

Analysis on clinical association of uterine scar diverticulum with subsequent infertility in patients underwent cesarean section

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Abstract

To evaluate the relationship between uterine cesarean scar diverticulum (CSD) and subsequent infertility in patients who underwent cesarean section, and determine the effects of pelvic fluid-releasing inflammations on infertility.

A retrospective analysis was designed among patients with CSD who were admitted to our hospital from January 1, 2018 to December 31, 2019. A total of 60 patients with CSD and uterine fibroids or benign ovarian tumors who underwent cesarean section were included, and divided into the CSD group and control group. Baseline characteristics of all patients were collected, and the pelvic adhesion scores and the percents of tubal patency were evaluated. Furthermore, the postoperative clinical outcomes were followed up. The levels of inflammatory factors in pelvic fluid were tested using Elisa kits.

Preoperative data indicated that the size of the uterine scar diverticulum was (1.68 ± 0.52) cm, the pelvic adhesion scores were higher in CSD group than control group (4.67 ± 0.90 vs 0.47 ± 0.90, $P < .05$), and 21 of 30 patients with unobstructed fallopian tubes. The levels of tumor necrosis factor- α , interleukin-1 β , and interleukin-6 in patients with CSD were obviously higher than control group ($P < .05$). After the follow-up, the data displayed that no CSD was found in all patients, the time of menstrual period in patients with CSD was shortened to 7.80 ± 1.27 days, and the myometrial thickness at uterine scar was significantly increased ($P < .05$). Additionally, the pregnancy rate was increased, and 12 of 30 patients were repregnant. Correlation analysis showed that the levels of inflammatory factors (tumor necrosis factor- α , interleukin-1 β , interleukin-6), the size of uterine scar diverticulum, and the myometrial thickness at uterine scar were significantly correlated with subsequent infertility ($r = 0.307, 0.083, 0.147, 0.405, 0.291, P < .05$).

Uterine scar diverticulum repair could improve menstrual prolongation, increased the thickness of myometrium and repregnant rate. Subsequent infertility was positively correlated with uterine scar diverticulum and the levels of inflammatory factors.

Abbreviations: CSD = cesarean scar diverticulum, IL-1 β = interleukin-1 β , IL-6 = interleukin-6, MRI = magnetic resonance imaging, TNF- α = tumor necrosis factor α .

Keywords: caesarean section, cesarean scar diverticulum, inflammation, menstruation, myometrial thickness, subsequent infertility

1. Introduction

Uterine scar diverticulum, also known as cesarean scar diverticulum (CSD), is one of the 3 major complications of cesarean section, and mainly due to the incision healing defect in

the lower section of uterine after cesarean section, leading to a depression that connected with the uterine cavity appeared at the uterine incision.^[1] According to epidemiological statistics, the incidence of CSD was approximately 89% among women with a

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BB and SG contributed equally to this work.

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All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The present study protocol was approved by the Ethics Committee of Tongde Hospital of Zhejiang Province.

Informed consent was obtained from all individual participants included in the study.

The authors have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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history of caesarean section when assessed by hysterosalpingogram, and about 61% to 64.5% when assessed by transvaginal ultrasonography.^[2] Furthermore, the incidence of CSD was 61% after undergoing 1 cesarean section, the incidence was 81% in 2 cases, and the incidence was 100% in 3 times.^[3] The main clinical manifestations were abnormal uterine bleeding, dysmenorrhea, menstrual disorders, hypogastric pain, and secondary infertility, which seriously affect women's quality of life.^[4]

At present, the treatment methods for CSD included hormonal and surgical, and the commonly used hormone drugs were mainly short-acting oral contraceptives. The surgical methods included transabdominal CSD repair, hysteroscopic CSD electrocoagulation repair, hysteroscopic combined with laparoscopic CSD repair, and transvaginal CSD repair.^[5] The previous study found that laparoscopic combined with hysteroscopic repair had better efficiency in improving the abnormal uterine bleeding, regulating the normal menstruation duration, and increasing the pregnancy rate.^[6] Other research demonstrated that hysteroscopy was more effective in the treatment of cesarean section scar diverticulum, while resectoscopic treatment was highly effective in women with abnormal uterine bleeding.^[7] Therefore, different surgical treatment methods have their own advantages and disadvantages, which should be selected according to the type of disease.

Secondary infertility refers to those patients who have the history of pregnancy and are not pregnant for at least 12 months without contraceptive. Clinically, due to the complexity and variety of the causes, the incidence of infertility in different countries and regions varies greatly, which has caused major problems for couples of childbearing age. Currently, with the introduction of China's "second child" policy, many women with scar uterus have reproductive requirements. Patients with CSD had long periods of menstrual, which not only prevented sperm from passing through the cervical canal, but also caused retrograde infection of uterine cavity by the vaginal bacteria, then destroyed the internal environment of the uterine cavity, and the effusions in the area of CSD interfered with the implantation of the embryo and even caused ectopic pregnancy.^[8]

A systematic review and meta-analysis indicated that cesarean scar defect might be related to secondary infertility, and CSD repaired by hysteroscopic and laparoscopic could improve uterine bleeding and increase the pregnancy rate.^[9] Therefore, more studies are still needed to identify the association between CSD and infertility, dysmenorrhea, menstrual disorders. Before eliminating other causes of postmenstrual bleeding or infertility, treatment of uterine scar defects should be performed. This study aimed to evaluate the relationship between CSD and subsequent infertility in patients who underwent cesarean section, and determined the effects of pelvic fluid-releasing inflammatory factors on infertility.

2. Methods

2.1. Study subjects and ethics committee

A retrospective study was conducted involving 60 infertility patients with CSD and uterine fibroids or benign ovarian tumors who were admitted to Tongde Hospital of Zhejiang Province, Hangzhou, China, from January 1, 2018 to December 31, 2019. All patients were divided into the CSD group and control group. The CSD group included 30 patients and underwent the surgery of CSD repair. The present study protocol was approved by the

Ethics Committee of Tongde Hospital of Zhejiang Province. All patients signed informed consent.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows. All patients were 20 to 40 years old. For CSD group, patients were diagnosed as CSD according to the diagnostic criteria of CSD: patients with a history of cesarean section surgery and clinical manifestations such as prolonged menstrual period and infertility; transvaginal ultrasound examination shows that there is a cystic, wedge-shaped, or triangular liquid dark area in the uterine cavity at the cesarean section incision; preoperative vaginal mycoplasma, chlamydia, gonococcus, and bacterial cultures were negative; patients with the cesarean history, the symptoms of menstrual period extension and secondary infertility. For control group, patients were diagnosed as uterine fibroids or benign ovarian tumors by preoperative vaginal B-ultrasound. The exclusion criteria were: diagnosed as endometriosis, adenomyosis, and pelvic inflammatory disease; patients with degeneration of uterine fibroids, gynecological malignancies, hypoovarian function, intrauterine adhesions, and other history of major organ diseases; loss of follow-up and insufficient clinical data.

2.3. Clinical outcomes

We collected the baseline characteristics of all included patients including age, body weight, past medical history, surgical history, menstrual history, fertility history, and infertility time, etc. The pelvic adhesion scores were assessed using the adhesion-related scores sheet according to the adhesion classification system. The main contents include the pelvic compactness, the range of adhesion, uterine ractal fossa, ovarian adhesion, fallopian tube adhesion, and fallopian tube atresia, ranging from 0 to 3 scores, respectively (Table 1). In addition, we evaluated the tubal patency, and the criteria included unobstructed, partially obstructed and inaccessible. After the surgery of CSD repair, all patients were followed up with 2 years. The outcomes of follow-up included the change of menstrual time, the recovery degree of CSD, and sequent pregnancy rate.

2.4. Elisa assay

Pelvic fluid in all surgical patients were collected and centrifuged, and then collected the supernatant and stored at -80°C . The concentrations of tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) were measured using Elisa kits according to the manufacturer's instructions.

Table 1

The criteria of pelvic adhesion score.

Contents	Score			
	0	1	2	3
Compactness of pelvic		Loose	Moderate	Severe
Range of adhesion		2–6 cm	6–10 cm	>10 cm
Uterine ractal fossa	Open	Partially closed	Completely closed	
Ovarian adhesion	No	One side	Both sides	
Fallopian tube adhesion	No	One side	Both sides	
Fallopian tube atresia	No	One side	Both sides	

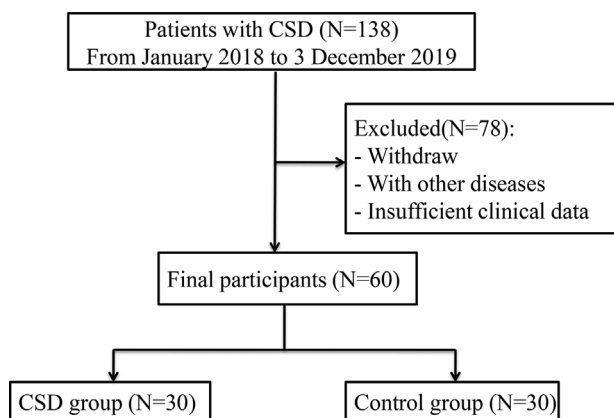


Figure 1. The flow diagram in this study.

2.5. Statistical analysis

All data were presented as mean ± standard deviation. Statistical analysis was conducted using the statistical software SPSS 19.0. For the variance data, comparisons between groups were carried out using Student test. The counting data were expressed as percentages, and significant differences between groups were measured by chi-square test. Correlation analysis between categorical variables was performed using spearman’s rank correlation coefficient. *P* < .05 was considered statistically significant in all results.

3. Results

3.1. Patient characteristics

A total of 138 patients were included in this study, of whom 78 patients were excluded due to withdraw, other disease, or insufficient data after follow-up (Fig. 1). Finally, 60 patients were included in the present study, of whom 30 patients were diagnosed as CSD and underwent the hysteroscopic or laparoscopic surgery to repair CSD (CSD group, N=30), and the other 30 patients received surgical or nonsurgical treatment (control group, N=30). The baseline data of patients were present in Table 2. In CSD group, the mean age of patients was 33.23 ± 4.25 years old, the body weight was 53.30 ± 7.55 kg, the number of cesarean sections was 1.47 ± 0.57 times, the number of abortions was 1.77 ± 1.28 times, the menstrual period was 16.07

Table 2
Baseline characteristics of the patients included in this study.

Characteristics	CSD group n=30	Control group n=30	P value
Age (yrs)	33.23 ± 4.25	32.33 ± 5.54	.851
Height (cm)	159.20 ± 4.82	160.93 ± 5.60	.283
Body weight (kg)	53.30 ± 7.55	56.87 ± 10.29	.457
Number of flat births	0.00 ± 0.00	0.70 ± 0.75	.039
Number of cesarean sections	1.47 ± 0.57	0.10 ± 0.31	.026
Number of abortions	1.77 ± 1.28	0.97 ± 0.96	.035
Menstrual period (d)	16.07 ± 1.95	5.60 ± 1.28	.007
Menstrual cycle (d)	30.43 ± 3.61	30.20 ± 5.45	.158
Infertility time (yrs)	2.73 ± 1.10	-	-

CSD=cesarean scar diverticulum.

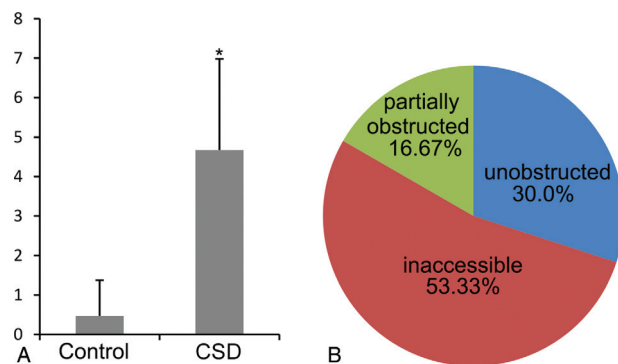


Figure 2. Assessment of the pelvic adhesion scores and the tubal patency. (A) The pelvic adhesion scores; (B) the tubal patency. Data are expressed as means ± SD. **P* < .05, compared with control group.

± 1.95 days, the menstrual cycle was 30.43 ± 3.61 days, and the infertility time before uterine scar diverticulum repair was 2.73 ± 1.10 years.

In control group, the mean age of patients was 32.33 ± 5.54 years old, the body weight was 56.87 ± 10.29 kg, the number of cesarean sections was 0.10 ± 0.31 times, the number of abortions was 0.97 ± 0.96 times, the menstrual period was 5.60 ± 1.28 days, and the menstrual cycle was 30.20 ± 5.45 days. There were no significant statistic differences in age, body weight, and the menstrual cycle between surgery group and control group (*P* > .05). However, obviously differences in the number of cesarean sections and abortions, the menstrual period, and the infertility time were observed (*P* < .05).

3.2. Assessment of the pelvic adhesion scores and the tubal patency

In the process of hysteroscopic surgery, we assessed the pelvic adhesion scores according to the criteria of pelvic adhesion. The results showed that the scores of CSD group were 4.67 ± 0.90, and the control group was 0.47 ± 0.90. There was significant difference between the 2 groups (*P* < .05) (Fig. 2A). We inferred that the pelvic adhesion of patients with CSD was serious. For the tubal patency, 9 of 30 (30%) patients were unobstructed, 5 of 30 (16.67%) patients were partially obstructed, and 16 of 30 (53.33%) patients were inaccessible (Fig. 2B). For patients with partially obstructed and inaccessible fallopian tubal, the methods of pressurization and salpingostomy were used to drain the old bloody mucus, improving the tubal patency.

3.3. Comparing the levels of inflammatory factors

During the surgery, we collected the pelvic fluid from all patients and measured the contents of inflammatory factors (TNF-α, IL-1β, IL-6). The data indicated that the levels of TNF-α, IL-1β, and IL-6 in patients with CSD were obviously higher than control group (*P* < .05) (Fig. 3). In the CSD group, the concentration of TNF-α was 976.68 ± 304.21 pg/mL, the IL-1β was 160.12 ± 126.10 pg/mL, and IL-6 was 259.36 ± 382.44 pg/mL. While in the control group, the concentrations of TNF-α, IL-1β, and IL-6 were 124.13 ± 98.12, 77.13 ± 86.65, and 80.93 ± 175.30 pg/mL. Thus, we surmised that CSD could increase the secretion of inflammatory factors and lead to inflammatory reactions.

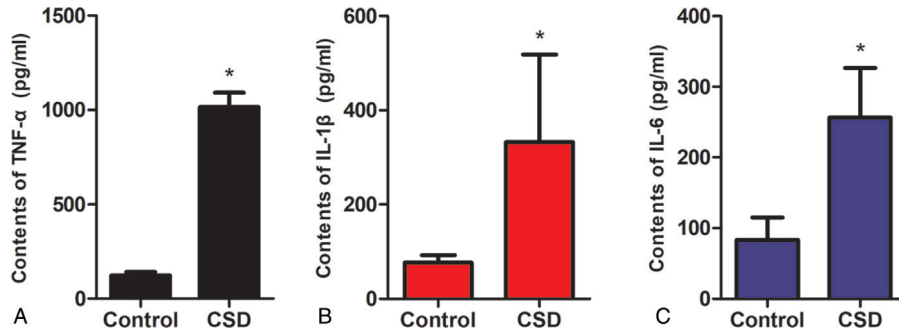


Figure 3. Measured the contents of inflammatory factors in the pelvic fluid. (A) TNF- α , (B) IL-1 β , (C) IL-6. Data are expressed as means \pm SD. * $P < .05$, compared with control group. IL-1 β = interleukin-1 β , IL-6 = interleukin-6, TNF- α = tumor necrosis factor- α .

3.4. Comparison of subsequent follow-up results

In the period of postoperation 2 years, we followed up all patients by telephone. Before surgery, we evaluated the size of the CSD in the patients through the three-dimensional vaginal B-ultrasound. The results showed that the sum of the 2 diameters of the CSD was (1.68 ± 0.52) cm. After 2 months of operation, all patients went to the hospital for review, and three-dimensional vaginal B-ultrasound showed that no CSD was found (Fig. 4A). From the data we collected, the menstrual period of patients with CSD was 7.80 ± 1.27 days. Comparison with preoperative menstrual period, the time was obviously shorter ($P < .05$) (Fig. 4B). In addition, three-dimensional vaginal B-ultrasound was used to review the CSD, and the results showed that the myometrial thickness at uterine scar was significantly increased ($P < .05$), the thickness of local thinnest part increased to 1.0 ± 0.12 cm (Fig. 4C).

For patients with reproductive requirements, contraception should be strictly performed for 1 year according to doctor’s

order. The follow-up results revealed that 12 patients had repregnant after surgery, of whom 6 patients had given birth, and 4 patients were pregnant, 2 patients had miscarriage in the first trimester (Fig. 4D). From these results, we inferred that CSD repair could improve the myometrial thickness at uterine scar, and increased the pregnancy rate.

3.5. Correlation between inflammatory factors and subsequent infertility

To evaluate the correlation between inflammatory factors and subsequent infertility, Spearman’s statistical analysis was used to determine the correlation coefficient. The results were shown in Table 3, the contents of inflammatory factors (TNF- α , IL-1 β , IL-6), the size of CSD, and the myometrial thickness at uterine scar were significantly correlated with subsequent infertility ($P < .05$). Moreover, the level of TNF- α and the size of CSD were moderate correlation with subsequent infertility ($r = 0.307, 0.405$), whereas the levels of IL-1 β and IL-6, and the myometrial thickness were low correlation with subsequent infertility ($r = 0.083, 0.147, 0.291$).

4. Discussion

CSD is one of the long-term complications after cesarean section, and the incidence is gradually increasing. At present, the diagnosis of CSD was mainly based on the patient’s previous history of cesarean section, the clinical manifestations such as prolonged menstruation and infertility, and imaging were also combined to confirm the defect of uterine incision. The commonly used auxiliary diagnosis of included: Transvaginal ultrasound examination: the linear, sac-like, wedge-shaped, or triangular liquid and dark areas at the incision of the lower part

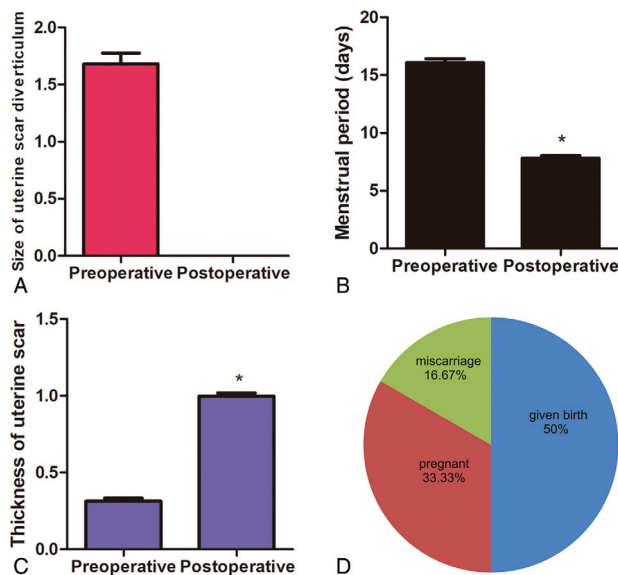


Figure 4. The results of subsequent follow-up during postoperation 2 years. (A) The size of cesarean scar diverticulum; (B) menstrual period; (C) thickness of cesarean scar; (D) the reproductive status. Data are expressed as means \pm SD. * $P < .05$, compared with preoperation.

Table 3
Correlation coefficients of variables associated with subsequent infertility.

N = 30	Correlation coefficients	P
TNF- α	0.307	.019
IL-1 β	0.083	.004
IL-6	0.147	.005
Size of CSD	0.405	.026
Myometrial thickness	0.291	.018

CSD = cesarean scar diverticulum.

of the anterior wall of uterine could be well observed through two-dimensional or three-dimensional vaginal ultrasound.^[10] Magnetic resonance imaging (MRI): MRI not only helped to observe the size of CSD, but also measured the thickness of the residual uterine muscle layer.^[11] However, the CSD was partially filled with fluid under angiography and displayed in an abnormal shape, which caused the measured size of CSD to be larger and the thickness of the local scar was thinner. Therefore, MRI is generally not recommended. Hysterosalpingography: this was one of the main auxiliary examinations to evaluate the unobstructed fallopian tubes and the uterine lesions in women. Hysteroscopy: hysteroscopy is considered as the “gold standard” for the diagnosis of CSD and is often used in combination with surgery.

In our study, all patients were diagnosed as CSD by the above methods, and the data indicated that pelvic adhesions were severe, the fallopian tubes were unobstructed, the myometrium at uterine scar was thinner, and the menstrual cycle was longer. CSD repair could improve menstrual prolongation and increased the thickness of myometrium. These results were consistent with the previous study.^[12] Other study found that hysteroscopy combined ultrasound might be an accurate method for diagnosis of CSD, and selection of the right operation methods according to the thickness of CSD was beneficial to improve the clinical symptoms.^[13] For women with retroflexed uteri, the failure rate of uterine scar remodeling was usually high by other surgeries; a novel of vaginal repair could increase the residual myometrium thickness and relieve clinical symptoms.^[14]

In recent years, the number of patients with secondary infertility had increased year by year, and tended to be younger, which had caused serious distress to families with fertility requirements. Early research found that secondary infertility was linked to CSD, which might be associated with persistent inflammatory reactions of local lesions in the uterine cavity.^[15] The mechanisms of CSD leading to infertility might include: repeated and abnormal uterine bleeding led to the inability to close the internal cervix, a persistent inflammatory reaction in the CSD was also linked, which caused tubal obstruction and pelvic inflammation, affecting the normal passage of sperm and the implantation of the embryo, and finally led to infertility.^[9] In addition, patients with CSD could cause the deformation of the uterine cavity and intrauterine inflammation, increasing the difficulty of embryo transfer and reducing the success rate of embryo transfer, and sustainably increased the risk of subsequent cesarean scar pregnancy after embryo transfer.^[16] Adopting hysteroscopic surgery to repair CSD could reduce the incidence of CSD pregnancy and increase the number of live deliveries.^[17] Our study found that the size of uterine scar diverticulum and the myometrial thickness at uterine scar were positively correlated with subsequent infertility, and uterine scar diverticulum repair could significantly increase repregnant rate.

Cytokines, as a class of hormone-like polypeptides with a wide range of biological activities, could regulate the ovarian endocrine or paracrine, thereby affecting follicle maturation, embryonic development, and implantation of fertilized eggs, which participated in the regulation of reproductive processes.^[18] IL-6 and IL-1 β are cytokines with inflammation-mediated activity; TNF- α is the initiation factor of the cytokine cascade, which can promote the secretion of IL-6 and IL-1 β , and closely related to the occurrences of reproductive tract infection, pelvic adhesion and infertility. In our study, the results found that the levels of TNF- α , IL-1 β , and IL-6 in CSD group were obviously

higher than control group ($P < .05$), and these results were consistent with previous research.^[19] Moreover, postoperative ultrasound examination revealed that no inflammatory lesions were observed.

Some studies have demonstrated that IL-6 plays an important role in the repair and regeneration of the fallopian tube endometrium, and the regulation of IL-6 can lead to adhesion, hyperplasia, fibrosis of local tissue, aggravating pelvic adhesion and tubal blockage.^[19,20] IL-6 can inhibit mouse embryo development and weaken the activity of sperm; the recombinant IL-6 inhibits the ability of sperm in penetrating egg cells and the development of early embryonic, finally leading to infertility.^[21] The high expression of IL-1 β could promote the inflammation reaction, and aggravated the pathological damage of fallopian tube.^[22] TNF- α is recognized as a marker for the formation of intra-abdominal adhesion, which can promote local inflammation of tissues, and leading to the development of tissue fibrosis.^[23] Current study has found that IL-1 β and TNF- α are strong inducers of IL-6, and the high concentration of IL-6 in serum is a risk factor for tubal factor infertility.^[24] Additionally, we evaluated the correlation between cytokines and infertility, and the results indicated that the contents of cytokines were positively correlated with subsequent infertility.

The limitations of the present study included the small size and selective group bias. Because pelvic effusions could not be collected from normal women, patients with uterine fibroids or benign ovarian tumors who use hysteroscopic surgery were included as a control group. In addition, we only evaluated the levels of pre-operative inflammation factors and postoperative inflammatory lesions; pelvic effusion was not collected to detect levels of inflammatory factors after surgery, and we could not further evaluate the patients' inflammatory changes. Therefore, other prospective clinical trial with large sample size and multicenter was needed to confirm the current results and achieve a rational conclusion.

In conclusion, women with CSD had severe pelvic adhesion, incomplete obstructed tubal, and high levels of cytokines. CSD repair could improve menstrual prolongation, increased the thickness of myometrium and repregnant rate. Subsequent infertility was positively correlated with the size of CSD and the levels of inflammatory factors.

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