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ORIGINAL RESEARCH

Risk Factors of Preterm Birth and Low Birth Weight in Singletons Conceived Through Frozen Embryo Transfer: A Retrospective Study

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Background: The risks of adverse perinatal outcomes in offspring conceived following frozen-thawed embryo transfer (FET) assisted reproductive technology (ART) are inconsistent. The aim of this study was to analyze the risk factors for preterm birth and low birth weight in singletons after FET.

Methods: 386 FET cycles was conducted at the Reproductive Medicine Center of Meizhou People's Hospital. The relationship between clinical characteristics and outcomes (term birth and preterm birth, normal birth weight and low birth weight) was analyzed.

Results: The rate of primary infertility, basal FSH and T levels, gestational age, birth weight, and proportion of male fetuses were significantly different in the preterm and full-term groups. Logistic regression analysis showed that high maternal age (≥35 years) (OR 3.652, 95% CI: 1.683–7.925, P=0.001), primary infertility (OR 2.869, 95% CI: 1.461–5.632, P=0.002), low FSH level (<6.215 mIU/mL) (OR 3.272, 95% CI: 1.743–6.144, P<0.001), and hormone replacement therapy (HRT) method (OR 2.780, 95% CI: 1.088–7.100, P=0.033) may increase risk of preterm birth after FET. Gestational age and birth weight were significantly different in fetuses with low birth weight (<2500g, n=38) and normal birth weight (≥2500g and <4000g, n=333). Logistic regression analysis showed that low basal FSH level (<6.215 mIU/mL) (OR 0.425, 95% CI: 0.209–0.865, P=0.018), and HRT method of endometrial preparation for FET (OR 0.272, 95% CI: 0.079–0.934, P=0.039) may reduce the risk of low birth weight after FET.

Conclusion: High maternal age, primary infertility, low FSH level, HRT method of endometrial preparation for FET, and male fetus may increase risk of preterm birth after FET. In addition, primary infertility, low basal FSH level, and HRT method of endometrial preparation may reduce the risk of low birth weight after FET.

Keywords: frozen embryo transfer, preterm birth, low birth weight, risk factors, assisted reproductive technology

Introduction

Infertility is medically defined as the failure to achieve pregnancy of a couple after 12 months of regular sexual intercourse without any form of contraception.[1] Infertility affects more than 6 million people in the United States, equivalent to 10% of the reproductive-age population.[2] In China, the prevalence of infertility among couples with childbearing age is about 25%.[3] The reasons of infertility include female factors (ovulation dysfunction, fallopian tube abnormalities, endometriosis, decreased ovarian function, uterine and cervix factors) and male factors (azoospermia and oligospermia).[4] The psychological stress caused by the fertility status and the side effects of some hormones and drugs may also increase the risk of infertility.[5,6] Assisted reproductive technology (ART) is one of the most effective methods for the treatment of infertility patients, and also an important means to achieve eugenic inheritance.[7]

Frozen-thawed embryo transfer (FET) is an important part of ART. It means that embryos will not be transferred during the oocyte retrieval cycle, it is a technique in which high-quality embryos are cryopreserved, thawed and transplanted into the uterine cavity of the patient to achieve conception.[8] FET reduces the number of ovulation induction,

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reduces the waste of excess embryos, and reduces the risk of complications.[9] FET has gradually become one of the important techniques of ART, which increases the transfer opportunity of patients and improves the cumulative pregnancy rate of embryo transfer.[10]

Fetuses conceived via assisted reproductive technologies are more likely to have perinatal adverse outcomes.[11] Study showed that FET has a higher fetal survival rate than fresh embryo transfer, but FET may be associated with an increased risk of adverse perinatal outcomes.[12] Given the increasing application of FET, it is critical to investigate whether FET was related to the development of perinatal adverse outcomes, and if elements of the treatment could be modified to optimize outcomes.[13] Therefore, the relationship between FET and perinatal adverse events and the study of the risk factors of perinatal adverse events after FET have become one of the research hotspots in reproductive medicine. Low birth weight and preterm birth were the most common perinatal adverse events.[14] It is necessary to investigate the risk factors for low birth weight and preterm birth in fetuses after FET. Several studies have investigated that, the characteristics of the treated couple and FET cycle parameters were associated with preterm birth and low birth weight in the FET cycles.[15,16] However, some studies have found no association between FET with preterm birth and low birth weight.[17] In general, there are still inconsistent results on the relationship between different indicators of FET and fetal preterm birth and low weight at home and abroad.

In order to meet the increasing fertility needs of the people, it is important to effectively improve the perinatal outcomes in offspring conceived following FET. Therefore, the related factors affecting the outcomes of FET have become the focus of research and discussion in the field of ART at home and abroad. Twin pregnancy is considered to be an independent risk factor for almost all ART-related pregnancy comorbidities, such as preterm birth, low birth weight and other perinatal adverse outcomes increased several times compared with singleton pregnancy.[18] Based on this, this study selected infertility patients who underwent FET in our hospital in the past 5 years (2016–2021) as the research objects to study the related influencing factors of preterm birth and low birth weight in singletons conceived by FET.

Materials and Methods

Between June 2016 and April 2021, about 2500 IVF treatment cycles were performed at the center. Compared to all IVF cycles, the proportion of FET was about 80.6%. And the singleton live birth rate was 61.9% among all FET single embryo cycles. A total of 386 FET cycles of pregnancy and singleton birth from June 2016 to April 2021 were selected, performed in the Reproductive Medicine Center of Meizhou People's Hospital. Detailed information on parental characteristics and FET procedures was collected from the electronic medical records of Reproductive Medicine Center. Pregnancy outcomes were obtained from the follow-up database.

The risk factors of infants with preterm birth and low birth weight investigated in this study were maternal age, paternal age, type of infertility, basal hormone level, total gonadotropin (Gn) dose, hormone level on day of human chorionic gonadotropin (HCG) triggering, method of endometrial preparation for frozen-thawed embryo transfer, blood HCG level, gestational age at birth, birth weight, gender of fetus, and so on.

Maternal age and paternal age was divided into four subgroups (<30 years, 30–35 years, 36–40 years, and >40 years), respectively. Primary infertility was defined as the failure to achieve pregnancy of a couple after 12 months of regular sexual intercourse without any form of contraception when a woman has never conceived, while secondary infertility was the incapability to conceive in a couple who have had at least one successful clinical pregnancy previously. Basal hormone including follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), estradiol (E2), testosterone (T), and progesterone (P). Hormone level on day of HCG triggering including E2, LH, and P. Method of endometrial preparation for FET including natural cycle (NC), hormone replacement therapy (HRT) cycle, and cycle with ovulation induction (OI).[19]

Demographics and clinical characteristics of pregnancies conceived through ART were calculated by χ^2 test. The distributions of continuous variables were evaluated by Student's *t*-test or the Mann–Whitney *U*-test. The optimal cutoff values of FSH and testosterone in the detection of preterm birth and low birth weight were determined by receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was applied to assess the associations between the risk factors and pregnancy outcome. The variables included in logistic regression analysis included categorical variables and the continuous variables with differences between preterm and full-term births. Data analysis was performed using SPSS 21.0 (IBM Inc., USA).

Results

Demographics and Clinical Characteristics of Infertility Patients and Infants

Table 1 showed demographics and clinical characteristics of infertility patients and infants in this study. The mean value of maternal age and paternal age was 31.10±4.20 and 33.86±5.33, respectively. There were 140 (36.3%), 184 (47.7%), 53 (13.7%) and 9 (2.3%) cases with maternal age <30 years, 30–35 years, 36–40 years and >40 years, respectively; 75 (19.4%), 181 (46.9%), 85 (22.0%) and 45 (11.7%) cases with paternal age <30 years, 30–35 years, 36–40 years and >40 years, respectively. The basal levels of FSH, LH, PRL, E2, T and P were 6.98±1.97 mIU/mL, 6.63±3.58 mIU/mL, 22.96 ±14.36 ng/mL, 39.01±17.51 pg/mL, 0.73±6.46 ng/mL and 0.47±0.84 ng/mL, respectively. The levels of E2, LH and P on day of HCG triggering were 4799.41±3329.00 pg/mL, 1.42±1.18 mIU/mL, and 1.07±0.68 ng/mL, respectively. The mean gestational age and weight of the fetuses at birth were 38.13±2.42 weeks and 3.13±0.58 kg, respectively. There were 213 male (55.2%) and 173 female (44.8%) fetuses (Table 1).

Table 1 Demographics and Clinical Characteristics of Infertility Patients and Infants in This Study

Variables	Number (Mean±SD)	Percentage
Maternal age (years)	31.10±4.20	
<30	140	36.3%
30–35	184	47.7%
36–40	53	13.7%
>40	9	2.3%
Paternal age (years)	33.86±5.33	
<30	75	19.4%
30–35	181	46.9%
36–40	85	22.0%
>40	45	11.7%
Infertility type		
Primary	170	44.0%
Secondary	216	56.0%
Basal hormone level		
Follicle-stimulating hormone (FSH) (mIU/mL)	6.98±1.97	
Luteinizing hormone (LH) (mIU/mL)	6.63±3.58	
Prolactin (PRL) (ng/mL)	22.96±14.36	
Estradiol (E2) (pg/mL)	39.01±17.51	
Testosterone (T) (ng/mL)	0.73±6.46	
Progesterone (P) (ng/mL)	0.47±0.84	
Total Gn dose	2474.06±841.42	
Hormone level on day of hCG triggering		
Estradiol (E2) (pg/mL)	4799.41±3329.00	
Luteinizing hormone (LH) (mIU/mL)	1.42±1.18	
Progesterone (P) (ng/mL)	1.07±0.68	
Method of endometrial preparation for frozen-thawed embryo transfer (FET)		
Hormone replacement therapy (HRT) cycle	268	69.4%
Natural cycle (NC)	79	20.5%
Cycle with ovulation induction (OI)	39	10.1%
Blood HCG level (mIU/mL)	472.22±937.99	
Gestational age at birth (weeks)	38.13±2.42	
Birth weight (kg)	3.13±0.58	
Gender of fetus		
Male	213	55.2%
Female	173	44.8%

Comparison of Demographic and Clinical Characteristics of Fetuses with Singleton Preterm and Term Births After Performed FET

There were 331 (85.8%) full-term fetuses and 55 (14.2%) preterm fetuses. The rate of primary infertility was higher in the preterm group than in the term group (60.0% vs 41.4%, P=0.012). Compared with full-term fetuses, mothers in the preterm group had lower basal FSH levels (6.31±2.13 mIU/mL vs 7.09±1.93 mIU/mL, P=0.001) and higher T levels (2.39±15.47 ng/mL vs 0.46±3.01 ng/mL, P=0.040) before performed FET. Gestational age (33.64±3.28 weeks vs 38.87 ±1.09 weeks, P<0.001) and birth weight (2.32±0.70 kg vs 3.27±0.44 kg, P<0.001) were significantly lower in the preterm group than in the term group. The proportion of male fetuses in the preterm group was significantly higher than that in the term group (70.9% vs 52.6%, P=0.013). There were no significant differences in the mean and distribution of maternal age, paternal age, basal LH, PRL, E2 and P levels, hormone levels on day of HCG triggering, and the proportion of methods of endometrial preparation for FET between the preterm group and the term group (Table 2).

Table 2 Comparison of Demographic and Clinical Characteristics of Fetuses with Singleton Preterm and Term Births After Frozen Embryo Transfer

Variables	Term Fetuses (n=331)	Preterm Fetuses (n=55)	*P* value
Maternal age (years)	31.01±4.24	31.64±3.97	0.244†
<30	122 (36.9%)	18 (32.7%)	0.381
30–35	158 (47.7%)	26 (47.3%)	
36–40	42 (12.7%)	11 (20.0%)	
>40	9 (2.7%)	0 (0%)	
Paternal age (years)	33.87±5.48	33.76±4.33	0.653†
<30	66 (19.9%)	9 (16.4%)	0.270
30–35	154 (46.5%)	27 (49.1%)	
36–40	69 (20.8%)	16 (29.1%)	
>40	42 (12.7%)	3 (5.5%)	
Infertility type			
Primary	137 (41.4%)	33 (60.0%)	0.012
Secondary	194 (58.6%)	22 (40.0%)	
Basal hormone level			
Follicle-stimulating hormone (FSH) (mIU/mL)	7.09±1.93	6.31±2.13	0.001†
Luteinizing hormone (LH) (mIU/mL)	6.72±3.66	6.09±3.02	0.279†
Prolactin (PRL) (ng/mL)	23.19±14.44	21.56±13.94	0.354†
Estradiol (E2) (pg/mL)	38.57±17.70	41.65±16.20	0.130†
Testosterone (T) (ng/mL)	0.46±3.01	2.39±15.47	0.040
Progesterone (P) (ng/mL)	0.48±0.90	0.41±0.32	0.542
Total Gn dose	2479.38±842.45	2442.05±842.15	0.622†
Hormone level on day of hCG triggering			
Estradiol (E2) (pg/mL)	4860.02±3417.11	4434.66±2738.12	0.439†
Luteinizing hormone (LH) (mIU/mL)	1.44±1.19	1.27±1.07	0.105†
Progesterone (P) (ng/mL)	1.05±0.66	1.20±0.79	0.351†
Method of endometrial preparation for frozen-thawed embryo transfer (FET)			
Hormone replacement therapy (HRT) cycle	224 (67.7%)	44 (80.0%)	0.134
Natural cycle (NC)	73 (22.1%)	6 (10.9%)	
Cycle with ovulation induction (OI)	34 (10.3%)	5 (9.1%)	
Blood HCG level (mIU/mL)	470.91±995.45	480.06±466.10	0.312†
Gestational age at birth (weeks)	38.87±1.09	33.64±3.28	<0.001
Birth weight (kg)	3.27±0.44	2.32±0.70	<0.001
Gender of fetus			
Male	174 (52.6%)	39 (70.9%)	0.013
Female	157 (47.4%)	16 (29.1%)	

Note: †Mann–Whitney *U*-test was performed.

In this study, there were 38 infants with low birth weight (<2500g) (including 4 extremely low birth weight (ELBW) (<1000g) infants, 5 very low birth weight (VLBW) (≥1000g and <1500g) infants and 29 low birth weight (LBW) (≥1500g and <2500g) infants), 333 normal birth weight (≥2500g and <4000g) infants and 15 macrosomia (≥4000g) infants. Gestational age (33.29±4.09 weeks vs 38.62±1.38 weeks, P<0.001) and birth weight (1.93±0.53 kg vs 3.22 ±0.37 kg, P<0.001) were significantly lower in fetuses with low birth weight than in the fetuses with normal birth weight. There were no significant differences in the mean and distribution of maternal age, paternal age, infertility type, basal hormone levels, hormone levels on day of HCG triggering, the proportion of methods of endometrial preparation for FET, and sex ratio between fetuses with low birth weight and normal birth weight (Table 3).

Table 3 Comparison of Demographic and Clinical Characteristics of Fetuses with Low Birth Weight and Normal Birth Weight After Frozen Embryo Transfer

Variables	Normal Birth Weight (n=333)	Low Birth Weight (n=38)	*P* value
Maternal age (years)	31.14±4.23	30.97±3.81	0.815
<30	119 (35.7%)	14 (36.8%)	1.000
30–35	161 (48.3%)	18 (47.4%)	
36–40	45 (13.5%)	5 (13.2%)	
>40	8 (2.4%)	1 (2.6%)	
Paternal age (years)	33.92±5.41	33.13±4.66	0.401†
<30	64 (19.2%)	8 (21.1%)	0.656
30–35	156 (46.8%)	18 (47.4%)	
36–40	73 (21.9%)	10 (26.3%)	
>40	40 (12.0%)	2 (5.3%)	
Infertility type			
Primary	141 (42.3%)	22 (57.9%)	0.084
Secondary	192 (57.7%)	16 (42.1%)	
Basal hormone level			
Follicle-stimulating hormone (FSH) (mIU/mL)	7.01±1.95	6.55±2.00	0.082†
Luteinizing hormone (LH) (mIU/mL)	6.74±3.67	5.68±2.65	0.087
Prolactin (PRL) (ng/mL)	22.91±13.78	24.60±18.65	0.705†
Estradiol (E2) (pg/mL)	38.85±17.72	40.88±16.72	0.501
Testosterone (T) (ng/mL)	0.46±3.00	3.31±18.61	0.351
Progesterone (P) (ng/mL)	0.48±0.89	0.46±0.36	0.916
Total Gn dose	2468.36±835.00	2513.16±985.44	0.785†
Hormone level on day of hCG triggering			
Estradiol (E2) (pg/mL)	4854.67±3427.89	4446.09±2846.84	0.480
Luteinizing hormone (LH) (mIU/mL)	1.43±1.19	1.44±1.21	0.700†
Progesterone (P) (ng/mL)	1.07±0.69	1.12±0.70	0.644
Method of endometrial preparation for frozen-thawed embryo transfer (FET)			
Hormone replacement therapy (HRT) cycle	225 (67.6%)	32 (84.2%)	0.083
Natural cycle (NC)	75 (22.5%)	3 (7.9%)	
Cycle with ovulation induction (OI)	33 (9.9%)	3 (7.9%)	
Blood HCG level (mIU/mL)	428.80±588.46	506.55±442.67	0.114†
Gestational age at birth (weeks)	38.62±1.38	33.29±4.09	<0.001
Birth weight (kg)	3.22±0.37	1.93±0.53	<0.001
Gender of fetus			
Male	178 (53.5%)	24 (63.2%)	0.304
Female	155 (46.5%)	14 (36.8%)	

Note: †Mann–Whitney *U*-test was performed.

Logistic Regression Analysis of Risk of Fetuses with Singleton Preterm and Low Birth Weight After FET

Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cut-off values of FSH, and T levels. When preterm birth was taken as the end point of FSH, and T levels, the cut-off value of FSH was 6.215 mIU/mL (sensitivity 65.5%, specificity 63.4%) (Figure 1A), and the cut-off value of T was 0.315 ng/mL (sensitivity 50.9%, specificity 66.5%) (Figure 1B). To gain insight into the independent influence of clinical characteristics on fetuses with singleton preterm after FET, logistic regression analysis was performed. The results of univariate analysis indicated that primary infertility, low basal FSH level (<6.215 mIU/mL), and high testosterone level (≥0.315 ng/mL) were risk factors for preterm birth. The results of multiple regressions analysis showed that high maternal age (≥35 years) (OR 3.652, 95% CI: 1.683–7.925, P=0.001), primary infertility (OR 2.869, 95% CI: 1.461–5.632, P=0.002), low FSH level (<6.215 mIU/mL) (OR 3.272, 95% CI: 1.743–6.144, P<0.001), and hormone replacement therapy (HRT) method of endometrial preparation for FET (OR 2.780, 95% CI: 1.088–7.100, P=0.033) may increase risk of preterm birth after FET (Table 4).

The results of univariate analysis indicated that low basal FSH level (<6.215 mIU/mL), and hormone replacement therapy (HRT) method of endometrial preparation for FET may reduce the risk of low birth weight. The results of multiple regressions analysis showed that low basal FSH level (<6.215 mIU/mL) (OR 0.425, 95% CI: 0.209–0.865, P=0.018), and hormone replacement therapy (HRT) method of endometrial preparation for FET (OR 0.272, 95% CI: 0.079–0.934, P=0.039) may reduce the risk of low birth weight after FET (Table 4).

Discussion

At present, the research on the influence of assisted reproductive technology on pregnancy outcome mainly focuses on the differences of pregnancy outcomes between frozen embryo transfer and fresh embryo transfer in assisted reproduction.[20,21] Etiology of preterm birth in IVF/ICSI which is related to both spontaneous and iatrogenic etiology.[22] This study analyzed the risk factors of preterm birth and low birth weight in frozen embryo transfer. This retrospective study of the risk of preterm birth and low birth weight in singletons conceived through frozen embryo transfer including 386 embryo transfer cycles, there were 55 preterm infants and 38 infants with low birth weight born after FET. The main findings of this study were that high maternal age (≥35 years), primary infertility, low FSH level (<6.215 mIU/mL), and hormone replacement therapy (HRT) method of endometrial preparation for FET may increase risk of preterm birth after FET. In addition, low basal FSH level (<6.215 mIU/mL), and HRT method of endometrial preparation may reduce the risk of low birth weight after FET.

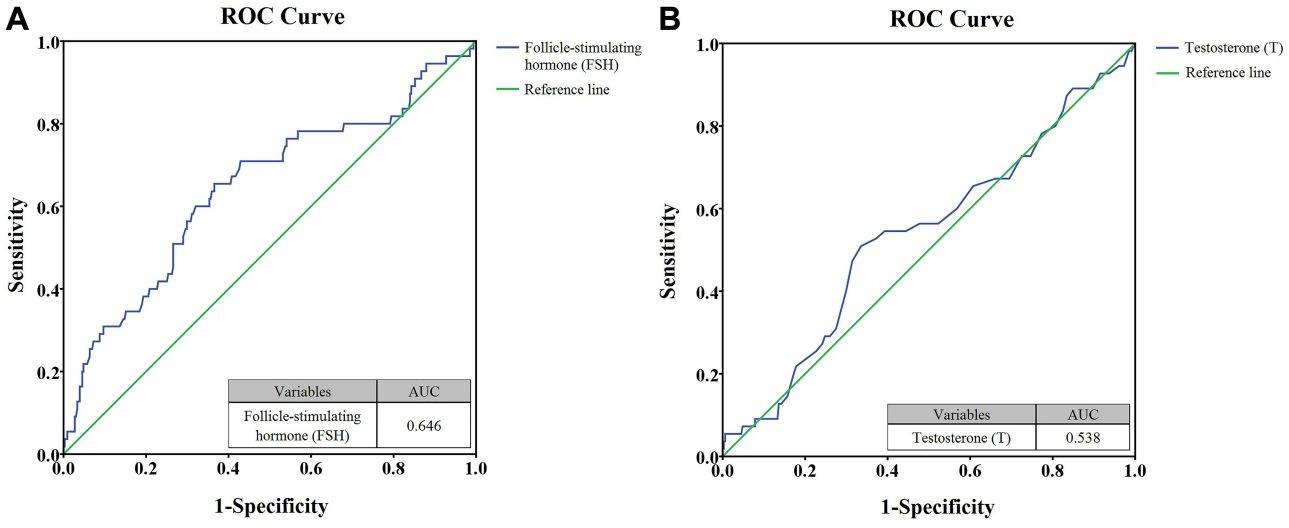

Figure 1 The ROC curve of follicle-stimulating hormone (FSH) (**A**), and testosterone (T) (**B**) for preterm birth and low birth weight.

Table 4 Logistic Regression Analysis of Risk of Fetuses with Singleton Preterm and Low Birth Weight After Frozen Embryo Transfer

Variables	Preterm Birth				Low Birth Weight			
	Univariate Analysis		Multivariate Analysis		Univariate Analysis		Multivariate Analysis	
	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value	Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Maternal age (years)								
<35	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
≥35	1.780 (0.935–3.389)	0.079	3.652 (1.683–7.925)	0.001	0.945 (0.414–2.155)	0.892	0.583 (0.234–1.449)	0.245
Infertility type								
Secondary	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
Primary	2.124 (1.187–3.802)	0.011	2.869 (1.461–5.632)	0.002	0.534 (0.271–1.054)	0.071	0.491 (0.234–1.029)	0.060
Basal hormone level								
Follicle-stimulating hormone (FSH) (mIU/mL)								
≥6.215	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
<6.215	3.288 (1.806–5.986)	<0.001	3.272 (1.743–6.144)	<0.001	0.412 (0.208–0.820)	0.011	0.425 (0.209–0.865)	0.018
Testosterone (T) (ng/mL)								
<0.315	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
≥0.315	2.055 (1.156–3.656)	0.014	1.639 (0.878–3.062)	0.121	0.549 (0.280–1.077)	0.081	0.708 (0.348–1.442)	0.342
Method of endometrial preparation for FET								
Natural cycle	1.000 (Reference)		1.000 (Reference)		1.000 (Reference)		1.000 (Reference)	
Hormone replacement therapy (HRT) cycle	2.390 (0.979–5.837)	0.056	2.780 (1.088–7.100)	0.033	0.281 (0.084–0.945)	0.040	0.272 (0.079–0.934)	0.039
Cycle with ovulation induction (OI)	1.789 (0.510–6.274)	0.363	1.578 (0.407–6.121)	0.510	0.440 (0.084–2.295)	0.330	0.494 (0.091–2.674)	0.413

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Maternal age is a determinant factor for success in ART.[23] Maternal age at natural-cycle frozen embryo transfers (NC-FET) independently impact pregnancy outcomes, such as odds of pregnancy and live birth.[24] However, studies have showed that maternal age was not associated with birth weight of singletons resulting from FET.[24,25] Increasing maternal age had no effect on preterm delivery or low birth weight risk after FET.[26] HCG levels are affected by female age and normal blastocyst development depends on HCG, so embryo development is affected by maternal age.[27] In addition, maternal age was not associated with live birth rate of infants resulting from FET.[28] In this study, high maternal age (≥35 years) may increase risk of preterm birth after FET. Elderly women older than 35 years old have decreased ovarian function, low ovulation number and poor quality, which is not conducive to obtaining high-quality embryos, and endometrial receptivity will be greatly reduced during pregnancy, all of which will lead to adverse pregnancy outcomes.[29,30]

HRT method for endometrial preparation during FET was associated with increased risk of low birth weight and preterm birth of singletons, compared to the natural cycle and cycle with ovulation induction protocols.[19,31] For women who received FET cycles, natural cycles were associated with a lower risk of preterm birth[13,32] and low birth weight.[13] On the contrary, HRT method FET group had a higher birth weight than those in the natural cycle FET group and stimulated cycle FET group.[16] In addition, no significant differences in infants with preterm birth and low birth weight between the different protocols.[33–35] Artificial cycle FET is a risk factor for preterm birth and low birth weight in multiple pregnancies but is not associated with outcome in singleton pregnancies.[36] In this study, HRT method may increase risk of preterm birth after FET, while it may reduce the risk of low birth weight after FET. The application of HRT method can artificially control and determine the time of endometrial proliferation and endometrial transformation, and the time of embryo thawing and transplantation can be arranged in advance to ensure the synchronicity of endometrial and embryo development, which is conducive to embryo implantation and development. It may be the reason why HRT reduces the risk of low birth weight. There are inconsistent results in related studies, and prospective studies with larger sample sizes are needed to reveal the relationship.[37] In addition, the pregnancy rate of natural cycle FET was significantly higher than that of HR method.[38]

Among other factors, a study has found that the type of infertility has no effect on the pregnancy outcome after ART.[39] There was no association between gestational trophoblastic disease and infertility types during assisted reproduction.[40] On the contrary, study has found that the type of infertility was associated with pregnancy outcomes in FET.[41] Basal serum FSH level is correlated to clinical pregnancy outcome in FET cycles.[42] Some scholars believe that decidualization of endometrium is a necessary condition for embryo implantation and placenta formation, and the factors associated decidualization need to interact with hormone receptors to play their functions, so hormone levels play an important role in regulating receptivity of endometrium.[43] Infant gender had significant effects on singleton birth weight.[44] Male fetuses showed a slower growth trajectory in terms of weight compared to females. In addition, study has showed that infants born to overweight mothers have a higher risk of low birth weight and preterm birth.[45] The rate of fetuses with preterm birth and lower birth weight in who performed double embryo transfer was higher than single embryo transfer.[46] Paternal age had no effect on neonatal outcomes.[47] The outcomes of FET may be influenced by the characteristics of dietary patterns.[48] Other perinatal adverse outcomes and their risk factors in offspring conceived following FET were not analyzed in this study.

In addition, the outcomes after FET were influenced by ethnicity.[49] Some studies have shown that polymorphisms in some genes are associated with outcomes after embryo transfer, such as human leukocyte antigen (HLA)-G gene,[50] leukaemia inhibitory factor (LIF) gene,[51] tumor necrosis factor (TNF),[52] insulin-like growth factor 2 (IGF2),[53] and chromosomal polymorphisms.[54] However, some studies have shown racial differences in live birth rates after fresh embryo transfer, but no significant differences in live birth rates after frozen embryo transfer.[55] The live birth rates of FET with different endometrial preparation protocols differed significantly in different populations.[56]

There are many influencing factors for preterm birth and low birth weight after FET assisted pregnancy. Our study found that high maternal age, primary infertility, low FSH level, and hormone replacement therapy (HRT) method of endometrial preparation for FET have a certain predictive value for preterm birth, while low FSH level, and HRT method of endometrial preparation for FET have a certain predictive value for low birth weight. In addition, other studies have found that other factors are associated with higher risks of preterm birth and low birth weight after FET, such as thin

endometrium,[57] polycystic ovary syndrome (PCOS),[58] number of embryos transferred,[46] uterine malformation,[59] and higher estradiol level.[60] The value of multi-factor combination in predicting preterm birth and low birth weight is better than that of independent factors, which deserves our close attention. In conclusion, in clinical practice, reproductive doctors and obstetricians should pay more attention to these influencing factors to reduce the incidence of perinatal adverse events.

This study only investigated the possible influencing factors of preterm birth and low birth weight in IVF/ICSI with FET. Of course, some studies have compared the effects of frozen versus fresh embryo transfer on perinatal outcomes. Study showed that IVF/ICSI conceptions from frozen-thawed as compared to fresh blastocyst transfer presented increased rate of large-for-gestational-age (LGA) and reduced rate of small-for-gestational-age (SGA) both prenatally and postnatally.[61] The proportion of SGA are lower in IVF/ICSI pregnancies conceived after FET as compared to fresh blastocyst transfer.[62] Another study showed that, at 6–14 weeks, thawed blastocyst transfers after IVF/ICSI conceptions present greater CRLs compared with fresh: this effect is particularly evident before 9 weeks and it may favor birth weight difference of thawed versus fresh blastocyst transfer pregnancies.[63] It can be seen that the differences in body weight and other fetal traits of fetuses transplanted through frozen embryos or fresh embryos may be related to the growth patterns of different gestational weeks, which requires the establishment of a unified reproductive, prenatal and postnatal monitoring mode to effectively prevent adverse events in pregnancy and perinatal period.

There are some limitations to this study. First, the present study did not collect and analyze data on the whole process of intrauterine development, which may have underlying pathological factors leading to preterm birth and low birth weight. Second, the number of fetuses with preterm birth and low birth weight is small, and the results of this study may be biased. Third, as a retrospective study, this study did not analyze all the reported possible influencing factors and could not provide a more comprehensive assessment of influencing factors. So, multicenter, large-sample, prospective randomized controlled trials are needed for further study.

Conclusions

In summary, high maternal age (≥35 years), primary infertility, low FSH level (<6.215 mIU/mL), and hormone replacement therapy (HRT) method of endometrial preparation for FET may increase risk of preterm birth after FET. In addition, primary infertility, low basal FSH level (<6.215 mIU/mL), and hormone replacement therapy (HRT) method of endometrial preparation may reduce the risk of low birth weight after FET. It is hoped that these findings will provide reproductive scientists with some advice on the risk of perinatal adverse outcomes in offspring conceived following FET.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital, Meizhou Academy of Medical Sciences. All participants signed informed consent in accordance with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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