Original Article

Comparing the occurrence rate of gestational hypertension during pregnancy with frozen embryo transfer and natural pregnancy

Farideh Moramezi[1], Roshan Nikbakht[1], Najimeh Saadati[1], Elham Farhadi[2], Negin Raad[1]

[1]Department of Obstetrics and Gynecology, Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran, [2]Golestan Hospital Research and Development Unit, Ahvaz, Iran

Abstract

Introduction: Recent researches have indicated that pregnancies with frozen embryo transfer are associated with the increment of risk of maternal and neonatal complications, especially hypertension during pregnancy. The present study aimed to compare the occurrence rate of gestational hypertension in pregnancy with frozen embryo transfer and normal pregnancy. **Materials and Methods:** This research, as a retrospective cross-sectional study, was performed on pregnant women with frozen embryo transfer ($n = 97$) and women with normal pregnancies ($n = 164$) referring to medical centers under the supervision of Ahvaz University of Medical Sciences in 2021. Women aged 18–35 were included in the study after week 20th of pregnancy. Maternal and neonatal outcomes including hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia), preterm birth (before the week 37th), low birth weight (lower than 2500 g), neonatal asphyxia (Apgar score >7 in minute 5th), intrauterine growth restriction (IUGR) and bleeding in the first trimester of pregnancy were evaluated. The association between frozen embryo transfer and pregnancy outcomes was evaluated using multiple logistic regressions. **Results:** The findings of this study indicated that pregnancy hypertension was observed in 23 people (23.7%) from the frozen embryo transfer group vs. 18 people (11.0%) from the normal pregnancy group ($P = 0.006$). Frozen embryo transfer pregnancy has a higher risk of gestational hypertension (OR = 2.521, 95% CI: 1.281-4.962; $P = 0.007$), preterm birth (OR = 2.264, 95% CI: 1.335-3.840; $P = 0.002$), and low birth weight (OR = 2.017, 95% CI: 1.178-3.455; $P = 0.011$). However, the incidence of birth asphyxia ($P = 0.850$), intrauterine growth restriction ($P = 0.068$), first-trimester bleeding ($P = 0.809$), and placenta accreta ($P = 0.143$) did not show a significant difference between two types of normal pregnancy and frozen embryo transfer pregnancy. **Conclusion:** Frozen embryo transfer pregnancy was associated with a higher risk of maternal and neonatal complications, hypertension, preterm birth, and low birth weight compared to natural and spontaneous pregnancies.

Keywords: Frozen embryo transfer, gestational hypertension, *In vitro* fertilization, preeclampsia

Introduction

Infertility and inability to reproduce have become one of the main health problems and important social threats in the world.[1] The incidence of infertility has been increasing since 1995, and nearly 10-15% of couples have this problem worldwide.[2] Besides, as it has been reported, the overall prevalence of infertility in Iran is 7.9% which is still increasing.[3] Recently, with the advancement of science and technology, scientists and researchers have investigated productiveness of antrauterine insemination (IUI) methods, which are generally known as assisted reproductive technology (ART) which is associated with favorable and significant achievements.[4]

Address for correspondence: Mrs. Negin Raad, Department of Obstetrics and Gynecology, Fertility, Infertility and Perinatology Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
E-mail: Negin Raad67@gmial.com

Received: 14-12-2022 **Revised:** 16-04-2023
Accepted: 01-08-2023 **Published:** 21-12-2023

Access this article online

Quick Response Code:

Website: http://journals.lww.com/JFMPC

DOI: 10.4103/jfmpc.jfmpc_2429_22

How to cite this article: Moramezi F, Nikbakht R, Saadati N, Farhadi E, Raad N. Comparing the occurrence rate of gestational hypertension during pregnancy with frozen embryo transfer and natural pregnancy. J Family Med Prim Care 2023;12:3312-8.

Nowadays, *in vitro* fertilization (IVF) is recommended as a definitive treatment for patients rather than other infertility treatment options.[5] During the last two decades, the rate of ART fertility cases has been constantly increasing, so during the years 1997 and 2016, the number of cases using these techniques has increased 5.3 times in Europe and 4.6 times in the United States.[6] Among the ART treatments, the frozen embryo transfer (FET) method has a growing pivotal role,[7] so in many reports from different places, the delivery rate after embryo transfer from freezing–thawing cycles have been more than fresh cycles.[6]

Recently, FET has been known to be one of the most important components of ART. This procedure provides the possibility of a reduction in the number of transferred embryos as well as a decrease in the risk of multiple pregnancies.[8] Although IVF and FET are successful treatment options for infertility that have increased the fertility rate, they also increased the risk of pregnancy and perinatal complications compared to spontaneous delivery such as premature delivery, low birth weight (LBW), intrauterine growth restriction (IUGR) and preeclampsia.[9] Besides, studies have shown that hypertensive disorders are the most common complications during pregnancy and involve more than 10% of pregnant women, and considered as one of the most crucial causes of maternal and neonatal morbidity and mortality worldwide.[10] The prevalence rate of preeclampsia in Iran has been reported to be 5.2%.[11] Hypertensive disorders include prepregnancy hypertension, pregnancy hypertension, preeclampsia, and eclampsia. Pregnant women with hypertension less than 140/90 mmHg are considered as normotensive.[12] The results of some studies have demonstrated that the FET is associated with a higher risk of preeclampsia compared to the fresh embryo transfer.[13] In some others, FET was reported as a risk factor for preeclampsia in women undergoing IVF, but no comparison has been performed with women with spontaneous labor.[14] On the other hand, in a study, it was revealed that the risk of preeclampsia and gestational hypertension is the same in two types of frozen and fresh embryo transfer. Therefore, despite the high prevalence of preeclampsia in pregnant women with artificial insemination, the freezing–thawing process has no effect on the increment of the risk of preeclampsia and hypertension during pregnancy.[15]

Bănică *et al.*[16] reported that IVF pregnancy in women was associated with a higher risk of maternal and neonatal complications compared to spontaneous pregnancies. The finding of another study also indicated that IVF is associated with the incidence of preeclampsia. Placental disorders and their insufficiency may make IVF patients at risk of preeclampsia, which appears to be bleeding in the first trimester of pregnancy.[9] Besides, previous studies have indicated the risk of hypertension in pregnant women with IVF who use FET (in both autologous or donor oocyte groups) and fresh donor oocyte transfer. Moreover, in the women in the IVF group, the risk of hypertensive disorders does not increase with fresh autologous oocytes embryo transfer.[17] Although some studies indicated that being pregnant through the IVF method increases the risk of hypertensive disorders and preeclampsia,[9] but the main cause of this disorder due to various underlying causes, unknown (unmeasured) confounding factors, or the IVF technology itself, or other treatment parameters is still unknown. In addition, past studies have faced limitations such as: considering hypertensive disorders in general or inappropriate control for confounding factors. Besides, compared to the happening of preeclampsia in spontaneous pregnancies, there is not enough information about the outcomes of preeclampsia in pregnancies with IVF. On the other hand, most of the studies have examined all IVF cases and have not investigated the happening of gestational hypertension in different techniques of embryo transfer separately. Also, just a few studies have compared gestational hypertension in delivery with FET and natural delivery. So, this study is aimed to compare the incidence of gestational hypertension in pregnancy with FET and normal pregnancy.

Materials and Methods

The present research, as a retrospective cross-sectional study, was performed on women with FET pregnancy technique and women with normal pregnancy referring to the medical centers under the supervision of Ahvaz University of Medical Sciences in 2021. Based on the previous studies,[9] the minimum number of people needed to perform this study was 164 people in the group of women with normal pregnancy and 76 people in the group of women with FET pregnancy. In total, in their study, 240 patients were investigated using consecutive sampling referred to the centers under the supervision of Ahvaz University of Medical Sciences. The inclusion criteria include the birth of at least one live baby after 28 weeks of pregnancy, age between 18 and 35 years, women after 20 weeks, and body mass index of 18-32 kg/m^2. On the other hand, the exclusion criteria include incomplete data in the patient's file, smoking women and patients with underlying conditions such as systemic lupus erythematosus, antiphospholipid syndrome, polycystic ovary syndrome (PCOS), women with a history of preeclampsia, and women with diabetes mellitus or hypertension before pregnancy.

Methods

The compulsory information was collected by evaluating the medical data of pregnant women in the archives of the centers under the supervision of Ahvaz University of Medical Sciences and was recorded in the data collection checklist. Demographic characteristics of mother, age, parity, BMI, gestational age at the time of preeclampsia diagnosis, laboratory parameters, pathological diagnoses, pregnancy complications, and perinatal outcomes such as premature birth (sooner than week 37th of pregnancy), newborn asphyxia (Apgar score <7 at 5 minutes after birth), IUGR (fetal weight <10th percentile or birth weight of <10th percentile for gestational age), LBW (birth weight <2500 g), bleeding in the first trimester of pregnancy and during delivery, and the placenta accreta were recorded. In addition to the doctor's report, the diagnosis and severity of preeclampsia were confirmed based on the symptoms of patients and their laboratory findings.

Gestational hypertension is defined as systolic blood pressure of more than 140 mmHg or 30 mmHg increase in blood pressure compared to the baseline value in the first trimester of pregnancy, diastolic blood pressure of more than 90 mmHg or 15 mmHg increase in blood pressure compared to the baseline value of in the first trimester of pregnancy (after week 20th) in women without previous hypertension. Gestational hypertension is confirmed by at least two measurements of blood pressure with a time interval of 4-6 hours.[18] Preeclampsia is defined as systolic blood pressure of more than 140 mmHg or diastolic blood pressure of more than 90 mmHg happening after week 20th of the pregnancy with proteinuria (24-hour urine protein ≥300 mg, or the result of urine dipstick tests at least + 1), or Multiple organ dysfunction syndrome in women with normal blood pressure before their pregnancy. Severe preeclampsia is defined as systolic blood pressure of more than 160 mmHg or diastolic blood pressure of more than 110 mmHg or a combination of at least one of the following symptoms: thrombocytopenia (<100 k/ml), kidney failure (creatinine >1.1 mg/dL), liver dysfunction (elevated liver transaminase levels twice the normal level), pulmonary edema, and cerebral or visual symptoms. The rapid occurrence of preeclampsia is also defined as the diagnosis of preeclampsia sooner than week 32nd of the pregnancy.[9] Finally, the collected data were compared between two groups of pregnant women with FET and women with natural pregnancy.

Data analysis

SPSS (SPSS Inc., Chicago, IL, U.S.A.) V22 was used to analyze the data. A *P*-value <0.05 was considered statistically significant.

Results

The participants of this study consisted of 261 pregnant women aged between 18 and 35 years. The basic characteristics of participants in two groups of FET pregnant women and natural pregnant women are presented in Table 1.

The prevalence of maternal and neonatal consequences in pregnancies with FET and natural pregnancies is represented in Table 2. Blood pressure during pregnancy was observed in 18 people (11.0%) from the normal pregnancy group versus 23 people (23.7%) from the FET group ($P = 0.006$). Besides, the frequency of preterm birth ($P = 0.002$) and LBW (weight <2500 grams) ($P = 0.010$) in women with FET pregnancies was significantly higher than in normal pregnancies.

The types of hypertensive disorders of pregnancy with FET and natural pregnancy are presented in Table 3. The type of hypertensive disorder was not observed in the two groups of normal pregnancy and FET pregnancy ($P = 0.612$). The gestational age at the time of diagnosis of gestational hypertension in the normal pregnancy group was 31.78 ± 3.63, and in the FET pregnancy group was 31.26 ± 3.54. Besides, the two studied groups were not statistically different ($P = 0.649$).

The frequency of disorders related to gestational hypertension in normal pregnancies and pregnancies with FET based on maternal age, parity, BMI, and type of pregnancy are presented in Table 4. As can be observed from table,[4] in the two groups of normal and FET pregnancies, there was no difference between the age of parity mothers with and without gestational hypertension ($P < 0.05$). In the FET pregnancies group, the difference in the BMI of mothers with and without gestational hypertension was not significant ($P = 0.975$). However, in the group of women with normal pregnancy, in women with higher BMI, the frequency of gestational hypertension was significantly higher ($P = 0.002$). In the two groups of women with FET and natural pregnancies, there was no significant difference in the type of pregnancy in mothers with and without gestational hypertension ($P < 0.05$).

The findings of this study [Table 5] indicated that in the group of women conceived by FET, the frequency of preterm birth in mothers with and without gestational hypertension was not significantly different ($P = 0.452$). However, in the normal pregnancy group, preterm birth in people with gestational hypertension was significantly higher than in those without gestational hypertension ($P = 0.001$). Besides, in the group of pregnancies with FET, the frequency of babies with LBW in mothers with and without gestational hypertension was not significantly different ($P = 0.068$). In the normal pregnancy group, the LBW of babies in the group with gestational hypertension was significantly higher compared to the group without gestational hypertension ($P < 0.0001$).

The findings of logistic regression analysis for evaluating the risk of gestational hypertension and other maternal and neonatal consequences in pregnancy with FET compared to normal pregnancy are presented in Table 6. The findings indicated that pregnancy with FET could be used as an independent predictor for gestational hypertension (OR = 2.521, 95%

Table 1: Basic characteristics of participants in two groups

Variable	Group	Normal pregnancy (164 people)	FET pregnancy	*P*
Mother's age (year)		27.59±4.96 (18-35)	29.71±3.06 (18-35)	<0.0001*
Parity		2.18±1.34 (1-6)	1.23±0.60 (1-4)	<0.0001*
BMI (kg/m^2)	18-24.9	60 (36.6)	25 (25.8)	0.178**
	25-29.9	67 (40.9)	44 (45.4)	
	30-32	37 (22.6)	28 (28.9)	
Number of embryos (singleton and multiple pregnancies)	Single	158 (96.3)	90 (92.8)	0.202**
	Multiple	6 (3.7)	7 (7.2)	

The numbers are presented in the form of standard deviation±average (minimum-maximum) or frequency (percentage). * Independent *t*-test. **Chi-squared test

Table 2: Maternal and neonatal consequences in pregnancy with FET and normal pregnancy

Variable	Normal pregnancy (164 people)	FET pregnancy (97 people)	*P**
Blood pressure during pregnancy	18 (11.0)	23 (23.7)	0.006
Preterm birth	44 (26.8)	44 (45.4)	0.002
Birth asphyxia	6 (3.7)	4 (4.1)	0.850
IUGR	20 (12.2)	20 (20.6)	0.068
Low birthweight (weight <2500 g)	41 (25.0)	39 (40.2)	0.010
First-Trimester Bleeding	6 (3.7)	3 (3.1)	0.809
Postpartum Hemorrhage	11 (6.7)	0 (0)	0.009
Accrete	7 (4.3)	1 (1.0)	0.143

*Chi-squared test. FET=Frozen Embryo Transfer, IUGR=Intrauterine Growth Restriction

Table 3: Prevalence of gestational hypertension in the women with FET pregnancy and normal pregnancy

Variable	Normal pregnancy (164 people)	FET pregnancy (97 people)	*P**
GHTN	7 (38.9)	6 (26.1)	0.612
Preeclampsia	9 (59.0)	15 (62.2)	
HELLP	2 (11.1)	2 (8.7)	

*Chi-squared test. FET=Frozen Embryo Transfer, GHTN=Gestational hypertension, HELP=Hemolysis, Elevated Liver enzymes, and Low Platelets

CI: 1.281-4.962; $P = 0.007$), preterm birth (OR = 2.264, 95% CI: 1.335–3.840; $P = 0.002$) and low birthweight (OR = 2.017, 95% CI: 1.178–3.455; $P = 0.011$).

Discussion

The findings of the present study indicated that blood pressure during pregnancy was present in 11% of women with normal pregnancy compared to 23.7% of women with FET pregnancy, a statistically significant difference. Past studies have indicated that ART is at high risk for many adverse maternal and neonatal consequences, including gestational hypertension,[17-19] preterm birth,[20] LBW, and small for gestational age.[21] In a recent cohort study, Bănică *et al.*[16] evaluated maternal and neonatal consequences of IVF and spontaneous pregnancy and indicated that IVF pregnancies were associated with a higher risk of gestational hypertension and placental abnormalities. These findings are consistent with the data achieved from the present study that indicate that IVF pregnancies are associated with a higher risk of gestational hypertension and other maternal and neonatal complications than spontaneous pregnancies. In a retrospective cohort study by Gui *et al.*,[9] 114,485 pregnant women, including 4,601 cases (4%) of IVF pregnancy, were investigated. Their findings indicated that the incidence of preeclampsia in IVF pregnancy was significantly higher than in spontaneous pregnancy (6.1% vs. 0.1). In the present study, it was concluded that placental dysfunction may make IVF patients susceptible to preeclampsia, which can be presented as bleeding in the first trimester of pregnancy. In their study Li *et al.*[22] reported FET as an independent risk factor for preeclampsia in women undergoing ART techniques. Besides, it was stated that high ovarian response may increase the risk of preeclampsia.

In another study, Luke *et al.*[17] reported the risk of hypertensive disorders of pregnancy (including gestational hypertension and preeclampsia) in pregnant women with IVF using FET method (in both groups of autologous or donor oocyte) and fresh donor oocyte transfer is increased compared to normal pregnancy. However, in the method of fresh autologous oocytes embryo transfer, the risk of hypertensive disorders did not increase. The findings of some studies have indicated that the risk of gestational hypertension and preeclampsia in FET is similar to fresh embryo transfer.[14,15] As a result, it was revealed that despite the high prevalence of preeclampsia in IVF pregnancies,[23] the freezing–thawing process has no effect on the increment of the risk of preeclampsia and blood pressure during pregnancy.[24] In a population-based cohort study, Opdahl *et al.*[19] compared the consequences of pregnancies with ART and spontaneous pregnancies, and reported an increment in the risk of hypertensive disorders in the group of ART pregnancy women. However, in their study Opdahl *et al.*[19] reported that pregnancies following frozen-thawed embryo transfer cycles compared to fresh embryo transfer had a higher risk of hypertensive disorders, and therefore the safety aspects of the frozen-thawed embryo transfer cycles require more attention.[19] Although, in the present study, different cycles of embryo transfer were not investigated.

The age of mothers over 35 years has been reported as a risk factor for hypertensive disorders of pregnancy.[25] Besides, Wennberg *et al.*[26] reported that advanced maternal age increases the risk of pregnancy complications regardless of the type of pregnancy (ART or natural).[26] So, to prevent the effect of this interfering factor, only pregnant women aged 18 to 35 years were included in the study. The findings of a retrospective cohort study also indicated that pregnancy with ART was associated with a high probability of preterm birth and gestational hypertension.[27] A meta-analysis consisting of 26 articles reported that singleton pregnancies with FET are associated with an increment in the risk of hypertensive disorders during pregnancy.[28] Theoretically, freeze–thaw cycle can cause epigenetic changes that may change the initial process of embryo development and lead to changes in IUGR.[29]

In the present study, pregnant women with FET had a higher average age and lower parity than those with normal pregnancy. Women undergoing IVF treatment, due to their older age and lower parity compared to women with normal pregnancies, are more likely to develop hypertensive disorders during pregnancy.[30] On the other hand, IVF cycles are also associated with the increment of risk of hypertensive disorders of pregnancy compared to natural pregnancy.[17] The cycles of embryo transfer consist of the protocols that use estradiols and progesterone to create the endometrium (programmed cycles), and there is no corpus luteum (CL) at the time to get pregnant.[31] Recent findings have indicated that being pregnant using the FET cycle without CL increases the risk of hypertensive disorders and preeclampsia during pregnancy.[32]

In this study, the increment of preterm birth in the group of FET pregnancies compared to natural pregnancies is consistent with

Table 4: Specifying of gestational hypertension in normal and FET pregnancies based on maternal age, parity, BMI, and type of pregnancy

Group	Normal pregnancy		FET pregnancy	
	Age SD±Mean	*P**	Age SD±Mean	*P**
Gestational hypertension				
No	27.43±5.10	0.241	29.76±3.20	0.795
Yes	28.89±3.53		29.57±2.66	
	Parity SD±Mean	*P**	Parity SD±Mean	*P**
Gestational hypertension				
No	2.18±1.34	0.896	1.23±0.65	0.932
Yes	2.22±1.35		1.22±0.42	
	Gestational hypertension Frequency (%)	*P**	Gestational hypertension Frequency (%)	*P**
BMI (kg/m²)				
18-24.9	2 (3.3)	0.002	6 (26.1)	0.975
25-29.9	7 (10.4)		10 (22.7)	
30-32	9 (24.3)		7 (25.0)	
Type of pregnancy				
Singleton	17 (10.8)	0.650	22 (24.4)	0.543
Multiple	1 (16.7)		1 (14.3)	

*Chi-squared test

Table 5: Determining the frequency of preterm birth and low birth weight based on gestational hypertension in normal and FET pregnancies

Group	Normal pregnancy		FET pregnancy	
	Gestational hypertension	*P**	Gestational hypertension	*P**
Preterm birth				
No	7 (5.8)	0.001	11 (20.8)	0.452
Yes	11 (61.1)		12 (27.3)	
Low birth weight (<2500 g)				
No	7 (39.9)	<0.0001	10 (17.2)	0.068
Yes	11 (61.1)		13 (33.3)	

*Chi-squared test

findings of previous studies that reported an increment in the risk of preterm birth in the IVF group compared to the control group.[20] A meta-analysis including 52 cohort studies consisting of 181,741 singleton pregnancies with IVF/intracytoplasmic sperm injection (ICSI) and about 4.6 million natural births in the world indicated that ART pregnancies were at higher risk of preterm birth, LBW, and perinatal mortality.[20] Due to the high prevalence of multiple pregnancies in the IVF technique, the increment of prematurity as one of the side effects of these high-risk pregnancies has also been reported in some associated studies.[16] Anyway, in this study, the difference in multiple pregnancies in the two studied groups was not significant. Moreover, the difference between both groups of FET and normal pregnancies in terms of the type of pregnancy (Twin vs. singleton pregnancy) in mothers with and without gestational hypertension was not significant. This difference in the findings can be due to the difference in the sample size and characteristics of the studied people. The number of multiple pregnancies in our study was small.

In our study LBW in the women of FET pregnancy group was significantly higher than those with normal pregnancy. Also, one of the main negative consequences related with FET pregnancy was identified. Maternal complications such as gestational hypertension, preterm birth, and the culture medium used forembryonic development can all affect the neonatal weight loss.[16] On the other hand, some previous studies have indicated that FET and freezing techniques are associated with the increment of birth weight and the risk of being large for gestational age.[28] Anyway, in their study Bănică *et al.*[16] did not show any effect of freezing embryos and FET techniques on the newborn weight gain.

Recent findings have indicated that FET pregnancy compared to fresh embryo transfer increases the risk of hypertensive disorders of pregnancy such as preeclampsia.[33] The findings of this research study also indicated that the occurrence of gestational hypertension and other negative consequences such as preterm birth and LBW in women with FET pregnancy is more than in women with normal pregnancy. So, these women should be monitored and checked carefully. On the other hand, the increment of these consequences questions the widespread use of FET in ART pregnancies.[28] Therefore, it is recommended that the FET technique should not be performed without preexamination for all patients but should only be used in women with clear indications to benefit from this technique. As this technique is widely used for fertility, prospective studies should be conducted with precise control of all the factors that affect the occurrence of hypertension disorders of pregnancy and other negative pregnancy and neonatal outcomes to specify the exact role of FET on maternal and newborn outcomes. Besides, long-term follow-up of babies born through FET can help monitor the consequences of this fertility technique.

Conclusion

The findings of this research demonstrated that women conceived with the FET technique are at higher risk of

Table 6: Risk assessment of maternal and neonatal consequences in FET pregnancy compared to the normal pregnancy

Variable	Unadjusted analysis		Adjusted analysis*	
	OR (CI95%)	*P***	OR (CI95%)	*P***
Gestational hypertension	2.521 (1.281-4.962)	0.007	2.129 (0.941-4.815)	0.023
Preterm birth	2.264 (1.335-3.840)	0.002	1.545 (0.820-2.912)	0.178
Asphyxia	1.133 (0.312-4.118)	0.850	0.581 (0.115-2.931)	0.511
IUGR	1.870 (0.949-3.687)	0.071	1.871 (0.761-2.802)	0.172
LBW	2.017 (1.178-3.455)	0.011	1.451 (0.752-2.802)	0.267
First-trimester bleeding	0.840 (0.205-3.440)	0.809	0.525 (0.090-3.063)	0.474
Accrete	0.234 (0.028-1.928)	0.177	0.501 (0.045-5.631)	0.576

*Adjusted analysis based on maternal age, parity, BMI, and number of fetuses. **P<0.05, significant. FET=Frozen Embryo Transfer, IUGR=Intrauterine Growth Restriction, LBW=Low birth weight, OR=Odds ratio, CI=confidence interval

pregnancy and neonatal complications such as hypertensive disorders of pregnancy, preterm birth, and LBW compared to normal pregnancy. So, considering the safety aspects of freezing and thawing cycles and the widespread administration of this technique in infertile women, precise monitoring of women conceived with FET is recommended. In this technique, in addition to preventive measures and timely diagnosis of blood pressure during pregnancy and other related complications, mother and the fetus are under control and a particular care to maintain healthy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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