Original Article

An application of uterine artery chemoembolization in treating cesarean scar pregnancy

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Abstract: Objective: To discuss the feasibility and safety of uterine artery chemoembolization in treating cesarean scar pregnancy (CSP). Methods: During the period between 1st of May 2009 and 17th of January 2014, uterine artery chemoembolization with methotrexate (MTX) and gelatin sponge was performed in 31 patients diagnosed with CSP in Xinqiao Hospital. Curettage of uterus was carried out within 24-48 hours after the procedure. Results: The success rate of bilateral uterine artery chemoembolization was 100%. The mean blood loss during curettage procedure was only 8.32±4.76 (2-20) ml. The mean time for serum β-HCG normalization was 33.81±17.47 (15-82) days, and the mean time for gestational sacs elimination was 29.52±20.93 (4-90) days. The mean time of hospital stay was 5.10±1.08 (4-8) days. Conclusions: No serious complications occurred. The uterine artery chemoembolization is an effective and safe treatment for CSP, which greatly reduces the necessity of hysterectomy.

Keywords: Cesarean scar pregnancy (CSP), uterine artery chemoembolization (UAE), methotrexate (MTX), curettage of uterus

Introduction

Cesarean scar pregnancy (CSP) was described for the first time in 1978 [1]. It is defined as the gestational sac being implanted into the myometrium and the fibrous tissue of a previous cesarean delivery and is one of the rarest types of ectopic pregnancy. Seow et al. [2] estimated that the incidence of CSP was 1 per 2216 pregnancies, with a rate of 6.1% for women with an ectopic pregnancy and at least one cesarean section (CS), while a rate of 0.15% for women with a previous CS. The incidence of CSP is increasing, because more and more deliveries are performed by CS. The baseline cesarean delivery rate is 15% worldwide but it accounts for approximately 40%-60% of births in China, and possibly even more than 70% of births in some hospitals [3].

CSP can lead to catastrophic complications, such as extensive vaginal bleeding during pregnancy or curettage, disseminated intravascular coagulation, uterine rupture that may result in compromising the patient’s reproductive future in cases of hysterectomy, or even to death [4, 5]. Early diagnosis and treatment is therefore very important to reduce life-threatening complications. Transvaginal ultrasound was the first widely used tool for diagnosing CSP, and is performed in conjunction with appropriate clinical investigation [6].

However, among most data on the clinical treatment of CSP, however, there is no consensus on the preferred therapeutic protocol. The main management for CSP includes systemic or local administration of methotrexate (MTX), uterine suction curettage, local resection of the mass, uterine artery embolization (UAE), and hysterectomy [7-10]. Conservative treatments avoid the need for unnecessary laparotomy, laparoscopy and/or hysteroscopy, but the control of profuse bleeding by conservative interventions has never been described precisely. Similarly, exploratory surgical approaches may lead to high mortality and the possible need for emergency hysterectomy.

UAE has been described in the literature as an effective treatment modality for ectopic implantation such as CSP, cervical pregnancies, cornual pregnancy and intramural pregnancy, postpartum hemorrhage, uterine leiomyoma and/or
adenomyosis, or for controlling growth and bleeding in malignancies during chemotherapy [8-11]. Transcatheter arterial chemoembolization which combines transarterial infusion chemotherapy with arterial embolization has recently been tried for localized gestational trophoblastic disease and CSP treatment [9, 12, 13].

Because of the rarity of the condition, most CSPs in the literature are case reports. In this study, we described 31 cases of viable cesarean scar pregnancies that are treated safely by selective uterine arterial chemoembolization. MTX is administered directly into the gestational foci through bilateral uterine arteries, in combination with subsequent dilatation and curettage, and/or mifepristone therapy.

Materials and methods

From 1st of May 2009 to 17th of January 2014, we performed a retrospective analysis of 31 CSP patients using records from Department of Obstetrics and Gynecology in Xinqiao Hospital. CSP was diagnosed based on patient history, including clinical manifestations, physical examination, and record of prior CS, serum β-HCG levels, and transvaginal ultrasound findings. The research protocol was approved by the ethics committee of Xinqiao Hospital, Third Military Medical University. All patients were well informed on the benefits and risks of the treatment, potential complications, and alternatives, and patient consent was obtained.

The diagnosis of CSP was confirmed if all criteria from ultrasound imaging were met [5, 6, 14, 15]: (1) empty uterus and cervical canal; (2) development of the sac in the anterior part of the isthmic portion; (3) presence of embryonic/fetal pole and/or yolk sac with or without heart activity; (4) a thin (1-3 mm) or absent myometrial layer between the gestational sac and the
Table 1. Clinical information on 31 patients with CSP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.42±5.94 (21-46)</td>
</tr>
<tr>
<td>Number of previous gravidity</td>
<td>4.48±1.86 (2-10)</td>
</tr>
<tr>
<td>Parity (times)</td>
<td>1.39±0.62 (1-3)</td>
</tr>
<tr>
<td>Number of previous cesarean delivery</td>
<td>1.10±0.23 (1-2)</td>
</tr>
<tr>
<td>1</td>
<td>24 (77.42%)</td>
</tr>
<tr>
<td>2</td>
<td>7 (22.58%)</td>
</tr>
<tr>
<td>Interval time (months)</td>
<td>55.61±45.98 (2-169)</td>
</tr>
<tr>
<td>Gestational age (days)</td>
<td>42.10±6.34 (30-60)</td>
</tr>
<tr>
<td>Original serum β-HCG (mIU/ml)</td>
<td>42351.89±46901.82 (437.22-210269.92)</td>
</tr>
<tr>
<td>Gestational sac/mass diameter (mm)</td>
<td>16.38±10.82 (6.0-56.67)</td>
</tr>
<tr>
<td>Number of cases with fetal cardiac activity (n)</td>
<td>12 (38.71%)</td>
</tr>
<tr>
<td>Number of cases with vaginal bleeding (n)</td>
<td>14 (45.16%)</td>
</tr>
<tr>
<td>Myometrial thickness (mm)</td>
<td>2.35±0.60 (1.0-3.0)</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD (rang) or number (percentage) unless otherwise indicated.
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Clinical information collected from all CSP patients includes maternal age, clinical presentation, gravidity and parity, gestational age, number of previous CS, the time interval between the last CS and current CSP, serum β-HCG, and ultrasound findings (gestational sac/mass diameter, yolk sac with or without cardiac activity, myometrial thickness) (Table 1).

All CSP patients have completed relevant examination before operation for UAE in Xinqiao Hospital. With the patient prone, the UAE procedure was performed by two experienced obstetrics and gynecology doctors. After sterilization of the groin, a percutaneous right femoral artery puncture was completed with the improved seldinger technique. A 5-F catheter and a guide wire were inserted and advanced into the aortic bifurcation. The left common iliac artery was entered and then the left inter- nal iliac was selectively catheterized. The catheter was positioned in the anterior division of the internal iliac artery. Digital subtraction arteriography (DSA) was then performed to confirm the left uterine artery and the location of the cesarean scar lesion and its feeding vessels. Before embolization, 50 mg of MTX (50 mg/m² body surface area) was injected into the uterine artery. After completing the embolization on the left side, right uterine artery catheterization was performed using a similar technique. Both uterine arteries were embolized with gelatin sponge particles (about 0.5-1.0 mm in size). Subsequently, the embolization was terminated when complete stasis of uterine artery flow was achieved (Figure 2). During the operation, the patient’s blood pressure, heart rate, consciousness, and electrocardiographic findings were monitored, and the total duration of the operation and bleeding were also recorded. After the removal of the catheter and wire, hemostasis was achieved by directed compression for 30 minutes. To prevent bleeding, patients were confined to bed rest for 6 hours after UAE. 24 hours after UAE, all patients were examined using transvaginal ultrasound to confirm the absence of intral- sional blood flow and their level of serum β-HCG was also assessed. Uterine suction curettage was performed under transabdominal ultrasound to confirm the absence of intral- sional blood flow and their level of serum β-HCG was also assessed. Uterine suction curettage was performed under transabdominal ultrasound to confirm the absence of intral- sional blood flow and their level of serum β-HCG was also assessed. Uterine suction curettage was performed under transabdominal ultrasound to confirm the absence of intral- sional blood flow and their level of serum β-HCG was also assessed. Uterine suction curettage was performed under transabdominal ultrasound to confirm the absence of intral- sional blood flow and their level of serum β-HCG was also assessed. Uterine suction curettage was performed under transabdominal ultrasound to confirm the absence of intral- sional blood flow and their level of serum β-HCG was also assessed.

Successful treatment was defined as a steady decline in no active vaginal bleeding, serum β-HCG concentration settling down to normal levels, gradual disappearance of the CSP mass, no severe complications, and exclusion of repeating embolization or laparotomy. Recorded data include curettage blood loss, serum β-HCG, transvaginal ultrasound, estimated vag- inal bleed loss, side effects (fever, nausea and vomiting, abdominal or pelvic pain, and abnormal liver or renal function, etc.), length of hospi- talization, frequency of CSP or hysterectomy, and resumption of menses. Monitoring of the serum β-HCG and transvaginal ultrasound were performed before the intervention, on day 1 after CSP and curettage, every 3 days during hospitalization, and finally every week until the

Table 2. Clinical outcomes of 31 patients with CSP

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD (after UAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of UAE (min)</td>
<td>30.48±12.60 (15-60)</td>
</tr>
<tr>
<td>UAE blood loss (ml)</td>
<td>9.48±3.91 (3-15)</td>
</tr>
<tr>
<td>Curettage blood loss (ml)</td>
<td>8.32±4.76 (2-20)</td>
</tr>
<tr>
<td>Time for serum β-HCG normalization (days)</td>
<td>33.81±17.47 (15-82)</td>
</tr>
<tr>
<td>Time for CSP mass disappearance (days)</td>
<td>29.52±20.93 (4-90)</td>
</tr>
<tr>
<td>Length of hospitalization (days)</td>
<td>5.10±1.08 (4-8)</td>
</tr>
<tr>
<td>Patients with hysterectomy (n)</td>
<td>0</td>
</tr>
<tr>
<td>Success rate (%)</td>
<td>100%</td>
</tr>
</tbody>
</table>

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recovery. All cases were followed up for at least a year. Statistical analysis of all data was performed using the Student t test and an $\chi^2$ test by the SAS 8.2 statistics package (SAS, Cary, NC).

Results

A total of 31 women with CSP were enrolled in this retrospective study and their clinical information is showed in details in Table 1. The average patient age of was 32.42±5.94 (21-46) years. The average gravidity was 4.48±1.86 (2-10), the average parity was 1.39±0.62 (1-3), and the average number of cesarean delivery was 1.10±0.23 (1.2). 24 patients (77.42%) had one cesarean delivery and 7 (22.58%) had two cesarean deliveries. The average time interval between the current CSP and last CS was 55.61±45.98 (2-169) months. The average gestational age was 42.10±6.34 (30-60) days. All CSP patients were initially diagnosed in our hospital, 14 patients had vaginal bleeding (45.16%), and only one had abdominal pain (3.22%). By transvaginal sonography, the mean gestational sac/mass diameter was 16.38±10.82 (6.0-56.67) mm and the mean myometrial thickness was 2.35±0.60 (1.0-3.0) mm. 12 gestational sacs had cardiac activity (38.71%), 14 sacs were yolk sacs (45.16%), and empty gestational sacs were found in the rest of patients (16.13%).

All 31 patients underwent bilateral uterine artery chemoembolization as the primary treatment, and then received suction curettage 24-48 hours after the UAE. No patients had recurrent vaginal bleeding after the UAE procedure. Table 2 presents the detailed clinical outcomes. The mean time of UAE operation was 30.48±12.60 (15-60) min. The mean blood loss during UAE procedure and curettage was 9.48±3.91 (3-15) ml and 8.32±4.76 (2-20)ml. The concentration of serum β-HCG was 42351.89±46901.82 (437.22-210269.92) mIU/ml before the UAE and the time for serum β-HCG normalization was 33.81±17.47 (15-82) days after the UAE. In these patients, the sizes of gestational sacs monitored by transvaginal ultrasound decreased gradually, and disappeared completely after 29.52±20.93 (4-90) days. The average duration of hospitalization was 5.10±1.08 (4-8) days. No patients were readmitted after discharge and all patients had uterine preservation.

No serious side effects due to MTX such as alopecia, nausea or vomiting, stomatitis, leukopenia, and liver or renal dysfunction, were observed in these CSP patients. The patients who showed signs of fever or experienced pain recovered after common symptomatic treatments within one or two days. After discharged from hospital, all patients were followed up for at least one year. 28 patients resumed their menses within 1-2 months after the intervention therapy and the other 3 patients had regular menses 3-4 months later. The serum sexual hormonal levels in all patients remained normal during the first year after the operation. During the follow-up, 4 patients were found able to conceive 3-9 months after the UAE, and they received painless induced abortion since the pregnancy was unexpected.

Overall, 31 patients were successfully treated, with a success rate of 100% and all experienced a rapid recovery.

Discussion

Cesarean scar pregnancy is an extremely rare presentation of ectopic pregnancy and associated with catastrophic complications, such as uterine rupture, massive bleeding and life-threatening complications [14, 16].

The mechanism of CSP remains uncertain. It is possible that the conceptus may penetrate the myometrium through a microscopic dehiscent tract of the cesarean section scar [14, 17]. If an embryo implants early into the myometrium via a microtubular tract in this tiny defect, CSP occurs. In this study, the average time interval between the current CSP and last cesarean delivery was 55.61±45.98 (2-169) months, it is unclear whether there is any correlation between the interval time and the occurrence of CSP. Out of the 31 patients, 24 women (77.42%) had only one cesarean delivery and 7 women (22.58%) had two cesarean deliveries. This indicates that multiple cesarean sections may not be a risk factor for CSP.

Due to the rate of cesarean deliveries and the severity of complications, it is important to diagnose CSP as early as possible. Transvaginal sonography is a useful tool for such purpose[2, 5] and has been used in this study to confirm the CSP of the 31 patients, besides considering their clinical symptoms such as menopause,
elevated serum β-HCG, vaginal bleeding, etc. Upon the diagnosis of CSP, termination of the pregnancy during the first trimester is strongly recommended due to the risk of uterine rupture associated with life-threatening hemorrhage. Clinical treatment may be drug-based and can also take surgical approaches. Medical treatment involves systemic or local administration of drugs such as MTX, mifepristone and the serum β-HCG is assayed. However, it takes about 1 to 4 months to reduce the serum level of β-HCG to normal and takes 2 months to 1 year for the mass to disappear, and vaginal bleeding lasts for 2 to 3 months. Therefore, the failure rate in medical treatment is very high and emergency hysterectomy was sometimes performed for profuse bleeding when conservative treatment failed [10, 18]. Surgical or invasive techniques, including dilation and curettage, hysteroscopic resection, laparotomy, or laparoscopic CS gestational product resection and hysterectomy, were not recommended for Cesarean scar pregnancy due to high morbidity and poor prognosis, except for cases of failure of conservative treatment or rupture of the uterus due to delayed diagnosis. Intra- or postoperative complications can occur, such as profuse hemorrhage, uterine perforation, shock, and even life-threatening events [19, 20].

UAE has recently gained widely acceptance as a conservative method for various obstetric and gynecologic conditions such as uterine myomas, postpartum hemorrhage, CSP, and cervical pregnancy [8, 21-24]. Some researchers consider it as the only alternative to hysterectomy to control bleeding in the case of trophoblastic tissue invading the vesicouterine space [25]. Recent studies suggest that the use of UAE is effective in the treatment of CSP through blocking the flow of blood in the uterine arteries and decreasing vascularization in pregnancy and produced satisfactory results in the treatment of CSP [17, 19]. In this study, we found that 14 patients had significant vaginal bleeding (45.16%) before the UAE, while the bleeding has been reduced below 10 ml per day after the UAE procedure. Transcatheter arterial chemoembolization combines transarterial infusion chemotherapy with arterial embolization. Recently, some reports have showed that UAE in combination with local MTX produced satisfactory results in the treatment of CSP [12, 13]. Delivery of intravascular MTX before occlusion facilitates high MTX concentration in the CSP mass, with less toxicity and fewer adverse effects than are common with systemic administration of MTX. During the past four years, UAE with embolic agents mixed with chemotherapeutic agents such as MTX has been used in Xinqiao hospital as the main approach to terminate CSP. In this study, 31 cases of CSP were treated with UAE in association with local MTX infusion. The intervention was successfully performed in all thirty one patients, with no serious complications and adverse effects during and after the procedure.

It takes a long time for the gestational sac or mass to be spontaneously reabsorbed, usually from several months up to a year [2]. Uterine suction curettage can remove most of the CSP mass, however, regular curettage used alone as a primary therapy to terminate CSP may result in serious hemorrhage, even necessitating an inevitable conversion to hysterectomy [2, 26]. Arslan et al. reported that uterine suction curettage has been shown to be unsuccessful with a failure rate as high as 70%, and could cause complications requiring secondary referrals or surgical treatment [27]. From our experience, curettage can be used as an additional treatment after transcatheter arterial chemoembolization and the interval between curettage and chemoembolization should not be too long in case that the embolic material starts to be absorbed and the uterine arteries reopen. In Xinqiao Hospital, all patients received curettage under transabdominal ultrasound guidance 24-48 hours after UAE. The blood loss during curettage was only 8.32±4.76 (2-20) ml, the time for serum β-HCG normalization was 33.81±17.47 (15-82) days after the UAE, the gestational sacs disappeared eventually after 29.52±20.93 (4-90) days, and the average length of hospitalization was 5.10±1.08 (4-8) days. This study showed that all CSP patients had much less bleeding during curettage and had a rapid decline of their serum β-HCG level. The time for CSP mass disappearance and the duration of hospitalization is also very short. Therefore, UAE can not only control the vaginal bleeding immediately but also reduced blood loss significantly during subsequent curettage.

However, it needs to be emphasized that no invasive procedure is risk-free. Associated complications consist of pain, fever, nausea and vomiting, and are most transient symptoms. Because UAE blocked temporary uterine
arterial blood flow, there is also a concern about whether ovarian perfusion is affected, which is directly connected to patient’s reproductive future. Zhang et al. [28] found that the normal menstrual cycle resumed two or four months after performing UAE in association with local MTX, and a normal pregnancy occurred in 50% of the patients within one year. In Xinqiao Hospital, 31 CSP patients recovered their menstruation 1-4 months after UAE and 4 patients were pregnant again within one year. It has been estimated that once the blood vessel has been embolized with gelatin sponge particles, it reopens its course after around 2-3 weeks, which helps the recovery of the reproduction system [29, 30]. Until now, few reports have addressed the potential impact of UAE combined with MTX infusion on fertility. MTX is a FDA Pregnancy Category X medication, so patients should be informed about the associated risks and use contraception for at least 3 months after MTX infusion [28, 31].

In summary, accurate early diagnosis of pregnancy within cesarean scar and its effective management is important to preserve the fertility of patients and reduce maternal mortality. This study suggests that UAE combined with intra-arterial MTX infusion is a safe and effective treatment for CSP patients. Further studies with a larger sample size are necessary to confirm our findings.

Disclosure of conflict of interest

None.

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References

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