A thinner endometrium is associated with lower newborn birth weight during in vitro fertilization–frozen-embryo transfer: cohort study

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Research Article

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Abstract

Background

The purpose of this study is to explore the influence of endometrial thickness (EMT) before embryo transfer on birth weight after *in vitro* fertilization–frozen-embryo transfer (IVF–FET).

Methods

This was a retrospective cohort study. We collected the medical records associated with singleton live births from Tianjin Central Obstetrics and Gynecology Hospital from June 2015 to February 2019 after IVF–frozen-embryo transfer (FET). Patients were ≤ 42 years at delivery. Outcomes related to newborns were birth weight, gestational age, delivery mode, low birth weight, and prevalence of macrosomia. Outcomes related to pregnant women were gestational hypertension, gestational diabetes mellitus, premature rupture of membranes and placenta previa.

Results

The birth weight of singleton newborns was higher for newborns delivered by patients with EMT > 12 mm before embryo transfer than newborns delivered by patients with a thinner endometrium. Regression analysis showed that the EMT ≥ 12 mm group had a gain in mean birth weight of 85.107 g compared with that in the EMT < 8 mm group, whereas the group with EMT of 8–12 mm had an increase in mean birth weight of 25.942 g compared with that in the EMT < 8 mm group. Hypertension during pregnancy, premature rupture of membranes, placenta previa, newborn sex, gestational age, delivery mode, number of implanted embryos, follicle-stimulating hormone (FSH) level, estradiol (E2) level, and pre-pregnancy body mass index (BMI) were all independent predictors of newborn birth weight. The regression model for predicting the newborn birth weight was: Y (birth weight) = 25.942×(EMT of 8–12 mm) + 85.107×(EMT > 12 mm) + 123.483×(hypertension during pregnancy) + 148.859×(premature rupture of membranes) + 182.342×(placental position) − 126.242×(newborn sex) + 23.837×(number of days of pregnancy) + 130.487×(delivery mode) − 55.023×(number of implanted embryos) − 6.215×FSH level − 1.124×E2 level + 22.218×BMI − 4468.101.

Conclusion(s)

EMT before embryo transfer in patients undergoing their first freeze–thaw embryo transfer cycle is related to the weight of newborn singletons. The newborn birth weight for patients with a thinner endometrium is lower. EMT should be increased before embryo transfer to improve neonatal outcomes after fertility treatment.

Background

The development of *in vitro* fertilization (IVF) technology has been beneficial for many infertile patients. With the increasing prevalence of IVF pregnancy and live births, increasing attention is being paid to

pregnancy and neonatal complications after IVF pregnancies. The safety of IVF offspring is an important area for investigation.

De Geyter et al. compared women who conceived with assisted reproductive technology (ART) with women who conceived naturally. They found that women who conceived after IVF carried a higher risk of premature delivery, and the mean birth weight was lower. If a pregnant woman delivered < 37 weeks after embryo transfer, the birth weight of the newborn was reduced considerably [1].

Other scholars have arrived at different conclusions. Ahlborg et al. investigated the changes in the parameters of fetal growth after IVF pregnancy. They found that the growth pattern of the fetus after IVF pregnancy was not significantly different from that observed in a natural pregnancy. Thus, IVF technology did not harm fetal growth [2]. A recent study of twin pregnancy after ART found that, compared with a natural pregnancy, twins conceived with ART did not show a higher risk of fetal-growth restriction, and there was no difference in the number of small-for-gestational-age (SGA) newborns. However, studies have reported that various ART types affect fetal-growth dynamics, which may influence the birth weight of the newborn [3, 4].

The mechanisms underlying the impact of IVF technology on mothers and children during pregnancy are not clear. Research has suggested that the reasons behind the poor outcomes of ART pregnancies involve factors related to IVF (e.g., superovulation, hormone supplements, freezing technology) and the infertility characteristics of the parents [4]. Therefore, exploration of the impact of IVF on pregnant women and newborns is important to optimize the IVF strategy and provide more information on pregnancy and neonatal complications during consultations with patients with various characteristics.

A successful IVF pregnancy is dependent upon implantation, which involves the interaction between the endometrium and embryo. This interaction is closely related to the quality of the embryo and receptivity of the endometrium. Research has indicated that endometrial thickness (EMT) might predict endometrial receptivity [5]. Chan et al. studied the effect of EMT on pregnancy outcomes on the day that human chorionic gonadotropin (hCG) was detected in patients undergoing a fresh-embryo transfer cycle. They showed that EMT < 8 mm on the day hCG was detected may adversely affect the overall chance of pregnancy [6]. Yoeli et al. found EMT to be directly proportional to the duration of follicular stimulation and inversely proportional to the age of the woman. Having increased EMT (> 14 mm) was not related to a decrease in the prevalence of implantation or pregnancy [7]. Rombauts et al. found that after embryo transfer, women with EMT > 12 mm were at a fourfold risk of placenta previa than that of women with EMT < 9 mm [8]. However, Liu et al. found that EMT > 12 mm before embryo transfer was a powerful protective factor against an ectopic pregnancy [9]. Therefore, the influence of EMT before embryo transfer on pregnancy outcomes and related obstetric complications is controversial.

Studies on the endometrium have focused mainly on the effect of EMT before transplantation on the prevalence of pregnancy and live birth. Zhang et al. found that EMT on the day of oocyte retrieval in fresh-embryo transfer cycles was associated with the prevalence of live births, whereas this association was weakened in freeze–thaw cycles. They proposed that EMT > 8.75 mm on the day of egg retrieval was the

cutoff value for predicting a live birth [10]. Fewer studies have focused on the effect of EMT on neonatal weight.

The main purpose of our study was to explore if EMT before embryo transfer during freeze–thaw cycles affected newborn birth weight, and which other factors may affect newborn birth weight during IVF. In this way, we wished to optimize each step in the IVF cycle and improve neonatal outcomes.

Methods

Ethical approval of the study protocol

The study protocol was approved by the Ethics Review Board of the Reproductive Center of Tianjin Central Obstetrics and Gynecology Hospital (Tianjin, China ZY2021001) and performed in accordance with the Helsinki Declaration. All women provided written informed consent for their data to be used in this study.

Exclusion criteria

The exclusion criteria were: (i) patient age at delivery >42 years; (ii) egg-donation cycle; (iii) uterine malformations; (iv) uterine submucosal fibroids and endometrial polyps; (v) chronic hypertension, mainly referring to basal blood pressure >140/90 mmHg before pregnancy or at <20 weeks of pregnancy; (vi) diabetes mellitus; (vii) newborns with congenital malformations.

Study design and population

This was a retrospective cohort study. We collected the medical records associated with singleton live births from Tianjin Central Obstetrics and Gynecology Hospital from June 2015 to February 2019 after IVF–frozen-embryo transfer (FET). Day-3 embryos were transplanted in all patients. If the patient underwent multiple freeze–thaw embryo-transfer cycles to obtain a single live birth, only the first transfer record was used.

Superovulation and IVF

Routine ovarian stimulation was undertaken according to underlying diseases and the clinical experience of the attending gynecologist. The program for ovarian stimulation involved four steps. The first step was the regimen for the long-acting gonadotropin (Gn)-releasing hormone agonist (GnRHa). Briefly, the short-acting GnRHa triptorelin (0.05 mg once a day or once every other day) was used from day-18 to day-23 of menstruation until follicle maturation. Oral contraceptives were used to control irregular menstrual cycles. The downregulation criteria were luteinizing hormone (LH) <5 mIU/mL, estradiol (E2) <50 pg/mL, no follicles >9–10 mm in both ovaries, and EMT ≤5 mm. The second step was the short-acting GnRHa regimen. Briefly, the short-acting GnRHa was used daily from day-2 or day-3 of menstruation until the day that hCG was detected. Simultaneously, Gn was used directly to promote ovulation from day-3 of menstruation. The third step was the antagonist regimen. Briefly, ultrasound and determination of hormone levels in blood on day-2 of standard menstruation or induced menstruation were not abnormal. Gn was

used directly to induce ovulation. When Gn was used for 4–6 days or the diameter of leading follicles was ≥12–14 mm (as observed using ultrasound), we considered addition of a GnRH antagonist (Cetrorelix (0.25 mg) or Ganirelix (0.25 mg)) as one injection (s.c.) per day until the day that hCG was detected. After oocyte retrieval, conventional IVF or fertilization by intracytoplasmic sperm injection was used according to semen quality. The cleavage-stage embryos cultured on day-3 were vitrified routinely. The freezing solution was a ready-to-use embryo thawing solution (VT602 Thawing Media; Kitazato, Tokyo, Japan).

Protocols for endometrium preparation and embryo thawing

At our center, two main endometrium-preparation programs are employed before transplantation. The first program is based on the natural cycle: the patient has regular menstruation and normal ovulation. First ultrasound monitoring occurs on day-11 to day-13 of the menstrual cycle, when the diameter of the follicle is ≥14 mm. hCG is used to trigger ovulation, and the thawed cleavage-stage embryos are transferred 48 h after ovulation. The second program is the hormone-replacement cycle: menstruation is sparse or irregular, and ovulation is obviously abnormal. Estrogen (3–10 mg per day) is used on day-2 to day-5 of the menstrual cycle. Ultrasound is used to check endometrial growth. Then, progesterone is administered to transform the endometrium and transfer the thawed cleavage-stage embryo. The thawing fluid is VT602 Thawing Media (Kitazato). Progesterone is used routinely to support the corpus luteum after transplantation.

EMT evaluation

EMT was measured using vaginal ultrasound. All ultrasound examinations were undertaken by the same experienced sonographer using identical ultrasound instrument. “EMT” was defined as the maximum distance from the junction of the endometrium and muscle layer on the sagittal plane of the uterus to the other side using vaginal ultrasound. “Natural-cycle EMT” denoted EMT measured on the day when hCG triggered ovulation. EMT in the hormone-replacement cycle was EMT on the day the progesterone level was transformed. Based on the literature and our clinical experience, we divided patients into three groups according to EMT before embryo transfer: <8, 8–12, and >12 mm.

Main outcomes

Outcomes related to newborns were birth weight, percentage of low birth weight (number of low-birth-weight children/total number of newborns delivered at term; “low birth weight” was defined as <2500 g at 37 weeks of pregnancy), and prevalence of macrosomia (number of newborns with macrosomia/total number of newborns delivered at term; “macrosomia” was defined as >4000 g at any gestational age).

Outcomes related to pregnant women were number of days of pregnancy, percentage of preterm births (number of cases delivered at 28–37 weeks of gestation/total number of cases), percentage of extremely premature deliveries (number of cases delivered at 28–32 weeks of gestation/total number of cases) as well as the prevalence of gestational diabetes mellitus (GDM), hypertension in pregnancy (including hypertension during pregnancy, preeclampsia, and eclampsia), placenta previa, and premature rupture of membranes.

Statistical analyses

Data analyses was undertaken using SPSS 25.0 (IBM, Armonk, NY, USA). Categorical variables are expressed as frequencies (percentages). Differences among the three groups were assessed using the chi-square test or Fisher's exact test. The P–P plot was used to observe the normality of continuous variables. Continuous variables with a normal distribution are expressed as the mean ± standard deviation. The three groups were compared using one-way analysis of variance. $P < 0.05$ was considered significant.

Univariate linear regression was used to identify the variables associated with newborn birth weight (dependent variable). The following independent variables were assessed: age; body mass index (BMI); infertility type; infertility factors; number of years of infertility; endometrium-preparation protocol; endocrine values; number of embryos transferred; number of implanted embryos; number of days of pregnancy; newborn sex; delivery mode; presence of GDM; presence of pregnancy-induced hypertension; whether the placental position was abnormal; premature rupture of membranes; EMT group. All variables deemed significant in the univariate analysis were used in the multivariate linear regression to establish a regression equation for predicting newborn birth weight. Dummy variables were set for all categorical variables. The results of regression analysis are presented as the regression coefficient of the variable and its P-value.

Results

Patient characteristics at baseline and characteristics of FET treatment

After application of the exclusion criteria and inclusion criteria, there were 3394 eligible cases. Of these, 506, 2661, and 227 patients had EMT <8, 8–12, and >12 mm, respectively. The process for case screening is shown in Figure 1.

The three groups had significant differences in age, BMI, infertility type, infertility factors, and testosterone level ($P < 0.05$). Differences among the three groups in terms of number of years of infertility, endometrium-preparation protocol, as well as levels of follicle-stimulating hormone (FSH), LH, prolactin, E2, and progesterone were not significant ($P > 0.05$). There were no significant differences in the number of transferred embryos or the number of implanted embryos among the three groups ($P > 0.05$) (Table 1).

Pregnancy complications and neonatal outcomes

We converted the gestational weeks into days to aid calculations and statistical analyses. The mean duration of pregnancy differed among the three groups, being longest in the 8–12 mm group. There was a significant difference in the prevalence of preterm births among the three groups ($P < 0.05$). Pregnant women with EMT <8 mm had the highest prevalence of preterm births, and those with EMT of 8–12 mm had the lowest prevalence of preterm births. There was no significant difference in the prevalence of very-preterm births among the three groups ($P > 0.05$). There was no significant difference in the sex distribution of newborns among the three groups ($P > 0.05$). The delivery modes were vaginal delivery and cesarean section. Patients with EMT <8 mm had the highest prevalence of cesarean section (73.3%), and

patients with EMT >12 mm had the lowest prevalence of cesarean section (63.4%). The difference in the prevalence of cesarean section was significant among the three groups ($P < 0.05$). Among the three groups, the mean birth weight of the fetus delivered by patients with EMT >12 mm was the highest, and the group with the lowest mean weight were patients with EMT <8 mm. The difference in newborn birth weight among the three groups was significant ($P < 0.05$). We further classified the birth weights of newborns and assessed the prevalence of low birth weight and macrosomia: the differences among the three groups were not significant ($P > 0.05$). With regard to pregnancy complications, we assessed the prevalence of GDM, hypertension during pregnancy, placenta previa, and premature rupture of membranes. The differences in the prevalence of GDM and premature rupture of membranes were significant ($P < 0.05$). There were no significant differences in the prevalence of hypertension or placenta previa among the three groups ($P > 0.05$) (Table 2).

Univariate linear regression analysis of birth weight

We discovered that birth weight may be related to EMT. Hence, we used birth weight as a dependent variable and univariate linear regression to screen for factors that may affect the birth weight of newborns. Table 3 shows the regression coefficient of each factor and P-value of the regression coefficient in the univariate linear regression. The pre-pregnancy BMI, FSH level, E2 level, number of embryos implanted, duration of pregnancy, newborn sex, delivery mode, pregnancy-induced hypertension, placental position, premature rupture of membranes, and EMT group were significant ($P < 0.05$).

Multivariate linear regression analysis of birth weight

Based on the results of the univariate linear regression of birth weight, all significant variables were included in the multivariate linear regression model. The Enter method was used to include all meaningful variables to establish a multivariate predictive model of newborn birth weight. After establishing dummy variables for the EMT groups, EMT <8 mm was used as the reference group. The mean birth weight of newborns in the 8–12 mm group increased non-significantly by 25.6 g compared with that in the <8 mm group ($P = 0.214$). In the >12 mm group, mean newborn birth weight increased significantly by 85.1 g compared with that in the <8 mm group ($P = 0.013$). Although the regression coefficient of the FSH level in the univariate regression was significant, it was not significant in the multivariate regression ($P = 0.075$). Other variables (hypertension in pregnancy, premature rupture of membranes, placental position, newborn sex, number of days of pregnancy, delivery mode, number of embryos implanted, E2 level, BMI before pregnancy) were significant in the multivariate analysis. The multivariate linear regression equation could be expressed as:

$$Y\ (\text{birth weight}) = 25.942 \times (\text{EMT of 8–12 mm}) + 85.107 \times (\text{EMT >12 mm}) + 123.483 \times (\text{hypertension during pregnancy}) + 148.859 \times (\text{premature rupture of membranes}) + 182.342 \times (\text{placental position}) - 126.242 \times (\text{newborn sex}) + 23.837 \times (\text{number of days of pregnancy}) + 130.487 \times (\text{delivery mode}) - 55.023 \times (\text{number of implanted embryos}) - 6.215 \times \text{FSH level} - 1.124 \times \text{E2 level} + 22.218 \times \text{BMI} - 4468.101.$$

The regression coefficients and P-values of the multivariate linear regression model are shown in Table 4.

The F value of the regression model was 183.355 ($P < 0.001$), indicating that establishment of this model was meaningful for better prediction of newborn birth weight. Adjusted R^2 was 0.404, indicating that the model explained 40.4% of the variance in newborn birth weight. The summary statistics of the model and the coding of categorical variables in the regression analysis are shown in Table 5.

Discussion

The main purpose of our study was to explore the influence of EMT before embryo transfer on the outcome of singleton live births resulting from freeze–thaw cycles. Mean birth weight of newborns was greater for mothers with EMT > 12 mm before embryo transfer compared with mothers with lower EMT. In addition, birth weight was affected by several confounding factors. Therefore, we established a multivariate linear regression model comprising all the clinical factors that may affect birth weight. After adjustment for confounding variables in the multivariate linear regression, the effect of EMT on newborn birth weight remained significant. At this point, we believed that a thicker endometrium before embryo transfer during freeze–thaw cycles was clinically significant with regard to increasing newborn birth weight and improving other newborn outcomes.

Few studies have focused on the influence of EMT before embryo transfer on pregnancy complications and neonatal outcomes after IVF–FET. Guo et al. studied EMT on the day of hCG detection in fresh-embryo transfer cycles. They found insufficient EMT to be a risk factor for neonatal SGA [11]. Thus, in accordance with our results, newborns with a thinner endometrium had a lower weight and an increased risk of SGA. After identification of a relationship between EMT and newborn birth weight, we assessed the relationship between EMT and prevalence of low birth weight or macrosomia among full-term newborns: there were no significant differences in the prevalence of low birth weight or macrosomia among the three groups. This finding may have been because our study involved FET because Ginod et al. found that fetal growth after FET was faster than that after fresh-embryo transfer cycles [3]. Hwang et al. also showed that, compared with fresh-embryo transfer cycles, FET led to a higher birth weight and lower risk of newborns with low birth weight (adjusted odds ratio: 0.72; 95% confidence interval: 0.59–0.88) [12]. Therefore, FET can improve newborn outcomes. As a result, in our study, we identified a relationship only between EMT and newborn birth weight but not with the prevalence of low birth weight or macrosomia.

A study by Moffat et al. on EMT as well as maternal and neonatal complications showed that increased EMT was not a predictor of birth weight in a normal pregnancy but, for those with pregnancy complications, EMT before embryo transfer was proportional to birth weight [13]. Therefore, birth weight is affected by multiple factors, and pregnancy complications, such as pregnancy-induced hypertension, pre-eclampsia, eclampsia, GDM, placenta previa, and premature rupture of fetal membranes, may all affect the growth and development of the fetus in the uterus, which is ultimately reflected in the difference in birth weight. Therefore, in the present study, pregnancy complications were also investigated. GDM prevalence was highest in the > 12 mm group and was significant. Saito and colleagues showed that hormone-replacement cycles can reduce GDM risk [14]. In our study, the number of hormone-replacement cycles was lower in patients with EMT > 12 mm than that in the other two groups. Thus, the > 12 mm group had a

higher proportion of GDM. He et al. explored the relationship between EMT and perinatal outcomes. They found that preimplantation EMT < 8 mm increased the risk of premature rupture of membranes significantly [15]: that finding is consistent with our results. In the present study, the prevalence of premature rupture of membranes was higher in the EMT > 12 mm group than that of patients with EMT 8–12 mm. This difference may be related to the higher prevalence of hypertension during pregnancy in this group. Oron et al. set an EMT cutoff of 7.5 mm, and found that the prevalence of obstetric complications in patients with EMT < 7.5 mm was increased significantly, including premature delivery, hypertension in pregnancy, placenta previa, and premature rupture of membranes [16]. In the present study, the EMT was divided into more detailed (i.e., three) groups, and the difference in pregnancy duration among the three groups was significant. Patients with a thin endometrium were more likely to have a preterm birth, a finding that is consistent with previous studies.

Newborn birth weight is affected by several confounding factors. In the present study, univariate regression was used to identify the factors that may affect birth weight. All significant variables were used in the multivariate linear regression to establish the following regression equation for predicting birth weight:

Y (birth weight) = 25.942×(EMT of 8–12 mm) + 85.107×(EMT > 12 mm) + 123.483×(hypertension during pregnancy) + 148.859×(premature rupture of membranes) + 182.342×(placental position) − 126.242×(newborn sex) + 23.837×(number of days of pregnancy) + 130.487×(delivery mode) − 55.023×(number of implanted embryos) − 6.215×FSH level − 1.124×E2 level + 22.218×BMI − 4468.101.

After adjustment for confounding factors, the EMT grouping remained meaningful for predicting birth weight, with increased EMT increasing the birth weight. Compared with patients with EMT < 8 mm, patients with EMT > 12 mm had an increase in the mean birth weight of 85.107 g. The regression coefficient was significant. This observation is consistent with the results of a similar study by Zhang et al. on freeze–thaw cycles [17]: they showed that EMT < 8 mm was associated with a lower mean birth weight.

We also found that the E2 level was an independent predictor of birth weight, with a regression coefficient of − 1.124. That is, for each unit change in the E2 level, the predicted weight of the newborn would decrease by 1.124 g. A study by Pereira et al. on fresh-embryo transfer cycles showed that the high estrogen level produced during superovulation can affect the environment of embryo implantation, thereby leading to platelet dysfunction and low birth weight [18]. In addition, experiments conducted by Weinerman et al. showed that the superovulation environment was not conducive for the growth and development of fetal mice [19]. Our study focused on freeze–thaw cycles. The high-estrogen effect of superovulation was absent, but a high E2 level regulated birth weight negatively. This finding is consistent with the low birth weight caused by a high-estrogen environment during fresh-embryo transfer cycles. Whether there is a definite connection requires further exploration in studies with large sample sizes. Spada et al. showed that the BMI of pregnant women in the first trimester was a strong predictor of newborn birth weight [20]. In our study, for each unit increase in BMI of a pregnant woman, the newborn birth weight increased by 22.218 g. This finding is consistent with data from other studies [20, 21].

The mean birth weight of male babies is higher than that of female babies, and IVF technology does not seem to change the sex-dependent differences in birth weight [21]. Our results also reflect those findings. According to our regression equation, the mean birth weight of female babies was reduced by 126.242 g compared with that of male babies. Gestational age is a confounding factor that affects birth weight. In our study, the newborn birth weight increased by 23.837 g for each additional day of pregnancy. Moreover, pregnancy complications and abnormal function of fetal appendages may affect the blood circulation between the mother and child during pregnancy, thereby leading to adverse neonatal outcomes [22]. The regression analysis in our study revealed that hypertension during pregnancy, premature rupture of membranes, and placenta previa were independent risk factors for decreased newborn birth weight. We also found that the delivery mode affected newborn birth weight. The birth weight of newborns delivered by cesarean section was relatively low, which may have been because that women who deliver by cesarean section have common pregnancy complications, and emergency pregnancy termination due to other reasons in the circumstance that the fetus is not yet mature. In addition, the number of implanted embryos was a predictor of newborn birth weight. The greater the number of implanted embryos, the greater was the probability of twins and an increased risk of pregnancy complications. Moreover, the number of embryos implanted can also affect early development of the newborn [23].

The mechanism underlying how EMT before embryo transfer affects newborn birth weight is thought to mainly involve changes in the intrauterine environment during embryo implantation and establishment of normal placental–fetal circulation. In the early stages of pregnancy, the hypoxic environment of the endometrium is a prerequisite for normal development of an embryo [24]. A thin endometrium increases the concentration of oxygen from the mother, which produces reactive oxygen species; this action affects the intrauterine environment during early embryonic development, resulting in impaired fetal growth [25]. Kelley et al. cultured mouse embryos under different oxygen concentrations, and found that an oxygen concentration of 20% compared with an oxygen concentration of 5% reduced the weight of fetal mice [26]. That observation suggests that excessive reactive oxygen species interfere with early embryonic implantation and development, and reduce newborn birth weight. The most important function of the placenta is the exchange of nutrients and oxygen between the mother and fetus. In the first trimester, establishment of a healthy placenta requires adequate remodeling of spiral arteries. If remodeling of the spiral arteries is impaired, placental function can be impaired, causing pregnancy complications and reducing the blood supply to the fetus in the third trimester, which can lead to fetal hypoxia, malnutrition, and low birth weight [24]. In patients with a thin endometrium, resistance to blood flow of the uterine basilar artery is increased, and blood vessels are often underdeveloped, which leads to poor remodeling of the spiral arteries and affects the placental blood supply [27].

Our study had four main strengths. First, we used strict inclusion criteria and exclusion criteria. Second, we excluded patients with underlying diseases (e.g., hypertension, DM) that may affect fetal development. Third, the treatment regimens were conducted in accordance with uniform standards to ensure treatment consistency. Fourth, EMT measurement was undertaken by the same experienced sonographer, which reduced measurement variability.

The main limitation of our study was that it was from a single center and retrospective. To obtain more precise evidence on the relationship between EMT and birth weight, a large-scale prospective study with multicenter collaboration may be required. Another limitation was that we did not explore the mechanism by which EMT affects birth weight.

Conclusion

EMT before embryo transfer has an impact upon newborn birth weight. Newborns born to mothers with a thinner endometrium weigh less. Yu et al. showed that newborn birth weight was associated with adverse newborn outcomes [28]. Therefore, gynecologists should try to increase the EMT of patients before transplantation to improve neonatal outcomes.

Declarations

Acknowledgements

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Availability of data and materials

All authors had full access to the data and materials. The data supporting the conclusions of this article is included within the article.

Authors' contributions

Yinfeng Zhang performed the experiments, collected the results and wrote the manuscript. Haining Luo contributed to data analysis and manuscript revision. Ying Han contributed to revise the manuscript. Bolun Zhang conceived the study and contributed to editing the manuscript. Junfang Ma collected the results. Pengpeng Qu and Yunshan Zhang critically revised the drafts of the manuscript and approved the final version of the manuscript.

Ethics approval and consent to participate

The study protocol was approved by the Ethics Review Board of the Reproductive Center of Tianjin Central Obstetrics and Gynecology Hospital (Tianjin, China ZY2021001) and performed in accordance with the

Helsinki Declaration. All women provided written informed consent for their data to be used in this study. All methods were performed in accordance with the literature and our clinical experience.

Consent for publication

Not applicable.

Competing of interests

The authors declare that they have no conflict of interest.

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Tables

Table 1. Characteristics of patients at baseline and characteristics of frozen embryo transfer treatment

Characteristic	Endometrial thickness (mm)			Statistic	P
	<8	8–12	>12		
Woman's age (years)	31.9±3.963	31.30±3.990	31.54±3.847	4.942	0.007[a]
Body mass index	22.643±3.0349	22.733±3.2749	23.417±3.3216	5.078	0.006[a]
Infertility type					
Primary	42.5% (215/506)	58.2% (1549/2661)	68.3% (155/227)	56.411	0[b]
Secondary	57.5% (291/506)	41.8% (1112/2661)	31.7% (72/227)		
Infertility factor					
Pelvis and fallopian tube	43.0% (172/506)	33.5% (891/2661)	39.6% (90/227)	23.653	0.003[b]
Ovary	9.5% (48/506)	8.4% (224/2661)	4.4% (10/227)		
Male	10.7% (54/506)	17.0% (453/2661)	17.6% (40/227)		
Multiple factors	41.7% (211/506)	36.9% (982/2661)	32.6% (74/227)		
Unexplained	4.2% (21/506)	4.2% (111/2661)	5.7% (13/227)		
Number of years of infertility	4.217±2.7961	4.471±2.7646	4.480±2.8647	1.811	0.164[a]
Endometrium-preparation protocol					
Natural cycle	66.6% (337/506)	70.5% (1876/2661)	162/227 (71.4%)	3.3	0.192[b]
Hormone-replacement cycle	33.4% (169/506)	29.5% (785/2661)	65/227 (28.6%)		
Follicle-stimulating hormone	6.37758±2.118024	6.33828±2.167308	6.07969±1.988762	1.647	0.193[a]
Luteinizing hormone	4.89±3.39	5.19±20.21	4.39±2.52	0.232	0.793[a]

Prolactin	14.77±8.78	15.42±12.81	14.31±7.41	1.282	0.277[a]
Estradiol	45.44±23.51	45.44±23.51	44.11±21.44	0.262	0.77[a]
Progesterone	2.30±1.39	2.56±6.02	2.22±1.08	0.765	0.465[a]
Testosterone	43.50±21.77	41.35±19.46	39.87±15.71	3.188	0.041[a]
Number of embryos transferred	1.92±0.474	1.89±0.510	1.82±0.459	2.87	0.057[a]
Number of implanted embryos	1.17±0.395	1.16±0.382	1.15±0.386	0.207	0.813[a]

[a]One-way ANOVA. Values are mean ± SD. [b]Pearson chi-square test. Values are frequency (percentage).

Table 2. Pregnancy complications and neonatal outcomes

Outcome	Endometrial thickness (mm)			Statistic	P
	<8	8–12	>12		
Number of days of pregnancy	270.04±15.246	272.7±12.875	272.31±14.222	8.448	0[a]
Prevalence of preterm birth	14.4% (73/506)	8.9% (236/2661)	8.8% (20/227)	15.22	0[b]
Prevalence of very-preterm birth	2.4% (12/506)	1.2% (32/2661)	1.3% (3/227)	4.261	0.119[b]
Newborn sex					
Male	50.2% (254/506)	49.8% (1324/2661)	54.2% (123/227)	1.643	0.44[b]
Female	49.8% (252/506)	50.2% (1337/2661)	45.8% (104/227)		
Cesarean section	73.3% (371/506)	68.8% (1832/2661)	63.4% (144/227)	7.714	0.021[b]
Newborn birth weight	3254.10±609.96	3342.34±529.198	3407.11±532.618	7.871	0[a]
Birth-weight classification					
Prevalence of low birth weight	2.1% (9/432)	1.5% (36/2422)	0% (0/205)	4.836	0.304[b]
Prevalence of normal birth weight	88.7% (838/432)	90.3% (2186/2422)	90.7% (186/205)		
Prevalence of macrosomia	9.3% (40/432)	8.3% (200/2422)	9.3% (19/205)		
Gestational diabetes mellitus	6.1% (31/506)	8.2% (218/2661)	12.8% (29/227)	9.212	0.01[b]
Hypertension in pregnancy	5.3% (27/506)	4.5% (120/2661)	7.0% (16/227)	3.319	0.19[b]
Placenta previa	0.6% (3/506)	0.8% (21/2661)	0% (0/227)	1.253	0.586[c]
Premature rupture of membranes	3.6% (18/506)	1.9% (51/2661)	3.1% (7/227)	6.021	0.049[b]

[a]One-way ANOVA. Values are mean ± SD. [b]Pearson chi-square test. Values are frequency (percentage). [c]Fisher's exact test. Values are frequency (percentage).

Table 3. Univariate linear regression for newborn birth weight		
Factor	β	P
Woman's age	−1.471	0.53
Body mass index	15.185	0
Infertility type	−32.85	0.081
Ovary factors (dummy variable	−43.438	0.229
Male factors (dummy variable	0.436	0.988
Multiple factors (dummy variable	−8.791	0.691
Unexplained infertility (dummy variable	−2.59	0.957
Number of years of infertility	3.76	0.263
Endometrium-preparation protocol	31.946	0.116
Follicle-stimulating hormone	−9.914	0.024
Luteinizing hormone	0.855	0.105
Prolactin	0.154	0.849
Estradiol	−0.974	0.013
Progesterone	1.152	0.521
Testosterone	−0.004	0.993
Number of embryos transferred	−27.882	0.133
Number of implanted embryos	−98.77	0
Number of days of pregnancy	23.976	0
Newborn sex	−97.784	0
Delivery mode	128.83	0
Gestational diabetes mellitus	6.652	0.845
Hypertension in pregnancy	325.019	0
Placental position	538.572	0
Premature rupture of membranes	855.715	0
EMT 8–12 mm	88.238	0.001
EMT >12 mm	153.011	0
Dummy variables were used for the infertility factors, with pelvic tubal factors as the reference group.		

Dummy variables were used for the EMT groups, with EMT <8 mm as the reference group. EMT: endometrial thickness.

Table 4. Multivariate linear regression model for newborn birth weight

Model	β	t	P
(Constant)	−4468.101	−17.741	0.000
EMT 8–12 mm	25.942	1.243	0.214
EMT >12 mm	85.107	2.494	0.013
Hypertension in pregnancy	123.483	3.523	0.000
Premature rupture of membranes	148.859	2.835	0.005
Placental position	182.342	2.018	0.044
Newborn sex	−126.242	−8.544	0.000
Number of days of pregnancy	23.837	39.586	0.000
Delivery mode	130.487	8.049	0.000
Number of implanted embryos	−55.023	−2.722	0.007
Follicle-stimulating hormone	−6.215	−1.779	0.075
Estradiol	−1.124	−3.659	0.000
Body mass index	22.218	9.299	0.000

Dummy variables were used for infertility factors, with pelvic tubal factors as the reference group. Dummy variables were used for EMT groups, with EMT <8 mm as the reference group. EMT: endometrial thickness.

Table 5. Model summary

R	R^2	Adjusted R^2	Standard error	F	P
0.637	0.406	0.404	418.018	183.355	<0.001

Independent variables: (constant), EMT group (<8 mm = 1, 8–12 mm = 2, and 12 mm = 3), E2, FSH, Number of implanted embryos, Placenta previa = 1, Normal placental position = 2, Male = 1, Female = 2, Premature rupture of membranes = 1, Non-premature rupture of membranes = 2, Hypertension in pregnancy = 1, Normal blood pressure = 2, Vaginal delivery = 1, Cesarean section = 2, Number of days of pregnancy = X.

Figures

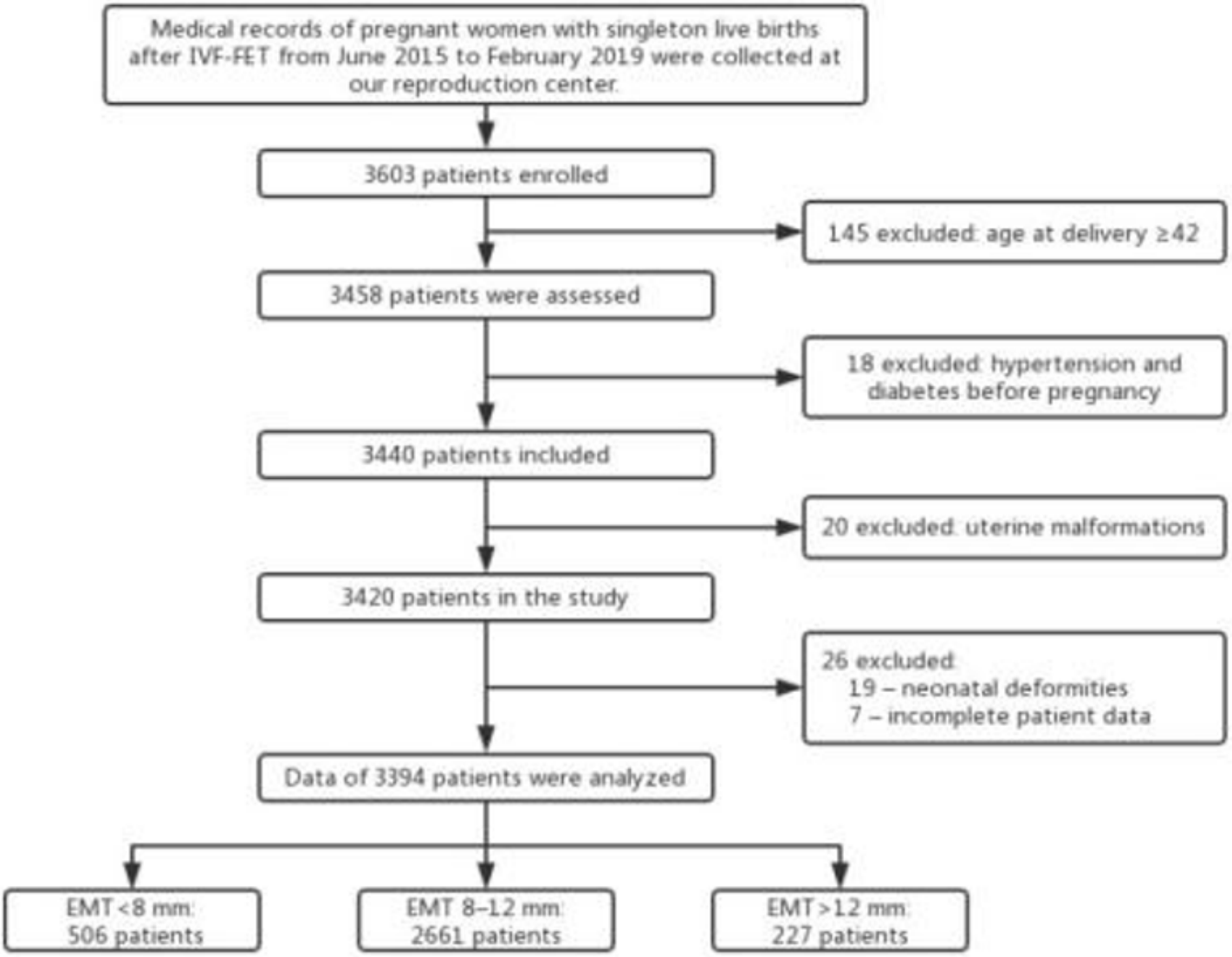

Figure 1

Study flowchart.