



Comparison of maternal complications between fresh and frozen embryo transfer during gestation

Gebelikte taze ve dondurulmuş embriyo transferiyle ilişkili maternal komplikasyonların karşılaştırılması

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Abstract

Objective: Maternal complications in infertile women undergoing in vitro fertilization are an important discussion, and patients should be informed about these complications depending on the method of embryo transfer. In this study, maternal complications during gestation were compared between frozen and fresh embryo transfer in infertile women who underwent in vitro fertilization at Shariati Hospital from 2018 to 2021.

Materials and Methods: This study was a retrospective cohort study, and patient data were collected using archive files. From 396 in vitro fertilization patients, 302 were in the frozen embryo transfer group and 94 were in the fresh embryo transfer group. Patients in both groups were similar in terms of the number of transferred embryos and age ($p>0.05$). Data regarding threatened miscarriage, early miscarriage, placenta previa occurrence, gestational hypertension, preterm birth, gestational diabetes, and pre-eclampsia were gathered and compared between the two groups.

Results: The rates of threatened miscarriage, placenta previa, gestational hypertension, gestational diabetes, preterm birth, and pre-eclampsia were not significantly different between the fresh and frozen embryo transfer groups ($p>0.05$). However, the early miscarriage rate in the fresh embryo transfer group was significantly higher (34% vs. 16.2%, $p<0.001$).

Conclusion: According to the results of this study, maternal complications, except early miscarriage, were not different between fresh and frozen embryo transfer. However, frozen embryo transfer is safer in terms of the early miscarriage rate.

Keywords: Embryo transfer, threatened miscarriage, placenta previa, gestational diabetes, gestational hypertension

Öz

Amaç: İn vitro fertilizasyon uygulanan infertil kadınlarda maternal komplikasyonlar önemli bir tartışma konusu olup, embriyo transfer yöntemine bağlı olarak hastaların bu komplikasyonlar hakkında bilgilendirilmesi gerekmektedir. Bu çalışmada, 2018-2021 yılları arasında Shariati Hastanesi'nde in vitro fertilizasyon uygulanan infertil kadınlarda, dondurulmuş ve taze embriyo transferleriyle ilişkili maternal komplikasyonlar karşılaştırıldı.

Gereç ve Yöntemler: Bu çalışma retrospektif bir kohort çalışması olup hasta verileri arşiv dosyaları kullanılarak toplandı. Üç yüz doksan altı tüp bebek hastasının 302'si donmuş embriyo transfer grubunda, 94'ü ise taze embriyo transfer grubunda yer aldı. Transfer edilen embriyo sayısı ve yaş açısından her iki gruptaki hastalar benzerdi ($p>0,05$). Düşük tehdidi, erken düşük, plasenta previa oluşumu, gebelik hipertansiyonu, erken doğum, gebelik diyabeti ve preeklampsi ile ilgili veriler toplandı ve iki grup arasında karşılaştırma yapıldı.

Bulgular: Düşük tehdidi, plasenta previa, gestasyonel hipertansiyon, gestasyonel diyabet, erken doğum ve preeklampsi oranları taze ve dondurulmuş embriyo transfer grupları arasında anlamlı farklılık göstermedi ($p>0,05$). Ancak taze embriyo transfer grubunda erken düşük oranı anlamlı derecede yüksekti (%34 vs. %16,2, $p<0,001$).

Sonuç: Bu çalışmanın sonuçlarına göre, taze ve dondurulmuş embriyo transferleri arasında erken düşük dışında maternal komplikasyonlar açısından farklılık bulunmadı. Ancak donmuş embriyo transferi erken düşük oranı açısından daha güvenli idi.

Anahtar Kelimeler: Embriyo transferi, düşük tehdidi, plasenta previa, gebelik diyabeti, gebelik hipertansiyonu

PRECIS: The early miscarriage rate in fresh embryo transfer was higher, but other complications were not different between the two groups.

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Introduction

Infertility is defined as failure to achieve pregnancy after a year of unprotected sexual intercourse without the use of contraceptive methods. Infertility affects an average of 10% of couples of the reproductive age. Risk factors for infertility include old reproductive age, genetic disorders, infections, and environmental pollutants⁽¹⁻³⁾.

There are few methods of assisted reproductive technology, such as in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), and intrauterine insemination. In IVF, eggs extracted from the ovary are fertilized with sperm in the laboratory. If infertility is also caused by a male factor, ICSI is also performed with IVF⁽¹⁻³⁾.

In IVF, there are two methods of embryo transfer: Frozen and fresh. In fresh embryo transfer, the embryos are transferred to the uterus in the same hormonal stimulation cycle. However, in frozen embryo transfer, the embryos are frozen and later taken to the uterus in a normal cycle or a cycle in which the endometrium has been prepared with hormone therapy. Factors affecting the selection of frozen or fresh embryos can depend on the progesterone level of the mother, endometrial thickness, polycystic ovary syndrome, and maternal age⁽¹⁻³⁾.

Many studies have compared fresh and frozen embryo transfer in terms of pregnancy outcomes and complications. However, their results vary and do not provide a firm conclusion on the matter. The goal of this study was to compare maternal complications in two methods of IVF pregnancies, frozen and fresh embryo transfer, during pregnancy.

Materials and Methods

This is a retrospective cohort study and was approved by the Ethics Committee of Tehran University of Medical Sciences (approval number: IR.TUMS.MEDICINE.REC.1400.061, date: 17.04.2021). All data were gathered through patient files in the hospital and phone calls. Patient information was kept private, and each patient was given a specific code to keep the information private. All stages of this study complied with the Declaration of Helsinki.

Study samples were infertile women treated with IVF/ICSI who were referred to Shariati Hospital Infertility Center from 2018 to 2021 and became pregnant. The exclusion criteria were unable to make phone calls, lack of data files, if embryo or egg was donated, and if pregnancy was surrogacy.

Three hundred ninety-six infertile women received IVF/ICSI treatment. Three hundred two of them (76%) received frozen embryo transfer and 94 of them (24%) received fresh embryo transfer. Patients in both groups were similar in terms of age (shown in Figure 1) and number of transferred embryos ($p>0.05$). Endometrial preparation for the frozen embryo transfer group was performed artificially using hormones. Data concerning maternal complications were gathered, and the two groups of fresh and frozen embryo transfer were compared in terms of threatened miscarriage, early miscarriage, placenta

previa occurrence, gestational hypertension, gestational diabetes, preterm birth, and pre-eclampsia.

The two groups were not similar in size due to the lack of fresh embryo transfer patients who were referred to the hospital for treatment. Frozen embryo transfer was much more popular; therefore, embryo transfers are mostly frozen. This matter should not significantly affect the statistical outcomes of this study because of the high patient count in both groups compared to past studies⁽⁴⁾.

Statistical Analysis

Data regarding infertility duration, number of oocytes retrieved, total gonadotrophin dose used, and number of blastocysts did not exist in the hospital files or were not gathered; therefore, they are not mentioned in this study. In addition, the pre-implantation genetic testing for aneuploidy) test was not performed for any patient.

Comparison of the groups was performed using Fisher's exact test, independent sample t-test, and chi-square test. Data analysis was performed using IBM SPSS 26 and significance level was less than 0.05.

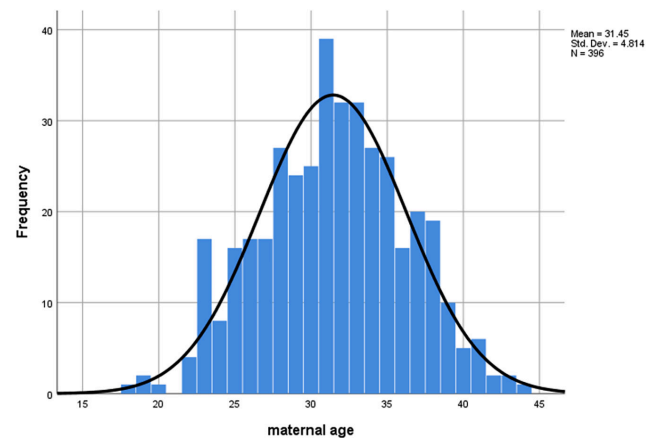


Figure 1. Maternal age in all patients

Threatened miscarriage: Vaginal bleeding in the first trimester without fetal loss while the cervix is closed.

Early miscarriage: Miscarriage before the 13th week of pregnancy.

Placenta previa: The placenta or part of it is placed on the cervical outlet.

Gestational diabetes: Glucose tolerance test disorder first diagnosed in the second or third trimester.

Gestational hypertension: Diastolic blood pressure greater than 90 mm Hg or systolic blood pressure greater than 140 mm Hg when diagnosed for the first time after the 20th week of pregnancy and not accompanied by proteinuria or end organ damage.

Pre-eclampsia: Diastolic blood pressure greater than 90 mm Hg or systolic blood pressure greater than 140 mm Hg when diagnosed for the first time after the 20th week of pregnancy and accompanied by proteinuria or end organ damage.

Results

The patient characteristics in both groups are shown in Table 1. Patient's age was 31.4 vs. 31.6 years and was similar in both groups ($p=0.722$). The number of transferred embryos was 2.7 vs. 2.5 and was similar between groups ($p=0.081$).

Maternal complications are listed in Table 2. Early miscarriage in the frozen vs. fresh group was 16.2% vs. 34%, and the fresh embryo transfer group was significantly higher than the frozen embryo transfer group ($p<0.001$). Threatened miscarriage was 9.9% vs. 7.4% and was not different between the two groups ($p=0.469$). Placenta previa occurrence was 4.3% vs. 4.8% and was not different between the two groups ($p=0.743$). Preterm birth was 26.8% vs. 24.5% and was not different between the two groups ($p=0.651$). Gestational diabetes was 16.9% vs. 15.3% and was not different between the two groups ($p=0.098$). Gestational hypertension was 8.2% vs. 6.7% and was not different between the two groups ($p=1$). Pre-eclampsia was 5.3% vs. 3.3% and was not different between the two groups ($p=0.744$).

It is worth mentioning that other maternal complications such as premature rupture of the membrane did not occur in any patient.

Table 1. Characteristics of IVF patients in two groups of frozen and fresh embryo transfer

	Frozen embryo transfer (302 patients)		Fresh embryo transfer (94 patients)		p-value
	Mean	SD	Mean	SD	
Female age (year)	31.4	4.7	31.6	4.9	0.722
Number of transferred embryos	2.7	0.5	2.5	0.6	0.081

IVF: In vitro fertilization, SD: Standard deviation

Table 2. Maternal complications of IVF patients in two groups of frozen and fresh embryo transfer

	Frozen embryo transfer (302 patients)		Fresh embryo transfer (94 patients)		p-value
	quantity	percentage	quantity	percentage	
Threatened miscarriage	30	9.9%	7	7.4%	0.469
Early miscarriage	49	16.2%	32	34%	<0.001
Placenta previa occurrence	11	4.3%	3	4.8%	0.743
Preterm birth	81	26.8%	23	24.5%	0.651
Gestational diabetes	41	16.9%	9	15.3%	0.098
Gestational hypertension	20	8.2%	4	6.7%	1
Pre-eclampsia	13	5.3%	2	3.3%	0.744

IVF: In vitro fertilization

Discussion

Early Miscarriage

In past studies, the early pregnancy loss rate in frozen vs. fresh embryo transfer was not significantly different⁽⁴⁻⁷⁾ and is as follows: 7.8% vs. 6.8%⁽⁴⁾, 13.3% vs. 19.4%⁽⁵⁾, 9.6% vs. 13.1%⁽⁶⁾ and 21.5% vs. 25.3%⁽⁷⁾. Zargar et al.⁽⁸⁾ found that first trimester loss was much higher in the fresh embryo transfer group (17.69% vs. 23.01%). Our results (16.2% vs. 34%) show that the chance of early miscarriage in the fresh embryo transfer group is 2.66 times higher than that in the frozen embryo transfer group. Higher early miscarriage rate in fresh embryo transfer may be due to the effect of hormones on the endometrium. Because in fresh embryo transfer, the embryos are taken to the uterus in the same ovarian stimulation cycle, the endometrium is under the influence of high levels of progesterone and estrogen. Theories have proposed that estrogen interferes with the angiogenesis of the endometrium and therefore has a negative effect on the continuation of pregnancy. In addition, ovulation stimulation by hormone therapy causes incoordination between the endometrium and embryo and thus has a negative effect on the implantation of the embryo in the uterus^(5,9,10).

Threatened Miscarriage

Korosec et al.⁽¹¹⁾ found that first trimester bleeding occurrence was not different between the frozen and fresh groups (6.6% vs. 8.1%). Our results show no difference between groups and are similar to those of a previous study (9.9% vs. 7.4%).

Placenta Previa

Wikland et al.⁽¹²⁾ concluded that placenta previa occurrence is not different between frozen and fresh embryo transfer (1% vs. 2.5%). However, according to Korosec et al.⁽¹¹⁾, Sazonova et al.⁽¹³⁾ and Sha et al.⁽¹⁴⁾, placenta previa occurrence was much higher in fresh embryo transfer [adjusted odds ratio (AOR) 0.32 [5% confidence interval (CI) 0.19-0.55]⁽¹¹⁾ and 0% vs. 3.5%⁽¹³⁾]. Ishihara et al.⁽¹⁵⁾ found that placenta previa occurrence was much higher in frozen embryo transfer (AOR

3.16, 95% CI 1.71-6.23). Also, Rombauts et al.⁽¹⁶⁾ concluded that increased risk of placenta previa is not related to the type of embryo transfer (fresh and frozen), but is related to the type of endometrial preparation. Our results showed no difference between frozen and fresh embryo transfer (4.3% vs. 4.8%).

Preterm Birth

Preterm birth rate was not different in frozen vs. fresh embryo transfer according to past studies^(6,11,17-19) (18.7% vs. 15.9%⁽⁶⁾, 9% vs. 12.1%⁽¹¹⁾, 21.2% vs. 18.8%⁽¹⁷⁾, 4.9% vs. 5.8%⁽¹⁸⁾, and 7.2% vs. 7.5%⁽¹⁹⁾). However, some studies found that the preterm birth rate was higher in fresh embryo transfer^(7,8,15) [0% vs. 11.1%⁽⁷⁾, 3.93% vs. 8.3%⁽⁸⁾ and AOR 0.90 (95% CI 0.82-0.98)⁽¹⁵⁾]. Our results showed no difference between frozen and fresh embryo transfer (26.8% vs. 24.5%).

Gestational Diabetes

Past studies have shown that gestational diabetes is not different between frozen and fresh embryo transfer^(4,7,8,12-14,18,19) (3.1% vs. 3.9%⁽⁴⁾, 1.8% vs. 0%⁽⁷⁾, 23.66% vs. 24.64%⁽⁸⁾, 2.9% vs. 2%⁽¹²⁾, 0.9% vs. 1.5%⁽¹³⁾, 1.3% vs. 1.8%⁽¹⁸⁾ and 7.2% vs. 8%⁽¹⁹⁾). Our results show no difference between groups and are similar to those of past studies (16.9% vs. 15.3%).

Gestational Hypertension

Many studies have found that gestational hypertension is not different between frozen and fresh embryo transfer^(4,6,7,12,18) (0.9% vs. 1.1%⁽⁴⁾, 2.3% vs. 1.2%⁽⁶⁾, 3.5% vs. 3.6%⁽⁷⁾, 1.9% vs. 1%⁽¹²⁾ and 0.8% vs. 1.3%⁽¹⁸⁾). However, another study by Ishihara et al.⁽¹⁵⁾ found that gestational hypertension was higher in frozen embryo transfer [AOR 1.58 (95% CI 1.35-1.86)]. Our study showed no difference between the frozen and fresh groups (8.2% vs. 6.7%).

Pre-eclampsia

Some studies have shown that pre-eclampsia is not different between frozen and fresh embryo transfer^(4,7,8,12,18,19) (4.4% vs. 3.3%⁽⁴⁾, 7.0% vs. 7.3%⁽⁷⁾, 7.3% vs. 7.66%⁽⁸⁾, 2.9% vs. 3%⁽¹²⁾, 0.5% vs. 0.3%⁽¹⁸⁾ and 2% vs. 1.4%⁽¹⁹⁾). However, other studies found a higher pre-eclampsia rate in frozen embryo transfer^(6,13,20) [4.4% vs. 1.4%⁽⁶⁾, AOR 1.32 (95% CI 1.07-1.63)⁽¹³⁾ and 3.1% vs. 1%⁽²⁰⁾]. Our study found no difference between the frozen and fresh groups (5.3% vs. 3.3%).

In fresh embryo transfer, the time to get pregnant is shorter compared with frozen embryo transfer. However, frozen embryo transfer has some advantages, such as reducing the risk of contracting OHSS, the ability to characterize embryo quality through genetics before implantation, and adjusting the natural physiological environment for better implantation.

In general, the early miscarriage rate, gestational hypertension rate, pre-eclampsia rate, and placenta previa rate for fresh and frozen embryo transfer differ in past studies. However, all studies concluded that the gestational diabetes rate and threatened miscarriage rate are similar in fresh and frozen embryo transfer.

Study Limitations

The retrospective nature of this study was a limitation. Prospective cohort studies and accurate long-term follow-up of patients can lead to a better understanding of the complications of embryo transfer methods. For future studies, it is suggested to evaluate the cost-effectiveness of these methods.

Conclusion

Fresh embryo transfer can increase the early miscarriage rate in IVF patients, and frozen embryo transfer is safer.

Ethics

Ethics Committee Approval: This is a retrospective cohort study and was approved by the Ethics Committee of Tehran University of Medical Sciences (approval number: IR.TUMS.MEDICINE.REC.1400.061, date: 17.04.2021).

Informed Consent: Informed consent was obtained from all participants.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.H., Concept: S.H., M.Z., S.M.G., Design: S.H., M.Z., H.Z., Data Collection or Processing: S.H., M.Z., S.M.G., Analysis or Interpretation: S.H., H.Z., Literature Search: M.Z., S.M.G., Writing: S.H., M.Z., S.M.G.

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