

Prognostic model on niche development after a first caesarean section: development and internal validation

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ABSTRACT

Objective: To develop and internally validate a prognostic prediction model for development of a niche in the uterine scar after a first caesarean section (CS).

Study design: Secondary analyses on data of a randomized controlled trial, performed in 32 hospitals in the Netherlands among women undergoing a first caesarean section. We used multivariable backward logistic regression. Missing data were handled using multiple imputation. Model performance was assessed by calibration and discrimination. Internal validation using bootstrapping techniques took place. The outcome was ‘development of a niche in the uterus’, defined as an indentation of ≥ 2 mm in the myometrium.

Results: We developed two models to predict niche development: in the total population and after elective CS. Patient related risk factors were: gestational age, twin pregnancy and smoking, and surgery related risk factors were double-layer closure and less surgical experience. Multiparity and Vicryl suture material were protective factors. The prediction model in women undergoing elective CS revealed similar results. After internal validation, Nagelkerke R^2 ranged from 0.01 to 0.05 and was considered low; median area under the curve (AUC) ranged from 0.56 to 0.62, indicating failed to poor discriminative ability.

Conclusions: The model cannot be used to accurately predict the development of a niche after a first CS. However, several factors seem to influence scar healing which indicates possibilities for future prevention such as surgical experience and suture material. The search for additional risk factors that play a role in development of a niche should be continued to improve the discriminative ability.

Introduction

After caesarean section (CS), approximately 60% of women develop

a niche in the caesarean scar, with varying prevalence rates described in different populations and using different methods [1]. A niche is recently defined by an expert panel to be “an indentation at the site of the

Abbreviations: AMT, adjacent myometrium thickness; AUC, area under the curve; eCRF, electronic Case Report Form; IQR, interquartile range; MAR, missing at random; MCAR, missing completely at random; MICE, multiple imputation by chained equations; OR, odds ratio; PDS, polydioxanone suture; PE, pre-eclampsia; PIH, pregnancy induced hypertension; RCT, randomised controlled trial; RMT, residual myometrium thickness; ROC, receiver operating characteristic; SHG, sonohysterography; TVUS, transvaginal ultrasound.

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CS scar with a depth of at least 2 mm” [2], and is also called ‘isthmocele’ or ‘caesarean scar defect’ [3,4]. Presence and size of a niche, but also residual myometrium thickness (RMT) overlying the niche, are associated with the presence of several gynecological symptoms such as postmenstrual spotting and dysmenorrhoea, [5–7] possibly impaired fertility, [8] as well as obstetric challenges in future pregnancies [9–11]. A niche can be visualized by ultrasound, preferably contrast-enhanced, which is considered as the gold standard [1,12]. Measurements of the niche (length, depth, width) and RMT can be performed for clinical assessment, before executing surgical treatment and for research purposes [2].

The etiology of a niche remains unknown, although several risk factors have been proposed in retrospective and prospective cohort studies [1,3,13–18]. These risk factors can be roughly divided into patient, labour or surgery related factors: previous CS, higher body mass index (BMI), hypertensive pregnancy disorder, and gestational diabetes [3,13–17] (patient related); advanced dilatation, duration of labour and deeper presenting part [3,18] (labour related); and short operative time and single-layer myometrium closure [1,18] (surgery related). However, due to the design of these studies, bias cannot be ruled out and information regarding some factors such as uterine closure technique was lacking, influencing the development of a reliable prediction model.

If we could identify women at risk for development of a niche, this could change future counselling regarding mode of delivery, especially in case of elective CS. The identification of women at risk enables us to inform women postoperatively and perform early sonographic check-up in case of symptoms, and to develop future preventive strategies.

Therefore, the primary objective of this study was to develop and internally validate a prognostic prediction model for the development of a niche in women undergoing a first CS. Our secondary aim was to develop a prediction model for women undergoing an elective first CS.

Material and methods

Study design

We conducted a randomized controlled trial (RCT) to determine the effectiveness of double-layer closure of the uterine incision compared to single-layer closure on postmenstrual spotting nine months after a first CS. The results of the primary aim of this RCT are published elsewhere [19]. In the current research paper we report the results of prognostic factor analysis. The study was carried out in 32 hospitals (university, teaching and district hospitals) in the Netherlands, within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology between May 25, 2016 and June 27, 2018. Follow-up ended on May 28, 2019.

The trial was registered (trialssearch.who.int; NTR5480) on the 29th of October 2015. The protocol of the study was approved by the institutional review board of Amsterdam UMC – location VUmc (2015.462) and subsequently by the boards of all participating hospitals. The study protocol has been published [20]. We followed the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) statement in the reporting of our results [21].

Participants

We recruited potential participants before they underwent a planned or unplanned first CS. We judged patients eligible for the study if it was the first CS, if they were 18 years or older and had good comprehension of the Dutch or English language. Exclusion criteria were: inadequate possibility for counselling, previous major uterine surgery, women with known causes of menstrual disorders, placenta in- or percreta during the current pregnancy or more than three foetuses during the current pregnancy. All participants provided written informed consent before enrollment.

Outcome variables

Clinical information about the CS was exported from an electronic case report form (eCRF). Three months after randomisation, participants were invited for transvaginal ultrasound (TVUS) examination of the uterine scar. We performed ultrasound evaluation in a standardized way, as proposed by Jordans et al. [2]. All sonographers were trained by a mandatory e-learning to create uniformity. Validation of ultrasound images and measurements was done by random checks of an ultrasound expert (J.H.).

In the sagittal plane we measured presence of a niche, length and depth of the indentation, RMT and adjacent myometrium thickness (AMT). In the transversal plane we measured the width of the niche. (See Fig. 1) These measurements were recorded in the eCRF. When no niche was visible or ultrasonography was not conclusive contrast-enhanced ultrasound was performed, either with gel or saline (i.e., sonohysterography [SHG]) and the same measurements were completed. When a participant declined or when she was in the luteal phase without adequate contraception, we did not perform an SHG. A predefined cut-off of niche depth was 2.0 mm to determine niche presence, according to the international recommendation [2]. Detection of a niche by SHG when no niche was seen using TVUS was defined as ‘a niche is present’, since SHG is considered to be superior over TVUS in evaluation of niches [1,2,12]. Sonographers were blinded for the allocated uterine closure method from the initial RCT from which data for this study on risk factors was derived. Other predictors might have been known by the sonographer, but they were not aware of the development of a prediction model for niche development at the time of ultrasound evaluation.

Predictor variables

Variables were candidate predictors when they were reported in previous studies or when we had clinically plausible explanations to include a variable as possible predictor variable. Risk factors investigated to be included in the prediction model were subdivided into patient related factors, labour related factors, and surgical factors. Patient related factors were maternal age, body mass index (BMI, kg/m²); smoking during or before pregnancy, gestational age (weeks), parity, singleton or twin pregnancy, presence of diabetes (gestational or mellitus), presence of hypertensive pregnancy disorders (pregnancy induced hypertension [PIH] or pre-eclampsia [PE]). These variables were assessed through digital questionnaires the first month after CS. Labour related factors possibly influencing the development of the lower uterine segment were type of CS (elective or during labour, failure to progress in first or second stage), presence of contractions and dilatation, induction and/or augmentation of labour, station of the presenting part, and fetal weight; surgical factors were operative time, single- or double-layer closure of the uterus, use of endometrial handling technique (in case of single-layer closure), experience of the surgeon (resident of gynecologist), type of suture material, and possible complications such as intraoperative blood loss (per 100 ml) and peripartum infection (temperature of > 38° Celsius or need for antibiotic treatment). Both labour related and surgical factors were assessed by the research nurses of the participating hospitals and were looked up in the electronic hospital file. Assessment of predictors was done before the ultrasound at 3 months follow-up was performed, so ultrasound performers were blinded for the group allocation and for baseline characteristics of the patients.

The primary objective was to develop a prediction model for niche development. An initial secondary objective was to develop a prediction model for development of a large niche, and for both outcomes (niche and large niche) additionally in a subset of women undergoing elective CS. We decided to present the methods section, results and discussion topics regarding a large niche in Appendix A due to several methodological limitations and therefore the results should be interpreted with caution: we did not perform an SHG in women where a niche was already identified on TVUS which might have caused underestimation of



Fig. 1. Niche on transvaginal ultrasound. *Left:* schematic drawing of a niche in the caesarean scar by transvaginal ultrasound, *middle:* transvaginal ultrasound without contrast in a participant with a niche after participating in the 2Close study, *right:* the same ultrasound as shown in the middle, with red (upper) line = residual myometrium thickness (RMT); yellow (middle) line = niche depth; blue (lower) line = niche length. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

the prevalence of a large niche, since the RMT using TVUS is in general substantially lower using SHG [5,6,12]. Additionally, the group of women with a large niche is per definition a subsample of the total population with a niche so the relative and absolute number of ‘events’ is smaller.

Missing data

Independent t-tests and chi-square tests with missing data indicator as group variable were used to differentiate between missing completely at random (MCAR) and not MCAR variables. The results of these tests revealed that missing data in our database was most likely missing at random (MAR) for the predictors maternal age, parity, hypertensive disorder, gestational age and operative time, for missing values on presence of a niche. Data was most likely MCAR for all other predictors. Multiple imputation is a good method to handle missing data in both situations [22]. We therefore performed multiple imputation for all missing predictor variables using the Multiple Imputation by Chained Equation (MICE) method with predictive mean matching [23]. We created ten datasets, since the total percentage of missing observations was 6%. We used Rubin’s rules to pool estimates of the regression coefficient from the imputed datasets [24].

Additional sensitivity analysis were performed to report the results of the original dataset excluding missing data.

Statistical analyses

We estimated 0.5 day/month reduction in postmenstrual spotting (the primary outcome of the initial RCT) to be clinically relevant. Using a significance level of 5%, we needed 1488 women to be included to achieve a power of 80%. We increased this number to 2290 women to be included, taking into account 35% of women unevaluable (due to drop-out or amenorrhoea) for the primary outcome. This sample was supposed to be also sufficient for performing the current study for development and internal validation of our prognostic model.

Model development

The linear relationship between continuous predictors and the outcome was tested with spline functions, and when no linear relationship was present the spline function was used in the regression models [25].

Univariate logistic regression analysis was used to determine associations between continuous, dichotomous and categorical variables and presence of a niche (depth ≥ 2 mm; not present = 0, present = 1).

To prevent overfitting of the model, we included at least 10 events per possible predictive variable for our logistic regression model [26].

For the multivariable analysis, we selected the variable with

clinically the highest expected predictive value in case of multicollinearity between predictors. Backward stepwise selection was performed using Wald test for removal of a predictor using Akaike’s Information Criterion ($p < 0.157$) as recommended by the TRIPOD statement [21,25,27]. We repeated the procedure for development of the model in a subset of women undergoing an elective CS.

Model performance

The performance of the models was assessed by testing overall performance, calibration and discrimination. Nagelkerke R^2 was computed to quantify the explained variance of the model and thereby overall performance. Calibration refers to the agreement between predicted and observed probabilities. We performed Hosmer-Lemeshow goodness-of-fit test, with a p-value > 0.05 indicating no significant difference between observed and predicted outcomes, thus a good fit of the final model. Discrimination of the model refers to the ability to distinguish between women who did and did not develop a niche. Discriminative ability was determined by plotting receiver operating characteristic (ROC) curve and corresponding median area under the curve (AUC) with c-statistic in each imputed dataset [28]. The AUC reflects the degree of discrimination; AUC < 0.60 reflects failing, $0.60 - 0.69$ poor, $0.70 - 0.79$ fair, $0.80 - 0.89$ good, and ≥ 0.90 excellent discrimination of the model.

Internal validation

To correct for optimism, internal validation using bootstrapping techniques (500 bootstraps) was performed on the first imputed dataset [29]. The resulting shrinkage factor was used to adjust the regression coefficients.

We used R (version 3.6.1) for the multivariable analyses and internal validation, and SPSS (IBM SPSS Statistics, version 26.0) for all other analyses.

Results

The flow of participants is visualized in Fig. 2. From May 2016 until June 2018, 2292 women were included in the study. Table 1 presents baseline characteristics of women with and without a niche. We performed 1961 (85.6%) TVUS, and additionally 535 (27.3%) SHG, and 80 (4.1%) women refused SHG or the procedure had to be terminated. The prevalence of a niche was 71.2% (1396/1961) and of a large niche 12.5% (244/1952) defined as RMT ≤ 3 mm. As presented in Table 1, 61.1% of all women that underwent sonographic examination underwent previous elective CS. Univariate analysis of the imputed data is shown in Table 2. Baseline characteristics and univariate analysis of the imputed data regarding women with a large niche are presented in table S1 and S2, respectively.

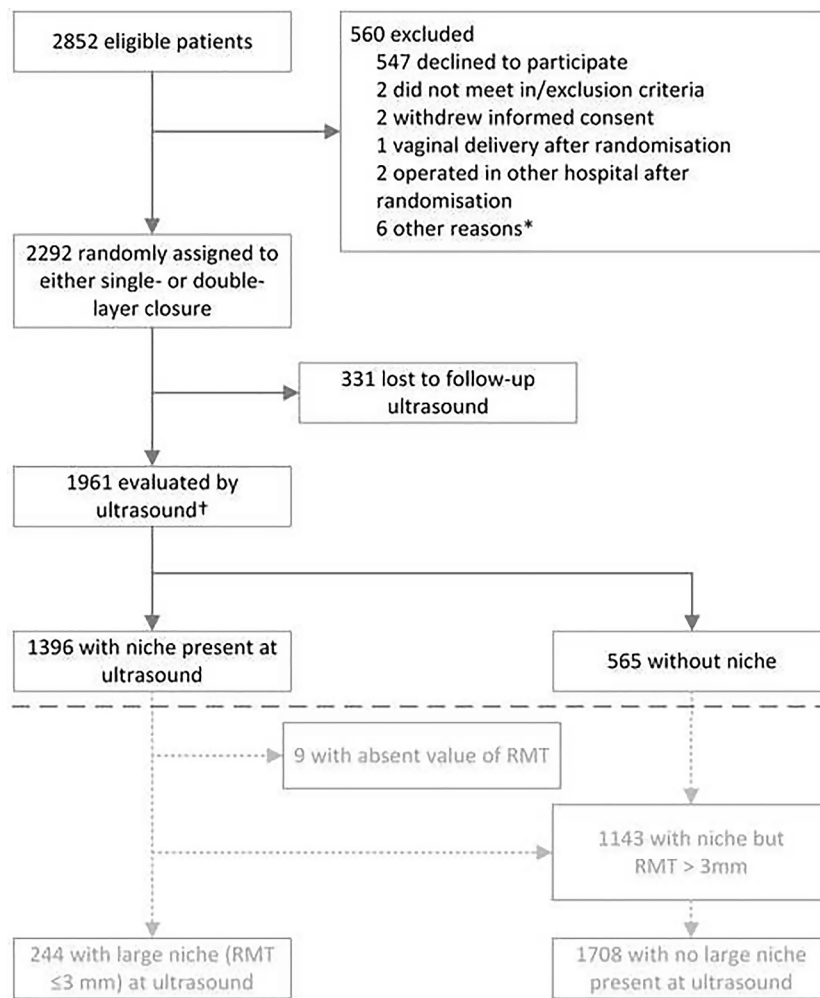


Fig. 2. Flowchart of the 2Close study. Modified for purposes of this study in which we investigated risk factors and attempted to develop a prediction model for niche development. *Logistical reasons, computer randomisation issues, passing through the allocated method to operating gynaecologist, or participant not traceable.

Missing data

Outcome variables

Data about the presence of a niche (defined as a depth of ≥ 2 mm) was missing for 331 (14.4 %) of the participants.

Predictor variables

Regarding patient related factors: maternal age, smoking status, body mass index and gestational age were all missing in 12.2%, presence of gestational diabetes or diabetes mellitus was missing in 12.5%, presence of PIH or PE in 12.6%, parity in 13.3%. Regarding labour related predictors: cervical dilatation was missing in 2.7%, station of fetal presenting part in 5.9%. Regarding surgery related predictors: operating time of the CS was missing in 2%, endometrial handling technique was missing in 8.6% within the participants that received single-layer closure. All other predictors were available for all 2292 participants.

Development

Predictor variables parity, gestational age at delivery, cervical dilatation, inclusion of endometrium, double-layer closure and suture material appeared to be most relevant for niche development after univariate logistic regression analyses when all predictors were analysed. We decided to leave out the predictor variables ‘contractions’, ‘augmentation with oxytocin’, ‘induction of labour’ and ‘type of CS’

from the multivariable analyses due to collinearity with the continuous predictor variable ‘dilatation’. The same was decided for ‘fetal weight’ due to collinearity with ‘twin pregnancy’. After applying backward regression analysis with all the remaining predictors, smoking status (overall Wald $p = 0.128$; during pregnancy OR 1.45; 95% CI 0.89 to 2.36, $p = 0.137$; prior to pregnancy OR 1.20; 95% CI 0.96 to 1.50, $p = 0.105$), gestational age (for each additional week OR 1.04; 95% CI 1.00 to 1.10, $p = 0.073$), twin pregnancy (OR 1.37; 95% CI 0.89 to 1.10, $p = 0.152$), double-layer closure (OR 1.28; 95% CI 1.04 to 1.57, $p = 0.029$) and surgical experience: resident (OR 1.28; 95% CI 0.99 to 1.64, $p = 0.058$) were independent risk factors, and being multiparous (OR 0.66; 95% CI 0.51 to 0.85, $p = 0.001$) and suture material: Vicryl (OR 0.65; 95% CI 0.50 to 0.84, $p < 0.001$) were independent protective factors for niche development. Being multiparous in this context means one or more previous vaginal deliveries, since all women in our study underwent a first CS.

We repeated the analyses in a subset of women that underwent elective CS. For the univariate and multivariable model, we excluded ‘dilatation’, ‘type of CS’ and ‘fetal station’ as a predictor, since all elective CS had no dilatation or it was not measured, and they were all scored as ‘elective CS’. Moreover, the predictor ‘intraoperative infection’ was not present in this subset, so it was deleted from the model.

After applying backward regression analysis with the remaining predictors in the subset of women that underwent elective CS, twin pregnancy (OR 1.38; 95% CI 0.89 to 2.14, $p = 0.148$), double-layer closure (OR 1.61; 95% CI 1.25 to 2.07, $p < 0.001$) and surgical

Table 1

Baseline characteristics of complete cases per variable in the total population and in a subset of women undergoing elective CS.

	Ultrasound performed – total population (n = 1961)		Ultrasound performed – subset elective CS (n = 1199)	
	With niche, n = 1396 (71.2%)	Without niche, n = 565 (28.8%)	With niche, n = 833 (59.5%)	Without niche, n = 366 (40.5%)
<i>Preoperative characteristics</i>				
Maternal age	32.0 (4.6)	32.4 (4.6)	32.3 (4.6)	32.5 (4.5)
Missing	135	66	62	32
Smoking status				
No smoking	702 (55.7)	299 (59.9)	428 (55.5)	203 (60.8)
During pregnancy	68 (5.4)	21 (4.2)	47 (6.1)	11 (3.3)
>1 years prior to pregnancy	491 (38.9)	179 (35.9)	296 (38.4)	120 (35.9)
BMI (kg/m ²) mean	26.6 (4.7)	26.1 (4.6)	26.1 (4.5)	25.6 (4.5)
Missing	136	66	62	32
Gestational age (weeks)	38.7 (2.3)	38.3 (2.8)	38.1 (2.2)	37.7 (2.9)
Missing	135	66	62	32
Multiparous	257 (20.6)	138 (28.0)	217 (28.6)	121 (36.8)
Twins	100 (7.2)	34 (6.0)	83 (10.0)	29 (7.9)
Diabetes				
No	1140 (90.8)	445 (89.2)	712 (92.7)	303 (90.7)
Gestational	89 (7.1)	51 (10.2)	44 (5.7)	28 (8.4)
Mellitus	27 (2.1)	3 (0.6)	12 (1.6)	3 (0.9)
Hypertensive disorder				
No	1040 (82.7)	410 (82.7)	654 (85.2)	285 (85.8)
Pregnancy induced hypertension	142 (11.3)	44 (8.9)	72 (9.4)	16 (4.8)
Pre-eclampsia	75 (6.0)	42 (8.5)	42 (5.5)	31 (9.3)
<i>Delivery characteristics</i>				
Induction of labour	353 (25.3)	138 (24.4)	–	–
Augmentation with oxytocin	489 (35.0)	167 (29.6)	–	–
Contractions present	641 (45.9)	235 (41.6)	106 (12.7)	44 (12.0)
Station of fetal presenting part				
Elective CS, not measured	690 (52.5)	309 (58.0)	690 (82.8)	309 (84.5)
0–1	446 (33.9)	170 (31.9)	134 (16.1)	51 (13.9)
2	150 (11.4)	50 (9.4)	9 (1.1)	6 (1.6)
3–4	28 (2.1)	4 (0.8)	–	–
Missing	82	32	–	–
Cervical dilatation (centimeters)	0 (0–5)	0 (0–4)	–	–
Missing	37	16	–	–
Type of CS				
Prelabour	833 (59.7)	366 (64.8)	–	–
Intrapartum, failure to progress 1st stage	329 (23.6)	113 (20.0)	–	–
Intrapartum, failure to progress 2nd stage	102 (7.3)	35 (6.2)	–	–
Intrapartum, other	132 (9.5)	51 (9.0)	–	–
Emergency CS	102 (7.3)	43 (7.6)	30 (3.6)	16 (4.4)
Fetal weight (grams)*	3380 (3021–3780)	3325 (2948–3765)	3275 (2945–3608)	3200 (2796–3575)
<i>Perioperative characteristics</i>				
Operating time (minutes)	40.9 (11.7)	40.0 (11.6)	40.7 (11.9)	39.7 (11.4)
Missing	30	9	13	8
Surgical experience: resident	625 (44.8)	221 (39.1)	415 (49.8)	157 (42.9)
Double-layer closure	702 (50.3)	250 (44.2)	447 (53.7)	149 (40.7)
Endometrial saving technique†	154 (11.5)	104 (19.1)	87 (10.9)	74 (20.9)
Suture material vicryl ‡	1074 (76.9)	472 (83.5)	683 (82.0)	322 (88.0)
Temperature > 38 °C	17 (1.2)	6 (1.1)	1 (0.1)	2 (0.5)
Blood loss (milliliter)	400 (300–600)	400 (300–500)	400 (300–500)	350 (300–500)

RMT: residual myometrium thickness, BMI: body mass index, CS: caesarean section. *Only for singletons. †All participants that received double-layer closure were coded as ‘no endometrial saving technique’ according to study protocol. ‡ Other means Novosyn, Polysorb, PDS, or other suture material.

experience: resident (OR 1.31; 95% CI 0.96 to 1.79, $p = 0.091$) were independent risk factors and smoking status was a risk factor (overall Wald $p = 0.105$, during pregnancy OR 1.86; 95% CI 0.96 to 3.58, $p = 0.064$; and prior to pregnancy OR 1.19; 95% CI 0.91 to 1.56, $p = 0.210$). Being multiparous (OR 0.67; 95% CI 0.51 to 0.87, $p = 0.003$) and suture material: Vicryl (OR 0.60; 95% CI 0.42 to 0.87, $p = 0.007$) were independent protective factors for niche development in this subset. Hypertensive disorder seemed to be a risk factor when present as PIH but a protective factor when present PE: (overall Wald $p = 0.031$, PIH OR 1.51; 95% CI 0.91 to 2.63, $p = 0.141$; and PE OR 0.56; 95% CI 0.32 to 1.01, $p = 0.052$). The predictor gestational age was not a risk factor in this subset anymore after backward selection. Results for the final models regarding a large niche (total population and subset with elective CS) are presented in [Table S3 in the Appendix](#).

When only the complete cases were used for backward regression analysis, this revealed slightly different results for all outcomes, but the

most important factors remained statistically significant in this sensitivity analysis.

Performance

Median Nagelkerke R^2 was low within the total group ($R^2 = 0.036$ [IQR 0.033–0.043], and within the subset of women after elective CS ($R^2 = 0.062$ [IQR 0.058–0.066])).

The Hosmer and Lemeshow goodness-of-fit test was not significant in all the imputed datasets for both outcomes (range p -values 0.817 to 0.993) indicating good model fit.

The median AUC was 0.60 (IQR 0.60–0.60) for niche development and in the subset of women undergoing an elective CS it was 0.63 (IQR 0.63–0.63). This means that the model has poor discriminative ability (AUC 0.60 – 0.69) in both populations.

When evaluating the original dataset and analyzing only complete

Table 2

Results of univariate logistic regression analysis after multiple imputation.

Parameter continue dich cat	Niche – total population			Niche – subset elective CS		
	OR	95 % CI	P- value	OR	95 % CI	P- value
<i>Preoperative characteristics</i>						
Maternal age	0.986	0.960–1.013	0.309	0.988	0.958–1.019	0.427
Smoking status			0.137			0.120
No smoking	Ref	ref	Ref	Ref	Ref	ref
During pregnancy	1.322	0.811–2.155	0.378	1.751	0.919–3.338	0.088
>1 years prior to pregnancy	1.232	0.986–1.540	0.066	1.213	0.925–1.591	0.163
BMI (kg/m ²)	1.013	0.990–1.037	0.261	1.014	0.984–1.045	0.365
Gestational age (weeks)	1.050	1.002–1.100	0.040	1.050	1.001–1.100	0.045
Parity: multiparous	0.644	0.506–0.820	<0.001	0.682	0.527–0.884	0.004
Twins	1.122	0.737–1.707	0.589	1.171	0.767–1.790	0.464
Diabetes			0.213			0.371
No diabetes	Ref	Ref	ref	ref	ref	Ref
Gestational	0.732	0.501–1.070	0.105	0.717	0.434–1.184	0.191
Mellitus	2.477	0.388–15.817	0.316	1.625	0.371–7.109	0.508
Hypertensive disorder			0.111			0.028
No hypertensive disorder	Ref	Ref	Ref	Ref	ref	Ref
Pregnancy induced hypertension	1.156	0.822–1.628	0.403	1.572	0.914–2.702	0.101
Pre-eclampsia	0.646	0.372–1.120	0.114	0.578	0.328–1.017	0.057
<i>Delivery characteristics</i>						
Induction	1.044	0.794–1.371	0.756	–	–	–
Augmentation	1.265	0.991–1.614	0.059	–	–	–
Contractions present	1.173	0.949–1.451	0.139	1.063	0.733–1.542	0.748
Station of fetal presenting part			0.202	–	–	–
Elective CS	Ref	Ref	Ref	–	–	–
0–1	1.133	0.888–1.446	0.312	–	–	–
2	1.308	0.915–1.871	0.140	–	–	–
3–4	2.327	0.750–7.218	0.139	–	–	–
Cervical dilatation (centimeters)	1.037	1.005–1.071	0.026	1.027	0.926–1.138	0.617
Type of CS			0.298	–	–	–
Prelabour	Ref	Ref	Ref	–	–	–
Intrapartum, failure to progress 1st stage	1.252	0.950–1.650	0.110	–	–	–
Intrapartum, failure to progress 2nd stage	1.275	0.842–1.932	0.249	–	–	–
Intrapartum, other	1.114	0.784–1.585	0.545	–	–	–
Emergency CS	0.933	0.650–1.339	0.705	0.798	0.437–1.455	0.461
<i>Perioperative characteristics</i>						
Operating time (minutes)	1.006	0.997–1.014	0.198	1.008	0.997–1.019	0.160
Surgical experience: resident	1.181	0.927–1.505	0.121	1.246	0.913–1.700	0.162
Double-layer closure	1.264	1.038–1.540	0.020	1.614	1.262–2.066	<0.001
Endometrial saving technique*	0.575	0.439–0.752	<0.001	0.500	0.357–0.700	<0.001
Suture material vicryl†	0.662	0.516–0.849	0.001	0.635	0.440–0.917	0.016
Temperature > 38 °C	1.143	0.467–2.795	0.770	0.225	0.020–2.526	0.227
Blood loss (per 100 ml)	1.012	0.986–1.039	0.373	1.004	0.973–1.035	0.810

Niche: defined as indentation of ≥ 2 mm in myometrium at site of incision. OR: odds ratio, CI: confidence interval, BMI: body mass index, CS: caesarean section, °C: degrees Celsius. *All participants that received double-layer closure were coded as ‘no endometrial saving technique’ according to study protocol. †Other means Novosyn, Polysorb, PDS, or other suture material.

cases, this revealed slightly different results due to a relatively large percentage of cases with missing data for any variable. In both populations (total group and subset of elective CS) one or two predictor variables had to be excluded from the model due to a p-value > 0.157. R^2 was 0.048 for niche development in the total population, and 0.109 in the elective CS subset. Median AUC was 0.615 in the total population and slightly higher and in the subset of elective CS: 0.660. Overall, sensitivity analyses revealed similar results as the primary analysis with a comparable low values of R^2 for overall performance as well as comparable low AUC, indicating poor discriminative ability of the derived models.

Validation

After performing bootstrapping, the median slope shrinkage factor in all the imputed datasets ranged from 0.88 to 0.90. Table 3 contains the adjusted ORs for all predictors and outcomes, including performance parameters R^2 and AUC derived after internal validation. The explained variance decreased to R^2 –values ranging from 0.03 to 0.05.

The median AUC of the model decreased after internal validation and

ranged from 0.59 to 0.62 for niche development in the total population and the elective CS subset, respectively. This means poor discrimination in the elective CS population and failed discriminative ability in the total group.

Discussion

Main findings

We developed a prediction model for niche development 3 months after a first CS, both in the total population of planned and unplanned first CSs, as in the subset of women with elective CS only. We identified risk factors for niche development: gestational age, twin pregnancy, smoking, double-layer closure and less surgical experience. Protective factors were multiparity (i.e., previous vaginal delivery or deliveries) and Vicryl as suture material. In the elective CS population, similar predictive factors were identified, but hypertensive pregnancy disorder was added as factor and gestational age was removed from the final model for niche development. For presence of a niche, both in the total study population and in the subgroup of elective CS, the prediction

Table 3

Multivariable logistic regression analysis of odds of niche presence in the total population and in subset of women undergoing elective first CS.

Variable	Final model niche presence – total population			R ²	AUC	Final model niche presence – subset elective CS			R ²	AUC
	OR	95% CI	p-value			OR	95% CI	p-value		
Smoking			0.128	–	–			0.105	–	–
No	Ref	Ref	Ref	–	–	ref	ref	ref	–	–
During pregnancy	1.447	0.887–2.363	0.137	–	–	1.857	0.964–3.579	0.064	–	–
Prior to pregnancy	1.201	0.962–1.500	0.105	–	–	1.188	0.907–1.557	0.210	–	–
Gestational age (weeks)	1.044	0.996–1.095	0.074	–	–	–	–	–	–	–
Parity: multiparous (1 = yes)	0.658	0.512–0.845	0.001	–	–	0.669	0.513–0.874	0.003	–	–
Twins (1 = yes)	1.366	0.890–1.097	0.152	–	–	1.381	0.891–2.142	0.148	–	–
Double-layer closure (1 = single- 2 = double-layer)	1.280	1.042–1.572	0.019	–	–	1.605	1.247–2.067	<0.001	–	–
Suture material: vicryl (1 = yes)	0.646	0.500–0.835	<0.001	–	–	0.602	0.416–0.872	0.007	–	–
Surgical experience: (1 = gynaecologist, 2 = resident)	1.275	0.991–1.640	0.058	–	–	1.310	0.957–1.794	0.091	–	–
Hypertensive disorder	–	–	–	–	–	–	–	–	–	–
No	–	–	–	–	–	Ref	Ref	Ref	–	–
Pregnancy induced hypertension	–	–	–	–	–	1.513	0.907–2.628	0.141	–	–
Pre-eclampsia	–	–	–	–	–	0.563	0.315–1.005	0.052	–	–
Performance	–	–	–	0.03	0.59	–	–	–	0.05	0.62

Odds ratio > 1: in favour of developing a niche. Performance parameters derived after internal validation. R²: Nagelkerke R², AUC: area under the receiver operating characteristic curve, OR: odds ratio, CI: confidence interval, ref: reference. The predicted probability of a niche ($\geq 2\text{mm}$) can be calculated using the following formula (after bootstrapping): $P(\text{niche}) = 1/(1 \exp(-(-1.1219 + \text{smoking} [\text{during}] \times 0.3697 + \text{smoking} [\text{prior to}] \times 0.1833 + \text{gestational age} \times 0.0431 + \text{multiparity} \times -0.4184 + \text{twins} \times 0.3121 + \text{double-layer closure} \times 0.2469 + \text{vicryl} \times -0.4374 + \text{surgical experience} \times 0.2430)))$. Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.90.

The predicted probability of a niche ($\geq 2\text{mm}$) in the subset of women undergoing elective CS can be calculated using the following formula (after bootstrapping): $P(\text{niche elective CS}) = 1/(1 \exp(-(-0.1757 + \text{smoking} [\text{during}] \times 0.6191 + \text{smoking} [\text{prior to}] \times 0.1726 + \text{multiparity} \times -0.4017 + \text{twins} \times 0.3231 + \text{double-layer closure} \times 0.4734 + \text{vicryl} \times -0.5069 + \text{surgical experience} \times 0.2700 + \text{hypertensive disorder} [\text{PIH}] \times 0.4139 + \text{hypertensive disorder} [\text{PE}] \times -0.5753)))$. Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.88.

models were neither accurate nor discriminating.

Strengths and limitations

The completeness of data from this large multicenter, well conducted and monitored RCT is a major strength of this study. The large sample size was sufficient for prediction in terms of number of events and predictors used in the model. All study measurements were performed by trained research staff that worked according to study protocol, and data was entered in an electronic case report form. We included only women with a first CS to avoid confounding of one or more previous CS on the outcome of interest. The inclusion of women with a planned and unplanned first CS allowed us to include this as a potential predictor. Additionally, ultrasound measurements were checked and validated by an expert (J.H.). Lastly, we applied multiple imputation and bootstrapping as state-of-the-art statistical techniques for development and validation of the model.

We also faced several limitations. The predictor variables were collected partly through patients and partly through trained research staff, which resulted in differences in missing data. However, the overall proportion of missing values was low (6%). We did, unfortunately, not record the duration of labour in case of an unplanned CS, although this has been suggested as a risk factor previously [15]. The same accounts for the collection of participants' blood samples to determine abnormalities, for example, hemoglobin, leukocyte or thrombocyte count. A limitation regarding the outcomes of interest is that multiple ultrasound examiners performed the structured ultrasound evaluation and this was therefore not limited to one or two sonographers, so interobserver variability is probably present. Given the large sample size, we attempted to limit this source of bias by a mandatory e-learning especially designed for the study. Moreover, ideally an SHG as golden standard for detecting a niche was performed in all women. From a cost- and patient friendly point of view, we decided only to perform SHG if TVUS was inconclusive. Lastly, we used the presence of a niche (surrogate outcome) as primary endpoint which might be argued as a limitation, [30] although the detrimental effects of a niche and thin RMT have been shown explicitly [1,7].

Interpretation and comparison with previous literature

We have learned from previous studies over the last two decades that several factors are associated with development of a niche. However, the combination of associations does not necessarily allow accurate prediction of the probability of development of a niche for individual patients. Furthermore, associations from previous studies were conflicting: diabetes has been reported as risk factor, [3] and as no risk factor [14]. Similarly, hypertensive pregnancy disorders and infectious morbidity have been and not been reported as risk factor [13,14,31]. The same accounts for maternal age [3,14,31,32] and intraoperative blood loss [14,31]. We tried to postulate hypotheses for the identified predictive factors found in our regression models: advanced gestational age and twin pregnancy may result in a thinner lower uterine segment, which probably makes closure of the uterotomy more difficult and as a consequence may impair wound healing. Smoking is in general known to negatively influence wound healing [33]. Double-layer closure, which is not the Dutch standard and by default included the endometrium [34], might have led to niche development but this is contradicting with previous studies [17,31,35,36]. Similarly, less surgical experience might lead to niche development, possibly due to inadequate approximation and tissue handling, compared to a surgeon with more experience (resident vs gynaecologist). For uterine closure, most hospitals used multifilament sutures (e.g. Vicryl USP 1 [Johnson and Johnson Medical GmbH] in 79.2% of patients or Novosyn USP 1 [Braun] in 18.8% of patients, Polysorb [Covidien] was used in 1.6% of patients), and monofilament sutures (PDS, monocril) was only used in 0.3% of the patients. Thus in case Vicryl was not used it was mostly Novosyn. Novosyn 1 might be experienced as slightly thinner than Vicryl 1, but it is unknown whether these two types of multifilament sutures really differ in quality aspects since studies are lacking. Previous vaginal delivery as a protective factor is difficult to explain and has not been identified previously [3,36].

In the subset of women undergoing elective CS, pregnancy induced hypertension was a risk factor, while PE turned out to be a protective factor for niche development. Hypothetically, patients with PE had severe illness that justified elective CS (protective factor) [14] or that more often medication was given in case of PE compared with PIH

(corticosteroids, magnesiumsulphate). But more likely the result of chance due to an infrequent occurrence of both conditions could have led to these findings.

Only one previous study, including 134 women without a previous CS, attempted to develop a model for the prediction of niche development. The accuracy of this previous model was comparable to our results (median AUC 0.63; IQR 0.62–0.64) [14].

Clinical implications and future research

The performance and discriminative ability of our prediction models are insufficient to implement them in daily practice. Apparently we did not evaluate all relevant prognostic factors influencing wound healing, which needs further elaboration and research as stated in the hypothesis article of Vervoort *et al.* [37]. We believe it is not the simple ‘one or two layers’ question, but the optimal approximation of the wound edges and uterine layers that needs attention during surgery throughout residency, endorsed by our finding that less surgical experience is a risk factor for niche development. Use of Vicryl sutures versus ‘other material’ seems to result in lower niche risk, although mainly Novosyn was used in the ‘other material’-group so no conclusions can be made regarding monofilament/PDS. A recent Italian trial did not find any differences between use of monofilament vs multifilament sutures for uterine closure regarding symptoms and ultrasound findings [38]. We did not measure the level of the uterotomy, which is thought to be of influence. A lower uterine incision in case of advanced dilatation, which was also a risk factor in our study for developing a large niche, should be avoided [14,39]. Future research is also needed to identify whether adhesion prevention after CS or individual patient factors (e.g. serum markers of coagulation or infection [13], use of medication, or other genetic factors that influence wound healing that are currently unknown) are important in the healing process and niche development [37]. Collection of participants’ blood samples was the initial set-up of our study but was not carried out due to logistical and financial reasons.

Furthermore, the outcome of future prediction models might be chosen differently. Linear regression models might predict the risk of thinning RMT, since larger decrease in RMT is associated with uterine rupture [40]. Certainly, future studies might focus on the prediction of long-term reproductive complications like uterine rupture, although this has been attempted before and remains difficult [41,42]. When sonographic markers are taken into account in predicting uterine rupture risk, this might improve accuracy and discriminative ability of the models.

Conclusion

The combination of various patient-related, labour-related, and surgery-related factors collected in our study cannot be used to accurately predict the development of a niche after a first caesarean section. Our study identified several factors (smoking, advanced gestational age, twin pregnancy, double-layer closure and surgeon with less experience as risk factors, and previous vaginal delivery and use of Vicryl sutures as protective factors) that do contribute to the development of a niche that may have implications for counselling of our patients and for the surgical approach and training of residents in performing a CS. Continuing to search for additional risk factors that play a role in development of a niche could improve the discriminative ability of prediction models and thus counseling of patients in whom CS is considered.

Author’s contributions

SIS collected data, analysed and interpreted data and drafted the report. LFvdV designed the study, collected data and participated in drafting and revising the report. MWH analysed and interpreted the data and participated in drafting and revising the report. KK, JOEHvL and WMvB collected data and participated in drafting and revising the

report. CJMdG designed the study and revised the first draft of the report critically. JAFH designed the study, was principle investigator, interpreted the data and participated in drafting and revising the report. All authors approved the final version of the manuscript.

Trial registration

Netherlands Trial Register NTR5480 (for the initial trial, not for the development/validation of a prediction model as secondary analysis)

Details of ethics approval

The study was approved by the Institutional Review Board (IRB) of Amsterdam UMC, location VU University Medical Centre, in December 2015 (registration no. 2015.462), and by the boards of all participating hospitals before the start of inclusion. No substantial changes were made to the protocol after commencement of the trial. All participants provided written informed consent before taking part in the study.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejogrb.2023.01.014>.

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