle versus stimulated or artificial cycle in frozen–thawed embryo transfer: A randomized prospective trial

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Abstract

Objective: The goal of this study was to see if there was a difference in pregnancy outcomes between natural cycle frozen–thawed embryo transfer (NC-FET) cycles, artificial cycle–FET cycles, and stimulated cycle (SC)–FET cycles in women with regular menstrual cycles.

Patients and methods: This prospective randomized clinical study was conducted in Assisted Reproductive Unit (ART), The International Islamic Center for Population Studies and Research, El Hussein Hospital, Al-Azhar University, in the period of September 2019 till August 2020.

Results: There was a significant increase in immotile sperms in the natural group ($P = 0.014$). Group I had much lower total count and total motility than the other groups, whereas group II had significantly greater total count and total motility. There was no statistically significant difference between the analyzed groups in terms of patients' basal ultrasonography, transplanted embryos, embryo grade, and embryo stage ($P > 0.05$). The majority of women in groups I and II had miscarriages (45 and 42.5%, respectively). The other half of group III did not have a clinical pregnancy, while half of group III did (50%).

Conclusion: In women with regular menstrual cycles, natural, artificial, and SCs all had similar pregnancy outcomes, including pregnancy rates, implantation rates, and cancelation rates, however, SCs had a greater incidence of endometrial thickness, semen volume, and pregnancy rates. NC-FET, on the other hand, is preferred since it does not require medication, is less expensive, and has less adverse effects.

Keywords: Artificial cycle, Embryo transfer, Natural cycle, Stimulated cycle

1. Introduction

Several individuals have profited greatly from frozen–thawed embryo transfer (FET) cycles to achieve pregnancy after successful in-vitro fertilization (IVF) or failed fresh embryo transfer (ET) cycles [1]. More cost-effective FET cycles result in a higher cumulative pregnancy rate per oocyte retrieval [2]. Hyperstimulation syndrome and multiple births are two IVF issues that can be effectively prevented with FET [3]. Endometrial receptivity, as well as synchronization of embryonic and endometrial development, are critical determinants in FET success [4]. Several endometrial preparation

methods have been proposed to achieve this. The transfer of embryos in FET cycles can be timed either in natural cycles following spontaneous ovulation or in artificial hormonally managed cycles utilizing exogenous estrogen and progesterone delivered sequentially [5,6].

Natural cycle-FET (NCFET) may be advantageous for women who have regular menstrual cycles because it requires less medication and is less expensive for patients. However, ovulation may not always occur in these women, or ovulation may occur unexpectedly. As a result, timing FETs can be challenging. Clinics also prefer artificial cycle–FET (AC–FET) cycles because of their predictability

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and consistency [2]. When compared with GnRHa-primed cycles, Simon et al. [7] discovered that endometrial preparation with an AC, including only estradiol and progesterone, is simpler, less expensive, and more convenient for patients and providers [7]. Other research has found no difference in pregnancy rates between GnRHa-primed cycles and artificial or stimulated cycles (SCs) [8].

Wright et al. [9] found similar implantation rates, pregnancy rates, and cycle-cancellation rates in artificial and SCs for endometrial preparation prior to implantation of frozen–thawed embryos. Although the two regimens had identical mean endometrial thickness, SCs had a much higher incidence of thick endometrium. The most intriguing discovery is that patients who need vaginal estradiol supplementation have a greater pregnancy rate than those who respond well to oral estradiol. Therefore, the goal of this study is to see if there was a difference in pregnancy outcomes between natural cycle frozen–thawed embryo-transfer (NC-FET) cycles, AC–FET cycles, and SC-FET cycles in women with regular menstrual cycles.

2. Patients and methods

The International Islamic Center for Population Studies and Research, El Hussein Hospital, Al-Azhar University, conducted this prospective randomized clinical study from September 2019 to August 2020 in the Assisted Reproductive Unit (ART), The International Islamic Center for Population Studies and Research, El Hussein Hospital, Al-Azhar University.

2.1. Ethical consideration

The study began when the Al Azhar University Faculty of Medicine's ethical council accepted the protocol. Each patient in the study underwent the following procedures: patients are counseled about the risks of laparoscopy and given detailed information about the technique to assist them and become more involved and cooperative in the research.

2.2. Inclusion criteria

The study included all women aged 22–35, with normal menses (25–34-day interval), and at least two cryopreserved embryos derived from intracytoplasmic sperm-injection treatment cycles.

2.3. Exclusion criteria

Endometriosis, immunological disorders, repeated abortions, uterine anomalies, all women who have

had previous IVF failures, any known contraindications or allergies to oral estradiol or progesterone treatment, and the presence of a Hydrosalpinx are all taken into account.

2.4. Methods

Using automated software, a total of 120 patients were randomly assigned in a 1 : 1 fashion. The aforementioned software developed the three-group allocation sequence, and the treating physicians ($n = 3$) delivered treatment based on the assigned chart. These patients were randomized to one of three groups at random: The NC-FET group A consisted of 40 women (NC-FET). Following a spontaneous menses, ultrasound tests were conducted on days 9–12 of the cycle to find the leading follicle in this group. When at least one dominant follicle reached 18 mm in diameter and the endometrial thickness was at least 8 mm, a bolus of 10 000 IU of human chorionic gonadotropin (hCG) was given intramuscularly for the induction of ovulation, and the embryos were thawed and implanted 4 days later.

Group B: consisted of 40 women who received oral estradiol valerate doses ranging from 2 to 4 mg/d twice daily commencing on day 2 of the following cycle after undergoing AC-FET. Transvaginal ultrasonography was used to determine endometrial thickness, and the estrogen dosage was changed correspondingly.

A second ultrasound examination was performed on days 8–12 after a baseline transvaginal ultrasound to measure endometrial thickness. The embryos were thawed and transplanted 4 days after the women received 400 mg of progesterone vaginal suppositories twice a day.

The SC-FET group C consisted of 40 women (SC-FET). The endometrial thickness was greater than 8 mm and the follicle had developed to 16–20 mm, at which point HCG was injected and the embryos were thawed and transferred 4 days later. The same attending physician performed a baseline transvaginal ultrasonography using a 7.5-MH transvaginal probe on all patients on the second or third days of their menstrual cycle to evaluate the endometrium and rule out the occurrence of an ovarian cyst.

The primary outcome was the detection of a fetal heartbeat by transvaginal ultrasonography during the sixth to seventh week of pregnancy.

The following are secondary outcomes: any pregnancy that is more than 12 weeks old and has an increased serum beta-hCG level 2 weeks following hCG treatment is considered an ongoing pregnancy. The rate of miscarriage is determined by transvaginal ultrasonography.

Table 1. Comparison between group I, group II, and group III regarding age, special habits, endometrial thickness, number and day of frozen embryos.

	Studied patients			F-test	P value
	Group I	Group II	Group III		
Age (years)				9.21	<0.001**
Mean ± SD	29.20 ± 4.65	24.77 ± 4.38	26.60 ± 4.25		
Range	20.00–37.00	18.00–33.00	20.00–34.00		
	$P_1 = 0.00, P_2 = 0.013, P_3 = 0.081$				
Special habits [n (%)]				16.59	<0.001**
No	31 (77.50)	39 (97.50)	24 (60)		
Passive smoker	9 (22.50)	1 (2.50)	16 (40)		
Endometrial thickness				3.42	0.036*
Mean ± SD	9.20 ± 1.07	9.37 ± 1.15	9.80 ± 0.94		
Range	7.00–11.00	7.00–11.00	8.00–11.00		
	$P_1 = 0.460, P_2 = 0.012*, P_3 = 0.074$				
No. of frozen embryos				9.91	<0.001**
Mean ± SD	4.32 ± 2.99	2.62 ± 1.33	2.55 ± 1.22		
Range	1.00–11.00	1.00–6.00	1.00–7.00		
	$P_1 = 0.00*, P_2 = 0.00*, P_3 = 0.868$ (NS)				
Day of frozen embryos				4.33	0.015*
Mean ± SD	3.95 ± 0.87	3.40 ± 0.77	3.70 ± 0.85		
Range	3.00–5.00	3.00–5.00	3.00–5.00		
	$P_1 = 0.004, P_2 = 0.184, P_3 = 0.112$				

F-test, analysis of variance F-test.

*Significant.

2.5. Statistical analysis

To tabulate and analyze our data, we used MICROSOFT EXCEL 2019 and SPSS v. 21 (SPSS Inc., Chicago, Illinois, USA). In the statistical study, descriptive and analytical tests were used. Descriptive terms include percentage (percentage), mean, and SD. Two examples of analytical tests are the χ^2 and analysis of variance F-tests. Statistical

significance is defined as a P-value of less than 0.05.

3. Results

With a mean age of 29.20 ± 4.655 years, group I had a statistically significant increase in age, as seen in Table 1. Furthermore, there was a statistically significant difference in special habits across the tested groups. Group-II participants did not smoke

Table 2. Comparison between the studied groups regarding duration, types, and causes of infertility.

	Studied patients			χ^2 -test	P value
	Group I (N = 40) [n (%)]	Group II (N = 40) [n (%)]	Group III (N = 40) [n (%)]		
Duration of infertility (years)				22.99	<0.001**
Mean ± SD	6.47 ± 2.68	6.77 ± 2.58	3.52 ± 1.73		
Range	1.00–11.00	1.00–11.00	1.00–8.00		
					$P_1 = 0.572, P_2 = 0.00, P_3 = 0.00$
Types of infertility				0.71	0.702 (NS)
Primary					
No	10 (25)	7 (17.50)	8 (20)		
Yes	30 (75)	33 (82.50)	32 (80)		
Secondary				4.81	0.090 (NS)
No	27 (67.50)	35 (87.50)	32 (80)		
Yes	13 (32.50)	5 (12.50)	8 (20)		
Causes of infertility				4.62	0.099 (NS)
Male					
No	11 (27.50)	18 (45)	20 (50)		
Yes	29 (72.50)	22 (55)	20 (50)		
Female				5.26	0.261 (NS)
No	27 (67.50)	18 (45)	20 (50)		
Tubal	6 (15)	8 (20)	6 (15)		
Ovarian	7 (17.50)	14 (35)	14 (35)		

*Significant.

Table 3. Comparison between the studied groups regarding hormonal profile and semen analysis.

Hormonal profile	Studied patients [n (%)]			F-test	P value
	Group I (N = 40)	Group II (N = 40)	Group III (N = 40)		
FSH				2.755	0.068 (NS)
Mean ± SD	6.17 ± 2.86	8.26 ± 7.57	5.97 ± 2.16		
Range	1.70–13.50	3.10–33.40	2.70–11.70		
	$P_1 = 0.056, P_2 = 0.851, P_3 = 0.036$				
LH				5.327	0.006*
Mean ± SD	3.83 ± 1.93	5.81 ± 3.75	5.83 ± 3.45		
Range	0.99–6.70	2.10–15.30	1.30–14.30		
	$P_1 = 0.006, P_2 = 0.005, P_3 = 0.978$				
PRL				8.641	<0.001**
Mean ± SD	19.28 ± 11.59	27.61 ± 14.31	17.75 ± 7.14		
Range	6.30–58.10	1.10–58.00	1.00–28.40		
	$P_1 = 0.001, P_2 = 0.551, P_3 = 0.00$				
E2				9.752	<0.001**
Mean ± SD	34.50 ± 14.66	36.68 ± 17.66	57.17 ± 37.39		
Range	6.98–66.70	4.00–74.00	27.00–200.00		
	$P_1 = 0.701, P_2 = 0.00, P_3 = 0.00$				
TSH				1.397	0.267 (NS)
Mean ± SD	2.33 ± 1.26	2.07 ± 1.19	2.51 ± 1.24		
Range	0.13–5.60	0.59–4.60	0.55–5.90		
	$P_1 = 0.347, P_2 = 0.495, P_3 = 0.106$				
AMH				2.397	0.077 (NS)
Mean ± SD	1.81 ± 0.94	2.05 ± 2.08	2.67 ± 2.12		
Range	0.50–4.40	0.32–8.10	0.60–8.00		
	$P_1 = 0.547, P_2 = 0.036, P_3 = 0.131$				
Semen volume				2.618	0.077 (NS)
Mean ± SD	2.53 ± 1.18	2.66 ± 1.11	3.14 ± 1.44		
Range	0.50–6.00	0.50–5.00	1.00–6.00		
	$P_1 = 0.631, P_2 = 0.031, P_3 = 0.092$				
Total count				4.208	0.017*
Mean ± SD	18.92 ± 17.86	35.82 ± 35.43	32.55 ± 26.77		
Range	1.00–50.00	1.00–95.00	2.00–100.00		
	$P_1 = 0.007, P_2 = 0.029, P_3 = 0.597$				
Total motility of sperms				3.673	0.028*
Mean ± SD	35.27 ± 21.17	47.87 ± 30.57	48.62 ± 21.33		
Range	1.00–80.00	5.00–90.00	10.00–80.00		
	$P_1 = 0.025, P_2 = 0.017, P_3 = 0.892$				
Immotile sperm				4.415	0.014*
Mean ± SD	66.00 ± 21.31	52.12 ± 30.57	51.737 ± 21.33		
Range	20.00–90.00	10.00–95.00	20.00–90.00		
	$P_1 = 0.014, P_2 = 0.09, P_3 = 0.983$				
Abnormal forms				7.254	<0.001**
Mean ± SD	98.95 ± 0.93	94.85 ± 6.02	95.92 ± 6.14		
Range	97.00–100.00	85.00–100.00	80.00–100.00		
	$P_1 = 0.00, P_2 = 0.008, P_3 = 0.338$				

AMH, anti-Müllerian hormone; FSH, follicle stimulating hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone.

Table 4. Comparison between the studied groups regarding basic ultrasound.

Basic US	Studied patients [n (%)]			χ^2 -test	P value
	Group I (N = 40)	Group II (N = 40)	Group III (N = 40)		
Uterine position				1.385	0.500 (NS)
RVF	7 (17.50)	5 (12.50)	9 (22.50)		
AVF	33 (82.5)	35 (87.50)	31 (77.5)		
Endometrial polyp				NA	–
No	40 (100)	40 (100)	40 (100)		
Ovarian cyst				3.158	0.206 (NS)
No	40 (100)	37 (92.5)	37 (92.5)		
Polycystic ovaries	0	3 (7.5)	3 (7.5)		

Table 5. Comparison between the studied groups regarding transferred embryos, embryo grade, and embryo stage.

	Studied patients [n (%)]			χ^2 -test	P value
	Group I (N = 40)	Group II (N = 40)	Group III (N = 40)		
Transferred embryos				1.054	0.352 (NS)
Mean \pm SD	2.30 \pm 0.56	2.20 \pm 0.69	2.40 \pm 0.59		
Range	1.00–3.00	1.00–3.00	1.00–3.00		
Embryo grade				1.920	0.383 (NS)
1.00	24 (60)	20 (50)	26 (65)		
2.00	16 (40)	20 (50)	14 (35)		
Embryo stage				1.067	0.587 (NS)
I	12 (30)	8 (20)	10 (25)		
II	28 (70)	32 (80)	30 (75)		

in the majority (97.50%). In addition, group III's endometrial thickness was significantly larger (9.80 ± 0.94) than the other groups ($P = 0.036$). Compared with the other groups, group I had a much higher number and day of frozen embryos ($P < 0.001$ and 0.015) (Table 2).

This table reveals that the duration of infertility in group II was substantially longer than in groups I and III ($P 0.001$). In terms of the types and causes of infertility, there was no statistically significant difference between the analyzed groups, although there was a statistically significant difference in terms of the types and causes of infertility.

Between the groups studied, there was no statistically significant difference. While luteinizing hormone (LH) was significantly higher ($P = 0.006$) in the stimulated group than in the other groups. In addition, there was a statistically significant increase in immotile sperms in the natural group ($P = 0.014$). Group I had considerably lower total sperm count and motility than the other groups (Table 3).

In terms of patient ultrasonography, there was no significant difference between the studied groups ($P > 0.05$) (Table 4).

In terms of transferred embryos, embryo grade, and embryo stage, there was no significant difference between the study groups ($P > 0.05$) (Table 5).

As seen in Table 6, the majority of women in groups I and II had negative pregnancy outcomes (45 and 42.5%). The other half of group III did not have a clinical pregnancy, while half of group III did (50%), despite the fact that there were no statistically

significant differences in pregnancy outcomes between the two groups.

4. Discussion

When compared with the other groups, we discovered that group II had a statistically significant increase in endometrial thickness. El-Toukhy et al. [10] discovered that cycles with an endometrial thickness of 9–14 mm had significantly higher LBR (25 vs. 14%, $P = 0.002$) than cycles with an endometrial thickness of 7–8 mm. Bu and Sun [11] found that endometrial thickness between 9 and 14 mm on transfer day was associated with significantly better LBR compared with 8 mm after adjusting for age, BMI, baseline follicle stimulating hormone (FSH), FET protocol, and number of embryos transferred. Furthermore, our findings differed from those of others. The letrozole group had a lower endometrial thickness (9.11.6 mm) than the artificial group (9.91.7 mm), according to Labrosse et al. [12]. The direct aromatase antagonistic activity of letrozole prevents testosterone from being converted to estrogen, resulting in reduced serum estrogen and endometrial thickness. In contrast to our findings, Hosseini et al. [13] found no statistically significant differences between the NC-FET and AC-FET groups in endometrial thickness, average number of transplanted embryos, or embryo grade. In addition, Wright et al. [9] demonstrated that the endometrial thickness in ACs was 8.71.1 mm, while the endometrial thickness in SCs was 8.71.0 mm.

Table 6. Comparison between the studied groups regarding pregnancy outcome.

	Studied patients [n (%)]			χ^2 -test	P value
	Group I (N = 40)	Group II (N = 40)	Group III (N = 40)		
Pregnancy outcome				2.508	0.643 (NS)
Negative	18 (45)	17 (42.50)	14 (35)		
Chemical pregnancy	6 (15)	9 (22.50)	6 (15)		
Clinical pregnancy	16 (40)	14 (35)	20 (50)		

Endometrial thickness did not differ significantly between these groups. However, there was a significant difference in the proportion of patients with endometrial thickness less than 8 mm between artificial and SCs: 5% in ACs versus 27% in SCs ($P = 0.01$). The huge number of people with thin endometrial thickness could explain the wide range of findings (<7 mm). Study-population group 1 had insufficient individuals to make a conclusive statement.

Group I had a much larger number and day of frozen embryos than the other groups, according to the current study. The number of FET conducted has been continuously growing over the previous few years, according to De Geyter et al. [14], which is consistent with our findings. The usage of FET has increased as a result of significant breakthroughs in cryopreservation, as well as positive pregnancy and neonatal results [15]. More frozen embryos will be accessible for FET cycles in the future as the number of elective single-embryo transfers increases. In contrast, Hosseini et al. [13] reported no significant changes in the average number of transferred embryos between the NC-FET and AC-FET groups. According to Labrosse et al. [12], no difference was found in the total number of embryos between the studied groups.

The duration of infertility in group II was found to be significantly longer than in the other groups in this study. While there was no significant difference in the types and causes of infertility between the groups studied, there was a significant difference in the types and causes of infertility. This backs up Hosseini and colleagues findings that found no significant differences between the two groups in terms of infertility type and causes. There was no significant difference in infertility status across the groups assessed, according to Labrosse et al. [12]. The majority of patients were treated for primary infertility (56.8%). Also, Groenewoud et al. [16] found that 383 of the patients were largely infertile (39.9%). While Hosseini et al. [13] found no significant differences in the duration of infertility among NC-FET and AC-FET groups.

In our study, hormonal profiles did not differ across the studied groups, but LH was significantly higher in the stimulated group than other groups. This agreed with Yu et al. [17], who found that serum FSH and serum total T differed among the two groups. Also, Hosseini et al. [13] reported no differences in FSH and LH among NC-FET and AC-FET groups. Our findings are similar with Aziz et al. [18], who found that estradiol levels were higher in ACs than in natural cycles. Embryo's grade or stage did not differ among the tested groups. Similarly, Aziz et al. [18] found transferring three embryos of

roughly the same size, all of which were grade A, and transferring them on day three for all patients aimed to neutralize all factors that could affect clinical outcomes. Yu et al. [17] also found that the number of transplanted embryos was not significantly different among artificial and HMG cycles.

Our research reported that most of groups I and II had a bad pregnancy result (45 and 42.5%). While half of group III had a clinical pregnancy. Also, Aziz et al. [18] found that group I had chemical and clinical pregnancy higher than group II, with no significant difference. Other studies found no differences in clinical pregnancy or live births among natural and ACs [19,20], which is consistent with our findings. Furthermore, clinical pregnancy did not differ between the ACs with and without GnRH [7,21]. Another study by Labrosse et al. [12] reported no difference in pregnancy or live-birth rates between MNC and STC.

Some researchers have discovered a link between ACs and the rates of preclinical and clinical pregnancy loss, which contradicts our findings [6]. As a result, given the lack of a clear benefit between one method and another in terms of pregnancy outcomes, other variables should be considered when choosing a strategy to prepare the endometrium prior to FET. Some NC-FET women saw a surge in LH on the day of their hCG treatment, but their pregnancy rates dropped drastically. CPRs appeared to be higher overall in this study, which could be due to embryo self-selection, with only day-3 embryos being transplanted, at least in part.

4.1. Conclusion

In women with regular menstrual cycles, natural, artificial, and SCs, all had similar pregnancy outcomes, including pregnancy rates, implantation rates, and cancelation rates, however, SCs had a greater incidence of endometrial thickness, semen volume, and pregnancy rates. NC-FET, on the other hand, is preferred since it does not require medication, is less expensive, and has less adverse effects.

Conflicts of interest

There are no conflicts of interest.

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