



Combined analysis of endometrial thickness and pattern in predicting clinical outcomes of frozen embryo transfer cycles with morphological good-quality blastocyst

A retrospective cohort study

Wei Yang, MMed, Tao Zhang, MMed, Zhou Li, PhD, Xinling Ren, PhD, Bo Huang, PhD, Guijin Zhu, MMed, Lei Jin, PhD^{*}

Abstract

To evaluate the combined effect of endometrial thickness and pattern on clinical outcomes in females following in vitro fertilization/ intracytoplasmic sperm injection and frozen-thawed embryo transfer (IVF/ICSI-FET).

FET cycles using at least 1 morphological good-quality blastocyst conducted between 2012 and 2013 at a university-based reproductive center were reviewed retrospectively. Endometrial ultrasonographic characteristics were recorded on the day of progesterone supplementation in FET cycles. In the combined analysis, endometrial thickness groups (group 1: equal or < 8 mm; group 2: >8 mm) were subdivided into 2 endometrial patterns (pattern A: triple-line; pattern B: no-triple line). Clinical pregnancy rate, spontaneous abortion rate, and live birth rate in different groups were analyzed.

A total of 1512 cycles were reviewed. The results showed that significant differences in endometrial thickness and pattern were observed between the pregnant group (n=1009) and no pregnant group (n=503) (P<.05), while no significant differences were found between the live birth group (n=844) and no live birth group (n=668). Combined analysis revealed those with endometrial thickness > 8 mm and triple-line endometrial pattern had significant higher clinical pregnancy rates, while spontaneous abortion rates and live birth rates showed no significant differences among these subgroups.

This study suggested neither individual nor combined analysis of endometrial thickness and pattern had predicting effects on live birth following IVF treatments, and embryo quality might be the one that really has effects.

Abbreviations: BMI = body mass index, COH = controlled ovarian hyperstimulation, FET = frozen blastocyst embryo transfer, FSH = follicle-stimulating hormone, hCG = recombinant human chorionic gonadotropin, ICM = inner cell mass, ICSI = intracytoplasmic sperm injection, IVF = in vitro fertilization, PGD = preimplantation genetic diagnosis, ROC = receiver operating characteristic curve.

Keywords: blastocyst, clinical pregnancy rate, endometrial pattern, endometrial thickness, in vitro fertilization, live birth rate

1. Introduction

The success of in vitro fertilization and embryo transfer (IVF-ET) cycles depends primarily on the quality of the embryo and the

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Reproductive Medicine Center, Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology, JieFang Avenue, Wuhan, People's Republic of China.

* Correspondence: Lei Jin, Reproductive Medicine Center, Tongji Hospital, Tongji Medicine College, Huazhong University of Science and Technology, 1095 Jiefang Avenue, Wuhan 430030, People's Republic of China (e-mail: leijintj@qq.com).

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receptivity of the uterus.^[1] Embryo quality has improved progressively with the rapid development of laboratory techniques and embryo culture media, leading to the reach of blastocyst stage for in vitro culture of embryos.^[2] Furthermore, studies have revealed the association between blastocyst embryo transfer and better IVF outcomes.^[3]

Also, uterine receptivity is widely accepted as one of the main limiting factors in IVF outcomes. Transvaginal ultrasound has long been performed in assisted reproduction technology (ART) treatments for the evaluation of endometrium receptivity due to its accurate evaluation and noninvasive detection. Generally, both endometrial thickness and endometrial pattern have been regarded as indicators for endometrial receptivity. Also, assessment of the association between these sonographic endometrial characteristics and clinical outcomes following IVF treatments has been the focus of interest for many years. However, no consensus was achieved on whether the endometrial ultrasound characteristics can predict the pregnancy outcome in IVF/ intracytoplasmic sperm injection (ICSI) treatment.

Some investigators have suggested positive associations between clinical outcomes in IVF cycles and endometrial thickness, pattern, or both,^[4–8] while others have shown no effect.^[9–11] Besides, the combined analysis of endometrial thickness and pattern also show conflicting results.^[9,12–14] Furthermore, few researches have

focused combined analysis of endometrial thickness and pattern for the prediction of frozen-thawed embryo transfer (FET) cycle clinical outcomes. Also, as the key IVF outcome, live birth rate is seldom assessed.

In this study, we design this large sample size investigation using FET cycles with at least 1 blastocyst of good morphological embryo quality, to demonstrate a more accurate correlation between IVF outcomes and endometrial thickness as well as pattern (both individually and together). Moreover, both clinical pregnancy rate and live birth rate is assessed as the key IVF outcome.

2. Materials and methods

2.1. Patient recruitment and counseling

Since this study was retrospective and vaginal sonographic assessment during IVF process was done routinely in our center, Institutional Review Board approval for the study was not necessary. Briefly, all FET cycles between 2012 and 2013 at Reproduction Medicine Center of Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology (Wuhan, China) were reviewed. Exclusion criteria included the presence of a known endometrial polyp or uterine anomaly, oocyte donation cycles, and preimplantation genetic diagnosis (PGD) cycles. Except for these exclusions, all FET cycles during this period with transfer of at least 1 good-quality blastocyst-stage embryos were included in the analysis, regardless of diagnosis, reproductive history, stimulation protocol, FET protocol, or insemination method. Patients underwent no therapeutic intervention other than routine procedures. Embryo quality was analyzed according to the Istanbul consensus workshop on embryo assessment.^[15] Only embryos transfers of at least 1 blastocyst expanding by day 5, and with at least fairquality (grade B) ICM (inner cell mass) and trophectoderm (grade C), were included in the study.

2.2. IVF treatment protocol

The methods of ovarian stimulation protocols, sperm preparation, IVF embryo culture, and FET protocols in our reproduction medicine center have been described elsewhere.^[16-18] Briefly, ovarian stimulation protocols were chosen depending on the maternal age, cause of infertility, ovarian response, and coexisting medical conditions. When 2 leading follicles reached a mean diameter of 18 mm, recombinant human chorionic gonadotropin (hCG) (250 mg; Ovidrel; Serono) was given to trigger ovulation. 36 hours later, transvaginal ultrasound-guided oocyte retrieval was performed. Fertilization of the oocytes took place either by IVF or ICSI, according to the sperm quality. Embryo cryopreservation by vitrification was performed for the additional good-quality embryos or blastocysts. FET protocols in our hospital are mainly divided into natural cycles after spontaneous ovulation and hormone replacement treatment cycles according to menstrual regularity. For the natural cycles, the evaluation of endometrial thickness, follicle growth, and ovulation by transvaginal ultrasound examination and measurement of the serum progesterone levels were initiated from cycle days 10 to 12. Thawing and transferring of blastocysts was planned 3 days after ovulation. Intramuscular administration of progesterone for luteal support was started from 1 day after ovulation. For hormone replacement treatment cycles, oral administration of estradiol (Progynova; Bayer) was initialed with 2 mg/day from cycle days 1 to 4, 4 mg/day from days 5 to 8, and 6

mg/day from days 9 to 12. Since day 13, transvaginal ultrasound examination was conducted to evaluate the endometrial thickness and ovulation and the dose of estradiol was adjusted according to the endometrial thickness. When the endometrial thickness reached 8.0 mm or more, 40 mg intramuscular administration of progesterone was given and maintained for the following 3 days. Thawing and transferring of blastocysts was performed on day 4 after 3 days of progesterone administration.

Clinical pregnancy was defined as the identification of a gestational sac with fetal heart activity on ultrasound examination 4 to 5 weeks after embryo transfer and clinical pregnancy rate is expressed per cycle. Spontaneous abortion was defined as spontaneous pregnancy loss after sonographic visualization of an intrauterine gestational sac and spontaneous abortion rate is expressed per clinical pregnancy cycle. Live birth rate was classified as those cycles resulting in the delivery of a viable infant after 24 weeks gestation and live birth rate is expressed per cycle.

2.3. Ultrasound measurement

Endometrial features assessed included endometrial thickness and pattern on the day of progesterone supplementation in FET cycles. Endometrial thickness was measured in the midsagittal plane of the uterus as the maximum distance between the 2 interfaces of endometrial-myometrial junction on the same day. All cycles were divided into 2 groups depending on the thickness: group $1 \le 8$ mm; group 2 > 8 mm. Endometrial patterns were classified according to the morphology of the endometrium as: pattern A (triple-line type characterized by a hypoechoic endometrium with well-defined hyperechoic outer walls and a central echogenic line); pattern B (no triple-line type characterized by a isoechoic or homogeneous hyperechoic endometrium with a nonprominent or absent central echogenic line).^[12]

2.4. Statistical analysis

Maternal age, baseline serum follicle-stimulating hormone (FSH), antral follicle count (AFC), body mass index (BMI), duration of infertility, endometrial thickness, and number of transferred blastocyst were compared between the clinical pregnancy group and no clinical pregnancy group as well as the live birth group and non-live-birth group by t-test. Endometrial pattern was compared by chi-square analysis. The association among maternal age, baseline serum FSH, AFC, BMI, duration of infertility, number of transferred blastocyst, endometrial thickness as well as pattern and subsequent clinical outcomes were assessed by multiple logistic regression analyses. Receiver operating characteristic (ROC) analysis was performed for the evaluation of discriminatory ability of endometrial thickness. A 2-tailed P < .05 was considered statistically significant. All analyses were performed using the Statistical Package for Social Sciences (SPSS) version 21.0 (IBM, Armonk, NY).

3. Results

3.1. Baseline cycle characteristics

Table 1 describes FET cycle characteristics according to cycle outcomes. Continuous data are presented as mean \pm standard deviation and categorical data are presented as percentage (%). A total of 1512 FET cycles were investigated in this study. The overall clinical pregnancy rate was 66.7% and the spontaneous abortion rate was 16.4%, with an overall live birth rate of 55.8%.

Table 1

Baseline cycle	characteristics	(n=1512).
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Variables	Mean \pm SD
No. of cycles	1512.0
Maternal age, years	30.3 ± 4.2
BMI, kg/m ²	21.5±5.8
Baseline FSH, IU/L	6.5±1.8
AFC	17.0 ± 7.2
Duration of infertility	4.5±3.4
Infertility diagnosis n (%)	
Tubal factor	708 (46.9%)
Ovulation disorder	52 (3.4%)
Pelvic and uterine factors	17 (1.1%)
Endometriosis	15 (1.0%)
Male factor	257 (17.0%)
Unexplained and other	52 (3.4%)
Multiple factors	411 (27.2%)
Endometrial thickness, mm	9.1 ± 1.6
Endometrial pattern in FET cycles n (%)	
Pattern A	901 (59.6%)
Pattern B	611 (40.4%)
No. of transferred blastocyst	1.8 ± 0.4

AFC = antral follicular count, BMI=body mass index, FET = frozen-thawed blastocyst transfer, FSH=follicle-stimulating hormone.

Pattern A = triple-line pattern, hypoechoic endometrium with well-defined hyperechoic outer walls and central echogenic line; Pattern B = no-triple line pattern, isoechogenic or homogeneous hyperechoic endometrium with a poorly defined or absent central echogenic line.

When subdividing cycles into pregnant ones (n = 1009) and no pregnant ones (n = 503) (Table 2), significant differences were observed between the 2 groups, including maternal age, duration of infertility, number of blastocysts transferred, AFC, endometrial thickness, and pattern (P < .05). Besides, when cycles were subdivided according to live birth group (n = 844) or no live birth group (n = 668) (Table 2), significant differences were observed between the 2 groups, which included maternal age, duration of infertility, number of blastocysts transferred, and AFC (P < .05), while no statistically significant differences in endometrial thickness (P=.26) and pattern (P=.07) were found between the 2 groups.

3.2. Binary logistic analysis and ROC curves of some variables on pregnancy outcomes

Binary logistic regression analysis was used to evaluate the effects of maternal age, endometrial thickness, and patterns in FET cycles (pattern B was defined as the dummy variable with an OR of 1), duration of infertility, AFC, baseline FSH, BMI, and number of transferred blastocyst in FET cycles, on clinical pregnancy or live birth following FET (Table 3). The modified Hosmer-Lemshow goodness-of-fit chi-square test statistics were 13.584 (P = .093 > .05) for the model of clinical pregnancy and 4.798 (P = .779 > 0.05) for the model of live birth, which suggested that the multivariable models were of good fit. The analysis indicated AFC and number of transferred blastocyst were associated with improved clinical pregnancy rate and live birth rate, while maternal age was negatively correlated with clinical pregnancy and live birth. Other variables involved including endometrial pattern, BMI, baseline FSH and duration of infertility did not contribute significantly to pregnancy outcomes. However, the data suggested endometrial thickness were positively correlated with clinical pregnancy, but showed no association with live birth.

3.3. Endometrial thickness and clinical outcomes

The ROC curve of endometrial thickness was constructed for the evaluation of its predictive value for clinical outcomes (Fig. 1). The area under the curve of endometrial thickness on starting day of progesterone supplementation in FET cycles was 0.534 (95% CI, 0.504–0.565) versus clinical pregnancy. The cut-off point of endometrial thickness was 8.25 mm (sensitivity of 73.0% and specificity of 32.8%) for clinical pregnancy, making the cut-off a poor overall indicator of pregnancy outcomes following FET.

Table 2

Comparison of IVF parameters by clinical outcomes.									
Variables	Pregnant	No-pregnant	P-value	Live-birth	No-live-birth	P-value			
No. of cycles	1009.0	503.0	_	844.0	668.0	-			
Maternal age at, years	29.8 ± 4.0	31.1 ± 4.4	<.001	29.7±3.9	31.0±4.4	<.001			
BMI, kg/m ²	21.5 ± 6.8	21.4 ± 2.9	.73	21.4±7.3	21.5 ± 3.0	.69			
Baseline FSH, IU/L	6.5 ± 1.7	6.6 ± 1.9	.42	6.5 ± 1.7	6.5 ± 1.9	.59			
AFC	17.6 ± 7.5	15.8 ± 6.5	<.001	17.7±7.5	16.2 ± 6.8	<.001			
Duration of infertility	4.3 ± 3.2	5.0 ± 3.7	.001	4.3 ± 3.1	4.8 ± 3.6	.004			
Infertility diagnosis n (%)			-			-			
Tubal factor	457 (45.3%)	251 (49.9%)		375 (44.4%)	333 (49.9%)				
Ovulation disorder	42 (4.2%)	10 (2.0%)		36 (4.3%))	16 (2.4%)				
Pelvic and uterine factors	9 (0.9%)	8 (1.6%)		6 (0.7%)	11 (1.6%)				
Endometriosis	12 (1.2%)	3 (0.6%)		10 (1.2%)	5 (0.7%)				
Male factor	188 (18.6%)	69 (13.7%)		163 (19.3%)	94 (14.1%)				
Unexplained and other	34 (3.4%)	18 (3.6%)		27 (3.2%)	25 (3.7%)				
Multiple factors	267 (26.5%)	144 (28.6%)		227 (26.9%)	184 (27.5%)				
Endometrial thickness (mm)	9.1 ± 1.5	8.9 ± 1.6	.02	9.1 ± 1.5	9.0 ± 1.6	.26			
Endometrial pattern in FET cycles n (%)			.02			.07			
Pattern A	622 (61.6%)	279 (55.5%)		521 (61.7%)	380 (56.9%)				
Pattern B	387 (38.4%)	224 (44.5%)		323 (38.3%)	288 (43.1%)				
No. of transferred blastocyst	1.8 ± 0.4	1.7 ± 0.5	<.001	1.9 ± 0.4	1.7 ± 0.5	<.001			

AFC=antral follicular count, BMI=body mass index, FET=frozen-thawed blastocyst transfer, FSH=follicle-stimulating hormone.

Pattern A=triple-line pattern, hypoechoic endometrium with well-defined hyperechoic outer walls and central echogenic line; Pattern B=no-triple line pattern, isoechogenic or homogeneous hyperechoic endometrium with a poorly defined or absent central echogenic line.

Table 3

Binary logistic analysis of factors related to clinical pregnancy and live birth in FET cycles.

	Clinical pregnancy				Live bir	th
	P value	OR	95% CI for Exp (B)	P value	OR	95% CI for Exp (B)
Maternal age, years	.002	0.952	0.923-0.983	.001	0.949	0.921-0.977
BMI, kg/m ²	.51	1.010	0.981-1.039	.97	1.000	0.982-1.019
Baseline FSH, IU/L	.63	1.016	0.952-1.084	.08	1.057	0.993-1.124
AFC	.01	1.023	1.005-1.041	.03	1.018	1.002-1.035
Duration of infertility	.29	0.981	0.946-1.017	.72	0.993	0.959-1.029
No. of transferred blastocyst	<.001	2.428	1.876-3.144	<.001	2.429	1.876-3.144
Endometrial thickness (mm)	.007	1.107	1.028-1.192	.17	1.049	0.980-1.123
Endometrial pattern						
Pattern A	.06	1.243	0.991-1.558	.15	1.169	0.943-1.449
Pattern B		1.000				1.000

AFC=antral follicular count, BMI=body mass index, FSH=follicle-stimulating hormone, FET=frozen-thawed blastocyst transfer.

Pattern A = triple-line pattern, hypoechoic endometrium with well-defined hyperechoic outer walls and central echogenic line; Pattern B = no-triple line pattern, isoechogenic or homogeneous hyperechoic endometrium with a poorly defined or absent central echogenic line.

Pattern B is chosen as the dummy variable with an OR of 1.

The area under the curve of endometrial thickness was 0.518 (95% CI, 0.488–0.547) versus live birth.

Clinical pregnancy rate, live birth rate, and spontaneous abortion rate were evaluated at each millimeter of endometrial thickness to have a more accurate comprehension of the association between endometrial thickness and pregnancy outcomes (Fig. 2). Clinical pregnancy rate ranged from 55.7% among patients with an endometrial thickness of \leq 7 mm to 71.2% among patients with an endometrial thickness of >12 mm, with live birth rate from 42.9% to 52.1%. Spontaneous abortion rate varied with endometrial thickness, but showed no consistent increase with increasing endometrial thickness.

3.4. Evaluation of clinical outcomes by combined analysis of endometrial thickness and pattern

For further assessing clinical outcome by combined analysis of endometrial thickness and pattern, the 2 endometrial thickness groups were subdivided into the respective endometrial patterns (Table 4) (Fig. 3). In group 1, clinical pregnancy rates, spontaneous abortion rates and live birth rates showed no significant differences between those with patterns A and B (clinical pregnancy rates: 62.3% vs. 60.0%, respectively; P > .05; spontaneous abortion rates: 16.7% vs. 16.2%, respectively; P > .05; live birth rates: 51.9 vs. 50.3%, respectively; P > .05;). In group 2, the pregnancy rates were significantly different between patterns A and B (clinical pregnancy rates: 70.4% vs. 64.6%, respectively; P < .05;), while spontaneous abortion rates and live birth rates showed no significant differences (spontaneous abortion rates: 16.2% vs. 16.7%, respectively; P > .05; live birth rates: 59.0 vs. 53.8%, respectively; P > .05;).

Clinical pregnancy rates increased significantly with increasing endometrial thickness only in patterns A group, but showed no significant increase with increasing endometrial thickness in patterns B group. No significant increase of live birth rates with increasing endometrial thickness was observed both in patterns A and B groups. Spontaneous abortion rates also showed no significant change with increasing endometrial thickness both in patterns A and B groups (Table 4).







Figure 2. Relationship between endometrial thickness and pregnancy outcomes in 1512 frozen-thawed blastocyst embryo transfer cycles.

4. Discussion

To the best of our knowledge, the present study has the largest sample size with 1512 FET cycles using morphological goodquality blastocysts to evaluate the combined effect of endometrial thickness and pattern on clinical outcome following IVF treatment. Although there were abundant studies focusing on the association among endometrial thickness, endometrial pattern and clinical outcomes of IVF treatments, most of them were limited by the influence of embryo quality. Nowadays, the rapid development of laboratory techniques and embryo culture media has allowed the in vitro culture of embryos reaching the

blastocyst stage.^[2] Also, researches have revealed the correlation between blastocyst embryo transfer and higher success rates. This might be explained by that developing to the blastocyst stage is an enhanced natural selection process with higher efficiency in selecting biologically superior embryos than morphological assessment of cleavage stage embryos.^[3] Here in this study, we selected cycles using at least one blastocyst of good morphological embryo quality, resulting in better homogeneity in embryo quality. Moreover, the inclusion of FET cycles reduced the possible effects of different ovarian stimulation protocols and high serum progesterone level on endometrium in fresh cycles. After controlling for embryo quality by using morphological good-quality blastocysts, our results suggested a correlation between endometrial thickness and clinical pregnancy, while no association was observed between endometrial pattern and clinical outcomes. Those with endometrial thickness >8 mm and the triple-line pattern had a significant higher clinical pregnancy rate. However, neither endometrial thickness nor endometrial pattern alone combined endometrial thickness and pattern could predict the live birth following FET cycles.

The predicting effect of endometrial thickness on uterine receptivity has been discussed for many years with conflicting conclusions. In the studies of fresh IVF cycles, many investigators have reported a positive correlation between endometrial thickness and IVF outcomes.^[1,2,13,14,19] In comparison, other

Table 4

The relationship between clinical outcome and endometrial thickness and pattern.

	Clinical pregnancy rate (%)			Spontaneous abortion rate (%)			Live birth rate (%)		
	Pattern A	Pattern B	Р	Pattern A	Pattern B	Р	Pattern A	Pattern B	Р
Group 1	62.3 (96/154)	60.0 (99/165)	.67	16.7 (16/96)	16.2 (16/99)	.92	51.9 (80/154)	50.3 (83/165)	.77
Group 2	70.4 (526/747)	64.6 (288/446)	.03	16.2 (85/526)	16.7 (48/288)	.85	59.0 (441/747)	53.8 (240/446)	.08
Р	.04	.30		.90	.91		.11	.44	

Endometrial thickness: Group 1: ≤8 mm; Group 2: >8 mm.

Pattern A = triple-line pattern, hypoechoic endometrium with well-defined hyperechoic outer walls and central echogenic line; Pattern B = no-triple line pattern, isoechogenic or homogeneous hyperechoic endometrium with a poorly defined or absent central echogenic line.





studies could not establish a significant association between endometrial thickness and clinical outcomes following IVF treatments.^[9,20,21] However, a thin endometrium is generally regarded to be associated with a lower implantation rate, clinical pregnancy rate or live birth rate, although no cut-off point of consensus exists. Several researches concluded that an endometrial thickness below a minimum value of 6-8 mm showed negative predictive value for IVF outcomes.^[1,2,13,14,19] However, a successful pregnancy can still be achieved despite a thin endometrium.^[22] In the studies of FET cycles, there is also no consensus on whether the endometrial thickness can predict the FET outcomes. Some studies suggested endometrial thickness as a positive predictor of clinical outcomes,^[5–8] while others showed no effect.^[4,10,11] But the endometrial thickness of 8 mm has been widely used as the cut-off point of endometrial preparation in FET cycles. In the present studies, we did find a significant correlation between endometrial thickness and clinical pregnancy. However, no association was observed between endometrial thickness and live birth rate, the key IVF outcome.

In addition to endometrial thickness, the correlation between endometrial pattern and the outcome of assisted reproductive techniques has also been the focus of interest for many years. However, their conclusions were not consistent. Generally, several investigators indicated that a triple-line pattern of the endometrium was correlated with better IVF outcomes,^[4,13,14] while other studies showed no correlation.^[12,23,24] In this study, no significant correlation was observed between endometrial pattern and the clinical outcomes following FET cycles. Previous studies have indicated that the advanced progesterone rise led to a premature secretory endometrial pattern, which had a detrimental effect in pregnancy rates. In the present study, blastocyst cryopreservation and subsequent ET in a frozen cycle removed the possible effects of high progesterone levels. Thus the mechanism underlying the notriple line endometrial pattern is not known and cannot be explained by higher progesterone levels.

In addition to independent evaluation of endometrial characteristics on clinical outcome, the combined predictive effect of the endometrial thickness and pattern is also assessed. Pattern A (triple line pattern) showed significant higher clinical pregnancy rate than pattern B (no-triple line pattern) in group 2 (>8 mm). There were no differences in clinical pregnancy rates between the 2 patterns in groups 1 (<8mm). However, no significant differences in live birth rates were observed between the 2 patterns in groups 1 and 2. These findings suggested combined endometrial thickness and endometrial pattern could not predict the live birth of IVF-embryo transfer correctly, although results showed that endometrial thickness >8 mm and endometrial pattern of triple-line predicted higher clinical pregnancy rate. This conclusion was not in agreement with previous researches,^[4,12–14] but most of them did not evaluate live birth rate as the key IVF outcomes. Our data indicated that in terms of live birth, perhaps embryo quality might be the one that really has effects. Although morphological good-quality blastocysts were used in our study, the research was still limited by the unknown genetic composition of embryos.

There are also some limitations in the present study. An important limitation of our study was that it is retrospective in nature. Besides, although morphological good-quality blastocysts were used in our study, the research was still limited by the unknown genetic composition of embryos. However, we believe that these findings were of interest as previous similar studies revealed conflicting conclusions. Well-designed and powered randomized clinical trials are still needed for further study.

In conclusion, this study suggested neither individual nor combined analysis of endometrial thickness and pattern have predicting effect on live birth following IVF treatments and embryo quality might be the one that really has effects.

5. Authors' contributions

WY participated in the conception and design of the study. TZ carried out the analysis and interpretation of data, and writing of the manuscript. ZL, BH, and XR have been involved in the ultrasound examination and critical manuscript revisions. LJ and GZ participated in its design and coordination, and helped to draft the manuscript. All authors have read and approved the final version of the manuscript.

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