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COMPARISON OF A 'FREEZE-ALL' STRATEGY VERSUS A 'FRESH TRANSFER' STRATEGY AMONG POOR RESPONDERS IN ASSISTED REPRODUCTIVE TECHNOLOGY (ART)

Dr Sudhir rakholia* Saket Hospital (Consultant),*Corresponding Author

Dr Manvi Tyagi Anulok hospital (Consultant),

ABSTRACT **Background:** The standard procedure in ART is the use of fresh embryo transfer (FET) which has stood the test of time. But in recent years, frozen embryo transfer has also been used by many quite successfully and it may be a viable alternative to FET. Aim and Objective: The main aim of the study is to find out if the clinical pregnancy rate per randomized patient after the first good quality blastocyst transfer is superior in a freeze-all as compared with same cycle transfer strategy in poor responders. The main objective of present study is to compare the 'freeze-all' strategy with same cycle transfer strategy among poor responders in artificial conception technology. **Methods**: An observational, prospective, cohort study was conducted between August 2018 and January 2019. In total, 102 poor responder patients (as per Poseidon criteria) were taken for COS with GnRH antagonist stimulation protocol and blastocyst stage embryo transfer was performed. **Results:** Clinical pregnancy rate and ongoing pregnancy rate were significantly higher in frozen embryo transfer group than fresh embryo transfer group. Conclusion: In poor responder group of patients, IVF outcomes can be improved by implementing freeze all policy. Major concern in poor responder patients is reduced oocyte competence due to availability of lesser oocyte. Therefore, better outcomes could be achieved with the help of Pre implantation genetic screening synchronized with latest endometrium receptivity markers which is only possible with freeze all policy.

KEYWORDS : ART, FET, OHSS, Freeze-all, IVF, GnRH

INTRODUCTION

The use of assisted reproductive technique for treatment of infertility is increasing all over the world, so that in some countries, up to 5% of overall births are thanks to ART. (European IVF-Monitoring Consortium (EIM) et al 2016).

The standard procedure in ART is the use of fresh embryo transfer (FET) which has stood the test of time. But in recent years, frozen embryo transfer has also been used by many quite successfully and it may be a viable alternative to FET. Better implantation rates and significant clinical pregnancy rates have been seen in frozen thaw cycles. Even better results compared to fresh embryo transfer have been noted (Roque M et al 2013).

Pregnancy rates in IVF treatment can be increased by using the genetically normal embryo via frozen technique instead of using the fresh embryo transfer. (Devroey P et al 2011) Use of frozen technique has the potential to become the simplest method to improve pregnancy rates in ART.

The most common complication that can occur during COS is ovarian hyperstimulation syndrome (OHSS). It is a possibly dreaded complication which is seen in around 1-12% of ART cycles. It is of utmost importance to prevent OHSS. If stimulation includes an antagonist protocol for stimulation and trigger with GnRH agonist for the physiological maturation of oocyte ; then the risk of early and late onset OHSS is almost prevented (Roque M et al 2015). Therefore, using trigger with GnRH agonist and “Freeze all” embryo strategy ; OHSS can be prevented (Huang B et al 2014).

The main objective of present study is to compare the 'freeze-all' strategy with same cycle transfer strategy among poor responders in artificial conception Technology.

MATERIALS AND METHODS

An observational, prospective, cohort study was conducted between August 2018 and January 2019, in a private IVF centre (Wings IVF Centre, Ahmedabad). Approval for the study was taken from the review board of our institute, and written and informed consent was taken from all patients.

In total, 102 poor responder patients (as per Poseidon criteria) were taken for COS with GnRH antagonist stimulation protocol and blastocyst stage embryo transfer was performed.

All the patients who presented to our IVF centre for fertility treatment meeting the POSEIDON criteria for POR, Day 5 embryo transfer in GnRH antagonist cycles, and fresh and frozen thawed ET done with good quality embryos according to Gardner blastocyst grading system, i.e, blastocyst cavity expansion larger than the embryo, along with thinning of the shell (4AA, 4AB) were included in this study.

All the patients having endometriosis stage 3 to 4, Ovarian cysts with a diameter more than 30 mm found on the starting day of stimulation, congenital/ acquired defect of uterus, fibroids (submucosal), presence of severe comorbidity (uncontrolled diabetes, cardiovascular, pulmonary, or any major system illness), uncontrolled thyroid disease, Contraindications or allergies to gonadotropins or GnRH antagonists, Ovum donor cycle, primarily male factor infertility (for e.g. severe oligozoospermia < 1million/mL, or azoospermia; asthenozoospermia etc) were excluded from the study. In the fresh transfer group (n=50), transfer of embryo was performed only when progesterone levels were <=1.5 ng/mL and the endometrium was 7mm or more on the day of trigger.

Those patients were included in the freeze-all group (n=52) who had all the embryos cryopreserved in the fresh cycle and the first embryo transfer was performed after priming the endometrial and embryo thawing. The freeze-all strategy was applied when the E2 levels were > 3000 picogram/ml or more than twenty follicles were seen in both the ovaries, serum level of progesterone was more than 1.5 ng/mL & the endometrium was less than 7 mm in thickness on the day of trigger. Data collection was done under the following categories: age of both partners seeking for ART treatment, serum AMH, AFC (on second day of menses), duration and cause of infertility, controlled ovarian stimulation protocol, retrieved oocytes, grade of day 5 embryo, transfer type (fresh or freeze thawed transfer), thickness of endometrium on the day of ET, implantation rate, clinical pregnancy rate and ongoing pregnancy rate.

Primary outcome was clinical pregnancy which is defined as confirmation of pregnancy by both, high level of serum beta HCG i.e more than 10 IU and gestational sac's presence along with cardiac activity of fetus 30 days after the embryo transfer, seen by USG. Ongoing pregnancy was the secondary outcome; which is defined as viable intrauterine pregnancy of at least twelve weeks duration confirmed on an ultrasonography scan.

The study protocol was approved by Ethics committee, The Indian Fertility Society, New Delhi. All subjects participating in the study signed the written consent forms.

For ovarian stimulation; GnRH antagonist stimulation protocol was used in both the groups. Stimulation was performed using combination of Inj. rFSH 225 IU (Gonal F, folligraft), and Inj.HMG 225 IU (Gynogen) or HMG 450 IU alone based on ovarian reserve markers,

which was started on day 2 or 3 of menses. Monitoring of ovarian response and adjustment of gonadotropin dose was done based on the reports of serum estradiol, serum progesterone level and TVS findings of the consecutive days. Injection cetrorelix in a dose of 0.25 MG was administered when at least 1 follicle reached 14mm or more in mean diameter and was continued till the day of trigger. Injection HCG 10,000 IU was injected for final oocyte maturation when at least three follicles of mean diameter 18mm or more and rest of the follicles more than 16 mm were seen, followed by oocyte pick up 34 – 36 hour later, under general anesthesia.

After oocyte collection 3 to 4 hours later sperm insemination was performed with the help of procedure known as intracytoplasmic sperm injection (ICSI), which employs micromanipulation techniques to inject a single sperm into each egg. Fertilization check and further embryo growth was monitored with the help of time lapse technique. Grading of embryo was done with the help of Gardner's blastocyst grading system which gives 3 different scores to each blastocyst embryo based on its stage of development; quality of inner cell mass and trophectoderm quality (Grade A, B, C).

Women who were chosen for fresh embryo transfer, at least 2 A grade blastocysts were transferred on day five. Luteal phase support in form of vaginal progesterone gel 90 mg daily along with oral dydrogesterone 10 mg BD was started just after ovum pick up and persisted to continue till the testing of serum beta HCG, which was done two weeks later to embryo transfer.

In women with positive serum beta HCG level luteal phase support was continued till the evaluation of clinical pregnancy which was done with the help of TVS. Further assessment of ongoing pregnancy was done at 12 weeks with the help of ultrasonography, which was defined as viable intrauterine pregnancy at that time.

Statistical analysis was done with the Statistical Package for Social Sciences (SPSS version 24.0). Statistical software was used for calculating the P values. Comparison of mean between the 2 groups was done using Unpaired 't' test and comparison of proportions between the 2 groups was done using Z test for two sample proportion. A p value of less than 0.05 was considered as statistically significant. The final data was presented in the form of tables and graphs.

RESULTS

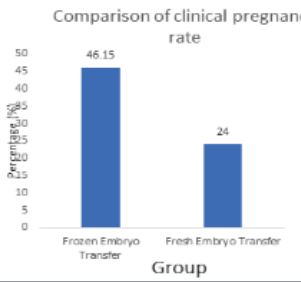
Distribution of women in the frozen embryo transfer group and fresh embryo transfer group were 51.0% and 49.0% respectively. In the frozen embryo transfer group, there were 8 (15.4%) women in the age group 22-30 years, 43 (82.7%) were in the age group 31-40 years and only 1 (1.9%) was in the age group more than 40 years.

In the fresh embryo transfer group, there were 20 (40.0%) women in the age group 22-30 years, 30 (60.0%) were in the age group 31-40 years. In both the groups, majority of the women who had undergone IVF were found in the age group of 31-40 years. Mean years of infertility duration was 6.81 and 7 in the frozen embryo transfer and the fresh embryo transfer group respectively.

Table No:01

Baseline Characteristics	Frozen Embryo Transfer	Fresh Embryo Transfer	P value
Mean age (±SD) years	34.04 ± 3.51	31.32 ± 3.39	<0.001
Mean years of active marital life	6.81 ± 2.80	7.00 ± 2.36	0.709, NS
Number of embryos transferred [Mean±SD]	1.69 ± 0.51	1.62 ± 0.49	0.468, NS

Chart No: 01



Clinical pregnancy rate was significantly higher in frozen embryo transfer group than fresh embryo transfer group. Ongoing pregnancy rate was 36.54% and 18.00% in frozen embryo transfer and fresh embryo transfer group respectively. The difference was statistically significant (p=0.031).

DISCUSSIONS

In our study we have found that there is a significant difference in IR, CPR and OPR between fresh and frozen thaw embryo transfer (FET) groups. It has been noted that implantation failure in early pregnancy is due to increased levels of PG released due to oocyte retrieval procedure in fresh embryo transfer cycle (Jaschevatzky OE et al 1983). It is also postulated that PG rise is responsible for early onset OHSS (Papanikolaou EG et al 2005 & Amor DJ et al 2009). Because of these reasons it has been theorized that FET cycles are similar to natural cycles and therefore gives better result.

In present study the mean age of patients in FET group and fresh embryo transfer group was 34.04 ± 3 and 31.3 ± 3 years respectively. In patients with advanced age, we have chosen frozen cycle transfer as it mimics natural physiology of implantation resulting in reduced abortion rate (Papanikolaou EG et al 2005 & Amor DJ et al 2009). Poor responder patients belonging to higher maternal age group i.e,< 35 years can be benefited from pre implantation genetic screening test, as aneuploidy rate significantly increases in advanced maternal age (Maheshwari A et al 2012).

The supra-physiological effects of the exogenous hormone administration in fresh ET cycle may adversely affect the implantation resulting in higher rates of miscarriage. As higher serum levels of estradiol (>2500 pg/ml) may affect endometrial maturation and implantation; there are lower chances of pregnancy rates in these cycles (Valbuena D et al 2001).

Celik et al (in 2015) reported no obvious difference in respect to IR in same cycle and frozen transfer cycle. However, in this study cleavage stage ET was done in fresh cycle whereas blastocyst stage transfer was done in FET cycle (Çelik S et al 2015). Clinical pregnancy rates and implantation rates were 36.4% and 25.2% respectively in fresh cycle whereas, 55.1% and 37.5% in frozen group; which is statistically significant (Zhu D et al 2011).

Muratet al (2017) had studied optimal embryo transfer strategy in poor responders including freeze all. The study showed IR of 24.1% in freeze cycle transfer and 47% in frozen ET cycle which was statistically significant and supports our study (Berkkanoglu M et al 2017).

In our study clinical pregnancy rates and ongoing pregnancy rates were 46.1% and 36.1% respectively in FET cycle while 24% and 18% in fresh cycle, which is statistically significant and supported by aforementioned study done by Murat et al.

With the recent advancements in ART like vitrification technique and cryopreservation technique we understand that we are not far from good culture and blastocyst vitrification in poor ovarian responders to gain better result. It is believed that future COS strategy will enhance the chances of more competent oocyte in patients with poor ovarian reserve which can result in clinical pregnancy rates comparable with that of normal responder patients.

CONCLUSIONS

In poor responder group of patients, IVF outcomes can be improved by implementing freeze all policy. As significantly higher rate of clinical pregnancy and ongoing pregnancy was observed in this group. This may be due to the negative effect of exogenous gonadotropins in ART cycle over the endometrium which gets prevented following freeze all policy.

Major concern in poor responder patients is reduced oocyte competence due to availability of lesser oocyte. Therefore better outcomes could be achieved with the help of Pre implantation genetic screening synchronized with latest endometrium receptivity markers which is only possible with freeze all policy.

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