Postoperative pregnancy outcome prediction model based on 3-dimensional ultrasound for intrauterine adhesion

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Abstract

Objective: The aims of this study were to establish a mathematical model to predict intrauterine adhesion (IUA) prognosis based on 3-dimensional (3D) ultrasound. Design:Derivate retrospectively and validate prospectively. Setting: University affiliated hospitals Population: 668 IUA in the derivation cohort and 426 IUA in the validation cohort. Methods: Logistic regression analysis was used to develop prediction models to forecast the live birth rate following HA according to postoperative 3D-TVUS characteristics and hysteroscopy characteristics. The performance of each of the prediction models was compared by calculating the area under the curve (AUC). A nomogram was then constructed for the excellent model. Main Outcome Measures: General clinical information, 3D-TVUS characteristics and hysteroscopy characteristics. Results: Live birth was achieved by 242 IUA patients in the derivation cohort (n = 668) and by 150 in the validation cohort (n = 426). Logistic regression analysis revealed that the AUC for the models based on 3D-TVUS characteristics in the derivation and validation cohorts were 0.8506 and 0.8963, respectively, which was better than the models based on hysteroscopy characteristics. The calibration curve of the nomogram based on 3D-TVUS characteristics and a non-significant Hosmer–Lemeshow test statistic showed good calibration (P = 0.3064). Conclusion: Our findings indicate that postoperative 3D ultrasound characteristics could be predictive factors for live births among IUA patients and provide valuable reproductive guidance for women after HA.

Introduction

In China, the incidence of infertility has reached around 15%[1, 2]. Intrauterine adhesion (IUA) is one of the leading causes of miscarriage and infertility in women of childbearing age, the prevalence of which is showing an increasing trend[3]. IUA occurs secondary to trauma to the basal layer of the endometrium in a gravid or non-gravid uterus[4]. Adhesions form abnormal fibrous connections in which vascular channels join tissue surfaces resulting in partial or total uterine cavity obliteration. Hysteroscopic adhesiolysis (HA) aims to restore uterine cavity volume and morphology with the goal of increasing fertility potential[5]. Early diagnosis and treatment of IUA can improve live-birth rate [6, 7].

Three-dimensional transvaginal ultrasound (3D-TVUS) has recently been adopted in gynecology because it enables multiplanar displays that help visualize the 3 orthogonal scan planes and yields precise anatomical views of the uterine cavity, which, theoretically, may be beneficial for later diagnoses and predictions [8]. However, ultrasound imaging also presents unique challenges, such as low image quality resulting from noise and artifacts, a high dependence on operator or diagnostician experience, and high inter- and intra-observer variability across institutes and ultrasound systems [9]. Image preprocessing technology has recently been applied to medical images to analyze various anatomical facets, including those of the brain, heart, cardiovascular system, muscle, and nerve structure [10].

In this study, we used image preprocessing technology to process 3D-TVUS images and extract feature information. The general information and clinical characteristic data were collected and combined into a global information set and correlated with the live birth rate of IUAs following HA. From this evaluation, we propose using postoperative 3D ultrasound as a novel modality that is superior to existing methods as a predictor of live births in IUA.

Materials and methods

Patients

The Ethics Committee of the Third Xiangya Hospital of Central South University (Main research hospital) approved the study (IRB No. 21046) and ethics committees at Hunan Guangxiu Hospital and Jiangwan Reproductive & Genetic Hospital (Participating hospitals) have documented the study. All procedures were performed in accordance with relevant guidelines and regulations. After the procedure had been fully explained to all patients, willing participants provided their informed consent.

Patients with IUA who had undergone 3D-TVUS evaluation and then confirmed by hysteroscopy, were 20–40 years of age, had a strong desire to conceive, and had normal hormone concentrations and ovulation were eligible for inclusion in the study. Patients were excluded from the study if they had any of the following: cervical or endometrial malignancies; serious heart and liver conditions or renal insufficiency; serious nervous system diseases (and were unable to care for themselves in daily life or unable to undergo relevant treatment); or congenital malformation of the uterus. In addition, patients who were not suitable for surgery or unable to follow doctors' advice at review or follow-up were excluded.

In all, 668 patients with IUA who were newly diagnosed by 3D-TVUS and underwent HA at The Third Xiangya Hospital of Central South University between January 2018 and January 2019 were retrospectively enrolled as the derivation cohort. Between February 2019 and February 2020, 426 IUA patients were prospectively enrolled from Hunan Guangxiu Hospital and Jiangwan Reproductive and Genetic Hospital for external validation of the prediction model. All these IUA patients underwent 3D-TVUS 1 month after the "see and treat" hysteroscopic follow-up strategy. After HA, patients were followed up by telephone every 3 months for 2 years. Pregnancy outcomes were tracked, including live births, abortion, or infertility. Patients' medical records, operative reports, and hysteroscopy videos were reviewed. The study workflow is shown in Figure 1.

3D-TVUS examination

The 3D-TVUS examinations were performed using a GE VOLUSON E8 ultrasound system (GE Healthcare, Chicago, IL, USA) with a 2-dimensional (2D) volume probe and real-time 3D volume probe. Patients underwent 3D-TVUS during the secretory phase of the menstrual cycle, using a 7.5 MHz IC5-9D vaginal probe. For 3D-TVUS, patients emptied their bladder and were placed in the lithotomy position. Routine 2D ultrasound examinations were performed first. After rotating the real-time 3D volume probe, panoramic technology was used to obtain overall image information and select the target area. The probe was fixed in the longitudinal section of the uterus, the best position to start the 3D program, while paying attention to adjusting the 3D sampling volume. The scope included the whole uterus and patients were asked to hold their breath. The 3D scanning measurement module was then executed to achieve a 3D reconstruction of the data. With the uterine cavity as the center point, the X , Y , and Z axes, which are perpendicular to each other, were rotated and the best observation angle was chosen, enabling acquisition of a 3D coronal plane image of the uterus. After image acquisition was completed, 3D images were obtained from the sagittal, cross-sectional, and coronary planes. The images were then adjusted and analyzed using 3 offline applications (i.e. OmniView, Render, and Multiplanar [GE Medical System, Zipf, Austria]).

3D-TVUS image preprocessing

Flip, grayscale, saturate, and rotate data augmentation techniques were used on the image datasets. The original images showed a large echo region, including the liver and other peripheral organ parts. To eliminate interference from irrelevant areas and reduce the computational burden of the model, we manually cropped the lesion region to a region of interest (ROI) and set the size to a uniform 192×192 pixels in the JPG format according to the input size of the selected models.

The 3D-TVUS images were processed with high error retention (a high-pass filtering algorithm in OpenCV; https://opencv.org/) and sharpened. The original image details retained after sharpening were adjusted using the threshold value of the high-pass filtering algorithm. The exposure and color were adjusted, and a clear image of the uterine cavity was obtained. To identify IUA, many 3D-TVUS images of the uterine cavity contour were first extracted and sorted. The information was then integrated by experts who repeatedly performed physical area identification, relationship extraction, event extraction, and other actions on the adhesions in the images. Finally, the key features of IUA were obtained by extracting a feature library through self-learning techniques. Image preprocessing is shown in Figure 2. For statistical analysis, image features (including endometrial thickness, intercornual distance, endometrial pattern [III-line sign], endometrial echo, fallopian tube ostia, endometrial–myometrial junction zone, uterine mobility, endometrial blood flow, endometrial peristalsis, and left/right uterine artery systolic/diastolic ratio [S/D], resistance index [RI], and pulsatility index [PI]) were quantified.

Cold scissors ploughing technique for HA and postoperative follow-up hysteroscopy

The HA and postoperative follow-up hysteroscopy were performed within 3–7 days after the onset of menstruation. Hysteroscopy was performed using an operative hysteroscope with an outer sheath diameter of 5.4 mm and a working channel diameter of 1.67 mm (Hunan KMS Medical Technology; Changsha, Hunan, China). When performing the HA, a "see and treat" strategy was implemented. Briefly, the hysteroscope was introduced into the cervical canal through the cervix with the aim of reaching the intrauterine cavity. Adhesions located in the central part of the uterine cavity were usually dissected first, followed by the lateral adhesions. First, the tubal ostia, which is the anatomical landmark during HA, needed to be located. Then, upon its visualization, the adhesions could be easily dissected. In cases of distortion of the intrauterine anatomy caused by adhesions, 5-Fr double-action forceps were used for blunt spreading dissection [11] to separate the adhesions and anatomically reveal the uterine cavity under transabdominal ultrasound monitoring. If the intrauterine anatomy was clear, the IUAs were separated with 5-Fr single-action sharp scissors and the scar tissue covering the intrauterine wall was treated with a cold scissors ploughing technique [12] until the entire uterine cavity had been opened successfully with a clearly visible bilateral fallopian tube ostia.

After HA, the size of the stent was determined based on the hysteroscopist's judgment combined with a predetermined intercornual distance through the 3D ultrasound. Intrauterine stents of various sizes, ranging from extra small (XXXS) to extra large (XXL), were selected depending on the size of the uterine cavity (Figure 3). The cervix was incrementally dilated with Hegar dilators up to No. 7.5, and the stent was then inserted into the uterine cavity with a pushrod. Hysteroscopy was performed immediately to confirm that the position and size of the stent matched the uterine cavity[13]. Then, 3 mL hyaluronic acid gel [14] was injected into the uterine cavity. Hormone therapy, administered for 3 menstrual cycles, started with estradiol valerate 3 mg b.i.d. for 21 days from day 1 of the patient's menstrual cycle, with progesterone 100 mg q.n. added for the last 6 days of the menstrual cycle to promote endometrial growth.

Postoperatively, a "see and treat" hysteroscopic follow-up strategy was used (3 months after the first surgery). During the follow-up procedure, patients' hysteroscopy videos were recorded. The parameters of hysteroscopy, including the length of the uterine cavity and the number of visible uterine horns and tubal ostia, were also measured and recorded. The severity of IUA in each patient was rated based on the American Fertility Society (AFS) score. The data for all these parameters were confirmed by 2 gynecologists.

Statistical analysis

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA). The significance of differences between the live birth and the no live birth groups was tested using chi-squared or Fisher's exact tests as appropriate. Logistic regression analysis was used to decide which postoperative variables were the dominant covariates, combined with the AFS score or 3D-TVUS image features, to establish the live birth rate prediction models. A nomogram incorporating these predictors was then constructed. The nomogram calibration curve and a Hosmer–Lemeshow test were used to show the calibration in the derivation and validation cohorts. The area under the receiver operating characteristic curve (AUC) of the nomogram in the derivation and validation cohorts was used to verify prediction accuracy. A P-value of <0.05 was considered statistically significant.

Results

Clinical characteristics of patients with IUA

Telephone follow-up for 2 years after HA in the derivation cohort (n = 668) revealed that 242 cases had a live birth. In the validation cohort (n = 426), 150 cases had a live birth. There were no significant differences in basic information between the live birth and no live birth groups in either the derivation or validation cohorts ($P < 0.05$), except for age and history of parity. The clinical characteristics of patients with IUAs in the derivation and validation cohorts according to pregnancy outcome (live birth or no live birth) are presented in Table 1. The postoperative 3D-TVUS characteristics of endometrial thickness (mm), endometrial echo, visibility of fallopian tube ostia, endometrial blood flow, intercornual distance (mm), and endometrial peristalsis were significantly related to the live birth rate in both the derivation and validation cohorts ($P < 0.05$). The postoperative hysteroscopy characteristics of visibility of the fallopian tube ostia and AFS scores were also significantly related to the live birth rate in both the derivation and validation cohorts ($P < 0.05$).

Logistic regression analysis

Logistic regression analysis was used to explore the influence of IUA on pregnancy outcomes (i.e., live birth and non-live birth pregnancy outcomes). The results of multivariate logistic regression analysis are presented in Table 2. Meaningful variables among the postoperative 3D-TVUS characteristics were as follows: (1) endometrial thickness was greater in the live birth group ($P = 0.0163$; odds ratio [OR] 1.131; 95% confidence interval [CI]: 1.023 to 1.251); (2) endometrial echo was more homogeneous in the live birth group ($P < 0.0001$; OR 0.426; 95% CI: 0.285 to 0.636); (3) segmentation of scar contraction was mainly in the lower area of the uterine cavity in the live birth group ($P = 0.0037$; OR 1.935; 95% CI: 1.239 to 3.022); (4) segmentation of absent endometrial tissue was mainly in the upper segment of the uterine cavity in the non-live birth pregnancy outcomes group ($P < 0.0001$; OR 0.187; 95% CI: 0.095 to 0.365); and (5) the number of bilateral invisible fallopian tube ostia was greater in the non-live birth pregnancy outcomes group ($P < 0.0001$; OR 0.360; 95% CI: 0.216 to 0.600).

Comparison between prediction models

Multivariate logistical regression analysis was conducted for the meaningful variables ($P < 0.05$) identified by univariate logistic regression analysis to establish a prediction model of postoperative 3D-TVUS characteristics and hysteroscopy characteristics. The AUC of the prediction model of hysteroscopy characteristics was 0.7279 and 0.7666 in the derivation and validation cohorts, respectively. The ROCs (receiver operating characteristic curves) of the prediction models were shown in Figure 4. There was a significant statistical difference in the AUCs for postoperative 3D-TVUS characteristics and hysteroscopy characteristics in the prediction of live birth rate in patients with IUAs in both derivation and validation cohorts ($P < 0.0001$; Table 3). Bivariate and binary logistic regression analyses revealed that postoperative 3D characteristics performed better in predicting the live birth rate in patients with IUAs

A nomogram establishmentand based on 3D-TVUS characteristics

A nomogram incorporating these predictors was then constructed (Figure 5a). The calibration curve of the nomogram and a non-significant Hosmer–Lemeshow test statistic showed good calibration in the derivation cohort ($P = 0.3064$; Figure 5b). The AUC of the nomogram in the derivation and validation cohorts was 0.8506 and 0.8963, respectively, indicating good discrimination. Decision curve analysis (DCA) for the nomogram is shown in Figure 5c. The DCA indicated that when the threshold probability for a doctor or patient was within 0.00–1.00 in the derivation cohort and 0.00–0.93 in the validation cohort, the nomogram added more net benefit than the "treat all" or "treat none" strategies.

Discussion

As a stubborn disease, IUA significantly affects fertility in women. Although it is mainly caused by induced abortion[15], the diagnostic yield of IUA is also increasing. Standardized treatment that could significantly improve the prognosis of patients is urgently needed [16, 17].

Early diagnosis and treatment are vital in managing and improving the health and pregnancy outcomes of IUA patients [18]. There are many methods to diagnose IUA, such as hysteroscopy [19], ultrasound [20], and hysterosalpingography [21]. Although diagnosis of IUA by hysteroscopy is the current gold standard, it is an invasive method, which may cause further intrauterine injury and infection. Moreover, hysteroscopy is associated with both high costs and difficulties with an initial diagnosis of IUA [22]. Compared with hysteroscopy and magnetic resonance imaging (MRI), 3D-TVUS has unique advantages when it comes to fellow up IUA pre- and post-HA: 3D-TVUS is non-invasive, relatively inexpensive, and easy to perform. Furthermore, 3D-TVUS not only produces accurate images of the conditions within the uterine cavity (including the angle of the uterus and the opening of the fallopian tube), but also gives surgeons a 3D image of the entire uterine cavity, which could identify the recurrence of adhesions and guide patient to pregnancy [23].

However, ultrasound imaging also presents unique challenges, such as low image quality resulting from noise and artifacts, a high dependence on operator or diagnostician experience, and high inter- and intra-observer variability across institutes and ultrasound systems [9]. With the assistance of image preprocessing technology, 3D-TVUS can be a quick and non-invasive modality that provides a vivid 3D perspective of the uterine cavity[24]. It can assess the visibility of the cornua and ostia, measure the size of the uterine cavity, and evaluate the basic features of the endometrium which are believed to be closely related to embryo implantation and affect pregnancy outcomes.

The primary concern of IUA patients is the pregnancy outcome after HA. According to several reports, live birth outcomes may be influenced by many factors, such as the age of mother [25], response to ovarian stimulation[26], and embryonic features. The AFS scoring system for clinical evaluation of IUA severity was established to predict pregnancy outcomes; although the main variable, menstrual status, was used to evaluate endometrial function, it was extremely subjective and inaccurate. With this in mind, we investigated postoperative 3D-TVUS as a means of evaluating the features of the endometrium and assessing the uterine cavity, and logistic regression analysis of postoperative 3D-TVUS features was used to explore the influence of IUA on pregnancy outcomes. The meaningful variables among the postoperative 3D-TVUS characteristics including the intercornual distance, endometrial thickness, endometrial echo, endometrial blood flow, trilaminar pattern of the endometrium, endometrial peristalsis, segmentation of scar contraction, segmentation of absent endometrial tissue and the visibility of the fallopian tube ostia.

The reported researches have confirmed these meaningful variables among the postoperative 3D-TVUS characteristics were relevant to pregnancy outcomes in patients with IUA. The intercornual distance is important for assessing the volume of the uterine cavity, which is an important line of reference for intrauterine cavity assessment. In this study, patients with a wider intercornual distance (greater endometrial volume) were more likely to have a favorable pregnancy outcome ($P = 0.0000$). Some studies have reported a significant correlation between endometrial thickness and pregnancy rate [27, 28]. A thin endometrium, usually associated with reduced blood flow, may fail to respond to hormone stimulation, leading to implantation failure or early miscarriage [29]. As reported previously, a well-functioning endometrium, with normal thickness and normal endometrial echo, positively affects implantation and conceptus survival[30]. The results of the present study are consistent with those of previous studies reporting a positive correlation between endometrial thickness and clinical pregnancy. The measurement of endometrial blood flow as a physiological dimension in addition to the anatomical parameters obtained with ultrasound plays an important role in the expectation of pregnancy outcome. Good blood supply to the endometrium is an essential requirement for implantation. Doppler velocimetry of uterine arteries is only slightly specific for predicting pregnancy[31]. The endometrial and subendometrial S/D, RI, and PI measured at one time point cannot be used alone to predict endometrial receptivity[32]. The blastocyst implants in the endometrium; hence, endometrial blood flow reflects uterine receptivity more appropriately[33]. In the present study, endometrial blood flow was significantly better in the live birth group ($P = 0.0000$). Ultrasound measurement of the endometrial pattern has been suggested to predict pregnancy outcome, but consensus has not been reached regarding its importance. Some studies have asserted that a trilaminar pattern of the endometrium is correlated with higher implantation and pregnancy rates [34], whereas other studies have not found a significant relationship between endometrial pattern and pregnancy rate[35]. In the present study, the trilaminar (III) sign was not significantly correlated ($P = 0.1479$) with live birth. Endometrial peristalsis contributes to enhanced fertility in females[36]. Intrinsic sperm motility and active sperm transport due to contractile movements inside the endometrial cavity have been reported as major factors in sperm transport from the cervix to the fallopian tube[37]. In the present study, endometrial peristalsis was better in the live birth group ($P = 0.0000$).

A previous study reported that depositing embryos in the uterine mid-fundal area improved pregnancy rates [38]. In the present study, segmentation of absent endometrial tissue and scar contraction in upper and middle segments of uterine cavity were greater in the no live births group ($P < 0.05$). A possible reason for this is that the fundal endometrium is suitable for implantation because there is a tendency for lower endometrial wave-like activity and higher endometrial tissue blood flow in this area [39]. The occurrence of IUA in the upper uterine cavity segment, particularly in the fundal area, destroyed the optimum area for implantation, and thus resulted in decreased pregnancy rates. Last but not least, the visibility of the fallopian tube ostia is the prerequisite for natural pregnancy.

A nomogram incorporating these predictors based on postoperative 3D-TVUS characteristics was constructed, with potent predictive power for live births in IUA patients that was even better than the prediction model based on hysteroscopy characteristics in both derivation and validation cohorts in our study. We believe our findings could supply some valuable information for the prediction of live birth rates in IUA patients. Further well-designed prospective clinical studies with a multicentric larger sample size will be needed to confirm the feasibility and efficacy of 3D-TVUS.

Conclusion

The use of postoperative 3D-TVUS images characteristics could be predictive factors for live births in IUA patients and can provide valuable reproductive guidance for patients after HA.

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related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Written informed consent for their medical records used for scientific research was signed voluntarily by each patient, and the ethics committee approved the study of the Third Xiangya Hospital of Central South University (IRB No. 21046). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013)

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Figure legends

Figure 1: The study workflow.

Figure 2. Extraction of key features of the IUA. To identify IUA, numerous 3D-TVUS images of the uterine cavity contour were first extracted and sorted in the following fashion: (A) acquisition of the 3D-TVUS image: coronal view of the uterine cavity, (B) identification of the outline of uterine cavity, (C) image of the endometrium, (D) identification of the adhesion contour, and (E) annotation of the original 3D-TVUS image. Finally, the key features of IUA were obtained by extracting the feature library with self-learning techniques.

Figure 3. Intrauterine stents of various sizes, ranging from extra small (XXXS) to extra large (XXL), the number represents the intercornual distance.

Figure 4: The ROCs (receiver operating characteristic curves) of the prediction models in the derivation cohort and in the validation cohort.

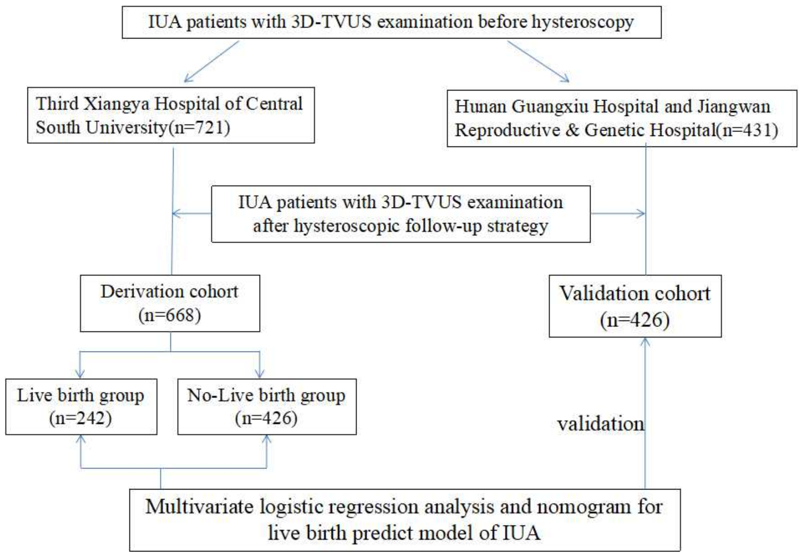
Figure 5-a: A nomogram incorporating these meaningful variables among the 3D-TVUS findings was constructed.

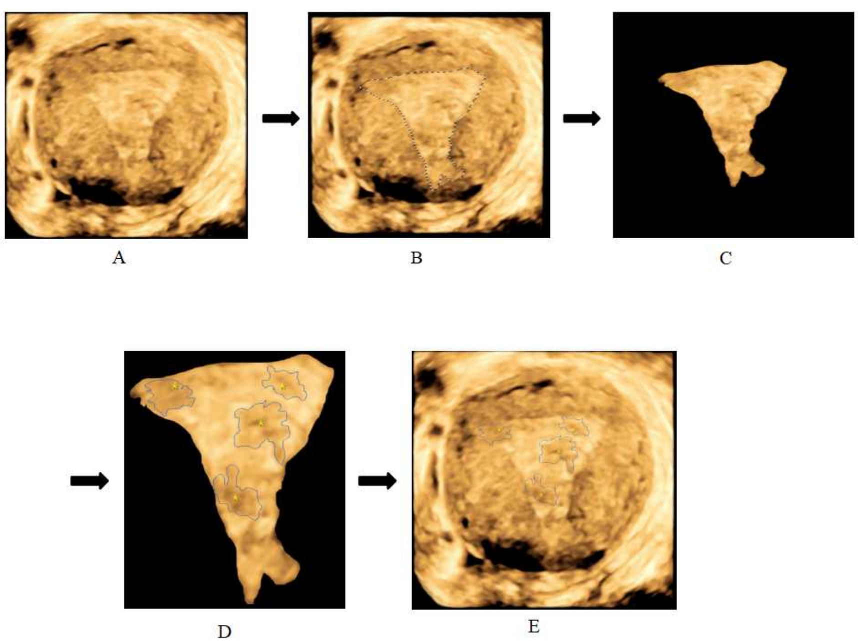
Figure 5-b: The calibration curve of the nomogram and a non-significant Hosmer–Lemeshow test statistic showed good calibration.

Figure 5-c: Decision curve analysis (DCA) for the nomogram indicated that when the threshold probability for a doctor or patient was within 0.00–1.00 in the derivation cohort and 0.00–0.93 in the validation cohort, the nomogram added more net benefit than the "treat all" or "treat none" strategies.

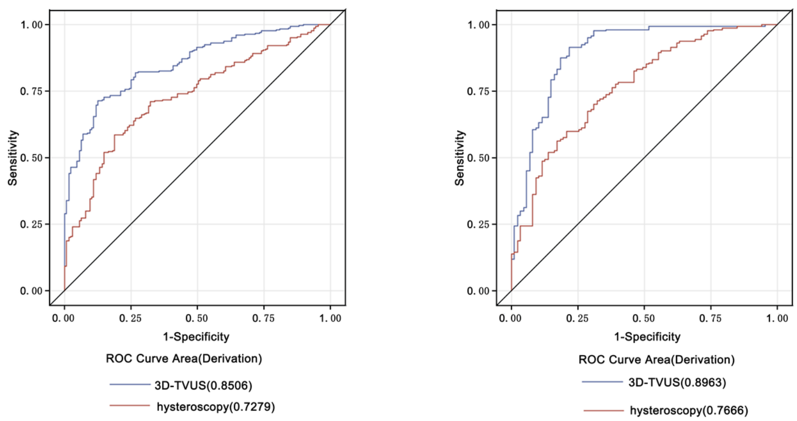
Hosted file

`tables.docx` available at https://authorea.com/users/517775/articles/592188-postoperative-pregnancy-outcome-prediction-model-based-on-3-dimensional-ultrasound-for-intrauterine-adhesion

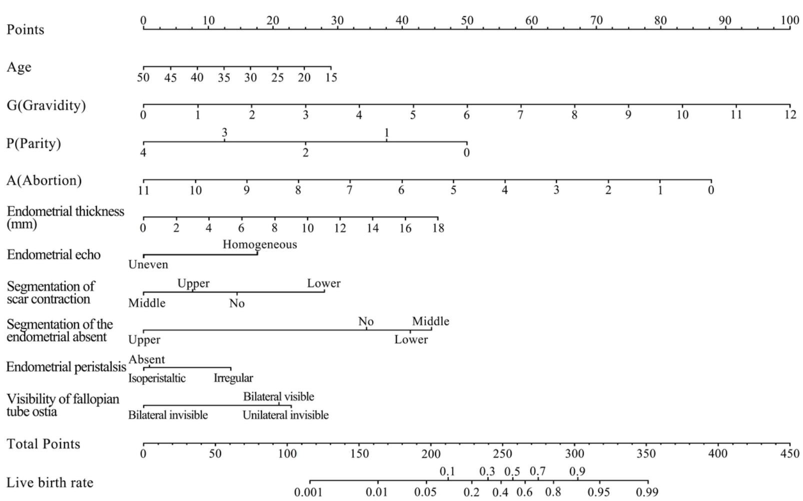




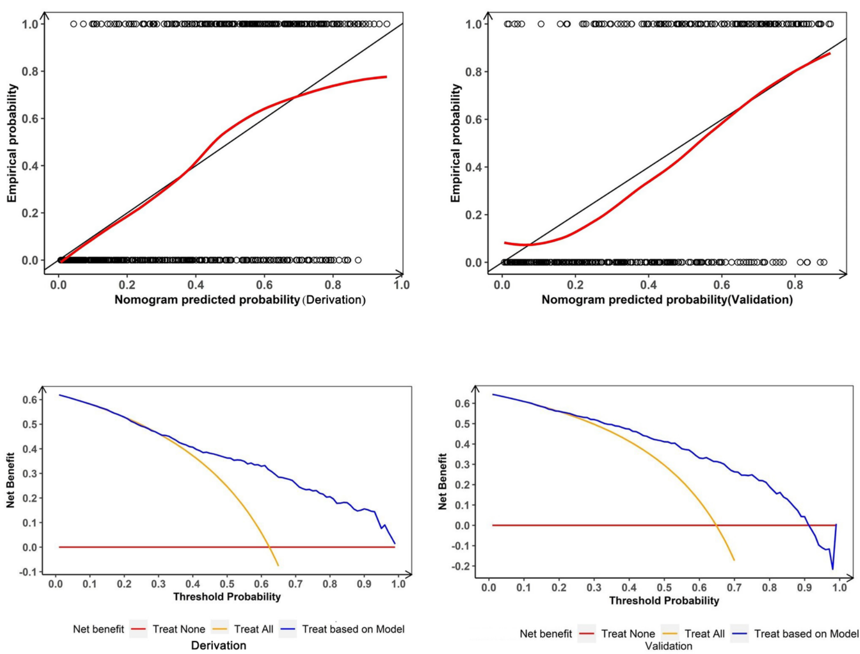
XXXS 14
XXS 16
XS 18
S 20
M 22
L 24
XL 26
XXL28
KMS



Sensitivity
1-Specificity
ROC Curve Area(Derivation)
3D-TVUS(0.8506)
hysteroscopy(0.7279)
ROC Curve Area(Derivation)
3D-TVUS(0.8963)
hysteroscopy(0.7666)



Points
Age
G(Gravidity)
P(Parity)
A(Abortion)
Endometrial thickness (mm)
Endometrial echo
Homogeneous
Uneven
Segmentation of scar contraction
Upper
Lower
Middle
No
Segmentation of the endometrial absent
No
Middle
Upper
Lower
Endometrial peristalsis
Absent
Isoperistaltic
Irregular
Visibility of fallopian tube ostia
Bilateral visible
Bilateral invisible
Unilateral invisible
Total Points
Live birth rate


Empirical probability
Nomogram predicted probability (Derivation)
Empirical probability
Nomogram predicted probability(Validation)
Net Benefit
Threshold Probability
Net benefit
Treat None
Treat All
Treat based on Model
Derivation
Net Benefit
Threshold Probability
Net benefit
Treat None
Treat All
Treat based on Model
Validation