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Original Article

Pregnancy outcomes following *in vitro* fertilization using fresh or frozen embryo transfer

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ABSTRACT

Objective: The aim of this study was to investigate the pregnancy outcomes in women undergoing IVF using fresh and/or frozen embryo transfer.

Methods: In this retrospective patient record study, we reviewed 2,872 infertile women's files, who were candidates for IVF. The patients were classified into two groups, including those who underwent fresh embryo transfer (n=1628) and/or frozen embryo transfer (FET) (n=1244).

Results: Fertility was achieved in 313 (19.23%) and 356 (28.62%) patients, who underwent fresh ET and FET, respectively. The rates of clinical pregnancy, ongoing pregnancy, and live births were significantly higher in the FET group than the fresh ET group. The incidence of multiple pregnancies, perinatal mortality, abortion in the first trimester, preterm delivery, and low birth weight were significantly higher among fresh ET group [38 (35.51%), 15 (14.50%), 72 (23.01%), 26 (8.30%), and 33 (10.54%), respectively] than in the FET group [25 (15.33%), 6 (6.87%), 63 (17.69%), 14 (3.93%), and 20 (5.61%); $p<0.05$]. In addition, the incidence of ectopic pregnancies, abortion in the second trimester, gestational diabetes, preeclampsia, and placenta previa were higher in the fresh ET group, but not significantly so ($p>0.05$).

Conclusions: Women who underwent IVF via FET showed more successful fertility and pregnancy outcomes compared to those who underwent IVF by fresh ET.

Keywords: fresh embryo transfer, frozen embryo transfer, pregnancy, *in vitro* fertilization

INTRODUCTION

Infertility refers to the failure to achieve pregnancy after one year of unprotected sexual intercourse (Pelkonen *et al*., 2010; Dunkel-Schetter & Lobel, 1991). Both female and male factors can cause infertility. Female and male factors are each solely responsible for 35% of infertility, and in 20% of cases a combination of female and male factors is involved; and in 10% of cases, there is no specific cause for the infertility found (Maheshwari *et al*., 2012; Roque *et al*., 2013; Lindsay & Vitrikas, 2015). Other factors that increase the likelihood of infertility include environmental and occupational factors, the effects of toxins from tobacco use, strenuous exercise, very high or very low weight, and low age of couples (Lindsay & Vitrikas, 2015; Pelkonen *et al*., 2010).

Successful fertility (successful embryo implantation) through the IVF method with fresh embryo is still low; cohort studies reported a chance of pregnancy between 18.9% and 41.8%, with an average likelihood of 32% (Pelkonen *et al*., 2010). The IVF outcomes depend on a variety of factors, including maternal age, frozen or fresh embryo, donated eggs, etc. (Maheshwari *et al*., 2012). Considering that young age is one of the main pre-existing risk factors of ovarian hyperstimulation syndrome (OHSS), preservation of the frozen embryos for the next 3 to 5 years for ART cycle programs can help increase the chance of pregnancy and reduce the risk of multiple pregnancies (Roque *et al*., 2015; Dieamant *et al*., 2017).

Qualified embryos or fertilized eggs in IVF is one of the key parts of a successful pregnancy. In this regard, there is information to be checked, including the number of cells available for evaluation of fresh ET health and embryo quality grading (Weitzman *et al*., 2010). 48 hours after fertilization, we examined cell number, cell size and the fragmentation degree of cells. Whenever the number of fragmentation is greater, the embryo quality is lower and pregnancy rates may be lower. Three day-old embryo grading based on the number of cells, embryo fragmentation and symmetry or proportion of cells are divided into five grades E, D, C, B, A. Therefore, the highest IVF embryo viability has the lowest fragmentation and natural growth rate, usually including embryos in grades B, A (Puissant *et al*., 1987). Embryo transfer is done in two ways: 1. Fresh embryos fertilized at the same menstrual cycle. 2. Frozen embryos fertilized in previous cycles (Roque *et al*., 2013). The present study is aimed at comparing the pregnancy outcomes in women who underwent IVF using fresh or frozen embryo transfer.

MATERIALS AND METHODS

This retrospective study was carried out in 2019 after approval by the group council and the ethics committee of the Ahvaz Jundishapur University of Medical Sciences - Ahvaz, Iran (Ethical Code: IR.AJUMS.REC.1398.782). In total, 2,872 infertile women's files, who were referred to the Ahvaz Infertility Center and were candidates for ART, were reviewed and evaluated.

Patients with incomplete information and egg donation cases were excluded from the study. The patients were classified into two groups including those who underwent fresh ET (n=1628) and/or frozen embryo transfer (FET) (n=1244).

The method and process of these measures were in accordance with global and central protocols. Thus, all cases were followed up via a phone call. Pregnancy outcomes such as spontaneous abortion, preterm delivery, gestational diabetes, gestational hypertension, prenatal mortality, and other pregnancy consequences were assessed and recorded. In addition, the study continued until the end of the pregnancy for pregnant patients who were undergoing IVF.

Pregnancy using human chorionic gonadotropin (HCG) levels was performed on the 11th day of embryo transfer, and clinical pregnancy was confirmed based on confirming

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an embryo heart rate at the 7th week of gestation. Ongoing pregnancy was considered as the continuation of the pregnancy process after the 12th week of gestation. Preterm delivery was considered as delivery before the 37th week of gestation. Mortality in the prenatal period included stillborn infant deliveries or infants who were born alive from the 22nd week of gestation and died on the 7th day of birth. Other parameters such as multiple births, ectopic pregnancy, gestational diabetes, placenta previa, abortion in the first trimester, abortion in the second trimester, and low birth weight were extracted from the files and compared between the two groups.

Statistical analysis

Categorical variables were compared using the Chi-square test and presented as frequency and percentages while continuous variables were compared with independent t-test, and presented as the mean. Analysis of all results was performed by the SPSS software version 22, and a *p*-value lower than 0.05 was considered statistically significant.

RESULTS

Reviewing the 2,872 files of infertile female candidates for IVF showed that fertility was achieved in 313 patients (19.23%) and 356 patients (28.62%) from the fresh ET group and the FET group, respectively. Statistically, the studied patients did not differ significantly in terms of maternal and paternal average age, type of infertility (primary or secondary), and the cause of infertility ($p>0.05$) (Table 1).

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 ($p=0.0001$). In addition, the live birth rate was significantly higher in the frozen embryo group [138 (38.76%)], compared with the fresh embryo group [49 (15.65%); $p=0.0001$].

The incidence of multiple pregnancies, perinatal mortality, abortion in the first trimester, preterm delivery, and low birth weight < 2500 g were significantly higher in the fresh ET group than the FET group ($p<0.05$). Although the incidence of ectopic pregnancies, abortion in the second trimester, gestational diabetes, preeclampsia, and placenta previa were higher in the fresh ET group, no statistically significant differences were found between the two groups ($p>0.05$). The mean birth weight was significantly higher in the FET group ($p=0.001$).

Causes of prenatal mortality were also investigated. The most important maternal cause of prenatal deaths in both fresh and frozen embryo groups was multiple pregnancies [(34.18% *vs*. 20.51%, respectively); Table 2].

From a total of 356 FET, 294 cases (82.58%) had previously experienced a pregnancy failure following the first fresh ET, while 62 cases (17.41%) had an early successful pregnancy. Subsequently, among these 62 cases, 38 and 24 cases showed successful pregnancies and live birth in frozen cycles, respectively. However, from 294 cases with a history of pregnancy failure, 128 cases became pregnant and 104 cases achieved a live birth.

Based on an intragroup statistical comparison between both subgroups of FET cases (with and/or without a history of early pregnancy), the clinical pregnancy rate was significantly higher in cases with a history of successful early pregnancy (61.30% *vs*. 43.53%; $p=0.0174$). However, the live birth rate was not significantly different between the two subgroups [$p=0.66$; Table 2]. All cases in the fresh ET group were in the first ET experience.

DISCUSSION

According to medical reports, IVF experts do not agree on which is better, fresh embryo transfer or frozen embryo transfer. Therefore, the present study aimed to investigate the outcomes of pregnancy following IVF with fresh and/or frozen embryos on 669 patients.

In Wang *et al*. (2017), the rate of ongoing pregnancy in the frozen embryo group (52%) was significantly higher than in the fresh embryo group (45.3%). They concluded that the frozen embryo protocol significantly increased the rate of implantation and pregnancy success compared to the fresh embryo. The results of Roque *et al*. (2015) showed that the probability of fertility among FET and fresh ET groups was 46.4% and 35.9%, respectively, and the results of IVF in cases undergoing frozen ET were significantly better than fresh ET group. Our study showed that the rate of clinically confirmed pregnancies and the ongoing pregnancy in the frozen embryo group were significantly higher than in the fresh embryo group, which is consistent with the mentioned reports. Based on a study in Canada, the pregnancy success rate was about 33% for fresh embryos, while it was reported as 24% for frozen embryos (Gunby *et al*., 2010), which was in contradiction with our findings.

According to Spijkers *et al*. (2017), the rate of preterm delivery (less than 37 weeks) was higher in the fresh embryo group. The results from Maheshwari *et al*. study (2012) showed that the rate of preterm delivery was lower in women who were fertilized using frozen embryos

Table 1. Demographic and clinical information of patients and infants studied.

Variable		Fresh embryo (n=313)	Frozen embryo (n=356)	*p*-value
Age (Mean)	**Female**	34.73	33.34	0.81
	Male	39.04	37.83	0.72
Types of infertility	**Primary**	224 (71.57)	248 (69.66)	0.41
	Secondary	89 (28.43)	108 (30.34)	
Infertility causes	**Male factor**	167 (53.35)	191 (53.65)	0.83
	PCO	102 (32.59)	111 (31.18)	
	Male factor/PCO	32 (10.22)	38 (10.67)	
	Other causes	44 (14.06)	54 (15.17)	

Data are expressed as mean or number (%).
Chi-Square test.
$p<0.05$ is considered as significant level.

Table 2. Determining and comparing the consequences of pregnancy in two groups.

Variables		Fresh embryo (n=313)	Frozen embryo (n=356)		*p*-value
Clinical pregnancy		111 (35.46%)	169 (47.47%)		0.0001***
Ongoing pregnancy		77 (24.60%)	141 (39.60%)		0.0001***
Live birth rate		49 (15.65%)	138 (38.76%)		0.0001***
Ectopic pregnancy		13 (4.15%)	5 (1.40%)		0.62
Abortion	**First-trimester loss**	72 (23.01%)	63 (17.69%)		0.022*
	Second-trimester loss	10 (11.60%)	9 (6.87%)		0.64
Twain		38 (35.51%)	25 (15.33%)		0.024*
Gestational diabetes		17 (24.64%)	31 (23.66%)		0.132
Placenta Previa		16 (5.11%)	17 (4.77%)		0.859
Preeclampsia		24 (7.66%)	26 (7.30%)		0.88
Preterm delivery		26 (8.30%)	14 (3.93%)		0.021*
Low birth weight < 2500 g		33 (10.54%)	20 (5.61%)		0.021*
Birth weight (kg)		2.8±1.03	3.2±1.8		0.001*
Perinatal mortality		15 (14.50%)	6 (6.87%)		0.0032*
			FET cases with successful early pregnancy history (n=62)	**FET cases with failed pregnancy history (n=294)**	
Clinical pregnancy after FET cycles			38 (61.30%)	128 (43.53%)	0.011*
Live birth rate after FET cycles			24 (38.70)	104 (35.37)	0.66

Data are expressed as number (%).
Fisher's exact test and/or Chi-Square.
FET: Frozen embryo transfer
*$p<0.05$ is considered as significant level.

(Maheshwari *et al*., 2012). The results of Spijkers *et al*. (2017) showed that the birth weight was higher in the frozen embryo group than in the fresh embryo group. The results of Luke *et al*. (2017) reported a higher risk of weight gain in the frozen embryo group compared to a fresh embryo in both the first and second pregnancies. Our findings have also confirmed these points, in which case the preterm delivery rate was higher in the fresh ET group, while the mean birth weight was significantly higher in the FET. In addition, the number of low birth weight infants in the fresh embryo group was significantly higher.

The results of Pelkonen *et al*. (2010) showed that the chance of low birth weight in infants born by FET was lower than in infants born from fresh embryo. In addition, the average birth weight for infants born by FET was 134 grams higher than in infants born from fresh embryos. In Maheshwari *et al.* (2012), low birth weight among infants born from fresh embryo was more evident than in FET infants.

In the present study, although the prevalence of patients with preeclampsia was higher in the fresh embryo group than in the FET group, this difference was not statistically significant. This result was consistent with the results from Blazquez *et al*. (2018); they showed that despite the high prevalence of preeclampsia in pregnant women with IVF, frozen embryos did not make a considerable reduction in the risk of preeclampsia, its duration, and gestational hypertension.

In the present study, perinatal mortality was significantly higher in the fresh embryo group. Multiple pregnancies were the most important maternal cause of prenatal deaths in both fresh and frozen embryo groups.

Based on Zamani Kiasari *et al*. (2010), the prenatal mortality rate was reported to be 7.2% in infants born from normal pregnancies. Our results showed that the mortality rate during the prenatal period in patients undergoing FET was almost lower than those who were undergoing fresh embryo transfers. In this regard, our results are confirming the results from Kansal Kalra *et al*. (2011); they evaluated 368 IVF pregnancies, including 238 cases of fresh ET and 130 cases of FET. The perinatal morbidity, first-trimester loss, and other adverse outcomes were significantly higher in IVF pregnancies with fresh ET compared with FET pregnancies. In addition, their results showed that the multiple pregnancy rate in the fresh ET group was considerably higher than the FET group, i.e. FET was more likely to result in a singleton pregnancy (Kansal Kalra *et al*., 2011).

Pelkonen *et al*. (2010) reported that the likelihood of premature birth was lower in the frozen embryo group than in the fresh embryo group. Frozen embryos also had no adverse effects on prenatal outcomes compared to fresh embryos, and was even better in some cases. Based on Maheshwari *et al*. (2012), the likelihood of perinatal mortality in infants born from frozen embryos were lower. In our study, the multiple pregnancy and abortion rates in the first trimester were significantly higher in the fresh embryo group than in the FET group. In addition, the rate of ectopic pregnancies, gestational diabetes, placenta previa, and abortion in the second trimester were higher in the fresh embryo group, but not significantly so. A systematic

and meta-analysis review study carried out by Roque *et al*. (2013) stated that the fertility results using IVF with frozen embryo were better than in the fresh embryo. They assumed that these results might be due to better access to synchrony between endometrium and embryo in the frozen embryo transfer method.

Our results regarding the effect of previous fresh cycles on FET cycles are in agreement with the findings reported by Ashrafi *et al*. (2011) and Bushaqer *et al*. (2020), but in contrast with the reports from Doherty *et al*. (2014) and Bdolah *et al.* (2015). Our results showed that the clinical pregnancy rate in cases of FET with a history of successful early pregnancy was significantly higher than cases with the failed pregnancy history (61.30% *vs*. 43.53%), which means that the previous fresh cycle protocol may affect the pregnancy outcomes arisen from subsequent FET cycles. However, the previous fresh cycle outcomes did not affect the live birth rate, which confirms the results reported by El-Toukhy *et al*. (2003) and Bushaqer *et al*. (2020). Their results showed that embryo survival arisen from frozen cycle is not affected by the fresh cycles (Bushaqer *et al*. 2020; El-Toukhy *et al*., 2003). In this regard, some researchers theorized that the good quality embryos in fresh and frozen cycles might lead to pregnancy in both cycles. However, opposite researchers believed that the top quality embryos would be often chosen for fresh cycles, and so, less reproductive embryos are left for FET cycles.

CONCLUSION

Women who underwent IVF by frozen embryo transfer showed more successful fertility and pregnancy outcomes compared to those who underwent IVF by fresh embryo transfer.

Study strength

Although a few studies have previously showed a strong influence of frozen ET on the consequences of fertility and pregnancy, this study is one of the rare studies, which more comprehensively and accurately examined the effect of embryo quality on all consequent pregnancies and childbirth following IVF.

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CONFLICT OF INTEREST

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