Original Article

Comparative Study Of The Clinical Pregnancy Rate For Patients Who Underwent Their First Cycle Of Frozen Embryo Transfer (Fet) After A Freeze-All Cycle And Those Who Underwent Their First Cycle Of Fresh ET

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ABSTRACT

Objective: Compare the conception rate in in vitro fertilization cycles using frozen versus fresh embryo transfer.

Study Design: A retrospective cross-section observational study.

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Materials and Methods: The study was conducted using records from Ganna IVF centers between January 2015 and June 2022 for patients who underwent their first cycle of frozen embryo transfer (FET) after a freeze-all cycle and those who underwent their first cycle of fresh ET. ovarian stimulation was done using the flexible antagonist protocol. Artificial hormone replacement cycles were used for FET, and high-quality cleavage stage embryos were used during embryo transfer. The measured outcome for this study was the clinical pregnancy.

Results: There was significant difference in the rate clinical pregnancy 50.2% (621/2777) in the FET group and 46.9% (2156/2777) in the fresh ET group.

Conclusion: Frozen embryo transfer strategy shows superior results regarding the clinical pregnancy rate when compared to fresh embryo transfer in the selected patients of this study.

Key Words: Fresh embryo transfer, frozen embryo transfer, pregnancy rate in IVF cycles.

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INTRODUCTION

The field of medicine concerned with in vitro fertilization (IVF) and Intra Cytoplasmic Sperm Injection (ICSI) cycles is subjected to intense studies to come out with evidence based data to guide the best practice, the step of embryo transfer (ET) timing has been studied by researchers in Taiwan to determine if the freeze-all policy followed by frozen-thawed embryo transfer (FET) is better than fresh embryo transfer regarding the cost aspect in each method. They found that the freeze-all policy is the cost-effective method[1].

A meta-analysis in 2018 found that Singleton pregnancies from FET had a decreased relative risk (RR) of preterm labor, neonatal small for gestational age and low birth weight in comparison to pregnancies from fresh embryo transfers, but they suffered from higher relative risk (RR) of hypertensive disorders of pregnancy, neonatal high birth weight and large for gestational age[2].

However, A meta-analysis by Matheus Roque, examined the available evidence to determine if FET leads to more favorable outcomes in comparison to fresh transfer in terms of clinical pregnancy rates and the results did suggest superiority to FET; that could be justified by a better embryo-endometrium synchrony[3].

Again in 2018, a comparative study between two groups found that there were no significant differences in the rates of implantation, clinical pregnancy rates between pregnancies after FET versus Fresh embryo transfer[4].

In special population FET has shown to result in a higher clinical pregnancy rates and live-birth rate than fresh-embryo transfer among anovulatory women with the polycystic ovary syndrome but FET resulted in a lower risk of the ovarian hyperstimulation syndrome[5,6].

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This study aimed to share in the determination and comparison of the clinical pregnancy rate in artificial reproductive technology (ART) cycles that had fresh embro transferred versus those that had frozen-thawed embryo transfer in Ganna IVF Centres, Egypt.

PATIENTS AND METHODS

Study Design:

A retrospective cross-section observational study was conducted using patient's records from Ganna IVF centers between January 2015 and June 2022. Patients who underwent their first cycle of FET after a freeze-all cycle and those who underwent their first cycle of fresh ET were included. only women aged 18–49 years were compared. Diabetic patients were excluded as well as all patients with any endocrine diseases such as thyroid disorders or hyperprolactinemia. Total number of embryo transfer cycles extracted from the database *n*=7249, excluded patients *n*=1418, Included patients *n*=5831, out of which FET cycles were1237cycles and fresh ET cycles were 4594 cycles.

IVF Treatment:

Stimulation of the Ovaries was done using the flexible antagonist protocol. Patients received ovarian stimulation on the second day of the cycle when ovarian quiescence was confirmed, and measurement of the endometrium was less than 5 mm on ultrasound, they were started on 150–225 IU/day of follicle-stimulating hormone (FSH). The initial and subsequent FSH doses were adjusted according to their age, body mass index (BMI), antral follicle count (AFC) and follicular growth response. Then when follicles started to reach 14mm, GnRH antagonist (cetrutide 0.25) was used daily for prevention of LH surge, then subcutaneous injection of 3 syringes of 0.1 mg/ml triptorelin acetate (Decapeptyl; Ferring, Saint-Prex, Switzerland) were used as the trigger when more than three follicles reached 18 mm in diameter.

Oocytes were fertilized by either conventional IVF or intracytoplasmic sperm injection (ICSI) according to the results of semen analysis. The Istanbul consensus was used as a guide for both evaluation and grading of the embryo[7]

In the fresh transfer cohort, patients received progesterone daily after oocyte retrieval. Cleavage stage embryos were transferred on Day 3 under transabdominal ultrasound visualization, the progesterone was administered for three more weeks as a luteal support.

In the frozen embryo transfer cohort, all the high-quality embryos were vitrified for cryopreservation on day 3 after oocyte retrieval using the two-step protocol of Mukaida *et al*.[8].

Artificial hormone replacement cycles were used for FET, 2mg of Estradiol valerate three times daily, was started on cycle day 2. The dose was sometimes modified according to the monitoring of the endometrial thickness. When it reached 8 – 14 mm., progesterone (oral dydrogesterone at a dose of 20 mg twice daily) started and then high-quality cleavage stage embryos were transferred on day 3. Both estrogen and progesterone was continued until 14 days after transfer then pregnancy test was done to confirm implantation so that estrogen and progesterone are continued for three more months.

Outcomes:

The measured outcome for this study was the clinical pregnancy defined as the visualization of a live fetus and/or a gestational sac in transvaginal ultrasound four weeks after embryo transfer. This data was extracted from the patients records then underwent statistical analysis.

Statistical Analysis:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA). Data was summarized using mean and standard deviation for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. Comparisons between groups were done using unpaired *t* test (Chan, 2003a). For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5 (Chan, 2003b). P-values less than 0.05 were considered as statistically significant[9,10].

RESULTS

Demographic and Clinical Data:

The basic features of the two groups are tabled in Table (1) and Figures (1&2). There was no significant difference in age or the number of embryos transferred per cycle.

Fertility Outcomes:

As mentioned in Table (2) and Figures (3) there was significant difference in the rate clinical pregnancy was 50.2% (621/2777) in the FET group and 46.9% (2156/2777) in the fresh ET group.

Table 1:

	Fresh group				Frozen group				
	Mean	**SD**	**Minimum**	**Maximum**	**Mean**	**SD**	**Minimum**	**Maximum**	***P value***
Age	31.61	6.12	18.00	50.00	31.25	5.94	18.00	49.00	0.071
Number Transferred	2.85	1.03	1.00	8.00	2.88	0.87	1.00	5.00	0.334

Table 2:

Count		Fresh group		Frozen group		
		%	Count	%	*P value*	
Outcome	Pregnant	2156	46.9%	621	50.2%	0.041
	Failed	2438	53.1%	616	49.8%	

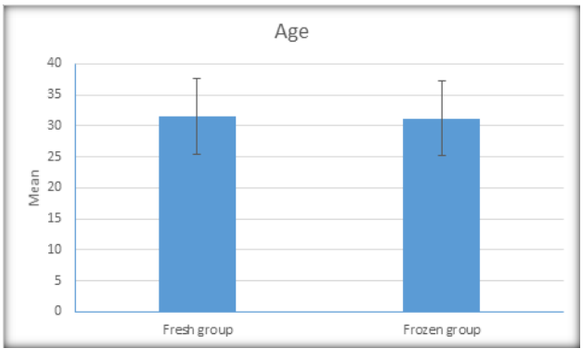

Fig 1: Mean age in both groups.

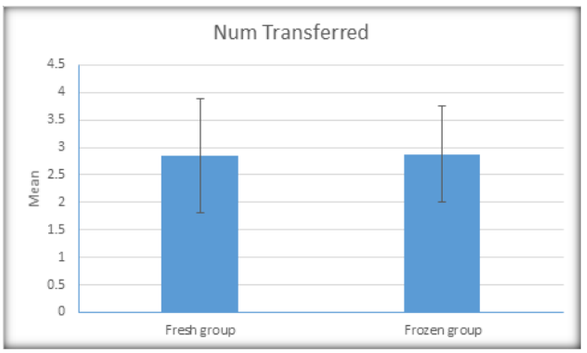

Fig 2: Mean number of embryos transferred.

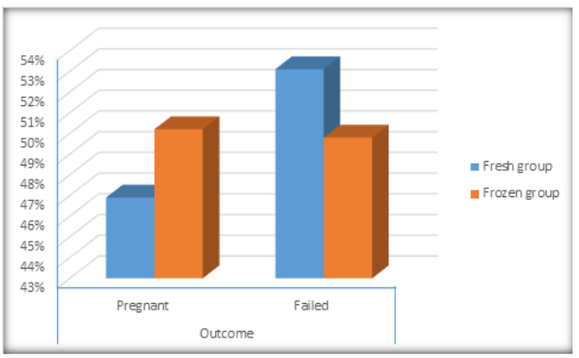

Fig 3: Clinical pregnancy rate in both groups.

DISCUSSION

There is widespread interest in the IVF field nowadays due to numerous social and medical factors, and the adopted protocols are continuously revised to tailor them to each case scenario of each group of patients, among the topics under study is the comparison between fresh embryo transfer and frozen embryo transfer technique, our study statistically analyzed the data from famous IVF centers from Egypt in a retrospective manner to include the records of more than five thousands patients and concluded that frozen embryo transfer technique had superior results regarding the clinical pregnancy rate.

According to earlier studies there were conflicting results regarding the superiority of either technique over the other across different outcomes.

For example, a study published in the journal of assisted reproduction and genetics in 2010 stated that biochemical pregnancy rate was comparable between FET and Fresh ET[11].

While Belva *et al*. and Aytoz *et al*. reported that biochemical pregnancy rate was significantly higher in the FET group than fresh ET group[12,13].

Another study compared the fertility rate and ART outcome of fresh ET and frozen ET in antagonist IVF cycles and found that Although not statistically significant, the percentage of chemical pregnancy and abortion was higher in the frozen ET group. The percentage of clinical pregnancy and live birth was higher in the fresh ET group[14].

Some studies had results similar to ours, among them is a study by Zargar in 2021 that stated that "in the fresh embryo and the frozen embryo groups, clinical pregnancy was respectively confirmed among the 111 cases (35.46%) and 169 cases (47.47%),

which was significantly different (p=0.0001). The ongoing pregnancy rate was significantly higher in the frozen embryo group. In addition, the live birth rate was significantly higher in the frozen embryo group, compared with the fresh embryo group[15].

Also Chandel in 2016 proposed that FET adds an advantage of providing good quality embryos for future and subsequent implantations in cases of failure, based on his finding that FET has better and significant conception rates compared to fresh embryo transfers in cases of infertility[16].

On contrary, a study focusing on young PCOS patients without risk of OHSS have a high clinical pregnancy rate with fresh transplant cycles. Frozen-thawed embryo transfer may increase the incidence of low placenta, fetal distress and neonatal jaundice[17].

Interestingly a study published in 2024 suggested that frozen embryo transfer yields better CPR and LBR when frozen blastocysts are transferred, but these rates are lower when frozen cleavage stage embryos are utilized. Therefore, the freeze-all strategy may not be suitable for universal application[18].

A courageous recommendation was published by a group of researchers in 2024 for patients under 35 years old with a low oocyte retrieval count, they said that embryo cryopreservation and FET are recommended when usable embryos are available. However, for patients aged 35 and above, it is advisable to undergo fresh embryo transfer to reduce the number of treatment cycles and related expenses without compromising the pregnancy rate[19].

A supporting paper to this aforementioned study, was published earlier in 2022 by the journal of clinical medicine clearly stated that the clinical pregnancies are higher after fresh ET in women of advanced maternal age (AMA), and they found no significant difference in the live birth rate between FET and fresh ET in women of AMA[20].

But it is worthy to mention that a recent study in 2024 suggested that the use of frozen-thawed single euploid ET in AMA patients to allow sufficient time for comprehensive genetic evaluation, while also enhancing implantation and pregnancy rates relative to fresh single euploid ET, in case they are undergoing preimplantation genetic screening (PGS)[21].

When women with a thin endometrium undergoing IVF were studied; the live birth rate, clinical pregnancy rate, and biochemical pregnancy rate after frozen ET were significantly higher than in the fresh embryo group[22].

On another aspect, if we are to choose between fresh embryo transfer versus FET, other fetal, perinatal and infant long term effects had to be considered not just the pregnancy rate or birth rate, that is why some studies monitored the percentage of major malformation rate after FET seems comparable with fresh ET group while preterm birth and LBW in singletons and multiple pregnancies were comparable between FET and fresh ET groups[10].

On a larger scale, Pelkonen and his colleagues published that Embryo freezing does not adversely affect perinatal outcome in terms of prematurity, low birthweight and being small for gestational age versus the fresh embryo transfer and the outcome is similar or even better, particularly regarding fetal growth[23].

Similarly, Shih and colleagues stated that LBW rates was found to be higher after fresh embryo transfer than after FET[24].

However, Fresh embryo transfer was favored by a published study in 2019, as the researchers discovered that infants in the FET group have greater odds for infectious disease, respiratory, and neurologic conditions than those in the fresh embryo transfer group[25].

Finally, - and obviously- the studies will continue to investigate these numerous points of comparison between the outcomes of each of these two techniques (fresh embryo transfer and FET) to reach better understanding of the expected benefits and drawbacks of each of them on both the short and long terms, thus tailoring the IVF protocol for each patient to reach the best patient care.

CONCLUSION

We concluded that frozen embryo transfer during IVF cycles lead to better outcomes regarding the clinical pregnancy rates when compared to fresh embryo transfer strategy with regard to the methodology of this study.

CONFLICT OF INTEREST

There are no conflicts of interests.

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