

A Validated Model for Individualized Prediction of Live Birth in Patients With Adenomyosis Undergoing Frozen-Thawed Embryo Transfer

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Abstract

Background

There is few predictive tools for live birth in women with adenomyosis, which provide further personalized and clinically specific information related to individualized decisions making during IVF/ICSI treatment.

Methods

A total of 424 patients with adenomyosis underwent frozen-thawed embryo transfer (FET) from Jan 2013 to Dec 2019 at a public university hospital were included. The patients were randomly divided into training (n = 265) and validation (n = 159) samples for the building and testing of the nomogram, respectively. Multivariate logistic regression (MLR) was developed on the basis of clinical covariates assessed for their association with live birth.

Results

In all, 183 (43.16%) patients became pregnant, and 114 (26.88%) had a live birth. In the multivariable analysis of the training cohort, probability of live birth was significantly correlated with the age < 37 years old (odds ratio [OR], 3.465; 95% CI, 1.215–9.885, P = 0.020), uterine volume prior ET < 102.02 cm³ (OR, 8.141; 95% CI, 2.170–10.542; P = 0.002), blastocyst transfer (OR, 3.231; 95% CI, 1.065–8.819, P = 0.023), twin pregnancy (OR, 0.328; 95% CI, 0.104–0.344, P = 0.005) and protocol in FET (P < 0.001). The statistical nomogram was built based on the five variates, age, uterine volume prior embryo transfer, twin pregnancy, stage of transferred embryo and protocol of FET, with an area under the curve (AUC) of 0.837 (95% confidence interval: 0.741–0.910) for the training cohort. The AUC for the validation cohort was 0.737 (95% confidence interval: 0.661–0.813), showing a satisfactory goodness-of-fit and discrimination ability in this nomogram.

Conclusions

Single blastocyst transfer, GnRH-a pretreated and smaller uterine size before embryo transfer contributed to increasing live birth rate in patients with adenomyosis. The user-friendly nomogram built on the risk factors of live birth in patients with adenomyosis, provides a useful guide for medical staff on individualized decisions making during the IVF/ICSI procedure.

Background

Adenomyosis is a common gynecological disorder where endometrial glands and stroma surrounded by hyperplastic smooth muscle were found within the myometrium [1, 2]. It affects up to 24.4% in infertile women, which represents a clinical issue associated with pelvic pain, excessive vaginal bleeding,

enlarged uterus and infertility [3, 4]. Adenomyosis has been reported to adversely impact fertility via abnormal uterine contractility, including altered endometrial function and receptivity, and impaired implantation [5]. Besides, patient with adenomyosis was also linked with poor obstetrical outcomes including preeclampsia, placental malposition, preterm delivery and preterm premature rupture of membrane [6–8].

Assisted reproduction technology (ART), including *in vitro* fertilization (IVF) and intracytoplasmic sperm injection (ICSI), is extensively being used for managing adenomyosis related infertility. ART results, however, vary according to reports, with some showing identical outcome as in patients without adenomyosis and others presenting increased miscarriage and lower clinical pregnancy rate[1]. Several studies provided evidences that enlarged uterus in adenomyosis had an adverse impact on pregnancy outcomes by the morphological and functional pathological changes [9, 10]. In addition, results from some trials on adenomyosis showed that applying gonadotrophin-releasing hormone agonists (GnRH-a) before IVF/ICSI cycle exert positive effects on increasing clinical pregnancy rate in patients with adenomyosis [11–13]. The success for a patient with adenomyosis - associated infertility in IVF/ICSI procedure to achieve pregnancy depend on a number of factors. Although several scoring systems have been published to evaluate the pregnancy rate after IVF/ICSI in infertile patients, current guidelines are based on general rather than individual clinic data. Despite the availability of these models, few of them are applicable for patients with adenomyosis and cannot evaluate the chances of live birth for individual adenomyosis patient. In this aspect, setting up of a predictive calculation model in live birth with a combination of all the risk factors in patients with adenomyosis will be beneficial for medical staff in the decision-making process and promoting adherence to medication through risk informed counselling.

The aim of the current study was, therefore, to develop a nomogram model on retrospective data analysis to predict the probability of live birth for patients with adenomyosis.

Patients And Methods

Data sources

Women diagnosed as adenomyosis undergoing frozen-thawed embryo transfer during 2013 and 2019 at Sun Yat-Sen Memorial Hospital, Guangzhou, China, were screened for this retrospective cohort study. Patients were included if they had received their first frozen-thawed embryo transfer (FET) cycle with autologous embryos. Exclusion criteria included congenital uterine malformation (unicornuate, bicornuate, septate uterus), intrauterine adhesion, uterine malformation, leiomyoma. Couples who received a preimplantation genetic screening or underwent preimplantation genetic diagnosis were excluded. Indications for IVF/ICSI included the tubal factor, male factor and immunity factor. Demographic data on age, body mass index (BMI), infertility duration, basal sexual hormone levels (tested on day 2-3 of menstrual cycle), uterine volume prior to embryo transfer (ET) (long diameter × width diameter × anteroposterior diameter × $\pi / 6$) [14], type of adenomyosis (diffusion or focal), endometrial thickness, protocol of FET were obtained from the clinical database.

The diagnosis of adenomyosis was ascertained by detailed chart review, including visit notes, ultrasound and operative reports, as well as pathology reports. The diagnosis was defined with two or more transvaginal sonographic criteria included heterogeneous myometrial area, globular asymmetric uterus, irregular cystic spaces, myometrial linear striations, poor definition of the endometrial-myometrial junction, myometrial anterior-posterior asymmetry, thickening of the anterior and posterior myometrial wall, and increased or decreased echogenicity [15, 16]. All identified adenomyosis cases were confirmed by two experienced sonographers. Diffuse adenomyosis was defined as outer myometrium extensive disease with endometrial glands and stroma scattered throughout the uterine musculature and focal adenomyosis included adenomyoma, was defined as grossly circumscribed adenomyotic masses within the myometrium [9, 17].

Frozen thawed embryo transfer procedure

FET was performed through a natural cycle (NC) or through hormone replacement therapy (HRT) cycles with endometrial preparation by exogenous estrogen and progesterone, or through the cycle adding gonadotrophin-releasing hormone agonists (GnRH-a) before estradiol. Among the patients with GnRH agonist pre-treatment, long-acting GnRH-a were administered of up to three injections of 3.75mg of triptorelin acetate (Ipsen Pharma Biotech, France)[18]. No more than two embryos were transferred. The luteal supported phase was administered by vaginal administration of micronized progesterone (400 mg/day). Pregnancies were diagnosed by an increasing concentration of serum β -hCG, which was tested 14 days after embryo transfer[18]. Clinical pregnancies were confirmed by the presence of the gestational sac on vaginal ultrasound examination during the fifth week. Twin pregnancy was confirmed by ultrasound examination during the twelfth week. A live birth is defined as any live born baby after 24th week of pregnancy.

Data analysis

Statistics with Gaussian distribution were presented as mean \pm SD and categorical variables were described as absolute frequencies (Table 1). Youden Index was used to determine the optimal cut-off point of the uterine volume related to live birth. External validation was chosen in the study so that patients enrolled were divided into a training set (n = 265) and validating set (n = 159) by the sampling techniques of random numbers. Statistical analyses were performed using the STATA 14.0 MP software and Regression Modeling Strategies (RMS, R version 3.6.3). For the nomogram establishment and the AUC measurements, we used the “regplot”, “pROC” and “rms” in R software[19]. Differences between groups were compared using Student’s *t*-test or Chi-squared test as appropriate.

Development and validation of the model

The training cohort of 265 patients was used to develop the nomogram for predicting patient-specific the probability of live birth in women with adenomyosis. The end-point of the study was live birth rate after FET cycles. Backward variable selection was performed to determine independent covariates. Multivariate analysis was performed using the logistic regression model and including the variables that

were significant at univariate analysis ($P < 0.05$). (Table S1). Coefficient for each independent covariates and the constant were generated in the equation by MLR analysis [20]. Variables entered into the nomogram model were age, uterine volume, stage of transferred embryo, twin pregnancy, and protocol of FET in the study. Values for each of the model covariates were mapped to points on a scale ranging from 0 to 100 and the total points obtained for each model corresponded to the probability of a live birth[19].

The model was applied to data from a sample of 159 patients (validating set) for external validation with a bootstrapping technique to obtain relatively unbiased estimates (1000 repetitions). The bootstrapping method is based on resampling obtained by randomly drawing data and replacing them with samples from the original dataset[21]. The predictive accuracy of the models was measured using the average optimism of the area under the curve (AUC). A precise prediction model would result in a plot where the observed and predicted probabilities fall along the diagonal [19].

Results

Description of the study population

A total of 424 patients with adenomyosis underwent frozen-thawed embryo transfer from January 2011 to December 2019 were identified as eligible and were analyzed in this study. In all, 183 (43.16%) patients became pregnant, and 114 (26.88%) had a live birth. Patients were divided into a training set and validation set by the sampling techniques of random numbers. The model was built from a training cohort of 265 patients and was validating on an independent validation cohort of 159 patients. Epidemiological, clinical, biological demographics and therapeutic strategies of the training and validation cohorts are summarized in Table 1. No significant difference was observed in the patients' characteristics between the two cohorts. 79 patients (29.81%) had live birth in the training cohort while 35 patients (22.01%) had live birth in the validation cohort.

Logistic regression analysis revealed blastocyst transfer, small uterine size and GnRH-a pretreated prior to FET improved live birth, but twin pregnancy negatively impacted live birth.

The optimal cut-off point of the uterine volume prior ET related to live birth was 102.02 cm^3 (AUC = 0.603, $P = 0.003$) according to the Youden Index. Table S1 summarizes univariable and Multivariable analysis. According to univariable logistic regression analysis, live birth was significantly correlated with age ($P = 0.018$), uterine volume prior ET $< 102.02 \text{ cm}^3$ ($P < 0.001$), twin pregnancy ($P < 0.001$), stage of transferred embryo ($P = 0.012$) and protocol in FET ($P < 0.001$). In the MLR analysis of the training cohort, probability of live birth was significantly correlated with the age < 37 years old (odds ratio [OR], 3.465; 95% CI, 1.215-9.885, $P = 0.020$), uterine volume prior ET $< 102.02 \text{ cm}^3$ (OR, 8.141; 95% CI, 2.170 - 10.542; $P = 0.002$), blastocyst transfer (OR, 3.231; 95% CI, 1.065 - 8.819, $P = 0.023$), twin pregnancy (OR, 0.328; 95% CI, 0.104-0.344, $P = 0.005$) and protocol in FET ($P < 0.001$) (Fig. 1). Blastocyst transfer, small uterine size and GnRH-a pretreated were associated with an increased the probability of live birth but twin pregnancy decreased the probability.

Development of the models from the training cohort

On the basis of the univariable and multivariable logistic regression analysis we performed, a nomogram incorporating the significant risk factors was established to predict the probability of live birth (Fig. 2). A total score was calculated using age, stage of transferred embryo, uterine volume, twin pregnancy and protocol of FET. The equation describing the probability of live birth was: $P = 1/(1 + \exp(-X))$, where $X = 0.4755302 + 0.1091108 \times V1 + 0.0882141 \times V2 - 0.3309371 \times V3 + 0.1281561 \times V4 + 0.2339871$, where $V1$ was age (1 if < 37 y and 0 if ≥ 37 y), $V2$ blastocyst transfer (0 if no and 1 if yes), $V3$ twin pregnancy (1 if no and 0 if yes) and $V4$ protocol of FET (2 if GnRH-a HRT, 1 if NC, 0 if HRT), $V5$ uterine volume (1 if $< 102.02 \text{ cm}^3$, 0 if $\geq 102.02 \text{ cm}^3$). The nomogram derived from this equation is reported in Fig. 2.

Validation of predictive accuracy

No significant difference was observed between the predicted probability obtained from the bootstrap correction and the actual probabilities of live birth ($P = 0.186$), which implied that the nomogram was well calibrated. The model demonstrated an AUC of 0.837 (95% confidence interval: 0.741 - 0.910) in the training cohort (Fig. 3A&B), which denoted good performance. The AUC of the receiver operating characteristic (ROC) curve in the validation set was 0.737 (95% confidence interval: 0.661 - 0.813), which indicated fair performance.

Discussion

On the basis of 424 infertile patients with adenomyosis underwent FET, we have first created a predictive nomogram tailored to the individual patient and capable of reliably generating numerical probabilities of live birth. The nomogram was developed in a training cohort including 265 patients and tested on an external independent validation cohort including 159 patients. Both calibration and discrimination were used to evaluate the performance. This graphical tool is simple and straightforward calculator, integrating five predictive variables that was easily accessible during ART treatment constituting of age, uterine volume, protocol of FET, type of pregnancy and stage of transferred embryo. Moreover, this model firstly integrated the potential risks in fetal loss of patient with adenomyosis into one graphical calculator, which is of particular interest for clinicians to make an informed decision on the timing and protocol of FET, stage and number of embryos to transfer.

Enlarged uterus in patients negatively impacted the live birth rate as revealed by MRL in our study. Endometrial tissues within the myometrium induce hyperplasia and hypertrophy of the adjacent smooth muscle resulted in uterus enlargement which is considered as an important feature of adenomyosis[10]. Morphological and functional pathological changes caused by hyperplasia and hypertrophy of the adjacent smooth muscle weaken the scalability and coordination of uterus, which adversely influence the patient's pregnancy and delivery procedure[1, 10, 22]. It's suggested that adenomyosis patient with an enlarged uterus suffered from high rate of miscarriage, preterm delivery and small-for-gestational age [10, 23]. In addition, Kim *et al.* indicated that preterm delivery in pregnant patients with adenomyosis can be

predicted through uterine wall thickness measurement in second trimester [22]. Recently, a retrospective study from Li *et al.* demonstrated that adenomyosis patients with larger uterine volume suffered lower live birth rate due to higher incidence of miscarriage [9]. A prospective study by Hawkins *et al.* also revealed that women with uterine lengths longer than 9 cm were more likely to experience spontaneous abortions [24]. Consistently, uterine volume larger than 102.02 cm³ was associated with a lower live birth rate in our study. Therefore, the use of uterine volume as a significant determinant factor in pre-pregnancy examinations should never be ignored. Routine checks for uterine size during ART treatment are beneficial for detecting patients at an increased risk, so that proper protocol for subsequent FET can be chosen and preventive measures can be taken in early pregnancy.

GnRH-a pre-treatment in FET cycles significantly improved the live birth rate in our retrospective study. Consistently, several studies suggested that administration of GnRH agonist increased the implantation rate, clinical pregnancy rate, and ongoing pregnancy rate of patients with adenomyosis in FET cycles[11, 25]. Adenomyosis tissue contained estrogen, progesterone and androgen receptors, develops in an estrogen-dependent manner[26]. Administration of GnRH agonist can suppress the hypothalamic-pituitary axis resulting in a hypoestrogenic status and then suppress the proliferation of cells derived from the endometrium reducing the size of pathologic lesions in patients with adenomyosis[27, 28]. Moreover, the expression of aromatase cytochrome P450, a protein overexpressed in women with adenomyosis and catalyzed the conversion of androgen to estrogen, can be decreased by GnRH agonist[29]. Our results show that after adjustment for confounding factors, GnRH agonist pre-treatment is associated with increased live births in patients with adenomyosis in FET cycles. With the increasing use of embryo freezing-thawing, pretreatment with GnRH agonist is recommended for adenomyosis patients in FET cycles.

Patient age has been considered to be a significant prognostic factor in reproductive medicine and frequently involved in assessing the probability of a live birth or pregnancy [30]. Uterine adenomyosis mostly occurs in women over the age of 35 years old and the average age of patients included in our study was up to 34, which was associated with adverse pregnancy outcomes in this study.

Consistent with previously published studies[31, 32], our study showed that the increased live birth rate was significantly associated with blastocyst transfer than cleavage embryo transfer. Besides, twin pregnancy a well understood risk factor of adverse obstetric outcomes[33] was a strong collective factor in our model. Therefore, single blastocyst embryo transfer, which is highly recommended in ET cycles for its high live birth rate, is encouraged in patients with adenomyosis, especially those with enlarged uterus.

Still, some limitations of the present study have to be underlined. First, we could not avoid the measurement bias of uterine diameter induced by different operated clinicians. Second, diagnosis for adenomyosis relied on ultrasound results so that mild adenomyosis might have been misclassified. Third, the retrospective nature of the study cannot exclude all biases. Despite these limitations, our nomogram model to predict the live birth rate could be a useful tool in helping physicians and patients

with adenomyosis undergoing the IVF/ICSI procedure to decide on embryo-transfer option and to pay special attentions during prenatal visits.

Conclusion

In conclusion, an objective and accurate prediction nomogram model for live birth rate was drawn up and validated in infertility patients with adenomyosis. Relative risk assessment could be performed during infertility consultation and appropriate measures could be carried out in advance to minimize the probability of fetal loss. Furthermore, our results support the concept that pretreatment of GnRH-a for reducing lesion size before FET effectively increased the probability of live birth.

Abbreviations

BMI, body mass index; FSH, follicular stimulating hormone; E2, estrogen; T, testosterone; HRT, Hormone replacement therapy; FET, frozen-thawed embryo transfer; IVF/ICSI, in vitro fertilization/ intracytoplasmic sperm injection; ART, assisted reproductive technology; GnRH-a, gonadotrophin-releasing hormone agonists; hCG, human chorionic gonadotropin; LBR, live birth rate; ROC, receiver operating characteristic curves; SD, standard deviation; ORs, odds ratios; CI, confidence interval.

Declarations

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments. This study was approved by the ethical standards of the Ethics Committee of The Sun Yat-Sen Memorial Hospital of China (SYSEC-KY-KS-2020-127). Requirement for inform consent has been waived by the institutional ethics committee due to the retrospective nature of the study, and pseudonymization of data.

Consent to Participate

Not applicable

Consent for Publication

Not applicable

Availability of Data and Materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure of interests

The authors declare that they have no conflict of interest.

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Authors' contributions

QZ supervised the entire study, including the procedures, conception, design and completion of the study data, HL and CC revised the article. RY JL and XJ was responsible for the collection of data. YW contributed the data collection and analysis and drafted the article. All authors contributed to the article and approved the submitted version.

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Tables

Table 1. Patient characteristics in the training and the validation cohorts

Characteristics ^a	Training set n = 265	Validating set n = 159	<i>P</i>
Live birth, n (%)	79 (29.81)	35 (22.01)	0.080
Age, years	34.05 ± 4.79	34.26 ± 4.52	0.652
Infertility duration, years	4.27 ± 3.41	4.57 ± 3.91	0.196
BMI, kg/m ²	21.41 ± 2.82	21.14 ± 2.74	0.331
AMH, IU/L	3.07 ± 2.83	3.76 ± 3.37	0.195
FSH, IU/L	8.65 ± 3.77	7.98 ± 2.13	0.087
LH, IU/L	5.27 ± 2.68	5.34 ± 2.87	0.822
E2, pg/mL	53.33 ± 15.78	46.60 ± 12.07	0.285
T, ng/mL	0.43 ± 0.24	0.46 ± 0.26	0.723
Type of Adenomyosis, n (%)			0.721
Diffuse	173 (65.29)	103 (64.78)	
Focal	92 (34.71)	59 (35.22)	
Uterine diameters prior ET			
Width diameter	5.41 ± 1.14	5.38 ± 1.13	0.415
Anteroposterior diameter	5.21 ± 1.11	5.30 ± 1.11	0.808
Long diameter	5.56 ± 1.05	5.67 ± 1.09	0.300
Uterine volume	84.81 ± 40.66	87.66 ± 40.35	0.485
Stage of embryo transfer			0.107
Cleavage, n (%)	53(20.00)	22 (13.84)	
blastocyst, n (%)	212 (80.00)	137 (86.16)	
Protocol of FET			0.219
HRT	115 (43.40)	58 (36.48)	
GnRHa-HRT	104 (39.25)	76 (47.80)	
NC	46 (17.35)	25 (15.72)	
Endometrial thickness (mm)	9.87 ± 2.72	9.91 ± 2.62	0.889
Pregnancy type			0.193

No pregnancy	142 (53.58)	99 (62.26)
Singleton pregnancy, n (%)	71 (26.79)	37 (23.27)
Twin pregnancy, n (%)	52 (19.62)	23 (14.47)

Abbreviations: BMI, body mass index; AMH, anti-mullerian hormone; FSH, follicular stimulating hormone; E2, estrogen; T, testosterone; ET, embryo transfer; HRT, hormone replacement therapy; NC, nature cycle;

^a Continuous variable are expressed as mean ± standard deviation, SD, categorical variables as absolute frequencies, n (%). *P < 0.05 was considered statistically significant.

Figures

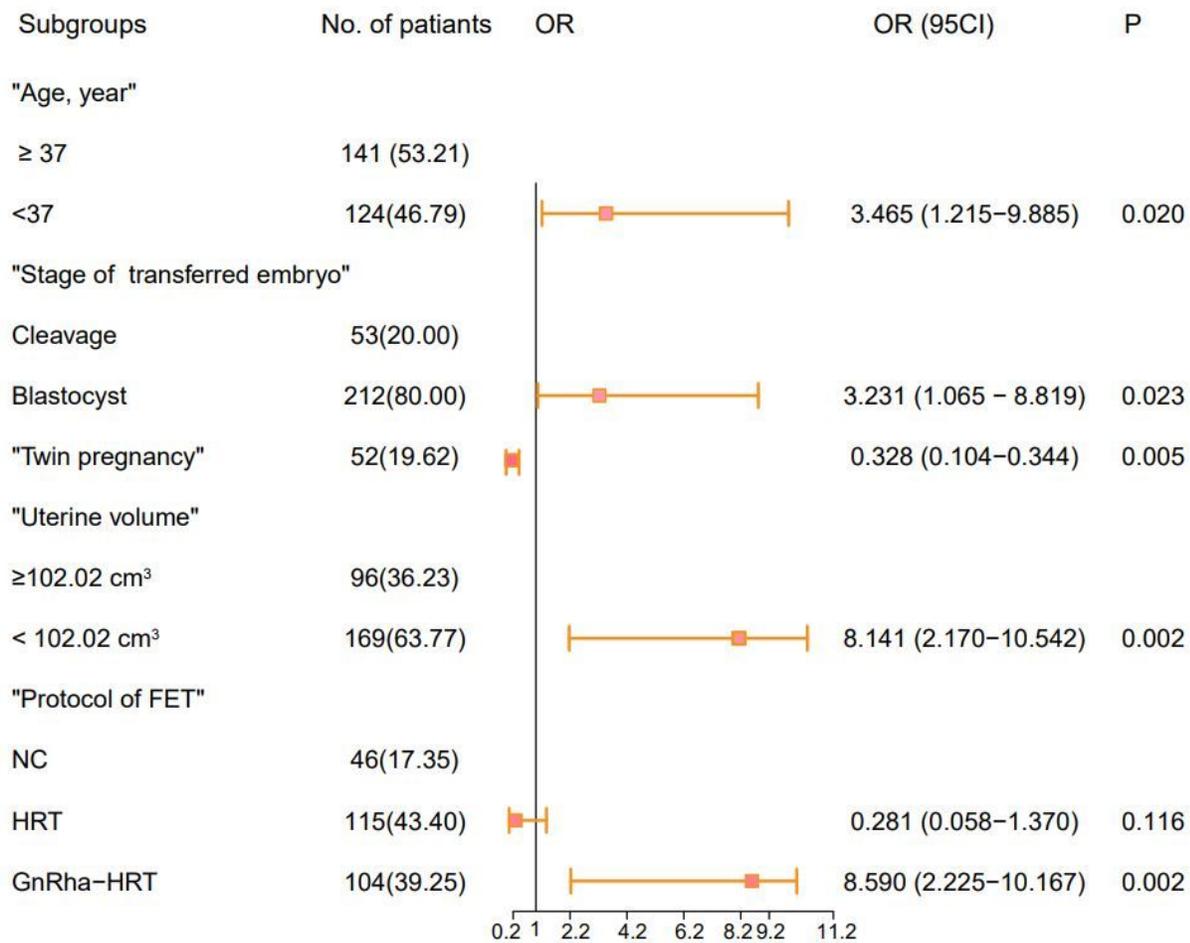


Figure 1

The Forest plot of predictive factors of live birth in Multivariable analysis of the training cohort. OR and 95% CI are presented to show the risk of predictive factors Abbreviations: FET, frozen-thawed embryo

transfer; OR, odds ratio; CI, confidence interval; *P < 0.05 was considered statistically significant

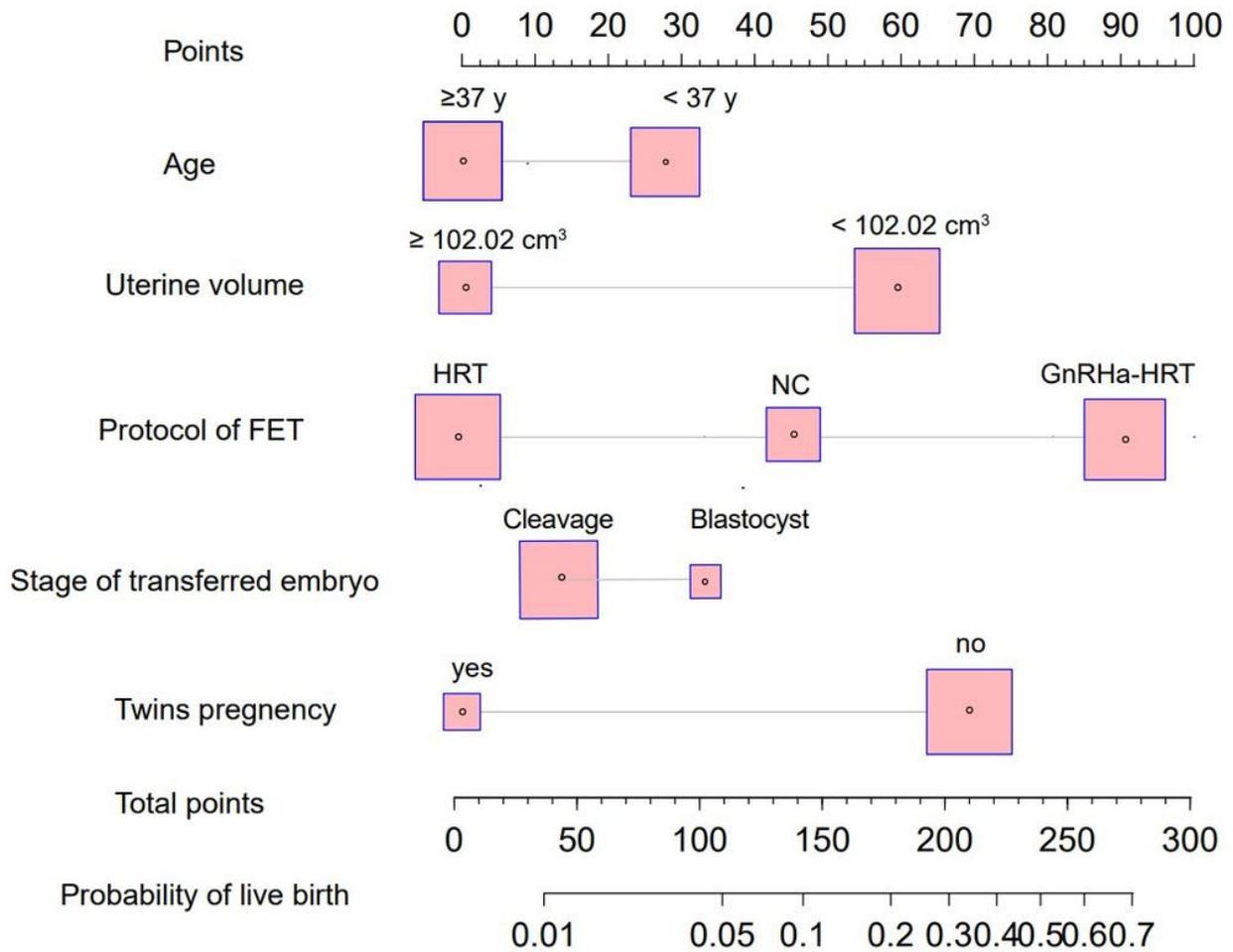


Figure 2

Nomogram to predict the probability of live birth in adenomyosis related infertility patients undergoing FET. The probability of a live birth is calculated by drawing a line to the point on the axis for each of the following variables: stage of transferred embryo, age, twin pregnancy, protocol of FET and uterine volume prior ET. The points for each variable are summed and located on the total points line. Next, a vertical line is projected from the total points line to the predicted probability bottom scale to obtain the individual probability of a live birth. Abbreviations: FET, frozen-thawed embryo transfer;

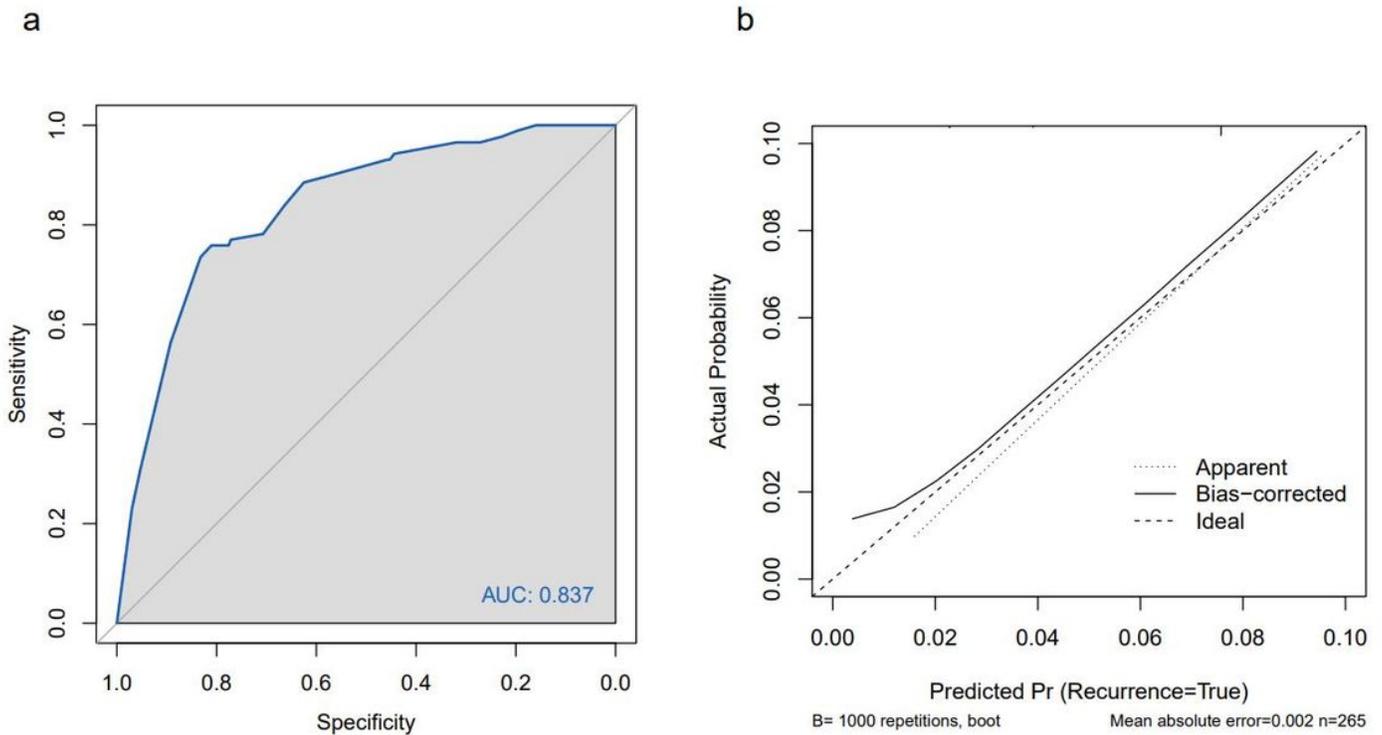


Figure 3

a: Discrimination for the training cohort. ROC curve of the model with an AUC of 0.837 (95% confidence interval: 0.741 - 0.910). b: Calibration of the nomogram to predict live birth in patients with adenomyosis undergoing FET Abbreviations: FET, frozen-thawed embryo transfer; CI, cervical insufficiency; ROC, Receiver Operating Characteristic Curve.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [TableS1.docx](#)