Investigating the risk factors for isthmocele development after cesarean delivery

Masoud Saadat Fakhr, MD; Mahya Mozafari, MD; Kiana Rezvanfar, MD; Zahra Amini, MD; Koosha Amiri, MD; Reza Shah Hosseini, MD; Hengame Sarnaz, MD; Poorya Gholami, MD; Zohreh Lavasani, MD

BACKGROUND: Cesarean delivery rates are increasing globally, raising concerns about associated complications such as isthmocele. Isthmoceles are pouch-like defects in the anterior uterine wall at the site of a prior cesarean delivery scar.

OBJECTIVE: This study aimed to determine isthmocele prevalence, associated symptoms, and risk factors among women with a history of cesarean delivery.

STUDY DESIGN: This cross-sectional study evaluated 297 women with prior cesarean delivery using transvaginal ultrasound to screen for isthmocele. Data on demographics, pregnancy details, comorbidities, and indications for cesarean delivery were collected. Isthmocele was defined sonographically as any niche or defect at the hysterotomy site. Descriptive and comparative analyses identified factors associated with isthmocele.

RESULTS: Isthmocele prevalence was 65.3% (n=194). Abnormal vaginal bleeding was reported in 21.1% of participants, pelvic pain by 4.1% of participants, and both by 4.1% of participants. Compared to women without isthmocele, those with isthmocele were older (35.9 vs 31.6 years), had higher body mass index (26.8 vs 25.5 kg/m^2), gravidity (1.8 vs 1.3), and parity (1.7 vs 1.2). Repeat cesarean delivery was more common (30.4% vs 12.6%) and elective cesarean delivery less common (33.5% vs 67.9%) among those with isthmocele.

CONCLUSION: Over half of the women with history of cesarean delivery had an isthmocele. Abnormal bleeding was common. Advanced maternal age, obesity, repeat procedures, and certain comorbidities appear to increase risk. Further research on prevention and treatment is warranted given the high prevalence.

Key words: abnormal uterine bleeding, cesarean delivery, cesarean scar defect, isthmocele, uterine niche

Introduction

Globally, cesarean delivery (CD) are the most commonly performed obstetric operative intervention.[1] Although CD is becoming increasingly popular, its rising cost and maternal, neonatal, and perinatal risks have caused a significant public health concern.[2] According to the World Health Organization, CD rates have increased from 7% in 1990 to 21% today.[3] There is an estimation that by 2030 the global average CD rate will increase to 28.5%, with more than 38 million births by CD.[4] The reasons for the rising CD rates are still subject to debate, with some authors suggesting fear of litigation, changing maternal characteristics, electronic fetal monitoring, and changing professional practice styles, whereas others suggest sociocultural and economic factors.[5–7] Healthcare providers can take preventive measures to minimize CD risks and complications, such as infection, excessive bleeding, organ injury, anesthesia reactions, blood clots, and prolonged recovery. It is also important for patients to be informed of possible long-term effects on future pregnancies, such as issues with placental implantation or uterine rupture risks. A comprehensive understanding of CD complications and risks facilitates informed decision-making for providers and patients.[8] One of the most common gynecologic sequelae of CD is a uterine

From the Faculty of Medicine, Tehran Medical Sciences Branch, Islamic Azad University, Tehran, Iran (Drs Fakhr, Mozafari, Rezvanfar, Amini, Amiri, Sarnaz, and Gholami); Faculty of Medicine, Istanbul Medipol University, Istanbul, Turkey (Mr Hosseini); Department of Obstetrics and Gynecology, Faculty of Medicine, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran (Dr Lavasani)

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No animals were used in this research. All human research procedures followed were by the ethical standards of the committee responsible for human experimentation (Islamic Azad University, Tehran Medical Branch (IR.IAU.TMU.REC.1401.166), and with the Helsinki Declaration of 1975, as revised in 2013. This study was approved by the research ethics board of Islamic Azad University.

Informed consent was obtained from each participant.

All relevant data and materials are provided in the manuscript.

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Corresponding author: Zohreh Lavasani, MD. zohrehlavasanii@yahoo.com

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Why was this study conducted?

This study aimed to investigate the rising rates of cesarean deliveries (CD) globally and associated complications, particularly isthmocele, a defect in the anterior uterine wall post-CD. It sought to determine isthmocele prevalence, symptoms, and risk factors among 297 women with prior CD, using transvaginal ultrasound and demographic data collection. The study aimed to offer insights into isthmocele's prevalence, symptoms, and risk factors to inform potential prevention and treatment strategies.

Key findings

These findings underscore the significance of isthmocele as a prevalent complication following CD, indicating a need for further research into prevention and treatment strategies.

What does this add to what is known?

This study deepens our understanding of isthmocele prevalence, symptoms, and risk factors among women with a history of cesarean delivery (CD). It quantifies isthmocele prevalence at 65.3% and identifies associated symptoms and demographic factors. These insights can guide future research and inform strategies for prevention and management in clinical practice.

scar with deficient healing, known as an isthmocele or CD defect.[9] Isthmocele is a triangular defect in the anterior uterine wall involving communication with the uterine cavity at the site of a previous CD scar.[10,11] Cesarean scar defects (CSDs) occur in 19% to 61% of women after 1 CD and in 100% of women after 3 CDs; however, these numbers may be underestimated in part due to asymptomatic women and a lack of awareness among practitioners.[12,13] A recent study demonstrated that higher maternal body mass index, gestational diabetes, and previous CDs were all associated with an increased risk for incomplete healing of the uterine incision. In addition, labor before CD could lead to a low hysterotomy and uterine closure with single-layer or locking sutures, as well as nonclosure of the peritoneum.[13] The most important risk factor for isthmocele is recurrent CD, which should be reduced by healthcare providers.[14] Although some isthmoceles remain asymptomatic, others can cause a variety of gynecological symptoms, including abnormal uterine bleeding (AUB), dysmenorrhea, chronic pelvic pain, dyspareunia, and infertility.[10] Furthermore, ectopic pregnancy, uterine rupture, and placental anomalies (including placenta accreta) may result from them.[15] According to the study, AUB was found to be the most common symptom of the condition.[14] The healing of uterine wounds plays a key role in isthmocele development. Following a CD, the uterine incision undergoes a complex set of intricate biological processes, including inflammation, cell migration, extracellular matrix remodeling, and tissue regeneration.[16,17] The exact mechanism behind isthmocele formation is not clear; however, impaired scar healing, inadequate vascularization, and suboptimal tissue repair all contribute to its development and persistence.[14] Isthmoceles or CSD, can be categorized into types such as simple, complex, wedge-shaped, pouch, dehiscent, partial, or complete, based on their appearance on transvaginal ultrasound. This classification uses characteristics such as shape, contents, borders, connection to the uterine cavity, and extent of lower uterine involvement. Ultrasound imaging helps classify the defect and guide treatment.[11,18] Considering these, there is limited and contradictory evidence regarding isthmocele risk factors and incidence. Moreover, few studies have evaluated isthmocele in the population. Identifying risk factors can facilitate isthmocele prevention. Therefore, we aimed to investigate the risk factors and causes of isthmocele following CD.

Materials and Methods

This cross-sectional analytical study was approved by the Ethics Committee of the Islamic Azad University of Tehran Medical Unit (IR.IAU.TMU.REC.1401.004).

All participants in this study signed a written informed consent form, and their information remained confidential. The sample size was calculated based on alpha of.05, the expected isthmus cell prevalence of 0.738 from previous studies[19] and d of 0.05; the required sample size of 297 patients was calculated. Inclusion criteria were history of CD and complete medical records. Exclusion criteria included unwillingness to continue participation and uterine anatomical defects. Study participants were selected using simple random sampling from the eligible population. Data collection was performed by the research team on-site at Amir Al Momenin Hospital in Tehran during the period from 2022 to 2023. Demographic information, including age, gravidity, parity, prior birth history, pregnancy complications, infant weights, and delivery details, were collected. Quantitative anthropometric data, including weight and height were measured by the researcher. Height and weight were measured using standard scales. Descriptive anthropometric data, including smoking status, family history of cardiovascular disease, hypertension, and dyslipidemia were collected via questionnaire. Isthmocele was sonographically defined as any CSD or niche, myometrial discontinuity or pouching, or an anechoic triangular defect in the anterior uterine wall connected to the cavity and located inferiorly. Isthmocele shape was categorized based on a prior publication as triangular, semicircular, rectangular, circular, droplet, or cystic. Isthmocele dimensions were measured in the sagittal plane, including residual myometrial thickness, isthmocele depth and width, cervical width, distance from fundus to isthmocele, and distance from isthmocele to internal os.

Transvaginal ultrasonography was performed to delineate isthmocele characteristics and additional uterine measures include location, length, width, endometrial thickness, and presence of intrauterine fluid.

Transvaginal ultrasound screening was performed to assess isthmocele in women with prior CDs. The ultrasound examinations were conducted by experienced sonographers using standard protocols. It is important to note that all ultrasound scans were performed without the use of saline or gel contrast in our study.

All patient information, including demographic and clinical factors were recorded on a checklist by the researcher and input into SPSS v26 (SPSS Statistics V26 2019). Statistical analysis was performed in descriptive and analytical sections. Isthmocele frequency as the main outcome was reported across groups. All demographic and clinical characteristics were summarized using descriptive measures. Analytical testing utilized appropriate parametric and nonparametric tests based on statistical assumptions. Qualitative data was analyzed using the chi-square test and quantitative data was compared using an independent sample t-test. If normality assumptions were violated, a nonparametric Mann-Whitney test was used. All tests were 2-sided at a 5% significance level. Furthermore, multivariable logistic regression modeling was employed to identify independent predictors of isthmocele, with all tests being 2-sided at a 5% significance level. This work was in line with the STROBE criteria.

Results

The study included 297 women with a history of CD who underwent transvaginal ultrasound screening for isthmocele. A total of 194 (65.3%) women had isthmocele (the isthmocele group), and 103 (34.7%) women did not have isthmocele. Based on Table 1, among women diagnosed with isthmocele, 41 (21.1%) reported abnormal vaginal

TABLE 1
Baseline characteristics and the risk factors for presence of an isthmocele[a]

	Isthmoscele		
Characteristics	+ n (%) 194 (65.3%)	_ n (%) 103 (34.7%)	*P* value
Types of symptoms, n (%)			
Bleeding	41 (21.1%)	—	—
Pelvic pain	8 (4.1%)	—	
Bleeding and pain	8 (4.1%)	—	
Mass feeling	4 (2%)	—	
Maternal factors (mean SD)			
Age (y)	35.9±5.9	31.6±5.5	<.001
Gravid (n)	1.8±0.7	1.3±0.6	<.001
Parity (n)	1.7±0.6	1.2±0.4	<.001
BMI (kg/m^2)	26.8±1.5	25.5±1.6	<.001
Gestational Age (wk)	38.2±1.1	38.3±1.7	.026
Cesarean delivery (n)	1.4±0.5	1.1±0.3	<.001
Weight of last baby (g)	3184.6±336.4	3156.2±374.1	.612
Reason for cesarean delivery, n (%)			
Elective	65 (33.5)	70 (67.9)	<.001
Repetition	59 (30.4)	13 (12.6)	<.001
Pregnancy twin	4 (2)	4 (3.8)	.45
PROM	8 (4.1)	4 (3.8)	.59
Breech	0 (0)	4 (3.8)	.01
Onset of pain	9 (4.6)	4 (3.8)	.51
Cerclage and uterine defect	11 (5.6)	0 (0)	.008
Overweight	4 (2)	0 (0)	.18
History PROM	13 (6.7)	0 (0)	.003
Prolonged delivery	4 (2)	0 (0)	.18
Comorbidity, n (%)			
Asthma	3 (1.5)	1 (0.009)	.56
Thyroid disorders	28 (14.4)	16 (15.5)	.79
Diabetes	8 (4.1)	0 (0)	.03
Depression	8 (4.1)	4 (3.8)	.59
Hypertension	13 (6.7)	0 (0)	.03
Anemia	12 (6.1)	0 (0)	.005
Heart disease	4 (2)	0 (0)	.18
Irritable bowel syndrome	1 (0.005)	3 (2.9)	.12

PROM, prelabor rupture of membranes; *SD*, standard deviation.

[a] Values are expressed as n (%) or mean±SD.

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TABLE 2
Univariable logistic regression model

Variables in the Equation	B	SE	Wald	*P* value	OR (95% CI)
Age	0.13	0.02	28.05	.000	1.14 (1.09–1.20)
Gravid	0.97	0.20	22.74	.000	2.64 (1.77–3.94)
Parity	1.31	0.24	29.92	.000	3.74 (2.33–6.00)
BMI	0.59	0.09	36.18	.000	1.80 (1.49–2.19)
Number of cesarean deliveries	1.53	0.30	25.98	.000	4.65 (2.57–8.41)
Elective cesarean delivery	−1.46	0.26	31.41	.000	0.23 (0.13–0.38)
Repeat of cesarean delivery	1.13	0.33	11.41	.001	3.10 (1.60–5.97)

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio; *SE*, standard error.

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bleeding, 8 (4.1%) had pelvic pain, 8 (4.1%) experienced both bleeding and pain, and 4 (2%) reported an abdominal mass. It is important to note that the information on symptoms was based on self-reported history during the study, and detailed data regarding the duration, amount, and significance of vaginal bleeding and pelvic pain were not systematically collected. In addition, specific types of pelvic masses were not systematically recorded.

The mean maternal age was higher among patients with isthmocele (35.9±5.9 vs 31.6±5.5 years; *P*<.001), Similarly, mean gravidity (1.8±0.7 vs 1.3±0.6; *P*<.001), mean parity (1.7±0.6 vs 1.2±0.4; *P*<.001), and mean body mass index (BMI) (26.8±1.5 vs 25.5±1.6 kg/m^2; *P*<.001) were higher among patients with isthmocele. The mean gestational age was slightly lower in the isthmocele group (38.2±1.1 vs 38.3±1.7 weeks; *P*=.026). Whereas only 13.6% (n=14) of the nonisthmocele group delivered at 34 to 36 weeks and 3.9% (n=4) delivered preterm before 34 weeks, 19.1% (n=37) of the isthmocele group delivered at 34 to 36 weeks and 7.7% (n=15) delivered before 34 weeks. Of the patients, 12.5% had a history of preterm labor, and 12.5% had a history of prelabor rupture of membranes (PROM). However, this difference was not statistically significant (9.7% vs 2.6%; *P*=.074). The mean weight of the last baby in patients was not statistically significant (3184.6±336.4 vs 3156.2±374.1 g; *P*=.612) (Table 1). The most frequent indication of CD overall was elective CD, accounting for 45.1% (n=134) of cases. However, the rate of elective CD was lower in women with isthmocele (33.5%, n=65 vs 67.9%, n=70; *P*<.001), which was statistically significant. The most common reasons for elective CD were previous myomectomy, placenta previa, suspected macrosomia, and maternal request. In contrast, repetition of CD was significantly more prevalent among women with isthmocele (30.4%, n=59 vs 12.6%, n = 13; *P*<.001). Other significant risk factors included prolonged labor, PROM, previous myomectomy, and previous uterine rupture. It is important to note that uterine anomalies were excluded as per the study's exclusion criteria and were not considered in the statistical analysis.

As presented in Table 2, there were 3 patients with asthma (1.5%), 28 with hypothyroidism (14.4%), 8 with A2GDM diabetes (4.1%), 8 with depression (4.1%), 13 with hypertension (6.7%), 12 with anemia (6.1%), 4 (2%) with heart disease, 1 (0.005%) with irritable bowel syndrome, 1 (0.005%) with arthritis, and 4 (2%) with human papillomavirus. In addition, patients without isthmocele had the following diseases during pregnancy: 1 (0.009%) had asthma, 16 (15.5%) had hypothyroidism, 4 (3.8%) had depression, 3 (2.9%) had arthritis, 3 (2.9%) had irritable bowel syndrome, and 73 (24.5%) had no diseases during pregnancy. Univariable logistic regression analysis (Table 2) showed that increased maternal age, gravidity, parity, BMI, number of previous CDs, and repeat CD were associated with significantly increased odds of isthmocele; whereas elective CD was associated with significantly decreased odds. Multivariable logistic regression modeling (Table 3) identified advanced maternal age (odds ratio [OR], 1.20; 95% confidence interval [CI], 1.08–1.33; *P*=.0), higher BMI (OR, 2.56; 95% CI, 1.73–3.78; *P*=.0), and asthma (OR, 28.07; 95% CI, 1.90–414.84; *P*=.015) as

TABLE 3
Multivariable logistic regression model

Variables in the Equation	B	SE	Wald	*P* value	OR (95% CI)
Age	0.18	0.05	12.72	.000	1.20 (1.08–1.33)
BMI	0.94	0.19	22.53	.000	2.56 (1.73–3.78)
Asthma	3.33	1.37	5.89	.015	28.07 (1.90–414.84)

BMI, body mass index; *CI*, confidence interval; *OR*, odds ratio; *SE*, standard error.

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independent predictors of isthmocele. After adjustment for other factors, each year increase in maternal age and unit increase in BMI was associated with 20% and 156% higher odds of isthmocele, respectively. Asthma had a very strong association, with over 28 times higher adjusted odds of isthmocele compared to women without asthma.

Discussion

A CSD is common after CD, occurring in 19% to 61% of women after 1 CD and nearly 100% after 3 CDs.[12,13] It may cause pain, infertility, and pregnancy complications, even if it is asymptomatic.[10] Despite limited evidence, it is still unclear whether high maternal BMI, gestational diabetes, labor before CD, and inadequate surgical closure contribute to this condition.[13] Pouch-like defects, or isthmoceles, have gained increased attention in recent years due to their potential impact on maternal health. Isthmocele and its associated risk factors are important to the well-being of post-CD patients and may facilitate prevention.

This study aimed to examine the risk factors and causes of isthmoceles, a condition that occurs frequently following CDs. In our study, 65.3% of 297 women with prior CDs who underwent transvaginal ultrasound screening had isthmocele. This rate is at the upper end of estimates from previous studies, which ranged from 19% to 61% for women after 1 CD.[12] This is likely reflecting the ability of ultrasound screening to detect even asymptomatic defects. The findings highlight that the majority of women may experience CSDs after CD, emphasizing the importance of clinical awareness.

A consensus statement by Jordans et al[20] outlined specific criteria for uterine niche evaluation, providing a standardized definition for this condition. According to their consensus, a niche was defined as an indentation at the site of a CD with a depth of at least 2 mm; and basic measurements, including niche length and depth, residual and adjacent myometrial thickness, and niche width were considered essential. Although our study utilized transvaginal ultrasound screening to detect isthmocele based on our defined criteria, it is crucial to acknowledge the importance of aligning with standardized definitions in the field.[20]

A review article by Thaysa Guglieri Kremer et al[11] published in 2019 reported that isthmocele is associated with AUB, dysmenorrhea, pelvic pain, and infertility. Moreover, Murji et al[21] demonstrated in 2022, in a systematic review and meta-analysis of 60 studies, that patients with CSD were more likely to experience AUB compared with those without CSD. There is a strong and consistent association, with a relative risk of 3.47 (95% CI, 2.02−5.97).[21] Our findings confirm findings from previous studies. According to our study, 21.1%women with isthmocele reported abnormal vaginal bleeding, 4.1% reported pelvic pain, and 4.1% reported both bleeding and pain, along with 2% feeling abdominal masses. Park et al,[19] in a randomized controlled trial (RCT), examined 404 women with a history of at least 1 low transverse CD. Isthmocele occurrence was not associated with maternal age, BMI, parity, or preterm experience as in our study.[19] In contrast, our research found several maternal factors that increased isthmocele risk, including advanced maternal age (35.9 years), a higher BMI (26.8 kg/m^2), repeated CDs (1.4), and an earlier gestational delivery age (38.2 weeks). All of these factors impair wound healing and scar formation. It is important to clarify that the term 'earlier gestational delivery age' in this context refers to the mean gestational age at delivery for the isthmocele group. These factors, including advanced maternal age, higher BMI, and repeated CDs, have been associated with impaired wound healing and scar formation in the literature.

In addition, Chen et al[22] (2017), in a retrospective study of 69 CSD cases and 107 cases without CSD, found that the occurrence of an isthmocele after CD is primarily due to multiple factors, including age ≥30 years, BMI ≥27.30, PROM, and elective CD. As a result of understanding isthmocele risk, providers can help patients to achieve a healthy BMI and reduce unnecessary repeat CDs. This study found that elective CD was less common, whereas repeat CD was more common in the isthmocele group. However, there were no significant differences in PROM, breech presentation, or labor pain onset. According to a case-control study by Liu et al[23] (2021), which included 216 women (87 patients with CSD and 129 cases without CSD), women with a history of CD, multiple CDs, elective CD, CD intervals of less than 5 years, and retroflexed positions of the uterus may be associated with an elevated risk of CSD. CD indications differed significantly between women with and without an isthmocele. Lumbanraja et al,[24] in a prospective cohort study in 2023 on 280 patients, found that there was no significant relationship between anemia status and CSD development. Similarly, in an RCT study on 404 women with a history of CD, Park et al[19] found no significant difference in diabetes or hypertension prevalence between the 2 groups (CSD vs no CSD).[11] This study revealed different results; we found higher comorbidity rates among women with isthmocele than the nonisthmocele group. These include A2GDM diabetes (4.1% vs 0%), hypertension (6.7% vs 0%), and anemia (6.1% vs 0%). According to our hypothesis, the increased prevalence of diseases impacting vascular health and wound healing, such as diabetes and hypertension, implies these conditions may exacerbate scar defect formation through mechanisms such as impaired angiogenesis and fibrosis.[25−27] Anemia could potentially affect tissue repair through reduced oxygen delivery.[28,29] However, additional studies are warranted to clarify these relationships and mechanisms. This study has several limitations. The data comes from a single medical center, limiting the generalizability of the findings to the broader population. The modest sample size reduces statistical power to detect significant associations. In addition, the transvaginal ultrasound screening approach may overestimate isthmocele prevalence compared to studies only including symptomatic cases. Verification with other imaging

modalities was not conducted. The analysis did not differentiate based on isthmocele characteristics such as size, depth, or morphology. Further large, multicenter prospective cohort studies are required to validate the relationships identified here between isthmocele, associated factors, and outcomes. Additional research should investigate optimal surgical techniques and standardized diagnostic criteria to improve isthmocele prevention, detection, and management.

Conclusion

In conclusion, this research found a high prevalence of isthmocele among women with prior CDs. Although some women with isthmocele reported symptoms such as abnormal bleeding and pelvic pain, a significant proportion of cases were identified without women reporting specific symptoms during the study. We also identified several associated factors, including abnormal bleeding, repeat procedures, fewer elective CDs, and certain comorbidities. These findings highlight the need for greater clinical awareness, risk factor optimization, and additional research to prevent and treat this common post-CD defect. Enhanced understanding of isthmocele can lead to improved care for affected women. ■

CRediT authorship contribution statement

Masoud Saadat Fakhr: Conceptualization, Investigation, Methodology, Supervision, Validation, Visualization.

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