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Comparison of maternal and perinatal outcomes of pregnancies with frozen and fresh embryo transfers at term pregnancy

Frozen and fresh embryo transfer results

Jule Eriç Horasanlı, Hasan Energin, Enes Ferlibaş
Department of Gynecology and Obstetrics, Meram Faculty of Medicine, Necmettin Erbakan Üniversity, Konya, Turkey

Abstract
Aim : In our study, we aimed to compare maternal and perinatal outcomes of frozen and fresh embryo transfers, induced by single or double embryo transfer with in vitro fertilization (IVF) at term pregnancy.
Material and Methods: After obtaining ethics, our study was performed retrospectively assessing pregnancies in women between the ages of 18 and 40 induced with single or double embryo transfer with IVF between the years 2010 and 2020. Maternal outcomes such as oligohydramnios, polyhydramnios, preeclampsia, placenta previa, placenta accreta syndrome (PAS), and hysterectomy were examined in all groups. Perinatal outcomes including birth weight, time of delivery, small for gestational age (SGA), large for gestational age (LGA), appropriate for gestational age (AGA), preterm labor, Apgar score of infant at five minutes, and intensive care requirement were also investigated.
Results: No difference was observed in terms of oocyte number collected, neonatal intensive care requirement, Apgar scores, postpartum hysterectomy, and blood transfusions. There was no difference between the groups in birth weight, preterm labor, and delivery time. There was no significant difference between the groups in SGA, LGA, and AGA. Polyhydramnios and oligohydramnios were significantly higher in the fresh transfer group ($p = 0.006$ and $p = 0.006$, respectively). Among perinatal parameters, the frequency of placenta previa was significantly higher in the frozen transfer group ($p = 0.001$). The frequency of placenta accreta and preeclampsia was not significantly different.
Discussion: Placenta previa was higher in the frozen transfer group, suggesting frozen embryo transfer increases the risk of placenta previa. Oligohydramnios and polyhydramnios were higher in the fresh transfer group.

Keywords
IVF, Frozen Transfers, Fresh Transfers, Outcomes, Term Pregnancy

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Corresponding Author: Jule Eriç Horasanlı, Department of Gynecology and Obstetrics, Meram Faculty of Medicine, Necmettin Erbakan Üniversity, Konya, Turkey.
E-mail: juleesen@gmail.com P: +90 555 479 33 94
Corresponding Author ORCID ID: https://orcid.org/0000-0002-8738-7126

Introduction

Despite regular sexual intercourse, one out of every six couples experiences infertility and wishes to have a healthy child with assisted reproductive technology (ART) [1]. Cryopreservation has become an essential part of ART and was used in approximately 40% of all in vitro fertilization (IVF) cycles in 2015 [2]. Embryo cryopreservation is an almost routine practice in IVF applications because it prevents multiple pregnancies by allowing for the transfer of fewer embryos. Protection from the risk of ovarian hyperstimulation syndrome (OHHS) is also an advantage [3]. Frozen embryo transfer (FET) may lead to better obstetric results by providing better placental development compared to fresh transfers since it creates a good endometrial microenvironment. However, some studies suggest that FET may have a negative effect on obstetric results. There can be a greater risk of congenital malformations in frozen embryo transfers compared with fresh embryo transfers Animal studies have shown increased large for gestational age results due to epigenetics [4,5].

Recent studies show that the risk of developing pregnancy-induced hypertension (PIH) and placenta accreta is higher in the FET group than in the fresh embryo transfer group [6,7]. IVF patients have more postpartum hemorrhage in their deliveries than the general population. During postpartum bleeding, hysterectomy, blood transfusions, and intensive care may be required. Thus, frequent applications of embryo cryopreservation and total freeze strategies may cause neonatal, perinatal, and maternal consequences [8,9].

Our aim in this study was to investigate retrospectively the maternal and perinatal outcomes of frozen and fresh embryo transfers, induced by single or double embryo transfer with in vitro fertilization (IVF) at term pregnancy.

Material and Methods

Patients

After obtaining ethics, our study was performed retrospectively assessing pregnancies in women between the ages of 18 and 40 induced with single or double embryo transfer with IVF between the years 2010 and 2020. (the Ethics Committee approved the study protocol (protocol no:2686- 09.07.2020) Perinatal and maternal results were obtained from screening patient information files for patients who had frozen or fresh embryo transfer and gave birth after 37 gestational weeks. Informed consent was obtained from all patients. In the patient groups, age, body mass index (BMI), education, smoking, number of eggs collected (oocyte count), embryo transfer day, and transfer type (frozen or fresh embryo transfer) were recorded. Maternal outcomes such as placenta previa, placenta ccrete spectrum (PAS), postpartum hemorrhage, and the associated need for blood transfusion and hysterectomy were investigated in all groups. As fetal parameters, delivery time, birth weight, small for gestational age (SGA: birth weight less than the 10-percentile adjusted for gestational week), large for gestational age (LGA: birth weight above the 90 percentile adjusted for gestational age), appropriate for gestational age (AGA), 5-minute Apgar score, and intensive care (NICU) requirement were investigated. Births before the 37th gestational week were accepted as term births. The presence of polyhydramnios and oligohydramnios were also examined. Single amnion vertical pocket fluid length over 8 cm was classified as polyhydramnios and values below 2 cm as oligohydramnios.

Inclusion criteria:

Patients who received single or double embryo transfer with IVF (fresh or frozen embryo transfer), gave birth after 37th weeks of gestation.

Exclusion criteria:

Patients with vanishing twins were excluded from the study, although their pregnancies continued individually. Miscarriages were not included. Multiple pregnancies were not included in the study. Chronic hypertensive patients and patients with previously diagnosed type 1 and type 2 diabetes were excluded from the study.

Statistical analysis:

Maternal and perinatal outcomes were described using mean, standard deviation, frequency, and percentages. Groups were compared using the chi-square and ANOVA tests. All analyses were performed using SAS University Edition 9.4 program. A p-value <0.05 was considered significant.

Results

A total of 297 patients were evaluated in the study. The fresh transfer group had 165 patients (55.6%), the frozen transfer (FET) group had 132 patients (44.4%). There was no difference in socio-demographic characteristics such as age, smoking, and education (p = 0.60 and p = 0.7, respectively). The BMI values were higher in the fresh transfer group (p = 0.01) (Table 1). Hysterectomy was not performed for any of the patients in the groups. There was no difference in terms of blood transfusions (p = 0.17). There was no significant difference in the number of oocytes obtained in the groups (p = 0.06). No significant difference was observed between the groups in the perinatal parameters SGA, LGA, and AGA (p = 0.41). There was no difference between the groups in terms of birth weight (p = 0.88), and time of delivery (p = 0.09). Although there was no statistically significant difference between the groups in neonatal intensive care requirement (p = 0.22), it was required for 20.45% of the FET group, 14.55% of the fresh transfer group. Newborn Apgar scores were similar in all groups (p = 0.08) (Table 2). There was no significant difference in gestational diabetes mellitus incedence between fresh ET and FET groups. Oligohydramnios and polyhydramnios were

Table 1. Baseline characteristics of the fresh ET group and FET group

Characteristics	Fresh ET (n=165)	FET* (n=132)	P value
Age, years	30.89± 5.41	30.77±3.71	0.60
BMI	30.61± 4.94	27.85±3.82	0.01
Duration of infertility	6.44± 4.54	7.01 ± 4.86	0.08
Cause of infertility n (%)			
Female factors	98 (59.3%)	75 (56.8%)	
Male factors	26 (15.7 %)	24 (18.1%)	
Mixed factors	33 (20%)	26 (19.6%)	
Unexplained	8 (4.8%)	7 (5.3 %)	
Oocyte Count	9.15 ± 2.63	10.14 ± 2.56	0.06

* (FET): Frozen Embryo Transfer, BMI: Body Mass Index

Table 2. Perinatal- Maternal Outcomes

		Fresh ET (n=165) n(%)	FET* (n=132) n(%)	P value
Fetal weight	Small for Gestational Age	12 (7.27)	21 (15.91)	0.41
	Appropriate for Gestational Age	147(89.09)	99 (75.00)	
	Large for Gestational Age	6 (3.64)	12 (9.09)	
NICU**		24 (14.55)	27 (20.45)	0.22
Amnion	Oligohydramnios	17 (10.3)	10 (7.57)	0.006
	Polyhydramnios	10 (6.6)	4 (3.03)	0.006
Placenta	Placenta Previa	5 (3.03)	8(6.06)	0.001
	Placenta Accreta Syndrome	3 (1.81)	2 (1.51)	0.06
Preeclampsia		12 (7.27)	10 (7.57)	0.32
Fetal weight (gr)		2916.18± 576.48	2909.77±665.13	0.88
Apgar score		6.58 ± 1.01	6.93 ± 0.85	0.08
Gestational Diabetes Mellitus		13 (7.87)	11 (8.33)	0.13

* (FET): Frozen Embryo Transfer, **NICU: Neonatal Intensive Care Unit, Maternal and prenatal outcomes are described using mean ± standard deviation or frequency (percentages).

significantly higher in the fresh transfer group (p = 0.006 and p = 0.006). The frequency of placenta previa was significantly higher in the frozen group (p = 0.001).

Discussion

Cryopreservation has recently become an important part of ART and has changed the transfer policies towards single embryo transfer. FET embryos have played an important role in modern ART therapy in protecting from over hyperstimulation syndrome and multiple pregnancy. After the first successful cryopreservation, embryo freezing procedures were performed for 20 years by various methods [10]. While slow freeze embryo cryopreservation was preferred in the first years, the vitrification method has recently depended not only on embryo quality, but also on endometrial receptivity and the uterine environment. Supra-physiological hormonal levels such as high estradiol levels observed during controlled ovarian stimulation (COS) can adversely affect embryo implantation, replacing it [11]. Obstetric outcomes in IVF are important for maternal and infant health, and success altering the microenvironment and implantation, leading to adverse obstetric and perinatal outcomes. Ovarian stimulation causes an increase in the risk of LBW in fresh embryo transfer cycles [12]. Since no ovarian stimulation was used in patients in whom a donor oocyte was used, no statistical difference was observed in LBW in either FET or fresh cycles and no increase in preterm delivery was observed. Preterm birth, LBW, and low Apgar scores are reported to be significantly lower in FET cycles [13]. However, Spijkers et al. found that the rate of preterm birth before 37 weeks of gestation was not different between fresh and FET transfers (2). Despite this, it is thought that endometrial receptivity improves in FET cycles (14,15). Improving endometrial conditions results in the proper placental development [16].

An increase in the risk of high birth weight and LGA is observed in FET cycles compared to fresh cycles [16,18]. Pinborg et al. attributed the development of LGA to the overgrowth of tissues to compensate for cell loss during freezing and thawing and to weight differences in culture media due to the influence of epigenetic factors [18]. Although the higher incidence of LGA fetuses in FET embryos does not appear to be clinically important, the risk of increased Cesarean section rates, metabolic disorders, stillbirth, traumatic deliveries, and birth asphyxia increases [15]. Other reasons may be the quality of the embryo itself or maternal factors [18]. In this study, we found no difference in the FET and fresh transfer groups in LBW, birth weight, and SGA, LGA, and AGA perinatal results.

Obstetric and reproductive results in IVF practice are important in terms of maternal and infant health [10]. The biggest concern in fresh transfers is the disruptive effect of COS on the endometrium and uterus. Some investigators report good IVF results because of a better endometrial environment in FET cycles compared to fresh embryo transfers [18]. Contrary to these findings, other studies report some side effects and negative obstetric outcomes in FET cycles [19]. Sazonova et al. mentioned an increased risk of PIH, preeclampsia, and placenta accreta in single FET cycles compared to fresh cycles [20]. We found no significant difference in the risk of developing preeclampsia between the Fresh ET group and the FET group.

Obstetric bleeding is reported with a higher rate in ART cycles, but the mechanism is not fully known. It has been suggested that fresh embryo transfers in IVF patients, endometriosis, hormone treatments, and events during the implantation period may be responsible for the bleeding and suboptimal endometrial function is a critical mechanism. A study reported that antepartum bleeding after fresh embryo transfers is due to increased estradiol concentrations in proportion to the number of oocytes collected that indirectly affects the endometrium [7,21]. Some researchers report that estrogen and progesterone are given in FET cycles, imitating normal physiology, and there is a question of a better endometrial environment [22]. Some authors found a high risk of developing placenta previa in ART and concluded that implantation occurs in the lower uterine segment due to uterine contractions during transfer [21]. Several studies report higher rates of placenta previa in ART singleton pregnancies compared to spontaneous pregnancies [7]. In a study comparing fresh cycles with FET cycles, a lower risk of placenta previa was found [19]. However, in some studies, the risk of developing placenta previa was not different between FET and fresh cycles [8-22]. In our study, we observed that the risk of placenta previa was significantly higher in FET pregnancies.

PAS is a rare complication after ART. This improper development of the placenta can cover a wide spectrum from hysterectomy to maternal emergencies. The study of Ishihara in 2014 demonstrated this increase in FET cycles. They also stated that the increased risk of placenta accreta in FET cycles is not related to patient characteristics, and the reason for this increase is due to low estradiol levels, thin endometrium, and uncontrolled extravillous trophoblast invasion or only cryopreservation [7]. In this study, there was no difference between the groups in the risk of developing PAS.

Studies have shown that problems such as polyhydramnios and oligohydramnios are more common in patients with ART than in normal gestational patients [23]. In another study, a 114% increased risk of polyhydramnios and oligohydramnios

was reported in ART [24]. In our study, a statistically significant increase was observed in both the FET and fresh groups compared to natural conception and was higher in the fresh embryo group.

Conclusion

Consequently, the safety of ART procedures is more important than pregnancy and implantation rates. There is an increased risk of placenta previa in the FET embryo group. This situation contains risks for the life of the mother and fetus. In the fresh embryo group, there was an increased risk of polyhydramnios and oligohydramnios. We think that more detailed studies should be done to understand the obstetric and perinatal consequences of cryopreservation. The limitation of this study was that it was retrospective and ignored various protocols of cryopreservation that could affect implantation. Before the studies evaluating obstetric and perinatal outcomes between FET cycles and fresh cycles become clear, "freeze all" strategies should be approached more cautiously.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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