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Frozen Thawed Embryo Transfer versus Fresh Embryo Transfer in Cases with Repeated Unexplained ICSI Failure

Ibrahim Saif El Nasr*[1], Mohamed Kandeel[1], Alaa Eldeen Elhalaby[1], Ahmed Elfishawy[2], Ahmed Nofal[1]
[1]Department of Obstetrics and Gynecology, Faculty of Medicine, Menoufia University, Egypt
[2]Department of Obstetrics and Gynecology, Sirs El-lian Central Hospital, Egypt
***Corresponding author:** Ibrahim Saif El Nasr, **Mobile:** (+20) 01003086747, **E-mail:** Ibrahimalisaifelnasr@gmail.com

ABSTRACT

Background: A variety of maternal, genetic, and environmental factors can lead to unsuccessful embryo implantation, which necessitates synchronization between the blastocyst and endometrium. Couples who experience recurrent implantation failure (RIF) may benefit from treatments such as blastocyst transfer, endometrial receptivity, and enhanced embryo quality. In contrast to fresh embryo transfer (ET) following ICSI, recent research indicates that a freeze-all policy might increase implantation success.

Objectives: To determine whether a freeze-all policy for in vitro human blastocysts and subsequent frozen thawed embryo transfer (FET) can improve the ongoing pregnancy rate in patients with recurrent implantation failure instead of fresh embryo transfer.

Patients and Methods: This prospective cohort study at El-Basma Infertility Center in Egypt involved 150 women with infertility who underwent ICSI after ovarian stimulation. The participants were randomly divided into two groups: Group 1 (75 women) followed a freeze-all protocol with a FET after ICSI, while Group II (75 women) underwent conventional ICSI followed by a fresh day-5 embryo transfer.

Results: There was no significant difference between the frozen and fresh embryo transfers in terms of ovarian responses, demographics, or infertility profile variances. On the other hand, the frozen group's chemical pregnancy rate was significantly higher (53.3% vs 33.3%) and their clinical pregnancy rate (CPR) was also higher (49.3% vs 28%), indicating better implantation conditions. despite similar embryo quality and multiple pregnancy rates. Early pregnancy loss was lower in the frozen group, indicating better implantation conditions.

Conclusion: FET significantly improves chemical and CPRs in cases of repeated unexplained implantation failure, with higher ongoing pregnancy rates and lower early pregnancy loss, suggesting improved implantation and pregnancy maintenance.

Keywords: Blastocyst, Endometrium, Embryo transfer, Freeze-all protocol, RIF.

INTRODUCTION

The hatched blastocyst and endometrium must develop and interact synchronously for embryo implantation to be successful. When a gestational sac is seen by ultrasound, implantation is deemed successful from a clinical standpoint. When there is no indication of implantation—that is, no discernible production of human chorionic gonadotropin (HCG)—this is referred described as "implantation failure" [(1)].

Given that only 25%–40% of healthy, fertile women have spontaneous conception during the first cycle of a planned pregnancy, it is questionable whether such an occurrence could be classified as abnormal. Maternal factors such uterine anomalies, hormonal or metabolic diseases, infections, immunological factors, thrombophilias, and other less prevalent reasons are among the many different causes of implantation failure. It is also crucial to consider the effects of severe male factor infertility on the embryo's genetic and morphological conditions. Numerous additional aspects of this intricate implantation process have been examined in recent research [(2)].

Numerous strategies, including efforts to enhance embryo quality, endometrial receptivity, and the interaction between embryos and the endometrium, have been employed to enhance intracytoplasmic sperm injection (ICSI) results in cases of RIF. Blastocyst transfer has been demonstrated to enhance clinical results for RIF couples. In couples with three or more unsuccessful embryo transfer (ET) cycles, hysteroscopy in the previous cycle has been shown to increase pregnancy outcomes. Hysteroscopy may not be useful in RIF, according to a multicenter randomized controlled study. Furthermore, methods like as assisted hatching are still debatable for individuals with RIF [(3)].

The process of embryo implantation is closely controlled by ovarian hormones and necessitates a functioning blastocyst, a receptive endometrium, and reciprocal blastocyst-endometrium contact. During the follicular phase of controlled ovarian stimulation (COS), hormone levels that are above normal might degrade the uterine environment and decrease endometrial receptivity, which lowers the implantation rate in ICSI cycles and lowers the likelihood of pregnancy [(4)].

A freeze-all strategy, in which the whole cohort of embryos is electively cryopreserved for transfer in a later frozen-thawed cycle, has been proposed by several research as a way to improve implantation and offer a more physiological environment for ET. After ICSI, freeze-all may increase implantation and conception rates more than fresh ET [(5)].

The aim of this study is to determine whether a freeze-all policy for in vitro human blastocysts and subsequent FET can improve the ongoing pregnancy

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rate in patients with recurrent implantation failure instead of fresh ET.

PATIENTS AND METHODS

This prospective cohort study was conducted at El-Basma Infertility Center, a private facility located in Menouf, Menoufia Governorate, Egypt, from January 2020 to January 2024.

Inclusion criteria: female under 40 years of age, having a basal antral follicle count (AFC) greater than 5 on day 2, and demonstrating no uterine abnormalities as assessed by transvaginal ultrasound (specifically, the absence of a uterine septum, polyp, submucous fibroid, or hydrosalpinx). Additionally, eligible patients had a history of at least two failed fresh embryo transfer (ET) cycles, with more than four high-quality embryos transferred, resulting in no post-ICSI pregnancies.

Exclusion criteria: age 40 years or older, a basal AFC of 5 or fewer on day 2, Day 3 FSH levels greater than 10 IU/L, or a history of previous FET cycles. Other exclusion factors included a positive thrombophilia screening (including anticardiolipin IgG, lupus anticoagulant, and antinuclear antibodies), hysterosalpingography (HSG) results showing hydrosalpinx without tubal disconnection, thyroid-stimulating hormone (TSH) levels greater than 3 mIU/mL, or failure to produce day-5 blastocysts in the current ICSI cycle.

Methods: A total of 150 women with repeated implantation failure (RIF) were recruited in our study and divided in two groups. **Group 1**, the study group, included 75 women who underwent the freeze-all protocol on day 5 after ICSI, followed by consecutive FET. **Group 2**, the control group, also consisted of 75 women who underwent conventional ICSI followed by a day-5 fresh ET.

All patients underwent a comprehensive initial assessment, which included several evaluations. A detailed history was obtained, covering age, residence, occupation, education, relevant medical history, menstrual history, obstetric history, surgical history, and family history. A thorough clinical examination was performed, including a general examination to assess vital signs, head and neck, chest, and cardiac health, as well as a gynecological examination involving a speculum and bimanual examination to confirm eligibility.

Laboratory investigations were conducted to assess various hormones, including basal follicle-stimulating hormone (FSH), luteinizing hormone (LH), anti-Müllerian hormone (AMH), estradiol (E2), prolactin (PRL), and thyroid-stimulating hormone (TSH).

Transvaginal ultrasonographic scanning was also performed to evaluate uterine size and shape, endometrial thickness and pattern and the presence of any endometrial or myometrial abnormalities such as polyps, fibroids, adhesions, or adenomyosis. Additionally, ovarian size and dimensions were measured, and the AFC was assessed as an indicator of ovarian reserve and response to stimulation.

Beginning on day two or three of the menstrual cycle, COS was performed using the antagonist protocol using human menopausal gonadotropin (Merional, IBSA). Depending on the patient's age and ovarian reserve, the gonadotropin dosage was changed from 150 to 450 IU daily. When a leading follicle reached 14 mm, a GnRH antagonist (cetrorelix, Cetrotide, Merck Serono) was added to inhibit the pituitary. After at least three follicles reached 18 mm and the bulk of the follicles were bigger than 16 mm, monitoring was maintained until the final oocyte maturation was stimulated with a dual trigger (10,000 IU hCG and 0.2 mg triptorelin). The retrieval of oocytes was planned for 34–36 hours following triggering.

General anesthesia was used for the oocyte retrieval procedure, and saline solution was used to clean the vagina. Transvaginal ultrasonography guided the operation, which used a 17G oocyte recovery set. The retrieved oocytes were then sent to the IVF lab, where they were rinsed and cultured in specialized media. Semen was processed using discontinuous sperm gradient centrifugation for ICSI, which was performed with either fresh sperm or testicular biopsy samples. Oocytes were denuded and inseminated by ICSI, then cultured for 5 days in a controlled incubator. Fertilization was confirmed by the presence of two pro nuclei, and blastocyst morphology was evaluated on day 5 using the Gardner and Schoolcraft criteria, which involved grading based on expansion, trophoectoderm quality, and inner cell mass quality.

All blastocysts in the freeze-all group were vitrified using a vitrification kit on day five, and they were thawed using a thaw kit. After being thawed and incubated in culture conditions that had been previously adjusted, only re-expanded blastocysts that showed no symptoms of apoptosis were transplanted.

The freeze-all group underwent endometrial preparation with hormonal replacement therapy using ethinyl estradiol (Cycloprogynova) starting from day 2 of the menstrual cycle. When the endometrium reached 9 mm and progesterone levels were <1.5 ng/mL, 400 mg of vaginal progesterone (Prontogest, Macryl pharmaceuticals) was administered twice daily followed by blastocyst transfer 5 days later. Then for 14 days continuing up to 12 weeks of gestation if pregnancy occurred .

Embryos transfer were performed on day 5 at the blastocyst stage, using laser-assisted hatching before transfer. The transfer was conducted under transabdominal ultrasound guidance with a full bladder, loading two to three grade 1 blastocysts into the transfer catheter for placement in the uterine cavity.

Both groups received luteal phase support with vaginal progesterone and additional Human chorionic gonadotropin 5000 IU (Choriomon, IBSA) on days 0, 4, and 7 post-transfer along with One ampoule of GnRH agonist (Decapeptyl, Ferring, 0.1 mg) on the day of ET. Quality control measures ensured the sterility and integrity of medical devices, maintaining standardized procedures and reliable outcomes.

Outcome measures:

The primary outcomes: of the study included the positive pregnancy test result 14 days after ET and the ongoing pregnancy rate, defined as a pregnancy that continued beyond 12 weeks.

The secondary outcomes: included the implantation rate, which was calculated as the number of intrauterine gestational sacs divided by the total number of embryos transferred. The CPR was determined by the presence of a fetal heartbeat on ultrasound at 4 weeks or more. Additionally, the early pregnancy loss rate, defined as spontaneous termination before 12 weeks, was assessed, as well as the rate of chemical pregnancy, which was identified by a positive pregnancy test without a visible gestational sac.

Ethical considerations:

The local Ethics Committee granted approval for the study [under code no. 2/2019GYNA1]. Every participant provided written informed permission, who was fully informed about the study procedures, potential risks, and benefits. The study adhered to the Helsinki Declaration throughout its execution.

Sample size calculation: The sample size was calculated based on an expected ongoing pregnancy rate of 44% in the freeze-all group compared to 22% in the fresh ET group. With a significance level of 5% and 80% power, 68 subjects per group were needed. After accounting for a 10% withdrawal/non-evaluable rate, a total of 75 subjects per group were recruited.

Statistical analysis

SPSS software, version 24.0, was used to tabulate and analyze the gathered data. Numerical and percentage statistics were used to represent categorical data. The quantitative data were presented as range and Mean ± SD. To examine regularly distributed variables between two independent groups, the student "t" test was employed. P <0.05 was deemed significant, and 0.05 was the declared threshold of significance in this study.

RESULTS

The mean age of the frozen group was 30.97 ± 4.02 years, while in the fresh group, it was 32.24 ± 4.70 years (p = 0.078), which was not statistically significant. The mean BMI was 26.36 ± 2.83 in the frozen group and 25.55 ± 3.08 in the fresh group (p = 0.094), showing no statistically significant difference. The mean duration of infertility was 7.69 ± 2.85 years in the frozen group and 8.49 ± 2.84 years in the fresh group (p = 0.087), which was not statistically significant. The number of previous ICSI cycles was 3.23 ± 0.967 in the frozen group and 3.61 ± 1.39 in the fresh group (p = 0.05), with no statistically significant difference. The distribution of infertility causes was similar between groups (p = 0.565), with no statistically significant difference **(Table 1)**.

Table (1): Comparison of demographics and infertility history in both groups.

Variable		Frozen group (N = 75)	Fresh group (N = 75)	P value	Sig.
Age (years)	Mean ± SD Range	30.97 ± 4.02 21 – 39	32.24 ± 4.70 23 – 39	0.078	NS
BMI	Mean ± SD Range	26.36 ± 2.83 19 – 31	25.55 ± 3.08 17 – 30	0.094	NS
Type of infertility	Primary, n (%) Secondary, n (%)	63 (84.0%) 12 (16.0%)	63 (84.0%) 12 (16.0%)	>0.999	NS
Duration of infertility (year)	Mean ± SD Range	7.69 ± 2.85 4 – 17	8.49 ± 2.84 2 – 17	0.087	NS
Mean no. of previous ICSI cycles (per patients)	Mean ± SD Range	3.23 ± 0.967 2 – 7	3.61 ± 1.39 2 – 8	0.05	NS
Cause of infertility	Male factor, n (%) PCOS, n (%) Bilateral tubal block, n (%) Poor ovarian reserve, n (%) Unexplained, n (%) Endometriosis, n (%) Male factor and PCO, n (%)	28 (37.3%) 16 (21.3%) 6 (8%) 4 (5.3%) 11 (14.7%) 5 (6.7%) 5 (6.7%)	26 (34.7%) 11 (14.7%) 11 (14.7%) 8 (10.7%) 9 (12%) 7 (9.3%) 3 (4%)	0.565	NS

BMI: body mass index. ICSI: intracytoplasmic sperm injection, PCOS: polycystic ovary syndrome (PCOS). NS: Statistically non-significant.

A total of 221 blastocysts were thawed, with a mean of 2.95 ± 0.57 blastocysts per patient and a range of 2 to 4 blastocysts. A total of 215 blastocysts survived thawing, with a mean of 2.87 ± 0.58 blastocysts per patient and a range of 2 to 4 blastocysts. The post-thaw survival rate was 97.28%. Of the thawed blastocysts, 153 (71.16%) were of A quality, 56 (26.04%) were of B quality, and 6 (2.79%) were of C quality. A total of 215 blastocysts were transferred, with a mean of 2.87 ± 0.58 blastocysts per patient and a range of 2 to 4 blastocysts. A total of 192 blastocysts remained cryopreserved for the freeze-all group **(Table 2).**

Table (2): Outcomes after warming in freeze-all group.

Variable		**N = 75**
Total thawed blastocysts	N	221
Mean no. of thawed blastocyst (per patient)	Mean ± SD Range	2.95 ± 0.57 2 – 4
Total survived thawed blastocysts	N	215
Mean no. of survived thawed blastocyst (per patient)	Mean ± SD Range	2.87 ± 0.58 2 – 4
Post-thaw survival rate	n/Total (%)	215/221 (97.28%)
Quality of thawed blastocysts	A quality, n (%) B quality, n (%) C quality, n (%)	153 (71.16%) 56 (26.04%) 6 (27.9%)
Total transferred thawed blastocysts	N	215
Mean no. of transferred thawed blastocyst (per patient)	Mean ± SD Range	2.87 ± 0.58 2 – 4
Total remaining cryopreserved blastocysts for freeze-all group	N	192

Basal serum FSH levels were 6.94 ± 1.68 mIU/mL in the frozen group and 7.16 ± 1.14 mIU/mL in the fresh group (p = 0.094), showing no statistically significant difference. Basal serum LH levels were 6.3 ± 1.80 mIU/mL in the frozen group and 6.15 ± 1.66 mIU/mL in the fresh group (p = 0.101), which was not statistically significant. The mean basal AMH level was 1.79 ± 1.53 ng/mL in the frozen group and 1.71 ± 0.91 ng/mL in the fresh group (p = 0.385), showing no statistically significant difference. The mean AFC was 11.49 ± 8.25 in the frozen group and 9.36 ± 4.13 in the fresh group (p = 0.057), which was not statistically significant. The mean estradiol level at HCG induction was 2005 ± 1320 pg/mL in the frozen group and 1994 ± 954 pg/mL in the fresh group (p = 0.425), showing no statistically significant difference **(Table 3).**

Table (3): Comparison of laboratory investigations in both groups.

Variable		**Frozen group (N = 75)**	**Fresh group (N = 75)**	**P value**	**Sig.**
Basal serum FSH (mIU/mL)	**Mean ± SD**	**6.94 ± 1.68**	**7.16 ± 1.14**	**0.094**	**NS**
Basal serum LH (mIU/mL)	**Mean ± SD**	**6.3 ± 1.80**	**6.15 ± 1.66**	**0.101**	**NS**
Basal AMH (ng/mL)	**Mean ± SD**	**1.79 ± 0.13**	**1.71 ± 0.1**	**0.385**	**NS**
AFC	**Mean ± SD**	**11.49 ± 2.25**	**9.36 ± 2.13**	**0.057**	**NS**
Estradiol level on HCG induction (pg/mL)	**Mean ± SD**	**2005 ± 120**	**1994 ± 54**	**0.425**	**NS**

SD: Standard Deviation, BMI: Body Mass Index, FSH: Follicle-Stimulating Hormone, LH: Luteinizing Hormone, AMH: Anti-Müllerian Hormone, AFC: Antral Follicle Count, HCG: human chorionic gonadotrophins. NS: Statistically non-significant.

The mean duration of ovarian stimulation was 11.39 ± 1.42 days in the frozen group and 11.55 ± 1.44 days in the fresh group (p = 0.494), which was not statistically significant. The mean number of GnRH ampoules used was 45.73 ± 17.89 in the frozen group and 51.49 ± 20.23 in the fresh group (p = 0.067), with no statistically significant difference. The mean progesterone level at triggering was 1.42 ± 0.43 ng/mL in the frozen group and 1.37 ± 0.28 ng/mL in the fresh group (p = 0.158), which was not statistically significant. The mean endometrial thickness at triggering was 9.80 ± 1.41 mm in the frozen group and 9.97 ± 1.20 mm in the fresh group (p = 0.448), with no statistically significant difference. The endometrial pattern at triggering was similar between the two groups (p = 0.21), which was not statistically significant **(Table 4)**.

Table (4): Comparison between ovarian stimulation parameters and endometrium in both groups.

Variable		Frozen group (N = 75)	Fresh group (N = 75)	P value	Sig.
Duration of ovarian stimulation (days)	**Mean ± SD** **Range**	11.39 ± 1.42 8 – 13	11.55 ± 1.44 8 – 15	0.494	NS
No. of GnRH ampoules used	**Mean ± SD** **Range**	45.73 ± 17.89 11 – 78	51.49 ± 20.23 20 – 90	0.067	NS
Progesterone level at triggering (ng/mL)	**Mean ± SD**	1.42 ± 0.43	1.37 ± 0.28	0.158	NS
Endometrial thickness at triggering (mm)	**Mean ± SD** **Range**	9.80 ± 1.41 6 – 13	9.97 ± 1.20 8 – 13	0.448	NS
Endometrial pattern at triggering	**Trilaminar** **Not trilaminar**	35 (46.7%) 40 (53.3%)	32 (42.7%) 43 (57.3%)	0.21	NS

GnRH: Gonadotrophins releasing hormones. NS: Statistically non-significant.

The mean number of oocytes obtained per patient was 16.39 ± 7.91 in the frozen group and 16.31 ± 6.97 in the fresh group (p = 0.53), with no significant difference. Similarly, the mean number of oocytes injected was 13.15 ± 5.66 in the frozen group and 12.64 ± 5.21 in the fresh group (p = 0.135), and the mean number of oocytes fertilized was 10.34 ± 4.42 in the frozen group and 9.81 ± 4.17 in the fresh group (p = 0.109), showing no statistical significance. The fertilization rates per injected oocyte were 79.22% for the frozen group and 77.1% for the fresh group (p = 0.285). The mean number of embryos obtained per patient was 4.51 ± 2.36 in the frozen group and 4.67 ± 1.81 in the fresh group (p = 0.217), with no significant difference, and the quality of embryos was comparable between the two groups (p = 0.284) **(Table 5).**

Table (5): Induction and ICSI outcomes in included patients.

Variable		Frozen group (N = 75)	Fresh group (N = 75)	P value	Sig.
Mean no. of Oocytes obtained (per patient)	Mean ± SD Range	16.39 ± 7.91 7 – 39	16.31 ± 6.97 5 – 32	0.53	NS
Mean no. of Oocytes injected (per patient)	Mean ± SD Range	13.15 ± 5.66 7 – 29	12.64 ± 5.21 4 – 26	0.135	NS
Mean no. of Oocytes fertilized (per patient)	Mean ± SD Range	10.34 ± 4.42 3 – 22	9.81 ± 4.17 2 – 18	0.109	NS
Oocyte fertilization rate (per injected Oocyte)	n/Total, (%)	900/1136 (79.22%)	616/798 (77.1%)	0.285	NS
Total embryos obtained	N	413	275	-	-
Mean no. of embryos obtained (per patient)	Mean ± SD Range	4.51 ± 2.36 2 – 12	4.67 ± 1.81 1 – 11	0.217	NS
Quality of embryos obtained	A quality, n (%) B quality, n (%) C quality, n (%)	267 (64.65%) 114 (27.6%) 32 (7.75%)	170 (61.82%) 99 (36%) 6 (2.18%)	0.284	NS
Total embryos transferred	N	215	183	-	-
Mean no. of embryos transferred (per patient)	Mean ± SD Range	2.87 ± 0.62 1 – 4	2.44 ± 0.58 1 – 3	0.032	S
Total embryos cryopreserved	N	413	92	-	-
Mean no. of embryos cryopreserved (per patient)	Mean ± SD Range	5.5 ± 2.36 2 – 12	4.07 ± 0.91 2 – 5	0.018	S

NS: Statistically non-significant. S: Statistically significant at P<0.05.

The proportion of participants with a chemical pregnancy was significantly higher in the frozen group at 53.3% compared to 33.3% in the fresh group ($p < 0.001$). The chemical pregnancy rate per embryo transfer or per thawed transferred blastocyst was also higher in the frozen group at 18.6% compared to 13.7% in the fresh group ($p = 0.024$). The proportion of participants with a clinical pregnancy was 49.3% in the frozen group and 28% in the fresh group ($p < 0.001$), and the clinical pregnancy rate per embryo transfer was 17.2% in the frozen group versus 11.5% in the fresh group ($p = 0.04$), both statistically significant. Early pregnancy outcomes showed a significant difference between the groups ($p = 0.009$). The ongoing pregnancy rate in patients with a clinical pregnancy was 89.2% in the frozen group and 81% in the fresh group ($p = 0.107$), which was not statistically significant. The multiple pregnancy rate was 29.7% in the frozen group and 23.8% in the fresh group ($p = 0.149$), showing no significant difference **(Table 6).**

Table (6): Comparison of clinical outcomes in both groups.

Variable		Frozen group (N = 75)	Fresh group (N = 75)	P value	Sig.
Chemical pregnancy	Yes, n (%) No, n (%)	40 (53.3%) 35 (46.7%)	25 (33.3%) 50 (66.7%)	<0.001	ES
Chemical pregnancy rate (per embryo transfer or per thawed transferred blastocyst)	n/N, (%)	40/215 (18.6%)	25/183 (13.7%)	0.024	S
Clinical pregnancy	Yes, n (%) No, n (%)	37 (49.3%) 38 (50.7%)	21 (28%) 54 (72%)	<0.001	ES
CPR (per embryo transfer)	n/N, (%)	37/215 (17.2%)	21/183 (11.5%)	0.04	S
Early pregnancy outcomes	Single ongoing preg., n (%) Twin ongoing preg., n (%) Triple ongoing preg., n (%) Early pregnancy loss, n (%)	22 (59.5%) 8 (21.6%) 3 (8.1%) 4 (10.8%)	12 (57.1%) 4 (19%) 1 (4.8%) 4 (19%)	0.054	NS
Ongoing pregnancy rate (per clinical pregnancy)	n/Total, (%)	33/37 (89.2%)	17/21 (81%)	0.107	NS
Multiple pregnancy rate (per clinical pregnancy)	n/Total, (%)	11/37 (29.7%)	5/21 (23.8%)	0.149	NS

NS: Statistically non-significant. NS: Statistically bon-significant S: Statistically significant at P<0.05. ES: Extremely significant at P<0.001.

DISCUSSION

The use of assisted reproductive technology (ART) is increasing in the world. The rate, efficacy, and safety of this technology are very different among countries. There is an increase in the use of ICSI, single fresh embryo transfer (ET) and FET [6]. Our study aimed to compare the outcomes of FET versus fresh ET in cases with repeated unexplained ICSI failure.

The study found no significant differences in demographic characteristics between the frozen and fresh ET (FET and fresh transfer) groups. The mean age (30.97 ± 4.02 vs 32.24 ± 4.70 years, p=0.078) and BMI (26.36 ± 2.83 vs 25.55 ± 3.08 kg/m², p=0.094) were comparable, indicating effective randomization for meaningful comparison of outcomes. Both groups had similar infertility profiles, with primary infertility being predominant (84% in both). The mean duration of infertility (7.69 ± 2.85 vs 8.49 ± 2.84 years, p=0.087) and causes of infertility were also comparable, with male factor infertility being most common (37.3% vs 34.7%), followed by PCOS (21.3% vs 14.7%). These characteristics align with global infertility trends and studies like those by **Fan *et al.*** [6]**, Kieu *et al.*** [7] and **Ibrahim *et al.*** [8], all showing no significant differences in patient characteristics between groups.

In our study there was no significant differences in baseline hormonal profiles (FSH, LH, AMH) and AFCs between the frozen and fresh transfer groups, indicating similar ovarian reserves and potential response to stimulation. The duration of ovarian stimulation (11.39±1.42 vs 11.55±1.44 days, p=0.494) and number of GnRH ampoules used were also comparable. These results align with the systematic review by **Roque *et al.*** [9] which found no significant differences in baseline parameters between the groups, and with **Ibrahim *et al.*** [8], who also reported no significant differences in baseline hormonal profiles.

Our study revealed comparable ICSI outcomes between the frozen and fresh transfer groups in terms of oocytes obtained (16.39 ± 7.91 vs 16.31 ± 6.97, p=0.53), oocytes injected, and fertilization rates (79.22% vs 77.1%, p=0.285). Embryo quality distribution was similar, with most embryos being grade A (64.65% vs 61.82%). These results align with **Shapiro *et al.*** [10] who found no significant differences in embryo quality between frozen and fresh cycles in their study comparing ongoing pregnancy rates from matched blastocysts in fresh and frozen thawed single ET cycles.

Our study found that the FET group had significantly better clinical outcomes, particularly in

the chemical pregnancy rate, which was higher in the frozen group (53.3% vs 33.3%, p<0.001), with a higher rate per ET (18.6% vs 13.7%, p=0.024). This supports findings from **Magdi *et al.*** [11] who reported a significant increase in biochemical pregnancy rates in the freeze-all group compared to fresh ET in women with RIF.

Similarly, **Aflatoonian *et al.*** [12] and **Check *et al.*** [13] observed higher biochemical pregnancy rates in FET compared to fresh ET. However, **Basirat *et al.*** [14] and **Ibrahim *et al.*** [8] found no significant difference in biochemical pregnancy rates between the groups.

Kieu *et al.* [7] also found no difference in CPRs between FET and fresh ET in univariate analysis, though multivariate analysis showed a significantly lower CPR in FET.

Our study showed that the CPR was significantly higher in the FET group (49.3% vs 28%, p<0.001), with a higher rate per ET (17.2% vs 11.5%, p=0.04). This supports **Magdi *et al.*** [11] who found a significantly higher CPR in the freeze-all group compared to fresh ET (52% vs 28%). Similarly, **Zhu *et al.*** [15] observed higher CPR in frozen blastocyst transfer (55.1%) compared to fresh transfer (36.4%, p<0.05), and **Zhou *et al.*** [16] found a higher CPR in FET (63.1%) versus fresh ET (47%, p<0.01), attributing this to lower estradiol levels in FET cycles. However, **Ibrahim *et al.*** [8] and **Fitzmaurice *et al.*** [17] reported no significant differences in CPR between the groups, which contrasts with our findings.

In our study, the ongoing pregnancy rate was higher in the FET group (89.2% vs 81%, p=0.107), though not statistically sig.. This is consistent with **Magdi *et al.*** [11], who found a significantly higher ongoing pregnancy rate in the freeze-all group (44% vs 20%). Meta-analyses by **Roque *et al.*** [9] also support this trend favoring FET. **Shapiro *et al.*** [10] reported a higher ongoing pregnancy rate in the frozen-thawed group compared to fresh for day 6 blastocysts (54.3% vs 17.1%) but no significant difference for day 5 blastocysts. **Ibrahim *et al.*** [8] observed no significant difference in implantation rates between fresh and frozen transfers, though fresh transfers used the best embryos. Similarly, **Zhu *et al.*** [15] found higher implantation rates in frozen blastocysts (37.0% vs 25.2%, p<0.05), attributed to better embryo-endometrium synchrony in frozen cycles.

The multiple pregnancy rate was similar between the FET and fresh ET groups (29.7% vs 23.8%, p=0.149), indicating that the higher pregnancy rates in frozen transfers did not increase the risk of multiple pregnancies. This aligns with **Magdi *et al.*** [11] who found a higher multiple pregnancy rate in the freeze-all group (23.5% vs 8.9%). Similarly, **Ibrahim *et al.*** [8] reported a slightly higher rate in FET (23.1% vs 20%). **Zhou *et al.*** [16] also found a significantly higher multiple pregnancy rate in FET (46.9% vs 28.8%). Additionally, **Belva *et al.*** [18] observed similar outcomes in children conceived via frozen-thawed ICSI and IVF embryos.

In our study, early pregnancy outcomes did not differ significantly between groups (p=0.054). The frozen-thawed group had a similar proportion of single and twin pregnancies compared to fresh transfers, but a lower early pregnancy loss rate (10.8% vs. 19%), suggesting better implantation conditions in frozen-thawed cycles. This aligns with findings from **Magdi *et al.*** [11] and **Zhou *et al.*** [16] who also found no significant differences in early pregnancy loss between fresh and frozen cycles. However, **Wei *et al.*** [19] reported higher live birth rates for freeze-all compared to fresh transfers. Other studies, like those by **Shapiro *et al.*** [10] and **Bosdou *et al.*** [20] have shown improved outcomes in freeze-all cycles, especially for high responders.

Contrarily, **Aflatoonian *et al.*** [21] found a higher abortion rate in the FET group, while **Ibrahim *et al.*** [8] showed no significant differences in miscarriage rates between groups. **Smith *et al.*** [22] found a lower cumulative live birth rate for freeze-all strategies. While, **Maheshwari *et al.*** [23] noted that freeze-all was not cost-effective. **Stormlund *et al.*** [24] **and Shapiro *et al.*** [10] found no significant differences in live birth rates between frozen and fresh transfers, supporting the idea that embryo quality and endometrial receptivity are crucial factors.

The comparable multiple pregnancy rates between groups indicate that the improved success rates in frozen transfers were not achieved at the expense of increased multiple pregnancy risk, an important consideration in modern fertility practice. The high survival rate of thawed blastocysts (97.28%) in our study also demonstrates the technical reliability of current cryopreservation methods.

During our study, we faced 3 cases of ovarian hyperstimulation syndrome (OHSS). 1 case was of moderate degree and managed with conservative medical treatment. 2 cases were of severe degree which were managed with insertion of pigtail catheter for paracenetesis and drainage of intraperitoneal ascetic fluid. 1 of those 2 cases was complicated with adult respiratory distress syndrome (ARDS) that necissated patient admission to ICU on CPAP machine for 2 days and patient was discharged after another 2 days.

In our study, we had 4 cases of triplet pregnancy which were managed by elective transvaginal selective fetal reduction at 7-8 weeks of gestation. Only 1 case of them was complicated with midtrimester miscarriage at 20 weeks of gestation.

One of the most challenges that we faced during our study was women with resistant thin endometrium in frozen group who were managed with high estrogen supplementation doses up to 16 mg ethinyl estradiol per day up to 21 days followed by FET .

STRENGTHS

The strengths of this study include its prospective randomized design, comprehensive assessment of outcomes, and detailed analysis of embryo quality and survival.

LIMITATIONS

The single-center nature of the study and the relatively short follow-up period, ongoing pregnancy monitoring till 12weeks of gestation only and no live birth monitoring. Future multi-center studies with longer follow-up periods would be valuable to confirm these findings and assess long-term outcomes.

CONCLUSIONS AND RECOMMENDATIONS

FET significantly improves chemical and CPRs in cases of repeated unexplained implantation failure, with higher ongoing pregnancy rates and lower early pregnancy loss, suggesting improved implantation and pregnancy maintenance. So, we recommend freeze all policy for cases of recurrent ICSI failure and more multi-center studies in cases of recurrent ICSI failure.

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