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MATERNAL-FETAL MEDICINE

The risk of placenta previa and cesarean section associated with a thin endometrial thickness: a retrospective study of 5251 singleton births during frozen embryo transfer in China

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Abstract

Purpose To determine whether the endometrial thickness (EMT) affects the occurrence of obstetric complications and neonatal outcomes in frozen embryo transfer (FET).

Methods We conducted a retrospective study that included singleton deliveries ($N=5251$) resulting from FET in a single center between August 2013 and March 2016. Obstetric complications and neonatal outcomes were compared among patients with different EMTs, which were measured the day before embryo thawing. The women were divided into three groups based on the EMT: group 1: < 9 mm; group 2: 9–12 mm; group 3: > 12 mm. Multiple logistic regression and subgroup analyses were performed to determine the potential confounding factors.

Results The incidence of placenta previa in groups 1, 2, and 3 was 3.8, 1.0 and 0.5%, respectively, and that of cesarean section was 87.0, 78.3 and 72.0%, respectively (both $P<0.001$). The gestational age and birth weight increased from group 1 to group 3 (both $P<0.001$). After adjusting for confounders, a thicker EMT was found to be associated with a decreased risk of placenta previa (adjusted odds ratio (aOR) 0.798; 95% confidence interval (95% CI) 0.651–0.979; $P=0.031$) and with a decreased risk of cesarean section (aOR 0.926; 95% CI 0.889–0.965; $P<0.001$). Regarding the incidence of placenta previa, compared to women in group 3, women in group 1 had an aOR of 6.208 (95% CI 2.169–17.766; $P=0.001$), and women in group 2 had an aOR of 1.862 (95% CI 0.851–4.076; $P=0.120$). Regarding the incidence of cesarean section, compared to women in group 3, women in group 1 had an aOR of 2.111 (95% CI 1.415–3.455; $P<0.001$), and women in group 2 had an aOR of 1.293 (95% CI 1.128–1.481; $P<0.001$). Subgroup analyses showed similar results.

Conclusions Our results demonstrate that a thin endometrial lining is associated with adverse obstetric and neonatal outcomes and might be related to poor placentation.

Keywords Endometrial thickness · Frozen embryo transfer · Obstetric complication · Neonatal outcome · Singleton live birth

Introduction

Pregnancies resulting from assisted reproductive technology (ART) are associated with a higher risk of adverse outcomes than spontaneously achieved pregnancies; these outcomes include preterm delivery [1], a lower birth weight and an increased incidence of pregnancy complications [2], mainly due to the increased incidence of multiple pregnancies [3–5]. However, numerous studies have shown an increased risk of adverse outcomes in singleton in vitro fertilization (IVF) pregnancies compared to spontaneously achieved pregnancies [2, 6–9].

Frozen embryo transfer (FET), which is a major technique utilized in ART, is also considered to be related to

Shuang Jing and Xiaofeng Li should be considered similar in author order.

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the occurrence of obstetric complications. FET is associated with an increased incidence of large for gestational age [10], hypertensive disorders of pregnancy [10, 11], a higher birth weight [10], macrosomia [10], and postterm birth [12]. These outcomes may occur because freezing and thawing cycles during FET affect implantation or placenta formation, thereby resulting in placenta-related complications [11, 13–15]. Numerous findings have shown that disturbed placental epigenetic regulation, which is caused by the process of freezing, may cause abnormal trophoblastic invasion [14]; moreover, subsequent abnormal remodeling of the uteroplacental spiral arteries during early gestation leads to defective deep placentation, which may contribute to the pathophysiology of spontaneous miscarriage, intrauterine growth restriction (IUGR) [16] and preeclampsia [17, 18].

Endometrial tissue also affects embryo implantation and placenta formation [15, 19]. The endometrial thickness (EMT) is regarded as one of the primary factors influencing endometrial receptivity [8]. The endometrium maintains complex autocrine, paracrine and endocrine signaling involving sex steroids, cytokines and chemokines [20]; it also plays a role in intracellular signaling, culminating in receptivity to embryo implantation and pregnancy-related diseases [21]. Many reports have shown that the EMT is significantly associated with the pregnancy rate and have described it as a prognostic factor [22–24]. A thin endometrium has been recognized as a critical factor of implantation failure [25] and ectopic pregnancy [19]. In addition, the EMT is associated with the risk of placenta previa or obstetric complications and birth weight, as shown in a retrospective study of singleton deliveries [15, 26, 27] resulting from fresh embryo transfer.

Although frozen embryos may affect placenta formation, little is known about the association between EMT and adverse pregnancy outcomes in FET. The aim of this study was to investigate the association between EMT measured prior to FET and adverse obstetric and neonatal outcomes.

Materials and methods

Study design

We conducted a retrospective study evaluating the outcome of singleton deliveries in women who underwent FET between August 2013 and March 2016 at a single center in a tertiary university-affiliated hospital: the Reproductive and Genetic Hospital of CITIC-Xiangya.

To exclude the influence of medicines used in different endometrial preparation schemes, only two common endometrial preparation protocols, natural and artificial cycles, were included in our study. We also excluded patients who were lost to follow-up or gave birth before 28 gestational weeks. There was a total of 17,280 freeze–thaw cycles during this time. There were 11,299 natural cycles, 4651 artificial cycles, and 29,793 total embryos transplanted. Women who were not pregnant or had multiple live births were not included in this study. The pregnancy rate was 54.8% (8746/15,950), the live birth rate was 44.3% (7061/15,950), the multiple birth rate was 25.3% (1788/7061), and there were 5273 cycles resulting in singleton live births. Finally, 5251 singleton delivery cycles met our requirements, as shown in Fig. 1. More than 99% of the women in our study population were of Han ethnicity. Smoking and alcohol use

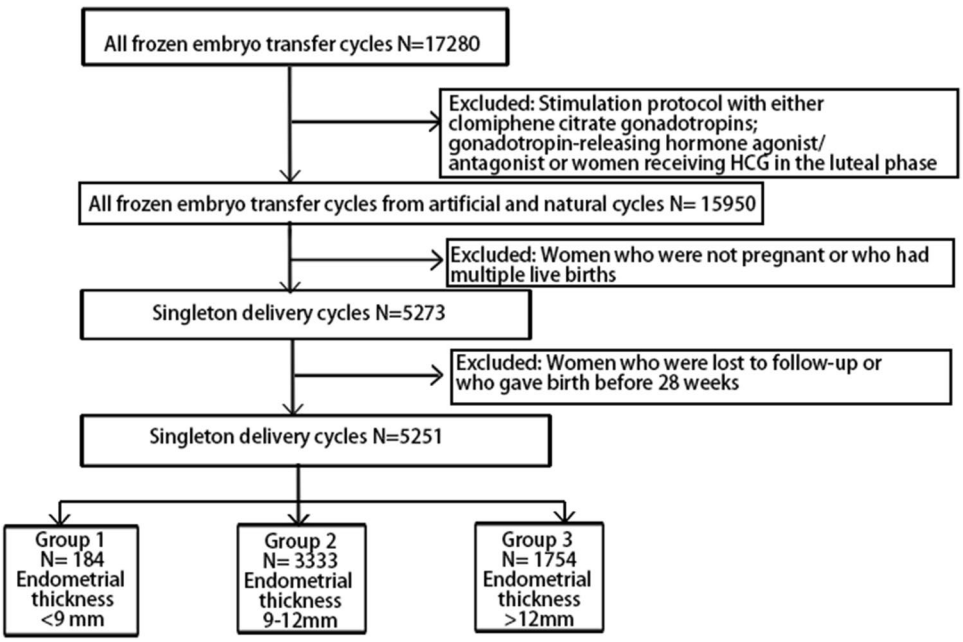

Fig. 1 Selection of study groups

were very uncommon in this population. Due to the one-child policy, 95% of the population was primipara (data not shown).

FET protocols

The embryos in our study were obtained from unsuccessful fresh embryo cycles, including IVF or intracytoplasmic sperm injection (ICSI). The embryos were vitrified using a Kitazato vitrification kit (Kitazato Biopharma) in combination with high-security vitrification straws (Cryo Bio System). The vitrification and thawing procedures were performed according to the manufacturer's instructions, as stated in our previous article [28].

Endometrial preparation

Natural cycle: women with a natural cycle did not take any medications during the follicular phase. Transvaginal sonography was performed on day ten. Subsequently, ultrasound examinations were performed until the EMT was at least 8 mm and the main follicle reached 18–22 mm. Ovulation predictor kits were also used to monitor ovulation. When ovulation occurred, FET was scheduled based on the embryo stage at freezing (i.e., day 3 for cleavage embryos and day 5 for blastocysts). The luteal phase was supported with progesterone (40 mg/day, 2 × 20 mg; Duphaston, Abbott Biologicals B.V., The Netherlands) administered orally 2 days before FET.

Artificial cycle: women undergoing an artificial cycle started on the first day of their natural menstrual cycle. Estrogen (Progynova, Delpharm Lille S.A.S., France) (2 mg estradiol valerate) was administered orally, as follows: one pill on days 1, 2, 3 and 4; two pills on days 5, 6 and 7; three pills on days 8, 9, 10 and 11; four pills on days 12, 13, 14, 15 and 16; and two pills on days 17 to 31. When the EMT reached at least 7.0 mm, dydrogesterone was administered orally (10 mg per 12 h; Duphaston, Abbott Biologicals B.V., The Netherlands), and progesterone was administered vaginally (200 mg, three times a day; Utrogestan, Capsugel, France) for luteal phase support.

Endometrial lining measurements

The EMT was measured on the day before embryo thawing in women with an EMT of at least 7 mm. Transvaginal sonography was performed using a GE Voluson E8/730 system (General Electric Tech Co., Ltd., New York, USA) equipped with a 5–9 MHz transvaginal color Doppler probe. Highly trained sonographers measured the EMT in a two-dimensional plane using an intracavity probe with a frequency range of 5–9 MHz. The patients were divided into three groups by the EMT (group 1: < 9 mm, group 2: 9–12 mm, and group 3: > 12 mm), according to Rombauts' article [15].

Data collection

The research group and the hospital information engineer extracted data from the hospital electronic medical records according to criteria set forth on the standardized data collection form. Discrete data (i.e., data that were not stored as free text) were pulled from the medical records directly. Trained nurses in the clinic who were routinely involved in conducting standardized detailed surveys telephoned the patients to obtain missing data regarding obstetric and neonatal outcomes. We also contacted the health and family planning department to obtain information when we could not contact the patients. Patients were defined as lost to follow-up only after the failure of numerous attempts to reach the patients by telephone or post or when the information could not be obtained from the health and family planning department.

Hypertensive disorders of pregnancy were defined as a sustained (on at least two occasions 6 h apart) blood pressure ≥ 140/90 mmHg after 20 weeks, with or without proteinuria and other signs or symptoms of preeclampsia and without a prior history of hypertension. Since the diagnostic criteria for preeclampsia and gestational hypertension varied across the study period and between countries [29], we considered hypertensive disorders of pregnancy a single, combined outcome (International Classification of Diseases, Tenth Revision, ICD-10: O11, O13–O16). The diagnosis of placenta previa was made by the treating obstetrician using generally accepted diagnostic criteria based on a transvaginal ultrasound examination in the third trimester. Preterm delivery (PTD) was defined as a gestational age < 37 weeks, and low birth weight (LBW) was defined as < 2500 g. Small for gestational age (SGA) was defined as a birth weight below the 10th percentile based on the gestational age, and large for gestational age (LGA) was defined similarly as a birth weight above the 90th percentile [30]. Vanishing twin was defined as the spontaneous reduction of a fetus while still in utero [31]. Indications for a cesarean section included a prior cesarean section, fetal malpresentation, placenta previa, cephalopelvic disproportion (CPD), dysfunctional labor, abnormal fetal heart rate (FHR) patterns, acute chorioamnionitis, pregnancy complications (such as gestational diabetes, hypertension, and eclampsia), and IUGR, maternal age > 35 years, and BMI > 25 (kg/m^2) [32].

Ethical consideration

The study was approved by the Ethical and Research Committee of Citic-Xiangya Hospital, Central South University, in July 2012. The ethical approval number is LLSL059.

Statistical analysis

Data were statistically analyzed using SPSS 22.0. Nonnormally and normally distributed data are presented as the mean (standard deviation), and the *t* test and Mann–Whitney *U* test were used for comparisons. Categorical variables are presented as percentages, and the Chi squared test and Fisher's exact test were used for comparisons. The *z* score was used to evaluate associations with the birth weight and EMT after adjusting for infant sex and gestational age: *z* score = (newborn birth weight − mean birth weight at the same gestational age for the same sex in the reference population)/standard deviation (SD) in the same reference population). The reference population was derived from the latest publication regarding gestational age-specific birth weights of Chinese singletons [30]. Multivariate logistic regression analysis (forward likelihood ratio) was used to adjust for potential confounding factors. Confounding factors were selected based on clinical relevance and previous knowledge, and they were unevenly distributed among the groups of women studied. $P < 0.05$ was considered statistically significant.

Results

Demographic and cycle characteristics and obstetric and neonatal outcomes

The characteristics and pregnancy outcomes of groups 1, 2 and 3 are shown in Table 1. Age, body mass index (BMI) and infertility etiology did not differ significantly among the groups, except for oviduct factors, polycystic ovary syndrome (PCOS), and Asherman syndrome (AS), the incidence of which was lower in group 3 and higher in group 1. Among the three groups, primary infertility and blastocyst transfer occurred more often in group 3, and there were more women with artificial cycles in group 1. The incidence of placenta previa and cesarean section increased from group 1 to group 3: the incidence of placenta previa and cesarean section in groups 1, 2, and 3 was 3.8, 1.0, and 0.5% ($P < 0.001$) and 87.0, 78.3, and 72.0%, respectively ($P < 0.001$). There were significant differences in the gestational age and birth weight among the three groups, with the lowest in group 1 and the highest in group 3 for both (gestational age, $P = 0.017$; birth weight, $P = 0.044$). The incidence of vanishing twin was comparable among the groups. There were no differences among the groups regarding the other obstetric and neonatal outcomes. The EMT ranged from 7 mm to 17.5 mm. The incidence of cesarean section with indications was 57.1, 53.9, and 48.7% ($P = 0.001$) in groups 1, 2, and 3, respectively, as shown in Table 1.

Logistic regression analysis

Logistic regression analysis to identify risk factors of placenta previa

The EMT (as a continuous variable), maternal age, BMI, AS, and artificial cycles were statistically associated with the incidence of placenta previa (all $P < 0.05$) on univariate logistic regression and were further entered into the multivariate analysis, as shown in Supplemental Table 1. After adjustment in the multivariate logistic model, a thinner EMT (as a continuous variable) increased the likelihood of placenta previa (adjusted odds ratio (aOR) 0.798, 95% confidence interval (CI) 0.651–0.979, $P = 0.031$), even after excluding patients with AS (aOR 0.781; 95% CI 0.631–0.966; $P = 0.022$), as shown in Table 2. Compared to women with an EMT of > 12 mm, the risk of placenta previa in women with an EMT of 9–12 mm had an adjusted odds ratio (aOR) of 1.862 and a 95% CI of 0.851–4.076 ($P > 0.05$), and women with an EMT < 9 mm had an aOR of 6.208 (95% CI 2.169–17.766, $P = 0.001$).

Logistic regression analysis to identify risk factors of cesarean section and cesarean section with indications

A thinner EMT, a more advanced maternal age, a higher maternal BMI before ET, treatment with artificial cycles, a previous cesarean section, and PCOS (primary infertility for cesarean section with indications) all had *P* values < 0.05 on univariate logistic regression and were entered into the multivariate analysis, as shown in Supplemental Tables 2 and 3. After adjusting for confounding factors, women with a thin endometrial lining were more likely to have a cesarean section (OR 0.926; 95% CI 0.889–0.965; $P < 0.001$), even after excluding patients with placenta previa (OR 0.928; 95% CI 0.891–0.967; $P = 0.001$), as shown in Table 2. Regarding the risk of cesarean section, compared to women with an EMT of > 12 mm, women with an EMT of 9–12 mm had an aOR of 1.293 (95% CI 1.128–1.481, $P < 0.001$), and women with an EMT < 9 mm had an aOR of 2.211 (95% CI 1.415–3.455, $P < 0.001$). The confounding factors were the incidence of primary infertility, oviduct factors, PCOS, AS, teratospermia, blastocyst transfer, the number of embryos transferred and treatment with artificial cycles. Similar results were found for the incidence of cesarean section with indications, as shown in Table 2.

The results of the subgroup analyses, including demographic characteristics, pregnancy complications and neonatal outcomes in singleton live births according to the EMT and cycle type, are shown in Tables 3 and 4. The incidence of placenta previa and cesarean section also decreased with increasing EMT in the subgroups. The gestational age and birth weight increased with increasing EMT in both women with natural and artificial cycles. The frequency of placenta previa in groups 1, 2, and 3 was 1.9, 0.9 and 0.3% in women

Table 1 Demographic characteristics, pregnancy complications and neonatal outcomes in singleton live births according to endometrial thickness

	Group 1	Group 2	Group 3	*P*
Cycles	184	3333	1734	
Endometrial thickness (mm)	8.70 ± 0.32	10.73 ± 0.80	13.32 ± 1.09	
Maternal age (years)	31.08 ± 4.56	30.93 ± 4.41	30.88 ± 4.38	0.786[a]
Body mass index (BMI) (kg/m^2)	21.48 ± 2.72	21.58 ± 2.69	21.61 ± 2.65	0.767[a]
Primary infertility	60 (32.6)	1393 (41.8)	759 (43.8)	0.012[b]
Basal FSH (mIU/ml)	6.44 ± 2.57	6.41 ± 2.44	6.35 ± 2.32	0.868[a]
Cause of infertility				
Oviduct factors	158 (85.9)	2859 (85.8)	1400 (80.8)	< 0.001[b]
Anovulation	5 (2.7)	44 (1.3)	15 (0.9)	0.063[b]
Endometriosis	1 (0.5)	94 (2.8)	61 (3.5)	0.054[b]
PCOS (%)	12 (6.5)	191 (5.7)	72 (4.2)	0.042[b]
Asherman syndrome	10 (5.4)	106 (3.2)	21 (1.2)	< 0.001[b]
Oligoasthenozoospermia	12 (6.5)	316 (9.5)	160 (9.2)	0.402[b]
Teratospermia	30 (16.3)	460 (13.8)	199 (11.5)	0.029[b]
Blastocyst transfer	73 (39.7)	1443 (43.3)	881 (50.8)	< 0.001[b]
Endometrial preparation method				
Artificial cycle	81 (44.0)	1020 (30.6)	305 (17.6)	< 0.001[b]
Natural cycle	103 (56.0)	2313 (69.4)	1449 (82.4)	
Chronic hypertension	0	9 (0.3)	1 (0.1)	0.215[b]
Pregestational diabetes	0	4 (0.1)	4(0.2)	0.546[b]
Previous caesarean section	6 (3.3)	130 (3.9)	70 (4.0)	0.870[b]
Number of embryo transfers				< 0.001[a]
1	30 (16.3)	608 (19.2)	427 (24.6)	
2	143 (77.7)	2540 (76.2)	1240 (71.5)	
3	11 (6.0)	185 (5.6)	67 (3.9)	
Pregnancy complications				
Gestational diabetes	15 (8.2)	328 (9.8)	156 (9.0)	0.509[b]
Pregnancy hypertension disorder	11 (6.0)	129 (3.9)	74 (4.3)	0.329[b]
Polyhydramnios	0	22 (0.7)	15 (0.9)	0.361[b]
Oligohydramnios	1 (0.5)	97 (2.9)	50 (2.9)	0.165[b]
Placental abruption	0	3 (0.1)	1 (0.1)	0.860[b]
Placenta previa[c]	7 (3.8)	34 (1.0)	8 (0.5)	< 0.001[b]
Vaginal infection	2 (1.1)	52 (1.6)	29 (1.7)	0.822[b]
Vanishing twins	21 (11.4)	408 (12.2)	213 (12.3)	0.942[b]
Cesarean section[d] (CS)	160 (87.0)	2609 (78.3)	1248 (72.0)	< 0.001[b]
CS without indications	55 (29.9)	812 (24.4)	403 (23.3)	0.124
CS with indications	105 (57.1)	1797 (53.9)	845 (48.7)	0.001
Neonatal outcomes				
Male sex	94 (51.1)	1776 (53.3)	950 (54.8)	0.459[b]
Gestational age (weeks)[e]	38.72 ± 1.69	38.94 ± 1.59	38.96 ± 1.62	0.017[a]
PTD	21 (11.4)	267 (8.0)	128 (7.4)	0.149[b]
Birth weight (g)[f]	3297.70 ± 521.94	3372.27 ± 498.57	3377.83 ± 515.12	0.044[a]
LBW	13 (7.1)	158 (4.8)	82 (4.8)	0.360[b]
Macrosomia[c]	10 (5.5)	233 (7.1)	146 (8.5)	0.112[b]
SGA	10 (5.5)	175 (5.3)	95 (5.5)	0.937[b]
LGA	29 (15.8)	580 (17.4)	327 (18.9)	0.330[b]
Z-score	0.17 ± 1.27	0.24 ± 1.42	0.27 ± 1.36	0.263[a]

Continuous measurements are summarized as the means ± standard deviation. Nominal measurements are summarized as n (%) unless stated otherwise

FSH follicle stimulating hormone, *PCOS* polycystic ovary syndrome, *PTD* preterm delivery (< 37 weeks), *LBW* low birth weight (< 2500 g), *SGA* small for gestational age (defined < 10%), *LGA* large for gestational age (defined > 10%)

Table 1 (continued)

Exact values of *P* values are given when > 0.001

[a]The differences between the groups were evaluated by the Mann-Whitney *U* test

[b]*P* values are from the chi-squared test or Fisher's exact tests for categorical variables

[c]Group 1 vs. Group 2, $P = 0.001$; Group 2 vs. Group 3, $P = 0.037$; Group 1 vs. Group 3; $P < 0.001$

[d]Group 1 vs. Group 2, $P = 0.005$; Group 2 vs. Group 3, $P < 0.001$; Group 1 vs. Group 3; $P < 0.001$

[e]Group 1 vs. Group 2, $P = 0.011$; Group 2 vs. Group 3, $P > 0.050$; Group 1 vs. Group 3; $P = 0.004$

[f]Group 1 vs. Group 2, $P = 0.023$; Group 2 vs. Group 3, $P > 0.050$; Group 1 vs. Group 3; $P = 0.014$

Table 2 Logistic regression analysis adjusting confounding factors to find the risk of placenta previa, cesarean section

Perinatal outcome	COR (95% CI)	*P*	AOR (95% CI)	*P*
Placenta previa[a]	0.755 (0.618–0.924)	0.006	0.798 (0.651–0.979)[b]	0.031
Placenta previa[c]	0.750 (0.607–0.926)	0.007	0.781 (0.632–0.967)[d]	0.023
Group 1	8.532 (3.058–23.807)	< 0.001	6.208 (2.169–17.766)	0.001
Group 2	2.224 (1.027– 4.814)	0.043	1.862 (0.851–4.076)	0.120
Group 3	Reference		Reference	
Caesarean section[a]	0.905 (0.870–0.942)	< 0.001	0.926 (0.889–0.965)[e]	< 0.001
Caesarean section[f]	0.908 (0.873–0.944)	< 0.001	0.928 (0.891–0.967)[g]	< 0.001
Group 1	2.596 (1.669–4.038)	< 0.001	2.211 (1.415–3.455)	< 0.001
Group 2	1.403 (1.228–1.603)	< 0.001	1.293 (1.128–1.481)	< 0.001
Group 3	Reference		Reference	
Caesarean section with indications[a]	0.906 (0.869–0.944)	< 0.001	0.926 (0.886–0.98)[e]	< 0.001
Caesarean section with indications[f]	0.903 (0.866–0.942)	< 0.001	0.929 (0.888–0.972)[g]	0.001
Group 1	2.516 (1.593– 3.975)	< 0.001	2.182 (1.353–3.520)	0.001
Group 2	1.428 (1.240–1.644)	< 0.001	1.325 (1.141–1.540)	< 0.001
Group 3	Reference		Reference	

Odds ratios were obtained via multiple logistic regression analysis

COR crude odds ratio, *AOR* adjusted odds ratio, *CI* confidence interval

[a]Endometrial thickness was considered a continuous variable

[b]Confounding factors included maternal age, Asherman syndrome, and artificial cycle

[c]Excluding patients with Asherman syndrome or endometrial thickness as a continuous variable

[d]Confounding factors included maternal age and artificial cycle

[e]Confounding factors included maternal age, body mass index, artificial cycle, previous caesarean section, PCOS

[f]Excluding patients with placenta previa and endometrial thickness as a continuous variable

[g]Confounding factors included maternal age, body mass index, artificial cycle, and PCOS

with natural cycles ($P = 0.058$) and 6.2, 1.4 and 1.0% for artificial cycles ($P = 0.002$), respectively. The frequency of cesarean section in groups 1, 2, and 3 was 84.5, 75.1 and 69.8% in women with natural cycles ($P < 0.001$) and 90.1, 85.5 and 82.3% in women with artificial cycles ($P = 0.164$), respectively. Similar results were found for the incidence of cesarean section with indications, although there were no significant differences.

In women with natural cycles, the gestational age was significantly higher in groups 2 and 3 than in group 1 ($P < 0.05$); although the birth weight was also higher in groups 2 and 3, there were no significant differences among the three groups.

In women with artificial cycles, the birth weight significantly increased from group 1 to group 3 ($P < 0.05$), and although the gestational age was also higher in groups 2 and 3, there were no significant differences among the three groups. The incidence of macrosomia increased from group 1 to group 3 (3.7, 7.4 and 10.8%), although there were no significant differences ($P = 0.051$). The incidence of SGA was highest in group 1, with a frequency of 12.3, 5.1 and 5.6% in groups 1, 2, and 3, respectively. We also discovered that the incidence of pregnancy complications was higher in women with artificial cycles than those with natural cycles.

Table 3 Demographic characteristics, pregnancy complications and neonatal outcomes in singleton live births according to endometrial thickness in the natural cycle

	Group 1	Group 2	Group 3	*P*
Cycles	103	2313	1429	
Endometrial thickness (mm)	8.74±0.30	10.80±0.79	13.35±1.12	
Maternal age (years)	31.60±5.12	31.00±4.31	30.92±4.36	0.382[a]
Body mass index (BMI) (kg/m^2)	21.39±2.84	21.44±2.62	21.47±2.61	0.821[a]
Primary infertility	33 (32.0)	966 (41.8)	623 (43.6)	0.058[b]
Basal FSH (mIU/ml)	6.66±2.54	6.41±1.95	6.36±2.18	0.738[a]
Cause of infertility (%)				
Oviduct factor[c]	89 (86.4)	1988 (85.9)	1162 (81.3)	< 0.001[b]
Anovulation	1 (1.0)	14 (0.6)	6 (0.4)	0.634[b]
Endometriosis	0 (0.0)	69 (3.0)	51 (3.6)	0.110[b]
PCOS	1 (1.0)	42 (1.8)	30 (2.1)	0.647[b]
Asherman syndrome	1 (1.0)	35 (1.5)	13 (0.9)	0.268[b]
Oligoasthenozoospermia	7 (6.8)	233 (10.1)	134 (9.4)	0.467[b]
Teratospermia	22 (21.4)	328 (14.2)	162 (11.3)	0.002[b]
Blastocyst transfer[c]	35 (34)	925 (40)	707 (49.5)	< 0.001[b]
Chronic hypertension	0	6 (0.3)	2 (0.1)	0.661[b]
Pregestational diabetes	0	0	5 (0.3)	0.015[b]
Previous caesarean section[d]	3 (2.9)	90 (3.9)	48 (3.4)	0.645[b]
Number of embryo transfers[c]				< 0.001[a]
1	18 (17.5)	420 (18.2)	345 (24.1)	
2	78 (75.7)	1760 (76.1)	1029 (72.0)	
3	7 (6.8)	133 (5.8)	55 (3.8)	
Pregnancy complications				
Gestational diabetes	8 (7.8)	219 (9.5)	131 (9.2)	0.821[b]
Pregnancy hypertension disorder	3 (2.9)	73 (3.2)	51 (3.6)	0.770[b]
Polyhydramnios	0	14 (0.6)	14 (1.0)	0.288[b]
Oligohydramnios	1 (1.0)	62 (2.7)	41 (2.9)	0.515[b]
Placental abruption	0	1 (0.0)	1 (0.1)	0.915[b]
Placenta previa	2 (1.9)	20 (0.9)	5 (0.3)	0.058[b]
Vaginal infection	1 (1.0)	34 (1.5)	24 (1.7)	0.787[b]
Vanishing twins	13 (12.6)	278 (12.0)	180 (12.6)	0.866[b]
Cesarean section[e] (CS)	87 (84.5)	1737 (75.1)	997 (69.8)	< 0.001[b]
CS without indications	33 (32.0)	577 (24.90)	333 (23.3)	0.105
CS with indications[c]	54 (52.4)	1160 (50.2)	664 (46.5)	0.050
Neonatal outcomes				
Male sex	51 (49.5)	1233 (53.3)	784 (54.9)	0.441[b]
Gestational age (weeks)[e]	38.67 ± 1.79	38.93 ± 1.52	38.94± 1.57	0.042[a]
PTD	10 (9.7)	175 (7.6)	105 (7.3)	0.680[b]
Birth weight (g)	3291.17± 645.63	3329.73 ± 605.32	3331.99 ± 596.19	0.522[a]
LBW	8 (6.0)	124 (5.4)	79 (5.5)	0.602[b]
Macrosomia	7 (6.8)	155 (6.8)	113 (7.9)	0.459[b]
SGA	5 (4.9)	118 (5.1)	78 (5.5)	0.878[b]
LGA	18 (17.5)	406 (17.6)	262 (18.3)	0.828[b]
Z-score	0.29± 1.11	0.23 ± 1.39	0.24 ± 1.47	0.690[a]

Continuous measurements are summarized as the means ± standard deviation. Nominal measurements are summarized as n (%) unless stated otherwise

FSH follicle stimulating hormone, *PCOS* polycystic ovary syndrome, *PTD* preterm delivery (< 37 weeks), *LBW* low birth weight (< 2500 g), *SGA* small for gestational age (defined < 10%); LGA, large for gestational age (defined > 10%). Exact *P* values are given when > 0.001

[a]The differences between the groups were evaluated by the Mann-Whitney *U* test

[b]*P* values are from the chi-squared test or Fisher's exact test for categorical variables

[c]Group 1 vs. Group 2, $P > 0.05$; Group 2 vs. Group 3, $P < 0.05$; Group 1 vs. Group 3, $P < 0.05$

[d]Group 1 vs. Group 2, $P < 0.05$; Group 2 vs. Group 3, $P > 0.05$; Group 1 vs. Group 3, $P < 0.05$

[e]Group 1 vs. Group 2, $P < 0.05$; Group 2 vs. Group 3, $P < 0.05$; Group 1 vs. Group 3, $P < 0.05$

Table 4 Demographic characteristics, pregnancy complications and neonatal outcomes in singleton live births according to endometrial thickness in the artificial cycle

	Group 1	Group 2	Group 3	*P*
Cycles	81	1020	305	
Endometrial thickness (mm)	8.65 ± 0.34	10.59 ± 0.80	13.17 ± 0.93	
Maternal age (years)	30.43 ± 3.66	30.80 ± 4.64	30.69 ± 4.33	0.963[a]
Body Mass Index (BMI) (kg/m^2)[c]	21.59 ± 2.56	21.89 ± 2.81	22.25 ± 2.70	0.050[a]
Primary infertility	27 (33.3)	427 (41.9)	136 (44.6)	0.188[b]
Basal FSH (mIU/ml)	6.17 ± 2.59	6.40 ± 3.28	6.28 ± 2.88	0.767[a]
Cause of infertility				
Oviduct factor[c]	69 (85.2)	871 (85.4)	238 (78.0)	0.009[b]
Anovulation	4 (4.9)	30 (2.9)	9 (3.0)	0.599[b]
Endometriosis	1 (1.2)	25 (2.5)	10 (3.3)	0.535[b]
PCOS (%)	11 (13.6)	149 (14.6)	42 (13.8)	0.647[b]
Asherman syndrome[d]	9 (11.1)	71 (7.0)	8 (2.6)	0.915[b]
Oligoasthenozoospermia	5 (6.2)	132 (12.9)	37 (12.1)	0.787[b]
Teratospermia	8 (9.9)	132 (12.9)	37 (12.1)	0.700[b]
Blastocyst transfer[c]	38 (46.9)	518 (50.8)	174 (57.1)	< 0.001[b]
Chronic hypertension	0	2 (0.2)	0	0.685[b]
Pregestational diabetes	0	4 (0.4)	0	0.468[b]
Previous caesarean section[c]	3 (3.7)	40 (3.9)	22 (7.2)	0.051[b]
Number of embryo transfers				< 0.001[a]
1	12 (14.8)	188 (18.4)	82 (26.9)	
2	65 (80.2)	780 (76.5)	211 (69.2)	
3	4 (4.9)	52 (5.1)	12 (3.9)	
Pregnancy complications				
Gestational diabetes	7 (8.6)	109 (10.7)	25 (8.2)	0.407[b]
Pregnancy hypertension disorder	8 (9.9)	56 (5.5)	23 (7.5)	0.156[b]
Polyhydramnios	0	8 (0.8)	1 (0.3)	0.516[b]
Oligohydramnios	0	35 (3.4)	9 (3.0)	0.228[b]
Placental abruption	0	2 (0.2)	0	0.685[b]
Placenta previa[d]	5 (6.2)	14 (1.4)	3 (1.0)	0.002[b]
Vaginal infection	1 (1.2)	18 (1.8)	5 (1.6)	0.934[b]
Vanishing twins	8 (9.9)	130 (12.7)	33 (10.8)	0.539[b]
Cesarean section (CS)	73 (90.1)	872 (85.5)	251 (82.3)	0.164[b]
CS without indications	22 (27.2)	235 (23.0)	70 (23.0)	0.693
CS with indications	51 (63.0)	637 (62.5)	181 (59.3)	0.604
Neonatal outcomes				
Male sex	43 (53.1)	543 (53.2)	166 (54.4)	0.933[b]
Gestational age (weeks)	38.77 ± 1.56	38.94 ± 1.72	39.03 ± 1.84	0.103[a]
PTD	11 (13.6)	92 (9.0)	23 (7.5)	0.237[b]
Birth weight (g)[f]	3265.31± 427.33	3329.89 ± 658.19	3426.49 ± 617.00	0.001[a]
LBW	6 (7.4)	74 (7.3)	18 (5.9)	0.709[b]
Macrosomia	3 (3.7)	75 (7.4)	33 (10.8)	0.051[b]
SGA[d]	10 (12.3)	52 (5.1)	17 (5.6)	0.025[b]
LGA	10 (12.3)	182 (17.8)	58 (19.0)	0.376[b]
Z-score	0.09± 1.04	0.29 ± 1.34	0.30 ± 1.41	0.192[a]

Continuous measurements are summarized as the means ± standard deviation. Nominal measurements are summarized as n (%) unless stated otherwise

FSH follicle stimulating hormone, *PCOS* Polycystic Ovary Syndrome, *PTD* preterm delivery (< 37 weeks), *LBW* low birth weight (< 2500 g), *SGA* small for gestational age (defined < 10%), *LGA* large for gestational age (defined > 10%)

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[d]Group 1 vs. Group 2, $P > 0.05$; Group 2 vs. Group 3, $P < 0.05$; Group 1 vs. Group 3, $P < 0.05$

Table 4 (continued)

[e]Group 1 vs. Group 2, $P < 0.05$; Group 2 vs. Group 3, $P > 0.05$; Group 1 vs. Group 3, $P < 0.05$
[f]Group 1 vs. Group 2, $P < 0.05$; Group 2 vs. Group 3, $P < 0.05$; Group 1 vs. Group 3, $P < 0.05$

Discussion

To the best of our knowledge, this is the first study to date to evaluate the effects of the EMT on obstetric and neonatal outcomes in FET. Notably, the incidence of both placenta previa and cesarean section was higher in women with a thin endometrial lining, even when the thickness was greater than 7.0 mm in FET. Our results suggest that the endometrial lining itself plays a crucial role in placenta formation and pregnancy complications and that an adequate EMT is important for decreasing the risk of placenta-related pregnancy complications in FET.

Placenta previa is a term used to describe abnormally low placentation. Placenta previa is a difficult diagnosis because it is associated with important maternal and fetal complications [15, 33, 34], including antenatal and postpartum hemorrhage, placenta accreta and percreta, peripartum hysterectomy, preterm delivery, IUGR, malpresentation and poor neonatal outcomes. The incidence of 0.7–1.6% in our study is comparable to that in previous studies: 0.24–1.57% in China [35] and 0.5–0.9% in other countries [15].

After we excluded patients with AS, which may increase the risk of placenta previa [36], and adjusted for other confounding factors, the EMT was still associated with the occurrence of placenta previa. These findings confirm that the EMT itself is a risk factor of placenta previa. Placenta previa may occur more commonly among women with a thin EMT because the blood supply may be insufficient, forcing the placenta to grow downward and expand the attachment area to include the lower uterine segment to obtain adequate nutrition during the pregnancy [8]. Miwa found that a 'thin' endometrium was characterized by high blood flow impedance in the uterine radial artery, poor epithelial growth, decreased VEGF expression, and poor vascular development [25]. Galia found that a thin endometrial lining was associated with obstetric complications [26]. However, Rombauts et al. [15] discovered that following IVF, the risk of placenta previa was fourfold greater in women with an EMT > 12 mm compared to women with an EMT < 9 mm, which is contrary to our conclusion. One possible reason for this difference is that in L. Rombauts' study, the approach consisted of primarily stimulated cycles with fresh embryo transfers, while all patients underwent FET in our study.

Another notable finding is that the EMT was associated with the incidence of cesarean section, suggesting either fertility problems in the patients who underwent ART or a thin EMT to be responsible for this increase, especially in women with natural cycles. Due to the high incidence of PCOS [37] and AS [36] in women with artificial cycles compared to women with natural cycles, the incidence of pregnancy complications and cesarean section increased. The incidence of diabetes and hypertension is increased in patients with PCOS [8, 38], and the incidence of placenta previa is increased in women with AS [36, 39]. Kazuki Saito also found an increased rate of cesarean section in women with artificial cycles [12]. After we adjusted for confounders, the cesarean section rate was still higher among women with a thinner than slightly thicker EMT, suggesting that a thin EMT itself is a risk factor of obstetric complications or adverse neonatal outcomes.

The incidence of cesarean section was 72.2–80.6% in our study, 85.3% in an ART population in a previous study in China [40], and 87.75% in Serbia [41]. A more advanced maternal age [42] and an increased BMI [43] are also risk factors of cesarean delivery [44].

We found a lower birth weight and younger gestational age among women with an EMT < 9 mm, regardless of the cycle type. This may be the result of the increased incidence of obstetric complications among women with an EMT less than 9 mm. For example, placenta previa [35] and hypertensive disorders of pregnancy [40] may lead to LBW. R. Moffat reported that a thin EMT was a risk factor of LBW [27], which is consistent with our findings. Further research is needed to confirm these findings.

Despite the large sample size, there are several limitations to our study. First, this was a retrospective analysis lacking detailed information about the cesarean sections. The possibility of bias and residual confounding factors is still a concern, even after multivariate logistic regression analysis. Second, the small sample of patients with placenta-related pregnancy complications, particularly placenta previa, may contribute to allocation bias. Third, in our hospital, to prevent the waste of embryos, we require an EMT greater than 7 mm for ET. Therefore, these results of our article cannot be extrapolated to thinner EMTs. In addition, although the endometrial lining was measured by the same team of trained sonographers providing routine sonography evaluations to all our fertility patients, the measurement is still subjective, which may contribute to allocation bias.

For the first time, we demonstrate the significant relationship between the EMT and obstetric/neonatal outcomes in FET. A thin endometrial lining was found to be associated with placenta previa and cesarean section even after adjusting for confounding variables. In conclusion, when the EMT is less than 9 mm, combined with other risk factors, obstetricians must remain aware of the possibility of adverse obstetric and neonatal outcomes.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Consent for publication Not applicable.

Ethics approval and consent to participate This retrospective study was approved by the Institutional Review Board of the Reproductive and Genetic Hospital of Citic-Xiangya. Ethical approval. All procedures performed in studies involving human participants 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. Informed consent was obtained from all participants included in the study.

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