

Comparison of transvaginal surgery and methotrexate/mifepristone-combined transcervical resection in the treatment of cesarean scar pregnancy

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Abstract. – OBJECTIVE: To explore the safety and efficiency of transvaginal surgical treatment of cesarean scar pregnancy (CSP).

PATIENTS AND METHODS: A retrospective analysis of 54 CSP patients that received treatment in our hospital from October 2011 to September 2015 was performed, dividing two groups: Group A (n=34) received transvaginal cesarean scar pregnancy focus clearance surgery while Group B (n=20) received transcervical resection following methotrexate/mifepristone-combined treatment. The basic clinical findings were collected and analyzed, along with the curative effects between the two groups.

RESULTS: Differences in age (30.91 ± 4.59 years vs. 31.91 ± 5.53 years) for gravidity (2.97 ± 1.24 times vs. 2.75 ± 1.48 times), cesarean section (1.24 ± 0.43 vs. 1.20 ± 0.41), time interval from last cesarean section (56.53 ± 32.93 months vs. 58.70 ± 39.44 months), menelipsis (51.35 ± 10.90 days vs. 57.85 ± 16.62 days), pre-operative serum-hCG (27953.65 ± 37517.10 mIU/L vs. 17368.24 ± 35094.14 mIU/L), operation time (43.34 ± 12.38 min vs. 40.07 ± 16.88 min), menstruation recovery time (1.23 ± 0.53 months vs. 1.55 ± 0.76 months) were not statistically significant ($p > 0.05$). The differences in the intraoperative blood loss (43.34 ± 12.38 ml vs. 40.07 ± 16.88 ml), average hospital stay (7.61 ± 2.47 days vs. 12.42 ± 3.64 days), time for β -hCG to return to normal (18.50 ± 8.19 mIU/L vs. 29.00 ± 12.96 mIU/L) between the two groups were statistically significant ($p < 0.05$). Group A was significantly lower than Group B.

CONCLUSIONS: Transvaginal surgery is an effective and relatively safe treatment option for CSP patients.

Key Words:

Cesarean scar pregnancy (CSP), Transvaginal surgical, Hysteroscopy, Methotrexate.

Introduction

Cesarean scar pregnancy (CSP) refers to fertilized egg and trophoblast cells that are seeded in the previous cesarean section scar and are enveloped by uterine muscle fibers and fibrous tissues. CSP is a long-term complication of cesarean section. It is a rare myometrial pregnancy, considered equal in causing patient harm as ectopic pregnancy. Larsen and Solomon¹ reported the first case of CSP in 1978. As the rate of cesarean sections increased, studies on CSP have also increased². According to statistics, the incidence of CSP accounts for 0.45%-0.56% of the total number of pregnancies^{3,4}. In China, with the increasing incidence of cesarean section (>50%)⁵, the number of CSP patients is also significantly increasing, making CSP treatment of particular medical importance. However, due to the paucity in clinical data, no uniform, international treatment guidelines exist for CSP. Furthermore, there is no consistent standard treatment for CSP. Current treatments are focused on individualized measures based on symptoms, serum β -human chorionic gonadotrophin (hCG), ultrasonic examination, and magnetic resonance imaging (MRI) examination. In this study, we retrospectively analyzed the clinical specimens of 54 CSP patients that received treatment at our Central Hospital of Xuzhou. Comparing the cu-

rative effects of several different treatment regimens, the advantages of transvaginal cesarean scar pregnancy focus clearance surgery was discussed.

Patients and Methods

Patients

Clinical specimens of 54 CSP patients that received treatment in our hospital from October 2011 to September 2015 were retrospectively analyzed. The patients were aged between 23-44 years, average age 31.28 ± 4.93 years; mean gravidity 2.81 ± 1.32 ; average parity 1.43 ± 0.49 ; average cesarean section 1.22 ± 0.42 ; time interval from last cesarean section was between 6 month-12 years, average 57.33 ± 35.13 months; menolipsis lasted for 34-98 days, on average 53.76 ± 13.8 days; vaginal bleeding time was 0-60 days, average 41.33 ± 10.31 ; preoperative serum β -hCG was 458-155300M IU/L (average 24033.13M IU/L). Exclusion criteria: (1) Patients that had received curettage or MTX treatment before admission, accompanied with a large amount of uterine bleeding. (2) Patients who could not tolerate surgery.

This study obtained informed consent for all patients.

Methods

The patients were divided into two groups: Group A (n=34) received transvaginal cesarean scar pregnancy focus clearance surgery, while Group B (n=20) received transcervical resection following methotrexate/mifepristone-combined treatment. Clinical specimens, clinical symptoms, and curative effects between the two groups were collected and analyzed. Differences in the age, gravidity, cesarean section, time interval from last cesarean section, menolipsis days, pre-operative serum-hCG level between the two groups were not statistically significant ($p>0.05$) (Table I).

Medical History and Clinical Manifestations

All patients had a history of cesarean section; one patient in the lactation period, all of the other patients had a history of menopause. Most patients had the following symptoms in the 5th-16th gestation week: (1) recurrent or persistent irregular bleeding, accompanied with or without abdominal pain; (2) continuous vaginal bleeding, accompanied with continuously elevated β -hCG after

artificial abortion and drug abortion. Gynecological examination showed lower uterine segment swelling, fornix shallowing, a normal cervical, and enlarged uterine body to various extents.

Laboratory Examination and Apparatus Examination

Examination results showed that all patients' serum β -hCG were elevated. Transvaginal sonography and/or nuclear magnetic resonance diagnosis confirmed as CSP. Basis and standard of CSP ultrasonic diagnosis^{4,6}: (1) Intrauterine and cervical canal had no gestational sac; (2) gestational sac or mixed mass was located in horizontal internal opening of cervix in the front wall of uterine isthmus or the scar of previous cesarean section; (3) between the gestational sac or mixed mass and bladder, muscular layer in the anterior wall of lower uterine segment was thinned or interrupted continuously; (4) Color Doppler flow imaging detected obvious annular blood flow signal around gestation sac trophoderm, pulse Doppler showed high-speed (peak flow velocity >20 cm/s) low resistance (pulsatility index <1) flow chart, similar to normal early pregnancy flow chart; (5) adnexa area showed no mass, rectouterine excavation had no free opaque dark area of fluid (except CSP rupture). All of the patients received transvaginal sonography. Forty-seven patients had an inhomogeneous mass in the scar in lower uterine segment or the cervix, the maximum thickness being 10-48 mm. Forty-two patients had the thickness from the mass edge to placenta percreta of 1.0-5.0 mm and five patients had the mass closely sticking to the placenta percreta. Color Doppler ultrasound on 7 patients showed heterogeneous hypoechoic in the lower segment of the uterus, and hematoma formation in the cesarean section scar. Under hypogastrium magnetic resonance imaging (MRI) examination, 10 patients were clearly diagnosed.

Treatment Method

Transvaginal Cesarean Scar Pregnancy Focus Clearance

After admission, all patients received relevant examinations and clarified diagnosis. Those with surgical contraindications were excluded, the remainder were prepared and draped for surgery vaginally. The patients were placed under general anesthesia or combined general-epidural anesthesia, the bladder emptied and a vaginal retractor was used to expose the vagina and cervix. A cer-

Table I. Comparisons on the basic materials of the two groups before treatment.

	Group A	Group B	p
Case (no.)	34	20	
Age (years)	30.91±4.59	31.91±5.53	0.477
Gravidity	2.97±1.24	2.75±1.48	0.561
Cesarean section (number)	1.24±0.43	1.2±0.41	0.738
Time interval from last cesarean section (months)	56.53 ±32.93	58.70 ±39.44	0.829
Menolipsis days (d)	51.35 ±10.9	57.85 ±16.62	0.125
Pre-operative serum-hCG level (mIU/L)	27953.65±37517.10	17368.24±35094.14	0.310

vical clamp was used to clamp the labium arterius with a No. 4-9.5 expanding-uterus rod to extend the uterus in sequence. Then, 30-40 ml of a 250 ml normal saline +0.5 mg adrenaline solution was injected into the junction of the cervix and vagina. The semi-circumference of vaginal wall was resected slightly below the bladder attachment point in anterior fornix. The bladder cervix space was bluntly separated to reach the peritoneum. When the cervical isthmus was swollen and soft with a diameter of about 4 cm, there were purple-blue nodules noted on the surface. The swollen section was opened and organized tissues and accumulated blood clots were observed; the focus tissues in the pregnancy scar and intrauterine decidual tissues were curetted and cleared. The uterine cavity was aspirated and curetted also. The cesarean scar tissue was trimmed in the incisional margin, and a No. 2-0 absorbable suture used to make a continuous suture. The excised focus was sent for pathological examination. A balloon catheter was placed inside the uterine cavity to prevent adhesion, two days later, the catheter was removed. After surgery, anti-inflammation, uterine contraction, and hemostatic therapy were performed. On the third post-operative day, the patients' serum β -hCG was taken. Once every week post-operatively, serum β -hCG was measured until it reached a normal level.

Transcervical resection following methotrexate/mifepristone-combined treatment

Before treatment, the blood, routine urine, liver and kidney function and serum β -hCG examinations were completed. Patients were excluded if they met the exclusion criteria. Patients were administrated 50 mg methotrexate by intramuscular injection, combined with oral administration of 25 mg mifepristone, once daily, hysteroscopic resection was performed until transvaginal ultrasound showed star shaped blood flow signals around the gestational sac or se-

rum β -hCG was below 2000 mIU/L or reduced by more than 60%. Before surgery, the vagina was prepared. On surgery day, intravenous general anesthesia was performed, the uterine cavity was detected under hysteroscopy, and the cervix was gently expanded with a No. 10 dilating stick. The uterine cavity was empty, but the normal, internal form of the uterus disappeared. The focus inside the myometrial wall in lower uterine segment protruded towards the direction of uterine cavity and, meanwhile, the scar marks from the previous cesarean section were observed. Under the monitoring of hysteroscopy and abdominal ultrasound, an electronic incision loop was used to excise the focus, until there was no obvious abnormality in uterine morphology under hysteroscopic visualization. Electric coagulation hemostasis using a dome-shaped electrode was used, and the blood clots in uterine cavity were removed. If the patient's focus was too large, a uterine balloon was placed in the uterine cavity and then removed within 24 hours. After excision, the focus was sent for pathological examination. Post-operatively, the patients were administrated antibiotic therapy, intramuscular injection of hemostatic drugs and drugs promoting uterine contraction. The amount of vaginal bleeding was recorded (used menstrual pad weighing method to calculate the volume of vaginal bleeding). If the volume of vaginal bleeding was over four pieces of menstruation pad, this was changed to a gauze packing weighing method). After forty-eight hours, the value of β -hCG was measured. One patient, due to copious bleeding, required laparoscopic combined surgery and excluded from this study.

Criteria for recovery: Clinical abdominal pain, abdominal distension, and other symptoms disappeared. Vaginal bleeding stopped, serum β -hCG returned to normal, no pregnancy tissue or residues were found under ultrasonic examination, and menstruation resumed.

Table II. Comparison on the treatment outcomes of the two groups (d, $\bar{x}\pm s$).

	Group A	Group B	<i>p</i>
Operation time (min)	43.34±12.38	40.07±16.88	0.423
Intraoperative blood loss (ml)	70.00±40.30	120.00±73.76	0.002
Hospitalization time (d)	7.61±2.47	12.42±3.64	<0.001
Time for blood β -HCG returned to normal (mIU/L)	18.50± 8.19	29.00± 12.96	0.001
Menstruation recovery time (month)	1.23±0.53	1.55±0.76	0.093

Statistical Analysis

SPSS 13.0 software (SPSS Inc., Chicago, IL, USA) was applied for the statistical analysis. The measurement data were presented by ($\bar{x} \pm s$); the *t*-test was applied in comparisons between groups; the χ^2 -test was applied in the enumeration data; $p < 0.05$ was considered to be statistically significant.

Follow-up

Patient post-operative, clinical follow-up and telephone follow-up occurred for 6-50 months. Follow-up was focused on the patients' serum β -hCG, gynecological ultrasound examination, menstruation, and any complications including abnormal vaginal bleeding, abdominal pain and distension, intrauterine adhesions, and secondary pregnancy. The patients without fertility concerns were followed up till their serum β -hCG value returned to normal, their menstrual cycle recovered, and they failed to demonstrate any abnormalities under transvaginal color Doppler ultrasound. The patients with fertility concerns were required to use birth control for over a year and were followed up until subsequent pregnancy. The condition of their incision, pregnancy and placental implantation were recorded.

Results

In Group A, four patients were lost to follow-up with the remainder successfully cured. In Group B, one patient was lost to follow-up and the remainder successfully cured. The hospitalization time of Group A was 5-17 days, without second hospitalization; the hospitalization time of Group B was 8-20 days, and two cases were hospitalized for the second time for the same cause with the difference between the two groups being statistically significant ($p < 0.05$). Except the cases lost to follow-up, all the remaining cases in the two groups were fully cured. The time that serum β -hCG returned to normal for Group A was 8-31

days, on average (18.50 ± 8.19); for Group B 5-58 days, on average (29.00 ± 12.96), and their difference was statistically significant ($p < 0.05$). The average menstruation recovery time of Group A was 1.23 ± 0.53 months; of Group B was 1.55 ± 0.76 months, and their difference was not statistically significant ($p = 0.093$) (Table II for details).

The treatment process of Group A was relatively stable, and no case had vaginal bleeding; one case in Group B had a large amount of vaginal bleeding (approximately 800 ml), which then required laparoscopic combined surgery. The bleeding rate of Group A was lower than Group B, and their difference was statistically significant ($p < 0.05$). During follow-up, three patients in Group A had a subsequent pregnancy, and no patient had recurrent cesarean scar pregnancy; five patients in Group B had a subsequent pregnancy, and no patient had recurrent cesarean scar pregnancy. One case in Group A had intrauterine adhesions, and three cases in Group B had intrauterine adhesions. Two cases in Group B still had persistent abdominal pain after serum β -hCG and menstruation returned to normal.

Discussion

CSP is a rare and dangerous form of ectopic pregnancy in the myometrium. Its exact pathogenesis is not yet known⁷. Fylstra⁸ deemed that placental implantation was the difference between CSP and normal intrauterine pregnancy. The caesarean section would lead to scanty or defective endometrial interstitial decida. The fertilized egg, after implanting there, would be subject to a decidual defect. Then the trophocyte directly invades the myometrium and continues to grow, resulting in the implantation of villi into uterine muscle layer, even penetrating the uterine wall. The diagnosis was mainly based on the medical history of patients, i.e. the history of menopause, history of cesarean section, without painful vaginal bleeding,

elevated serum β -hCG value, transvaginal color Doppler ultrasound/nuclear magnetic resonance imaging results and postoperative pathology. Like other pregnancies, serum β -hCG values of CSP patients increase after menolipsis. After artificial abortion, the value remains the same or even increases. It is mainly used to determine pregnancy, monitor treatment effect and understand the prognosis. Transvaginal color Doppler ultrasound examination is the most important method for early diagnosis of CSP⁹. Ultrasound has become the first choice of auxiliary examination for the diagnosis of cesarean scar pregnancy. MRI has a good soft tissue resolution and can directly display the anatomical structure of the pelvic organs as well as the hierarchical relationship between tissues, and is very suitable for intractable cases. MRI could clearly distinguish the relationship between endometrium, cesarean scar and pregnancy sac through multidimensional images and also for the specific observation of ectopic pregnancy as well as the structures inside the blood clots, which are difficult to visualize using transvaginal ultrasound (TVS)¹⁰. After surgery, the focus tissue was sent for pathological examination. If there were villi tissues inside the muscular layers of cesarean scar, it was confirmed as CSP.

CSP is a rare disease. At present, there are many treatment methods¹¹⁻¹⁷, but an ideal treatment method has not been determined. If patients with uterine surgical scars are subject to vaginal bleeding or have a low pregnancy sac under ultrasound examination, TVS examinations are performed to understand the relationship between the pregnancy and muscular layer on the scar, membranae serosa, bladder and other peripheral tissues, and also to understand the extent of blood flow. In the absence of a clear B ultrasound examination, artificial abortion or curettage should not be conducted blindly¹⁸. During treatment, we should start from the patient's individual condition and choose the most appropriate, safe and effective methods to reduce the suffering of patients and to avoid excessive medical treatment.

The muscular layer in the isthmus uteri is thin, and surgical scarring has abundant connective tissues. Decidua is subject to mal-development after pregnancy, and when the pregnancy sac is implanted, the villous tissues implant into the muscular layer or are enveloped by the muscular layer placental tissues. This could cause the villi or placenta to exfoliate completely. The lower ute-

rine segment fails to effectively contract due to a lack of muscle fibers, and the open blood sinus fails to close on its own, and results in unmanageable blood loss, threatening the life of patients.

Methotrexate is a kind of folic acid antagonist¹⁹. Trophocytes are relatively sensitive to methotrexate. Therefore, methotrexate could effectively kill the trophocytes. Mifepristone has a strong anti-progesterone effect, which could cause the villi tissues to metamorphosis and decidual tissues to atrophy and necrose, resulting in embryonic death. Through different working mechanism, both drugs could prevent the embryo from development, and further lead to atrophy, degeneration, and necrosis. However, the cycle for pure methotrexate/mifepristone combined treatment is too long and clinical experiments have shown that the curative effects are not ideal. Hysteroscopic surgery allows the operators to get direct visualization of the focus and clear away the pregnant products. This also allows the surgeon to ensure adequate hemostasis. Yang et al²⁰ deemed that the large blood loss during uterine curettage was related to pre-operative serum β -hCG. Considering that β -hCG is secreted by villi and decidua, Yang et al²⁰ indicated that the degree of gestational sac implantation (i.e. the degree of development of villi and placenta) would influence the amount of bleeding. Transcervical resection following methotrexate/mifepristone-combined treatment could be an ideal treatment method for CSP. However, the space of uterine cavity is limited, and hemostasis under direct vision is not always easy on the pregnancy scar after excising the focus. In our study, one case in Group B had a large amount of vaginal bleeding (more than 600 ml), which then required conversion to laparoscopic combined surgery. Before surgery, the serum β -hCG value of the patents was significantly reduced. Before hysteroscopy, the serum β -hCG value was lowered to 823 mIU/ml. This would indicate that serum β -hCG is not necessarily associated with large intra-operative blood loss. Multiple factors likely affect the amount of bleeding during the operation. However, this report had a small sample size, which suggests that a larger work is required.

Our hospital has used this transvaginal procedure in the treatment of cesarean scar pregnancy since 2013. Advantages include: 1. The focus site of CSP patients was relatively low, making it easier to reach the site of the lesion through the vagina and the focus site more convenient for exposure.

Moreover, this allows the surgeon to clear the focus under direct visualization. 2. The operative space was larger, allowing for various hemostasis methods. 3. During the procedure, surgeons could repair the cesarean scar, reducing the incidence of recurrent CSP. 4. There was no need to open the uterovesical peritoneal reflection, so impact on the intestinal tract was minimized. The results of our study indicate that the amount of bleeding during the operation and the hospitalization time of Group A were less than that of Group B and the differences were statistically significant (Table II); operation time between the two groups was not significantly different (Table II). Although focus clearance of patients in both groups was carried out under direct visualization, our results showed that the time required for β -hCG to return to normal in Group A was significantly less than in Group B and their difference was statistically significant (Table II). Possible reasons: 1. Intraoperative ultrasound resolution was limited. Though it could guide the operator to clear away large pregnancy products, it could do nothing on minor residues. While implementing hysteroscopic electric resection to prevent injuring the bladder, the operator would subconsciously select a smaller resection focus. 2. Few patients, due to the amount of bleeding and the residues were closely incorporated and therefore not resectable, were removed from the study. Compared with Group B, Group A separated the bladder and cervix, so the patients had no bladder injury, and focus clearance was more thorough. Meanwhile, our clinical observations found that transvaginal surgery was more prone to produce injuries to the peripheral tissues and neighboring organs. In Group A, 2 among the 5 cases that accepted surgery the earliest were subject to bladder and cervix injuries during surgery. After surgery, they received an indwelling catheter and recovered two weeks later. The remaining 32 cases in Group A had no significant peripheral tissue or organ damage.

Although bladder and cervix space were isolated to reduce the risks of bladder or other organ injuries, an increased awareness to protect the bladder and peripheral tissues is tantamount. For Group B, treating the local defects of cesarean section was not enough. Patients were more vulnerable to abnormal vaginal bleeding, abdominal pains and other symptoms. Follow-up results showed that 2 cases in Group B still had persistent abdominal pain after serum β -hCG and menstruation returned to normal. Compared with Group B, Group A had better ameliorati-

ve effects. Through transvaginal cesarean scar pregnancy focus clearance surgery not only the pregnancy products were removed, but also tissue damage was repaired, thus greatly reducing the incidence of sequelae. Data showed that no patient in Group A had persistent abdominal pain or abnormal vaginal bleeding after serum β -hCG and menstruation recovered to normal. Five patients in Group B had a secondary pregnancy, without recurrent CSP. Three patients in Group A had a secondary pregnancy, also without recurrent CSP.

Conclusions

Since the number of patients is limited and the rate of subsequent pregnancy is relatively low, it is difficult to evaluate the influence of the two methods on subsequent pregnancy. Based on the above data analysis, combined with the satisfactory results of transvaginal cesarean scar pregnancy focus clearance treatment, we believe that transvaginal cesarean scar pregnancy focus clearance treatment is a safe and effective treatment method for cesarean scar pregnancy.

Conflict of interest

The authors declare no conflicts of interest.

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