Prognostic factors for niche development in the uterine caesarean section scar: a prospective cohort study including women with one caesarean section

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Published as Brief Communication based on this chapter
Abstract

Objective
To develop a prognostic model for the development of a niche in the uterine caesarean scar.

Study Design
Prospective cohort study performed in a teaching hospital in the Netherlands including 134 women after their first caesarean section to undergo a sonohysterography 6-12 weeks for standardised evaluation of the uterine scar. Main outcome measurement was a niche with a depth of at least 2 mm. Secondary outcomes were large niche defined as depth ≥ 5mm and large niche defined as ratio residual myometrium and adjacent myometrium < 0.50%. Evaluated predictors were: age, gestational age, parity, birth weight, labour, cervical dilatation, augmentation of labour, induction of labour, failure to progress, closure of uterus, pre-eclampsia, diabetes, haemorrhage, infection.

Results
After multivariable logistic regression analysis and multiple imputation the following prognostic factors were identified for niche development: cervical dilatation, labour and induction of labour. Cervical dilatation > 3 cm (OR 8.93 [95% CI 1.89-42.19]), cervical dilatation > 7 cm (OR 9.26 [95% CI 1.88-45.94]) and induction of labour (OR 4.76 [95% CI 1.25-18.21]) Previous contractions resulted in less niches (OR .114 [95% CI .023-.570]). The conducted prognostic model with these factors has an area under the receiver operating curve of 0.63.

Conclusion
Cervical dilatation of more than 3 cm and induction of labour are independent predictors for niche development measured with sonohysterography 6-12 weeks after CS, while contractions without dilatation may be preventive.
Introduction

Due to the rise in caesarean section (CS) rates in the last decades, there is a growing interest in the caesarean scar. The uterine caesarean scar is easy to detect with ultrasound in a non-pregnant uterus and has different features. In approximately half of the women a niche, defined as an anechoic area at the site of a previous CS scar, can be observed. 1,2 The reported prevalence of a niche in non-pregnant women varies dependent on the diagnostic method used. Using sonohysterography (SHG) in a random population the prevalence varies between 56 and 84%.1,2,3,4

The predominant symptom associated with a niche is postmenstrual spotting.1,8 Other symptoms reported in women with a niche are dysmenorrhea, chronic pelvic pain and dyspareunia.7 In addition, an association between the presence of a niche and subfertility has been suggested and a niche may cause obstetric problems.9,11 A thinner residual myometrium between the niche and the bladder may increase the risk of uterine rupture or uterine dehiscence during a subsequent pregnancy.10,11 As the presence of a niche is associated with symptoms, it is of interest to elucidate prognostic factors in order to develop preventive strategies. The aim of the current study is to identify prognostic factors and to conduct a prognostic model for niche development after a CS.

Methods

To study prognostic factors for developing a niche we evaluated a subgroup of women included in a previous prospective cohort study which aimed to study the prevalence of a niche and its relation with abnormal uterine bleeding in women who were previously delivered by a CS.4 For the current study we analysed a subgroup of women who received a GIS at 6-12 weeks following CS, had only one previous CS and had had a singleton pregnancy. Women with a placenta previa were excluded. (see Figure 1)

The study was performed between October 2007 and September 2010 at Sint Antonius Hospital, Nieuwegein, a teaching hospital.4 The design of the study will be briefly outlined below, for details we refer to the previous publication.4

All women who had a CS performed during the study period were consecutively asked to participate within three days after their CS. After informed consent women underwent a transvaginal sonography (TVS) followed by a gel installation sonohysterography (GIS) six to twelve weeks after their CS. The uterus was scanned in a standardised way using a Philips Sonicare HD 11.XE (Philips Medical Systems, Eindhoven, the Netherlands). The position, length, and width of the uterus and double thickness of the endometrium were recorded in the midsagittal plane. A niche was defined as an anechoic space (with or without fluid) at least 2 mm deep at the presumed site of the caesarean section scar. A niche was measured both during TVS and during GIS in the sagittal plane in the section with the largest depth of the niche; the depth of the niche and the thickness of the residual myometrium and adjacent myometrium were measured in real time (see Figure 2).4
Baseline characteristics and specifics about the pregnancy and CS were distracted from the medical charts and registered in a web based data base by 2 research nurses immediately after the visit 6-12 weeks after CS.  

**Outcome measurement**

The primary outcome was the presence of a niche with a depth of ≥2 mm measured by GIS 6-12 weeks after the CS. Secondary outcomes were the presence of a large niche. Since there is no international consensus on the definition of a large niche we decided to use two separate definitions: a depth ≥5 mm measured by GIS and a residual myometrium < 50% of adjacent myometrium measured by GIS.  

**Prognostic factors**

We evaluated all possible prognostic factors for niche development as reported in a previous systematic review, that included studies reporting on women who had only one CS and assessed risk factors based on multivariate analyses. These prognostic factors include one or two-layer closure of the uterus, cervical dilatation divided into 0-3 cm, 4-7 cm, 8-10 cm, age (years), gestational age (days), parity, birth weight (gram), labour (yes or no), augmentation of labour with oxytocin (yes or no), induction of labour (yes or no), pregnancy induced hypertension (PIH)/pre-eclampsia (defined as systolic tension >160 mm Hg or systolic tension >95 mmHg, or urine albumen > 0.3 gram/24 hour (yes or no), diabetes with use of insulin (yes or no), haemorrhage (defined as blood loss > 1000 cc or need for...
Prognostic factors for niche development

transfusion) (yes or no), fever more than 38 degree Celsius (yes or no), antibiotic use more than 24 hours (yes or no). Duration of active labour and the station of the presenting part at CS were not recorded in our study. Both factors may affect the development of the low uterine segment (LUS). We did record failure to progress as indication for CS and added this factor to our analyses since this may also affect the development of LUS. Reporting of this study was conform the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) statement.15

Statistics
Data were analysed using SPSS 22 (SPSS Inc., Chicago,IL, USA). Stepwise backward logistic regression analysis was performed to identify potential prognostic factors with niche ≥ 2 mm as dependent variable and p< 0.157 for inclusion. All analyses were repeated for large niches defined as depth ≥ 5 mm and also for large niches defined as ratio RM/AM < 50% as dependent variables. All potential factors as mentioned above were included. We used at least 10 events per candidate variable to develop a model, resulting in a maximum of eight factors for niche ≥ 2mm, three factors for niche ≥ 5 mm and two factors for niche < 50% in the final model to avoid over fitting. To test the discriminative ability of the logistic regression models, receiver operating characteristics (ROC) curves were used. The explained variation of the prognostic model was expressed as Nagelkerke R².

Missing values were substituted by multiple imputation by generating 15 imputed data sets. The Multivariate Imputation by Chained Equation (MICE) method was applied with predictive mean matching.16 Multiple imputation was applied concerning all included possible prognostic factors in the imputation model. Logistic regression analysis were performed in each imputed dataset, and subsequently results were pooled.

Figure 2 Measurement of the niche
1 = depth, 2 = residual myometrium, 3 = adjacent myometrium
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The median area under the receiver operating curve and interquartile range were calculated for the 15 imputed data sets as for the Nagelkerke $R^2$. Internal validation of the model was tested using bootstrapping on the first imputed data set. A shrinkage factor was derived and used to correct the regression coefficients.

Results

Of the 263 women included in the original study, 134 women could be included in the current study. (See Figure 1)
The prevalence of a niche was 63% (85/134) in this subgroup and the prevalence of a large niche was 23% (31/134) if defined as depth $\geq$ 5 mm and 18% (24/134) if defined as a ratio RM/AM $<$ 50%. None of the women had a residual myometrium $<$ 2.5 mm. Baseline characteristics and univariate analysis are shown in Table 1. The use of locking or unlocking sutures was not recorded, all uteri were closed with polyglactin 910. Backward regression analysis including all possible previous defined prognostic factors resulted in the following eight most significant factors, in order of significance; labour, cervical dilatation, induction of labour, augmentation of labour with oxytocin, diabetes, failure to progress in the third stage/fourth stage, fever, blood loss.
With these eight factors the final model was developed resulting in the following statistically significant independent prognostic factors for niche development; cervical dilatation 4-7 cm (OR 8.9, 95% CI 1.9-42.2), cervical dilatation 8-10 cm (OR 9.3, 95% CI 1.9-46.0) and induction of labour (OR 4.8, 95% CI 1.3-18.2). Contraction before caesarean section reduced the risk for niche development (OR 0.11, 95% CI 0.02-0.57). These prognostic factors were included in the final model. (see Table 2) The predictive value of the model was low with a median area under the curve (AUC) of 0.63 (IQR 0.62-0.64). The mean Nagelkerke $R^2$ was 0.14 (IQR 0.12-0.15). Prognostic factors for a large niche defined as depth of niche $\geq$ 5 mm were induction of labour (OR 12.6, 95% CI 1.3-122) and augmentation of labour with oxytocin (OR 15.1, 95% CI 1.6-145.3). Contraction before CS also reduced the risk on a large niche ($\geq$ 5 mm) (OR 0.04, 95% CI 0.0-0.4). (see Table 2), AUC of this model was 0.64 (IQR 0.64-0.64). We could not find any significant prognostic factor for the development of a large niche defined as ratio RM/AM $<$ 50%. (data not shown). Internal validation with bootstrapping gave a shrinking factor of 0.72 for a niche $\geq$ 2 mm and a shrinkage factor of 0.74 for a large niche defined as niche $\geq$ 5 mm. After bootstrapping the AUC was 0.58 for niche $\geq$ 2 mm and 0.60 for a niche $\geq$ 5 mm. The Nagelkerke $R^2$ reduced to 0.07 for a niche $\geq$ 2 mm and 0.08 for a large niche $\geq$ 5 mm after bootstrapping.
## Table 1: Patients characteristics

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<td>.831</td>
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<td>gestational age (days) mean (SD)</td>
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<td>276(12)</td>
<td>277(13)</td>
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<td>.663</td>
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<td>1.2( 0.4)</td>
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<td>.967</td>
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<td>.968</td>
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<td>.980</td>
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<td>augmentation of labour with oxytocine</td>
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<td>29</td>
<td>2</td>
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<td>.217</td>
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<td>induction</td>
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<td>21</td>
<td>0</td>
<td>.116</td>
<td>.121</td>
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<td>4.4(3.9)</td>
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<td>4.6(3.9)</td>
<td>3</td>
<td>.384</td>
<td></td>
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<td>34</td>
<td>3</td>
<td>.108</td>
<td></td>
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<tr>
<td>dilatation 4-7 cm</td>
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<td>9</td>
<td>24</td>
<td>3</td>
<td>.197</td>
<td>.083</td>
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<td>3</td>
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<td>.221</td>
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<td>.600</td>
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<td>failure to progress third/fourth stage</td>
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<td>9</td>
<td>13</td>
<td>1</td>
<td>.665</td>
<td>.644</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>*  degrees Celsius</td>
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</tbody>
</table>


Chapter 6

Discussion

Main findings

Identified prognostic factors for niche development were cervical dilatation > 3 cm and > 7 cm and induction of labour. Contractions before the CS reduced niche development. Predictive value of the conducted prognostic model using these factors was low. Prognostic factors for the development of a niche ≥ 5mm were induction and augmentation of labour with oxytocin and contractions before CS were preventive.

Strengths and limitations

This is one of the few prospective studies that investigated prognostic factors for niche development with sonohysterography (SHG), using clear definitions and multivariate analyses. Most previous studies used TVS only or used SHG only in a selection of the patients.13,17-19 SHG improves the identification of niches and the intra- and inter-observer agreement, due to its better delineation.4,12,20 Another strength is that we only included women with one CS in our analysis to exclude risk factors that occurred during the previous CSs. We also studied prognostic factors for various definitions of (large) niches given the lack of international consensus on this topic. Although it is one of the largest prospective study assessing prognostic factors for niche development we consider the relatively small sample size as a limitation Due to this small sample size we were not able to assess the effect of possible patient related factors, such as diabetic and hypertensive disorders.

Table 2 Prognostic model

<table>
<thead>
<tr>
<th>Niche ≥2 mm</th>
<th>Niche ≥2mm∞</th>
<th>Niche ≥5mm∞</th>
</tr>
</thead>
<tbody>
<tr>
<td>No niche</td>
<td>niche</td>
<td>Missing</td>
</tr>
<tr>
<td>N=49</td>
<td>N=85</td>
<td>0</td>
</tr>
<tr>
<td>labour*</td>
<td>31</td>
<td>55</td>
</tr>
<tr>
<td>induction*</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>cervical dilatation(mean)(SD)*</td>
<td>4.0(4.0)</td>
<td>4.6(3.9)</td>
</tr>
<tr>
<td>dilatation 0-3 cm</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>dilatation 4-7 cm</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>dilatation 8-10 cm</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>augmentation of labour with oxytocine*</td>
<td>22</td>
<td>29</td>
</tr>
</tbody>
</table>

SD=standard deviation. ∞Results after multiple imputation (15x). The predicted probability of a niche can be calculated using the following formula (after bootstrapping). P(niche ≥2 mm) 1/(1 exp(-(-0.483 + labour x-1.65 + induction x1.19 + dilatation 4-7 cm x1.66 + dilatation8-10 cm x 1.70))). Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) of 0.761. P(niche ≥5 mm) 1/(1 exp(-(-0.935 + labour x-2.37 + induction x 1.85 + augmentation of labour with oxytocine x 2.0))). Regression coefficient multiplied with a shrinkage factor (obtained from the bootstrapping procedure) f 0.74. *Predictor value is one when present and zero when absent

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Another limitation is that we were not able to study the effect of closure technique on niche development since only three women received a double layer closure and detailed information on the use of locking sutures was missing. In addition, we did not record the descent of the presenting part at the time of CS. Our original study already started before this factor was reported as a predictive factor for large niches.17

Relation to other literature
The only other study developing a prognostic model for (large) niches also reported advanced cervical dilatation as an independent prognostic factor.17 Contractions seem to be protective for niche development in our model that included cervical dilatation. Vikhareva et al reported a prolonged labour of more than 5 hours as a prognostic factor for a large scar defect, defined as RMT < 2.3.17 We could not study this factor due to lack of registration. Based on the fact that advanced cervical dilatation increased the risk on niche development while contractions itself are preventive we postulate that contractions are only preventive in the absence of advanced dilatation. In line with Vikhareva’s and our findings, a recent cohort study including 409 women, reported a CS in the second stage to be a risk factor for the development of a niche.19 In contrast to these findings, a small RCT reported a lower mean dilatation before CS in the group with a niche compared to the group without a niche.18 However the maximum dilatation was less than 3.5cm in >95% of women.18 Another prognostic factor reported in the literature is a retroflexed position of the uterus.1,21 The retroflexed uterus may also be the consequence of niche formation rather than a prognostic factor. This is underlined by two studies reporting an increase of retroflexed positions of the uterus after the CS in comparison to vaginal delivery and in comparison to women without a niche.22,23 We did not include a retroflexed uterus in our prognostic model since we did not record the position of the uterus before or in the first trimester of the pregnancy.

Interpretation of our findings
Our findings, underline our previously postulated hypothesis that the location of the uterine incision during the CS may be of influence on the prevalence of niches.21 (see Figure 3) Based on the fact that having some contractions may be beneficial in the prevention of niche development we assume that an incision through the middle part of a developed LUS is beneficial for wound healing ability of the uterus. (Figure 3b). We assume that advanced cervical dilatation or prolonged labour or oxytocin augmentation or a very low position of the presenting fetal part may result in an unintended low incision through cervical tissue which may be less optimal for wound healing (see Figure 3c). This is in line with the reported higher incidence of uterine scars/niches at the level of the cervix/internal os if women were in labour or had a prolonged labour.17,24 In theory a lower incision through cervical tissue containing mucus producing glands may impair wound healing.17,21 A total lack of contractions may result in an incision trough a thick non developed LUS and may be less optimal either (Figure 3a). If our hypothesis is correct and if contractions are confirmed to be preventive for niche development, this may have challenging consequences.
for the timing of elective CS. Additionally if the optimal location of the uterine incision is confirmed it encourages the development and evaluation of surgical strategies in order to prevent too low incisions. For example avoiding dissection of the bladder flap may prevent a low uterine incision.25

The low predictive value of our prediction model indicates that niche development is a multi factorial process and apart from the identified factors apparently there are more factors of influence. Closure technique of the uterus could be a very relevant factor that unfortunately could not be included in our analyses.21,26-28.

Future perspectives

The effect of various surgical techniques including the location of incision and suturing techniques or use of adhesion barriers requires future RCTs. Larger prospective studies assessing relevant prognostic factors, including factors affecting wound healing using uniform definitions and methods of niche measurement are needed to develop more optimal prognostic models. Also a core outcome set of outcomes to be recorded after pregnancy and delivery has to be developed to be able to study the long term complications of a CS in order to enable future meta-analysis. 29

Conclusion

Cervical dilatation and induction of labour are independent prognostic factors for the development of a niche ≥ 2 mm deep after the first CS. Induction of labour and oxytocin augmentation are prognostic factors for a large niche of at least 5 mm deep, while being
in labour prevents niche development. We could not evaluate the effect of suturing techniques or patient related factors affecting wound healing. This possibly explains why our model could only partly explain niche development.

Acknowledgements
We thank K.W. Van den Berg-Swart and C. van Dam-Bourens, research nurses, for recording all the collected data in the database. We thank M. de Vries MD for performing ultrasounds.

Disclosure of interest
JHU received two grants of ZonMw, a Dutch organization for Health Research and development for 1) To compare the effect of a hysteroscopic niche resection versus no treatment in women with postmenstrual spotting (Hysniche study, ZonMw project number 80-82305-97-12030and 2) The (cost)effectiveness of double layer closure of the caesarean (uterine) scar in the prevention of gynaecological symptoms in relation to niche development (ZonMw project number 843002605) and received grants from Samsung Medison and Gedeon Richter outside the submitted work. HBR received grants from Olympus and Gynesonics and non-financial support from Samsung Medison, outside this study. SV is consultant for Bayer and Norvartis. He is member of the advisory board of Hologic and Johnson and Johnson. And SV is patentee for a new hystroscope.

Contribution to authorship
This study was conceived by LV, HB SV and JH. LV and SV performed the ultrasounds and collected the data. Analysis of the data was performed by LV,JH and MH The first draft was written by LV and JH, and MB, MH, HB, and SV supervised the article to the final draft.

Details of Ethics Approval
The study received ethics approval from the united committee on research involving human subjects (VCMO), Nieuwegein, the Netherlands (27 September 2007; ref. no. NL18722.100.07 R-07.14A/SCAR). The study was registered at the Nederlands trialregister, (www.trialregister.nl, NT2887).

Funding
No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.
References


