Selection of high-risk individuals for a large niche development based on a scoring classification model: a retrospective cohort study.

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Abstract

Objective: To develop a risk prediction model to identify the high-risk individuals of large niche formation after cesarean section (CS). Design A retrospective study. Setting Women's health research in Anhui, China. Population: Women received CS between Jan 2012 to Jun 2017. Methods: Women were arranged to receive uterine scar examination by transvaginal ultrasonography, and those diagnosed with niche were divided into two groups according to whether they suffer from postmenstrual spotting. The cut-off values of depth, RMT (residual myometrium thickness), and depth/AMT (adjacent myometrium thickness) were chosen to define a large niche. Then, all participants were classified into three groups, including a control, a small niche, and a large niche group. The scores of each variable in the prediction model were calculated by dividing the minimum β-coefficient from the multivariate logistic analysis. Main outcome: Primary outcome was a prediction scoring model for large niche formation. Results: In total, 727 women were recruited in this study, and the large niche was defined as more than 0.50 cm in depth, less than 0.21 cm in RMT, more than 0.56 in depth/AMT. The large niche prediction model included eight variables of age at delivery, retroflexed uterine, meconium-stained amniotic fluid, history of CS, B-Lynch suture, operation duration, premature rupture of membranes and cervical dilatation more than 4 cm. The cut-off value of 5 in this score-based model presented sensitivity and specificity as 67.48% and 90.07% respectively. Conclusions: This score-based risk prediction model could present the risk of large niche formation of individuals after CS.

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Conclusions: This score-based risk prediction model could present the risk of large niche formation of individuals after CS.

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Key words: Cesarean, large niche, definition, risk prediction, scoring, an individualized assessment

Introduction

Cesarean section (CS) is one of the most common operations performed on reproductive-aged women[1,2]. In China, nearly 35% of the deliveries are by CS[3]. Long term complications of CS, including postmenstrual spotting[4], scar pregnancy[1,5], and scar dehiscence or rupture in later pregnancies[6], are usually caused by incomplete healing of the previous cesarean incision. It forms a triangular anechoic structure at the site of the uterus scar with depth more than 2 mm and is defined as a niche[1]. The prevalence of the niche varies between 24% and 70% in random populations by transvaginal ultrasonography (TVS)[1,7,8].

Small niches may indeed be quite common but would be clinically unimportant, however, the large niches are most likely to give rise to those complications and should be taken seriously[9,10]. So far, only three small sample studies have defined large niche as a depth of at least 50-80% of anterior myometrium or the remaining myometrial thickness (RMT) less than 2.2 mm when evaluated by TVS[11-13]. Large niche incidence has been reported varying from 11% to 45% depending on the definition mentioned above[6]. A recent study indicated that the size of the niche can guide clinical decision and the sum of depth and length greater than 40 mm can increase the failure risk of surgical outcomes[9]. However, research data on large niche development based on large sample sizes is lack.

Large niche is pathological[14], the selection of individuals at high-risk based on scoring classification model could be efficient for developing preventive strategies. Several studies have summarized numerous risk factors related to niche formation[5,15,16], and emphasized that a double layer closure of the cesarean incision was advantageous to decrease the incidence of niche and increase the RMT[17]. As we know, cervical dilation, CS history, and uterus position have been commonly accepted as niche risk factors in the previous studies[16,18,19], however, there is debate on the other factors, such as twin pregnancy, obesity, surgeon experience[6,16] owing to small sample size in different studies.

Hence, this study aims to define the large niche based on large sample size statistical analysis and develop a score-based prediction model to identify an individual's risk of developing a large niche after CS.

Materials and Methods

Study population

This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University before the study began. All participants provided informed consent before entering the study. This study has lasted more than 4 years from Jan. 2016 to Jun. 2020. Randomly drawing 1641 non-pregnant women who have received CS more than one year[20] in our department between Jan 2012 to Jun 2017 were asked to complete questionnaires: menstruation cycle, methods of contraceptive, dysmenorrhea, abnormal uterine

bleeding, infertility, dyspareunia, gynecological endocrine disease, whether have another baby or have suffered other surgeries. Finally, 812 women accepted the invitation and were arranged to receive TVS examination. Excluding criteria were other surgeries on the uterus, intrauterine device (IUD), oral contraceptive, irregular vaginal bleeding related to the endocrine disorder, and endometrium polyp or carcinoma. Postmenstrual spotting was defined as more than 2 days of brownish discharge at the end of menstruation with a total length of menstruation (including spotting) of more than 7 days, or intermenstrual bleeding which starts within 5 days after the end of menstruation[21]. The flow chart was shown in Fig.S1.

Cesarean scars measurement

All the participants were arranged during their mid-follicular phase to receive TVS examination (Fig. 1A, B). The standardized approach for measuring CS scars was from midsagittal plane to both sides of the uterus with good visualization of the cervical canal, recording the information about uterus position, endometrium thickness, RMT, adjacent myometrial thickness (AMT) of the scar, depth, length for the niche[22,23](as shown in Fig. 1C., and Table 1). The width of the niche should be visualized in the transverse plane. All values were taken as the average of three times of examination. The uterine cavity was examined carefully for the presence of other intrauterine abnormalities, such as Naeschner's cyst of the cervix, submucosal fibroids or polyps. Niche was defined as an indentation at the site of the cesarean scar with a depth of at least 2 mm in the sagittal plane[8].

Data collection and selection of candidate predictors of a large niche

In the present study, candidate variables predictive of the large niche were identified based on the current literature, meta-analyses, high-quality studies[1,15]. Thirty-one variables were divided into four parts as shown in Table 2, including Operation (history of once CS, bilateral tubal ligation (i.e. for sterilization), B-Lynch suture, emergent CS, duration of CS and surgeon experience), Infection (meconium-stained amniotic fluid (MSAF), cervical dilatation, premature rupture of membranes (PROM), and vaginal examination), Tension (pre-pregnancy bass mass index (BMI), BMI at delivery, retroflexed uterine, macrosomia, twin pregnancy, breech, presence or duration of labor at CS, and oxytocin augmentation during labor), and Healing (pre-eclampsia, diabetes, intrahepatic cholestasis of pregnancy (ICP), anemia (Hb $<$ 90 g/mL), postpartum hemorrhage, placenta previa, steroid treatment during pregnancy and assisted reproduction technology (ART)). In this study, all the participants received a continuous locked single-layer uterine suture with peritoneal closure and inclusion of the decidua.

Statistical analysis

Analysis of the niche parameters

Women with niche were grouped into two parts according to whether they complained of obvious postmenstrual spotting symptoms. The average menstruation days (including dot bleeding days) and parameters of the niche (depth, length, width, RMT, AMT, and depth/AMT) were compared between the asymptomatic group and symptomatic group using*t-test* , and $p < 0.05$ was regarded as significantly different (Table 1). As shown in Table S2 and Fig 2, we used receiver-operating characteristics (ROC) curves to establish cut-off values for depth, RMT, depth/AMT, width, length, and AMT for classification of large niche.

Univariate analyses and multivariate logistic regression analyses of risk factors of a large niche

In this study, women with niche but the parameters of the niche didn't meet our definition of the large niche were divided into small niche group. Therefore, all the participants were classified into three groups including, the control group, small niche group, and large niche group as shown in Table S3. Univariate analyses between different groups were conducted using the *t-test* for continuous variables, and the*chi-squared test* for categorical variables. Two-sided tests were used and $p < 0.05$ was considered statistically significant. Then, variables with $p < 0.05$ in univariate analyses were included in the multiple logistic regression analyses. The odds ratio (OR) and 95% CI for the association of a large niche development with candidate predictors were estimated using multivariate logistic regression, and $p < 0.05$ was deemed to be statistically significant (Table S4).

Score-based model for prediction of the risk of a large niche

The risk scores of each predictor in the model were calculated by dividing the minimum β -coefficient from the multivariate logistic analyses and rounding to the nearest 0.5. The total risk score of each participant was calculated by summing the scores of each risk factor, and then, a score-based prediction model was developed. The cut off value of the high risk of large niche development was assessed by the area under the ROC curve (AUC) and its 95% CI.

All statistical analyses were performed using the computer package SPSS version 23.0 (IBM Corp., Armonk, New York). The data were presented as mean ± SD for normally distributed variables and frequency (percentage, %) for categorical variables.

Results

Demographic characteristics in this study

Following the inclusion and exclusion criteria, 727 women were included in this study, and 85 women were excluded as shown in Fig. S1. The prevalence of niche at CS scar was about 36.2% in our hospital during 2012.01- 2017.06 by TVS evaluation. In the analysis of clinical symptoms, prolonged postmenstrual spotting was the most common symptom (29.6%, 215/727), and the incidence was the highest (75.5%, 123/163) in the large niche group as shown in Table S3. The age of all participants ranged from 22 to 44 years, with a mean age of 29.66 ± 3.84 years, and gestational age ranged from 30 to 42 weeks at CS, with a mean value of 38.77 ± 1.86 weeks. Of these women, 35 had once previous vaginal delivery, 117 had undergone once CS history, and 301 had abortion history before the last CS (ranged from 1 to 9 times).

Large niche definition

Table 1 showed the average menstruation days, endometrium thickness, and niche parameters including depth, length, width, RMT, AMT, and depth/AMT in two groups. The mean menstruation days of asymptomatic women with niche was about 6.09 ± 1.10, and 9.51 ± 2.11 for the symptomatic women with niche ($p < 0.05$). There was no significant difference between the two groups in endometrium thickness on the examination day. The mean values of depth, length, and width of niches were significantly greater in the symptomatic group than those of the asymptomatic group ($p< 0.05$). The mean values of RMT and AMT of the symptomatic group were significantly lower than those of the asymptomatic group ($p < 0.001$). The ROC curves of these variables were shown in Fig.2 and Table S2, and the largest AUC was considered to be the best predictor of a large niche. According to the AUC statistics, the cut-off for depth was 0.50 cm (AUC: 0.731, 95% CI: 0.661-0.790), RMT was 0.21 cm (AUC: 0.683, 95% CI: 0.614-0.747), and Depth/AMT ratio was 0.56 (AUC: 0.798, 95% CI: 0.725-0.804). Therefore, we define the large niche more than 0.50 cm in depth, or less than 0.21 cm in RMT, or more than 0.56 in depth/AMT. This definition had 61.17% (95% CI: 0.52-0.70) specificity, 76.87% (95% CI: 0.70-0.84) sensitivity and 70.72% (95% CI: 0.65-0.76) accuracy.

Risk factors related to a large niche formation

According to the definition for the large niche mentioned above, 163 women were classified in a large niche group, 100 women were classified in a small niche group, and 464 women were classified in the control group. Table S3 showed the candidate predictive variables compared among the three groups by univariate analyses. There was no significant difference in gestational age at delivery, times of abortions, and vaginal delivery history among different groups. The differences of age at delivery, one CS history, bilateral tubal ligation, B-Lynch suture, operating duration, emergent CS, MSAF, PROM, cervical dilatation more than 4 cm, retroflexed uterine, breech, oxytocin augmentation, presence or duration of labor at CS, anemia, and postpartum hemorrhage were significant between control and large niche group ($p < 0.05$). However, we didn't find any relevance between large niche and obstetric complications, such as pre-eclampsia, diabetes, ICP, and placenta previa. Moreover, our results showed that twin pregnancy, macrosomia, surgeon experience, and ART didn't influence the risk of large niche development.

Multivariate logistic model and assigned scores

The model predicting large niche development included the following eight variables: age at delivery (0 for < 35 years old; 1.0 for [?] 35 years old), history of once CS (1.0 for yes), operation duration (0 for < 120 min; 1.0 for [?] 120 min), B-Lynch suture (2.0 for yes), MSAF (2.0 for yes), PROM (1.0 for yes), cervical dilatation more than 4 cm (2.0 for yes), and retroflexed uterine (4.0 for yes) (Table 2).

Effectiveness of the score-based prediction model of a large niche

Table 3 showed the discriminative performances of each score as the cut-off value in identifying individuals at high-risk of large niche formation in our study. As the cut-off value increased, the risk of large niche formation increased. We comprehensively estimated some predominant indices for each score cut-off value in the score-based model, including the number and proportion of high-risk individuals, sensitivity, specificity, Youden's index (sensitivity + specificity – 1). The candidate cut-off value of 5 from the score-based model was selected as the criteria for identifying high-risk individuals for large niche formation after CS. If a cut-off value of 5 was applied to select individuals in this study, 166 individuals were selected as the high-risk populations. In this study, 110 individuals have been identified to have large niches by TVS, and 107 individuals accompanied by dot bleeding symptoms. The sensitivity and specificity were 67.48% and 90.07%, respectively. The AUC of this score-based model was 0.875 (95% CI: 0.848–0.902; Fig. 3).

Discussion

The main results of this retrospective study proposed a large niche definition based on the largest sample size so far, and it showed good sensitivity and specificity. Besides, a score-based individual risk prediction model was developed according to the multivariate analysis results of twelve risk factors and was used to quantitatively evaluate the risk of a large niche formation for women undergoing CS. This model included eight variables and showed the good discriminative ability to predict high-risk individuals. More importantly, this model provided detailed information for the doctors to develop preventive strategies for high-risk individuals during or after CS.

So far, only three studies focused on the large niche, and one of them gave the definition of a large niche, and others proposed the risk factors related to the large niche formation[24-26]. Our definition was similar to the previous one[16], however, we proposed more detailed values based on a large sample size. Large niches were uncommon with a reported varying incidence of 11-45%[27] depending on the definition used. The prevalence of large niche in our hospital during 2012-2017 was about 22.4% using our diagnostic criteria. It appeared that there was a correlation between the size of the defect and postmenstrual spotting[4,15,27]. Studies demonstrated that when using TVS in a group of women with gynecological symptoms, half of them had a large niche, involving more than 50% of the myometrial thickness[7]. Clinically, we often found abundant newly formed fragile vessels in the large niches under hysteroscopy as show in Fig.1D. Therefore, postmenstrual spotting was the most common symptom in large niches[4,27] and was used as a term to distinguish the large niches from small ones in our study.

It should be emphasized that TVS examination was done during the mid-follicular phase of the examinees, owing to a clear visualization of the niches in case of the fluid in the uteri cavity[28,29]. The size of the niche was affected by the thickness of endometrium[30], however, we didn't find significant difference among the participants. As we know, depth, RMT, and AMT values can be easily obtained from sagittal plane[31], however, the values of length and width often varying with the pressure of the uterine cavity in case of intracavitary fluid, which was not included in our definition. Besides, the AUC statistics of the depth, RMT, and depth/AMT were the top three among all the parameters of the niche. Therefore, the definition of a large niche was the parameters of a niche meet anyone of the three items.

In this study, several well-known risk factors[5,15,23,32] were included in the final model, including age at delivery, duration of CS, cervical dilation more than 4 cm, CS history, and uterine retroflection. The other potential risk factors of niche[6], emergent CS, the presence of labor, anemia, oxytocin augmentation during labor, breech excluded from multivariable logistic analysis (Table S4). These findings might suggest that the associations between these factors and the risk of a large niche might be weaker than the association with other robust risk factors in our study. Some researchers reported that niche may almost happen in the

women with more than three times CS[11,18], and most women in our country are more likely to have twice CS during their lifetime. So, we only include once history of CS in the model. The surgical technique of uterine incision closure is the most important determinant of the CS defect formation[33,34]. However, the method of wound closure could not be analyzed because the standard way of uterine wound closure at our hospital was continuously locked sutures during the 2012-2017 year. Moreover, double-layer uterine closure was recommended by several important studies[33,35,36] and was accepted by the most obstetricians in China. So, this factor was not recruited in the model. Interestingly, B-Lynch suture and MSAF were the first time verified to associate with a large niche. Notably, it is not possible to evaluate the position of uterus immediately during or after the CS, but some studies considered that the formation of niche is one year after the operation. Therefore, scoring the position of uterus three months after delivery does not affect the prediction of a large niche.

Compared to the conclusions of previous studies or the meta-analyses, our model might have some merits. First, from the aspect of the study design and data resources used in the model development, our study was the first large size sample-based cohort study to develop a prediction model of a large niche, thus rendering the model more convincible. Second, from the aspect of selection of predictors, we chose all the well-known predictors according to high-quality literature reviews, meta-analyses, and the latest Chinese expert consensus. Besides, some unwell-known variables such as B-Lynch suture and MSAF based on our clinic experience were also included in the model. Therefore, we estimated the model accuracy and practice value as a prediction method in the large niche formation. The score of each predictor in this model represented different degrees of impact on large niche formation, which provided important information for the doctors to develop individualized prevention strategies. In the future, this scoring model for large niche formation will allow a large size of prospective studies in the clinical practice.

Strength and Limitations

This study has several strengths. First, the sample size and full-scaled risk factors were relatively large and detailed to date. Second, the measurement of niche and the time of examination was consistent with the guideline in practice in Europe. Third, the definition of a large niche was practicable and low-cost. Finally, the scoring model for the prediction of niche formation was designed for the individual after CS.

Our study has some limitations. First, we lost a large number of women who refused to interview the uterine scar measurement. The number of the participants was still insufficient, so the results for design the scoring model was limited. Second, the niche parameters in this study are not full-scale, like the distance between the niche and the vesico-vaginal fold, and distance between the niche and the external os were excluded in the data collection. Third, the loss of the follow-up of the different treatment protocols for the women with large niche and dot bleeding symptoms, and the relationship of niche parameters with the next pregnant result. Finally, the best suture method recommended at present is the first-layer suture avoiding the decidua followed by a second layer for the approximation of the myometrium. However, the suture method of CS in our hospital was continuous single-layer uterine closure using locking sutures, and closure of the peritoneum during 2012-2017. At present, the proposed cut-off value in the large niche scoring model is still arbitrary, and it should be verified furtherly in the clinic to make sure its meaning of guidance for treatment opinions. Because the uterus position can't be determined during or after CS, and the uterus position sometimes may change after CS. Therefore, the uterus position score may be determined by TVS during the first three months of CS.

Conclusion

Further studies should focus on investigating the definition of large niche in relation to severe long-term complications after CS, such as obvious dot bleeding, scar pregnancy and late pregnancy uterine rupture. In addition, the score-based prediction system of large niche should be validated in prospective cohort study.

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Disclosure of interest

There are no conflicts of interest to declare.

Contribution to authorship

Jing Wang planned this study and wrote the manuscript. Qiushi Pang and Shijie Yan took an active role in collecting medical history and contacting participants. Most of the transvaginal ultrasound examinations were done by Wenwen Wei. Mingjun Hu and Fen Huang analyzed all the data. Linghui Cheng, Yunxia Cao and Zhaolian Wei planned, and modified the manuscript.

Details of ethics approval

The study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University (PJ-2019-03-12).

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Table 1 Comparison of niche parameters

	Asymptomatic group (n =103)	Symptomatic group (n =160)	*p*
Menstruation days, mean ± SD, d	6.09 ± 1.10	9.51 ± 2.11	0.000
Endometrium thickness, mean ± SD, cm	0.66 ± 0.23	0.71 ± 0.20	0.064
Depth, mean ± SD, cm	0.37 ± 0.18	0.54 ± 0.22	0.000
Length, mean ± SD, cm	0.36 ± 0.20	0.49 ± 0.26	0.000
Width, mean ± SD, cm	0.54 ± 0.67	0.68 ± 0.38	0.038
RMT, mean ± SD, cm	0.34 ± 0.15	0.25 ± 0.13	0.000
AMT, mean ± SD, cm	0.91 ± 0.17	0.84 ± 0.14	0.000
Depth/AMT, mean ± SD	0.40 ± 0.17	0.65 ± 0.27	0.000

RMT: remaining myometrial thickness; AMT: adjacent myometrial thickness.

Table 2 Multivariate logistic model and assigned scores

	Regression coefficient	Adjusted OR (95% CI)	Assigned Scores
Age at delivery (y)			
< 35		1.00 (reference)	0
[?] 35	0.064	1.066 (1.005-1.132)	1.0
History of once CS			
No		1.00 (reference)	0
Yes	0.919	2.506 (1.398-4.492)	1.0
Operating duration (min)			
< 120		1.00 (reference)	0
[?] 120	0.015	1.015(1.002-1.027)	1.0
B-Lynch suture			
No		1.00 (reference)	0
Yes	1.444	4.238 (1.423-12.621)	2.0
PROM			
No		1.00 (reference)	0
Yes	0.758	2.134 (1.238-3.676)	1.0
MSAF			
No		1.00 (reference)	0
Yes	1.447	4.250 (1.768-10.216)	2.0
Cervical dilatation 4-10 cm			
No		1.00 (reference)	0
Yes	1.258	3.523 (1.584-7.833)	2.0
Retroflexed uterine			
No		1.00 (reference)	0
Yes	2.383	10.836 (6.863-17.108)	4.0

CS: cesarean section; PROM: premature rupture of membranes; MSAF: meconium-stained amniotic fluid.

Table 3 Performance of a risk scoring prediction model of large niche with different score cut-offs in the study cohort

Score Cut-off	High risk individuals (n, %)	True large niche (n)	Sensitivity (%)	Specificity (%)	Youden's index
1	470 (64.65)	163	100.00	45.57	0.46
2	340 (46.77)	147	90.18	65.78	0.56
3	269 (37.00)	129	79.14	75.17	0.54
4	231 (31.77)	117	71.78	79.79	0.52
5	**166 (22.83)**	**110**	**67.48**	**90.07**	**0.58**
6	91 (12.52)	67	41.10	95.74	0.37
7	48 (6.60)	37	22.70	98.05	0.21
8	18 (2.84)	16	9.82	99.65	0.09
9	9(1.24)	9	5.52	100.00	0.06
10	3(0.41)	3	1.84	100.00	0.02

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FIG3.pdf available at https://authorea.com/users/366485/articles/486224-selection-of-high-risk-individuals-for-a-large-niche-development-based-on-a-scoring-classification-model-a-retrospective-cohort-study