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The Effect of monitoring serum Estrogen and Progesterone 24hrs before FET on outcome of ART

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ABSTRACT

Frozen embryo transfer is widely used fertility technique with good pregnancy outcomes. Monitoring of hormones prior to embryo transfer has shown better outcomes. To evaluate whether monitoring serum estrogen and progesterone one day before frozen embryo transfer predicts the outcome. This study is an observational prospective cross sectional study conducted in three fertility centers in Baghdad city-Iraq (Kamal al-Samarrai hospital fertility center, Baghdad privet fertility center and Al-Nada privet fertility center) during the period of ten months from1st of December, 2020 till 1st of October, 2021on convenient sample of one hundred infertile women. The outcome and duration of follow-up were done until fetal heart positive. Hormonal monitoring was done by taking blood sample from enrolled patients one day before embryo transfer in frozen cycle. The pregnancy outcome for all studied infertile women was positive in 35% of them and negative in 65% of them. The age, body mass index, embryo number and infertility diagnosis were not related to hormonal monitoring. The positive pregnancy outcome of infertile women was significantly related to hormonal monitoring (p=0.02). The monitoring of serum estrogen and progesterone one day before frozen embryo transfer is helpful in predicting pregnancy outcome.

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1. INTRODUCTION

Infertility is the failure of couples to conceive after one-year duration associated with unprotected vaginal sexual relation that need for investigations and treatment. The common etiological factors for both types of infertility (primary and secondary) are male factor, ovulatory disorders, tubal diseases, uterine and/orperitoneal disorders [1]. The global prevalence of infertility in reproductive age couples is (15%). It was estimated that 6% of women in United States were infertile and 12%of women were nulliparous till menopause, while the infertility prevalence among Chinese women was (25%) [2]. Advanced technology and improving of culture conditions and implantation are accompanied with high pregnancy rates and increase the use of in vitro fertilization and intracytoplasmic sperm injection (ICSI) cycles associated with frozen embryo transfer (FET) as the main option for infertility treatment all over the world [3]. The FET is the common assisted reproductive technology (ART) applied nowadays [4]. As compared fresh embryo

transfer, the FET is characterized by better live birth rate [5], maximum oocyte retrieving, lower risk of multiple pregnancy, genetic testing ability [6] and chance for unsynchronized embryo donations [7]. However, some authors reported similar live birth rates for both techniques8. Recently, the FET is widely used, despite routine uses of fresh embryo transfer [6- 8]. The FET mechanism is classified into artificial and natural cycles. The artificial or hormonal replacement treatment cycle aimed to suppress the proliferation of endometrium and growth of follicles by supply of estrogen hormone, while the natural cycle involves the monitoring of menstrual cycle with no medical intervention [9]. The luteinizing hormone (LH) levels are obviously increased during proliferative phase of artificial cycles without suppressing the pituitary effect like ovulation by natural cycle. In spite of that, the LH is not an appropriate predictor of FET outcome because the estrogen (E2) hormone supply restrains the follicular development. On other hand, the progesterone (P) hormone monitoring at proliferative phase is more accurate in detection of escape ovulation [10].

Monitoring of E2 at proliferative phase is also essential in assessment of endometrial receptivity as the estrogen hormone stimulates the endometrium reproduction and induces the expressing of progesterone receptors of endometrium that are needed for reproduction of a transferred embryo [11]. Some literatures revealed that the mid-cycle serum E2 hormone level is not related to pregnancy outcome of assisted reproductive technology [12], while other literatures found higher E2 mean level at proliferative phase could be negatively correlated to pregnancy course and live birth rates following artificial frozen embryo transfer [13]. The discrepancies in findings of these literatures might be due to differences in timing of estrogen hormone measurements [13]. Delayed FET is applied due to complications of increased endogenous hormonal levels in controlled ovarian stimulation (COS) cycles [14], [15]. These complications are changes in hypothalamic-pituitary-ovarian axis, dysfunction of corpora lutea and the altering of endometrial receptivity [14]. Changes in hypothalamic-pituitary-ovarian axis lead to delayed ovulation in next natural cycle after COS [15]. The purpose of this study was to determine whether blood E2 and P levels measured one day before to frozen embryo transfer predicts pregnancy outcome.

2. Methodology

Design of current study was an observational prospective cross sectional study conducted in three fertility centers in Baghdad city-Iraq (Kamal al-Samarrai hospital fertility center, Baghdad private fertility center and Al-Nada privet fertility center) during the period of ten months from 1st of December, 2020 till 1st of October, 2021. The infertile women presented to Kamal al-Samarrai hospital fertility center, Baghdad private fertility center and Al-Nada privet fertility center were part of the study population. The inclusion criteria were adults (≥18 year's age) infertile couple for more than 2 years, underwent autologous vitrified-warmed cleaved programmed FET and the cleavage stage (day 3) warming and transfer was scheduled to be performed on fourth day of progesterone supplementation. Younger or older age women, lost for follow up, E2 level below 200 pg/ml, progesterone level less than 15 ng/ml and women refused to participate were the exclusion criteria. The ethics of study were implemented in regard to Helsinki Declaration; an approval was taken from Arab Board of Health Specializations with an agreement from Infertility centers authorities and an oral informed approval was taken from women enrolled in the study in addition to completing management of women accordingly. This was a study that collect a hundred women and grouped into two subgroups: Standard group (a fifty women who underwent FET without measuring serum level of E2 and P one day prior Embryo Transfer); and Surveillance subgroup (a fifty women who underwent FET with measuring serum level of E2 and P one day prior Embryo Transfer). Women in Surveillance subgroup that had serum E2 level less than 200pg/ml and /or Serum P4 level less than 15 pg/ml were exclude from the study. The hormones were assessed in Ibn-Hyan private laboratory in Baghdad city. A blood sample of 8 ml was taken from the selected women.

The progesterone hormone kits used were Elecsys P III (Cobas) laboratory kits, while the E2 hormone kits used were Elecsys E2 III (Cobas) laboratory kits. These kits were analyzed by Cobase 411 analyzer (Roche, Germany). The outcome and duration of follow-up were done until fetal heart rate positive. All women that included in this study underwent the same protocol of FET Cycle. A simpler regime commencing estrogen was done on day 2 of the cycle (which prevent follicular requirement) with addition of P later for both study groups. High dose fixed regimen starting from 6 mg/day of Estrofem (17B-oestradiol) orally which given continuously for 12days, after which transvaginal scan was repeated to see endometrial thickness and pattern. If endometrial thickness reaches a minimum of 7 mm and no dominant follicle, no signs of ovulation, embryo transfers were scheduled. Micronized progesterone was vaginally administrated in next day in cyclogest supcyclogest (Progesterone 400 mg) pessaries. Cleaved stage (day3) warming and transfer was scheduled on fourth day of P supplementation. Data analysis was done by using statistical package for social sciences version 26 and the statistical tests were used to analyze the categorical variables accordingly with p value significant if ≤ 0.05.

3. Results

The current study enrolled 100 infertile women with mean age of (32.6 years) with range of (24-40 years); 35% of women were less than 30 years age, 56% of women were 30-39 years age and 9% of women were forty years age. Mean body mass index of infertile women was 27.9±4.7 Kg/m2; 44% of them were overweight and 32% of them were obese. Mean embryo number of infertile women was 1.7±0.5; 38% of them had one embryo and 62% of them had two embryos. The diagnosis of infertility for studied infertile women was unexplained (20%), polycystic ovarian syndrome (21%), male factor (20%), diminished ovarian reserve (DOR) (19%), endometriosis (16%) and male factor and Polycystic ovarian syndrome (PCOS) (4%). Mean progesterone hormone of infertile women monitored was (1.1 ng/ml) and mean estradiol hormone was (456 Pg/ml). The pregnancy outcome for all studied infertile women was positive in 35% of them and negative in 65% of them. (Table 1).

No significant differences were observed between infertile women hormonally monitored (Surveillance group) and infertile women not monitored (standard group) regarding age (p=0.7), body mass index (p=0.5), embryo number (p=0.4) and infertility diagnosis (p=0.7). (Table 2).

As shown in table 3; there was a significant association between positive pregnancy outcome and infertile women and of surveillance group (p=0.02), 46% of monitored women had positive pregnancy outcome, while 24% of women not monitored (standard group) had positive pregnancy outcome.

4. Discussion

The hormonal replacement therapy is essential in preparing endometrium in the protocol of FET due to many advantages such as better monitoring, more flexible schedules, decreased rate of cancelled cycles and low cost [16]. In spite of these advantages, correct coincidence between embryo transfer and endometrial preparation is needed through time control and control of progesterone dose [17]. This study revealed a significant relationship between positive pregnancy outcome of infertile women and hormonal monitoring (p=0.02). Out study result is close to findings of [18] retrospective time-series study in USA on 379 standard FET and 524 surveillance FET cycles which reported that surveillance cycles (monitored E2 and P) were associated with better live birth. Another prospective cohort study implemented by [19] in Iran on 258 infertile women undergone first or second FET cycles found that measurement of progesterone is required to acquire better pregnancy outcomes, while measuring the E2 before frozen embryo transfer is still controversial. However, a single tertiary center study carried out by [20] in Belgium on 1222 infertile women undergone FET cycles stated that measurement of E2 prior to cycles is important in yielding better

outcomes. Nowadays, the relationship between measuring serum levels of E2 and P during luteal phase and outcome of pregnancy in FET cycles is highly explored. [21] retrospective study in Australia documented that progesterone level range of 70-99 nmol/l is linked to good pregnancy outcome for infertile women. Recently, many authors developed researches to detect the effect of P level on embryo transfer and on pregnancy outcome [22]. The main study limitations were financial difficulties and loss to follow up of women.

5. Conclusion

One day before to frozen embryo transfer, blood E2 and P levels should be monitored to predict pregnancy outcome. This study suggested that physicians adopt serum E2 and P monitoring one day before to FET and that more research on serum E2 and P monitoring one day before FET be funded.

6. Conflicts of interest

None

7. Acknowledgment

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Table 1: General characteristics and FET outcome of infertile women

Variable	**No.**	**%**
Age mean±SD (32.6±4.7 years)		
<30 years	35	35.0
30-39 years	56	56.0
40 years	9	9.0
Total	100	100.0
Body mass index mean±SD (27.9±4.7 Kg/m^2)		
Normal	24	24.0
Overweight	44	44.0
Obese	32	32.0
Total	100	100.0
Embryo mean±SD (1.7±0.5)		
One embryo	38	38.0
Two embryos	62	62.0
Total	100	100.0
Diagnosis of infertility		
Unexplained	20	20.0
PCOS	21	21.0
Male factor	20	20.0
DOR	19	19.0
Endometriosis	16	16.0
Male factor and PCOS	4	4.0
Total	100	100.0
Hormonal monitoring		
Estradiol (pg/ml)	465	161.9
Progesterone (ng/ml)	19.504	1.66
Total	50	100.0
Pregnancy outcome		
Positive	35	35.0
Negative	65	65.0

Total	100	100.0

Table 2: Distribution of general characteristics according to study groups

Variable	Study groups				P
	Surveillance		Standard group		
	No.	%	No.	%	
Age					0.7 NS
<30 years	16	32.0	19	38.0	
30-39 years	30	60.0	26	52.0	
40 years	4	8.0	5	10.0	
Body mass index					0.5 NS
Normal	10	20.0	14	28.0	
Overweight	22	44.0	22	44.0	
Obese	18	36.0	14	28.0	
Embryo					0.4 NS
One embryo	17	34.0	21	42.0	
Two embryos	33	66.0	29	58.0	
Infertility diagnosis					0.7 NS
Unexplained	7	14.0	13	26.0	
PCOS	10	20.0	11	22.0	
Male factor	11	22.0	9	18.0	
DOR	11	22.0	8	16.0	
Endometriosis	9	18.0	7	14.0	
Male factor and PCOS	2	4.0	2	4.0	

NS=Not significant.

Table 3: Distribution of pregnancy outcome according to study groups

Variable	Study groups				P
	Surveillance		Standard group		
	No.	%	No.	%	
Pregnancy outcome					**0.02** S
Positive	23	46.0	12	24.0	
Negative	27	54.0	38	76.0	

S=Significant.