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Original Research Article

Prospective Analysis of the Relationship between Caesarean Scar Defect and Abnormal Uterine Bleeding

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Abstract

Objective: To evaluate the relationship between cesarean scar defect and abnormal uterine bleeding at one year after cesarean section (CS).

Study Design: A prospective observational cohort study was conducted in 401 women who delivered by CS for one year. Women were screened for isthmocele with sonohysterography six months after CS and followed by electronic questionnaires at 12, 13 and 14 months after CS. The main outcome measure was the prevalence of postmenstrual spotting. Secondary outcome measures were the duration of menstrual bleeding, prevalence of postcoital bleeding, dyspareunia or dysmenorrhea, usage of painkillers, and absence from work or other activities.

Results: The response rate was 88 %. In the isthmocele group, the prevalence of postmenstrual spotting was 20.0 % compared to 8.3 % in women without isthmocele (OR 2.75 [95 % CI 1.39-5.44]; P = 0.004). Additionally, women with isthmocele reported more frequently postcoital bleeding (8.3 % vs. 2.4 %; OR 3.73 [95 % CI 1.18-11.83]; P = 0.026). The prevalence of postmenstrual spotting was even higher in the subgroup of large isthmoceles, (25.9 % vs. 9.5 %; (OR 3.34 [95 % CI 1.72-6.49]; P < 0.001).

Conclusion: The prevalence of postmenstrual spotting among isthmocele patients was 20.0 %. Additionally, post-menstrual spotting was associated with the presence of isthmocele inquired at 1 year after CS.

Keywords: Abnormal uterine bleeding; Cesarean scar defect; Cesarean section; Isthmocele; Postmenstrual spotting.

Introduction

Cesarean section (CS) is the most frequently performed obstetric procedure [1]. Millions of women undergo this operation annually. Recently, multiple studies have been published concerning cesarean scar defect, also known as isthmocele. It represents inadequate healing of myometrium at the site of uterine incision. Isthmocele is frequently identified by ultrasonography [2]. The reported prevalence of isthmocele has varied considerably, between 6.9–69 % depending on the study population and the method used for evaluation [2,3]. Patients are not always symptomatic, but an association between isthmocele and various gynecological symptoms like abnormal uterine bleeding (AUB) has been suggested [4–6]. In particular, postmenstrual spotting has been associated with isthmocele and it has been found to correlate with the size of the defect [3,5,6]. Other reported symptoms are chronic pelvic pain, dysmenorrhea and prolonged periods [3–5,7]. However, in most studies evaluating the isthmocele-associated symptoms, selection bias is likely to play a role, as these studies have mainly included symptomatic women. This may have resulted in a falsely accentuated prevalence of postmenstrual spotting. In fact, a retrospective study showed no correlation between isthmocele and AUB but AUB was related to CS itself when compared to women with a history of only vaginal delivery [8]. We found only two previous prospective studies investigating the isthmocele-related symptoms in randomly selected populations [5,6]. Vaate *et al*. reported a two-fold increase in the prevalence of postmenstrual spotting among women with isthmocele compared to women without isthmocele [5]. In the study by Van der Voet *et al*. the prevalence of postmenstrual spotting was 28.9 % among women with isthmocele compared to 6.9 % among women without the defect [6]. Symptomatic women with isthmocele arefrequently treated with invasive surgical techniques, although large prospective trials concerning the clinical outcome of isthmocele are lacking [9–11]. Hence, we found it justifiable to investigate the association between isthmocele and postmenstrual spotting in a prospective setting and in large, unselected population.

Materials and methods

This prospective observational cohort study was designed to assess the clinical outcome of isthmocele with respect to bleeding patterns. This study is a continuation of our previous studies, in which the prevalence and risk factors for isthmocele were investigated [12,13]. The study was carried out at tertiary care hospital, which is a tertiary referral center for high-risk pregnancies, with annual rates of approximately 5000 deliveries and 700 CSs. Women who had a CS performed in our hospital for one year were asked to participate within 3 days of CS or prior to an elective CS. Exclusion criterion were a known uterine anomaly, a lack of common language, a known hematologic disorder and an age under 18. All participants provided a written informed consent before enrollment. Six months after the CS, participants were evaluated by saline contrast sonohysterography (SHG) using Samsung WS80 Elite (Samsung Medison CO., Ltd, Gangwon-do, Republic of Korea). The uterus, uterine scar, and an isthmocele, if present, were examined in a standardized way as previously described in detail (Fig.1) [14]. Isthmocele was defined as an anechoic defect at least 2.0 mm deep at the site of the CS scar (Fig. 2) [15]. Isthmocele was defined as a large defect if the ratio between the thickness of residual myometrium (RMT) and the thickness of the myometrium adjacent to the defect (AMT) was <0.50 as previously described (Fig. 2) [6].

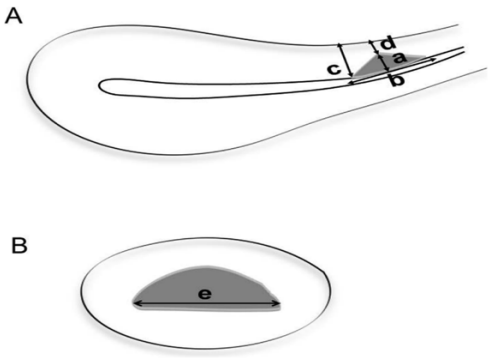

Figure 1: Schematic presentation of isthmocele measurements. Isthmocele dimensions in longitudinal (A) and transverse (B) planes. a. Depth of isthmocele, b. Width of isthmocele, c. Thickness of adjacent myometrium, d. Thickness of residual myometrium, e. Length of isthmocele.

All examinations were performed by the first author, who was blinded to any clinical information. Women were not informed about the ultrasound findings. At 12,13 and 14 months after the CS women received an electronic questionnaire by e-mail (three separate questionnaires) in which menstrual bleeding pattern and other gynecological symptoms were inquired. Additionally, age, current medication, breastfeeding, the use of contraception, smoking habits and body mass index (BMI) were asked as confounding factors. Details of menstrual bleeding pattern prior to the pregnancy were not collected because it would be susceptible to recall bias. Participants had been screened for sexually transmitted anogenital infections in early pregnancy at maternity health care as well as during the isthmocele assessment. The presence of preexisting medical conditions possibly affecting the bleeding patterns (e.g. hypothyreosis, celiac disease, inflammatory bowel disease) was assessed from hospital medical records.

Women who completed the questionnaire at least once, were included in the statistical analyses. Those who were pregnant at the time of questionnaire or had undergone miscarriage or ectopic pregnancy during the past two months were excluded, because it would not have been possible to reliably analyze the menstrual pattern.

The primary outcome measure was the prevalence of postmenstrual spotting which was defined as ≥2 days of brownish discharge after the end of the menstrual period. For statistical analysis it was combined with intermenstrual bleeding, according to a previous prospective study [5]. Postmenstrual spotting was chosen as the primary outcome measure due to two previous prospective studies indicating an association between isthmocele and postmenstrual spotting [5,6]. Secondary outcome measures included prolonged menstruation (>7 days), presence of dysmenorrhea/dyspareunia/post-coital bleeding, a need for painkillers because of dysmenorrhea, and absence from work or other activities because of bleeding/dysmenorrhea.

Statistical analyses

The DICE study was primarily designed to assess the relation of isthmocele to AUB. Specifically, here the primary outcome measure was the prevalence of postmenstrual spotting. A detection of a two-fold difference in the prevalence of postmenstrual spotting between the isthmocele and non-isthmocele groups was aimed at in the statistical analyses. The sample size calculations were based on the

following assumptions: the prevalence of postmenstrual spotting among women with isthmocele corresponds to 30 % and the prevalence of isthmocele was estimated to be approximately 50 % according to previous data [5]. To achieve an 80 % power with a two-sided alpha of 0.05, we needed to enroll 266 women in the study. Considering the dropout rate, which we anticipated to be up to 30 %, we aimed to recruit 400 women.

Data was analyzed using SPSS version 22.0 (IBM Corp, Armonk, NY). The independent student's t-test was used for the comparison of continuous variables in case of normal distribution. Otherwise, non-parametric tests were used. Associations between categorical variables and isthmocele were compared with Chi-square or Fisher's exact test when appropriate. Two-tailed p values of <0.05 were considered as statistically significant. A binary logistic regression model was used to evaluate the effect of isthmocele on various symptoms. Results are shown as ORs (odds ratio) with 95 % confidence intervals (CI).

Potential confounding factors were predefined, and included age, breastfeeding, smoking, BMI, oral contraceptive use (combined oral contraceptive pill or progestin-only pill), and use of levonorgestrel-releasing (LNG) or copper (Cu) IUD. These potential confounding factors were analyzed using logistic regression in multivariate analysis.

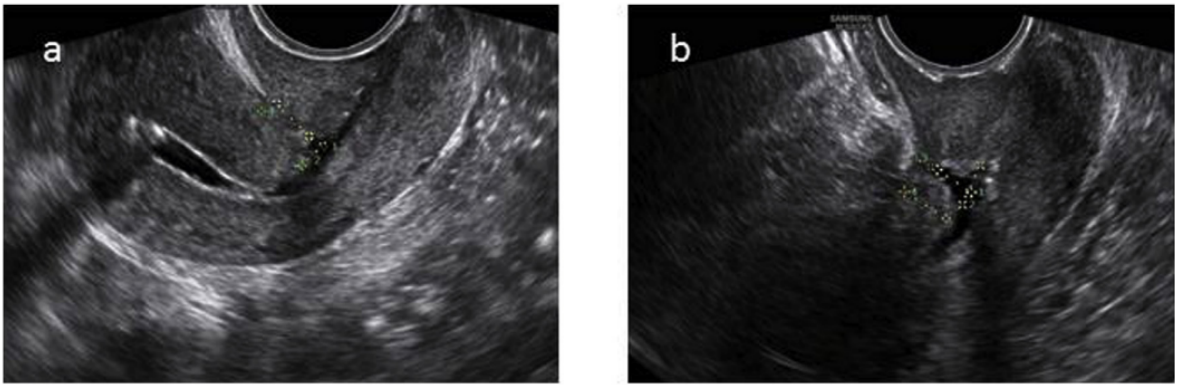

Figure 2: Sonohysterographic image showing a small (a) and a large isthmocele (b)

Results

For one year, four hundred and one women who delivered by CS gave an informed consent. Three hundred and seventy-one participants were successfully examined with SHG on average 6.7 months after the CS. The prevalence of isthmocele was 46.3 %. The prevalence and risk factors of isthmocele from the present data set have been reported previously [13]. In total, 88.4 % (328/371) of participants completed the symptom questionnaire at least once. Forty-three women were lost to follow-up (non-responder or incorrect e-mail address). Later,15 women were excluded (14 because of pregnancy and 1 because of miscarriage). The background variables among all participants and isthmocele/non-isthmocele groups are shown in Table 1.

There were no differences between the study participants who completed the questionnaire and those who were lost to follow-up regarding age, parity, previous CS, previous vaginal delivery, induction of labor, type of CS (elective versus emergency) or BMI (data not shown). At CS, a low transverse uterine incision and uterine closure with double layer continuous unlocked sutures were used for all participants. At the time of questionnaire, 29.7 % were breastfeeding and 19.2 % were in amenorrhea. Following methods of contraceptive use were reported: no hormonal contraception, 66.8 %; progestin-only pills, 9.9 %; combined oral contraceptive pills, 4.5 %; contraceptive implant, 1.0 %; LNG-IUD 15.0 % and Cu-IUD 2.9 %.

No other uterine pathologies (such as polyps or fibroids) were found at SHG. The prevalence of postmenstrual spotting in the whole study cohort was 13.7 %. According to hospital medical records, there were no differences in pre-existing medical conditions possibly affecting the bleeding patterns between women who suffered from AUB and those who did not (data not shown). In the isthmocele group, 20.0 % of women reported postmenstrual spotting, compared to 8.3 % without an isthmocele (OR 2.75 [95 % CI 1.39–5.44]; P = 0.004; Table 2). Moreover, the prevalence of postcoital bleeding was associated with isthmocele (8.3 % vs. 2.4 %; OR 3.73 [95 % CI 1.18–11.83]; P = 0.026; Table 2). In a subgroup analysis excluding the women with amenorrhea (n = 252), the association between postmenstrual spotting and isthmocele remained statistically significant (21.9 % vs. 10.1 %; P = 0.012). Using logistic regression analysis none of the predefined confounding factors or baseline characteristics were related to postmenstrual spotting (method of contraception, breastfeeding, smoking, age, BMI; data not shown).

There was no difference between the isthmocele and non-isthmocele groups concerning the prevalence of prolonged periods, dysmenorrhea, dyspareunia, use of painkillers and absence from work or activities (Table 2). All in all, 80.2 % of study participants were totally free from AUB and 74.5 % of women with isthmocele did not suffer from AUB at all. In the subgroup analyses of large defects, women with large isthmocele reported even more often postmenstrual spotting compared to women with small isthmocele or no isthmocele at all (OR 3.34 [95 % CI 1.72–6.49]; P<0.001; Table 3). Nearly half of the women with postmenstrual spotting (48.8 %) had a large isthmocele (data not shown).

Table 1: Background characteristics at the time of electronic questionnaire

Parameter	All	(n = 313)	Isthmocele (n = 145)		No isthmocele (n = 168)		p-value
Age, years; mean (SD)	32.7	(5.2)	33.4	(4.7)	32.0	(5.5)	0.018
Parity; median (range)	1	(1–7)	2	(1–6)	1	(1–7)	<0.001
Number of previous CS; median(range)	0	(0–3)	0	(0–3)	0	(0–2)	<0.001
Body mass index, kg/m^2; mean (SD)	26.6	(6.0)	27.9	(6.42)	25.5	(5.3)	0.001
Smoking; n (%)	19	(6.1)	8	(5.5)	11	(6.5)	0.703
Contraception							0.002
No hormonal contraception n (%)	209	(66.8)	85	(58.6)	124	(73.8)	
Oral contraceptive pills n (%)	14	(4.5)	10	(6.9)	4	(2.4)	
Progestin-only pills n (%)	31	(9.9)	13	(9.0)	18	(10.7)	
Hormonal IUD n (%)	47	(15.0)	32	(22.1)	15	(8.9)	
Copper IUD n (%)	9	(2.9)	5	(3.4)	4	(2.4)	
Contraceptive implant n (%)	3	(1.0)	0	(0.0)	3	(1.8)	
Women in amenorrhoea n (%)	60	(19.2)	31	(21.4)	29	(17.4)	0.370
Breastfeeding n (%)	93	(29.7)	45	(31.0)	48	(28.6)	0.634

CS = caesarean section, IUD = intrauterine devise.

Table 2: Uterine bleeding pattern and gynecological symptoms at 12 months after cesarean section among 145 women with isthmocele and 168 women without isthmocele.

	Isthmocele (n = 145)		No isthmocele (n = 168)		p-value	OR	95 % CI
Postmenstrual spotting; n (%)[a]	29	(20.0)	14	(8.3)	0.004	2.75	1.39-5.44
Prolonged periods (> 7 days); n (%)	10	(7.2)	12	(7.2)	0.998	1.00	0.42-2.39
Postcoital bleeding; n (%)	12	(8.3)	4	(2.4)	0.026	3.73	1.18-11.83
Dysmenorrhea; n (%)	80	(55.2)	93	(55.4)	0.974	0.99	0.64-1.55
Dyspareunia; n (%)	24	(16.6)	18	(10.7)	0.133	1.65	0.86-3.19
Absence from activities; n (%)	2	(1.4)	7	(4.2)	0.172	0.33	0.07-1.62
Need for painkiller; n (%)	49	(34.0)	54	(32.1)	0.724	1.09	0.68-1.75
Absence from work; n (%)	0	(0.0)	1	(0.6)	0.996	0.99	0.98-1.01

[a] Primary outcome measure. Others are secondary outcome measures.

Table 3: Uterine bleeding pattern and gynecological symptoms at 12 months after cesarean section in the groups of large isthmocele (n = 81) and small/no isthmocele (n = 232)

	Large isthmocele (n = 81)		Small/no isthmocele (n = 232)		p-value	OR	95 % CI
Postmenstrual spotting; n(%)	21	25.9	22	9.5	<0.001	3.34	1.72-6.49
Prolonged periods (>7 days); n(%)	5	6.5	17	7.4	0.785	0.87	0.31-2.43
Postcoital bleeding; n(%)	7	8.8	9	3.9	0.097	2.38	0.86-6.61
Dysmenorrhea; n(%)	43	53.1	130	56.0	0.646	0.89	0.53-1.48
Dyspareunia; n(%)	11	13.6	31	13.4	0.960	1.02	0.49-2.14
Absence from activities; n(%)	2	2.6	7	3.0	0.833	0.84	0.17-4.14
Need for painkiller; n(%)	23	28.8	80	34.5	0.348	0.77	0.44-1.34
Absence from work; n(%)	0	0.0	1	0.4	0.997	1.00	0.99-1.00

Comment

In this prospective observational cohort study, we showed that postmenstrual spotting and post-coital bleeding were associated with isthmoceles, surveyed at 1 year after CS. The prevalence of postmenstrual bleeding among isthmocele patients was slightly lower than expected (20.0 %).

To the best of our knowledge, this study represents the largest study performed to date in which isthmocele was evaluated prospectively with contrast-enhanced SHG in relation to symptoms. We

recruited participants within 3 days of CS aiming at avoiding possible selection bias. We decided to perform SHG six months after the CS because it has been suggested that the wound healing process will take at least six months [16]. Earlier assessment would have probably led to over diagnosis, and delayed assessment to higher dropout rate due to subsequent pregnancies. Here, the prevalence rate of isthmocele was 46.3 %, which is in line with a previous prospective study using SHG [5]. Women were not informed about the possible presence of isthmocele in order to prevent possible bias in later reports on the bleeding pattern. Additionally, other reasons for AUB were taken into account.

The use of electronic questionnaire in reporting the symptoms can also be considered as strength of the present study. Our aim was to minimize the risk for recall bias. We consider that the collected data was reliable because women were able to answer the questionnaire right after the menstruation instead of later recalling the bleeding days and symptoms. The inquiry time point at one year after CS was chosen in order to minimize the rate of lactation amenorrhea and subsequent pregnancies. The response rate was as high as 88.4 %, which is prone to increase the reliability of the outcome assessment.

A possible limitation of our study is a lack of any validated tool to assess postmenstrual spotting. The validated patient-reported outcome measures assessing AUB have been developed only for heavy menstrual bleeding. These questionnaires measure the volume of blood loss and are not suitable for the purpose of the current study [17,18].

Another limitation is the fact that not all women who delivered by CS during the study period participated in the study. There were 742 CSs at our hospital during the study period out of which 401 women gave an informed consent. However, women participating in the study did not differ from non-participating women with respect to baseline characteristics such as elective or emergency cesarean section rate, age and parity.

The main outcome measure was the relation of postmenstrual spotting to the presence of isthmocele. Postmenstrual spotting inquired at 1 year after CS was associated with the presence of isthmocele detected with SHG at 6 months after CS. One out of five women with isthmocele reported postmenstrual spotting, compared with one out of twelve women without isthmocele. Additionally, postmenstrual spotting was reported even more often by women who presented with a large isthmocele. On the whole, the prevalence of postmenstrual spotting in our study cohort was slightly lower compared to previous prospective trials. Van der Voet *et al*. reported a prevalence of 28.9 % in the isthmocele group compared to 6.9 % in women without isthmocele [6] in a study population of 137 women. Also, Bij de Vaate *et al*. reported that one third of women with isthmocele suffer from postmenstrual spotting compared to one in seven in women without isthmocele [5]. However, participants were recruited several months after the CS, which may have resulted in the selection of symptomatic patients. We suggest that selection bias may have less pronounced effect on the present study, which may explain the lower rate of postmenstrual spotting reported here.

According to our results, the isthmocele-related postmenstrual spotting is reported by 20.0 % of women with isthmocele and by25.9 % of women with large isthmocele, at least when inquired at one year after the CS. The association remained significant when women with amenorrhea were excluded. This is in line with the previous prospective studies [5,6]. The relationship between the size of isthmocele and postmenstrual spotting is in line with the hypothesis that spotting is induced by the accumulated blood inside the isthmocele pouch [19]. The positive association of isthmocele defects with menstrual bleeding disorders allows us to consider invasive surgical interventions when encountering symptomatic patients. However, only one randomized controlled trial (RCT) addressing the impact of hysteroscopic resection of isthmocele on postmenstrual bleeding is presently available [20]. More prospective studies and RCTs with long-term follow-up should be carried out before establishing guidelines on the clinical management of symptomatic isthmocele.

A longer follow-up of the participants would possibly have given us more information on the magnitude of the clinical disorders. Available studies, such as ours presented here, have followed the patients up to one year after the CS, and more data on long-term effects of isthmocele is warranted.

Conclusion

The presence of isthmocele was significantly associated with postmenstrual and postcoital bleeding.

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