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RESEARCH ARTICLE

Natural cycle versus new artificial protocol in frozen embryo transfer

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Abstract

Background: preparation of the endometrium for better receptivity and implantation is important step for high pregnancy rate in frozen cycle embryo transfer for ICSI procedures. Many methods known for preparation but which the best still a debatable issue. The present study is represent a fixed dose sequential artificial cycle.

Material and methods: 80 cases scheduled for frozen cycle transfer divided into two groups group one (natural cycle) monitored only by ultrasound and when leading follicle reached 20mmhCG injection given and embryos transferred .group two received progynova2 tablets twice per daily for 8 days from the first day menses then uterogestan tablets added three times per day for 5 days the embryo transfer done at the fourteenth day. Quantitative hCG done after 14 days.

Results: On comparing endometrial thickness and pregnancy rate among studied groups group two (augmented fixed cycle) showed pregnancy rate 62.25% compared to 37.5% in group one with p value <0.02(statistically significant difference as shown in (table 2).

Conclusion: the new method of endometrial preparation for frozen embryo transfer is better than natural cycle preparation

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INTRODUCTION

In Vitro Fertilization (IVF) or Intra Cytoplasmic Sperm Injection (ICSI) treatment cycles often produce more embryos than can be transferred during the fresh treatment cycle. Moreover, in some patients embryo transfer is postponed for medical reasons (e.g. ovarian hyperstimulation syndrome).

Cryopreservation of these embryos provides both physicians and patients a safe, successful and cost-efficient option [1-3].

Single embryo transfer strategies in IVF and IVF -ICSI programs have increased the importance of successful frozen thawed embryo transfer (FET) programs. Synchronization between the endometrial development and the embryo is mandatory for better endometrial receptivity and implantation [4-7].

In natural cycle FET (NC-FET) planning of embryo thawing and transfer requires the identification of a period of optimal receptivity. Window of implantation starts shortly after ovulation usually from day 22 to day 24. [4-7].

Planning NC-FET can either be done based on recognition of the LH surge that precedes ovulation(using serum or urine LH monitoring) or by triggering ovulation.

Using modified NC-FET, the development of the dominant follicle is closely monitored by regular ultrasonic evaluation. On reaching a diameter of 16-20 mm human chorionic gonadotrophin (hCG) is administered and ovulation takes place approximately 36 h later.

Embryo thawing and transferring can be planned accordingly. Despite ultrasonic monitoring, spontaneous ovulations do occur. In such an event the start of the window of implantation cannot be estimated accurately.

In NC-FET cycles, 5-6% of all patients have insufficient development of the dominant follicle and/or endometrium thickness and treatment has to be cancelled however, a clear advantage of NC-FET is the fact that it does not require patients to take medication for several weeks. [8].

In summary, NC-FET has the advantage of not requiring medication but this advantage is balanced against the need for frequent ultrasonic evaluation of the dominant follicle, the risk of unexpected ovulation and the risk of insufficient development of the endometrium and/or dominant follicle.

Due to these factors NC-FET is more difficult to plan.

During AC-FET patients start with daily estrogens which are supplemented with progesterone when the endometrial thickness is considered sufficient. Patients have to take these drugs for several weeks. The main advantage of this treatment is that it requires little ultrasonic monitoring and therefore is more easily scheduled placing less burden on both patients and doctors agenda's.

Supplementing estrogen reduces cancellation rates due to insufficient endometrium thickness compared to NC-FET. The main disadvantages of AC-FET are possible side-effects and higher risk of thrombo-embolic events [10, 11].

Subjects and methods

Objectives: to compare two different methods for endometrial preparation in frozen cycle embryo transfer

Rationale and hypothesis: natural cycle preparation is under endogenous hormonal milieu of the patients and may show elevations and depressions so making endometrium unstable.

Setting: Elshorok fertility Centre in Benha –Qualubia –Egypt under supervision of Dr Ahmad Youssef

Sample size: 80 patients undergoing frozen cycle embryo transfer divided into two groups according to the method of endometrial preparation.

Method of randomization: randomization tables generated by software called randlist

The inclusion criteria required the subjects to:

1. Age younger than 40 years.
2. High-quality frozen embryos.

The exclusion criteria included:

1. a history of endocrine diseases.(like uncontrolled diabetes mellitus)
2. cardiovascular, renal and liver diseases.(chronic disease with organ failure)

Patients groups:

Group one (natural cycle group): forty patients

Group two (augmented cycle group): forty patients

Intervention:

Group one (natural cycle group):

Patients allocated to intervention 1 will undergo their FET in a natural cycle. Starting on day 8, 1 or 12 of their cycle regular ultrasonic evaluation of the endometrium thickness and mean diameter of the dominant follicle is performed. When the endometrium is 8mm or more and the diameter of the dominant follicle is 16-20 mm ovulation is induced using hCG injection (pregnyl 5000 IE, MSD USA or ovitrelle 250 µgram, Serono Benelux bv, Germany). Thawing and transferring is performed subsequently. A maximum of two embryos will be transferred.

If during ultrasonic evaluation no follicle is visible ovulation is deemed to have occurred. In this event no thawing or transferring will take place.

Group two (augmented artificial group):

Patients commence oral estradiol (progynova, Bayer, Germany) 2 mg two tablets twice per day from the first day of menses for 8 days. At the eighth day, ultrasound evaluation done and if endometrial thickness reached 8mm micronized progesterone (utrogestan Besins International, Belgium) is added to the regime for 5 days then thawing and transferring is done at the fourteenth day. Two embryos grade one quality chosen for transfer.

Luteal support continued with the same regimen in addition to prontogest ampoules every day

Quantitative HCG done 14 days after transfer. Arranged ultrasound examination scheduled with patients after additional 14 days to document pregnancy state and number.

Outcome

In case BHCG was tested and proved to be positive, estradiol valerat and progesterone were continued until the 11th week of pregnancy. Then, four weeks after the embryo transfer, the number of gestational sacs was determined by vaginal ultrasound.

Results

The epidemiological data of patients showed no significant difference as shown in (table 1). basal FSH and LH showed insignificant difference. On comparing endometrial thickness and pregnancy rate among studied groups group two (augmented fixed cycle) showed pregnancy rate 62.25% compared to 37.5% in group one with p value <0.02 (statistically significant difference as shown in (table 2)

(Table 1) characteristics of patients at the beginning of the cycle

	GROUP ONE(natural cycle)	Group two (augmented artificial cycle)	P value
Infertility duration(months)	71	73	0.3
Age(years)	28	29	0.47
Basal FSH(IU/L)	5.4	5.6	0.4

(Table 2) endometrial thickness and pregnancy rate among groups

	Group one	Group two	P value
Endometrial thickness (Mean mm)	8	9.8	<0.0001
Chemical pregnancy	15(37.5%)	25(62.25%)	<0.02

Discussion

Optimization of embryo transfer for better pregnancy rate and outcome is the main goal of IVF specialists. Frozen cycle embryo transfer is a choice when cycle postponed for special conditions such as hyperstimulation syndrome .freeze/thaw cycles show significant improvement nowadays.

The challenge in the freeze/thaw cycle transfer is endometrial preparation for better receptivity and implantation. There are two ways for endometrial preparation; the first called natural cycle in which follicle growth monitored with ultrasound and when the leading follicle reached 18-20mm human chorionic gonadotropin (HCG) given then embryos thawed and transferred.

The drawback of this method is the hormonal fluctuation that can negatively affect the endometrium. Spontaneous unpredictable ovulation also occurred frequently and cancellation of the cycle is high

Despite ultrasonic monitoring, spontaneous ovulations do occur. In such an event the start of the window of implantation cannot be estimated accurately.

The second method called (conventional) artificial cycle preparation in which patients commence oral estradiol (progynova, Bayer, Germany) 2 mg three times daily from day one of the cycle. After 11, 12 or 13 days an ultrasound is performed. If no leading follicle is present and the endometrial thickness is ≥ 8 mm, micronized progesterone (utrogestan, Besins International, Belgium) is added to the regime and thawing and transferring is commenced 4 or 5 days later according to the stage of cryopreservation [20].

If the endometrial thickness is less than 8 mm, the progynova dose is raised to 2 mg 4 times daily for 7 days. After a week the endometrium is checked once again. When the endometrium thickness is >8 mm and no dominant follicle (≥ 14 mm) is present, utrogestan can be added and thawing and transferring is performed. If a follicle is visible during ultrasound, serum luteinizing hormone (LH) and progesterone levels are determined. If these are raised, (serum LH ≥ 13 E/l or progesterone ≥ 15 nmol/l) luteinization of the follicle is considered to have taken place and because of the associated diminished pregnancy rates, thawing and transferring will not be performed. (21-24)

In recent years several, retrospective, studies comparing live birth rates in both NC-FET and AC-FET have been published. Both Morovoz et al. and Chang et al. concluded that NC-FET results in higher pregnancy rates [12, 13]. However, in a retrospective analysis of 1677 FET cycles, Givens et al. observed no difference in pregnancy rates between NC-FET and AC-FET. Pregnancy rates did not differ significantly between both groups [14].

A recent Cochrane review on treatment regimes in FET concluded that current evidence does not demonstrate a significant difference in pregnancy rates between these methods of endometrial preparation. (19)

The new third method applied in this study is easy and simple and done with infrequent ultrasound monitoring. The endometrial thickness was better in group two than in group one (8 mm in group one versus 9.8 mm in group two) (table 2).

The advantage of the fixed protocol over the natural method were in many ways

1-the first advantage was the elimination of ovarian factors affecting the endometrium such as hormonal fluctuations.

2-second advantage was better endometrial thickness.

The pregnancy rate in group one was 62.25% in group two compared to 37.5% in group one with statistically significant difference (p value <0.02) table 2.

So the present study of frozen embryo transfer represented a new method with best results in terms of endometrial receptivity and implantation rate.

Conflict of interest

No conflict of interest to declare about this work.

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