Indication Criteria of Hysteroscopic Surgery for Secondary Infertility Due to Symptomatic Cesarean Scar Defect Based on Clinical Outcomes: A Retrospective Cohort Study

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Precis: Hysteroscopic surgery is indicated for patients with infertility due to symptomatic cesarean scar defects and residual myometrial thickness of ≥2.2 mm, particularly for patients aged <38 years.

Abstract

Study objective: Hysteroscopic surgery criteria for patients with cesarean scar defect (CSD) are unclear. Therefore, this study aimed to explore the indication of hysteroscopic surgery for secondary infertility due to CSD.

Design: Retrospective cohort study

Setting: Single university hospital

Patients: Seventy patients with secondary infertility due to symptomatic CSD who underwent hysteroscopic surgery under laparoscopy between July 2014 and February 2022 were included.

Interventions: Clinical data, including basic patient information, preoperative residual myometrial thickness (RMT), and postoperative pregnancy status, were collected from medical records. Patients were divided into postoperative pregnancy and non-pregnancy groups. A receiver operating characteristic (ROC) curve was drawn, and the optimal cutoff value was calculated based on the area under the curve (AUC) to predict pregnancy after hysteroscopic surgery.

Measurements and main results: No complications were observed in any cases. Among the 70 patients, 49 (70%) patients became pregnant after hysteroscopic surgery. There was no significant difference in patient characteristics between the pregnancy and non-pregnancy groups. In the ROC curve analysis for patients aged <38 years, the value of AUC was 0.77 (sensitivity: 0.83 and specificity: 0.78) when optimal cutoff of RMT was 2.2 mm. There was a significant difference in preoperative RMT between the pregnancy and non-pregnancy groups (3.3 mm and 1.7 mm, respectively) in patients aged <38 years.

Conclusion: For RMT ≥2.2 mm, hysteroscopic surgery was reasonable for secondary infertility due to symptomatic CSD, particularly in patients aged <38 years.

Keywords: cesarean scar syndrome; cesarean section; hysteroscopic surgery

Introduction

The cesarean section procedure can cause cesarean scar defects (CSD), which can result in several symptoms including abnormal uterine bleeding (AUB), dysmenorrhea, chronic pelvic pain, and secondary infertility [1-3]. The presence of these symptoms is known as cesarean scar syndrome (CSS) [4]. There is increasing evidence of the safety and effectiveness of hysteroscopic surgery for secondary infertility in women with CSS [2, 5]. However, the hysteroscopic surgery criteria in these patients are unclear.

The indication for hysteroscopic surgery is residual myometrial thickness (RMT) of ≥3 or ≥2.5 mm according to Donnez [2] or Tanimura et al. [6], respectively. However, both criteria seem to rely on the concept of uterine perforation prevention due to thinned myometrium rather than clinical data. Therefore, establishing clinical outcome-based indications for hysteroscopic surgery is necessary. For patients who desire pregnancy, the clinical outcome of interest is successful conception. There is a strong association between aging and fertility as aging reduces ovarian reserve and fertility declines with age, particularly in women aged >35 years [7]. Therefore, the factor of age should be considered for pregnancy prognosis prediction.

The receiver operating characteristic (ROC) curve is widely used to determine the efficacy of clinical diagnosis and prognosis, and the area under the ROC curve (AUC) is useful for interpretation of prognosis [8, 9]. Therefore, we explored clinical outcome-based hysteroscopic surgery criteria for secondary infertility due to symptomatic CSD based on AUC values.

Materials and Methods

Patients

This retrospective study was approved by the Ethics Committee of Shiga University of Medical Science (approved number R2022-097) and performed at Shiga University of Medical Science. Although written informed consent was obtained from all patients prior to surgery, it was waived for this study due to its retrospective nature. Alternatively, an opt-out methodology was used. This method provided patients the opportunity to decline participation in this study. All data were fully anonymized after collection. We enrolled patients with secondary infertility due to symptomatic CSD between July 2014 and February 2022. The inclusion criteria were the presence of both CSD and AUB or liquid pooling in CSD detected by transvaginal ultrasonography. Inspection for AUB was performed in accordance with the FIGO classification system

(PALM-COEIN) [10]. Patients with endometrial polyps, cervical polyps, abnormal cervical cytology, endometrial hyperplasia, uterine fibroids, adenomyosis, and coagulopathy were excluded. Furthermore, the enrolled participants had all tried to conceive for at least 12 months after surgery. Patients who no longer desired pregnancy <1 year after surgery were excluded. All patients were divided into two groups: postoperative pregnancy and non-pregnancy.

Surgical procedure

The procedure for hysteroscopic surgery has been previously reported [11]. In our hospital, there is no minimum RMT value for performing hysteroscopic surgery. Briefly, all hysteroscopic surgeries were performed using laparoscopy because it was necessary to monitor perforation in CSD and treat endometriosis whenever it was intraoperatively recognized in the pelvis. First, only the inferior edge of the CSD was resected to enable visualization of the diverticulum. Second, the entire isthmus, including CSD, was cauterized using a ball electrode. Patients were then allowed to conceive 2 months after surgery. Elective cesarean delivery was recommended for all postoperative deliveries.

Data collection

Information on participants such as age, body mass index (BMI), gravidity, parity, number of cesarean sections, period of infertility, preoperative history of artificial reproductive technology (ART) treatment, and RMT was collected. RMT was measured using magnetic resonance imaging on a 1.5-T instrument (SIGNA HDxt; GE Healthcare Waukesha, WI, USA) with an 8-channel phased array coil, which was performed preoperatively. In addition, we collected information regarding perinatal prognosis and how the pregnancy was achieved. For patients who did not continue to visit our hospital, we confirmed their current situation via a medical information provision form provided by their referral hospital or by telephone.

Statistical analysis

Statistical analyses were performed using GraphPad Prism version 7 (GraphPad Software, Inc., San Diego, CA, USA). The D'Agostino–Pearson test was used for statistical analysis. Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median (interquartile range). The postoperative pregnancy and non-pregnancy groups were compared using an unpaired two-tailed t-test or the Mann–Whitney U test for parametric and nonparametric data, respectively. Categorical data were analyzed using Fisher's exact test. Statistical significance was set at $p < .05$. The ROC curve was graphically displayed with sensitivity estimates plotted against 1 − specificity. AUC was calculated as a prognostic marker. An AUC >0.75 was defined as a good indicator, as previously reported [12-15]. Cutoff values were calculated using the Youden index method.

Results

No patients meeting the inclusion criteria were lost to follow-up. Of the eligible patients, the mean age was 36.2 ± 4.3 years, median BMI was 21 (interquartile range: 19–23) kg/m^2, median number of gravidities was 2 (interquartile range: 1–2), median number of cesarean sections was 1 (interquartile range: 1–1), and median period of infertility was 18 months (interquartile range: 8–36 months). Regarding preoperative history of ART treatment, 40 patients (57.1%) underwent ART before surgery. All surgeries were performed without any complications such as uterine perforation. Of the 70 patients, 49 (70%) patients became pregnant after surgery. There was no significant difference between the pregnancy and non-pregnancy groups in terms of basic patient characteristics including preoperative and postoperative RMT (Table 1). Postoperatively pregnant and non-pregnant cases were distinguished, and scatterplots related to age and RMT were generated (Figure 1). The ROC curve was drawn for each age group, and the AUC was calculated (Figure 2). In patients aged <36 years, the AUC was 0.95 (sensitivity: 0.75 and specificity: 1.00) when the optimal RMT cutoff was 2.3 mm (Figure 2A). In patients aged <37 years, the AUC was 0.86 (sensitivity: 0.81 and specificity: 0.88) when the optimal RMT cutoff was 2.2 mm (Figure 2B). In patients aged <38 years, the AUC was 0.77 (sensitivity: 0.83 and specificity: 0.78) when the optimal RMT cutoff was 2.2 mm (Figure 2C). In patients aged <39 years, the AUC was 0.71 (sensitivity: 0.83 and specificity: 0.73) when the optimal RMT cutoff was 2.1 mm (Figure 2D). In patients aged <40 years, the AUC was 0.36 (sensitivity: 0.20 and specificity: 0.36) when the optimal RMT cutoff was 2.2 mm (Figure 2E). The AUC was 0.43 in all patients (sensitivity: 0.92 and specificity: 0.28) when the optimal RMT cutoff was 5.5 mm (Figure 2F). Although there was no significant difference in preoperative RMT between the pregnancy and non-pregnancy groups in any patients (3.6 ± 1.5 mm and 3.7 ± 2.8 mm, respectively) (Figure 3A), there was a significant difference in preoperative RMT between the pregnancy and non-pregnancy groups (3.3 [2.3–4.4] mm and 1.7 [0.9–1.9] mm, respectively) in patients aged <38 years (Figure 3B).

Forty-eight patients received ART and 22 received non-ART as postoperative treatment (Figure 4). Subsequently, 34 (70.9%) patients became pregnant with ART and

15 (68.2%) became pregnant with non-ART. No significant between-group difference was observed. Regarding obstetrical outcomes, 42 patients had live births by elective cesarean section and 7 had spontaneous abortion. The median birth weight among live birth cases was 2,877 g. Of 42 patients, cesarean section scar dehiscence was observed in two cases at the time of elective cesarean section; however, there was no case of uterine rupture and cesarean scar pregnancy.

Discussion

This study revealed that preoperative RMT correlated with pregnancy after hysteroscopic surgery. However, it was also found that aging affected postoperative pregnancy. Therefore, we were able to show a novel indication that hysteroscopic surgery can be performed if the preoperative RMT is ≥2.2 mm, especially under the condition of aged <38 years. This study is the first report that preoperative RMT is a predictor of pregnancy outcome after hysteroscopic surgery.

We previously demonstrated that greater RMT predicted pregnancy prognosis [11]. However, it is difficult to predict whether RMT is greater before surgery. Therefore, in this study, we attempted to determine the indication for hysteroscopic surgery based on preoperative information only. However, pregnancy is associated with various factors such as ovarian reserve. When we first created a scatter plot of age and preoperative RMT (Figure 1), we realized that preoperative RMT could predict pregnancy in young patients. However, it is not clear at what age they should be sorted. Hence, an ROC curve was drawn for each age group. However, it is debatable whether AUC is a good predictor. Fischer et al. [14] and Akobeng [13] described an AUC of 0.7–0.9 as an indicator of moderate accuracy. Considering all aforementioned factors, we concluded that an RMT of 2.2 mm with an AUC of ≥0.75 and age of <38 years could indicate hysteroscopic surgery. However, the appropriate RMT cutoff value depends on patient age. If an AUC of >0.9 represents a good indicator, this study indicates that hysteroscopic surgery is recommended for patients with an RMT of >2.3 mm, particularly in patients aged <36 years. This phenomenon is considered a limitation of this study because a good indicator cannot be established based on a specific AUC value.

Many studies have demonstrated the effectiveness of hysteroscopic surgery for secondary infertility due to symptomatic CSD [6, 16-20], and the effectiveness of laparoscopic repair for women with CSS [6, 20, 22-27]. Because hysteroscopic surgery is generally less invasive than laparoscopic surgery, hysteroscopic surgery is recommended if the case is operable. Perforation of CSD by hysteroscopic surgery has been reported for a recent case of severe CSD [28], defined as RMT ≤3.0 mm. Our surgical procedure and this novel indication may be appropriate from a risk management perspective.

A strength of this study is that it is the first report regarding an indication for hysteroscopic surgery using preoperative RMT. In this study, we found that an RMT of <2.2 mm was associated with low pregnancy expectations after hysteroscopic surgery in young women. Although age affects the establishment of pregnancy, based on the data of non-elderly patients, 2.2 mm can be considered an indication for hysteroscopic surgery. Regarding the limitations of this study, because CSD alone could not prove the cause of infertility, especially in elderly infertile patients, it was difficult to determine the indication for surgery based on preoperative RMT data alone. Therefore, for elderly infertility cases, it is necessary to consider treatment individually, such as performing ART treatment with hysteroscopic surgery due to decreased ovarian reserve. In other words, preoperative RMT is not a good predictor of pregnancy prognosis after hysteroscopic surgery in elderly patients. Furthermore, we did not exclude hysteroscopic surgery in elderly patients.

Although the mechanism leading to pregnancy by hysteroscopic surgery has not been completely clarified, clinical data indicate the novel indication of hysteroscopic surgery for secondary infertility due to symptomatic CSD. The study results suggest that hysteroscopic surgery is reasonable when the RMT is ≥2.2 mm, particularly in patients aged <38 years. We believe that this novel indicator will be helpful for surgical procedure selection.

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Figure Legends

Figure 1.

A scatter diagram with pregnancy as ○, non-pregnancy as ●, age on the horizontal axis, and residual myometrial thickness on the vertical axis.

Figure 2. A receiver operating characteristic (ROC) curve of the pregnancy rate after hysteroscopic surgery in women with cesarean scar syndrome in each age group.

A. The area under the ROC curve (AUC) was 0.95 in patients aged <36 years (sensitivity: 0.75, specificity: 1.00, optimal RMT cutoff: 2.3 mm). **B**. The AUC was 0.86 in patients aged <37 years (sensitivity: 0.81, specificity: 0.88, optimal RMT cutoff: 2.2 mm). **C**. The AUC was 0.77 in patients aged <38 years (sensitivity: 0.83, specificity: 0.78, optimal RMT cutoff: 2.2 mm). **D**. The AUC was 0.71 in patients aged <39 years (sensitivity: 0.83, specificity: 0.73, optimal RMT cutoff: 2.1 mm) **E.** The AUC was 0.36 in patients aged <40 years (sensitivity: 0.20, specificity: 0.36, optimal RMT cutoff: 2.2 mm). **F.** The AUC was 0.43 in all patients (sensitivity: 0.92, specificity: 0.28, optimal RMT cutoff: 5.5 mm).

Figure 3.

Residual myometrial thickness (RMT) before surgery in the postoperatively pregnant and non-pregnant patients. **A**. There was no significant difference in RMT between the pregnancy and non-pregnancy groups of all ages (n=70). An unpaired two-tailed t-test was used for analysis. The bar represents mean and standard deviation. **B.** There was a significant difference between postoperatively pregnant and non-pregnant patients in the group aged <38 years (n=39, $p < 0.0001$). The Mann–Whitney test was used for analysis. Bar represents median and interquartile range.

Figure 4.

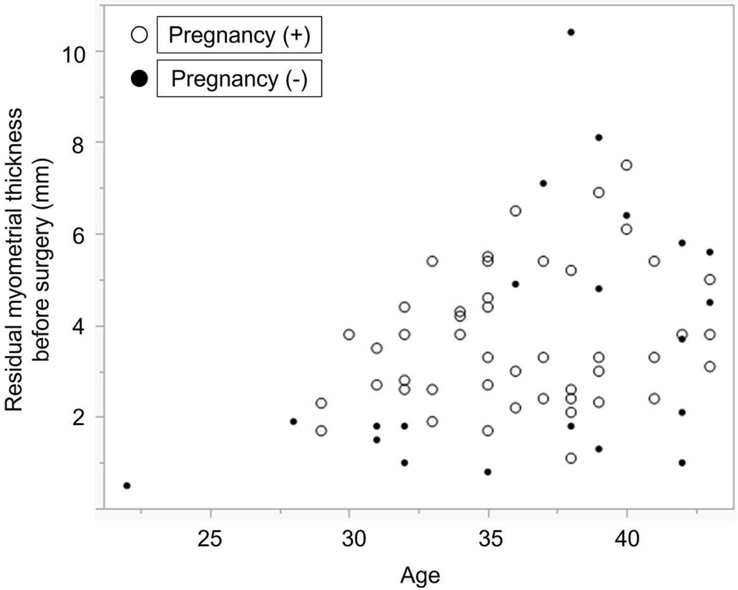
The association of pre- and postoperative ART and postoperative pregnancy.

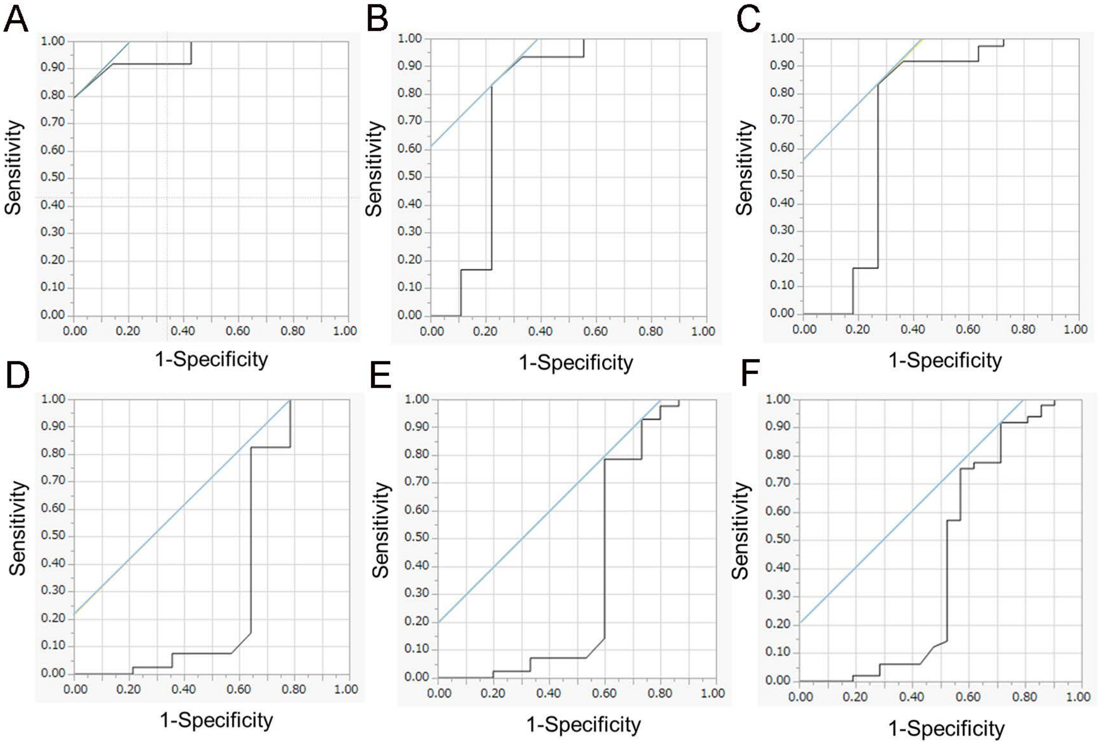
Table 1 Background details of the participants

Characteristics	Pregnancy	Non-pregnancy	p-value
Number	49	21	
Age, years	36.1 ± 3.7	36.7 ± 5.6	n.s.
BMI, kg/m^2	21 (20–25)	20 (19–22)	n.s.
Gravidity	2 (1–2)	2 (1–2)	n.s.
Parity	2 (1–2)	2 (1–2)	n.s.
C/S number	1 (1–1)	1 (1–2)	n.s.
Period of infertility, months	18 (7–36)	20 (8–37)	n.s.
Endometriosis (%)	33 (67%)	16 (76%)	
r-ASRM classification 1–2	29	13	n.s.
3–4	4	3	
Preoperative history of ART Treatment	29 (59.2%)	11 (52.4%)	n.s.
Preoperative RMT, mm	3.6 ± 1.5	3.7 ± 2.8	n.s.
Postoperative RMT, mm	5.3 ± 1.8	4.3 ± 3.0	n.s.

ART, assisted reproductive technology; BMI, body mass index; C/S, cesarean section; n.s., not significant; r-ASRM, revised American Society for Reproductive Medicine; RMT, residual myometrial thickness.

Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median (interquartile range).


Pregnancy (+)
Pregnancy (-)
Residual myometrial thickness before surgery (mm)
10
8
6
4
2
25
30
35
40
Age



A
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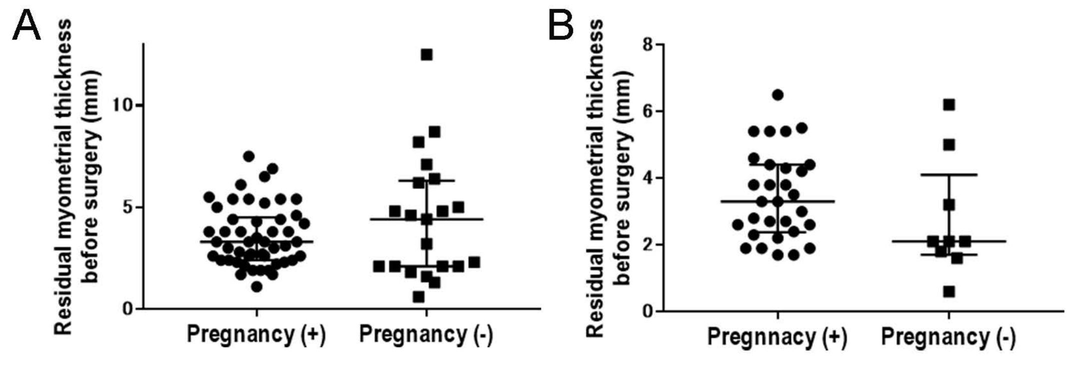

A
Residual myometrial thickness before surgery (mm)
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10
Pregnancy (+)
Pregnancy (-)
B
Residual myometrial thickness before surgery (mm)
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4
6
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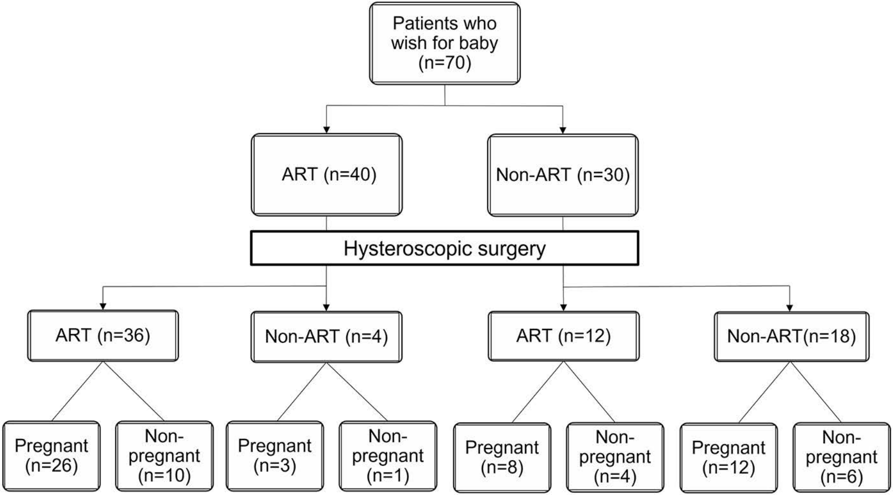
Pregnnacy (+)
Pregnancy (-)


Patients who wish for baby (n=70)
ART (n=40)
Non-ART (n=30)
Hysteroscopic surgery
ART (n=36)
Non-ART (n=4)
ART (n=12)
Non-ART(n=18)
Pregnant (n=26)
Non-pregnant (n=10)
Pregnant (n=3)
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