Thin Endometrium and Cleavage Embryo Transfer Are Associated With Ectopic Pregnancy After *in Vitro* Fertilization-embryo Transfer Cycles: a Matched Case–control Study Using Propensity Score Matching

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Research

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Abstract

Objective: To evaluate the relationship between the endometrial features (endometrial thickness(EMT), pattern and endometrium growth amplitude and rate) and the embryo stage transferred and ectopic pregnancy after IVF-ET based on the data of 628 matched cases.

Methods: This was a 1:1 matched case-control study that enrolled 314 EP patients and 314 matched IUP patients from the ART center of Xiangya Hospital of Central South University from January 2014 to April 2020. Univariate analysis and multiple-stepwise logistic regression analysis was used to analyze the risk factors of EP, and a receiver-operating characteristic (ROC) curve was generated to predict EP.

Results: 1. The EP group had a higher cleavage stage embryo transfer rate(94.57% vs 86.22%), a thinner endometrium on transformation day(the day when progesterone was added in the frozen embryo cycle or the trigger day in the fresh embryo cycle) (9.40(2.60) mm vs 9.80(2.60)mm) compared with IUP group. In fresh embryo cycles, the EP group had a higher endometrium pattern C proportion on transformation day, a smaller endometrium increment, and a slower endometrial growth rate compared with the IUP group. 2.The ROC curves were used to analyze the cut-off values of the EMT on transformation day, the endometrial growth amplitude and rate in fresh cycles, the results were 9.35mm, 4.90mm and 0.491 mm/d, respectively. The incidence of EP was significantly different between groups according to cut-off values. 3.The transferred embryo stage and EMT on transformation day were independent factors affecting outcome in the general population. The area under the curve(AUC) of the EMT and the stage of embryos transferred for EP prediction was 0.604, sensitivity was 0.702, and specificity was 0.465. The EMT on trigger day was an independent factor affecting outcome in the fresh cycles. The AUC of the EMT for EP prediction in fresh cycles was 0.605, sensitivity was 0.805, and specificity was 0.420.

Conclusions: 1. Transferring cleavage stage embryo, and thin EMT on the transformation day were risk factors for EP. 2. Thin EMT and pattern C on transformation day may be related to abnormal endometrial receptivity and endometrial peristaltic waves. 3.The combined indicator of EMT and embryonic development stage could not well predict the occurrence of EP after ET.

Background

Ectopic pregnancy (EP) is a kind of pregnancy in which the embryo implants outside the uterine cavity [1]. It is reported that EP deaths account for 5% and 10% of all maternal deaths in developed and developing countries, respectively[2].

The risk factors of EP include fallopian tubes factors[3–8], older maternal age[9, 10], infertility history [4], endometriosis[4, 11, 12] and assisted reproductive technology treatment[3]. In theory, ART treatment can reduce the risk of ectopic pregnancy, because neither fertilization nor embryo transfer involves the fallopian tubes.

In fact, the first pregnancy achieved by IVF was ectopic[13], 2 years before the birth of the worldwide first IVF-baby reported [14]. The ectopic pregnancy rate is about 1–2% in spontaneous pregnancy and as high as 1.0–11% in ART[15, 16]. ART plays an important role in the occurrence of ectopic pregnancy[17]. However, data on risk factors for EP after IVF were inconsistent. Risk factors associated with ectopic pregnancy after ART include tubal infertility[5,18–22], multiple embryos transferred[18], and fresh embryo transfer compared with thawed embryo transfer cycles in stimulated cycles[23–28]. It is controversial whether the development stage of the embryos transferred affects the incidence of EP[29–32].

Few studies were focus on the correlation and predictive ability of combined endometrial and embryotic features to ectopic pregnancy after ART treatments, and there is no consensus on the cut-off value of EMT associated with ectopic pregnancy.

Thus, it is important to identify risk factors for EP, and best to find out the relevant combined endometrial and embryonal indicators that can predict EP related to ART, so as to guide embryo transfer to a certain extent. Considering the relatively low incidence rate of EP, and many factors are associated with EP, we designed a matched case-control study using propensity score matching to assess the relationship between endometrial features (endometrial pattern, thickness and endometrium growth amplitude and daily rate) and stage of embryo transferred and EP based on 628 *in vitro* fertilization-embryo transfer cycles.

Methods

Ethical approval

The present study was approved by the Ethics Committee of Xiangya Hospital, Central South University. For patients who receive ART (IVF/ICSI) treatment in our center, their medical records are allowed to be used for research. All patients received informed consent before ART treatment. All patients were registered in data management system, which is used to store all medical information about patients trying to conceive through ART.

Definition of clinical outcomes

When one or more gestational sacs that were confirmed in the uterus by ultrasonic examination, intrauterine pregnancy was defined. The definition of ectopic pregnancy was the observation of one or more gestational sacs outside the uterine cavity under ultrasound. Heterotopic pregnancy was defined as the coexistence of pregnancy inside and outside the uterine cavity. According to the ART follow-up flow path in our center, all patients were asked to come back for a blood β-human chorionic gonadotropin (β-hCG) test 12 days after ET. β-hCG levels below 5 IU/L were considered negative, those between 5 and 15 IU/L were considered indeterminate, and those above 15 IU/L were considered positive. Patients with indeterminate β-hCG levels were considered positive if their β-hCG increased after 48 h. Those patients with increasing β-hCG were followed sonographically 28 days after ET for the first time, especially for

those with a history of EP or previous tubectomy to rule out EP earlier. In addition, 35 days after ET, they underwent a second ultrasound scan to confirm the presence of a gestational sac with fetal heart in the uterus (especially transvaginal). Only a small number of the diagnoses of ectopic/heterotopic pregnancy were made in other hospitals; for those cases, we confirmed that the diagnostic criteria were the same as those in our hospital. As the main purpose of our study was to investigate endometrial and embryo factors associated with the occurrence of EP, heterotopic pregnancy was excluded in our analysis.

Risk factor selection

We used the female age[9,10,33], body mass index (BMI)[34], the duration of infertility, gravidity[35], previous history of ectopic pregnancy[36,37], ovarian stimulation/endometrial preparation protocol[38], number of embryos transferred[18,35], the main causes of infertility[18], and frozen-thawed/ fresh embryos transferred[39,40] as matching factors because previous study have determined that these factors are associated with the occurrence of EP, and our goal in the present study was to analyze the relationship between endometrial features and embryonic development stage and EP. Our study reduced bias of population selection by adjustment of matching the time for infertility treatment. The sample sizes were 314 and 314 in the EP and IUP groups with a ratio of 1:1, based on the propensity score with a standard caliper width of 0.2.

Study design and patients

This was a 1:1 case-control study of all patients who received IVF treatment between January 2014 and April 2020 at the Center for Assisted Reproductive Technology, Xiangya Hospital, Central South University, China. Data were extracted from clinical records. The selection process for IVF cycles is illustrated in Fig. 1. From the initial 21704 patients, we selected 11699 patients with a positive hCG value (12 days after embryo transfer). Patients were eligible if they met the following criteria: (1) good physical and mental health (not disabled and without psychological disorders and mental illness); (2) IVF/intracytoplasmic sperm injection (ICSI) cycle; and (3) positive hCG test 12 days after an embryo transfer. The exclusion criteria were as follows: (1) biochemical pregnancy; (2) cornual pregnancy; (3) cesarean scar pregnancy; (4) cervical pregnancy and (5) heterotopic pregnancy. We further selected patients resulted in a clinical pregnancy of either EP or IUP. Endometrial thickness, growth and pattern were assessed at two time points (the day of gonadotrophin stimulation and HCG administration in fresh embryo cycle, the first day use estrogen and the day of progesterone addition in the hormone treatment frozen embryo cycle, or the 10th day of menstruation and the day of ovulation of frozen embryos in the ovulation cycle), the increment and growth rate of endometrium within cycle were calculated simultaneously. The EMT was obtained in a sagittal midline plane on transvaginal sonography, with the maximal anteroposterior thickness used, in the method described by Bredella et al[41]. The echoes of the endometrium was observed, the endometrial patterns were divided into three types based on the Gonen system[42]: type A, trilaminar pattern (endometrial three-layer pattern), consisting of hyperechoic outer and middle layers, hypoechoic inner layers, and evident echo at the intrauterine midline; type B, relatively homogeneous hyperechoic endometrium, with unclear endometrial layers, obscure intrauterine midline echo, but clear

interface between endometrial and muscular layers; and type C, homogeneous hyperechoic endometrium without intrauterine midline echo. The developmental stage of the embryos transferred were recorded at the same time.

Statistics

All statistical analyses were carried out using R 3.6.2 statistical software. For the quantitative data, the mean ± SD and median (quartile interval) are used to describe the normal distributed data and non-normal distributed data respectively. For categorical data, the number of cases (percentage) is used to describe it.

In the comparison of univariate differences, two independent samples t-test was used for those who is normally distributed, Mann-Whitney U test for those who was not in the normal distribution, and Pearson Chi-square test was used for the categorical variables. Fisher's exact probability method was used when $n < 40$ or $T < 1$ in the Chi-square test table(n is the total number of samples, T is the theoretical frequency). Stepwise multiple logistic regression analysis was used to analyze the risk factors for EP, and a receiver-operating characteristic(ROC) curve was generated for the predictors of EP. The validity of the model was assessed by AUC. In this research, $P < 0.05$ was considered statistically significant difference.

Results

A total of 314 ectopic pregnancies and 314 matched intrauterine pregnancies were included in this study. The baseline characteristics of the two groups are shown in Table 1. There were no significant differences in the female ages, body mass index (BMI), infertility duration, number of embryos transferred, times of previous pregnancies and ectopic pregnancies, fresh/frozen embryo, protocol and main cause of infertility between the two groups. 7po

Table 1 The baseline characteristics of the patients in the two groups

	IUP (n=314)	EP (n=314)	*P*
Female age	30.00(6.00)	30.00(6.00)	0.309
BMI	21.50(4.26)	21.09(3.74)	0.178
Infertility duration	4.00(4.00)	4.00(4.00)	0.617
Number of embryos transferred	2.00(0.00)	2.00(0.00)	0.707
Gravidity			0.694
0	141(44.90)	133(42.36)	
1	59(18.79)	70(22.29)	
2	68(21.66)	63(20.06)	
3	23(7.32)	26(8.28)	
4	11(3.50)	15(4.78)	
5	5(1.59)	4(1.27)	
6	7(2.23)	3(0.96)	
Times of previous ectopic pregnancies			0.977
0	243(77.39)	239(76.11)	
1	47(14.97)	49(15.61)	
2	21(6.69)	23(7.32)	
3	3(0.96)	3(0.96)	
Cycle			0.805
Frozen-thawed embryo transfer	172 (54.78)	165 (52.55)	
Fresh embryo transfer	142 (45.22)	149 (47.45)	
Protocol			0.539
Hormone treatment frozen embryo cycle	113 (35.99)	106 (33.76)	
Frozen embryo cycle after ovulation	60 (19.11)	57 (18.15)	
Antagonist	10 (3.18)	18 (5.73)	
Agonist	93 (29.62)	89 (28.34)	
Others	38 (12.10)	44 (14.01)	
Main course of infertility			0.060
Sequelae stage of pelvic inflammatory disease	301 (95.86)	307 (97.77)	

Endometriosis	0 (0.00)	2 (0.64)
Others	13 (4.14)	5 (1.59)

EP ectopic pregnancy, *IUP* intrauterine pregnancy, *BMI* body mass index

Compared with the IUP group, EP women had a significantly higher cleavage stage embryo transfer rate (P< 0.001), significantly thinner EMT on transformation day (P<0.001)(Table 2).

For fresh cycles, EP women had a significant higher ratio of endometrial pattern C on transformation day (10.96% v 4.29%, P=0.047), smaller endometrial growth amplitude (P=0.009), and slower endometrial daily growth rate (P=0.022) compared with IUP women. There were no difference in the above indicators for women who transferred frozen embryos(Table 2).

EMT and pattern at the first time point(the day of gonadotrophin stimulation in fresh embryo cycle, the first day using estrogen in the hormone treatment frozen embryo cycle, or the 10th day of menstruation of frozen embryos in the ovulation cycle) in the two groups were similar either by integral analysis or analyzed in subgroups according to the fresh/frozen embryo cycle (Table 2).

Table 2 Comparison of endometrial and embryotic parameters in EP and IUP women

	EP (n=314)	IUP (n=314)	*P*
The stage of embryos transferred			<0.001*
cleavage stage embryo	269(86.22)	296(94.57)	
blastocyst	43(13.78)	17(5.43)	
EMT on the first point	5.30(2.70)	5.30(2.85)	0.913
EMT on the first point (Fresh embryo cycles)	4.70(1.98)	4.90(2.23)	0.468
EMT on the first point (Hormone treatment frozen embryo cycle)	5.40(3.33)	5.30(3.20)	0.600
EMT on the first point (Frozen embryo cycle after ovulation)	6.60(2.40)	6.20(2.70)	0.136
Endometrial pattern on the first point			0.990
A	18(6.45)	18(6.64)	
B	93(33.33)	89(32.84)	
C	168(60.22)	164(60.52)	
Endometrial pattern on the first point (Fresh embryo cycles)			0.472
A	0(0.00)	2(1.71)	
B	26(22.03)	23(19.66)	
C	92(77.97)	92(78.63)	
Endometrial pattern on the first point (Hormone treatment frozen embryo cycle)			0.533
A	10(10.10)	7(7.45)	
B	25(25.25)	30(31.91)	
C	64(64.65)	57(60.64)	
Endometrial pattern on the first point (Frozen embryo cycle after ovulation)			0.663
A	8(12.90)	9(15.00)	
B	42(67.74)	36(60.00)	
C	12(19.35)	15(25.00)	
EMT on transformation day	9.80(2.60)	9.40(2.60)	0.004*
EMT on transformation day (Fresh embryo cycles)	10.90(2.60)	9.80(2.90)	0.002*
EMT on transformation day (Hormone treatment frozen embryo cycle)	9.30(1.80)	9.05(1.90)	0.468

EMT on transformation day (Frozen embryo cycle after ovulation)	9.70(2.15)	9.30(2.10)	0.384
Endometrial pattern on transformation day			0.311
A	123(39.30)	109(35.05)	
B	172(54.95)	176(56.59)	
C	18(5.75)	26(8.36)	
Endometrial pattern on transformation day (Fresh embryo cycles)			0.047*
A	62(44.29)	50(34.25)	
B	72(51.43)	80(54.79)	
C	6(4.29)	16(10.96)	
Endometrial pattern on transformation day (Hormone treatment frozen embryo cycle)			0.884
A	31(28.18)	30(28.85)	
B	72(65.45)	69(66.35)	
C	7(6.36)	5(4.81)	
Endometrial pattern on transformation day (Frozen embryo cycle after ovulation)			0.999
A	30(47.62)	29(47.54)	
B	28(44.44)	27(44.26)	
C	5(7.94)	5(8.20)	
Endometrial growth amplitude	4.30(3.70)	3.90(3.23)	0.082
Endometrial growth amplitude (Fresh embryo cycles)	6.05(2.70)	4.90(4.05)	0.009*
Endometrial growth amplitude (Hormone treatment frozen embryo cycle)	3.90(2.92)	3.35(3.22)	0.481
Endometrial growth amplitude (Frozen embryo cycle after ovulation)	2.91±1.97	3.15±1.82	0.480
Endometrial daily growth rate	0.47(0.38)	0.43(0.40)	0.173
Endometrial daily growth rate (Fresh embryo cycles)	0.56(0.32)	0.47(0.41)	0.022*
Endometrial daily growth rate (Hormone treatment frozen embryo cycle)	0.36(0.25)	0.32(0.30)	0.474
Endometrial daily growth rate (Frozen embryo cycle after ovulation)	0.50(0.46)	0.57(0.40)	0.532

*** *P*<0.05.**

For the quantitative data, the mean ± SD and median (quartile interval) are used to describe the normal distributed data and non-normal distributed data respectively. For categorical data, the number of cases (percentage) is used to describe it.

Using the ROC curve to generate cut-off values for the significant indicators above, the results for EMT on trigger day, endometrial growth amplitude, and daily growth rate in fresh cycles were 9.35mm, 4.90mm and 0.491mm/d, respectively(Fig. 2,3,4).

Stepwise logistic regression analysis was performed to further investigate the risk factors for EP. The regression model selected the variables which were significant in univariate analysis. Finally, cleavage embryo transfer and a thin EMT on transformation day were independent risk factors for developing EP following ART[Table 3]. Stepwise logistic regression analysis was also performed in subgroups. For fresh cycles, a thin EMT on trigger day was an independent risk factor for developing EP[Table 4].

Table 3 Stepwise logistic regression analysis for the general population

	OR(95CI%)	*P*
The stage of embryos transferred	1.00	0.000
cleavage stage embryo		
blastocyst	0.334(0.180,0.593)	
EMT on the transformation day	0.868(0.799,0.942)	0.001

EP is more likely to occur in patients who transferred cleavage embryos or had a thinner EMT on the transformation day.

Table 4 Stepwise logistic regression analysis for fresh cycles

	OR(95CI%)	*P*
EMT on transformation day	0.842(0.742,0.95)	0.0063

In fresh cycles, EP is more likely to occur in patients had a thinner EMT on the transformation day.

As showed in Fig. 5, a prediction model was generated based on EMT on transformation day and the embryo stage for ectopic pregnancy, ROC curve was used to assess the ability of the model. The area under the curve which calculated as sensitivity/(1-specificity), is a measure that can show ‘superior’ (AUC close to 1) or ‘inferior’ (AUC close to 0.5) the model is. In the present study, the results from ROC curve analysis suggest these endometrial and embryo parameters have poor predictive value for ectopic pregnancy(AUC 0.604, 95% CI 0.64–0.72); The subgroup analysis of fresh embryo cycles based on the endometrium thickness on trigger day showed similar result s (AUC 0.605, 95% CI 0.64–0.72)(Fig. 6).

Discussion

With the hope to provide suggestions for EP prevention, this matched case-control study was designed to identify risk factors related to EP in women undergoing ART working backwards from the outcome to exposure. To our knowledge, this is the first study to analyze only endometrial and embryonic developmental factors associated with ectopic pregnancy after precise matching of other risk factors.

In this study, transferring cleavage stage embryo was found to be a risk factor of EP. This is consistent with some previous studies, which have shown that blastocyst transfer may reduce EP in IVF/intracytoplasmic sperm injection (ICSI) cycles[39,43,44], and day-3 embryo transfers was an ectopic pregnancy risk factor in IVF[45]. In the case of cleavage-stage ETs, the embryos are not temporally prepared for immediate implantation regardless of whether the endometrium is in a receptive state and can migrate within the upper female reproductive tract before implantation. Selecting blastocysts has the advantage of physiological synchronization with the uterine endometrium, therefore, it may lead to better pregnancy outcomes[46]. Meanwhile, it has been reported that uterine contractile decreased on day 5, which may be another reason for the decreased EP rate after blastocyst transfer[30]. But in contrast, many studies [30,47-50] considered the stage of embryos did not affect the EP rate. In addition, other researches have indicated that blastocyst transfer may increase the risk of EP compared with the cleavage stage embryo transfer on account of the potentially higher implantation rate of each blastocyst [31,51]. The reason why they did not come to the same conclusion may be related to different research sample sizes, patients' age, experimental designs and analysis methods among studies, even blastocyst culture techniques in reproductive centers. In our center, almost all embryos transferred in the fresh cycle are cleavage stage, blastocysts can only be transferred in the frozen cycle, which leads to the lack of data of blastocyst transfer in the fresh cycle, which may be one of the reasons why our results are different from some previous studies. Although EP risk was lower when the blastocyst was transferred, all-blastocyst-incubation strategy is likely to lead to zero blastocyst formation and canceling of transfer for the elderly women, this will be a huge blow to the elderly couples hoping to have a baby.

The success of in vitro fertilization and embryo transfer (IVF-ET) cycles depends primarily on embryo quality and uterine receptivity, both are indispensable. It's speculated that mismatch between the embryo stage transferred and the receptive state of the endometrium can lead to increased incidence of EP after ART treatment, as it will lead to inadequate embryonal-endometrial crosstalk, the blastocyst travels in the uterine cavity for a longer time to wait for the endometrial implantation window, it is also possible that the endometrium is not capable of receiving embryo implantation, increasing the likelihood that the embryo migrating outside the uterus, eventually leading to an EP.

A variety of studies have suggested that ultrasound can be used as a noninvasive and simple method to assess the endometrial receptivity[52]. Several sonographic parameters have been evaluated, including EMT, endometrial pattern, endometrial volume and endometrial and subendometrial blood flow[53-57]. Many studies have proposed that a correlation exists between EMT and uterine receptivity[58-63]. Few

studies use EMT during ART therapy to predict future EP, the cutoff value for EP associated EMT is also debated. One study showed that the EMT > 12 mm (OR 0.27; 95% CI 0.13–0.56) prior to embryo transfer was a protective factor against EP[64]. Our study showed that, for fresh cycles, the EMT of the EP group on transformation day was significantly lower than that of the IUP group, the best cutoff point was 9.35mm, the thinner the endometrial was, the more likely EP would occur. However, for frozen cycles, we came to the opposite conclusion from Hongfang Liu's study[65], no significant difference was found in EMT between the two groups.

It's known the endometrium can be divided into basal layer and functional layer. The functional layer is a highly dynamic tissue that changes periodically under the action of steroid hormones, creating an endometrial implantation window[66]. The ultrasonic appearance of the endometrium reflects these periodic changes. It can be considered that the endometrium measured on the first time point was the basal layer, and endometrial growth amplitude represents the functional layer thickness at the late proliferative stage (EMT on transformation day minus EMT on the first time point). Take into account the different length of stimulation in each patient, we included the average daily growth rate of the endometrium in our analysis. The results showed that there was no difference in EMT on the first time point between the two groups, suggesting that the thickness of the basal layer is always constant in most patients. In fresh cycles, the endometrial growth amplitude and daily growth rate of EP patients were significantly smaller/slower than that of IUP group, the cutoff value were 4.9mm and 0.491mm/d, respectively. However, for the frozen embryo cycles, these indicators had no difference between two groups. In general, all the studies showed that thinner EMT may be associated with worse endometrial receptivity in fresh cycles. A previous study confirmed that an increased EMT was positively correlated with an increased risk of placenta praevia [67], hypothesized that increased EMT is a sign of the frequency and/or amplitude of uterine peristalsis wave, which may increase the risk of the embryos being dislodged from their initial transfer location. Combined with our results, it can be speculated that EMT may be related to the direction of endometrial peristaltic waves, thicker endometrium may represent fundus-to-cervix uterine peristalsis, leading to a higher incidence of placenta praevia [67], as well as a lower EP rate in the present. In frozen embryos cycle, endometrium growth depends on exogenous estrogen stimulation, rather than the hyperphysiological levels of endogenous estrogen caused by multiple follicles develop simultaneously, it can be assumed that only very high levels of hormones affect the direction of the endometrial peristaltic waves. A prospective study to determine the actual endometrial implant window by combining molecular biology with pregnancy outcome tracking and to measure the endometrial peristaltic wave, and to analyze their association with different endometrial parameters should be interesting. Further larger studies should confirm a more accurate cutoff value, to guide clinical embryo transfer so as to avoid the occurrence of EP as much as possible.

Our study indicated that in fresh cycles, when endometrial pattern on transformation day was C, EP was more likely to occur. It has been reported that women with lower implantation rates and pregnancy rates show homogenous patterns, although there are conflicting results[68-70]. It is generally believed that the hyperechoic middle line represents the uterine cavity, and the other two hyperechogenic line are related to

the endometrium-myometrium interface, but the main reason for the hyperechoic structure of secretory endometrium is still controversial. Fleischer et al.[71] suggested that the homogeneous hyperechoic endometrium during the late secretory phase might indicate the stromal edema by comparing the endometrial chronological date with glandular histology and stromal histology respectively[72]. The transformation process of endometrial from proliferative phase to secretory phase under the influence of hormones is called endometrial decidualization. The disability of decidualization is related to recurrent spontaneous abortion (RSA), infertility and so on.

Progesterone is the hormone responsible for the secretory changes in the endometrium, it is expected that high progesterone levels in responsible to the hyperechogenic endometrium. Investigations have shown a relationship between the serum progesterone level and secretory changes in the endometrium in controlled ovarian hyperstimulation (COH) cycles[73]. Some study suggested that a premature secretory endometrial pattern is caused by the advanced rise of P[74], and this premature conversion is bad for pregnancy[75]. Moreover, another team[76] found that ovarian stimulation would increase PRB expression and lead to the proliferative endometrium persistence. Therefore, delayed endometrial maturation may not be synchronized with embryonic developmental stages. Our study did not analyze the correlation between progesterone levels and endometrial patterns, but in either situation(earlier or later), endometrial development does not match embryo, consequently lead to the increasing EP rate. But there was no difference in frozen embryo cycles, this may be related to the less frequently early P rise in the frozen embryo period. Different unknown mechanisms produced hyperechogenicity, although the exact mechanism is unknown, it is believed that other hormones, such as androgens and exogenous gonadotropins, cause premature echogenicity of the endometrium by direct effects on the endometrium[77,78]. Further studies should be done to explore these mechanisms.

Clinically, combining endometrial and embryo information are often considered together. However, in the present study, a suggestion of combining EMT and embryo stage to predict ectopic pregnancy could not be made since the AUC of combining the two factors was as low as 0.604. Many factors known to affect EP such as the sequelae stage of pelvic inflammatory disease and maternal age cannot be cured before ET. In this study, our initial aim was to analyze only the effects of endometrial and embryonic parameters on EP after matching other well-known influencing factors, hoping that EP can be prevented by changing the parameters of endometrium and embryo to some extent in the IVF-ET cycle, in further study, when we use more of the risk parameters such as number of embryos transferred to set up a model, it would be likely to get a better prediction effect.

In addition, it is necessary to note that the correlation between EMT and pattern and embryo stage and pregnancy outcome shown in our study does not imply a causal relationship, we must acknowledge its function more than its mere thickness and pattern. The relationship may also result from some other factors that are responsible for endometrial receptivity (such as blood flow or some other underlying physiological machinery responsible for periodic endometrial changes). Despite a higher pattern C rate in EP group, we disagree with the idea that embryo cryopreservation and subsequent ET in a frozen cycle.

We agree with Friedler[79] that endometrial pattern offers important predictive information but should not be used as an absolute predictor of conception. We believe that such patients should be adequately counseled and given the most adaptive advice, routine endometrial peristaltic wave examination in patients with endometrium pattern C or thickness less than 9.35mm on transformation day may be of certain significance.

This study has some limitation, the most important of which is that it is retrospective in nature, moreover, lifestyle factors such as alcohol consumption, smoking, risky sexual behaviors and some other factors which were previously reported to be associated with higher EP risks[80] were not evaluated. However, we believe the results are of interest because similar but not the same studies have published with debate results, there is no consensus about the optimal cutoff value of EMT and the prediction or prevention strategy of EP after ART. A well-designed and powered randomized clinical trial will be needed to achieve these ends.

Conclusions

A thin EMT on the day of endometrial transformation and cleavage embryo transferring were independent risk factors for ectopic pregnancy after ART. Combined endometrial and embryonic features were not sufficient variables to predict the ectopic pregnancy during IVF-ET treatment cycles. Efforts to increase the EMT and prolong embryo culture to blastocyst stage may further reduce ectopic pregnancy risk after ART. Endometrial peristaltic wave examination and corresponding treatment before embryo transfer in patients with risk factors may help preventing EP.

List Of Abbreviations

EP ectopic pregnancy; *IUP* intrauterine pregnancy; *BMI* body mass index; *ART* assisted reproductive technology; *IVF-ET in vitro* fertilization-embryo transfer; *EMT* endometrial thickness

Declarations

Ethics approval and consent to participate

The study was approved by Ethics Committee of Xiangya Hospital, Central South University.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contribution

Y.Z. analyzed and interpreted all the patients' data, and was the major contributor in writing the manuscript. All authors participated in data analysis and results discussion, read and approved the final manuscript.

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Figures

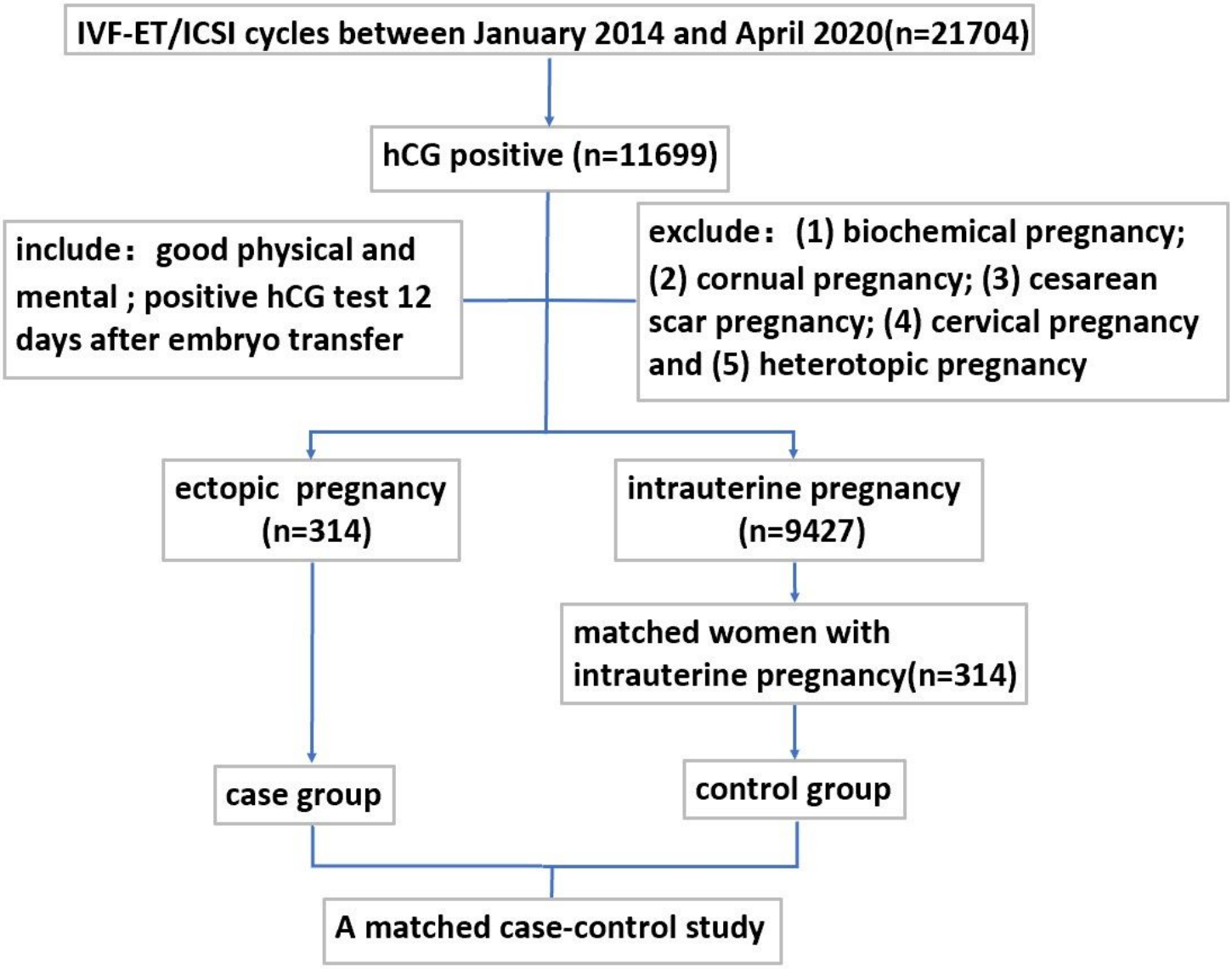

Figure 1

Patient selection flowchart. IVF-ET in vitro fertilization-embryo transfer, ICSI intracytoplasmic sperm injection, hCG human chorionic gonadotropin

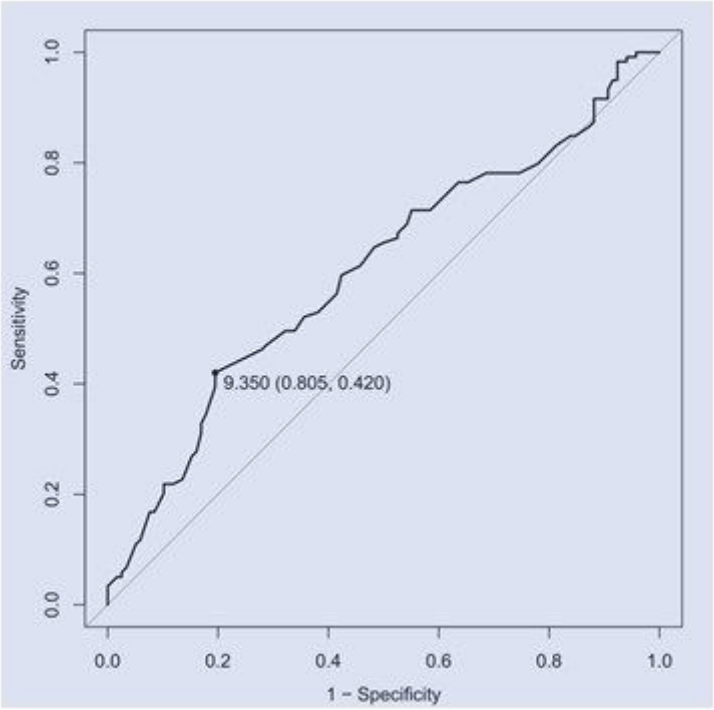

Figure 2

The cutoff value of the EMT on trigger day in fresh cycles. The cutoff value was 9.35mm.

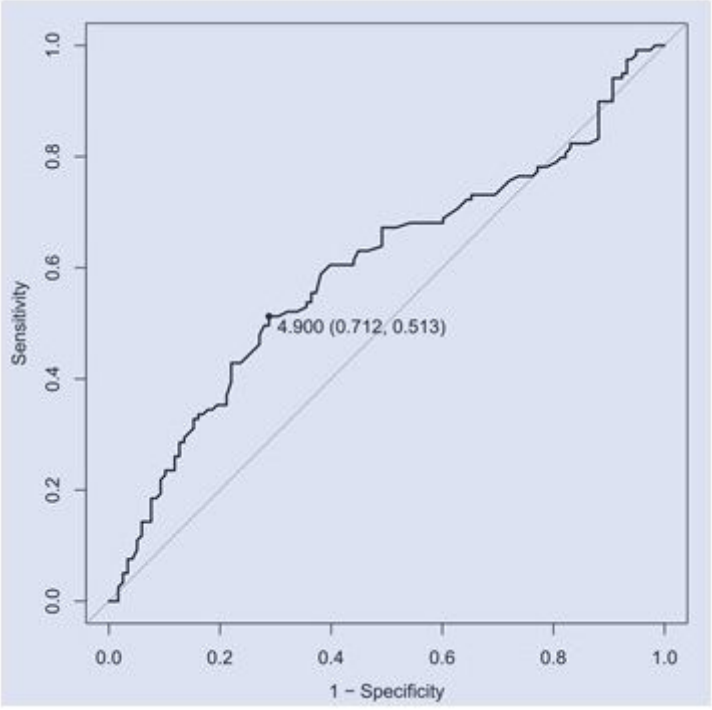

Figure 3

The cutoff value of the endometrial growth amplitude in fresh cycles. The cutoff value was 4.9mm.

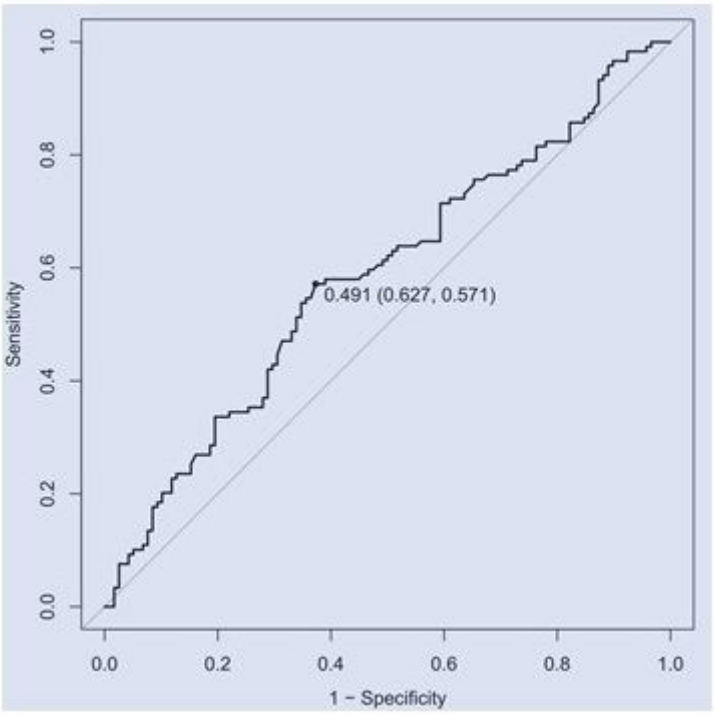

Figure 4

The cutoff value of the endometrial growth rate in fresh cycles. The cutoff value was 0.491mm/day.

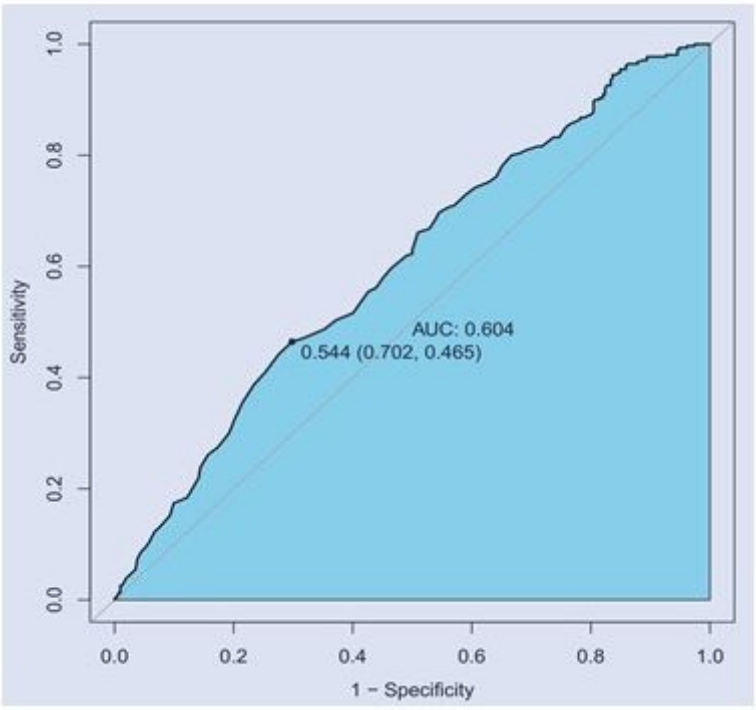

Figure 5

Receiver operator characteristic curve of EMT on transformation day and stage of embryos transferred. The area under the curve was 0.604. Diagonal segments are produced by ties.

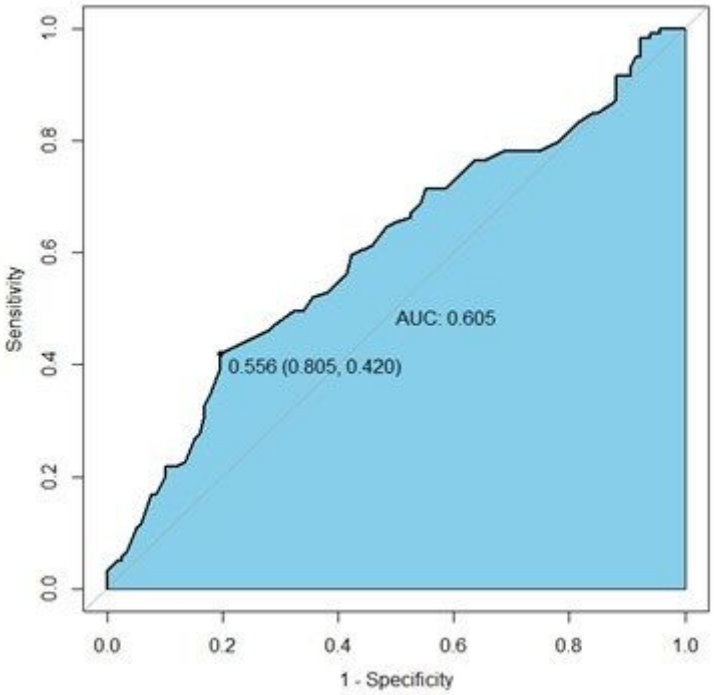

Figure 6

Receiver operator characteristic curve of EMT on trigger day for fresh cycles. The area under the curve was 0.605. Diagonal segments are produced by ties.