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A Retrospective Cohort Study: Frozen Thawed Embryo Versus Fresh Embryo Transfer in Assisted Reproductive Technology

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ABSTRACT
Aim of study was to compare outcomes between frozen-thawed ET with fresh ET for women undergoing ART. Some evidences suggests that frozen embryo transfer improve live birth rate and reduce complication such as OHSS, as there are improvements in preservation techniques. This was a retrospective cohort study of patients who underwent embryo transfer from Aug 2022-Sep 2023 at a fertility centre in Vapi, Gujarat. 350 cycles of embryo transfer(238 fresh and 112 frozen) were included in the study. Outcomes were measuredpregnancy rate. There was no satisfactory difference between positive pregnancy rate(55.5% versus 60.5%)Odd ratio(OR)0.77, Clinical pregnancy rate(48.73% versus 57.14% OR 0.53%, 95%CI 0.1-2.5), Ongoing clinical pregnancy rate (45.4% Versus 51.8% OR 1.4, 95% CI 0.29-6.66 in Fresh and FET cycles respectively. Although the FET cohort showed higher rates of positive biochemical, clinical ongoing pregnancies per transfer, these differences did not achieve statistical significance. Therefor, both the option strategies can be used.

INTRODUCTION

According to WHO, infertility is defined as disease of male or female reproductive system who fail to achieve pregnancy after 12 months or more of regular reproductive sexual intercourse[1]. Globally infertility is a public health problem as age of marriage is delayed in both men and women compared to previous generation and due to modified lifestyle changes , the incidence of infertility has increased drastically. Around 17.5% of the adult population roughly 1 in 6 world wide experience infertility showing the urgent need to increase access to affordable, high quality fertility care for those in need[2]. The life time prevalence was 17.8% in high income countries and 16.5% in low and middle income countries[2]. Currently, Assisted reproductive technique has delivered over 8 million babies worldwide[3]. The most dreaded complication of IVF cycles is OHSS(Ovarian hyper stimulation syndrome). Devroey[4] developed the freeze all" stratergy in order to avoid ovarian hyper stimulation syndrome. It is a potentially life threatening condition where in fluid shifts from blood vessels to abdominal cavity. This can result in bloating, a higher risk of thrombosis, liver and kidney ischemia. The hallmark of OHSS is an increase in the permeability of capillaries, resulting in a fluid shift from intra vascular space to extra vascular space compartments. Vascular endothelial growth factor (VEGF) plays a critical role in a pathogenesis of OHSS by increasing vascular permeability. VEGF is secreted by the granulosa cells and human chorionic gonadotropin (HCG) stimulates its secretion. Severe OHSS is associated with higher levels of VEGF[5]. The other suggested factors that may act directly or indirectly on the development oe severity of OHSS are, insulin like growth factor, transforming growth factor alpha and beta, basic fibroblast growth factor, platelet derived growth factor inter lukin-1B and interlukin-6[6,7]. The intra-ovarian renin angiotensin system(RAS) is another pathophysiological mechanism implicated in OHSS . Furthermore, HCG activates the RAS, which is confirmed by the association of high renin activity in the follicular fluid of women with OHSS. Higher levels of VEGF and the RAS seems to play a role in development of OHSS[8]. The transfer of the fresh embryos is the usual practice in most IVF units when such embryos are available. In some cases, all embryos may be cryo preserved without a fresh embryo transfer, most commonly to prevent ovarian hyper stimulation syndrome when excess follicle development has occurred. After ovarian recovery, embryos are thawed and transferred to the uterus after a programmed physiologic cycle of hormone replacement to prepare the endometrium. With fresh-embryo transfer the medication given for ovarian stimulation or the resulting supra physiological sex steroids may alter the endometrial receptivity[9,10] and adversely affect trophoblastic invasion or placentation[11]. The study aims to compare the pregnancy rate of fresh embryo transfers following ovarian stimulation with antagonist potocols to those of frozen-thawd embryo transfers into an artificially prepared endometrium and after embryo cryo preservation during stimulated cycle.

Objectives: The primary objective of this retrospective cohort study is to compare the live birth rates between fresh and frozen-thawed embryo transfer. Secondary objective includes comparing outcomes such as

- Biochemical pregnancy.
- Clinical pregnancy.
- Miscarriage rates.
- Ectopic pregnancy and to know incidence of multiple pregnancies like twins/triplets By analyzing these parameters, the study aims to provide robust evidence to guide clinical practice and enhance patient outcomes in ART.

Statement of Problem: In ART, embryo transfer techniques in a critical component for success rate of IVF cycles. Fresh embryo transfers involve transferring embryos shortly after fertilization in the same cycle of ovulation induction. In frozen-thawed embryo transfers, embryos are frozen for future use and thawed before being transferred. There are many studies with mixed varying results for fresh vs frozen-thawed embryo transfer regarding effectiveness and safety of these procedures and the decision -making process for clinicians remain complex and multifaceted. It is therefore essential to analyze large scale data retrospectively to determine the efficacy and Safety of these two methods.

Hypothesis:

- There is significant difference in the live birth rate of fresh vs frozen-thawed embryo transfers in ART.
- There are low incidences of OHSS in frozen-thawed ET when compared to fresh ET.
- The overall pregnancy rates in biochemical, clinical and ongoing clinical pregnancies may vary between procedures.

The result of the study would contribute to our understanding of the comparative effectiveness and safety of these two approaches, which will help in clinical decision making.

MATERIALS AND METHODS

Study Design: It was a retrospective cohort study.

Data Collection: We collected the data from a register at a fertility centre from August 2022 to September 2023 in Vapi, Gujarat.

Inclusion Criteria:

- Women from 21-to 49-year-old who underwent ICSI by ovarian stimulation with antagonist protocol with D3 and blastocyst transfers.
- Serum progesterone of <or equal to 1.5ng/ml on the day of trigger in a fresh cycle and day 12 for frozen ET.
- Endometrium >/=8mm, grade 1vasularity on the day of transfer.
- Transfer of 1 or 2 good quality embryos only 6-10 cells with </=20% fragmentation.

Exclusion Criteria:

- Patients with a history of recurrent pregnancy loss.
- Uterine pathology-Asherman syndrome, thin endometrium, endometrial polyps and fibroid.
- Patients undergoing ART using embryo donation /gamete /surrogate pregnancy.

Procedure:

- Ovarian stimulation was done with recombinant gonadotrophins or highly purified urinary gonadotrophins from day 2 or day 3 of menstrual cycle after confirming the FSH level between 3-10 IU/L and LH level <5-7 IU/ml and serum estradiol level between 20-80 pg/ml.
- The dose of gonadotrophins was selected on patients age, BMI, AMH, AFC and modified according to follicular response.

Protocol: Mainly antagonist protocol was used. Follicular growth monitoring was done using transvaginal sonography. When follicle reached 14mm, Inj cetrorelix acetate (0.25mg) s.c was added daily till the day of trigger. Once follicles reached 18-20mm with adequate number, ovulation was triggered using human chorionic gonadotrophin (hcG) (Inj Ovitrelle 500mcg i.e. 13000 IU) or combination of hcG and Inj Buserelin acetate(0.5mg) s.c endometrial thickness was measured along with serum LH, estradiol and progesterone values on the day of trigger. Ovum pick up was performed 34-36 hours after trigger injection.

The Process of Embryo Transfer:

Fresh ET Cycle: Embryo transfer was done if serum progesterone level on day of trigger was <1.5ng/ml. Following the egg retrieval, either a day 3 embryo transfer or day 5 blastocyst transfer was done depending on availability of high-quality embryo. A maximum of 2 embryos were transferred per cycle to optimize the chances of successful implantation. Any excess embryos were cryo preserved using kitazato embryo vitrification kit (cryotop method). When the endometrial thickness exceeded 8mm, luteal phase support commenced with the administration of micronized natural progesterone supporting twice daily each containing 400mg administered vaginally. This regimen began from the day of oocyte retrieval until 12th week post conception.

Frozen ET Cycle: During frozen embryo transfer cycle, patients underwent FET if they did not achieve pregnancy in prior attempts and surplus embryos were available for cryo preservation. The ET could not be performed during the initial attempt due to suspected risk of ovarian hyper stimulation, serum progesterone levels greater than 1.5ng/ml, inappropriate endometrium on the day of transfer. Following ovarian down regulation with daily injections of triptorelin acetate 0.1mg daily starting 4-5 days before the date of expected menses for 5 doses, patients were administered astraddle valerate tablet 4mg BD for 5days followed by TDS for next 15 days starting from day 2 of menses. If the endometrial thickness exceeded serum, vaginal progesterone was administered using the same regimen as in fresh ET cycles. Following four days of progesterone regimen, frozen embryos were thawed and transferred. Luteal phase support with astraddle valerate and micronized vaginal progesterone persisted until 12 weeks post conception. Frozen embryo thawed using kitazato embryo thawing media and transferred. Upon consideration of the availability of high quality embyos and maximum of 2 embryos were transferred per cycle following provision of written informed consent.

Statistical Analysis: The statistical analysis of the data was conducted utilizing SPSS (Statistical Package for Social Science version 28.0, Chicago Illinois, USA) software. Differences between variables in the two groups were assessed using the students t-test, while the chi square test was employed-to compare categorical variables. A p-value <0.01 was deemed statistically significant for all analyses.

RESULTS AND DISCUSSIONS

There were no notable differences observed in patient's characteristics between the groups ($p<0.05$). In Fresh ET group, unexplained infertility was most prevalent cause while in Frozen ET group, it was male factor infertility (Table 1).

(Table 2): Pregnancy Rates in Fresh and Frozen Thawed ET: It represents while there were no statistically significant differences between:

Table 1: Patient Characteristics

		Fresh ET	Frozen ET	P-values
1	Types of infertility			
	Primary	192	94	0.259
	secondary	56	18	0.259
2	Causes of Infertility			
	Male factor	94	42	0.2
	Female factor	34	28	
	Unexplained	110	42	
3	Age of females	30.2+/-4.4	29.82+/-4.02	0.475
4	Age of males	33.3+/-3.17	32.8+/-4.02	0.652
5	Duration of fertility	4.08 +/- 1.44	4.39 +/- 1.82	0.22
6	S.AMH	2.52 +/-0.81	2.4 +/- 0.72	0.355
7	Antral follical count (both ovaries)	9.45 +/- 1.72	8.93 +/- 1.42	0.052

Table 2: Pregnancy Rate in Fresh and Frozen Embryo Transfers

	Fresh ET	Frozen ET	ODDS ratio	P-value
Biochemical pregnancies B-hcg positive	130	68	0.77	0.45
hcg negative	108	44	-	-
Clinical pregnancies Gestational sac present	116	64	0.53	0.42
Gestational sac absent	14	4	-	-
Ongoing clinical pregnancies				
Featl cardiac activity present	108	58	1.4	0.6
Fetal cardiac activity absent	8	6	-	-

Table 3 : Secondary Outcome Measures

	Fresh ET	Frozen ET	ODDS Ratio	P-value
1.viable pregnancy	108	58	1.4 (0.29-6.666)	0.674
2.Miscarriage	8	6	1.4 (0.29-6.666)	0.674
3.Ectopic pregnancy	0	0	1.4 (0.29-6.666)	0.674
4.Singleton	60	40	0.56 (0.23-1.36)	0.234
5.Twin	54	16	0.56 (0.23-1.36)	0.234
6.Triplets	14	2	0.56 (0.23-1.36)	0.234

- Positive pregnancy rate (55.5% vs 60.5%).
- Clinical pregnancy rate (48.73% vs 57.14%).
- On going pregnancy rate (45.4% vs 51.8%).

CONCLUSION

Although the frozen ET cohort displayed higher rates of positive biochemical, clinical and ongoing pregnancy per transfer, these differences did not achieve statistical significance. Therefore, both the transfer strategies remain viable option, although there is a tendency favoring towards the freeze all strategy.

Recommendation:

- There is scope for additional prospective studies with large sample sizes to validate the findings of this retrospective study and provide more robust evidence.
- The long term follow-up assessments to evaluate not only short-term outcomes such as pregnancy rates but also outcomes such as obstetric complications, neonatal outcomes and child development can be done.

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