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Original Article

Uterine artery embolization with and without local methotrexate infusion for the treatment of cesarean scar pregnancy

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ABSTRACT

Objective: To compare the clinical value of uterine artery embolization (UAE) with local methotrexate (MTX) infusion to embolization without MTX in the treatment of cesarean scar pregnancies (CSPs).
Materials and methods: From January 2009 to December 2013, 50 patients with CSP treated with UAE receiving or not receiving local MTX infusion prior to curettage were analyzed retrospectively. Twenty-two patients were offered UAE with local MTX infusion prior to curettage (UAE + MTX group), whereas 28 patients received UAE alone prior to curettage (UAE group). Clinical data and the outcomes were analyzed, followed by a brief review of the published literature summarizing what is known about UAE with and without MTX for the treatment of CSP.
Results: UAE was successful in 42 of 50 cases (84%), with complications occurring in only five patients. There were no significant differences in the success rate, complication rate, recovery time, or hospitalization costs between the UAE + MTX group and the UAE group. However, blood loss in the UAE + MTX group was significantly higher than in the UAE group.
Conclusion: UAE with or without local MTX infusion might be an effective treatment for CSP. Compared with UAE alone, UAE with local MTX infusion did not dramatically improve the therapeutic effect of UAE. A larger and more comprehensive random control study is warranted to better evaluate the therapeutic effects of UAE in the treatment of CSP.

Introduction

Cesarean scar pregnancy (CSP) is a rare but potentially life-threatening complication of a previous cesarean birth, in which the gestational sac is implanted at the site of the previous cesarean scar and is surrounded by uterine muscular fiber, scar tissue, and the thin myometrium adjacent to the bladder [1,2]. CSP may lead to excessive hemorrhaging, shock, and/or uterine rupture with the potential necessity for hysterectomy; in the worst case, CSP can result in maternal death [3,4]. Therefore, it is imperative that CSP be diagnosed and effectively treated as early as possible. The number of identified CS pregnancies ranges from 1/1800 to 1/2216 of every pregnancy [5,6], and is likely to exponentially rise in the near future, because of the increasing rate of cesarean delivery worldwide and enhanced detection through the widespread use of transvaginal ultrasound [7,8].

However, to date, the optimal management of CSP remains to be determined. In this study, the clinical value of uterine artery embolization (UAE) with or without local methotrexate (MTX) infusion prior to curettage in the treatment of CSP are discussed, along with a brief review of the published literature on the management of CSP.

Materials and methods

Patients

This study, which was approved by the Ethics Committee of Taizhou Hospital of Zhejiang Province, Zhejiang, China is a retrospective case series of 50 patients diagnosed with CSP treated over a period of 5 years (from January 2009 to December 2013). Patients with a ruptured uterus, inevitable abortion, active inflammation, severe cardiac, lung, kidney, or liver disease, or allergy to iodinated contrast medium, MTX, or embolic material were excluded. All

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patients were given extensive counseling, and written informed consent was obtained from participants prior to the treatment. The medical records and ultrasound images of all patients with CSP were collected from the original hospital charts, operation notes, and outpatient medical records via telephone questionnaires.

The average patient age was 31.68 ± 4.58 years (range 22–40 years). The average time between CSP and previous cesarean delivery was 4.87 ± 3.04 years (range 0.6–12 years). In terms of the number of cesarean deliveries prior to CSP, 38 patients had one, 11 patients had two, and one patient had three. The range of symptoms was wide. Twenty-six patients complained of intermittent slight vaginal bleeding, in which five cases were transferred to our hospital because of a failed artificial abortion, and nine cases suffered from excessive vaginal hemorrhage owing to misdiagnosis and underwent dilatation and curettage (D&C) or medical abortion prior to referral from another hospital. Three patients only experienced light abdominal discomfort, and 12 were asymptomatic.

Diagnosis

Alongside a positive pregnancy test, CSP was confirmed by the following transvaginal ultrasound criteria [9–11]: (1) an empty uterine cavity without contact with the sac, (2) a clearly visible empty cervical canal without contact with the sac, (3) the presence of the gestational sac in the anterior uterine isthmus with or without a fetal pole or fetal cardiac activity (depending on the gestational age), and (4) an absent or diminished myometrial layer between the bladder and the sac (Figure 1).

Procedure

UAE with or without local MTX infusion before curettage was performed. A right transfemoral approach was used for artery access, and the uterine artery was selectively catheterized with a 5F Yashiro catheter (TERUMO, Tokyo, Japan) and embolized with gelfoam sponge particles (1–2 mm in diameter), with or without 25 mg of MTX infused bilaterally into via each uterine artery for a total of 50 mg prior to the embolization procedure. Uterine artery angiogram was performed prior to and after UAE. Embolization was performed until the bilateral uterine arteries were occluded (Figure 2). Curettage was performed under the guidance of abdominal ultrasound 24–120 hours later by qualified doctors.

Treatment assessment and follow-up

The dynamic levels of serum β-human chorionic gonadotropin (β-hCG) were determined every 3 days until the level had decreased by > 50% from pretherapy levels, then weekly until levels returned to normal. Ultrasound was used to monitor the size of the gestational mass weekly until serum β-hCG had returned to normal levels, then monthly until the mass had disappeared. The outcomes of subsequent patient reproduction were recorded. Failure of the initial treatment was considered in the case of complications, such as significant vaginal bleeding (blood loss > 200 mL), when 7th day serum β-hCG continued to rise or decreased by ≤ 50%, or when the gestational mass became larger than pretherapy levels. In these cases, additional therapies were given. All patients were asked not to have intercourse until termination of the CSP was confirmed.

Data analysis

Mean ± standard deviation ($\overline{\chi} \pm S$) is presented for continuous and ordinal data, and categorical data are presented as the absolute count and percentage. The Chi-square test was used to compare categorical data. The two-sample t test was used to compare continuous and ordinal data. SPSS 19.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A p value < 0.05 was considered statistically significant.

Results

Fifty patients underwent UAE with or without local MTX infusion prior to curettage. This was successful in 42 cases (84%); eight cases required additional treatments with complications occurring in five cases; four of them were complicated with severe vaginal bleeding during curettage and were given hysterotomy. Postoperative pathologic examination of excised CSP specimens from these four patients showed clusters of trophoblast cells invading the myometrium. One patient's gelatin sponge separated from the uterine artery and embolized the right leg after UAE. Therefore, this patient went to other hospitals in Shanghai, China for a second UAE upon request. In the remaining three cases, treatments were considered a failure: In the first case, the patient was given an additional intra-amniotic MTX injection (50 mg) and later a second D&C. In the second case, the patient underwent systemic MTX treatment (50 mg/m^2) and later another D&C. In the third case, the patient underwent hysterotomy after extensive counseling.

Among the 50 patients, 22 patients were offered UAE combined with local MTX infusion prior to curettage (UAE + MTX group), and 28 patients received UAE only prior to curettage (UAE group). The clinical characteristics and findings of the two groups are presented in Table 1.

There was no significant difference in the serum β-HCG levels, gestational age, diameter of the sac, or myometrium thickness between the two groups. In the UAE + MTX group, 77.3% cases were successfully treated, representing a lower success rate than in the

Figure 1. Transvaginal ultrasound image of a cesarean scar pregnancy at 7 postmenstrual weeks. (A) Empty uterine cavity with gestational sac between cavity and cervix. (B) Triangular shape of the sac; the embryonic pole and fetal cardiac activity are visible (arrow). (C) Gestational sac embedded in the scar; thin (3 mm) myometrium (arrow) between the sac and bladder.

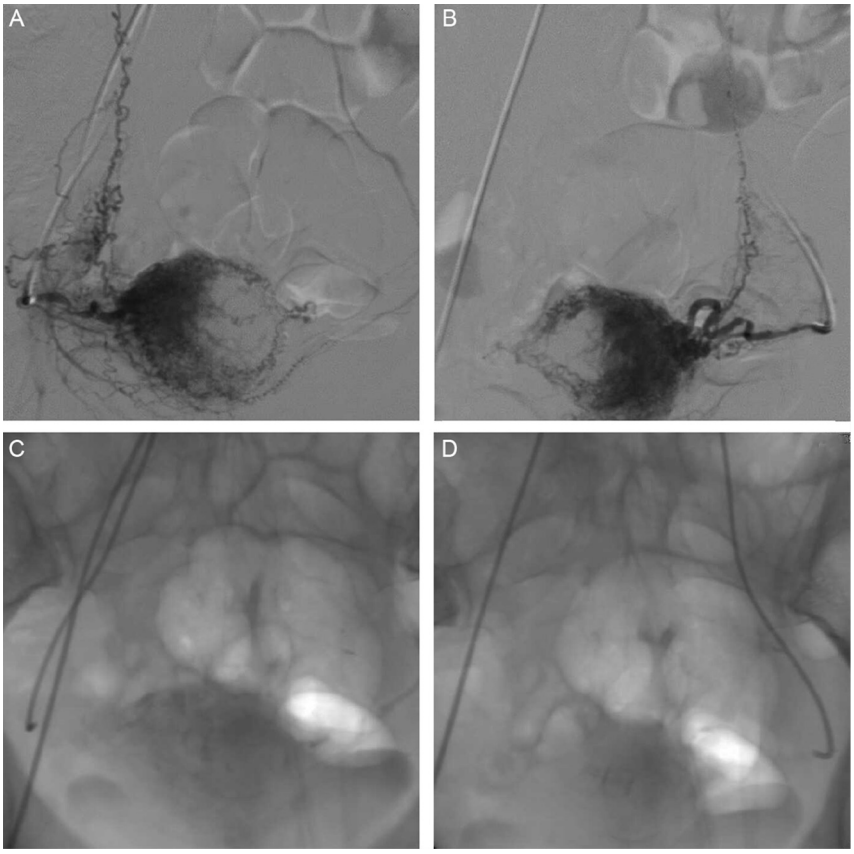

Figure 2. (A, B) Uterine artery angiography prior to uterine artery embolization (UAE). (C, D) Arterial embolization was confirmed after UAE.

UAE group (89.3%). The rate of complication in the UAE + MTX group was higher than in the UAE group (18.2% vs. 3.6%). The time of recovery in the UAE + MTX group was shorter than that in the UAE group, whereas hospitalization costs were higher in the UAE + MTX group than in the UAE group. However, these differences were not statistically significant ($p > 0.05$). The amount of bleeding in the UAE + MTX group was significantly higher than in the UAE group. This might be accounted for by the four cases that suffered from excessive vaginal hemorrhage in the UAE + MTX group.

During the long-term follow-up, we lost contact with four patients. In the remaining 46 women, the average time of recovery was 35.49 ± 15.60 days, whereas the recovery of menstruation was 20–45 days. Most patients who underwent therapy indicated that they no longer wished to conceive. Four cases did conceive again and underwent artificial abortion. One patient developed an ectopic pregnancy and received laparoscopic ipsilateral salpingectomy. There were no cases of CSP recurrence.

Discussion

UAE prior to curettage is currently accepted as an effective treatment for CSP, and it is also usually used to control acute bleeding [12,13]. UAE has a number of advantages [14–16]. First, it blocks the blood supply of the gestational sac, which causes embryo ischemia, hypoxia, and finally atrophy and necrosis, and at the same time reduces the risk of bleeding during curettage. Second, in the case of excessive bleeding, UAE can accurately detect and embolize the pelvic arteries to stop bleeding. Third, as an embolic agent, gelatin sponge can embolize arteries effectively, while at the same

Table 1
Clinical characteristics and findings of women with CSP treated with UAE with or without MTX prior to curettage.

Characteristic	UAE + MTX[a] group	UAE[b] group	*p*
No. of cases	22	28	—
Serum β-hCG (U/L)	45,710.14 ± 58,538.86	38,347.06 ± 42,500.99	0.663
Gestational age (d)	59.86 ± 17.67	54.33 ± 17.51	0.279
Diameter of the sac (mm)	28.56 ± 16.99	27.73 ± 12.30	0.88
Thickness of myometrium (mm)	3.22 ± 1.57	2.35 ± 1.48	0.166
Success rate (%)	77.3 (17/22)	89.3 (25/28)	0.223
Complication rate (%)	18.2 (4/22)	3.6 (1/28)	0.109
Hospitalization cost (yuan)	8582.13 ± 3101.72	7212.98 ± 1918.13	0.061
Time of recovery (d)	31.18 ± 14.80	39.00 ± 15.62	0.081
Amount of bleeding (mL)	80.25 ± 113.92	32.04 ± 21.41	0.036

β-hCG = β-human chorionic gonadotropin; CSP = cesarean scar pregnancy; MTX = methotrexate; UAE = uterine artery embolization.
[a] UAE with local MTX infusion prior to curettage.
[b] UAE alone prior to curettage.

Table 2
Published reports of cesarean scar pregnancy treated with UAE grouped by initial treatment strategy.

Reference	Period of case collection	No. of cases	Initial treatment modalities used[a]	Additional treatment needed	Hysterectomy or supracervical hysterectomy performed
UAE + MTX					
Wu et al [17]	2009–2012	6	UAE + MTX + Intramuscular MTX ($n = 2$); UAE + MTX + Intramuscular MTX to D&C ($n = 4$)	0	0
An et al [18]	2010–2012	23	UAE + MTX	7	4
Wang et al [19]	2007–2012	128	UAE + MTX to D&C	15	5
Lan et al [12]	2004–2010	79	UAE + MTX to D&C	0	0
Le et al [20]	2008–2012	10	UAE + MTX to D&C	0	0
Zhang et al [16]	2009–2012	11	UAE + MTX to D&C	1	0
Shen et al [21]	2008–2010	46	UAE + MTX to suction curettage ($n = 36$); UAE + MTX ($n = 10$)	1	1
Wu et al [22]	2000–2010	22	UAE + MTX ($n = 6$); UAE + MTX to D&C ($n = 16$)	0	0
Yin et al [23]	2002–2008	13	UAE + MTX to vacuum aspiration	1	0
Li et al [24]	2002–2009	31	UAE + MTX to D&C	5	0
Shao et al [25]	2003–2010	32	UAE + MTX to D&C ($n = 26$); UAE + MTX ($n = 6$)	2	0
Liang and He [26]	2005–2009	42	UAE + MTX to D&C	0	0
Zhang et al [27]	2005–2008	60	UAE + MTX to D&C	0	0
Yang et al [28]	2003–2008	38	UAE + MTX ($n = 14$); UAE + MTX to D&C ($n = 24$)	4	0
Yin et al [29]	2003–2008	30	UAE + MTX to D&C ($n = 13$)	0	0
Present study	2009–2013	50	UAE + MTX to D&C ($n = 22$)	5	0
UAE					
Cao et al [30]	2007–2012	54	UAE to D&C ($n = 52$); UAE ($n = 2$)	0	0
Wu et al [31]	2012	1	UAE + intramuscular MTX	1	1
Kochhar et al [32]	2012	1	UAE + intramuscular MTX	0	0
Yu et al [33]	2003–2011	56	UAE to D&C	2	0
Li et al [34]	2004–2010	12	UAE to endoscopy	0	0
Sadeghi et al [35]	2007–2008	1	UAE + systemic MTX	1	1
Yin et al [29]	2003–2008	30	UAE to D&C ($n = 17$);	0	0
Zhuang and Huang [36]	2003–2007	37	UAE to D&C	3	0
Hois et al [37]	2006	1	UAE + intramuscular MTX	0	0
Yan [38]	2006	1	UAE + intra-amniotic MTX	0	0
Sugawara et al [39]	2005	3	UAE + intra-amniotic MTX	3	0
Chou et al [40]	2003	1	UAE	0	0
Yang and Jeng [41]	2003	1	UAE + laparotomy	0	0
Ghezzi et al [42]	2001	1	UAE + Systemic MTX + intra-amniotic KCl	0	0
Marcus et al [43]	1999	1	UAE + systemic MTX	1	1
Present study	2009–2013	50	UAE to D&C ($n = 28$)	3	0

D&C = dilatation and curettage; MTX = methotrexate; KCl = potassium chloride; UAE = uterine artery embolization.
[a] "to" indicates subsequent inventions; "+" indicates concurrent interventions.

time it can be absorbed naturally 14–21 days later, so that the blood flow of the uterus can recover and uterine function is not affected. To better compare the value of UAE with or without MTX in the treatment of CSP, we performed a brief review of the published literature from 1995 to 2014 via the MEDLINE/PubMed database, searching the terms "cesarean scar pregnancy" and "uterine artery embolization/embolism." To identify additional articles and case reports, the secondary references of these publications were also reviewed. We identified 44 articles, 29 of which involved UAE in the treatment of CSP and were included, as shown in Table 2 [12,16–43].

A total of 792 cases were identified and analyzed based on their initial management and outcome (Table 3). Among the 792 cases, only 55 cases (6.94%) required additional treatment(s), and the uterus was preserved in 779 patients (98.36%). Overall, according to these findings, UAE might be an effective and safe treatment for CSP.

MTX has been used widely as a first-line conservative drug in the treatment of tubal pregnancy. UAE combined with local MTX infusion has been used extensively in recent years, and it has been suggested that the effects of MTX are synergistic to UAE [17,25,30,35–37,39]. However, in our review of the current literature, although UAE + MTX was used in 576 patients, and UAE alone was used in 216 patients in the treatment of CSP, there were no significant differences in the occurrence of additional treatment or hysterectomy between the two groups. Therefore, we propose that the addition of MTX does not improve the therapeutic outcomes of UAE; in fact, it may actually increase the risk for complications related to bleeding.

In conclusion, based on the present results and a review of the literature, UAE with or without local MTX infusion prior to curettage might be an effective treatment for CSP. UAE can be used to block the blood supply to the uterus to reduce the risk of bleeding during curettage. Compared with UAE alone, UAE with local MTX

Table 3
Outcome of all reported cases of cesarean scar pregnancy.

Initial treatment	Total no. of cases	Additional treatment needed, *n* (%)	Hysterectomy or supracervical hysterectomy performed, *n* (%)
UAE + MTX	576	41 (7.12)	10 (1.74)
UAE	216	14 (6.48)*	3 (1.39)*
Total	792	55 (6.94)	13 (1.64)

* $p > 0.05$, compared to UAE + MTX.
MTX = methotrexate; UAE = uterine artery embolization.

infusion shows no enhanced therapeutic effect, which does not support the use of MTX in the treatment of CSP. However, this study has its limitations. First, it is a retrospective study with a small sample population, which reduces the overall robustness of this approach. Second, this study does not assess the potential effect of MTX dose or specific patient characteristics on the overall outcome. In addition, our study did not take into account the number of deep implantations, or the viability of the fetus inside the sac prior to therapy, which can affect the treatment of CSP and increase the risk of complication or the failure to resolve the condition. A larger random control study is therefore warranted in a larger patient population affected by CSP.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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