



CLINICAL OUTCOME IN DIRECT VERSUS SUPPRESSED HRT FOR FROZEN EMBRYO TRANSFER CYCLES

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ABSTRACT

Aim: To evaluate the effect of Direct versus suppressed Hormone Replacement therapy (HRT) on clinical outcome in Frozen embryo transfer cycles (FET). **Material and methods:** **Study design:** Retrospective observational study. A Total of 101 patients included in the study from August 2016 to Dec 2017. All patients were divided into two groups, Direct HRT group A (n-45) and Suppressed HRT group B (n-56). **Outcome:** Treatment duration and clinical outcome like implantation rate, chemical and Clinical pregnancy rates, Miscarriage rate. **Results:** All Suppressed HRT patients required significantly longer days of preparation (18.98 ± 4.56 versus 16.93 ± 2.12 ; $p < 0.05$) in comparison to Direct HRT group. Higher ongoing pregnancy rate in suppressed HRT compared to direct HRT (42.8% versus 31.1% ; $p = 0.48$) However, There were no statistical differences in clinical outcomes and cycle characteristics between the two groups. **Conclusions:** Direct HRT, a method of Artificial FET is equally beneficial in FET cycle along with suppressed HRT as it has shorter duration of preparation and is more patient friendly.

KEYWORDS: Hormone Replacement therapy, Frozen embryo transfer.

INTRODUCTION

The first successful pregnancy from a frozen-thawed embryo transfer (FET) was reported in 1983. More than three decades have passed, and significant changes have been introduced into our clinical practice. Developments and improvements in cryopreservation methods have helped improve the efficiency of in vitro fertilization (IVF).^[1-4] These quantifiable modifications have led to vitrification being introduced as the main cryopreservation technique in almost every laboratory in the world.

More efficient cryopreservation strategies (i.e. vitrification) and reassuring safety data have progressively increased the use of frozen embryo transfer, namely beyond cases with a surplus amount of good quality embryos following an elective single

embryo transfer policy. The use of an antagonist protocol with agonist triggering followed by a 'freeze- all' strategy and transfer of the embryo(s) in a subsequent FET cycle is a promising option with high live birth rates. Although elective embryo cryopreservation was mainly developed for patients with an increased risk of developing ovarian hyper-stimulation syndrome, its use has now been also extended to cycles with pre-implantation genetic diagnosis/screening, late- follicular progesterone elevation and embryo-endometrial asynchrony. Moreover, there is an ongoing debate whether frozen embryos transferred in a 'more physiologic' non-stimulated endometrium, may not only result in higher pregnancy rates, but also potentially decrease maternal and neonatal morbidity.^[5]

An important factor for implantation in frozen-thawed

embryo transfer (FET) is exact synchronization between endometrial maturation and embryo development.^[6-7]

Frozen Embryo Transfer (FET) cycle is performed using different cycle regimens: Frozen/thawed embryos may be transferred into the uterus in a natural cycle, stimulated cycle and a hormone replacement cycle(HRT). The advantages of Direct HRT cycles are it is more patient friendly as fear of cancellation can be drastically reduced and patient anxiety can be minimized. Less frequent monitoring in terms of ultrasonography and hormonal profile is required and can be given even in irregular cycles.^[8] Whereas, treatment with a GnRH agonist is costly and there is a risk of hypoestrogenic side effects before hormonal replacement, and the preparation is lengthy.^[9]

AIM: To evaluate the effect of Direct versus suppressed Hormone Replacement therapy (HRT) on clinical outcome in Frozen embryo transfer cycles (FET).

OBJECTIVE: To Observe the Ongoing/clinical pregnancy rate, Implantation Rate, Miscarriage rate, Total Days of stimulation.

MATERIALS AND METHODS

This is a Retrospective observational study. All patients undergoing their first FET cycles during the period between August 2016-September 2017 were included in the study. Women who have associated disorders which can affect pregnancy like endometriosis, fibroid, Adenomyosis, TB endometrium were excluded. On Retrospective analysis after considering inclusion and exclusion criteria 101 Patients who have undergone FET cycles were considered under the study. These patients were divided into Group A including 45 patients undergoing direct HRT and Group B including 56 patients undergoing FET cycle after Pituitary suppression.

Protocol for Endometrial Preparation

Group A patients underwent HRT from the day 2 of a spontaneous menstrual cycle. Group B Patients received Inj. Luprolide acetate 3.75mg intramuscularly on 15th

day of oral contraceptive pill and HRT was started after withdrawal bleeding. HRT in both the groups was started only after a baseline ultrasound to confirm that there is no ovarian cyst or dominant follicle. Patients in both groups were prescribed T. Estradiol Valerate 4mg/day for 5 days and increased to 6mg/day thereafter. On day 11 of HRT trans-vaginal ultrasound was performed in all patients in both the groups. The dose of estradiol valerate was adjusted according to the Endometrial thickness(ET) until it reached an optimal value of 8mm. Progesterone replacement was done for days equal to day on which embryos were frozen and on the following day embryo transfer was done (p+day of embryo). Serum β hcg was performed 14 days preceding embryo transfer. Serum β hCG values more than 5mIU/ml was considered as positive test for pregnancy. In Patients with positive serum Beta-hCG, same dose micronized progesterone and estrogen were continued till 12 weeks. Trans-vaginal ultrasonography was done after 2 weeks of serum beta hCG estimation to confirm site of pregnancy, number of sacs and cardiac activity.

Statistical analysis

The collected data were analyzed with SPSS statistics software 23.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & SD were used continuous variables. To find significant difference between the bivariate samples in independent groups the unpaired t-test was used. To find the significance in categorical data Chi-Square test and Fishers exact test was used. In all above statistical tools the probability value 0.05 is considered as significant level.

RESULTS

There were no significant differences in Demographic characteristics and Indications of IVF/ICSI between direct cycle and suppressed cycles (Table-1&2). In FET cycle characteristics the total days of HRT and Endometrial thickness were slightly higher in suppressed cycles and was statistically significant ('p' value < 0.05) depicted in Table-3. Number of embryo's transferred in both the groups were similar.

Table 1: Demographic characteristics.

Demographic Characteristics		Direct Cycle (n=45)	Suppressed Cycles (n=56)	'p' Value
AGE (years)		31.31±4.83	30.95±3.763	0.18
BMI(kg/m ²)		24.16±2.24	25.66±2.94	0.06
DURATION OF INFERTILITY(years)		6.31±1.97	5.59±1.91	0.55
TYPE OF INFERTILITY	PRIMARY	35(77.8%)	42(75%)	0.74
	SECONDARY	10(22.2%)	14(25%)	0.74

Table 2: Indication of Ivf/Icsi.

Indication	Direct(n=45)	Suppressed(n=56)	'p' value
Male factor	10(22.2%)	13(23.3%)	0.89
Female factor	23(51.1%)	29(51.7%)	0.95
Combined factor	12(26.7%)	14(25%)	0.84

Table 3: FET cycle characteristics.

Fet cycle Characteristics	Direct Cycle (n=45)	Suppressed Cycle (n=56)	'p' Value
Total days of HRT	16.93±2.12	18.98±4.56	0.006
Endometrial thickness (mm) on the day of progesterone	9.64±1.44	10.69±1.41	0.0004
Number of embryos transferred	2.89±0.73	2.78±0.7	0.42

Table 4: Clinical outcomes.

Clinical outcomes	Direct Cycle (n=45)	Suppressed Cycle (n=56)	'p' value
Pregnancy Rate	18(40%)	29(51.7%)	0.56
Biochemical Pregnancy	2(4.44%)	2(3.57%)	0.82
Implantation Rate	32/115(27.8%)	48/141(34.04%)	0.50
Clinical Pregnancy Rate	16(35.5%)	27(48.2%)	0.14
Miscarriage Rate	2(4.44%)	3(5.35%)	0.91
Ongoing pregnancy Rate	14(31.1%)	24(42.8%)	0.48

Clinical outcomes were comparable between two groups and none reached statistical significance.

DISCUSSION

Artificial cycle FET has been traditionally increased after suppression to prevent interference from endogenous hormones. But the duration of treatment and Hypo-estrogenic symptoms were more in suppressed cycle. Hence to reduce the duration and hypo-estrogenic symptoms, Direct HRT has been tried.

In our study we have evaluated the outcome of direct versus suppressed HRT in Frozen embryo transfer cycles. None of the patients ovulated during preparatory phase of HRT cycles.

In our study ongoing pregnancy rate in direct HRT cycles was 31.1% and in suppressed HRT cycles is 42.8% which is higher than the direct HRT cycle, but statistically not significant ($p=0.48$). To prove the statistical significance with this pregnancy rate we need larger study with sample size of 532 (266 in each group, 0.5 α error and 80% power). In study done by AzimiNeeko et al clinical pregnancy rate was slightly higher in direct HRT compared to suppressed cycle (Direct 30.1% versus suppressed 22.6%). Mean Implantation rate in direct versus suppressed HRT was 27.8% versus 34.04% and Miscarriage rate was 4.44% versus 5.35% respectively and none reached statistical significance.

In addition, During our study we have observed that when compared to Direct HRT, suppressed HRT was associated with longer days of stimulation. Mean duration of HRT in Direct versus suppressed cycle (16.93±2.12 days vs 18.98±4.56 days). Mean Endometrial thickness in Direct versus suppressed cycles (9.64±1.44mm vs 10.69±1.41mm).

There is limited body of evidence of data in the literature on Direct versus suppressed HRT cycles. Most of the studies in the literature compared Natural cycles and

artificial cycles with regard to clinical pregnancy, ongoing pregnancy or live births.^[10-13] Our findings on clinical outcomes were correlating with the study conducted by AzimiNeeko et al.^[1] Endometrial thickness in both groups of our study was more than 8mm. In study conducted by Son et al^[14] average endometrial thickness in pregnant and non-pregnant groups was 9.15mm and 9.31mm. Clinical outcomes were comparable between both the groups and none reached statistical significance like our study. Son et al^[14] concluded that Endometrial thickness is not an effective predictor of pregnancy. Similarly in the study by Azimi Neeko et al^[1] Endometrial thickness in direct and suppressed cycles were similar.

To conclude Direct HRT have comparable outcomes with Suppressed HRT in FET cycles. Lesser duration of HRT with adequate endometrial thickness suggest direct HRT is advantageous and can be a considerable mode of choice in FET cycles.

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