Potential risk factors for caesarean scar pregnancy: a retrospective case–control study

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STUDY QUESTION: What are the important risk factors for having a caesarean scar pregnancy (CSP)?

SUMMARY ANSWER: Independent risk factors were smoking in the first trimester, higher parity, and previous caesarean section (CS) before the index caesarean delivery.

WHAT IS KNOWN ALREADY: A spectrum of risk factors for CSP has been suggested but not proven: parity, number of previous caesarean section, elective as opposed to emergency CS, IVF-pregnancy, breech presentation, previous gynaecological surgery as well as suture technique.

STUDY DESIGN, SIZE, DURATION: This retrospective case-control study included 31 women with a CSP during the period 2003–2018 treated at a tertiary care centre for gynaecology and reproduction. A control cohort of 8300 women with a history of a CS and a subsequent delivery during the same time period was formed.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Variables describing demography, lifestyle factors, and reproductive and obstetric history were retrieved from medical records and the obstetric hospital database. Logistic regression analyses were applied to identify potential risk factors.

MAIN RESULTS AND THE ROLE OF CHANCE: In a multivariable analysis, smoking in first trimester (adjusted odds ratio (OR) 3.03, 95% CI 1.01–9.07), higher parity (adjusted OR 1.30, 95% CI 1.03–1.64) and previous CS in addition to the preceding CS (adjusted OR 3.43, 95% CI 1.35–8.66) were independently predictive of a CSP. An elective CS at the index pregnancy was associated with an increased risk of CSP but did not remain significant in the multivariable analysis.

LIMITATIONS, REASONS FOR CAUTION: CSP is a very rare phenomenon and several of the risk factor estimates are imprecise. Nevertheless, significant risk factors could be identified. Another limitation is the lack of electronically recorded details on suture techniques.

WIDER IMPLICATIONS OF THE FINDINGS: The identified factors, namely higher parity and previous CS before the index caesarean section, are in accordance with previously suggested risk factors. Whether there is a true risk association between elective CS and future CSP needs to be investigated further. Smoking in the first trimester is a new finding, which has a plausible rationale. These factors should be recognised when counselling women after a caesarean delivery, particularly in a subsequent pregnancy with early complications.

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Key words: Caesarean scar pregnancy / ectopic pregnancy / risk factor / caesarean section / case-control study / smoking / parity / epidemiology

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WHAT DOES THIS MEAN FOR PATIENTS?

After a caesarean section, there will always be a scar in the womb and sometimes the wound healing may be poor. In a subsequent pregnancy, it may occur, albeit rarely, that the pregnancy implants in the scar. This may be a life-threatening condition with severe bleeding. It is, thus, important to recognise this type of pregnancy early and to be aware of factors that may increase the risk for having a caesarean scar pregnancy.

In the present study, we have compared the characteristics of 31 women with a caesarean scar pregnancy to 8300 women with a normal pregnancy after a previous caesarean delivery. We found that having undergone several childbirths, more than one caesarean section and being a smoker in early pregnancy were factors that increased the risk of having a caesarean scar pregnancy.

Introduction

Caesarean scar pregnancy (CSP) is defined as implantation of the gestational sac in a poorly healed caesarean scar. This rare type of ectopic pregnancy was first described in 1978 (Larsen and Solomon, 1978). Since then the occurrence has become more common, possibly because of the increased caesarean section (CS) rate the last 25 years (Timor-Tritsch and Monteagudo, 2012; Betrán et al., 2016). Caesarean scar defects have been associated with various gynaecological and obstetric problems. CSP represents about 6.1% of all ectopic pregnancies among women with a previous CS. For pregnant women with experience of at least one CS there is a 0.15% risk to have a CSP (Seow et al., 2004).

The following ultrasonographic criteria are used for diagnosis of CSP: empty uterine cavity; empty cervical canal; presence of gestational sac in the anterior part of the uterine isthmus; and absence or thinning of healthy myometrium between bladder and gestational sac (Vial et al., 2000; Fylstra, 2002).

The pathophysiology behind CSP is a migration of the fertilised egg inside the myometrium through microscopic lacunas to the position where there is a scar defect after a caesarean section (Rotas et al., 2006; Ash et al., 2007). It has also been reported that other uterine surgical procedures, for example curettage, vacuum aspiration and manual removal of placenta, can be other causal factors (Fylstra, 2002; Rotas et al., 2006; Ash et al., 2007).

CSP is a heterogenous condition, which can be divided into two subgroups, endogenous and exogenous CSP (Vial et al., 2000; Gonzalez and Tulandi, 2017). Endogenous CSP, also called Type 1, originates from the wound tissue (scar) but bulges into the cavity (Fig. 1). If this pregnancy proceeds it can develop into morbidly adherent placenta such as accreta/increta/percreta (Timor-Tritsch et al., 2014a, 2014b). In the exogenous subgroup, also called Type 2, the embryo is implanted deep inside the scar tissue in the myometrium and the growth of the pregnancy is through the evolving placenta directed towards the isthmic frontside and further into the abdominal cavity and/or bladder (Vial et al., 2000; Gonzalez and Tulandi, 2017). This type of CSP may cause catastrophic consequences, such as uterine rupture, long before the time for delivery (Fig. 2).

Presently there are no clinical guidelines to identify women at risk of a CSP. The aim of the present study was to identify potential risk factors for CSP.
Materials and methods

Cases
As these cases are very rare, the diagnostic and therapeutic management in our region is often centralised to Sahlgrenska University Hospital. The diagnostic criteria presented in the introduction were applied (Vial et al., 2000; Fylstra, 2002). The clinical experience at the hospital resulted in a collection of cases. This series was expanded by a search in the medical records from the gynaecological department. CSP does not have a specific International Statistical Classification of Diseases and Related Health Problems (ICD) code. Instead the codes for ectopic pregnancy were applied: O00.8 (other ectopic pregnancy) and O00.9 (ectopic pregnancy without further specification). The time period 2003–2018 was chosen based on the introduction of electronic records in 2003. All events with these ICD codes were reviewed to identify the CSP cases. The obstetric records of these women were retrieved and scrutinised. Demographic, gynaecological and obstetric history variables were collected manually (Table I). If a woman had two or more CSPs only the first was included. Variables such as BMI and smoking at the time of the CSP were not routinely recorded in the medical charts.

Controls
A control cohort from the same time period as the cases was identified from the obstetric hospital database, including data both from the antenatal primary clinics and the obstetric and maternity wards at the Sahlgrenska University Hospital. Women with a history of a CS (referred to as the index CS) and a subsequent delivery during the same time period were eligible for inclusion. The subsequent pregnancy could end in either a caesarean or vaginal delivery. The same variables as for the cases were searched in the hospital database and available variables were retrieved electronically and included in the dataset. The CSP cases were excluded from the control cohort. The sample size was, thus, determined by the time period during which electronic hospital records were available.

Statistical methods
All statistical analyses were conducted using SAS System Version 9.4, (SAS Institute, Cary, NC, USA). Descriptive statistics were used to describe the groups. To compare the two groups Student’s t-test or Mann–Whitney U test (continuous variables), Fisher’s exact test (dichotomous variables) and Mantel-Haenzel Chi² test for categorical variables were used. All tests were two-sided and conducted at a significance level of 0.05. Univariable logistic regression was used to analyse the action of individual variables on the dependent variable CSP, excluding individuals with a missing value for the specific variable. BMI was categorised based on established classes, and gestational weeks was dichotomised to define premature delivery (</≥ 37). Other continuous variables (age, calendar year and time from CS to result of subsequent pregnancy) were categorised in clinically relevant intervals in which the middle of three intervals comprised the most frequent occurrence. Stepwise multivariable logistic regression was used to analyse which factors were independently predictive of CSP, considering pre-specified covariates and the total number of events. In the main analysis, cases and controls with missing values were excluded. Potentially correlated covariates were analysed with Pearson correlation coefficient. In a sensitivity analysis, missing values were imputed by means of stochastic imputation using fully conditional specification. The results are presented as adjusted odds ratio (aOR) with 95% CI and AUC.

Ethical approval
Study approval was sought and received from the Regional Ethical Committee at the University of Gothenburg (number 2019/01995, 20 May 2019). No informed consent from patients was required.

Results
The search in the medical records for the ICD codes O00.8 and O00.9 resulted in 2067 records, corresponding to 1267 unique patients. Twenty-eight cases were identified by reading the medical records and 10 additional cases were added by personal recognition resulting in a series of 38 women with 39 CSPs. During the study period there were 140 540 births at Sahlgrenska University Hospital. Among these there were 8330 women who had a CS and a subsequent birth, either a vaginal delivery or CS, excluding diagnosed CSPs. The incidence of CSP among women with a CS was, thus, 1:219. The incidence expressed as the number of CSP per births during the same period would then be 1:3605.

The dominant symptoms among the 38 patients were vaginal bleeding and/or pain during early pregnancy. The CSP diagnosis was made at the emergency department, at the abortion clinic or after referral within the region. Seven of 38 cases were excluded from further analysis due to missing information about the index CS. One of the 31 women had experienced two CSPs, but only the first was included in the analysis.

The entire cohort was characterised at the index CS by a mean age of 30.6 (SD 4.3) years and mean BMI of 24.7 (SD 4.5). The mean gestational age was 39.2 weeks, 80% were primiparous and 89% had their first CS. The mean time between CS to next pregnancy (CSP or delivery) was 3.23 (SD 1.78) years. The presented values for the entire cohort coincide with the values of the control group in Table I, owing to the large difference in sample sizes (31 vs. 8300). Table I shows the distribution of demographic, gynaecological and obstetric history variables at the index CS. The variables BMI, previous CS, termination of pregnancy, previous miscarriage and smoking in the first trimester had a large proportion of missing values.

In univariable logistic regression analyses, smoking, higher parity, previous CS and type of CS (elective vs. emergency) were associated with an increased risk of having a CSP the subsequent pregnancy (Table II). The influence of BMI varied in different categories, without demonstrating any statistical significance. The variables age, gestational length, time from index CS to next pregnancy, blood loss, suturing technique, breech birth, previous termination of pregnancy, previous miscarriage, and previous gynaecological surgery were not associated with CSP. In the main multivariable analysis, smoking in first trimester (adjusted OR 3.03, 95% CI 1.01–9.07), higher parity (adjusted OR 1.30, 95% CI 1.03–1.64) and previous CS in addition to the preceding CS (adjusted OR 3.43, 95% CI 1.36–8.66) were independently predictive of a CSP (Table III). The AUC was 0.731. The correlation
Table I Demographic, gynaecological and obstetric history variables at the index caesarean section.

| Variable                        | CSP (n = 31)          | Controls (n = 8300) |
|---------------------------------|-----------------------|---------------------|
| Age (years)                     | 31.8 (4.6)            | 30.6 (4.3)          |
|                                 | 33.0 (23.6; 39.8)     | 30.8 (14.7; 50.5)   |
|                                 | n = 31                | n = 8300            |
| BMI (kg/m²)                     | 24.3 (3.8)            | 24.7 (4.5)          |
|                                 | 24.8 (18.4; 30.9)     | 23.8 (14.0; 51.2)   |
|                                 | n = 24                | n = 5389            |
| Gestational length (weeks)      | 38.8 (1.8)            | 39.2 (2.7)          |
|                                 | 39.0 (32.9; 42.4)     | 39.3 (24.1; 45.6)   |
|                                 | n = 31                | n = 8287            |
| Time from CS to CSP/next delivery (years) | 3.48 (2.18)         | 3.23 (1.78)         |
|                                 | 2.81 (0.82; 9.16)     | 2.77 (0.56; 15.77)  |
|                                 | n = 31                | n = 8300            |
| Parity: 0                       | 16 (51.6%)            | 6595 (79.5%)        |
|                                 | 1 (6.2%)              | 1202 (14.5%)        |
|                                 | ≥2 (9.0%)             | 503 (6.1%)          |
| IVF: no                         | 29 (93.5%)            | 8091 (97.5%)        |
|                                 | Yes (2.6%)            | 205 (2.5%)          |
| Type of CS: emergency Elective  | 15 (51.7%)            | 5796 (70.1%)        |
|                                 | Missing               | 2 (6.5%)            |
|                                 | 2 (6.5%)              | 32                  |
| Previous CS: no                 | 17 (65.4%)            | 5640 (88.8%)        |
|                                 | Yes (9.4%)            | 711 (11.2%)         |
|                                 | Missing               | 5 (1.2%)            |
|                                 | 5 (1.2%)              | 1949                |
| Blood loss during CS (ml)       | 536 (270)             | 609 (450)           |
|                                 | 500 (1000; 1000)      | 500 (0.00; 12 000)  |
|                                 | n = 28                | n = 7987            |

Locked, non-continuous sutures:  
Layer 1: yes  
No  
Layer 2: yes  
No  
Missing  
Breech birth: no  
Yes  
Previous termination of pregnancy: 0  
I  
≥2  
Missing  
Previous miscarriage: 0  
I  
≥2  
Missing  
Previous ectopic pregnancy: no  
Yes  
Smoke in first trimester: no  
Yes  
Missing  

For categorical variables n (%) is presented. For continuous variables Mean (SD)/Median. (Min: Max)/n = is presented. CS, Caesarean section; CSP, caesarean scar pregnancy.

Discussion

We found smoking, higher parity, and more than one previous CS to be independently associated with an increased risk of having a CSP in the next pregnancy.

Smoking in the first trimester of the pregnancy resulting in the index CS was estimated to increase the risk for CSP 3-fold. We have not found smoking being investigated as a risk factor for CSP in previous publications. It is well recognised that smoking delays wound healing (Bohlin et al., 2016). As a vasoconstrictor, nicotine reduces nutritional blood, resulting in tissue ischemia and impaired healing of injured tissue. The adhesiveness of the platelets also increases, raising the risk of thrombotic microvascular occlusion and tissue ischemia (Silverstein, 1992).

Higher parity was associated with a 30% increased risk for each additional birth of having CSP. Our dataset did not include delivery mode in previous pregnancies, so we cannot analyse parity in relation to number of previous CS. Shah et al. (2019) described in their case series of ectopic pregnancies that parity and the number of prior caesarean deliveries were significantly higher in CSP patients. None of our cases had a previous ectopic pregnancy.

If a woman had had at least one CS before the index CS, there was a 3-fold risk increase for CSP. This is probably an underestimation since we had limited access to complete obstetric history in the control group. The hypothesis, whether several CS implies higher risk, is that the scar tissue acts attracting, and reiterated uterotomies lead to a larger scar area. In several case series, most of the cases has only one previous CS before the CSP (Seow et al., 2004), while a few case series reported on multiple CS (Zhou et al., 2020). Jurkovic et al. (2003) reported that 72% of their cases with CSP had a history of multiple (two or more) CS; they suspected that multiple CS procedures led to impaired healing of the uterine incision.

Elective compared with emergency CS was associated with an increased risk, only in the univariable analysis. In our department from which the cohort was derived, approximately 39% of all CS are elective. The proportion of elective CS was 48.3% among cases and 29.9% in the control group. Downes et al. (2015) described a risk association between elective CS and placenta previa. There is also a common denominator between CSP and placenta previa (Timor-Tritsch et al., 2014b). Begam et al. (2019) also found that elective CS, for any reason, was overrepresented among cases. Whether is true risk association between elective CS and future CSP needs to be investigated further. The theory behind a potential association is that the wound healing is impaired in the myometrium that has not been exposed to contractions (Begam et al., 2019).

Four of 38 cases (11%) had been conceived through IVF. In Sweden, IVF-pregnancies constitute 4% of all births (Q-IVF, 2021). In other CSP case series, IVF has been a more frequently occurring...
| Variable                              | Value          | n (% of event) | OR (95% CI) | P-value |
|---------------------------------------|----------------|----------------|-------------|---------|
| **Age**                               |                |                |             |         |
| 14.7–<25.0                            | 5 (0.6%)       |                |             |         |
| 25.0–<35.0                            | 19 (0.3%)      |                |             |         |
| 35.0–50.5                             | 7 (0.5%)       |                | 1.06 (0.98–1.16) | 0.14    |
| BMI (category)                        |                |                |             |         |
| 18.5–24.9                             | 11 (0.3%)      |                | 1.00        |         |
| <18.5                                 | 1 (0.8%)       |                | 2.30 (0.29–17.95) | 0.43    |
| 25.0–29.9                             | 10 (0.7%)      |                | 2.16 (0.91–5.10) | 0.079   |
| ≥30.0                                 | 2 (0.3%)       |                | 0.95 (0.21–4.31) | 0.95    |
| **Pregnancy week at birth**           |                |                |             |         |
| <37 weeks                             | 3 (0.3%)       |                |             |         |
| ≥37 weeks                             | 28 (0.4%)      |                | 1.29 (0.39–4.24) | 0.68    |
| **Calendar year of index CS**         |                |                |             |         |
| 1999–<2005                            | 9 (0.4%)       |                |             |         |
| 2005–<2011                            | 15 (0.4%)      |                |             |         |
| 2011–2017                             | 7 (0.3%)       |                | 0.98 (0.90–1.06) | 0.61    |
| **Time from CS to CSP/delivery (years)** |            |                |             |         |
| 0.6–<2.0                              | 9 (0.5%)       |                |             |         |
| 2.0–<5.0                              | 17 (0.3%)      |                |             |         |
| 5.0–15.8                              | 5 (0.5%)       |                | 1.07 (0.90–1.28) | 0.43    |
| **Parity, category**                  |                |                |             |         |
| 0                                     | 16 (0.2%)      |                |             |         |
| 1                                     | 6 (0.5%)       |                |             |         |
| 2 or more                             | 9 (1.8%)       |                | 2.66 (1.75–4.06) | <0.0001 |
| **IVF**                               |                |                |             |         |
| No                                    | 29 (0.4%)      |                |             |         |
| Yes                                   | 2 (0.9%)       |                | 2.67 (0.63–11.26) | 0.18    |
| **Type of sections**                  |                |                |             |         |
| Emergency                             | 15 (0.3%)      |                |             |         |
| Elective                              | 14 (0.6%)      |                | 2.19 (1.05–4.54) | 0.035   |
| **Previous CS**                       |                |                |             |         |
| No                                    | 17 (0.3%)      |                |             |         |
| Yes                                   | 9 (1.3%)       |                | 4.20 (1.87–9.46) | 0.0005  |
| **Blood loss during CS (ml)**         |                |                |             |         |
| 0–<500                                | 11 (0.3%)      |                |             |         |
| 500–<1000                             | 15 (0.4%)      |                |             |         |
| 1000–12 000                           | 2 (0.2%)       |                | 0.95 (0.86–1.06) | 0.38    |
| **Locked, non-continuous sutures:**   |                |                |             |         |
| Layer 1                               |                |                |             |         |
| Yes                                   | 0 (0.0%)       |                |             |         |
| No                                    | 29 (0.4%)      |                | +infinity    | 1.00    |
| Layer 2                               |                |                |             |         |
| Yes                                   | 6 (0.4%)       |                |             |         |
| No                                    | 23 (0.3%)      |                | 0.98 (0.40–2.41) | 0.96    |
| Breech birth                           |                |                |             |         |
| No                                    | 25 (0.4%)      |                |             |         |
| Yes                                   | 6 (0.3%)       |                | 0.79 (0.32–1.94) | 0.61    |
| **Previous termination of pregnancy** |                |                |             |         |
| 0                                     | 19 (0.4%)      |                |             |         |
| 1                                     | 4 (0.4%)       |                |             |         |
| 2–6                                   | 1 (0.4%)       |                | 1.10 (0.58–2.09) | 0.78    |
| **Previous miscarriage**              |                |                |             |         |
| No                                    | 17 (0.4%)      |                |             |         |
| Yes                                   | 7 (0.6%)       |                | 1.55 (0.64–3.73) | 0.33    |
| **Previous gynaecological surgery**   |                |                |             |         |
| No                                    | 15 (0.3%)      |                |             |         |
| Yes                                   | 7 (0.6%)       |                | 1.93 (0.78–4.74) | 0.15    |
| **Smoking in first trimester**        |                |                |             |         |
| No                                    | 20 (0.4%)      |                |             |         |
| Yes                                   | 4 (1.2%)       |                | 3.41 (1.16–10.03) | 0.026   |

OR, odds ratio.
conception method (9–28%) (Fylstra, 2002; Shah et al., 2019), and IVF has been suggested to increase the CSP risk (Ouyang et al., 2015). Only two cases of CSP with IVF-conception were included in our analysis. The unadjusted OR of 2.67 indicated an increased risk of CSP after IVF, but with very few events, no inference could be made.

Contrary to other suggestions, we could not verify breech birth as a risk factor, having a lower or similar incidence of breech presentation among cases (19.4%) compared with controls (23.2%) (Rotas et al., 2006; Ash et al., 2007). Begam et al. (2019) studied the indications of the preceding CS and found that elective CS for breech presentation with a non-contraceptile uterus could possibly be associated with an increased risk of CSP.

Neither miscarriage nor termination of pregnancy seemed to increase the risk of CSP in our cohort, contrary to the findings of others (Zhou et al., 2020). We could not confirm previous gynaecological surgery to be a risk factor. The risk was estimated to be increased 2-fold, although this was not statistically significant. No previous study has reported on BMI in relation to CSP. Our results are inconclusive, but a negative effect of overweight cannot be precluded. This is in line with the findings of Antila-Långsjo et al. (2018), who found rising BMI to increase the risk for isthmocele (scar defect). Gestational age at the index CS (< vs. ≥ 37 weeks) did not influence the risk of CSP.

The surgical technique for closing the uterotomy may influence wound healing and the development of CSP. Several reports discuss the effect of the suturing technique on myometrial thickness and a potential benefit of double- as compared with single-layer closure (Roberge et al., 2016; Vachon-Marceau et al., 2017; Hanacek et al., 2020).

Also, advanced stage of labour has been associated with large scar defects (Vikhareva et al., 2019). In our case series, the uterine first layer was always sealed with unlocked continuous suture, but the second layer was in some cases closed with locked non-continuous sutures. The hospital database did not provide this detailed information for the controls on how the uterotomies had been sutured and no further analysis could be conducted.

The incidence of CSP for all births in other publications has varied between 1:1800 and 1:2216, which is much higher than reported here (1:3605) (Jurkovic et al., 2003; Seow et al., 2004). Since CSP does not have a unique ICD code, the coding by the physicians may vary widely, resulting in cases not being captured in the hospital database search. Furthermore, cases might have been misdiagnosed as miscarriage, bleeding in pregnancy and termination of pregnancy. Some cases may have escaped our notice during uncomplicated curettage or vacuum aspiration of endogenous CSP. Sweden also has a lower CS rate than many other countries, and our result did not detect an increased incidence over time. Owing to national differences, such as CS rates and smoking habits, further studies are warranted to verify the identified risk factors. Also, the suture technique may vary. In our obstetric unit it changed in the 1990s, when the Joel Cohen technique replaced the Pfannenstiel incision. Since then the uterotomies are always stitched in two layers.

**Strengths and limitations**

To the best of our knowledge, this is the one of the first studies aimed at identifying risk factors for CSP in a population from the Western world. There are three large Chinese studies (with sample sizes of 200–300 CSPs) to which regression analyses have been applied (Luo et al., 2019; Xie et al., 2019; Zhou et al., 2020). They report level of care and number of previous induced abortions to be important risk factors. The Chinese population may differ from populations in the Western world because of the previous one-child policy, resulting in a different risk factor panorama.

CSP is a very rare phenomenon and several of the risk factor estimates are imprecise. Nevertheless, significant risk factors could be identified. The lack of a predefined ICD code for CSP made the search for cases difficult and it cannot be precluded that individual cases were not recognised. This type of verification bias is more likely to affect precision than the result in a skewed comparison. Another limitation is the lack of electronically recorded details on suture techniques.

The incidence of CSP in this cohort of births with a previous CS was 1:219. We could identify that smoking in the first trimester, higher parity, and previous CS before the index pregnancy were independently associated with an increased risk of having CSP. These factors should be recognised when counselling women after a caesarean delivery, particularly in a subsequent pregnancy with early complications. It is important to develop diagnostic strategies to detect CSP at the earliest possible gestation, to prevent life-threatening complications.

**Data availability**

The data underlying this article will be shared on reasonable request to the corresponding author.

### Table III Multivariable logistic regression with CSP as the dependent variable.

| Variable                  | Model excluding individuals with missing values (n = 23 + 5738) Adjusted OR (95% CI) | P-value | Model including all cases after imputation of missing values (n = 31 + 5730) Adjusted OR (95% CI) | P-value |
|---------------------------|--------------------------------------------------------------------------------------------|---------|-------------------------------------------------------------------------------------------------|---------|
| Parity                    | 1.30 (1.03–1.64)                                                                           | 0.025   | 4.14 (1.89–9.05)                                                                                | 0.0004  |
| Previous CS              | 3.43 (1.36–8.66)                                                                           | 0.009   | 4.02 (1.63–9.92)                                                                                | 0.0025  |
| Smoking in first trimester| 3.03 (1.01–9.07)                                                                           | 0.048   |                                                                                                  |         |
| AUC for the model         | 0.731                                                                                      |         | 0.644                                                                                           |         |

*Main analysis with exclusion of individuals with missing values and sensitivity analysis with imputed values.*
Risk factors for caesarean scar pregnancy

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Authors’ roles

B.G. collected the clinical case series, contributed to the conception of the study, to the analysis and interpretation of data and revised the article critically for intellectual content. V.K. was responsible for acquisition of data regarding the matched controls, contributed to the analysis and interpretation of data and drafted the article. A.J. was responsible for acquisition of data regarding the case series, drafted and revised the article. A.S. was responsible for the conception and design of the study, analysis and interpretation of data and drafted the article. A.J. was responsible for acquisition of data regarding the matched controls, contributed to the analysis and interpretation of data and revised the article. A.S. was responsible for the conception and design of the study, analysis and interpretation of data, revised the article critically for intellectual content. All authors approved the final version.

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Conflict of interest

None of the authors has any conflict of interest to declare.

References

Antila-Långsjö RM, Mäenpää JU, Huhtala HS, Tomás El, Staff SM. Cesarean scar defect: a prospective study on risk factors. Am J Obstet Gynecol 2018;219:458.e1–8.
Ash A, Smith A, Maxwell D. Caesarean scar pregnancy. BJOG 2007;114:253–263.
Begam MA, Mirghani H, Al Omari W, Khair H, Elbiss H, Naeem T, Salahudeen SM. Cesarean scar pregnancy: time to explore indications of the caesarean sections? J Obstet Gynaecol 2019;39:365–371.
Betrán AP, Ye J, Moller A-B, Zhang J, Gülmezoglu MA, Torloni AM. The increasing trend in caesarean section rates: global, regional and national estimates: 1990–2014. PLoS One 2016;11:e0148343.
Bohlin KS, Ankandarl M, Sjördahl JH, Lindkvist H, Milsom I. Influence of the modifiable life-style factors body mass index and smoking on the outcome of hysterectomy. Acta Obstet Gynecol Scand 2016;95:65–73.
Downes KL, Hinkle SN, Sjaarda LA, Albert PS, Grantz KL. Previous prelabor or intrapartum caesarean delivery and risk of placenta previa. Am J Obstet Gynecol 2015;212:669.e1–669.e6. doi: 10.1016/j.ajog.2015.01.004.
Fylstra DL. Ectopic pregnancy within a cesarean scar: a review. Obstet Gynecol Surv 2002;57:537–543.
Gonzalez N, Tulandi T. Cesarean scar pregnancy: a systematic review. J Minim Invasive Gynecol 2017;24:731–738.
Hanacek J, Vojtech J, Urbanková I, Krcmar M, Krepelka P, Feyerisl J, Krofta L. Ultrasound caesarean scar assessment one year postpartum in relation to one- or two-layer uterine suture closure. Acta Obstet Gynecol Scand 2020;99:69–78.
Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. First trimester diagnosis and management of pregnancies implanted into the lower uterine segment caesarean section scar. Ultrasound Obstet Gynecol 2003;21:220–227.
Larsen JV, Solomon MH. Pregnancy in a uterine scar sacculus – an unusual cause of postabortal haemorrhage. A case report. S Afr Med J 1978;53:142–143.
Luo L, Ruan X, Li C, Chen S, Hu Q, Mueck AO. Early clinical features and risk factors for cesarean scar pregnancy: a retrospective case-control study. Gynecol Endocrinol 2019;35:337–341.
The National Quality Registry for Assisted Reproduction (Q-IVF). https://www.medscinet.com/qivf/ (20 January 2021, date last accessed).
Ouyang Y, Li X, Yi Y, Gong F, Lin G, Lu G. First-trimester diagnosis and management of Caesarean scar pregnancies after in vitro fertilization-embryo transfer: a retrospective clinical analysis of 12 cases. Reprod Biol Endocrinol 2015;13:126.
Roberge S, Demers S, Girard M, Vikhareva O, Markey S, Chaillet N, Moore L, Paris G, Bujold E. Impact of uterine closure on residual myometrial thickness after caesarean; a randomized controlled trial. Am J Obstet Gynecol 2016;214:507.e1–507.e6.
Rotas MA, Haberman S, Levgrn M. Caesarean scar ectopic pregnancies: etiology, diagnosis, and management. Obstet Gynecol 2006;107:1373–1381.
Seow KM, Huang LW, Lin YH, Lin MY, Tsai YL, Hwang JL. Caesarean scar pregnancy: issues in management. Ultrasound Obstet Gynecol 2004;23:247–253.
Shah J, Nasab S, Papanna R, Chen H-Y, Promecene P, Berens P, Johnson A, Balwal A. Management and reproductive counselling in cervical, cesarean scar and interstitial ectopic pregnancies over 11 years: identifying the need for a modern management algorithm. Human Reprod Open 2019;2019:hoz028.
Silverstein P. Smoking and wound healing. Am J Med 1992;93:225–245.
Timor-Tritsch IE, Monteagudo A. Unforeseen consequences of the increasing rate of caesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. Am J Obstet Gynecol 2012;207:14–29.
Timor-Tritsch IE, Monteagudo A, Cali G, Palacios-Jaraquemada JM, Mayrmon R, Arslan AA, Patil N, Popiolek D, Mital KR. Caesarean scar pregnancy and early placenta accreta share common histology. Ultrasound Obstet Gynecol 2014a;43:383–395.
Timor-Tritsch IE, Monteagudo A, Cali G, Vintzileos A, Viscarello R, Al-Khan A, Zamudio S, Mayberry P, Cordoba MM, Dar P. Caesarean scar pregnancy is a precursor of morbidly adherent placenta. Ultrasound Obstet Gynecol 2014b;44:346–353.
Vial Y, Petignat P, Hohlfeld P. Pregnancy in a caesarean scar. Ultrasound Obstet Gynecol 2000;16:592–593.
Vachon-Marceau C, Demers S, Bujold E, Roberge S, Gauthier RJ, Pasquier JC, Girard M, Chaillet N, Boulvain M, Jastrow N. Single versus double-layer uterine closure at caesarean: impact on lower
uterine segment thickness at next pregnancy. *Am J Obstet Gynecol* 2017;217:E5.e1–E5.e5.  
Vikhareva O, Rickle GS, Lavesson T, Nedopekina E, Brandell K, Salvesen KÅ. Hysterotomy level at caesarean section and occurrence of large scar defects: a randomized single-blind trial. *Ultrasound Obstet Gynecol* 2019;53:438–442.  
Xie R, Guo X, Li M, Liao Y, Gaudet L, Walker M, Lei H, Wen SW. Risk factors and consequences of undiagnosed cesarean scar pregnancy: a cohort study in China. *BMC Pregnancy Childbirth* 2019;19:383.  
Zhou XY, Li H, Fu XD. Identifying possible risk factors for cesarean scar pregnancy based on a retrospective study of 291 cases. *J Obstet Gynaecol Res* 2020;46:272–278.