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Ultrasound-guided local methotrexate treatment for cesarean scar pregnancy in the first trimester: 12 years of single-center experience in China

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ABSTRACT

Objective: To investigate the efficacy and safety of ultrasound-guided local injection of methotrexate (MTX) in the treatment of cesarean scar pregnancy (CSP) diagnosed in the first trimester.
Study design: The clinical and imaging data of 101 CSP patients who received ultrasound-guided local injection of MTX in our hospital between January 2007 and December 2018 were retrospectively analyzed. The decline in serum β human chorionic gonadotropin (βHCG) level, size and blood flow of lesions, vaginal bleeding, liver/kidney functions, and other indicators were observed or tested after treatment on a weekly basis.
Results: The duration of amenorrhea was 6.1 ± 0.8 weeks (range: 5.7–8.1 weeks) and the initial serum βHCG level was 20,321 ± 965 U/L in 97 patients, The mean time t to βHCG normalization was 40 ± 14 days (range: 21–140 days), Minor intermittent vaginal bleeding occurred after local MTX injection, lasting 25 ± 17 days (range: 10–61 days), and the lesions at the scar sites had completely disappeared with an average interval of 39 ± 29 days ; The treatment failed in four patients. The average duration of amenorrhea was 7.5 weeks and the average initial serum βHCG level was 91,359 U/L.
Conclusion: Ultrasound-guided local injection of MTX is an effective and minimally invasive treatment for CSP. However, it is not feasible for patients with long-term amenorrhea (>8 weeks) and markedly increased blood βHCG level.

Introduction

Cesarean scar pregnancy (CSP) is a special form of ectopic pregnancy resulting from the implantation of an embryo on a previous CS [1]. The incidence of CSP has been rising in China with the increasing rate of cesarean section and the implementation of the two-child policy [2]. When CSP occurs, the gestational sac is implanted at the site of a previous CS and grows into the deep muscular layer of the scar. The feeding blood vessels grow around the gestational sac, and the muscular layer becomes thin. If CSP found during the first trimester is not treated effectively, serious life-threatening complications such as placental implantation, uterine rupture, and major bleeding may occur in the coming weeks [3,4]. Therefore, early diagnosis of CSP and reasonable and effective management are important. In the past, treatment of CSP included uterine artery embolization (UAE) followed by dilation and curettage (D&C), hysteroscopic and laparoscopic removal of the embryo, and excision of the pregnancy site; in critically ill cases with major bleeding, even the uterus needs to be excised. These surgical treatments are highly risky due to massive intraoperative blood loss and large trauma. [5]. The main medical treatment for scar pregnancy was intramuscular injection of methotrexate (MTX) combined with oral administration of embryocidal drugs, which had low success rates [6]. MTX is a folinic acid antagonist and has been used as a first-step therapy in the treatment of ectopic pregnancy for years. In 1987, Feichtinger reported for the first time that ultrasound-guided local injection of MTX successfully treated ectopic pregnancy [7], and later, some case reports described the application of this technique in treating CSP [8–11]. Local injection of MTX for CSP diagnosed in the first trimester is minimally invasive and less painful as it is surrounded by fibrous scar tissue rather than the normal myometrium, leading to blockage of the uterus circulation and accumulation of MTX inside the intragestational sac [10]. In poorly indicated patients, however, this treatment is less effective and may cause more pain, even requires hysteroscopy and/or laparotomy [10]. Due to

Abbreviations: CSP, Cesarean scar pregnancy; MTX, methotrexate.

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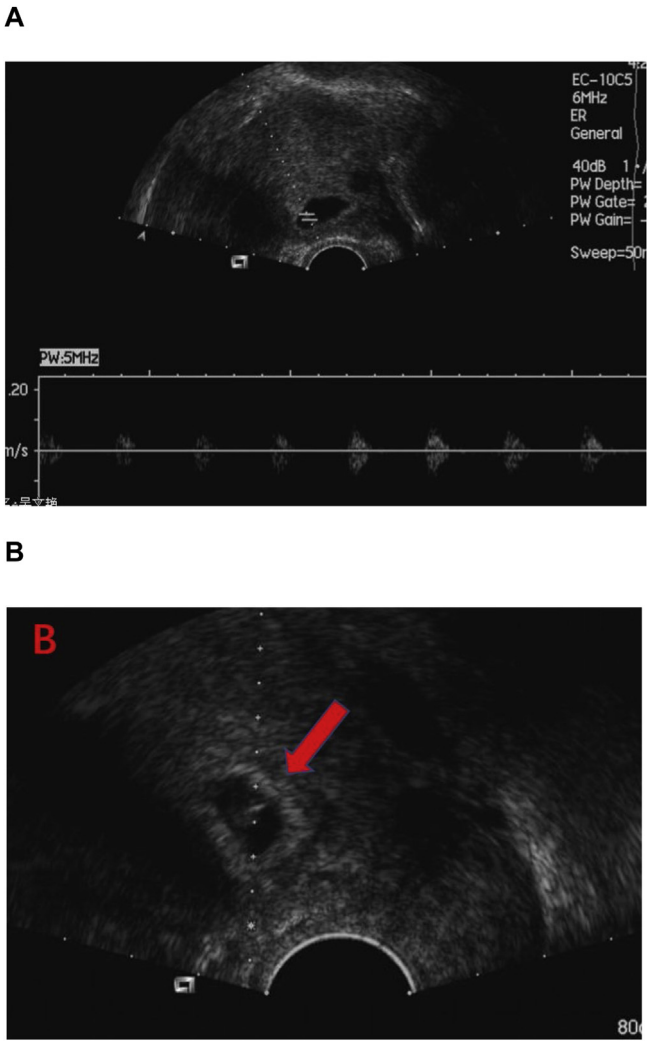

Fig. 1. A 35-year-old patient, 3 years after cesarean section. She had been amenorrheic for 6 weeks, with a blood βhcg level of 15,915 U/L. (A) A gestational sac was found by ultrasound. Embryo and fetal heartbeats were noted in the gestational sac; (B) puncture needle entered the gestational sac under the guidance of ultrasound, 0.8 ml amniotic fluid was drained, methotrexate (75 mg) was dissolved in 1.5 ml water for injection.

inconsistency regarding the dose, site and timing of MTX administration or concomitant interventions, the selected patients who were managed solely with local MTX administration as a first-line treatment were limited in number.

In this study, we retrospectively analyzed the clinical data of 101 patients who underwent ultrasound-guided local injection of MTX for treatment of CSP over the past 12 years. The clinical efficacy and safety of the treatment were analyzed based on the changes in clinical manifestations and symptoms after treatment.

Materials and methods

Clinical data

The clinical and imaging data of 101 CSP patients who received ultrasound-guided local injection of MTX in our hospital between January 2007 and December 2018 were retrospectively analyzed. The disease condition was stable, without major vaginal bleeding. All the patients voluntarily underwent ultrasound-guided local injection of MTX and gave signed informed consent. Before treatment, patients were informed of the risk of spontaneous hemorrhage due to CSP. The mean age of these patients was 31.1 ± 4.1 years (range: 22–45 years). Ninety-two patients had one prior cesarean section, and the others had two. The average time interval between current CSP and previous cesarean section was 3.5 ± 1.3 years (range: 1–10 years). The duration of amenorrhea was 42.6 ± 6.3 days (range: 40–59 days). The ultrasound images of CSP showed masses in 11 cases (type 2, with the mass within the scar after curettage for CSP) and gestational sacs in 90 cases (type 1, with the gestational sac embedded in the myometrium of the previous cesarean scar). The average diameter of these masses was 1.7 ± 0.9 cm (range: 1.0–3.1 cm) and the average diameter of the gestational sacs was 2.5 ± 1.7 cm (range: 0.9–4.5 cm). In patients with gestational sacs, embryo and fetal heartbeats were noted. The average length of embryos was (0.4 ± 0.2) cm (range: 0.3–1.4 cm). During surgery, 1.1 ± 0.7 ml (range: 0.2–10 ml) of amniotic fluid was drained from the gestational sacs. The β human chorionic gonadotropin (βHCG) level in patients with gestational sacs was 21,523 ± 976 U/L (range: 1700 – 184,013 U/L); in contrast, the βHCG level in patients with masses was low after curettage and before puncture (mean: 93 ± 27 U/L (range: 15–321 U/L).

Ethical approval

This study was approved by the Ethics Committee of the PLA General Hospital, and written informed consent was obtained from all patients.

Instruments and equipment

For the purpose of the ultrasound-guided interventional therapy, we used color Doppler ultrasound diagnostic instruments

Table 1
Characteristics of the four failed CSP patients and 97 successful CSP patients after local MTX treatment.

Characteristics		Failed cases (n = 4)				Successful cases (n = 97)
		Case 1	Case 2	Case 3	Case 4	
Age(year)		25	33	37	40	31.0 ± 4.1
Time since the last cesarean (year)		2	3	5	10	3.4 ± 1.2
Symptoms before MTX treatment	Vaginal bleeding	+	+	+	+	+
	Abdominal-pelvic pain	+	+	+	+	+ (21/97)
Initial serum βHCG (U/L) before MTX treatment		37,969	44,687	98,768	184,013	20,321 ± 965
Sonographic findings	Gestational age (week)	7.0	7.2	7.5	8.3	6.1 ± 0.8
	Fetal cardiac activity	+	+	+	+	+ (30/97)
Time interval of massive hemorrhage after MTX treatment (days)		5	9	10	20	N/A
The duration of intermittent vaginal bleeding after MTX treatment (days)		N/A	N/A	N/A	N/A	25 ± 17
Serum βHCG (U/L) after MTX treatment		26,763	38,265	43,632	27,423	N/A
Time to βHCG normalization (days)		N/A	N/A	N/A	N/A	40 ± 14
Outcome		UAE + D&C	UAE + D&C	UAE + second local MTX injection	UAE + hysterectomy	cured

CSP: Caesarean section, βHCG: beta-human chorionic gonadotropin, UAE: uterine artery embolization, D&C: dilation and curettage, N/A: Not applicable.`

including Sequera512 and Esaote MyLab90, for intracavitary or abdominal wall ultrasound procedures equipped with corresponding guiding stents. A 21-gauge PTC needle was used for puncture.

Pre-treatment examination

Before treatment, venous blood was tested for βHCG level, complete blood cell count, liver/kidney functions, coagulation function, and serum infection test. Color Doppler ultrasonography was performed to assess the location, size, and blood flow of lesions, blood supply around the lesion, and thickness of the muscular wall at the scar, and to select the appropriate needling path.

Therapeutic method

The patient was asked to empty the bladder before treatment. MTX (50 or 75 mg) was dissolved in 1–2 ml water for injection. For women with a gestational sac, a 21 G PTC needle was used to puncture the sac, and after sufficient amniotic fluid draining, MTX was injected (Fig. 1). In women with masses, MTX was directly injected into the lesion region with the most abundant blood flow, and multiple injections were administered to blood-rich lesions. Oral mifepristone (25 mg) was initiated at day 2 for 3 consecutive days.

Therapeutic evaluation

Complete recovery was defined when the level of serum βHCG decreased to normal, and the lesion and local nourishing blood vessels completely disappeared. Liver/kidney functions and complete blood cell count were routinely tested to establish the toxicity of MTX therapy.

Statistical analysis

The statistical analysis was performed using SPSS version 19.0 software. The measurement data were normally distributed and expressed as mean ± standard deviation and compared using a *t* test. $P < 0.05$ was considered significantly different.

Results

Local injection of MTX into the CSP lesions was completed in the outpatient ultrasound intervention room in all 101 patients. The patients were observed for 1 h after treatment and then safely discharged to the ward or home. After treatment, blood βHCG level was detected weekly to observe its dynamic changes until it returned to normal. Ultrasound scan was performed 1–2 weeks after treatment to observe the lesion size and the change in peripheral nourishing blood flow.

Finally, 97 patients were cured and four failed treatment (Table 1). Four patients (4.0%) with normal fertility desire became pregnant and delivered their babies after treatment. The intervals from the last CSP were 1, 2, 2.5 and 3 years. The duration of amenorrhea in 97 patients with local MTX success was 6.1 ± 0.8 weeks (range: 5.7–8.1 weeks).

Hemorrhage

Follow-up observations were carried out. A small amount of intermittent vaginal bleeding was observed in all the 97 patients who were cured after local MTX injection, with a duration of 25 ± 17 days (range: 10–61 days). The medical treatment failed in four patients with gestational sacs, in whom massive hemorrhage occurred at different times after treatment, which was treated by UAE. Two of these patients were cured after D&C following embolization; one was cured by a second session of ultrasound-guided local MTX injection following embolization; and one underwent hysterectomy. The duration of amenorrhea exceeded 7 weeks in all four patients (mean: 7.5 weeks), who had a mean

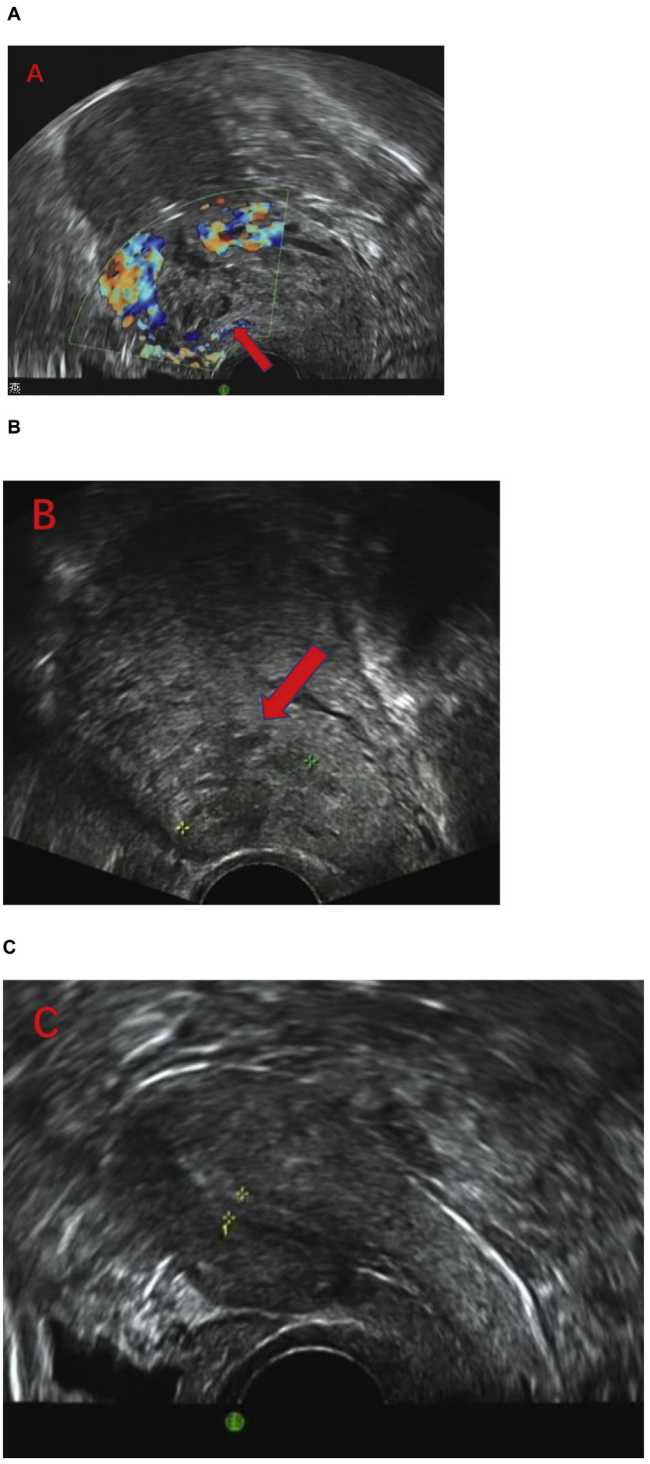

Fig. 2. A 38-year-old patient, 2 years after cesarean section. She had been amenorrheic for 5 weeks, with a blood βHCG level of 578 U/L, Ultrasound showed mass scar pregnancy after complete curettage of uterine cavity. (A) A mass was found by ultrasound, Methotrexate (50 mg) was dissolved in 1.0 ml water and injected into the lesion site with rich blood supply; (B) the mass size markedly decreased 3 weeks after treatment; and (C) the mass at the scar region disappeared 4 weeks after treatment.

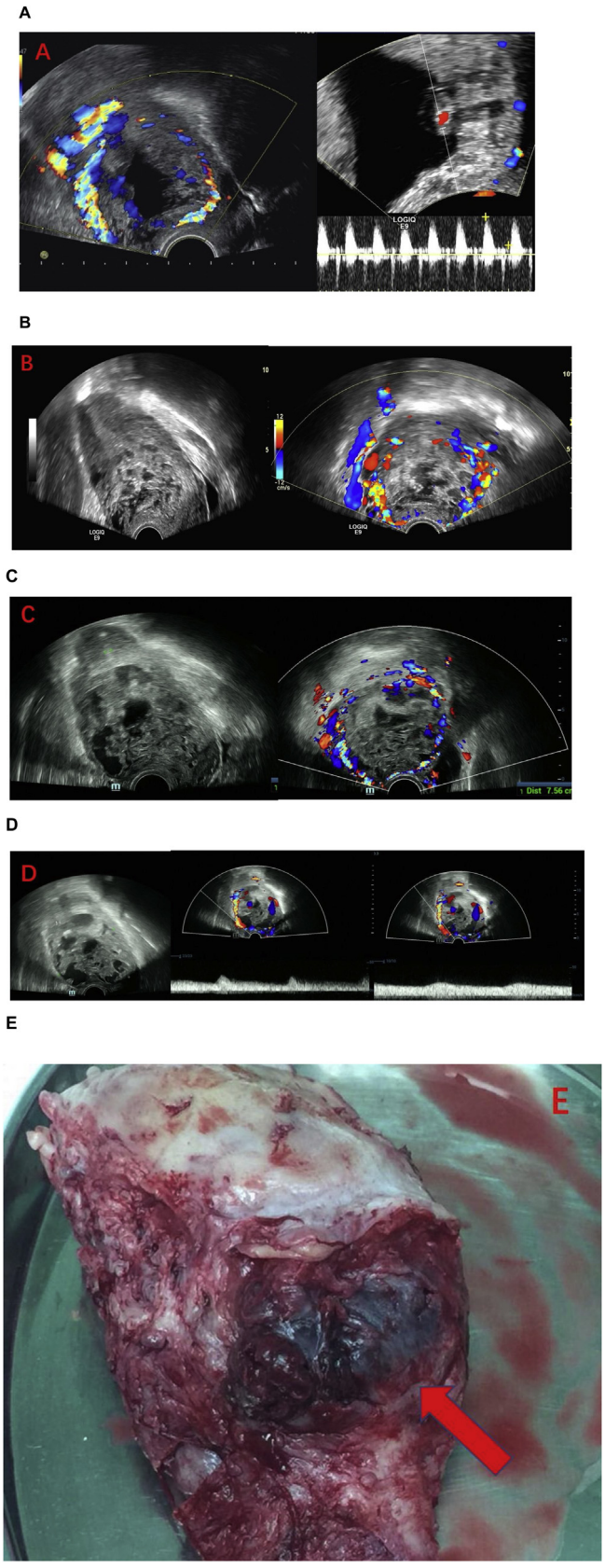

Fig. 3. A 41-year-old patient, 10 years after cesarean section. She had been amenorrheic for 7 weeks, with a blood βHCG level of 184,013 U/L. A gestational sac was found by ultrasound, with rich surrounding blood flow signals. (A) Embryo and fetal heartbeats were noted in the gestational sac; (B) the lesion became a mass 1 week after treatment; the change in size was not obvious; the surrounding blood flow signals were rich; and blood βHCG level dropped to 154,922 U/L; (C) 2 weeks after treatment, the change in mass size was not obvious; the surrounding blood flow signals were rich; and blood βHCG level decreased to 96,493 U/L; (D) 3 weeks after treatment, the mass was not decreased in size; the surrounding blood flow signals remained rich (with arterial and venous blood flow signals available); and blood βHCG level decreased to 27,009 U/L; (E) at day 23, the patient underwent hysterectomy due to massive vaginal hemorrhage, and the gross findings of the specimen confirmed scar pregnancy.

βHCG level of 91,359 U/L before treatment, along with vaginal bleeding, embryo, and fetal heartbeat.

βHCG decline

In the above four treatment failure cases, blood βHCG levels were high before treatment: 37,969, 44,687, 98,768 and 184,013 U/L; after local MTX injection, the blood βHCG levels markedly decreased before UAE. The βHCG level in 97 cured patients was 20,321 ± 965 U/L before puncture. Among the remaining 86 patients with gestational sacs, the βHCG levels slightly increased in 30 patients 1 week after treatment, with an increase of 57–60,645 U/L (15,523 ± 679 U/L); further tests after week 2 showed that βHCG continued to decline to normal. In 10 patients with gestational sacs, βHCG decreased slowly and a small amount of continuous vaginal bleeding, A second vaginal ultrasound scan showed rich blood flow signals at the scar site. The second session of local MTX injection was performed 3–7 weeks after the first session; as a result, βHCG continued to decline to normal. In 11 patients with masses, the level of βHCG continued to decrease after local MTX injection, and the shortest time following initial MTX injection for βHCG normalization was 21 days. The mean time required for βHCG normalization was 40 ± 14 days (range: 21–140 days).

Lesion volumes

In four patients with gestational sacs who failed treatment, the lesion volumes showed no significant change and the blood flow signals were still rich. In another three inpatients with gestational sacs, the mean βHCG level was >50,000 U/L and the mean diameter of the gestational sacs was >3 cm before treatment. After treatment, a small amount of vaginal bleeding was observed. Ultrasound examination showed that the gestational sacs had been partially exfoliated. When the βHCG level was below 5000 U/L after local treatment with MTX, ultrasound-guided curettage was performed, as requested by the patients, to removal of the gestational sac. The intraoperative blood loss was 60–100 ml. The remaining patients did not receive any other treatment. Further ultrasound examination revealed that the lesions at the scar sites had completely disappeared (Fig. 2), with an average interval of 39 ± 29 days (range: 21–168 days).

Comment

It is generally believed [4,12] that cesarean section damages the endometrium and muscle layer, and poor scar healing leads to formation of tiny fissures or sinuses that communicate with the uterine cavity; the fertilized ovum can implant in the corresponding muscle layer and grow to form CSP. Curettage or medical abortion following a misdiagnosis of ordinary intrauterine pregnancy can cause major bleeding or even uterine rupture. Once a proper diagnosis is missed, however, the trophoblasts penetrate the muscular layer and even invade the bladder, causing perforation/rupture of the uterus, uncontrolled bleeding, hysterectomy, and even maternal death [13,14].Therefore, reasonable and effective clinical treatment of CSP in the first trimester is important. Bilateral uterine artery chemoembolization combined

with curettage is the common surgical procedure for CSP [15]. After embolization of bilateral uterine arteries with gelatin sponge particles, the blood flow in the lesion is rapidly blocked, which not only promotes ischemic necrosis of the lesion but also avoids massive bleeding during curettage, thus ensuring the safety of curettage. The inflammatory process of UAE eventually leads to the breakdown of the gelfoam within 1–3 weeks after embolization with subsequent vascular recanalization [16]. Compared with UAE, medical treatment is cheaper, less invasive, and easier to operate and requires no anesthesia and hospitalization. Therefore, it is more easily accepted by the patients. As a structural analogue of folic acid, MTX is an anti-cell metabolism drug that prevents DNA synthesis and inhibits trophoblastic cell division. It has been widely used in the conservative treatment of ectopic pregnancy [17]. Gilbert et al. reported that direct MTX injection into the gestational sac for nontubal ectopic pregnancy is safe and effective [18]. Peng et al. [19] reported that the cure rate achieved by local MTX injection and systemic MTX treatment in CSP patients was 69.2% and 67.3%, respectively, and they concluded that local treatment was more effective than systemic treatment. Compared with systemic medication, local injection of MTX avoids the hepatic first-pass effect and achieves high drug concentration in the lesion, which accelerates necrosis of the lesion; it also preserves the integrity of the uterus while killing the embryo, thereby preserving the fertility of the patients. Finally, local injection decreases drug-induced damage to liver and kidney function and reduces adverse reactions [20]. Mifepristone has an established role in termination of pregnancy during the early first, and the second trimesters [21]. Koch M et al. [22] reported a significantly longer duration of βHCG clearance in patients who received local MTX, which is inconsistent with our study, The possible reasons are: (1) the initial βHCG levels of their patients were higher than ours; and (2) the dose of MTX was lower than that used in our study.

Previous studies have suggested that ultrasound-guided local MTX treatment is feasible for patients with a mean βHCG < 5000 U/L [23]. In the current study, however, most patients with gestational sacs had a mean βHCG level >5000 U/L. After the treatment, only four patients with gestational sacs suffered from massive hemorrhage at different times, which was treated by UAE. The remaining patients only experienced a small amount of intermittent vaginal bleeding. Follow-up observation showed that the lesions gradually shrank and their peripheral blood flow decreased after treatment. No liver/kidney dysfunction, hematopoiesis, or other serious complication was observed in any of the treated patients. In patients with gestational sacs, the baseline βHCG level was high; as a result, the βHCG decline was slower and the recovery time was longer in these patients than in patients with masses. Among the 90 patients with gestational sacs, 10 had high preoperative blood βHCG level (51,432 ± 679 U/L); after treatment, follow-up of these 10 patients showed that blood βHCG level decreased slowly, lesion size did not change significantly, and duration of intermittent vaginal bleeding was long. A second session of local MTX injection was performed to accelerate removal of the lesion. This was consistent with a study in which three consecutive cycles of medication, at an interval of 1 week, were superior to a single cycle in treating a patient with local lesions containing a viable embryo or with high βHCG level [24]. Therefore, local injection of MTX for CSP is not only feasible for patients with βHCG levels <5000 U/L but also a safe and effective treatment for patients with mean βHCG levels >5000 U/L.

In 30 patients with gestational sacs, blood βHCG levels increased 1 week after local MTX injection. However, blood βHCG levels dramatically decreased 2 weeks later. The possible explanations are: (1) blood βHCG level was measured 3–5 days before treatment and could not reflect the actual blood βHCG level immediately before treatment; and (2) it takes time for MTX to exert its effect. The trophoblasts are still proliferating and secreting hormones before such effects are exerted. Therefore, the elevation of blood βHCG level is not a problem as long as it can be effectively decreased in the second week after treatment, although close observation and follow-up is required.

After local MTX injection, most CSP patients have a small amount of vaginal bleeding before the lesion is completely cured, which may be related to the symptoms of incomplete abortion caused by embryonic tissue death. In the current series, four patients suffered from massive vaginal bleeding 5–20 days after local injection of MTX. These patients had the following common features: long duration of amenorrhea (mean: 7.5 weeks); presence of gestational sacs; embryo and fetal heartbeats in the gestational sacs before treatment; high blood βHCG level (mean: 91,359 U/L) before treatment; and vaginal bleeding before treatment. All four of these patients underwent UAE after massive hemorrhage. Two patients were cured after D&C following embolization; one was cured by a second session of ultrasound-guided local MTX injection following embolization; and one underwent hysterectomy due to continuous bleeding after D&C following embolization (the patient with preoperative βHCG level 184,013 U/L). This older patient was pregnant with her second child. Initially she was unwilling to abandon her fetus. Later, due to the presence of continuous vaginal bleeding, she expressly wished to preserve her uterus by local MTX injection. After drug administration, the weekly follow-up visits showed her blood βHCG level decreased constantly and markedly. However, the lesion volume showed no significant change and the blood flow signals were still rich. At day 20, she underwent hysterectomy due to continuous massive vaginal bleeding despite arterial embolization and D&C (Fig. 3).

In 101 CSP patients, ultrasound-guided local injection of MTX was an effective and minimally invasive treatment for CSP. Treatment failure occurred in four patients with long-term duration of amenorrhea (8 weeks), history of massive vaginal bleeding, and high blood βHCG level before treatment. These data suggest that ultrasound-guided local injection of MTX should be contraindicated in such patients, for whom a multidisciplinary strategy including UAE is feasible.

In conclusion, Ultrasound-guided local injection of MTX is an effective and minimally invasive treatment for CSP in the first trimester. However, it is not feasible for patients with long-term amenorrhea (>8 weeks) and markedly increased blood βHCG level. For these patients, a multidisciplinary approach including UAE is more reasonable.

Founding

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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