The Egyptian Journal of Hospital Medicine (July 2022) Vol. 88, Page 4057- 4061

Artificial Versus Modified Natural Cycles for Endometrial Preparation for Frozen-Thawed Embryo Transfer

Magdi Ragab Elsayed, Walid Mohamed Sayed Ahmed Elnagar,
Hanan Abraheem Almahtot Imbayyah*, Shahenda Ahmed Elsayed Ibrahim
Department of Obstetrics and Gynecology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Hanan Abraheem Almahtot, **Mobile:** (+20)1159698272,
E-mail: hananibrahimimbiya2005@gmail.com

ABSTRACT

Background: Improvements in IVF have led to an increased number of embryos not available for immediate transfer due to concern about multiple pregnancies. Cryopreservation of supernumerary embryos with subsequent frozen–thawed embryo transfer (FET) is an excellent solution to surplus embryos and has become a common practice in infertility centers.

Objectives: The aim of the current work was to evaluate the success rate of hormonal replacement therapy (HRT) and modified natural cycle protocol in frozen–thawed embryo transfer (FET).

Patients and methods: Randomized controlled trial study was done at department of Obstetrics and Gynecology, Zagazig University and in a private Center in the period from January 2021 to March 2022. Included 84 women who underwent Frozen-thawed embryo transfer (FET). The women were divided into 2 groups; Natural cycle group included 42 women, 3 of them escaped from the study. Artificial cycle group included 42 women, 2 of them escaped from the study.

Result: This study showed that there were no statistically significant differences in the number of embryo thawing, the number of embryo transfers, the degree of embryos, as well as the rate of biochemical and clinical and continuous pregnancy among the studied groups.

Conclusion: It could be concluded that both modified natural and artificial cycle for endometrial preparation in frozen-thawed embryo transfer cycles appears to be equally successful about pregnancy rates.

Keywords: Endometrial preparation, Modified Natural Cycles, Frozen-thawed embryo transfer.

INTRODUCTION

In vitro fertilization (IVF) is a type of assistive reproduction technology (ART). In this procedure, eggs are taken from a woman's ovaries and fertilized with sperm. Known as an embryo, this fertilized egg is a cell. The embryo can subsequently be placed in a woman's uterus or preserved for later use [(1)].

Frozen-thawed embryo transfer (FET) is a procedure used for the storage and transfer of excess embryos obtained during IVF and ICSI cycles. Which prevents embryo waste [(2)]. The cumulative pregnancy rate of IVF/ICSI treatment is believed to be increased by the transfer of frozen thawed embryos that enables the excess embryos generated by IVF and ICSI to be stored and utilized later [(3)].

A progressive increase in FET cycles was observed in recent years ,due to limitations on the number of embryos to be transferred, also the use of agonist trigger in antagonist protocol and "freeze all" strategy in patients with high risk to develop ovarian hyperstimulation syndrome (OHSS), and transfer the embryos in subsequent FET cycle. FET is offered also in cases with late follicular progesterone rise, embryo-endometrial asynchrony, recently its use is extended to involve cycles with preimplantation genetic screening (PGS) or preimplantation genetic diagnosis (PGD). Similar live birth rates in FET have been observed when comparing to fresh cycles when frozen top-quality embryos are transferred [(4)].

In order to optimize pregnancy rates, adequate synchronization between the development of embryo and endometrium should be present. This can be achieved in various ways. Different endometrial preparation strategies have been described, however, there is still some controversy as to the ideal endometrial preparation protocol [(5)].

The aim of this study was to evaluate the success rate of hormonal replacement therapy (HRT) and modified natural cycle protocol in Frozen-thawed embryo transfer (FET).

PATIENT AND METHODS

Randomized controlled trial study was done at department of Obstetrics and Gynecology, Zagazig University and in a private Center in the period from January 2021 to March 2022. It Included 84 women who underwent Frozen-thawed embryo transfer (FET).

The women were divided into 2 groups; Natural cycle group included 42 women, 3 of them escaped from the study. Artificial cycle group included 42 women, 2 of them escaped from the study.

Inclusion criteria; Age from 20-37 years old. Women who were regularly menstruating with a cycle length of 21~35 days. Women who were undergoing in vitro fertilization (IVF)/ intra cytoplasmic sperm injection (ICSI) cycle.

Exclusion criteria: Congenital uterine abnormality or pathology either inborn or acquired. Presence of a hydro salpinx. Women who needed pre implantation genetic testing. Women who with recurrent miscarriages.

Received: 19/04/2022
Accepted: 16/06/2022

Women who with recurrent implantation failure. Chronic diseases which are not suitable for pregnancy. ICSI cycles with fresh or frozen testicular sperm extract (TESE) samples.

All the women in this study were subjected to full history taking including age, parity, duration of infertility, special habits of medical importance as smoking, medical diseases as diabetes mellitus, hypertension, cardiac diseases and history of previous Assisted reproductive technologies and the use of fertility drugs.

Endometrial preparations:

All participants were divided randomly (closed envelope) into modified natural group and the HRT cycle group according to the endometrial preparation protocols.

The primary outcome was to assess the best protocol for FET (modified natural cycle or hormonal replacement therapy (HRT) cycle regarding optimizing ongoing pregnancy rate in FET cycles. The secondary outcomes were biochemical pregnancy rate, clinical pregnancy rate, miscarriage rate and live birth rate.

Ethical consent:

An approval of the study was obtained from Zagazig University Academic and Ethical Committee. Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Data were analyzed using SPSS software (USA). The parametric data expressed as mean ± SEM. The statistical comparisons between different groups were carried out using unpaired Student's t-test for parametric data. Categorical data were represented by frequency and percentage, as well as was compared by chi square (X^2) and fisher exact (X^2) test. The level of significance was identified at $P<0.05$.

RESULT

Table 1; showed that there was no significant difference between the studied groups regarding age and BMI.

Table (1): Age and BMI among the studied groups

Variables	Natural Cycle (n=39)	Artificial Cycle (n=40)	t	P
Age (Years) Mean ± SD Median (Min-Max)	 30.2 ± 3.1 31 (22-35)	 30.4 ±2.9 31 (23-35)	t=0.28	0.78
BMI (kg/m^2) Mean ± SD Median (Min-Max)	 24.3 ± 2.4 24.1 (20.4-31.3)	 24.9 ± 2.7 24.3 (20.4-30.8)	t=1.07	0.28

Data are represented as mean ± SD. Data analyzed using unpaired student t test.

Table 2; showed that there was no significant difference between the studied groups regarding duration of infertility, thickness of endometrium, type and cause of infertility.

Table (2): Duration, type and cause of infertility among the studied groups

Variables	Natural Cycle (n=39)	Artificial Cycle (n=40)	t / X^2	P
Duration of infertility (Years) Mean ± SD Median (Min-Max)	 3.7 ± 1.3 3 (2-6)	 3.9 ± 1.3 4 (2-6)	t=0.58	0.56
Thickness of endometrium (mm) Mean ± SD Median (Min-Max)	 9.28 ± 1.14 9 (8-12)	 9.25 ± 1.12 9 (8-12)	t=0.12	0.9
Type of infertility Primary Secondary	 24 (61.5%) 15 (38.5%)	 28 (70%) 12 (30%)	X^2= 0.62	0.42
Cause of infertility Male factor Female factor Mixed Unexplained	 16 (41.1%) 14 (35.9%) 4 (10.2%) 5 (12.8%)	 15 (37.5%) 14 (35%) 6 (15%) 5 (12.5%)	X^2= 0.42	0.93

Data are represented as mean ± SD or number (%). Data analyzed using unpaired student t test or chi square (X^2).

Table 3; showed that there was no significant difference between the studied groups regarding number of embryos thawing, number of embryos transfer and embryo grade.

Table (3): Number of embryos at thawing, number of embryos transfer and embryo grade among the studied groups

Variables	Natural Cycle (n=39)	Artificial Cycle (n=40)	t / X^2	P
Number of embryos at thawing Mean ± SD Median (Min-Max)	3.48 ± 0.82 3 (2-5)	3.5 ± 0.84 3 (2-5)	t= 0.06	0.94
Number of embryos transfer Mean ± SD Median (Min-Max)	2.35 ± 0.53 2 (1-3)	2.47 ± 0.5 2 (2-3)	t=0.98	0.32
Embryo Grade I II	26 (66.6%) 13 (33.4%)	24 (60%) 16 (40%)	X^2= 0.37	0.53

Data are represented as mean ± SD or number (%). Data analyzed using unpaired student t test or chi square (X^2) or Fischer exact test #.

Table 4; showed that there was no significant difference between the studied groups regarding biochemical, clinical and ongoing pregnancy rate.

Table (4): Biochemical, clinical and ongoing pregnancy rate among the studied groups.

Variables	Natural Cycle (n=39)	Artificial Cycle (n=40)	X^2	P
Biochemical Pregnancy Rate Yes No	19 (48.7%) 20 (51.3%)	18 (45%) 22 (55%)	0.11	0.74
Clinical Pregnancy Rate Yes No	16 (41%) 23 (59%)	16 (40%) 24 (60%)	0.009	0.92
Ongoing Pregnancy Rate Yes No	14 (35.8%) 25 (64.2%)	13 (32.5%) 27 (67.5%)	0.1	0.75

Data are represented as number (%). Data analyzed using chi square (X^2).

Table 5; showed that there was no significant difference between the studied groups regarding miscarriage and live birth rate.

Table (5): Miscarriage and live birth rates among the studied groups

Variables	Natural Cycle (n=39)	Artificial Cycle (n=40)	X^2	P
Miscarriage Rate Yes No	6 (15.4%) 33 (84.6%)	6 (15%) 34 (85%)	X^2= 0.002	0.96
Live Birth Rate Yes No	13 (33.4%) 26 (66.6%)	12 (30%) 28 (70%)	X^2= 0.1	0.75

Data are represented as number (%). Data analyzed using chi square (X^2).

DISCUSSION

Our results demonstrated that there were no significant differences between the studied groups regarding age and BMI.

In the present study, there were no significant differences between the studied groups regarding number of embryos, number of embryos transfer and embryo grade.

Also, **Hatoum *et al.*** [6] demonstrated that there was no significant difference in the number of embryos transferred between the studied groups.

Also, there were no significant differences between the studied groups regarding biochemical, clinical, and ongoing pregnancy rate.

In agreement with our study, a recent meta-analysis could not find robust data on live birth, ongoing pregnancy and clinical pregnancy rates to favor stimulated or artificial endometrial preparation protocols prior to FET [7].

Vaginal absorption of exogenous progesterone is variable, and the peak serum progesterone level is reached 6 to 8 h after administration. This means that the uterine peak was reached even earlier. The LH activity provided by HCG after stimulation in the presence of a corpus luteum leads to more constant circulatory concentration of progesterone. These arguments are in favour of a local CL production of progesterone **Andersen *et al.*** [8] without exceeding the level of 20 ng/dl which is associated with an increased risk of abortion [9].

When exogenous progesterone is administered intramuscularly or subcutaneously and even vaginally, there is variable, limited endometrial exposure with earlier uterine peak, leading to less synchronization between embryo and endometrial development [10].

The results showed that there were no significant differences between the studied groups regarding miscarriage and live birth rate.

In agreement with our study, **Agha-Hosseini *et al.*** [11] demonstrated that there were no significant differences between the two cycle types in terms of chemical, clinical, and ongoing pregnancy rates, miscarriage and live birth rates.

In **Groenewoud *et al.*** [12] randomized controlled trial, artificial cycles were not found to be superior to modified natural cycles in terms of clinical pregnancy and live birth rates. A retrospective study by **Jouan *et al.*** [13] demonstrated the superiority of clomiphene citrate cycles over artificial cycles—notably with higher overall pregnancy rates (24.3 vs. 20.8%, respectively). Clomiphene citrate cycles were also associated with a significantly higher ongoing pregnancy rate (18.6%). This can be explained by that clomiphene citrate was known to decrease the transfer cancellation rate and to improve the follicular phase quality. However, this molecule is a selective estrogen-receptor modulator that inhibits estradiol-induced cellular-proliferation in the endometrium, resulting in reduced thickness in mid-luteal phase [13].

Eight retrospective studies, including 8152 cycles, and one randomized controlled study including 111 cycles were investigated in the literature, no differences were observed between the natural cycles and artificial cycles with regard to clinical pregnancy (OR 1.2, 95% CI 0.86–1.6), ongoing pregnancy (OR 1.2, 95% CI 0.95–1.5), or live births (OR 1.2, 95% CI 0.93–1.6) [14]. In four studies comparing natural cycles with GnRH agonist-supported artificial cycles, clinical pregnancy and live births did not differ [15].

CONCLUSION

It could be concluded that both modified natural and artificial cycle for endometrial preparation in frozen-thawed embryo transfer cycles appears to be equally successful with regard to pregnancy rates.

RECOMMENDATIONS

Larger randomized controlled studies would be needed to confirm the validity of our results. Further clinical trials are required to illuminate the clinical and biochemical benefits of modified natural and artificial-FET.

Conflict of interest: The authors declare no conflict of interest.

Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution: Authors contributed equally in the study.

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