Nomogram to Predict an Endometrial Thickness >7.5 mm in the Frozen Embryo Transfer Cycle for Thin Endometrial Women

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Research

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Abstract

Background A sufficient endometrial thickness (EMT) is essential for successful pregnancy. For patients with a thin endometrium (EMT ≤7.5 mm on human chorionic gonadotropin [HCG] trigger day) in IVF, some studies have suggested freezing all embryos and preparing the endometrium in the subsequent frozen-thawed cycle, but not all patients can obtain a thicker endometrium during endometrial preparation in the frozen embryo transfer cycle than on HCG trigger day in the fresh embryo transfer cycle. This study aimed to investigate which characteristics of patients with a thin endometrium suggest the possibility of EMT >7.5 mm in the subsequent frozen cycle, and build up a prediction nomogram.

Methods Data were collected from the university-based reproductive medical center between January 2013 and September 2019. Multivariable logistic regression was used to generate the final prediction model and construct the nomogram. Model performances were quantified by discrimination and calibration.

Results The predictive variables that entered the final model were: hysteroscopic adhesiolysis history, PCOS status, application of clomiphene in the ovarian stimulation process, the ovarian stimulation protocol, and the endometrial preparation protocol. The receiver operating characteristic curve for the final model and validation cohort was 0.76 (95% confidence interval [CI]: 0.722–0.797) and 0.71 (95% CI: 0.66–0.76), respectively. Discrimination performed well in both the modeling and validation cohorts.

Conclusion We conclude that in women with a thin endometrium (EMT ≤7.5 mm on HCG trigger day), the absence of a hysteroscopic adhesiolysis history, and the presence of PCOS, the application of clomiphene in the ovarian stimulation process, the application of a GnRH agonist short protocol, mild stimulation protocol, natural cycle protocol, and natural cycle for endometrial preparation are prognostic for an increased possibility of EMT >7.5 mm in the subsequent frozen cycle.

Background

Endometrial thickness (EMT) and embryo quality are two important factors affecting the pregnancy outcomes of *in vitro* fertilization (IVF) and embryo transfer. With the continuous development of assisted reproductive technology and laboratory embryo cultivation technology, the quality of embryos is being continuously improved so the endometrium is considered an important fertility-determining factor [1]. A sufficient EMT is essential for successful pregnancy.

In 2014, Kasius et al. conducted a systematic review and meta-analysis which revealed a significantly lower pregnancy rate with EMT < 7 mm than with EMT > 7 mm [2]. Another systematic review showed that both clinical pregnancy and live birth rates decreased significantly for each millimeter of endometrial thickness below 8 mm in fresh IVF cycles and below 7 mm in frozen-thawed IVF cycles [3]. A thin endometrium reduces the clinical pregnancy rate and live birth rate, but there is no consensus on this definition [4] and it is currently thought to be around 7–8 mm [5–8]. We use a cutoff of 7.5 mm on human chorionic gonadotropin (HCG) trigger day to diagnose a thin endometrium in our reproductive center. Our

latest research [9] found that the risk of being born small for gestational age was significantly increased in the EMT ≤ 7.5 mm group compared with the EMT > 12 mm group (adjusted odds ratio [aOR] 2.391; 95% confidence interval [CI], 1.155–4.950).

The most common factors leading to a thin endometrium (EMT ≤ 7.5 mm on HCG trigger day) are inflammation and iatrogenic disease as well as poor vascularity and low estrogen levels [10]. Improvement of the pregnancy outcome in patients with a thin endometrium has always been a contentious issue in the field of reproductive medicine. Some studies have suggested freezing all embryos and preparing the endometrium in the subsequent frozen-thawed cycle [11], but not all patients can obtain a thicker endometrium during endometrial preparation in the frozen embryo transfer (frozen) cycle than on HCG trigger day in the fresh embryo transfer (fresh) cycle. Moreover, some clinicians and patients prefer to use a fresh cycle to save time and costs.

The present study aimed to identify which characteristics of patients with a thin endometrium suggest the possibility of an EMT > 7.5 mm in the subsequent frozen cycle, and to provide individualized and targeted advice for patients on transfer type.

Materials And Methods

Patients

All women who had received IVF or intracytoplasmic sperm injection (ICSI) treatment at the university-based reproductive medical center between January 2013 and September 2019, and whose EMT on HCG trigger day was £7.5 mm were screened. The aim was to identify which characteristics of patients with a thin EMT suggest the possibility of endometrial growth in subsequent frozen cycles; therefore, the first frozen cycle of patients with a thin EMT who adopted the “freeze all” strategy was included. Exclusion criteria were uterine malformations, untreated submucosal uterine fibroids, and endometrial polyps. To develop an optimal prediction model and validate its accuracy, patients with a thin EMT who received IVF/ICSI treatment from January 2013 to September 2017 were included in a modelling cohort (n = 628) and those treated from October 2017 to September 2019 were absorbed into a validation cohort (n = 454).

IVF/ICSI treatment procedure

Different ovarian stimulation protocols were selected according to the patient’s age and ovarian function, including gonadotrophin-releasing hormone (GnRH) agonist long protocols, GnRH agonist short protocols, flexible GnRH antagonist protocols, mild stimulation protocols, and natural cycle protocols, which have been reported in detail previously [9]. Transvaginal ultrasound was used to monitor the growth and development of follicles. When at least two follicles measured ³18 mm, 4000–8000 IU of HCG was given intramuscularly to trigger ovulation. Transvaginal oocyte retrieval was carried out 34–36 h after HCG injection.

For fresh cycles, luteal phase support was started after oocyte retrieval and lasted for 10 weeks of gestation. Indications for the “freeze all” strategy included moderate to severe ovarian hyperstimulation syndrome (OHSS), a high risk of moderate to severe OHSS, a thin endometrium, the presence of progesterone elevation, and other factors affecting embryo implantation. For frozen cycles, no luteal phase support was provided after oocyte retrieval. In the second menstrual cycle after oocyte retrieval, endometrial preparation was performed through a natural cycle, an artificial cycle, or an ovulation induction cycle. Endometrial preparation protocols of the study center have been reported previously [12]. If oral estradiol valerate (Progynova, Delpharm Lille) was applied for 10–12 days in the artificial cycle, the EMT did not reach 8 mm so the amount of oral estradiol valerate would be increased as appropriate. If the EMT still did not reach 8 mm, the decision to carry out endometrium transformation using progesterone was made by taking into account the EMT on HCG day during the ovarian stimulation period and the patient’s wishes.

Measurement of endometrial thickness

EMT was defined as the maximal distance from one endometrial–myometrial interface to the other in the midsagittal plane of the uterus as measured by ultrasonography. To avoid error, all patients were measured by the same operator group. Each patient was measured three times and the average value was taken. In fresh cycles, the EMT was taken from the day of HCG administration, while in frozen cycles the EMT of the last ultrasound before the use of progesterone was recorded.

Statistical analyses

Development of the model

The study endpoint was the probability of EMT >7.5 mm in women with a thin endometrium in the subsequent frozen cycle. Multivariable logistic regression (MLR) analysis was performed to test the association between EMT thickening and patient characteristics. MLR was used to generate the final prediction model and construct the nomogram.

The predictive variables included in the MLR analysis were based on the variables that were significant at univariate logistic regression analysis ($p < 0.1$) and clinical knowledge. Backward variable selection was performed to determine independent covariates. The Akaike information criterion was used to select the best mode. Before logistic regression analysis, the multicollinearity was checked among the variables. A simple measure of collinearity diagnosis is variance inflation factors (VIF), which is defined as a ratio between the variance in the mode with the multiple variables and the variance in the model with the single variable [13]. For models with 3 or more categories of categorical variables, generalized VIF (GVIF) is more appropriate. To make GVIFs comparable in all dimensions, it is recommended to use GVIF^(1/(2∗Df)), where Df is the degree of freedom. In general, variables with GVIFs < 10 are considered acceptable [14]. A P-value of 0.05 was considered to be statistically significant. The values of each model covariable were mapped to a point in the range from 0 to 100. The total point of each model corresponded to the probability of EMT >7.5 mm in the subsequent frozen cycle.

Evaluation of the model

The predictive ability of the model was assessed on the validation cohort. The validation was based on a cohort of women with a thin endometrium undergoing their first frozen cycle from October 2017 to September 2019 (temporal validation).

The model performances were quantified in two aspects: discrimination and calibration [15]. The discriminatory ability was accessed by using the receiver operating characteristic curve and the area under the curve (AUC). Calibration was detected using calibration curves accompanied by the Hosmer–Lemeshow test (H–L test).

All statistical analyses were performed using the RMS package in R version 3.4.1 and the IBM SPSS version 24.0.

Results

General characteristics of womenwith a thin endometrium

The model was built from a training cohort of 628 patients with a thin endometrium from January 2013 to September 2017, and tested from an independent validation cohort of 454 patients with a thin endometrium from October 2017 to September 2019. Through literature study and clinical experience, research variables that affect EMT growth were included, such as patient age, body mass index, infertility duration, infertility type, cause of infertility, induced abortion, medical abortion, with or without endometriosis, polycystic ovary syndrome (PCOS), history of tuberculosis, history of hysteroscopic adhesiolysis, basic follicle-stimulating hormone, thyroid-stimulating hormone, prolactin, ovarian stimulation protocol, application of clomiphene, total gonadotropin dose, days of stimulation, estradiol level on HCG trigger day, number of oocytes, number of embryos, and protocol of endometrial preparation. These characteristics are shown in Table 1. Among the 628 cycles of the modeling cohort, 297 (47.3%) had an EMT >7.5 mm before frozen embryo(s) transfer. For the validation cohort, 190 (41.9%) of the 454 cycles had an EMT >7.5 mm before frozen embryo(s) transfer.

The pregnancy outcomes of womenincluded in this study based on EMT

Among the 1082 cycles of the modeling and validation cohorts, 487 had an EMT >7.5 mm and 595 had an EMT ≤7.5 mm before frozen embryo(s) transfer. We compared the pregnancy outcomes of patients included in this study based on EMT. The women with EMT >7.5 showed a higher live birth rate (35.7% vs. 28.9%, $p < 0.05$), clinical pregnancy rate (46.6% vs. 38.8, $p < 0.05$), and biochemical pregnancy rate (56.1% vs. 47.1%, $p < 0.05$) than the women with EMT ≤7.5, as shown in Table 2.

Feature selection and MLR model construction

In MLR analysis of the modeling cohort, EMT >7.5 mm in the frozen cycle was significantly correlated with hysteroscopic adhesiolysis history (adjusted odds ratio [aOR] 0.186; 95% CI 0.101–0.341; p<0.001);

PCOS (aOR 2.363; 95% CI 1.405–3.973; p = 0.001); application of clomiphene (aOR 3.769; 95% CI 1.444–9.834; p = 0.007); ovarian stimulation protocol, and endometrial preparation protocol (Table 3). By using the collinearity diagnosis, the value of GVIF for the hysteroscopic adhesiolysis history, PCOS, application of clomiphene, ovarian stimulation protocol, and endometrial preparation protocol were less than 10 (hysteroscopic adhesiolysis history: 1.0284; PCOS: 1.3077; application of clomiphene: 3.1647; ovarian stimulation protocol: 3.7211 ; endometrial preparation protocol: 1.1750), indicating there is no severe collinearity between variables. Without a hysteroscopic adhesiolysis history, PCOS, the application of clomiphene in the ovarian stimulation process, and the application of a GnRH agonist short protocol, mild stimulation protocol, natural cycle protocol, and natural cycle for endometrial preparation were associated with an increased possibility of EMT >7.5 mm in the frozen cycle for women with a thin endometrium.

The equation describing the probability of EMT >7.5 mm in the frozen cycle was: $P = 1/ (1+ \exp (-X))$ where $X = - 0.2443 - 1.6556 * V_1 + 0.9278 * V_2 + 1.3067 * V_3 + 0.5181 * V_{4-1} + 0.0338 * V_{4-2} + 1.0904 * V_{4-3} + 2.4961 * V_{4-4} - 0.5030 * V_{5-1} - 0.8144 * V_{5-2}$, where V_1 was the hysteroscopic adhesiolysis history, V_2 was the status of PCOS, V_3 was the application of clomiphene in the ovarian stimulation process, V_{4-1} was the application of a GnRH agonist short protocol, V_{4-2} was the application of a GnRH antagonist protocol, V_{4-3} was the application of a mild stimulation protocol, V_{4-4} was the application of a natural cycle protocol, V_{5-1} was the application of a programmed cycle for endometrial preparation, V_{5-2} was the application of a minimal ovarian stimulation for endometrial preparation.

Development of nomogram

Based on MLR analyses, a nomogram including the significant risk factors was established to predict the probability that women with a thin endometrium could have an EMT >7.5 mm in the subsequent frozen cycle (Fig. 1). The final score was calculated using the following variables: hysteroscopic adhesiolysis history (with or without); PCOS (with or without); application of clomiphene (with or without); ovarian stimulation protocol and endometrial preparation protocol. The influence of variables on the outcome is represented in the form of coordinate axes, and points are assigned according to the predicted importance of variables. For example, the combination nomogram in Figure 1 assigns to each variable (hysteroscopic adhesiolysis history, PCOS, application of clomiphene in ovarian stimulation process, ovarian stimulation protocol and endometrial preparation protocol) a unique point value that represents its prognostic significance. Accumulate the points of each variable and located them on the “total points” line. Next, the individual probability of EMT >7.5 mm is obtained by projecting a vertical line from the “total points” line to the predicted probability bottom scale.

Validation and evaluation of the model

Discrimination

The predictive model showed an AUC of 0.76 (95% CI: 0.722–0.797) in the modeling cohort (Figure 2A). The AUC of the ROC curve was 0.71 (95% CI: 0.66–0.76) in the validation cohort (Figure 3A). Discrimination performed well in both the modeling and validation cohorts.

Calibration

The calibration curves demonstrated a good consistency between the predicted probabilities of EMT >7.5 mm in the frozen cycle for women with a thin endometrium and actual probabilities in both modeling and validation cohorts (Figure 2B & Figure 3B). The goodness-of-fit test (H–L test) showed no significant miscalibration (P = 0.57 in the modeling cohort and P = 0.29 in the validation cohort).

Discussion

The EMT is an effective means of predicting endometrial receptivity, and patients with a thin endometrium were associated not only with lower pregnancy outcomes [3] but also with higher perinatal and neonatal risks [16]. We defined a thin endometrium in this study as EMT ≤ 7.5 mm on hCG trigger day which is the threshold commonly used in the literature [2, 9, 16].

Some studies have pointed out that the pregnancy rate of patients with an EMT of 7–8 mm is lower than that of patients with an EMT > 8 mm in FET cycle [17]. According to Liu et al., the pregnancy rates decline as the EMT decreases below 7 mm in FET cycles [18]. The etiology of thin endometrium is complicated, mainly including endocrine disorder and endometrial injury caused by various reasons, as well as age factors and idiopathic thin endometrium. The main pathophysiological features of thin endometrium are: poor growth of glandular epithelium, high blood flow impedance of uterine radial artery, decreased expression of vascular endothelial growth factor and poor vascular development [19]. Thin endometrium affect pregnancy outcomes, may be associated with the local high oxygen concentrations near the endometrial basal layer. The endometrial oxygen tension is mainly affected by the uterine spiral arteries. When the basal layer is thin or absent, the implanting embryo is much close to the spiral artery and the high vascularity and oxygen concentrations near the basal endometrium, compared with the normal endometrial surface with low oxygen tension [20]. However, some scholars believe that there is no obvious correlation between EMT and pregnancy rates, or there is only a correlation when EMT is combined with other relevant parameters for statistical analysis [21]. Gingold et al. [22] suggested that endometrial pattern, rather than endometrial thickness, affects the pregnancy outcomes. EMT is not the only factor that affects endometrial receptivity, but it is one of the main factors. Thin endometrium may reduce the implantation rate of the embryo, thus adversely affecting the pregnancy outcomes. Our study found that women with EMT ≤ 7.5 mm on hCG trigger day, if the EMT increased to 7.5 mm during the subsequent FET cycle, the pregnancy outcomes of them were better than that of women whose EMT cannot reach 7.5 mm on FET cycle. This is a summary of our central data and a supplement to previous studies. Our data show that if the EMT of patients with thin endometrium can be increased to 7.5mm during FET cycle, the pregnancy outcomes can be improved.

To the best of our knowledge, the nomogram we developed here is the first to predict the probability of an EMT > 7.5 mm in the subsequent frozen cycle for women with a thin endometrium. In our analysis of 628 thin endometrial patients who adopted the “freeze all” strategy, we found that the absence of a hysteroscopic adhesiolysis history, and the presence of PCOS, the application of clomiphene in the ovarian stimulation process, and the application of a GnRH agonist short protocol, mild stimulation protocol, natural cycle protocol for ovarian stimulation, and natural cycle for endometrial preparation in the next frozen cycle increased the possibility of EMT > 7.5 mm in the subsequent frozen cycle. The AUC of the predictive model was 0.76, denoting good discrimination. The model was tested on an independent validation cohort of 454 patients, and also showed a good discriminative capacity (AUC 0.71). Additionally, the model calibrated well in both the modeling and validation cohorts.

Our nomogram is a user-friendly graphical model based on clinically significant characteristics. We predict that it will help determine whether it is necessary to cancel the fresh cycle and freeze the embryo for endometrial preparation to obtain an EMT of ≥7.5 mm in patients undergoing IVF/ICSI treatment when the EMT ≤ 7.5 mm on HCG trigger day. Our model could also provide individualized and targeted consultations for patients with a thin endometrium.

We screened a number of characteristics that might affect endometrial growth (Table 1), and identified those for MLR analysis by preliminary screening through univariate logistic regression analysis combined with a study of the literature and clinical experience. Stepwise backward variable selection was used to determine independent predictors, which identified five meaningful variables: hysteroscopic adhesiolysis history, PCOS, application of clomiphene in ovarian stimulation process, ovarian stimulation protocol, and endometrial preparation protocol.

Repeated or severe intrauterine operation will cause damage to endometrium. For example, when performing curettage, surgical instruments will directly contact endometrium. Improper operation hurts basal layer and muscular layer of the endometrium, which may result in intrauterine adhesions (IUAs). Due to the limited repairment of the endometrium, scar wound is formed, which will eventually lead to local or complete occlusion of the uterine cavity, and develop into thin endometrium [23]. With the development of hysteroscopic technology, hysteroscopic adhesiolysis has become the standard method for the treatment of IUAs. Patients with intrauterine adhesions are only allowed to undergo IVF/ICSI after hysteroscopic adhesiolysis and re-examination of hysteroscopy indicate that the uterine cavity morphology has returned to normal. In patients with IUAs, the morphology of the uterus may be restored by hysteroscopic adhesiolysis, but the function of the endometrium may not be completely restored. Our study found that patients with thin endometria who have a history of IUAs were less likely to have an EMT > 7.5 mm in the frozen cycle. If the patient’s endometrium is “hypotrophic” because of the IUA history, they can try direct fresh embryo transfer. Interestingly, we found that thin endometrial women with PCOS were significantly more likely to have an EMT > 7.5 mm in the following frozen cycle versus thin endometrial women without PCOS. The “freeze all” strategy was originally proposed for patients with PCOS [24]. Frozen embryo transfer can recover the ovary from ovarian stimulation and the exposed

endometrial lining may also be shed, providing a new starting point for both. For thin endometrial women with PCOS, frozen embryo transfer may obtain a thicker endometrium and reduce the risk of OHSS.

During IVF/ICSI, clomiphene can promote the growth of ovarian follicles, resulting in auxiliary stimulation. However, clomiphene is a selective estrogen receptor modulator that exhibits both estrogenic agonist and estrogenic antagonist activities at the endometrial level, thereby affecting endometrial thickness and receptivity [25, 26]. Based on our findings, we recommend frozen embryo transfer for patients with thin endometria receiving clomiphene for ovarian stimulation to allow the endometrial lining to grow and possibly thicken. Another factor influencing the probability of EMT > 7.5 mm in the frozen cycle is the ovarian stimulation protocol. In our study, the applications of a GnRH agonist short protocol, mild stimulation protocol, and natural cycle protocol were associated with an increased probability of EMT > 7.5 mm in the frozen cycle compared with a GnRH agonist long protocol. This may be related to the clomiphene applied in the mild stimulation protocol.

The type of endometrial preparation protocol most suitable for patients with a thin endometrium is controversial. We found that a natural cycle was more likely to be associated with an EMT > 7.5 mm for thin endometrial women during frozen embryo transplantation compared with those using programmed and minimal ovarian stimulation cycles. Some studies [27–29] reported that pregnancy outcomes and the endometrial thickness of patients with a natural cycle were significantly higher than in those with a programmed cycle, and that the decrease in clinical pregnancy rate in those with a programmed cycle may be related to endometrial receptivity damage and early closure of the “implantation window”. However, it is noteworthy that the populations of these studies include patients with a thin endometrium but are not restricted to them. Another study [30] identified no difference in pregnancy outcome between patients with a natural and programmed cycle. Additionally, Zheng et al. [31] found that embryo implantation and clinical pregnancy rates of thin endometrial patients with a programmed cycle were significantly higher than in those with a natural cycle, suggesting that the programmed cycle is more suitable. However, there was no difference in endometrial thickness between the two groups.

Our predictive model can evaluate the probability of EMT > 7.5 mm in frozen embryo transfer for each patient with a thin endometrium. Our study found that when the EMT of patients with a thin endometrium increased to 7.5mm during the frozen embryo transfer cycle, the pregnancy outcomes were better. Therefore, our nomogram could help clinicians refer patients with a thin endometrium either to receive fresh embryo transfer directly or to adopt a “freeze all” strategy for frozen embryo transfer. Of course, the application of a “freeze all” strategy needs to consider many factors, and our findings only provide advice at the endometrial level. However, our model cannot be used to predict pregnancy outcomes, and further research is needed. Our study is also limited by its retrospective nature that cannot exclude all potential biases, and the fact that the conclusions should be further tested in a randomized controlled study. Additionally, our study only included data from one reproductive center, and there were no independent verification cohorts from other hospitals.

Conclusions

In conclusion, our study resulted in a well-calibrated model. We conclude that in women with a thin endometrium (EMT ≤ 7.5 mm on HCG trigger day), the absence of a hysteroscopic adhesiolysis history, and the presence of PCOS, the application of clomiphene in the ovarian stimulation process, the application of a GnRH agonist short protocol, mild stimulation protocol, natural cycle protocol, and natural cycle for endometrial preparation are prognostic for an increased possibility of EMT > 7.5 mm in the subsequent frozen cycle.

Abbreviations

EMT: endometrial thickness

HCG: human chorionic gonadotropin

IVF: in vitro fertilization

ICSI: intracytoplasmic sperm injection

aOR: adjusted odds ratio

GnRH: gonadotrophin-releasing hormone

OHSS: ovarian hyperstimulation syndrome

MLR: multivariable logistic regression

VIF: variance inflation factor

AUC: the area under the curve

H-L test: Hosmer–Lemeshow test

PCOS: polycystic ovary syndrome

IUA: intrauterine adhesion

Declarations

Ethical approval

This retrospective study was approved by the institutional review board of the Center for Reproductive Hospital Affiliated to Shandong University.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contributions

ZG and LY planned and designed the study. YW, XX and LZ were responsible for data acquisition. WC and RC analyzed and interpreted the data. JM and ZG were primarily responsible for writing the paper. All authors were involved in drafting and revising the manuscript, and all authors approved the final report.

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Tables

Table 1 General characteristics of thin endometrial women included in this study

	Total n=1082	Modeling cohort n=628	Validation cohort n=454
Age; (years)	33.38±5.34	33.21±5.41	33.61±5.24
BMI; (kg/m2)	23.58±3.40	23.30±3.36	23.96±3.42
Duration of infertility; (years)	3.69±2.94	3.75±2.99	3.61±2.89
Primary infertility; n (%)	351(32.4)	238(37.9)	113(24.9)
Cause of infertility			
Tubal; n (%)	794(73.4)	467(74.4)	327(72.0)
Male; n (%)	112(10.4)	70(11.1)	42(9.3)
Multiple causes; n (%)	65(6.0)	61(9.7)	4(0.9)
Unexplained; n (%)	11(1.0)	5(0.8)	6(1.3)
Other; n (%)	100(9.2)	25(4.0)	75(16.5)
Endometriosis; n (%)	54(5.0)	31(4.9)	23(5.1)
PCOS; n (%)	212(19.6)	112(17.8)	100(22)
History of tuberculosis; n (%)	47(4.3)	28(4.5)	19(4.2)
History of hysteroscopic adhesiolysis; n (%)	207(19.1)	99(15.8)	108(23.8)
Induced abortion; n (%)			
0 previous induced abortion	734(67.8)	470(74.8)	264(58.1)
1 previous induced abortion	254(23.5)	103(16.4)	151(33.3)
≥2 previous induced abortion	94(8.7)	55(8.8)	39(8.6)
Medical abortion; n (%)			
0 previous medicine abortion	941(87.0)	543(86.5)	398(87.7)
1 previous medicine abortion	94(8.7)	55(8.8)	39(8.6)
≥2 previous medicine abortion	47(4.3)	30(4.8)	17(3.7)
Basic FSH; IU/liter	7.38±3.76	7.22±3.39	7.61±4.22
TSH; n (%)			
2.5 mU/L	695(64.2)	402(64.0)	293(64.5)
≥2.5 mU/L	387(35.8)	226(36.0)	161(35.5)

PRL; n (%)			
30 ng/ml	1025(94.7)	589(93.8)	436(96.0)
≥30 ng/ml	57(5.3)	39(6.2)	18(4.0)
Ovarian stimulation protocol			
GnRH agonist long protocol	351(32.4)	211(33.6)	140(30.8)
GnRH agonist short protocol	281(26.0)	171(27.2)	110(24.2)
GnRH antagonist protocol	223(20.6)	114(18.2)	109(24.0)
Mild stimulation protocol	184(17.0)	104(16.6)	80(17.6)
Natural cycle protocol	43(4.0)	28(4.5)	15(3.3)
Application of clomiphene; n (%)	128(11.8)	85(13.5)	43(9.5)
Total gonadotropin dose; IU	1833.19±1022.16	1732.71±939.78	1972.16±1112.41
Days of stimulation	9.65±3,14	9.88±3.30	9.33±2.85
Oestradiol level on HCG trigger day; (pg/ml)			
1000; n (%)	163(15.1)	79(12.6)	84(18.5)
1000-2000; n (%)	216(20.0)	123(19.6)	93(20.5)
2000-3000; n (%)	174(16.1)	102(16.2)	72(15.9)
3000; n (%)	529(48.9)	324(51.6)	205(45.2)
Number of oocytes; (n)	10.76±7.90	11.06±7.79	10.34±8.04
Number of embryos; (n)	3.68±3,20	3.77±3.18	3.56±3.23
Protocol of endometrial preparation			
Natural cycles	418(38.6)	236(37.6)	182(40.1)
Programmed cycles	433(40.0)	239(38.1)	194(42.7)
Minimal ovarian stimulation	231(21.3)	153(24.4)	78(17.2)
EMT on frozen embryo-transfer day > 7.5mm	487(45.0)	297(47.3)	190(41.9)

BMI: body mass index; PCOS: polycystic ovary syndrome; FSH: follicle stimulating hormone; TSH: thyroid stimulating hormone; PRL: prolactin; GnRH: gonadotrophin-releasing hormone;

HCG: human chorionic gonadotropin; EMT: endometrial thickness.

Table 2 The pregnancy outcomes of thin endometrial women included in this study based on endometrial thickness.

Pregnancy outcomes	EMT≤7.5mm n=595	EMT>7.5mm n=487	*P*-value
Live birth rate; n (%)	172(28.9)	174(35.7)	0.017*
Clinical pregnancy rate; n (%)	231(38.8)	227(46.6)	0.010*
Biochemical pregnancy rate; n (%)	280(47.1)	273(56.1)	0.003*

EMT: endometrial thickness.

*p <.05

Table 3 Adjusted odds ratios of endometrium > 7.5 mm in frozen cycles for thin endometrial women by multivariate analysis of predictor variables

Predictor variable	aOR (95% CI)	*P*-value
History of hysteroscopic adhesiolysis		
Without	1	
With	0.186(0.101-0.341)	0.001*
PCOS		
Without	1	
With	2.363 (1.405-3.973)	0.001*
Application of clomiphene		
Without	1	
With	3.769(1.444-9.834)	0.007*
Ovarian stimulation protocol		
GnRH agonist long protocol	1	
GnRH agonist short protocol	1.636(1.035-2.586)	0.035*
GnRH antagonist protocol	1.019(0.612-1.695)	0.943
Mild stimulation protocol	2.786(1.179-6.582)	0.020*
Natural cycle protocol	11.838(3.741-37.460)	0.001*
Endometrial preparation protocol		
Natural cycle	1	
Programmed cycle	0.587(0.378-0.910)	0.018*
Minimal ovarian stimulation	0.423 (0.260-0.688)	0.001*

PCOS: polycystic ovarian syndrome; GnRH: gonadotrophin-releasing hormone;

*p <.05

Figures

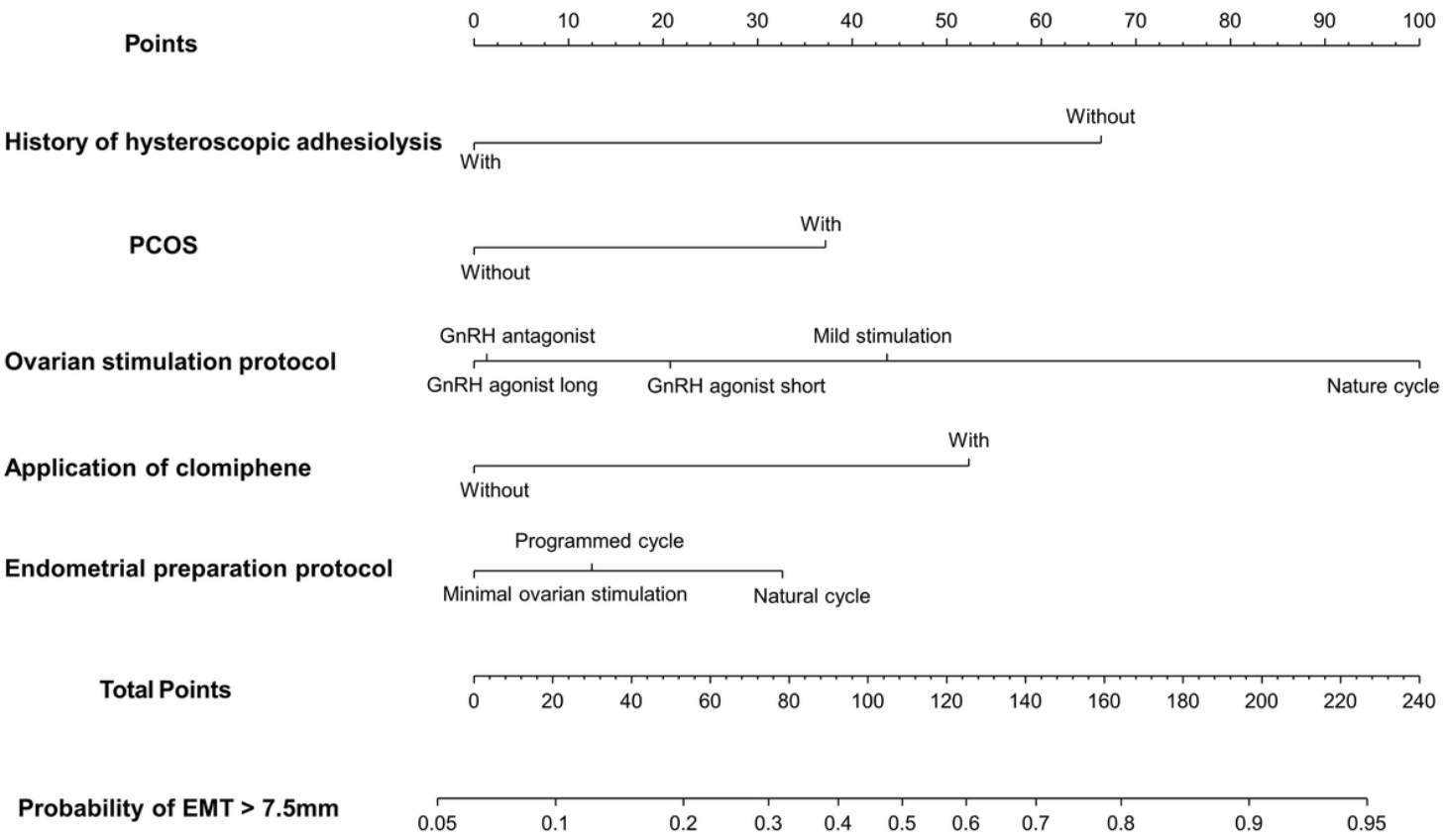

Figure 1

The combination nomogram to predict endometrial thickness (EMT) >7.5 mm in frozen cycles for thin endometrial women, combining hysteroscopic adhesiolysis history, PCOS, application of clomiphene in ovarian stimulation process, ovarian stimulation protocol and endometrial preparation protocol. Accumulate the points of each variable and located them on the “total points” line. Next, the individual probability of EMT >7.5 mm is obtained by projecting a vertical line from the “total points” line to the predicted probability bottom scale.

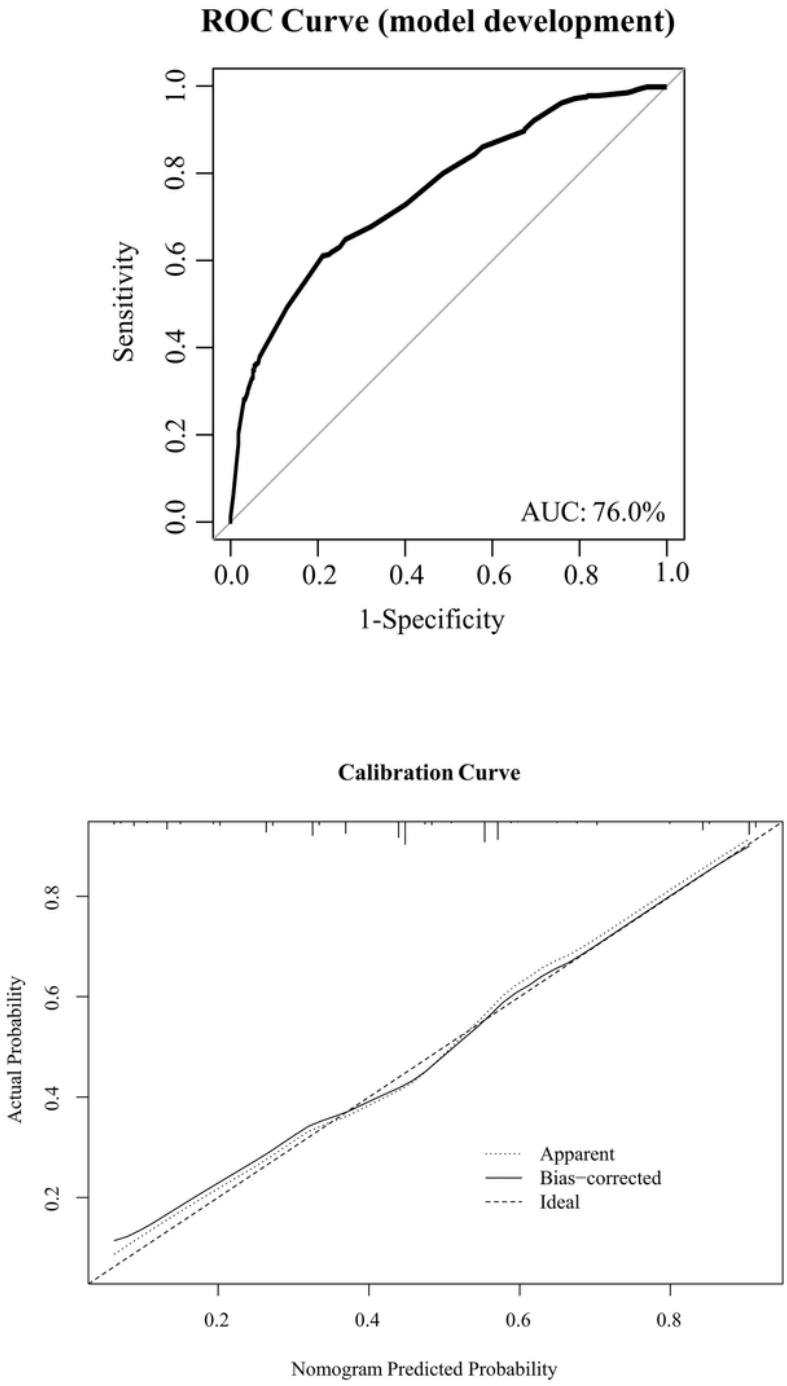

Figure 2

Discrimination and validation of the modeling cohort. A. ROC curve of the modeling cohort, and the AUC of the predictive model was 0.76 (95% CI: 0.722-0.797). B. Calibration for the modeling cohort. No difference observed between the predicted and the actual probabilities (P = 0.57).

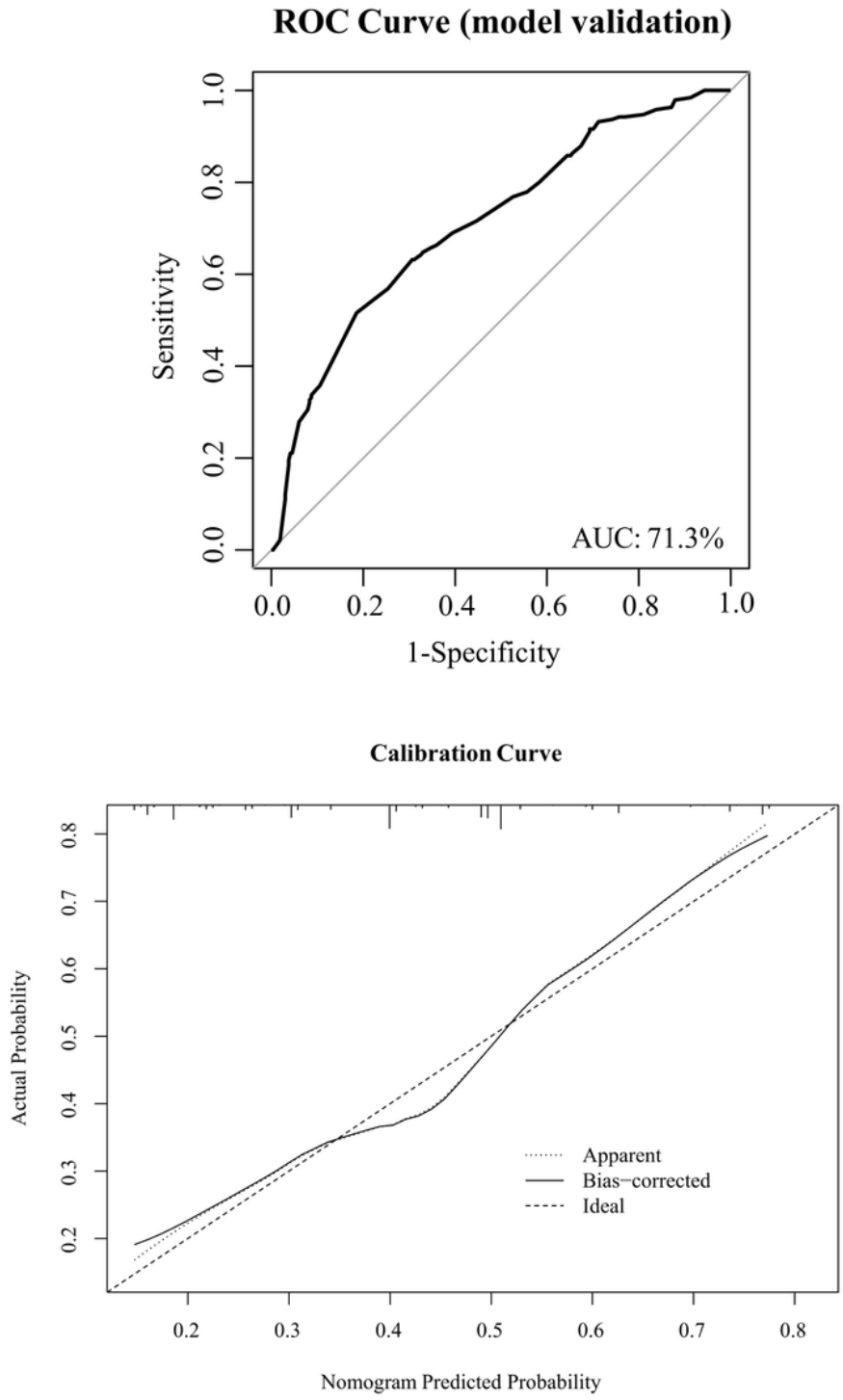

Figure 3

Discrimination and validation of the validation cohort. A. ROC curve of the validation cohort, and the AUC of the predictive model was 0.71 (95% CI: 0.664-0.759). B. Calibration for the validation cohort. No difference observed between the predicted and the actual probabilities (P = 0.29).