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ORIGINAL RESEARCH

Early Magnetic Resonance Imaging Measurements and Prediction of Second Trimester Pregnancy Loss: a Nomogram Model Analysis

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Objective: To investigate the magnetic resonance imaging (MRI) features of women with prior second-trimester pregnancy loss, and to establish a nomogram prediction model for subsequent miscarriage.

Methods: A retrospective cohort study of women with prior second-trimester pregnancy loss from January 2018 to December 2021 in Second Affiliated Hospital of Soochow University was performed. A total of 245 patients were included. Data from January 2018 to December 2019 were used to construct the model, and data from January 2020 to December 2021 were used to evaluate the model. Data on maternal demographic characteristics, MRI cervical measurements were extracted. The prediction model was constructed with independent variables determined by multivariate logistic regression analyses. Through receiver-operating characteristic (ROC) curve analysis, the predictive ability of the model for subsequent second trimester pregnancy loss in women was evaluated, and internal validation was performed through validation data.

Results: Thin cervix was observed in 77 (31.42%) women with prior second-trimester pregnancy loss, the mean longitudinal diameter of cervical canal on MRI was 11.76±2.75mm. The model reached a sensitivity of 80%, specificity of 75.90%, positive predictive value (PPV) of 55.80% and negative predictive value of 90.90%; ROC characteristics proved that the model was superior to any single parameter with an AUC of 0.826.

Conclusion: Our observations showed that thin cervix and longitudinal diameter of cervical canal reliably predicted second trimester pregnancy loss. We developed and validated a nomogram model to predict the individual probability of second trimester pregnancy loss in the next pregnancy and hopefully improve the prediction and indication of interventions.

Keywords: cervical insufficiency, MRI, nomogram, magnetic resonance imaging, CI

Introduction

Pregnancy loss occurring after the 12th and prior to the 24th week of gestation is referred to as a second-trimester pregnancy loss.[1] The likelihood of miscarriage in the second trimester is about 0.5% in a group at low risk.[2] Cervical insufficiency (CI), fetal and placental defects, uterine deformities, chromosomal abnormalities, and inherited and acquired thrombophilias are known causes of second-trimester loss. CI has been defined as painless dilatation and shortening of the cervix in the second-trimester, and it accounts for a large part of the abortion in the second-trimester pregnancy loss.[3] The chance to administer interventional treatment is limited because the early symptoms in patients with CI are typically apparent prior to the occurrence of contractions or any other clinical signal of miscarriage or preterm labor. Patients with cervical dilatation may occasionally have emergency cervical cerclage, but infections and post-operative contractions with eventual miscarriage are other possible outcomes. A clearly defined demographic for whom the operation is clearly advantageous is yet lacking.[4]

There is no diagnostic test for CI. Part of the diagnosis is based upon the exclusion of other causes of preterm delivery or mid-trimester pregnancy loss. For women with a history of one second trimester pregnancy loss, the SOGC guideline

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recommend detailed evaluation of risk factors should be undertaken, but elective cerclage was not suggested.[5] Without a reliable diagnostic test, it becomes necessary to screen for or to predict the likelihood of second trimester pregnancy loss. In the therapy of women who are thought to have CI but whose history is not thought to indicate enough risk to call for immediate prophylactic cerclage, a conservative approach that includes cervical length (CL) evaluation may be used.[6] The ultrasound CL measurement of such women will identify a cohort that is more likely to experience a subsequent miscarriage, some of whom may benefit from the installation of a cerclage. These studies suggested that sonographic cervical shortening is a marker for CI.[7, 8] However, only 27% of the women with short cervix in the preterm prediction research gave birth before 37 weeks, and less than 18% of women gave birth before 35 weeks.[9] CL exhibited little predictive efficacy as a single indicator, with extremely short cervix less than 15 mm only conferring a 50% chance of delivery prior to 33 weeks.[10] Therefore, more accurate tools are needed to evaluate the anatomy and function of the cervix.

Prior studies have showed that magnetic resonance imaging (MRI) has been used to assess prenatal abnormalities.[11] According to several research, MRI was used to treat congenital vaginal atresia, placenta accreta and pelvic neoplasms.[12] After a radical trachelectomy for cervical cancer, researchers conducted some research on the MRI measurement of remaining CL.[13] Through signal intensity spectroscopy, accurate assessment of the biometry, and individualization of the stromal zone, MRI of the cervix has shown particular morphological features that may signify access to the cervix's microstructure.[14] In this aspect, exploration of the potential risk factors contributing to miscarriage prior to conception and further setting up of a predictive calculation model with a combination of all the risk factors will be of great importance.

In order to create a forecast that is more precise and may be used to guide clinical judgment, it is essential to incorporate a variety of useful elements. The purpose of this study was to investigate maternal features and MRI measurement of patients who had a history of second trimester pregnancy loss, and to set up a nomogram model based on retrospective data analysis to predict the incidence of miscarriage.

Materials and Methods

Study Population

This was a retrospective study of women with prior second-trimester pregnancy loss. It was conducted in the Department of Obstetrics and Gynecology, the Second Affiliated Hospital of Soochow University between January 2018 and December 2021. Eligible women were sent for MRI examination with a protocol directed towards evaluating the cervix. Two hundred sixty-two women who became pregnant in the study period underwent routine TVU every 2 weeks since 12 weeks of gestation. For the present analysis, we excluded 17 patients and thus, 245 patients met the inclusion criteria. One hundred fifty-nine samples were assigned to the training group while 86 samples were gathered for the external validation group. Women enrolled would be offered cerclage if their CL is <25 mm during the TVU screening before 24 weeks of gestation. The operation method was McDonald approach. All operations were performed by the same doctor. This study was approved by the ethics committee of the Second Affiliated Hospital of Soochow University.

Female patients were eligible if they fulfilled the following criteria:women had at least one previous second-trimester pregnancy loss with painless cervical dilation, following with discharge of the fetus and appendages; Female patients with any of the following conditions were excluded: incomplete records, stillbirth, genital tract malformation, multiple pregnancy, abortion caused by infection or trauma. All patients were followed up until after delivery or miscarriage, and the outcomes of pregnancy were recorded, including pregnancy loss, preterm birth. The flowchart demonstrating how the development cohort and validation cohort were derived is displayed in Figure 1

Method for the Measurement of Cervix

All patients underwent MRI measurements during non pregnancy. MRI examinations of the cervix were performed using the 1.5 GE Signal high-field magnet. Plain scan was performed in axial, sagittal and coronal positions. FOV: 24 ~ 36 cm; Layer thickness / spacing = 5 mm / 1 mm. T1 weighted image (T1WI) adopts spin echo (SE) sequence, and the scanning parameters are repetition time (TR) / echo time (TE): 400 / 10 ms, matrix 240 × Average, 240. T2 weighted image

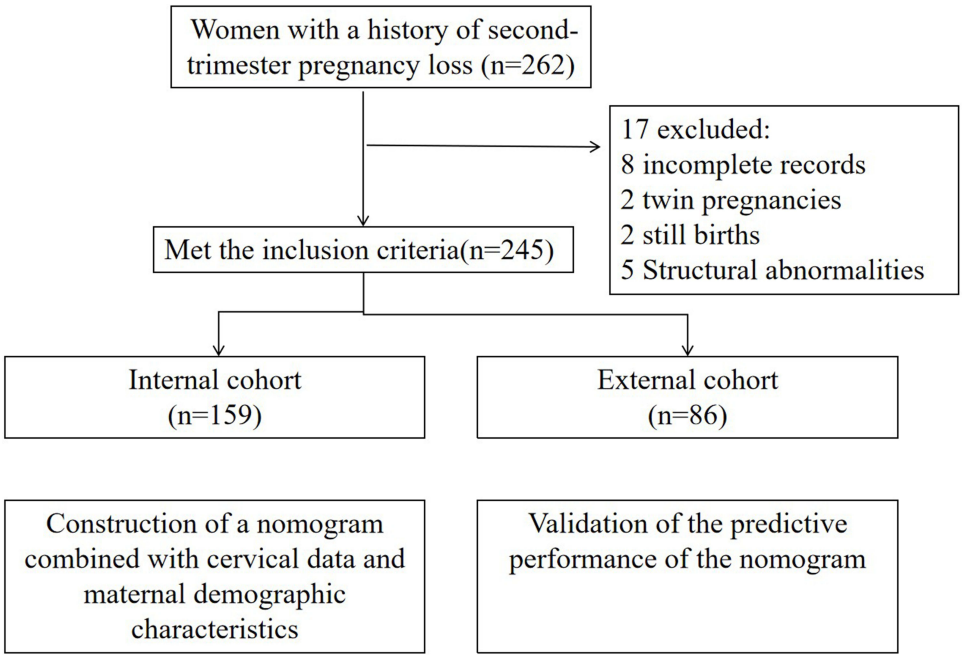

Figure 1 Study flowchart.

(T2WI) adopts fast spin echo (FSE) sequence, scanning parameters: TR / TE = 3000 / 90 IIIS, matrix 260 × 260, acquisition mean 4.

MRI images were analyzed by three researchers with 10 years of experience of Gynaecological imaging. Each individual researcher independently identified the best sagittal cervical image that captured the entire cervical canal and measured the CL, the longitudinal diameter of the cervical canal, the length of the anterior and posterior lips of the cervix and the thickness of the cervix. All three were blinded to the obstetric outcomes.

The MRI assessment was performed to measure the longitudinal diameter of the cervical canal from the internal and external orifices and measure the length of the anterior and posterior lips of the cervix in the standing position. The longitudinal diameter of cervical canal was defined as the minimum linear distance between internal and external orifices and can be described by fully exposing the most central cervical canal. CL was defined as the maximal linear distance between the isthmus uteri and the external orifices and assessed in sagittal T2-weighted TSE pictures without fat suppression, and their maximum width in axial T2-weighted TSE. The central endocervical mucosa, which is contiguous with the endometrium, appears hyperintense on T2WI. The middle fibromuscular stroma is hypointense on T2WI, the outer fibromuscular stroma demonstrates hypointense to intermediate intensity T2WI, and is contiguous with the outer myometrium. Thin cervix was defined as the cervix maximum width≤ 6 mm (Figure 2).

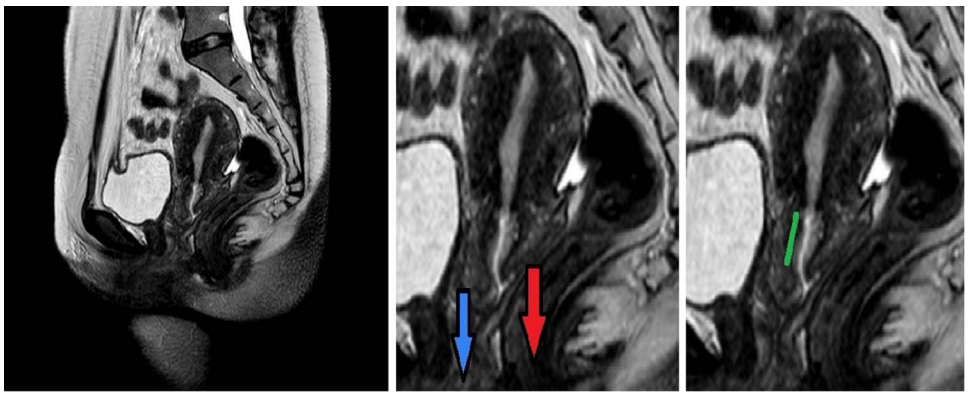

Figure 2 Sagittal T2 shows the MRI anatomy of the cervix. Hyperintense T2 endocervical canal, and hypointense T2 fibrous stroma, the thin posterior lip of the cervix. The blue arrow represents the anterior lip of the cervix, the red arrow represents the posterior lip of the cervix, and the green line represents longitudinal diameter of cervical canal.

Data Collection

Demographic characteristics included maternal age, prepregnancy BMI, history of PCOS and history of Loop Electrosurgical Excision Procedure (LEEP). Clinical data included history of prior second-trimester pregnancy loss, gestational age at delivery. The length of cervix, the anterior lip and the posterior lip of the cervix in non-pregnant period using MRI. Gestational age was calculated from the last menstrual period (LMP) and confirmed by the fetal crown-rump length measurement at the first trimester ultrasonic scan. Second-trimester pregnancy loss is defined as pregnancy loss occurring after the 12th and prior to the 24th week of gestation.

Statistical Analysis

Model Development

Women who were included in the study were divided into a training cohort and a validation cohort. We performed a differential analysis of the clinical variables of the modelling database and the verification database. Quantitative data are expressed as the means ± standard deviation (SD) or medians with interquartile range (IQR), and The Wilcoxon–Mann–Whitney test or Fisher's exact test was performed to measure the distribution differences of variables between the development and external validation groups. Univariate and multivariate logistic regression analyses were performed to detect the correlations between routine clinical variables and the occurrence of pregnancy loss. Based on the selected independently significant variables, the nomogram model for the prediction of pregnancy loss was established.

Model Validation

To assess the predictive accuracy and estimate the sensitivity and specificity values for each, and combinations of the variables, receiver-operating characteristic (ROC) curves were generated. On the basis of these predictive factors, a nomogram was constructed to predict pregnancy loss. Nomogram model performance was assessed by examining discrimination and calibration in the development and validation cohorts. The calibration was constructed to examine the agreement between the predicted probabilities with the observed outcome, which was assessed by the Hosmer–Lemeshow goodness-of-fit test and calibration plots. The calibration plot was calculated by the 1000 repetitions bootstrap resampling.

Results

Characteristics of the Development and External Validation Groups

In total, 245 patients were eligible for the study, of which 159 were assigned to the training group, while 86 were assigned to the external validation group (Figure 1). In the whole study population, the numbers of positive cases of second trimester pregnancy loss were 65 (26.53%). In the follow-up of transvaginal ultrasound, the proportion of CL <25mm was about 14.28%, which was far lower than the miscarriage rate.

There were no significant differences in maternal demographic and clinical characteristics between the training and validation groups (P>0.05), indicating that the features of the training and external validation groups were similar and that subsequent external validation would be representative (Table 1).

Predictive Factors Associated with Second Trimester Pregnancy Loss

We used univariate and multivariate regression analysis to examine the relationships between clinical factors and the probability of second trimester pregnancy loss in the training group (Table 2). Then, based on the findings of multivariate analysis, we created ROC curves for predicting second trimester pregnancy loss (Figure 3). We made the decision to create a predictive model for forecasting second trimester pregnancy loss after carefully weighing the predictive power and the number of positive cases of second trimester pregnancy loss. The longitudinal diameter of the cervical canal and thin cervix were found to be independent risk factors for miscarriage in the second trimester by multivariate logistic regression analysis.

Table 1 Characteristics of Non-Pregnant Women in Training and Validation Group

	Training Group (n = 159)	External Validation group (n = 86)	P-value
Maternal age (years)	29.03±3.10	30.12±2.92	0.286
Prepregnancy BMI*(kg/m2)	24.2±2.91	23.9±3.02	0.270
PCOS			0.961
No	150 (94.34)	81 (94.18)	
Yes	9 (5.66)	5 (5.81)	
Prior second-trimester pregnancy loss	1.67±0.81	1.67±0.67	0.984
History of LEEP			0.610
No	147 (92.46)	81 (94.18)	
Yes	12 (7.54)	5 (5.81)	
MRI Cervical length (mm)	25.59±4.59	25.19±4.88	0.510
MRI The longitudinal diameter of cervical canal(mm)	11.76±2.75	12.06±3.18	0.601
MRI thin cervical myometrium			0.085
No	115 (72.33)	53 (61.63)	
Yes	44 (27.67)	33 (38.37)	
MRI anterior lips of the cervix(mm)	9.79±2.76	9.68±2.76	0.815
MRI posterior lips of the cervix(mm)	10.14±2.69	10.53±2.81	0.967

Abbreviation: *BMI, body mass index.

Table 2 Potential Predictors and Multivariable Logistic Regression Model for Pregnancy Loss

Variable	Univariate analysis OR (95% CI)	*P*	Multivariable analysis OR (95% CI)	*P*
Female age(years)	1.08 (0.94–1.24)	0.264		
Prepregnancy BMI (kg/m2)	0.69 (0.61–0.82)	0.382		
PCOS		0.402		
No	1.00			
Yes	1.92 (0.29–15.19)			
Prior second-trimester loss	1.95 (1.15–3.39)	0.014	1.99 (1.00–4.17)	0.055
History of LEEP		0.637		
No	1.00			
Yes	1.37 (0.34–4.73)	0.634		
MRI Cervical length (mm)	0.96 (0.86–1.05)	0.37		
MRI The longitudinal diameter of cervical canal	0.60 (0.46–0.75)	0.000	0.59 (0.45–0.75)	0.002
MRI thin cervical myometrium		0.007		0.016
No	1.00		1.00	
Yes	3.45 (1.39–8.61)		4.01 (1.32–13.02)	
MRI anterior lips of the cervix (mm)	1.22 (1.04–1.44)	0.013	1.15 (0.94–1.42)	0.405
MRI posterior lips of the cervix (mm)	1.04 (0.89–1.22)	0.577		0.648

Development and Validation of a Nomogram for Second Trimester Pregnancy Loss

We created a nomogram to forecast the risk of pregnancy loss in the second trimester based on significant independent factors in multivariate regression analysis (Figure 4). The intersection of the vertical line from the variable to the point axis could be used to determine each point. The final stage was to add each variable point to determine the overall risk score. The total point axis could be used to read the risk of pregnancy loss in the second trimester. According to the calibration curves, the probability predicted by the nomogram and the actual probabilities in both the internal cohort and the exterior cohort were in good agreement (Figure 5). In the training group and external validation group, the AUCs of the nomogram predicting the probability of second trimester pregnancy loss were 0.826 (95% CI 0.730–0.923) and 0.825

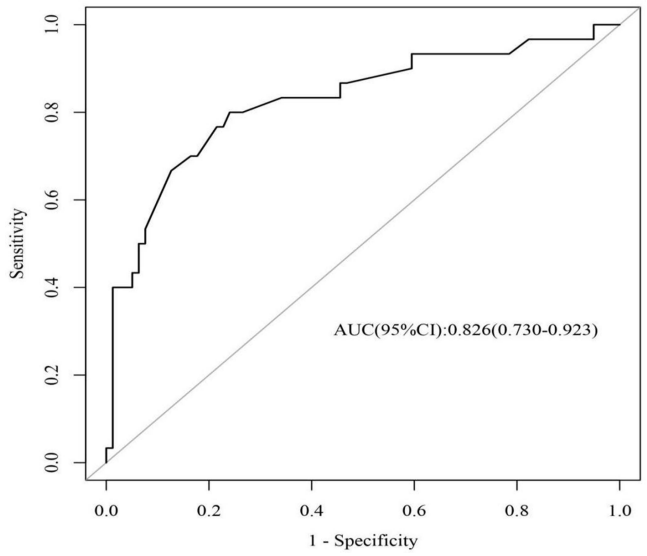

Figure 3 ROC curves for second trimester pregnancy loss.

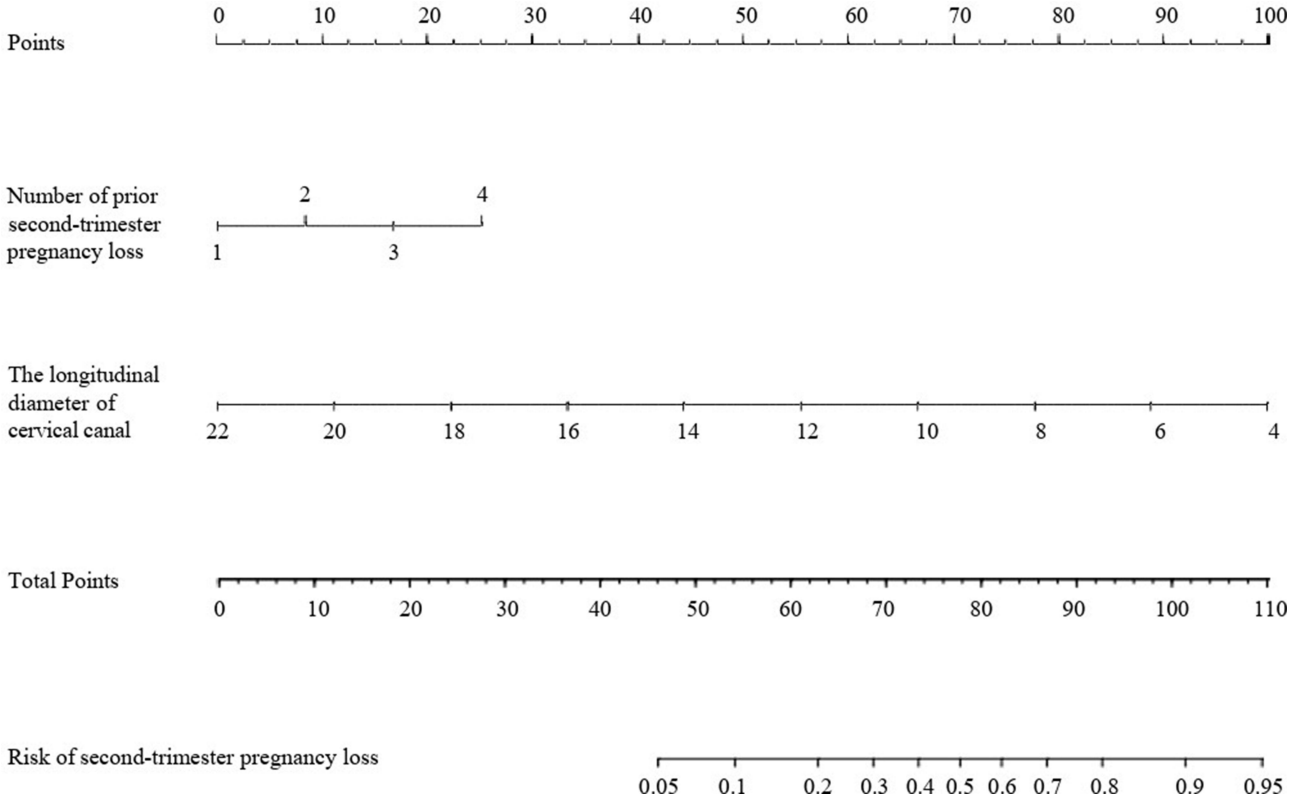

Figure 4 Nomogram for the prediction of second trimester pregnancy loss based on two independent risk factors.

(95% CI 0.664–0.986), respectively. The model reached a sensitivity of 80%, specificity of 75.90%, positive predictive value (PPV) of 55.80% and negative predictive value (NPV) of 90.90%.

Discussion

This study aimed to identify and describe the primary morphological indicators of CI in MRI. And to explore whether there is a means of assessing abortion before pregnancy. The selected population in the study are all those who have a history of second trimester loss, which is representative of a specific population.

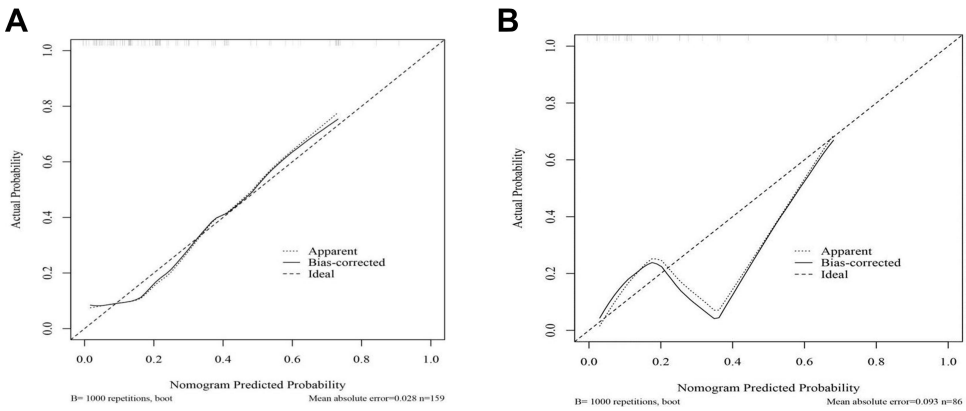

Figure 5 Calibration plots for the predicted and observed overall risk of the nomograms in (**A**) the training group; (**B**) the external validation group. The x-axis demonstrates the nomogram-predicted probability, and the y-axis shows the actual observed probability.

CI has been defined as painless dilatation and shortening of the cervix in the second trimester.[15] Diagnosis of CI is difficult because of the lack of standard diagnostic criteria. The incidence of CI is approximately 0.1% to 2%. Approximately 15% of them will recurrent abortion between 16 and 28 weeks of gestation.[3] CI factor accounts for approximately 8% of all late abortions and preterm birth.[16] As the gold standard for cervical measurement during pregnancy, transvaginal ultrasound is widely accepted, and has obtained evidence that CL is related to premature birth[17]. However, research employing TVUS to quantify CL and time to delivery have produced mixed results, as some women's cervical shortening is slow while in others, it is hastened. MRI is a non-invasive technology with the potential to reveal the initial state of the cervix in non pregnancy by detecting the thickness of the cervical myometrium, in addition to detecting the measurement of the cervix.

The cervix provides an important mechanical barrier to prevent ascending infections between the uterus and the microbe-rich vagina[18, 19] Cervix is composed of about 90% extracellular matrix (ECM) and about 10% cervical myometrium, while smooth muscle cells (SMCs) play a supporting role by secreting ECM contents.[20] Some results indicated that a history of intrapartum cervical laceration appeared to be an independent risk factor for CI, preterm delivery, recurrent cervical laceration in the subsequent pregnancy.[21, 22] For a cervix that already has an old laceration or congenital dysplasia, it may not be able to bear even in the first and second trimesters.

Our study was to access the cervix using MRI signs characterized in terms of both morphology and signal intensity, allowing for a better understanding of the cervix in women with CI. Because it produces no radiation, allows multi-directional, multidimensional scanning, and has exceptional soft tissue resolution, MRI is the preoperative imaging method of choice for CI. Additionally, it has been stated that an MRI scan can provide information on the cervix muscle, making it possible to improved comprehension of the physiological initial state of cervix. CI women are likely to have changes in the structure of the cervix before pregnancy, resulting in imaging abnormalities. We discovered that CI has several MRI features, including thin cervix which was probably correlated with such abnormalities.

In our retrospective analysis and external validation study, we developed a predictive model of second trimester pregnancy loss based on maternal characteristics and MRI features. The reason we comprehensively considered all the above factors when building the model was that the predictive performance of a single maternal factor or cervix measurement is not satisfactory. In the general population, etiologies of second-trimester pregnancy loss include CI, multiple pregnancy, autoimmune factors, fetal abnormalities, and maternal medical illness.[23–25] Patients with PCOS with hyperandrogenism were reported to have a higher prevalence of CI and an approximately 6% higher risk of preterm delivery compared to women without PCOS.[26, 27] Combined with previous studies and our results, women with second trimester pregnancy loss who are known to be associated with shorter longitudinal diameter of cervical canal, may be at a higher risk of second trimester loss and should garner the focused attention of clinicians. Presence of a short cervix is certainly compatible with CI, but in non-pregnant women with a history of second trimester loss, other signs need to be sought, even before the shortening of the cervix.

More applications of MRI to cervical structure are also under active development.[28, 29] A recent study has shown diffusion MRI images detected changes in tissue organization as gestation progressed suggesting the potential application of this technique to non-invasively monitor cervical changes that precede the onset of labor in women at risk for preterm delivery.[14] Our study is concordant with existing research indicating that MRI is a promising tool to assess the cervix. Women experiencing second-trimester miscarriage are at increased risk in subsequent pregnancies of recurrence.[30] At present, there is still no good method for predicting second trimester pregnancy loss of CI women. Our research incorporated maternal characteristics and measurement of cervix to develop a nomogram model that reached favourable PPV and NPV.

Still, some limitations of the present study have to be underlined. Most importantly, post-pregnancy monitoring is mainly carried out by transvaginal ultrasound, and no follow-up monitoring of MRI during pregnancy has been carried out. And the small patient sample size requires more cases to assess the predictive value of non-pregnant cervical measurements.

Despite these limitations, our results provide the early signs of CI seen on cervical MRI. Our nomogram model to predict the probability of second trimester pregnancy loss occurrence could be a useful tool in aiding physicians and patients who have history of second trimester pregnancy loss.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the second affiliated hospital of Soochow university (JD-LK-2018-030-03) on August 6, 2018. The study was conducted according to the ethical principles stated in the Declaration of Helsinki. Informed consent was obtained from all subjects.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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