Developing and validating a prediction model of live birth in patients with moderate-to-severe intrauterine adhesions: a new approach with endometrial morphology measurement by 3D transvaginal ultrasound

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Background: There is no reliable method to predict the live birth rate among patients with moderate-to-severe intrauterine adhesions (IUA) after second-look hysteroscopy. Therefore, we aimed to construct a practical prediction model mainly based on the features of 3D transvaginal ultrasound (3D-TVUS). and other clinical characteristics.

Methods: From January 2018 to February 2020, a total of 870 IUA patients with fertility requirements were retrospectively enrolled based on the same method. First, the predictors were screened by logistic regression analysis. A nomogram was constructed based on the screened predictive factors in the derivation cohort. Next, receiver operating characteristic (ROC), calibration curve, and decision curve analysis (DCA) were used to assess the predictive accuracy and discriminability of the model. Finally, correlation analysis was performed to analyze the correlation between the results of 3D-TVUS and second-look hysteroscopy.

Results: A total of 558 (64.14%) participants had live births. Age, endometrial thickness, assisted reproductive technology, a homogeneous endometrial echo, a lower segment of scar contraction, and upper segmentation of the endometrial absence were included in the model. The predictive model showed good predictive performance in the derivation cohort (area under the curve, 0.837) and validation cohort (0.857). DCA demonstrated its clinical utility. A homogeneous endometrial echo was related to no segmentation of scar contraction (r=0.219; P<0.001) or no segmentation of the endometrial absence (r=0.226; P<0.001). Thicker endometrium was associated with no segmentation of the endometrial absence (r=−0.145; P=0.007).

Conclusions: The proposed method can effectively predict live birth. 3D-TVUS should be an important means for evaluating the endometrium of moderate-to-severe patients with IUA preparing for pregnancy after operation.

Keywords: Live birth; 3D transvaginal ultrasound (3D-TVUS); predictive model; hysteroscopic adhesiolysis (HA); intrauterine adhesion (IUA)

Introduction

Intrauterine adhesions (IUA) are intrauterine or cervical adhesions caused by damage of the endometrial basal layer. They are usually accompanied by endometrial fibrosis, and mainly manifested by reduced menstrual volume, amenorrhea, and periodic lower abdominal pain, which has a significant impact on female fertility and can lead to recurrent miscarriage or infertility (1). Induced abortion or curettage significantly increases the incidence of IUA (2). IUA may cause pregnancy complications, such as spontaneous abortion, premature delivery, and placenta implantation, which increases the probability of uterine curettage and further compromises the fertility of patients (3,4). Therefore, we believe that the pregnancy outcome of patients with IUA should be paid more attention. Live birth is a valuable indicator of pregnancy outcome and the main appeal for patients with IUA with fertility needs. Therefore, in the clinical work, how to comprehensively evaluate the postoperative live birth rate of patients with IUA and provide more practical suggestions for patients is worthy of further discussion.

Some researchers have investigated the factors influencing the postoperative live birth of patients with IUA. Cao et al. (5) studied the correlation between different IUA evaluation systems following hysteroscopic adhesiolysis (HA) and live birth after surgery in 128 patients with IUA and found that Nasr classification (Nasr) had the highest predictive value for live birth. Zhang et al. (6) studied the high-risk factors of obstetric complications in 265 patients with IUA and found that the degree of intrauterine involvement and the number of surgical abortions were risk factors for placenta accreta spectrum. In another study, the clinical characteristics of 394 patients with moderate-to-severe IUA were analyzed retrospectively by constructing a decision tree model. The menstrual pattern after HA was found to be the key factor in predicting live birth (7). Another study, which included 71 patients who underwent HA, identified age as a key factor in assessing fertility after surgery (8).

We have discussed the predictive ability of live birth after HA from the aspects of pregnancy patterns, uterine cavity parameters, preoperative 3D transvaginal ultrasound (3D-TVUS) parameters, and endometrial gland density (9-12). Assisted reproductive technology (ART) might be a better choice for patients with recurrent IUA (9). Visible bilateral fallopian tube ostia or American Fertility Society (AFS) scores of <4 in the hysteroscopic reexamination might predict better live birth (10). Thin endometrium and the upper and middle segments of endometrial absence have been found to be risk factors for live birth (11). We also found that the density of endogenous glandular openings can be a novel variable to predict live births in patients with IUA (12).

A 3D-TVUS examination is commonly completed before hysteroscopy to evaluate the disease, but not enough attention has been paid to the value of 3D-TVUS examination after HA. Furthermore, the ability of the post-HA 3D-TVUS to predict the live birth rate of patients with IUA is still unclear. Moreover, most of the previous articles used univariate and multivariate logistic regression analysis to evaluate the risk factors affecting the likelihood of postoperative live birth for patients with IUA; they did not establish and validate a clinical prognosis. Finally, this study has a larger sample size (870 patients) than that in our previous research, which can help to build a more practical prognosis model. A nomogram using the results of 3D-TVUS after second-look hysteroscopy was built based on 870 patients with moderate-to-severe IUA to predict the live birth rate. We present this article in accordance with the TRIPOD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1014/rc).

Methods

Patients

A total of 870 patients with fertility requirements were retrospectively enrolled in this study. From January 2018 to February 2020, all participants underwent HA in the Department of Gynecology, Third Xiangya Hospital, Central South University. The included patients were selected through the same method.

All cases were followed up for 2 years by the same person, and the pregnancy outcome was recorded. The patients were followed up every 3 months from 1 year after second-look hysteroscopy. The pregnant patients were followed up until the termination of the pregnancy. Patients without pregnancy were followed up to 2 years after operation. For patients with multiple pregnancies, only the first pregnancy outcome was recorded. The time of the end of follow-up was April 2022.

The inclusion criteria of this study were as follows: (I) patients with reproductive needs; (II) patients who underwent HA at the Third Xiangya Hospital of Central South University; (III) patients with IUA diagnosed by

hysteroscopy; (IV) patients with moderate-to-severe IUA; and (V) availability of 3D-TVUS results during the interval between second-look hysteroscopy and pregnancy. The exclusion criteria were as follows: (I) endometrial tuberculosis; (II) severe adhesion rendered the restoration of the normal uterine cavity impossible; (III) infertility with other causes, such as male infirmity, tubal factor infertility; (IV) primary infertility; (V) uterine cavity volume either too large or too small, inability to place an intrauterine device (IUD) after surgery; or (VI) loss to follow-up.

Clinical data collection

We obtained each patient's demographic information (age), clinical history (disease course, pregnancy patterns, pregnancy outcomes, gravidity, parity, spontaneous abortion, surgical abortion/curettage, and recurrence of IUA), 3D-TVUS results after second-look hysteroscopy (uterine length, endometrial thickness, distance between two uterine cornua, triline sign, endometrial echo, uterine mobility, blood flow of endometrium, and endometrial mobility), results of the second-look hysteroscopy (segmentation of scar contraction, segmentation of the endometrial absence, IUA score, and the number of visible tubal ostia) from the electronic medical record. The medical records, operative reports, and hysteroscopy videos of all patients were reviewed by two doctors. The main outcome indicators were pregnancy outcomes, including live birth and non-live birth. Non-live birth was defined as infertility, induced abortion, spontaneous abortion, induced labor, and stillbirth. Disease course referred to the time interval between the occurrence of reduced menstrual volume, amenorrhea, or IUA detected by B-ultrasound examination or hysteroscopy. The IUA scores, also known as the AFS score, were categorized as follows (13): 1–4 (mild), 5–8 (moderate), and 9–12 (severe).

Surgical procedure for the last HA

Second-look hysteroscopy was conducted 1 month after the initial HA for patients with severe IUA (score 9–12) and 3 months after the initial HA for patients with moderate IUA (score 5–8) (12).

HA was performed within 3–7 days following menstruation. An operative hysteroscope (Karl Storz SE & Co. KG. KG-Tuttlingen, Baden-Württemberg, Germany) was used. A blunt spreading dissection technique (14) and the cold scissors ploughing technique (15) were used to dissect adhesive tissues and reconstruct the normal uterine cavity. An IUD was placed during the first HA and removed during the second-look hysteroscopy.

For patients who wished to become pregnant, bilateral intubation of the fallopian tubes under hysteroscopy was completed (9). After the HA, 3 mL of hyaluronic acid gel was then injected into the uterine cavity via the catheter (16).

3D-TVUS examination

In this study, 3D-TVUS was performed at the middle stage of the endometrial secretory phase after the second-look hysteroscopy and before pregnancy using a GE volume E8 ultrasonic instrument (GE Healthcare GmbH & Co OG, Tiefenbach, Styria, Austria). The 3D-TVUS examination was conducted by ultrasound doctors with more than 10 years of clinical experience during the period from the last HA to the pregnancy.

The endometrium was divided into patterns A, B, and C, which were distinguished by two hyperechoic lines between the endometrium and the myometrium and by different images of a hyperechoic central line between the two layers of the endometrium (17). Pattern A meant that three lines of endometrium can be clearly displayed. Pattern B referred to an endometrial echo that is uniform and moderate, and the strong echo line of the uterus is discontinuous or unclear. In pattern C, the endometrium showed a strong homogeneous echo, no midline echo in the uterine cavity, and three lines disappeared (17).

Endometrial blood flow was divided into grades 0, 1, 2, and 3 (18). Grade 0 means that the blood flow signal can hardly be detected in the endometrium. Grade 1 refers to the blood flow reaching the basal layer of the endometrium. Grade 2 refers to the blood flow reaching the functional layer of the endometrium. Grade 3 refers to the blood flow reaching the central lining of the urinary cavity (18). We combined grades 2 and 3 patients into the grade ≥2 group. Endometrial wave-like movements were classified according to the classification system constructed by Ijland et al. (19): no activity, no activity detected during at least 2 minutes when recording; fundo-cervical, waves moving from the fundus to the cervix; cervico-fundal, waves moving from the cervix to the fundus; opposing, waves produced from both cervix and fundus; and random, waves generated at any point on the uterus. In this study, bidirection included fundo-cervical and cervico-fundal; irregular included opposing and random.

Analysis plan

The statistical software SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) were used to analyze the data and draw graphs. The normality test was carried out by Shapiro-Wilk method. The count data were expressed by frequency percentage (%), and the comparison between groups was performed using a *Z* test. Continuous variables were compared by the independent-samples *t*-test, or the Mann-Whitney *U* test. The predictors were screened by univariate and multivariate logistic regression analysis, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. The predictive factors were included in the clinical predictive model, and a nomogram was constructed. The model was evaluated by the receiver operating characteristic (ROC) curve, calibration curve, the Hosmer-Lemeshow (HL) test statistic, and decision curve analysis (DCA). Spearman correlation analysis was used to analyze the correlation between clinical parameters and ultrasound parameters, which was shown by a heat map. A P value <0.05 was considered statistically significant.

Ethical statement

This study was approved by the Ethics Committee of Third Xiangya Hospital of Central South University (IRB No. I 21053). All participants signed an informed consent form. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and all the terms related to human study participants.

Results

According to the inclusion criteria, 922 patients with IUA were initially included in this study, and 52 patients were excluded according to the following criteria: (I) male competence (n=8); (II) tubercular IUA (n=1); (III) tubal factor infertility (n=6); (IV) other lesions, including endometrial polyps, atypical hyperplasia, or endometrial malignancy (n=14); and (V) lost to follow-up (n=23). Finally, 870 patients were included in the final study and divided into groups according to the ratio of 7:3, including 609 in the derivation cohort and 261 in the validation cohort (*Figure 1*). *Table 1* shows the clinical characteristics of 870 patients with IUA with complete follow-up data on their pregnancy outcomes. In the two groups, the average age of the patients was 31.0 years old (28.0–35.0 years), and all patients were

of reproductive age. A total of 84.71% of patients were hoping to achieve a spontaneous pregnancy after HA, and only 15.29% chose ART. There were 558 live births, about twice the number of non-live births. Most cases had non-recurrent IUA (64.70% *vs.* 35.30%). The constituent ratio of moderate and severe patients with IUA was similar between the two groups (48.74% *vs.* 51.26%). There was no significant difference in all clinical parameters between the derivation and validation cohorts (P>0.05).

In the derivation cohort, there were significant differences in some clinical indicators between the live birth and non-live birth groups. Patients with non-live births had the following characteristics: (I) older (median age, 32.0 *vs.* 30.0 years; P<0.001); (II) more patients chose spontaneous pregnancy (70.77% *vs.* 29.23%; P<0.001); and (III) the proportion of patients with pregnancy ≥3 times (67.73% *vs.* 32.27%; P=0.005) and delivery ≥2 times (72.73% *vs.* 27.27%; P<0.001) were higher. In the non-live birth group, more patients had experienced abortion, surgical abortion/curettage, and recurrence of IUA, but there was no significant difference between the two groups (P>0.05). For 3D-TVUS indicators, the endometrium was thicker (5.6 *vs.* 4.8 mm; P<0.001), and the intercornual distance was larger (P<0.001) in the live birth group, but patients in the non-live birth group were more likely to be heterogeneous endometrial echo (70.92% *vs.* 29.08%; P<0.001), poor uterine mobility (92.00% *vs.* 8.00%; P=0.01), poor endometrial blood flow (P<0.001), and worse endometrial mobility (P<0.001). For the variates in the second-look hysteroscopy, more patients in the non-live birth group had the following characteristics: (I) IUA in the middle segment of the uterus (80.00% *vs.* 20.00%; P<0.001) and the upper segment of the uterus (84.38% *vs.* 15.63%; P<0.001); (II) the missing part of the endometrium was located in the upper segment of the uterus (89.94% *vs.* 10.06%; P<0.001); (III) bilateral fallopian tube ostia could not be seen (82.26% *vs.* 17.74%; P<0.001); and (IV) more patients had severe IUA (71.84% *vs.* 28.16%; P<0.001; *Table 2*).

Multivariate logistic regression analysis showed that age (OR 0.929; 95% CI: 0.893–0.967; P<0.001), endometrial thickness (OR 1.276; 95% CI: 1.150–1.416; P<0.001), ART (OR 7.016; 95% CI: 3.856–12.766; P<0.001), homogeneous endometrial echo (OR 1.797; 95% CI: 1.171–2.759; P=0.007), lower segment of scar contraction (OR 2.259; 95% CI: 1.390–3.672; P=0.001), and upper segmentation of the endometrial absence (OR 0.159; 95% CI: 0.080–0.318; P<0.001) were independent predictors for pregnancy outcomes of patients with IUA after HA in the derivation
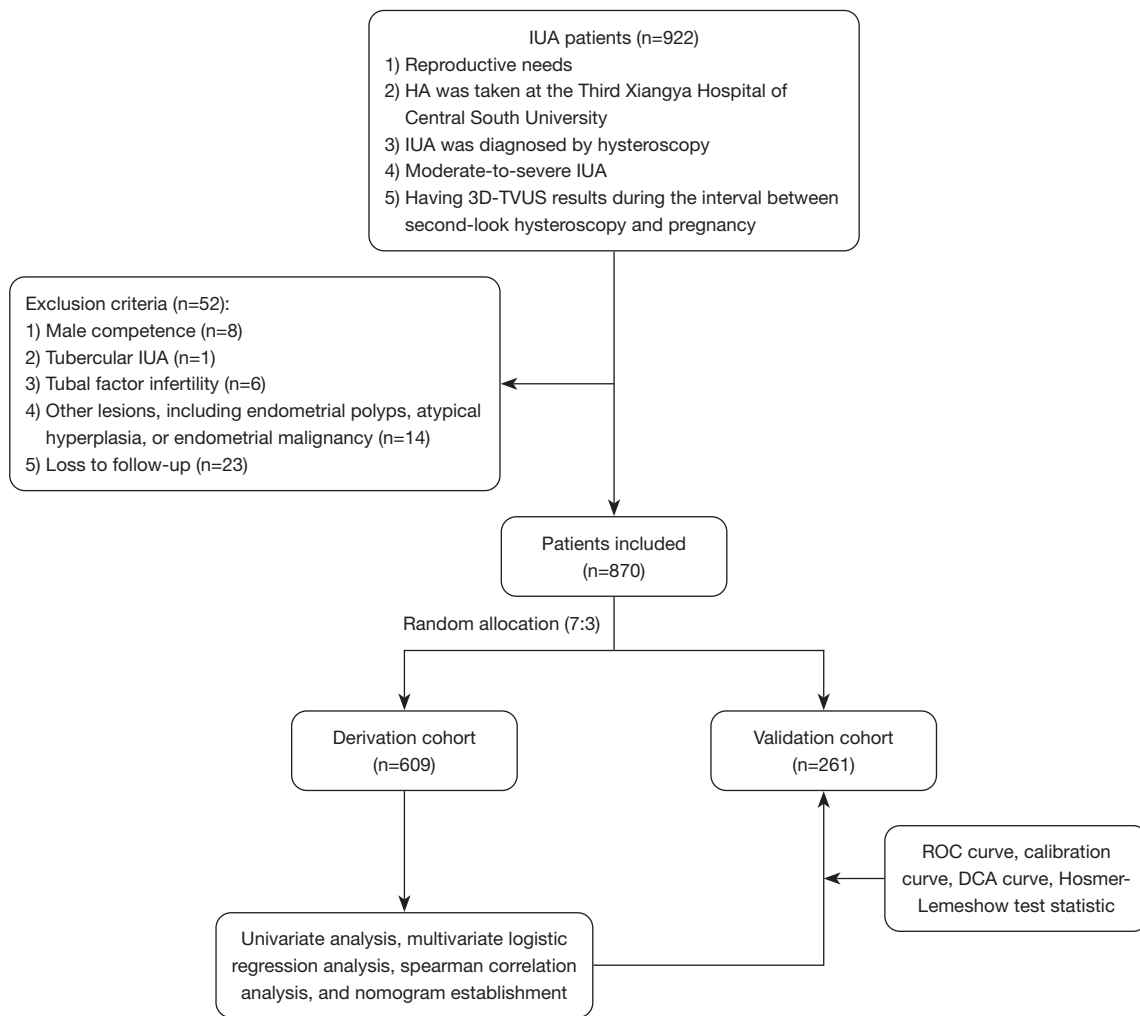
Figure 1 Study workflow. IUA, intrauterine adhesions; HA, hysteroscopic adhesiolysis; 3D-TVUS, three-dimensional transvaginal ultrasound; ROC, receiver operating characteristic; DCA, decision curve analysis.

Table 1 Clinical characteristics of model derivation and internal validation populations

Variable	Total (n=870)	Derivation (n=609)	Validation (n=261)	Z/χ^2	P value
Age (year)	31.0 (28.0–35.0)	32.0 (28.0–36.0)	31.0 (28.0–34.0)	1.377	0.168
Disease course (year)	0.8 (0.3–2.0)	0.7 (0.3–2.0)	0.8 (0.3–2.0)	0.824	0.410
Pregnancy patterns				0.711	0.399
Spontaneous pregnancy	737 (84.71)	520 (85.39)	217 (83.14)		
ART	133 (15.29)	89 (14.61)	44 (16.86)		
Pregnancy outcomes				0.161	0.688
Non-live birth	312 (35.86)	221 (36.29)	91 (34.87)		
Live birth	558 (64.14)	388 (63.71)	170 (65.13)		

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total (n=870)	Derivation (n=609)	Validation (n=261)	Z/χ²	P value
Gravidity				2.180	0.536
0	25 (2.87)	19 (3.12)	6 (2.30)		
1	162 (18.62)	111 (18.23)	51 (19.54)		
2	247 (28.39)	166 (27.26)	81 (31.03)		
≥3	436 (50.11)	313 (51.40)	123 (47.13)		
Parity				2.333	0.311
0	523 (60.11)	356 (58.46)	167 (63.98)		
1	302 (34.71)	220 (36.12)	82 (31.42)		
≥2	45 (5.17)	33 (5.42)	12 (4.60)		
Spontaneous abortion				2.062	0.560
0	41 (4.71)	31 (5.09)	10 (3.83)		
1	261 (30.00)	176 (28.90)	85 (32.57)		
2	244 (28.05)	169 (27.75)	75 (28.74)		
≥3	324 (37.24)	233 (38.26)	91 (34.87)		
Surgical abortion/curettage				0.112	0.990
0	45 (5.17)	32 (5.25)	13 (4.98)		
1	412 (47.36)	287 (47.13)	125 (47.89)		
2	195 (22.41)	138 (22.66)	57 (21.84)		
≥3	218 (25.06)	152 (24.96)	66 (25.29)		
Previous HA history				2.071	0.150
No	576 (66.21)	394 (64.70)	182 (69.73)		
Yes	294 (33.79)	215 (35.30)	79 (30.27)		
Uterine length (mm)	28.0 (24.5–31.5)	28.0 (25.0–31.5)	28.0 (24.0–30.5)	1.336	0.182
Endometrial thickness (mm)	5.0 (4.0–6.2)	5.0 (4.0–6.2)	5.0 (3.9–6.1)	0.499	0.618
Intercornual distance (mm)				0.071	0.965
≤22	347 (39.89)	242 (39.74)	105 (40.23)		
23–25	224 (25.75)	156 (25.62)	68 (26.05)		
≥26	299 (34.37)	211 (34.65)	88 (33.72)		
Triline sign				3.896	0.273
Not clear	782 (89.89)	548 (89.98)	234 (89.66)		
Pattern A	17 (1.95)	9 (1.48)	8 (3.07)		
Pattern B	34 (3.91)	27 (4.43)	7 (2.68)		
Pattern C	37 (4.25)	25 (4.11)	12 (4.60)		

Table 1 (*continued*)

Table 1 (*continued*)

Variable	Total (n=870)	Derivation (n=609)	Validation (n=261)	Z/χ^2	P value
Endometrial echo				1.657	0.198
Heterogeneous	548 (62.99)	392 (64.37)	156 (59.77)		
Homogeneous	322 (37.01)	217 (35.63)	105 (40.23)		
Uterine mobility				0.480	0.787
Poor	35 (4.02)	25 (4.11)	10 (3.83)		
Not good	643 (73.91)	446 (73.23)	197 (75.48)		
Well	192 (22.07)	138 (22.66)	54 (20.69)		
Blood flow of endometrium				1.195	0.550
Grade 0	227 (26.09)	156 (25.62)	71 (27.20)		
Grade 1	592 (68.05)	414 (67.98)	178 (68.20)		
Grade ≥2	51 (5.86)	39 (6.40)	12 (4.60)		
Endometrial mobility				1.233	0.540
No	531 (61.03)	379 (62.23)	152 (58.24)		
Irregular	290 (33.33)	197 (32.35)	93 (35.63)		
Bidirection	49 (5.63)	33 (5.42)	16 (6.13)		
Segmentation of scar contraction				3.336	0.343
No	341 (39.20)	238 (39.08)	103 (39.46)		
Lower segment	357 (41.03)	259 (42.53)	98 (37.55)		
Middle segment	125 (14.37)	80 (13.14)	45 (17.24)		
Upper segment	47 (5.40)	32 (5.25)	15 (5.75)		
Segmentation of the endometrial absence				3.588	0.310
No	267 (30.69)	197 (32.35)	70 (26.82)		
Lower segment	57 (6.55)	37 (6.08)	20 (7.66)		
Middle segment	306 (35.17)	206 (33.83)	100 (38.31)		
Upper segment	240 (27.59)	169 (27.75)	71 (27.20)		
Number of visible tubal ostia				1.273	0.529
0	170 (19.54)	124 (20.36)	46 (17.62)		
1	162 (18.62)	109 (17.90)	53 (20.31)		
2	538 (61.84)	376 (61.74)	162 (62.07)		
AFS scores				0.316	0.574
5–8	424 (48.74)	293 (48.11)	131 (50.19)		
9–12	446 (51.26)	316 (51.89)	130 (49.81)		

Continuous data are presented as the median (interquartile range) and categorical data are presented as number (%). ART, assisted reproductive technology; HA, hysteroscopic adhesiolysis; AFS, American Fertility Society.

Table 2 Univariate analysis of pregnancy outcomes after HA in the derivation cohort

Variates	Non-live birth (n=388)	Live birth (n=211)	Z/χ^2	P value
Age (year)	32.0 (29.0–37.0)	30.0 (28.0–34.0)	4.536	<0.001
Disease course (year)	0.8 (0.3–2.0)	0.6 (0.2–2.0)	0.403	0.687
Pregnancy patterns			76.671	<0.001
Spontaneous pregnancy	368 (70.77)	152 (29.23)		
ART	20 (22.47)	69 (77.53)		
Gravidity			12.872	0.005
0	7 (36.84)	12 (63.16)		
1	60 (54.05)	51 (45.95)		
2	109 (65.66)	57 (34.34)		
≥3	212 (67.73)	101 (32.27)		
Parity			18.014	<0.001
0	202 (56.74)	154 (43.26)		
1	162 (73.64)	58 (26.36)		
≥2	24 (72.73)	9 (27.27)		
Spontaneous abortion			3.967	0.265
0	16 (51.61)	15 (48.39)		
1	106 (60.23)	70 (39.77)		
2	111 (65.68)	58 (34.32)		
≥3	155 (66.52)	78 (33.48)		
Surgical abortion/curettage			1.882	0.597
0	17 (53.13)	15 (46.88)		
1	184 (64.11)	103 (35.89)		
2	87 (63.04)	51 (36.96)		
≥3	100 (65.79)	52 (34.21)		
Recurrence of IUA			2.001	0.157
No	243 (61.68)	151 (38.32)		
Yes	145 (67.44)	70 (32.56)		
Uterine length (mm)	28.0 (24.5–31.5)	29.0 (25.0–32.0)	1.168	0.243
Endometrial thickness (mm)	4.8 (3.7–5.8)	5.6 (4.5–7.2)	6.742	<0.001
Intercornual distance (mm)			18.635	<0.001
≤22	174 (71.90)	68 (28.10)		
23–25	103 (66.03)	53 (33.97)		
≥26	111 (52.61)	100 (47.39)		
Triline sign			3.751	0.290
Not clear	355 (64.78)	193 (35.22)		
Pattern A	6 (66.67)	3 (33.33)		
Pattern B	15 (55.56)	12 (44.44)		
Pattern C	12 (48.00)	13 (52.00)		

Table 2 (*continued*)

Table 2 (*continued*)

Variates	Non-live birth (n=388)	Live birth (n=211)	Z/χ^2	P value
Endometrial echo			24.718	<0.001
Heterogeneous	278 (70.92)	114 (29.08)		
Homogeneous	110 (50.69)	107 (49.31)		
Uterine mobility			9.232	0.010
Poor	23 (92.00)	2 (8.00)		
Not good	281 (63.00)	165 (37.00)		
Well	84 (60.87)	54 (39.13)		
Blood flow of endometrium			22.471	<0.001
Grade 0	115 (73.72)	41 (26.28)		
Grade 1	260 (62.80)	154 (37.20)		
Grade ≥2	13 (33.33)	26 (66.67)		
Endometrial mobility			20.115	<0.001
No	267 (70.45)	112 (29.55)		
Irregular	102 (51.78)	95 (48.22)		
Bidirection	19 (57.58)	14 (42.42)		
Segmentation of scar contraction			18.946	<0.001
No	146 (61.34)	92 (38.66)		
Lower segment	151 (58.30)	108 (41.70)		
Middle segment	64 (80.00)	16 (20.00)		
Upper segment	27 (84.38)	5 (15.63)		
Segmentation of the endometrial absence			73.280	<0.001
No	112 (56.85)	85 (43.15)		
Lower segment	15 (40.54)	22 (59.46)		
Middle segment	109 (52.91)	97 (47.09)		
Upper segment	152 (89.94)	17 (10.06)		
Number of visible tubal ostia			28.006	<0.001
0	102 (82.26)	22 (17.74)		
1	74 (67.89)	35 (32.11)		
2	212 (56.38)	164 (43.62)		
AFS scores			18.751	<0.001
5–8	161 (54.95)	132 (45.05)		
9–12	227 (71.84)	89 (28.16)		

Continuous data are presented as the median (interquartile range) and categorical data are presented as number (%). HA, hysteroscopic adhesiolysis; ART, assisted reproductive technology; IUA, intrauterine adhesions; AFS, American Fertility Society.

Table 3 Risk factors for pregnancy outcomes of patients with IUA in the derivation cohort

Variable	Category	Estimate	SE	Wald	P value	OR	95% CI	
							Low	Up
Intercept		–0.142	–	0.035	0.851	0.867	–0.615	2.349
Age		–0.073	–0.213	12.801	<0.001	0.929	0.893	0.967
Endometrial thickness		0.244	0.264	21.080	<0.001	1.276	1.150	1.416
Pregnancy patterns	ART	1.948	0.380	40.691	<0.001	7.016	3.856	12.766
Endometrial echo	Homogeneous	0.586	0.155	7.182	0.007	1.797	1.171	2.759
Segmentation of scar contraction	Lower segment	0.815	0.222	10.803	0.001	2.259	1.390	3.672
	Middle segment	–0.673	–0.125	3.124	0.077	0.510	0.242	1.076
	Upper segment	0.148	0.018	0.069	0.793	1.160	0.384	3.502
Segmentation of the endometrial absence	Lower segment	0.249	0.033	0.337	0.562	1.283	0.553	2.980
	Middle segment	0.358	0.093	2.217	0.137	1.430	0.893	2.290
	Upper segment	–1.838	–0.454	27.007	<0.001	0.159	0.080	0.318

IUA, intrauterine adhesions; SE, standard error; OR, odds ratio; CI, confidence interval; ART, assisted reproductive technology.

cohort (*Table 3*).

Next, we constructed a nomogram containing the six predictive factors (*Figure 2A*). The total score of the nomogram was the sum of the corresponding scores assigned to each risk factor. The higher the score, the higher the risk of live birth. In the HL test, there was no significant difference between the actual live birth rate and the predicted live birth rate (χ^2=5.912; P=0.657), indicating that the goodness of fit of this model is high. In both cohorts, the blue line is a straight line with a slope close to 1, which indicates that there is a good correlation between the probability of actual live birth and the probability of predicted live birth (*Figure 2B*). According to ROC analysis, the area under the curve (AUC) was 0.837 (95% CI: 0.805–0.869) in the derivation cohort and 0.857 (95% CI: 0.810–0.903) in the validation cohort, which revealed good discrimination (*Figure 2C*). The DCA curve was used to evaluate the clinical practicability of the model. When the predictive rate of the model was about 0.35–0.90, there was a net benefit from clinical measures (*Figure 2D*).

Finally, to explore whether the 3D-TVUS results after the second-look hysteroscopy were consistent with the results during the second-look hysteroscopy, correlation analysis was used to study the correlation between the two kinds of parameters (*Figure 3*). The results showed that five of the 3D-TVUS results after the second-look hysteroscopy (endometrial thickness, distance between two uterine cornua, endometrial echo, blood flow of endometrium, and endometrial mobility) had a closer correlation with the results of the second-look hysteroscopy.

On the whole, endometrial echo or endometrial mobility had a positive correlation with the results in the second-look hysteroscopy (P<0.05). Endometrial thickness, the distance between two uterine cornua, or blood flow of endometrium had a negative correlation with the results in the second-look hysteroscopy (P<0.05). Homogeneous endometrial echo was related to the no segmentation of scar contraction (r=0.219; P<0.001) or no segmentation of the endometrial absence (r=0.226; P<0.001). Thicker endometrium was associated with no segmentation of the endometrial absence (r=–0.145; P=0.007). The results suggested that the outcomes of noninvasive 3D-TVUS and invasive hysteroscopy were consistent in their judgments of endometrial conditions.

Discussion

In this study, the predictive model suggested that endometrial thickness was an important factor affecting live birth. This finding is consistent with the results of other studies (20-22). However, it is often difficult to achieve a satisfactory endometrial thickness in patients with IUA (23), so the thin endometrium has become a difficult problem for doctors and patients (24). Endometrial thickness <7 mm
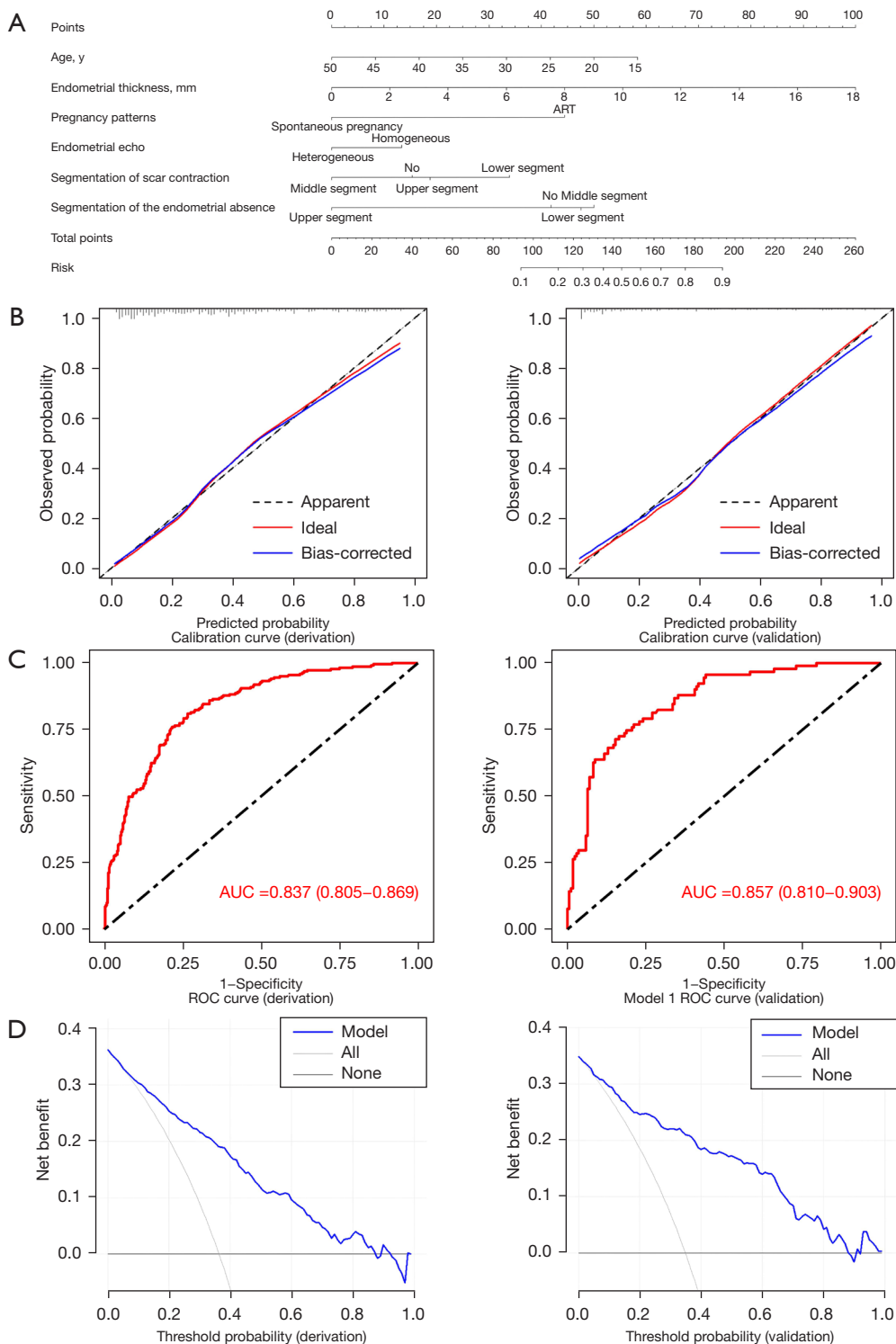
Figure 2 Development and validation of the prognostic nomogram. (A) A nomogram for the prediction of a live birth after second-look hysteroscopy. (B) Calibration curves of the nomogram. The 45° black dotted line represents a perfect prediction, and the blue lines represent the predictive ability of the model. ROC curves (C) and DCA curves (D) of the nomogram. The x-axis of the DCA curve represents the threshold probability of postoperative live birth, and the y-axis indicates the net benefit of the model. ART, assisted reproductive technology; ROC, receiver operating characteristic; AUC, area under the curve; DCA, decision curve analysis.
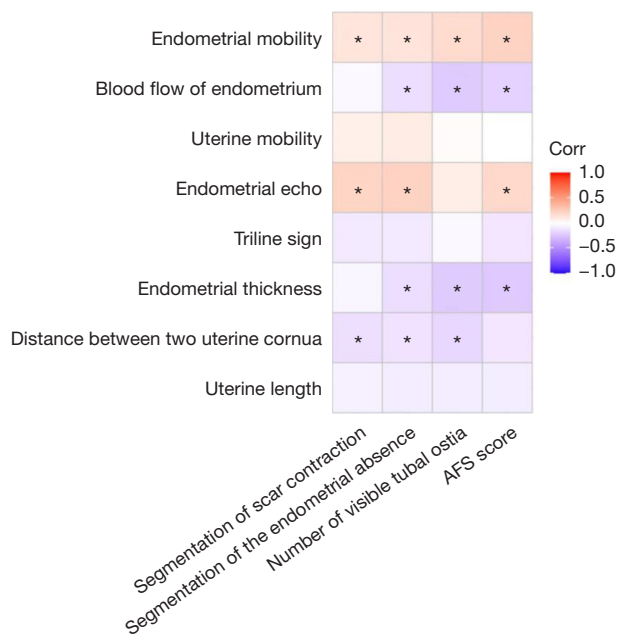
Figure 3 Correlation heatmap of 3D-TVUS parameters and clinical parameters. *, P<0.05. 3D-TVUS, three-dimensional transvaginal ultrasound; AFS, American Fertility Society.

is associated with lower pregnancy rates (24). The mean endometrial thickness of the 870 participants was only 5 mm (4.0–6.2 mm). The mean endometrial thickness was 5.6 mm (4.5–7.2 mm) in the live birth group, which was higher than the 4.8 mm (3.7–5.8 mm) in the non-live birth group, but lower than 7 mm. At present, sodium hyaluronate, estrogen, stem cell transplantation, amniotic membrane transplantation, and organoid transplantation have been reported to improve thin endometrium (25-28), but the effects are not significant. Therefore, how to improve the endometrial thickness of patients with IUA and improve the pregnancy outcome requires further investigation.

In addition, we should pay attention to the evaluation of endometrium by 3D-TVUS after HA and timely intervention. Usually, 3D-TVUS is performed before HA. However, during the period from the completion of HA to the time before pregnancy, 3D-TVUS has not attracted enough attention. After surgery, anatomical and physiological changes can be found in the uterine cavity, so the outcomes of postoperative 3D-TVUS can be closer to that of the uterine cavity in preparation for pregnancy than the results of preoperative 3D-TVUS. This study found that a thicker and homogeneous endometrium after HA was related to a higher live birth rate. It is suggested that more

attention should be paid to evaluation of the uterine cavity, especially the endometrium, by means of 3D-TVUS to guide reproductive pursuits.

The correlation analysis found that the postoperative 3D-TVUS results were consistent with the intraoperative results of second-look hysteroscopy. Our research found that homogeneous endometrial echo was related to the no segmentation of scar contraction or no segmentation of the endometrial absence. Thicker endometrium was associated with no segmentation of the endometrial absence. 3D-TVUS is a safe and noninvasive examination, which produces results consistent with those of invasive hysteroscopy. Based on the results of this study, we recommend using noninvasive ultrasound to evaluate the uterine condition after HA, as it has more advantages than hysteroscopy, which can reduce the trauma and pain of the operation, lower the cost, and is easy to popularize. In addition, 3D-TVUS has irreplaceable advantages of hysteroscopy, such as the evaluation of uterine contour, endometrial blood flow, and diagnosis of uterine malformation (11). Therefore, for moderate-to-severe patients with IUA who have completed HA treatment, hysteroscopy is not recommended to evaluate the uterine cavity before pregnancy, but 3D-TVUS is the first choice.

We previously found that an AFS score <4 was a favorable factor for live birth (10). However, this study did not find any correlation. For the first time, 3D-TVUS parameters after the second-look hysteroscopy were included, which was closer than the last operation to the intrauterine conditions before pregnancy. The AFS score was evaluated during the last HA, and there may be recurrence of IUA after an operation. Furthermore, the AFS score cannot more clearly describe the sites of adhesion and endometrial loss, which are important to evaluate pregnancy outcomes, whereas 3D-TVUS can clearly assess those two parameters. For example, even if the AFS score is less than 4, the endometrial loss is mainly located in the upper segment of the uterine cavity, which is still not conducive to embryo implantation. When the AFS score is more than 4, the adhesions were mainly located in the lower segment of the uterus, which may have little effect on pregnancy. Therefore, the last 3D-TVUS outcomes are more practical and accurate than the AFS score in predicting pregnancy outcomes.

IUA can reduce endometrial receptivity and affect embryo implantation and development. The possible mechanism is as follows (23,29): (I) endometrial

microenvironment changes can reduce endometrial receptivity; (II) the location of the lesion affects uterine contractility and embryo implantation; (III) IUA reduces the volume of the uterine cavity and interferes with sperm movement and embryo implantation; (IV) inflammation of the endometrium affects the endocrine function of the endometrium. The implantation of fertilized eggs mainly occurs in the middle or upper segment of the uterine cavity (29,30). When the adhesive tissues are located in the middle or upper segment of the uterine cavity, it may affect embryo implantation and development, thus reducing the live birth rate (23,29,30). Our study found that the lower segment of the adhesion location is a protective factor of live birth, whereas the missing part of the endometrium in the upper segment is a risk factor for live birth, confirming the findings of existing studies (23,29,30).

Moreover, the findings of this study are consistent with our previous research. ART can increase the live birth rate (9), suggesting that regardless of the number of visible tubal ostia during the second-look hysteroscopy, ART can still improve the pregnancy outcome. However, we need to recognize that it is still of important clinical value to judge the number of visible tubal ostia. For example, when the two tubal ostia are invisible, it is recommended to choose ART instead of spontaneous pregnancy. Therefore, this parameter can provide a certain value for guiding patients to choose the appropriate method of conception.

The predict model included age, endometrial thickness, pregnancy patterns, endometrial echo, segment of scar contraction, and segmentation of the endometrial absence. The nomogram indicated a younger IUA patient who has thicker endometrium, a homogeneous endometrial echo, a lower segment of scar contraction, and a lower segmentation of the endometrial absence might be easier to have a live birth by ART. The model is helpful for clinicians to give reasonable fertility guidance to IUA patients, so patients can have a better understanding of their fertility outcomes. Sometimes, unnecessary loss of time and money can be avoided. As a non-invasive and non-radiological examination, 3D-TVUS it is more easily accepted by patients during pregnancy preparation.

The research also has some limitations. The diagnosis of 3D-TVUS depends on the professional ability of sonographers and the advancement of equipment, so it is meaningful to predict the live birth rate on the premise of accurate ultrasound diagnosis. Whether the 3D-TVUS parameters will be changed dynamically with the extension of the time before pregnancy after HA and what is the best time point to perform the 3D-TVUS examination remains to be further discussed. This is a retrospective study; prospective studies are needed to further confirm the conclusions of this research.

Conclusions

In conclusion, the clinical predictive model has more practicability. With the help of noninvasive ultrasound examination, the postoperative live birth rate of patients with IUA can be predicted. Doing so can reduce the pain and economic cost of patients, and this method is easy to promote. Therefore, we suggest that 3D-TVUS be performed during the preparation for pregnancy after HA in patients with moderate-to-severe IUA.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1014/rc

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related

to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was approved by the Ethics Committee of Third Xiangya Hospital of Central South University (IRB No. I 21053). All participants signed an informed consent form. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and all the terms related to human study participants.

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