






Clinical and historical features of cesarean scar pregnancies in a tertiary hospital with a high rate of cesarean section: A case-control survey

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Abstract

Background and Aims: Cesarean scar pregnancy (CSP) is a rare medical condition accounting for 1:2000 of all pregnancies with prior history of cesarean deliveries (CS). As the rate of CS is increasing worldwide, it is important to know the nature of CSP and its complications.

Methods: In this retrospective case-control study, we evaluated 264 pregnant women; 86 cases with ultra-sonographic findings of CSP and 178 controls: normal pregnancies with gestational age less than 12 weeks. The variables consisted of demographic characteristics, the features and causes of the prior CS, the time distance to the current pregnancy, sonographic features, and the final management. All data analyzed using SPSS version 21.

Results: There was a significant difference between the two study groups regarding to parity, abortions and D&Cs ($p < 0.001$). In the case group, 19.8% of patients had positive results for STDs versus 16.3% in the control group ($p > 0.990$). The mean average of intervals between the last CS and current pregnancies were 48.22 ± 37.03 in the case group versus 61.25 ± 36.25 months in the control group ($p < 0.001$). Regression Logistic analysis showed advanced maternal age ($p < 0.001$), positive history of abortions and D&C ($p < 0.001$), elective type of prior c/s ($p < 0.001$) and the short time interval between prior CS and current pregnancy ($p < 0.001$) could significantly predict the patients at higher risk of presenting CSP in the case group.

Conclusions: Based on our findings, advanced maternal age, positive history of abortion, the elective type of the former CS, and short time intervals between previous CS and current pregnancy are the main risk factors of CSP.

KEYWORDS

cesarean scar pregnancies, ectopic pregnancy, pregnancy, risk factors

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1 | INTRODUCTION

The implantation of gestational components in places other than the endometrium is defined as ectopic pregnancy (EP).¹ The common anatomical sites of EP are fallopian tubes (95%) or some other possible areas (5%) such as ovaries, cervix, intra-abdominal spaces, prior cesarean scar surfaces. One particular type of EP occurs on the myometrium of the prior incised Cesarean sections (CS) fibrous scar.¹⁻³

It's estimated that cesarean scar pregnancy (CSP) occurs in 1:2000 of all pregnancies with a prior history of CS deliveries, accounting for approximately 6.1% of all EPs.³ Similar to EP, the diagnosis of CSP is tricky, as the patient usually presents no specific symptoms, therefore, the physician clinical judgment along with further radiologic evaluations are the main stem part of CSP diagnosis.^{3,4} Finding the gestational sac at the previous CS scar sites (the lower anterior part of uterine isthmus) on ultra-sonography (US) or magnetic resonance imaging (MRI) makes the accurate diagnosis of CSP.⁵

Two types of CSP have been defined as (a) endogenous (type1) and (b) exogenous (type 2). As the terms reveal, growing the gestational sac towards the endometrial cavity, started basically from the superficial part of the prior CS scar tissue site is referred to as endogenous, while, when the implantation occurs in, rather, deeper parts of the myometrium, tending to grow, aiming the abdominal structures, exogenous CSP is implied.^{4,5}

There are several treatment options, such as expectant management, Methotrexate therapy in multiple dosages, uterine artery embolization, curettage, wedge resection, and their combination^{4,5} but the optimal management still remains unclear. Of course, each treatment method has its own advantages and side effects, but, misdiagnosis or mismanagement of CSP leads to major complications including uterine rupture, hysterectomy, life-threatening hemorrhage, loss of future fertility, and even maternal death.⁵

Although this disease seems as an "emerging challenge," the studies conducted for CSP evaluations appear to be in their initial steps.⁶⁻¹⁰

Of course CSP is an iatrogenic complication through prior cesarean section and better understanding of the risk factors may lead to a good prevention protocol. Also, early CSP diagnosis and termination is highly important to avoid serious complications. Here, in our tertiary hospital, the CSP is not a rare complain, and so, we aimed to investigate the possible risk factors of CSP among a northern Iranian population, in Rasht, alongside with a brief report of our treatment options for patients with CSP.

2 | MATERIALS AND METHODS

In this retrospective case-control study, we evaluated all the women with ultra-sonographic results confirming CSP, referred to Al-Zahra hospital during January 2020 to December 2022. Al-Zahra hospital is a tertiary hospital of Guilan University of Medical Sciences in the

north of Iran with a high rate of cesarean section more than 2500 cases during 2020.

Based on the "SAMPLE protocol," numbers of cases and controls do not have to be equal. So, as a cost-effective way to improve the study, we matched two other pregnant women referred at the same day for each case, with gestational age lower than 12 weeks, as control group. Both case and control groups had a positive history of prior CS with the transection of the lower uterine segment through a pfannenstiel incision.

2.1 | Exclusion criteria included

The subjects who refused to confirm CSP diagnosis by ultra-sonography, the ones who did not continue treatment in our medical center, the files who did not had all the required data and the women who simply were not willing to participate in the study.

Following proper confirmation of the ethical committee of Guilan University of Medical Sciences (GUMS), the case files of subjects were reviewed and analyzed.

2.2 | Sample size

Based on Rotas et al.⁶ the sample size of the study with the test power of 90% and confidence interval (CI) 95% was estimated at least 72 patients in each group.

2.3 | Study group classifications

We defined two groups as case (86 subjects with ultra-sonographic results confirming CSP) and, control: 178 women with gestational age lower than 12 weeks referred at the same day with each case. We did not matched subjects in terms of demographic features and so on.

2.4 | Study variables

To facilitate our final analysis process and also to organize our data collection, we designed a checklist containing all the variables and filled it out for each patient. These variables included: age, body mass index (BMI), age at menarche, parity, No. of abortions, No. of prior CSs, types of CS (elective vs. emergency), underlying causes of previous CS (breech presentation, arrest of labor, multiple gestations, fetal distress, prior CS, meconium passage, placenta previa, abruption), gestational age in the prior CS, prior CS to current pregnancy intervals, previous pregnancy/labor related variables (history of premature rupture of membrane [PROM], postpartum infections [wound infection, metritis, etc.], postpartum hemorrhage [needed to packed cell infusion]), history of D&C, history of sexual transmitted disease (STD), current method of pregnancy (natural, assisted), sonographic results consisted of diameter of gestational

sac (millimeter), fetus with heart rate (FHR), gestational age, myometrial diameter between gestational sac and bladder. Also, the final management of all cases recorded in their collecting data sheet; Methotrexate therapy in multiple dosage, uterine artery embolization (UAE), D&C, wedge resection, UAE + D&C, UAE and wedge resection.

2.5 | Ethical consideration

The study was approved by the ethics committee of Guilan University of Medical Sciences (IR.GUMS.REC.1401.138). All stages of this research have been performed according to the Helsinki Declaration. All procedures of the study were explained clearly to the participants who had the eligible inclusion criteria. Moreover, all participants voluntarily filled out the written informed consent form before they join the study and they were free to decide whether or not to attend or withdraw at any time and for any reason without changing the medical care. All authors have read and approved the final version of the manuscript had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. Also, the study had no funding or support. Dr. Seyedeh Hajar Sharami and Dr. Sima Fallah Arzpeyma (the first and the corresponding authors) affirm that this manuscript is an honest, accurate, and transparent account of the study being reported, no important aspects of the study have been omitted and any

discrepancies from the study as planned have been explained. The authors confirm that the data supporting the findings of this study are available within the article its Supporting Information Materials.

2.6 | Statistical methods

All data were statistically analyzed using the SPSS software package version 23.0 for windows (IBM). Percentage and frequency were used to report the results of the qualitative data and standard deviation and the mean were used to report the quantitative data. Chi-square, Fisher exact test and independent *T* test were used to compare variables. $p < 0.001$ is considered statistically significant.

3 | RESULTS

A total number of 86 pregnant women with CSP as case group and 178 pregnant women as control group enrolled. Table 1 shows the demographic features distribution among all subjects. Applying nonparametric Mann–Whitney statistical test, there were significant differences between the two study groups regarding to age ($p < 0.001$) and parity ($p < 0.001$), which shows that the patients in the case group showed higher mean age and parity. Also, a positive history of abortions ($p < 0.001$) and prior D&C ($p < 0.001$) was more frequent in the case group. All patient 17 patients (19.8%) in the case

TABLE 1 Comparison the Demographic features between the two study groups.

| Variables | Total = 264 | Groups | | p value |
|--|--------------|---------------|-------------------|---------|
| | | Case (n = 86) | Control (n = 178) | |
| Age (y/o), M ± SD | 32.82 ± 5.6 | 35.35 ± 4.64 | 31.87 ± 5.7 | <0.001* |
| BMI (kg/m ²), M ± SD | 25.92 ± 3.24 | 24.82 ± 2.96 | 26.71 ± 2.98 | >0.990 |
| Menarche age (y/o), M ± SD | 11.6 ± 1.11 | 11.51 ± 1.26 | 11.63 ± 1.05 | >0.990 |
| Age at the time of prior pregnancy (y/o), M ± SD | 25.66 ± 4.6 | 25.83 ± 4.37 | 25.59 ± 4.69 | >0.990 |
| Parity (n), M ± SD | 2.82 ± 0.91 | 3.31 ± 1.08 | 2.63 ± 0.77 | <0.001* |
| Number of previous CS, M ± SD | 1.39 ± 0.695 | 1.43 ± 0.695 | 1.37 ± 0.579 | >0.990 |
| Number of previous CS (n (%)) | | | | |
| 1 | 175 (66.28) | 54 (62.79) | 121 (67.97) | >0.990 |
| ≥2 | 89 (33.72) | 32 (37.21) | 57 (32.02) | |
| Previous D&C (n), M ± SD | 0.36 ± 0.67 | 0.72 ± 0.92 | 0.23 ± 0.48 | <0.001* |
| Previous abortions (n (%)) | 77 (29.3) | 41 (48.2) | 36 (20.2) | <0.001* |
| History of PROM (n (%)) | 13 (4.92) | 6 (6.97) | 7 (3.93) | >0.990 |
| Post-partum infection (n (%)) | 11 (4.16) | 3 (3.48) | 8 (4.49) | >0.990 |
| Post-partum hemorrhage | 17 (6.43) | 6 (6.97) | 11 (6.17) | >0.990 |
| Assisted pregnancy (n (%)) | 53 (20.07) | 19 (22.09) | 34 (19.10) | >0.990 |
| STD (n (%)), M ± SD | 46 (17.4) | 17 (19.8) | 29 (16.3) | <0.001* |

*The difference is statistically significant.

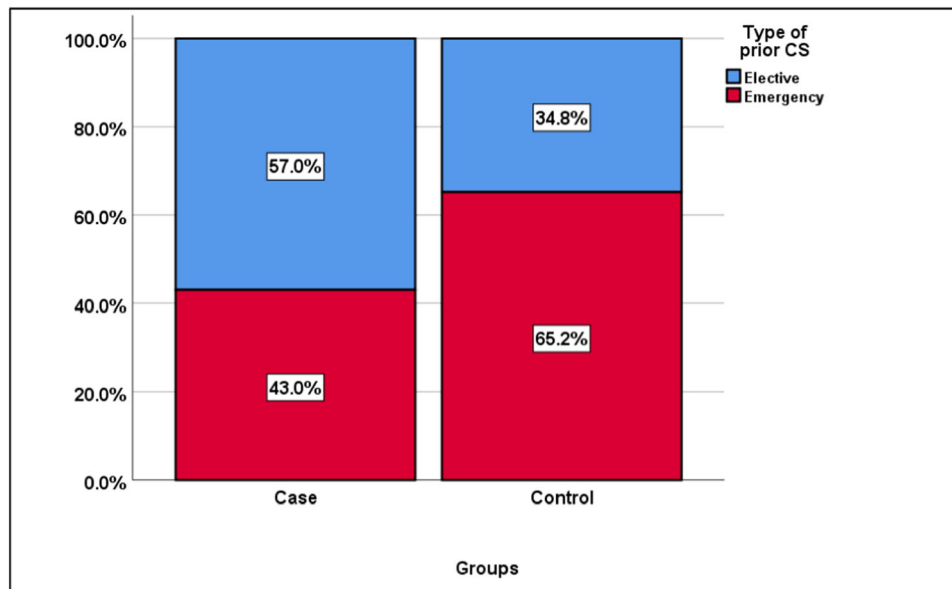


FIGURE 1 The type of prior cesarean section between the two study groups.

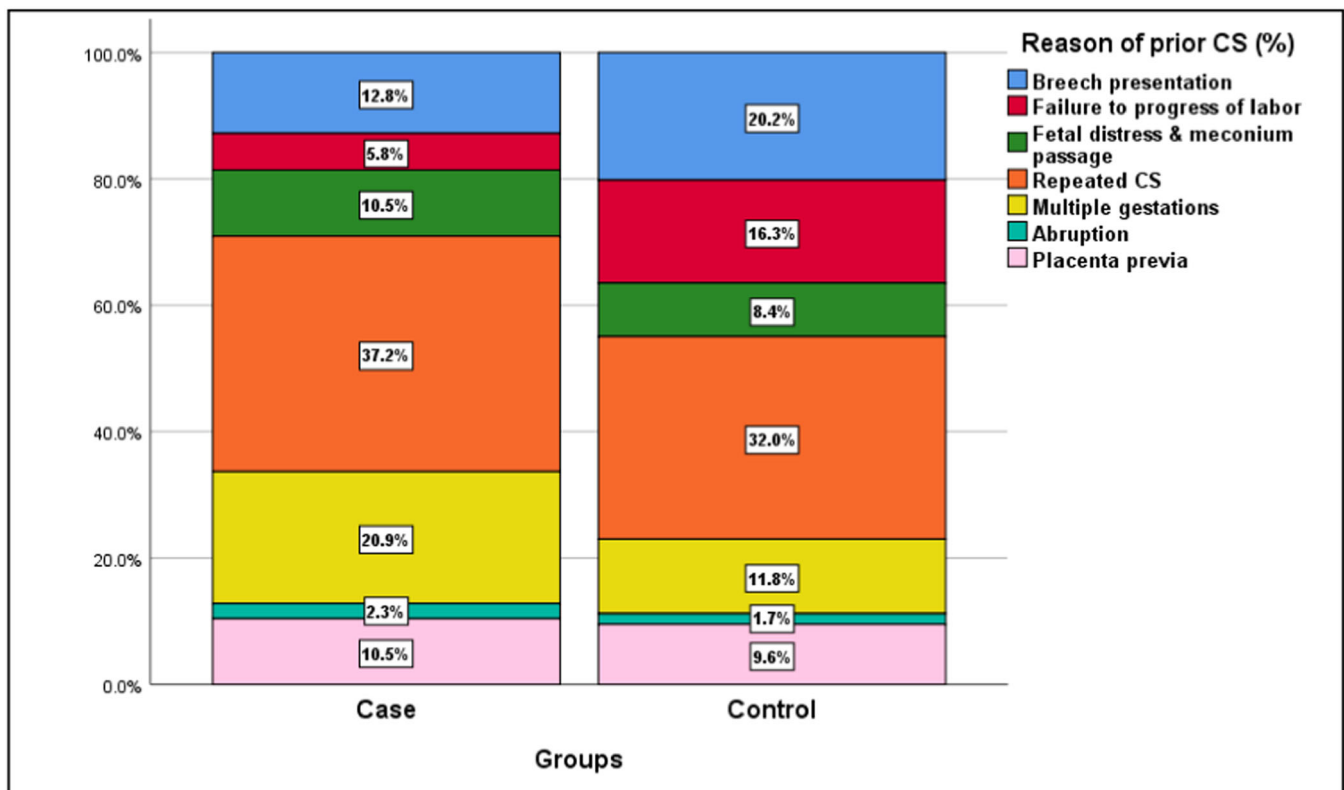


FIGURE 2 The reason of prior cesarean section between the two study groups.

group had positive results for STDs, compared to the 29 (16.3%) patients in the control group ($p > 0.990$) (Table 1 and Figures 1 and 2).

Table 2 shows the sonographic features of CSP in the case group. As the table shows, the mean gestational age among CSP patients was 6.42 ± 1.29 and 31.4% of the gestational sacs showed fetal heart rate (Table 2)! Table 3 indicates a significant statistical difference

between the two study groups regarding to the type of CS in the previous labor (57% of case group and 34.8% of control group was elective type also, emergency CS was more frequent in control group; $p < 0.001$). Outcomes of the study groups revealed no significant differences comparing the underlying causes of CS between the groups ($p < 0.001$) (Table 3).

TABLE 2 The sonographic features of CSP in the case group.

| Variables | Case (n = 86) |
|---|---------------|
| Diameter of gestational sac (M ± SD) | 22.94 ± 12.57 |
| Gestational age (M ± SD) | 6.42 ± 1.29 |
| With Fetal heart rate (n (%)) | 27 (31.4) |
| The myometrial thickness between the gestational sac and bladder (M ± SD) | 3.17 ± 2.06 |

TABLE 3 Comparing the features of the previous CS among the two groups.

| Variables | Total = 264 | Groups | | p value |
|--|---------------|---------------|-------------------|---------|
| | | Case (n = 86) | Control (n = 178) | |
| Type of prior CS (n (%)) | | | | |
| Emergency | 153 (38.3) | 37 (43) | 116 (65.2) | <0.001* |
| Elective | 111 (61.7) | 49 (57) | 62 (34.8) | |
| Reason of prior CS (n (%)) | | | | |
| Breech presentation | 47 (17.80) | 11 (12.79) | 36 (20.22) | >0.990 |
| Failure to progress of labor | 34 (12.87) | 5 (5.81) | 29 (16.29) | <0.001* |
| Fetal distress and meconium passage | 24 (9.09) | 9 (10.46) | 15 (8.42) | >0.990 |
| Repeated CS | 89 (33.71) | 32 (37.22) | 57 (32.05) | >0.990 |
| Multiple gestations | 39 (14.72) | 18 (20.94) | 21 (11.79) | <0.001* |
| Abruption | 5 (1.85) | 2 (2.32) | 3 (1.68) | >0.990 |
| Placenta previa | 28 (10.54) | 9 (10.46) | 17 (9.55) | >0.990 |
| Gestational age at prior CS (weeks) (M ± SD) | 39.09 ± 1.36 | 38.95 ± 2.06 | 39.15 ± 0.84 | >0.990 |
| Prior CS to current pregnancy interval (months) (M ± SD) | 52.46 ± 37.21 | 48.22 ± 37.03 | 61.25 ± 36.25 | <0.001* |

*The difference is statistically significant.

TABLE 4 Results of regression logistic model analysis in the CSP group.

| Variables | B | Standard error (SE) | WALD | p value | EXPB | 95% Confidence interval (95% CI) | |
|----------------------------------|--------|---------------------|-------|---------|-------|----------------------------------|---------|
| | | | | | | Minimum | Maximum |
| Age | 0.089 | 0.034 | 6.84 | <0.001* | 0.915 | 0.856 | 0.978 |
| Parity | 0.019 | 0.213 | 0.008 | >0.990 | 0.981 | 0.646 | 1.489 |
| Prior abortions | 1.35 | 0.415 | 10.69 | <0.001* | 3.888 | 1.723 | 8.775 |
| Previous D&C | 0.12 | 0.022 | 5.82 | <0.001* | 2.24 | 1.432 | 4.567 |
| Type of prior CS | 0.945 | 0.361 | 6.84 | <0.001* | 2.57 | 1.267 | 5.221 |
| Time interval of the previous CS | -0.242 | 0.021 | 2.87 | <0.001* | 0.652 | 0.232 | 0.878 |
| History of STDs | 0.45 | 0.558 | 0.10 | >0.990 | 1.046 | 0.426 | 2.569 |

*The difference is statistically significant.

The mean intervals between the last CS and current pregnancies were 48.22 ± 37.03 in the case group versus 61.25 ± 36.25 months in the control group ($p < 0.001$). There was no statistically significant difference between the two study groups in terms of gestational age at the prior CS (Table 3).

Finally, we applied regression Logistic analysis, aimed at group prediction, assuming CSP as a dependent variable and maternal age, parity, history of abortions, type of prior CS and the interval, history of STDs and D&Cs as independent variables. As shown in Table 4, advanced maternal age ($p < 0.001$), positive history of abortions and

D&C ($p < 0.001$), elective type of prior c/s ($p < 0.001$) and the short time interval between prior CS and current pregnancy ($p < 0.001$) could significantly predict the patients at higher risk of presenting CSP in the case group.

Surprisingly, despite the statistically significant difference between the two study groups, based on logistic regression analysis, parity ($p > 0.990$) and positive history of STDs ($p > 0.990$) were not predictive variables of CSP!

Finally, different treatment methods performed for CSP patients: 41 (47.67%) cases managed with a combination of UAE and D&C. Multiple dosage of MTX together with UAE and D&C used for 25 (29.06%) cases and 20 (23.25%) patients underwent wedge resection. No hysterectomy or massive hemorrhage happened.

4 | DISCUSSION

The main objective of the present study was to better understand the possible risk factors of CSP. To achieve this, we intended to cover some basic demographic features of the patients visiting our medical center and evaluated the potential, yet determining, variables related to CSP. These were considered to provide a comprehensive overview of a rather newly introduced EP subtype.

In total, 264 patients were enrolled in two groups (case vs. control). Among various aforementioned variables in the results section; maternal advanced age, positive history for prior abortions or D&Cs, elective type of CS and the short time interval have been shown to be as risk factors of CSP in a pregnant woman with a prior history of CS.

Similar to Zhou et al.,⁷ our results revealed that, higher maternal age was associated with increased risks of developing CSP. However, in their study, they defined an age range of over 35 years old, as a risk factor of CSP, while we found an ongoing negative effect of aging on CSP rates among our subjects, so that as patients age, the rates of CSP raised.

The mean and standard deviation of the age of our patients in the case group were 35.35 ± 4.64 years old, while these figures were 35.7 ± 3.8 in Kim et al.⁸ and 34.16 ± 4.4 in Lanrong et al.⁹ and 32.90 ± 4.80 in Tang et al.¹⁰

We assume that economic reasons, leading to delays of pregnancies could be an underlying cause. Then, with advanced age, not only the quality of the prefertilized/fertilized egg, but also the implantation sites at the endometrium could be compromised. Moreover, as in general, the chances of normal pregnancies decline with age, the possibilities of abortions and infertility and the procedures to treat these medical issues and their complications might increase.

Furthermore, Zhou et al.⁷ reported that the anatomy and physiology of the endometrium in an older mother paves the ways for higher rates of CS itself, let alone the possible accompanying complications. This is rather due to tissue stiffness of the endometrial cavity as women age, compromising the flexible structure of a normal uterus in a rather younger mother. On the other hand, as we know, maternal age rises the rate of early or induced abortion which as our

results showed, may be related to CSP! Our findings demonstrate a significant relationship between a history of previous abortion, D&C and previous elective type of CS with CSP. A prior abortion can be a weak point for future implantation, possibly due to the remain placental tissue or a hematoma which are entrapped in the myometrium. A similar concept has been mentioned in Wang et al. and Ma et al. studies.^{11,12}

During an emergent CS, which is usually due to the failure to labor progress or fetal distress, dilation on the lower segment happens and the incision will be on the lower parts of uterine with thin myometrium layer, while, in an elective CS, lower segment is not dilated and the incision will be on a thick myometrium, therefore, healing with fibrosis will weaken the myometrium, leading to a defect formation, known as "Niche" which carries high risks of CSP on the affected implantation site.¹¹⁻¹³

After reviewing of the literature, we assumed that infections could lead to the development of postcesarean scar defects or even changes in the structures of healthy endometrial tissues leading to not only difficulties in implantation, but also developing possible adhesion sites in the anatomy of affected sites in individual with STDs. This negative cycle of events could reinforce the CSP occurrence by delaying tissue repair of the CS scar, however, despite the statistically significant difference between the two study groups, we found no significant relationships between the frequencies of STDs and the occurrence of CSP ($p = 0.921$).

Similar to Zhou et al.,⁷ there was a significant statistical difference, with regard to the short intervals between previous CS and current pregnancy ($p = 0.001$).

The possible mechanism is that endometrial injury is an unavoidable consequence of CS itself, in which poor wound healing happens due to the misaligned incision edges of the uterine cannot overlap very well, or the infected incision. Therefore, a cesarean scar defects forms in the anterior wall of the lower uterine segment and it takes time to complete healing. So, when the time interval is too short, the fertilized egg can easily implant here and leads to CSP¹³⁻¹⁵!

These results might indicate this possible theory that by encouraging plans, aiming at decreasing the average age of women at the time of their pregnancies along with increasing the overall knowledge of women about the benefits of normal vaginal deliveries instead of CS, we might lead the way to significant declines in the incidence of CSPs. Also, probable illegal abortions in Iran, somehow due to cultural and religious beliefs, might results in incomplete evacuations of the products of conception (POC) or even cause damages to the endometrial-myometrial layers, interfering with normal implantation processes. Therefore, seeking novel solutions or recommendations to decrease such abortions should be considered.

5 | CONCLUSION

Based on our findings, advanced maternal age, positive history of abortion, the elective type of the former CS, and short time intervals between previous CS and current pregnancy are the main risk factors of CSP.

AUTHOR CONTRIBUTIONS

Seyedeh Hajar Sharami: Conceptualization. **Sima Fallah Arzpeyma:** Writing—review and editing. **Sina Montazeri:** Conceptualization. **Zahra Haghparast Ghadim-limudahi:** Writing—review and editing. **Habib Eslami-Kenarsari:** Formal analysis. **Seyedeh Maryam Attari:** Resources. **Harir Tanhaye Kamakoli:** Investigation.

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DATA AVAILABILITY STATEMENT

Data available on request. The data underlying this article will be shared on reasonable request to the first or corresponding authors.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author Sima Fallah Arzpeyma affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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