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# Hysteroscopic removal of cesarean scar pregnancy after primary therapy with methotrexate: a case series

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**Summary**

*Purpose of Investigation*: To present the clinical outcome of cesarean scar pregnancies (CSP) managed by methotrexate (MTX) administration followed by hysteroscopy removal. *Materials and Methods*: A retrospective study was undertaken in eight consecutive patients admitted to the present Hospital with a diagnosis of CSP, based on ultrasound assessment. The patients underwent systemic (five patients) or local (three patients) MTX administration for pregnancy termination, followed by hysteroscopy removal. A 27Fr resectoscope was used for hysteroscopy surgery. *Results*: Mean gestational age was of 7.8 weeks and five patients showed a viable embryo. All pregnancies were terminated after MTX; since drug administration, hysteroscopy removal was carried-out after a mean time of 36.1 days. Hysteroscopy view found type 1 and type 2 CSP in one and six patients, respectively. In one patient hysteroscopy assessment demonstrated a cervical pregnancy instead of a type 1 CSP suspected by ultrasound. Mean operating time was of 20.8 minutes, no further intervention was needed, and neither complications were reported. The mean time of menses resumption was of 35.5 days. After the first menstrual period all patients showed β-hCG level in the non-pregnant range and empty uterine cavities. *Conclusions*: Termination of CSP by MTX, combined with its hysteroscopic removal, resulted to be safe and effective.

*Key words:* Cesarean scar pregnancy; Cervical pregnancy; Ectopic pregnancy; Hysteroscopy; Methotrexate.

## Introduction

Aberrant uterine placentation can occur within a scar of cervico-isthmic junction caused by a previous cesarean delivery. Firstly described in 1978, cesarean scar pregnancy (CSP) [1] is now classified as ectopic placental implantations, showing an incidence of 1:500 to 1:2000 in patients with history of CD [2, 3]. Vial *et al.* first described two varieties of CSP, the superficial (type 1) and the deep (type 2) type. The placental growth of type 1 progresses into the cervico-isthmic space and then into endometrial cavity, whereas in type 2 the placenta attaches and develops directly within a cesarean scar niche, growing towards the inner surface of the uterine serosa [4]. If untreated, CSP exposes the patient to obstetric complications such as uterine rupture and hemorrhage during the first months of pregnancy or to the development of a placenta previa/accreta near term [5-7]. The mainstay management aimed at sparing fertility and reducing maternal morbidity, is an early diagnosis of CSP and its termination [2, 8]. An early diagnosis can be achieved by ultrasounds, following established imaging criteria [8, 9], whereas no consensus on the best management for termination and removal of CSP is currently shared [3]. The surgical techniques described to conservatively remove a CSP include uterine dilatation and curettage (D&C) [10, 11], hysteroscopy [12, 13], vaginal [14], laparoscopy [15], and laparotomy [2] excisions. Medical therapy for CSP termination is based on systemic [2, 3], regional [16], and local [17] methotrexate (MTX) administration. In addition, in recent years, uterine arteries embolization (UAE) has been introduced to reduce the placental blood supply before CSP surgical removal [18]. Herein, the authors present their clinical experience in the management of CSPs observed throughout a six-year period. All patients underwent hysteroscopy removal after MTX administration.

## Materials and Methods

A retrospective observational study was conducted at the present Obstetric and Gynecology Department. Between January 2010 and December 2015, a consecutive series of eight patients were admitted with a diagnosis of CSP. Medical records, ultrasound images, and hysteroscopy video-records were collected and reviewed. In all patients the diagnosis was based on transvaginal ultrasound and color Doppler findings, following established criteria [8]. All patients underwent MTX administration delivered at 50 mg/m$^2$, either by intramuscular route in five ml saline or by local injection within the gestational sac, under transabdominal ultrasound or hysteroscopy guidance in two ml saline [19]. The serum level of beta-human chorionic gonadotropin (β-hCG) was measured before MTX administration. Thereafter, a weekly β-hCG assessment was planned. If the authors detected less than 25% decrease of the basal level of β-hCG two weeks after the first administration, a second 50 mg/m$^2$ systemic dose of MTX was administered [20]. When a steady decline of β-hCG resulted in at

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Table 1. — *Demographic, clinical, and operative findings of the eight patients suffering from CSPs are shown.*

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|---|---|---|---|---|---|---|---|---|
| Age (years) | 39 | 31 | 22 | 38 | 36 | 32 | 28 | 44 |
| Gravidity and parity | G2P2 | G1P1 | G1P1 | G3P2 | G2P2 | G4P3 | G3P1 | G5P4 |
| Previous CS | 2 | 1 | 1 | 2 | 1 | 3 | 1 | 1 |
| Gestational age (weeks) | 7 | 8 | 7 | 9 | 7 | 9 | 9 | 7 |
| Viable pregnancy | Yes | Yes | Yes | No | Yes | No | No | Yes |
| Sonographic findings | Type2 CSP | Type 2 CSP | Type 2 CSP | Type 2 CSP | Type 2 CSP | Type2 CSP | Type 1 CSP | Type1 CSP |
| Implantation at hysteroscopy view | Type2 CSP | Type 2 CSP | Type 2 CSP | Type 2 CSP | Type 2 CSP | Type 2 CSP | Type 1 CSP | CP |
| Primary therapy | Systemic MTX | US guided MTX | Systemic MTX | Systemic MTX | Hysteroscopy guided MTX | Systemic MTX | US guided MTX | Systemic MTX |
| β-hCG before MTX (IU/ml) | 21300 | 17300 | 15800 | 20000 | 18000 | 22000 | 12500 | 13000 |
| β-hCG before hysteroscopy (IU/ml) | 420 | 1200 | 70 | 133 | 500 | 39 | 1100 | 189 |
| Time elapsed from MTX and hysteroscopy (days) | 37 | 21 | 62 | 38 | 26 | 48 | 25 | 32 |
| Operating times (minutes) | 25 | 12 | 15 | 41 | 8 | 50 | 7 | 9 |
| Deficit of saline (ml) | 150 | 0 | 0 | 200 | 0 | 300 | 0 | 0 |
| First menstrual period (days) | 42 | 32 | 48 | 30 | 30 | 45 | 29 | 28 |

Legend: CS = cesarean section; D&C = dilatation and curettage; CSP = cesarean scar pregnancy; CP = cervical pregnancy; MTX = methotrexate; US = transabdominal ultrasound.

least two consecutive assessments showing serum levels' halving, a hysteroscopy removal of pregnancy was scheduled. In order to assess the embryonic demise of viable pregnancies and to estimate the evolution of CSP and placental blood supply following MTX administration, ultrasound assessment with qualitative color Doppler application was accomplished on a weekly basis. Before treatment, all patients signed an informed consent and an informative chart highlighting the risk of hemorrhage associated with their obstetrical conditions. All hysteroscopies were carried-out under conscious sedation, using a 27Fr resectoscope, armed with a 2.5-mm or four-mm bipolar loop set at 100 watt power. Saline solution was delivered as uterine distension medium at 60-80 mm/Hg working pressure, by an electronic irrigation-suction device. After the clearance of blood clots and tissue debris, the uterine fundus and tubal ostia endometrial landmarks were identified. Progressing outward with the hysteroscope, the topography of placental implantation and its anatomical relationships with the cesarean scar and cervico-isthmic uterine walls were carefully assessed. After entering the cleavage plane between the trophoblastic tissue of placental implantation site and the basal decidua, a separation was carried-out using the cold-loop. Cutting and coagulating currents were used (I) to slice bulky placental tissue or organized blood clots far from uterine walls and (II) to coagulate actively bleeding spiral or venous vessels encountered during placental separation, respectively. The estimation of intraoperative blood loss was based on determination of HGB levels measured before and three hours after surgery. At the discharge, all patients were requested to undergo clinical and sonographic assessment after the first menstrual period. At the same time, a β-hCG determination was obtained.

## Results

The clinical patients' characteristics are presented in Table 1. The mean age was 33.7 (range 22 to 44) years. The mean gestational age was 7.8 (range seven to nine) weeks. Viable embryos were found in five patients whereas no heart embryonic activity was found in three patients. Upon admission, three patients were asymptomatic whereas intermittent light vaginal bleeding was reported in five patients. Ultrasound gray-scale imaging suggested a diagnosis of CSP in all patients; in all of them color Doppler and spectral analysis showed high-flow and low-impedance vascular patterns around the gestational sac. In six patients the gestational sac was found growing within a cesarean scar niche, bulging ventrally toward the bladder base and thinning the uterine wall (type 2 CSP) (Figure 1A). In two patients the gestational sac overlapped caudally with the cesarean scar but showed a growth toward the endometrial cavity, without evidence of uterine wall thinning (type 1 CSP) (Figure 2A). Systemic MTX was administered in five patients and a repeated dose was required for three of them. In two patients local MTX was administered by ultrasound trans-abdominal guidance within the gestational sac and in one patient under hysteroscopy guidance within the subchorionic space of placental implantation site; in these three patients no additional MTX doses were required. In all pregnancies showing a viable embryo, heart activity disappeared after the first dose of MTX. No adverse event was recorded after MTX administration. The mean time elapsed from MTX and hysteroscopy removal was 36.1 days (range 21 to 62 days) and an intermittent light vaginal bleeding was the only complaint reported by all patients. At the ultrasound follow-up, all patients showed the persistence of the gestational sac or a cervico-isthmic mass indicating placenta and blood clots residuals. Power and color Doppler application showed a progressive decrease in the signal of peritrophoblastic blood flow in all patients (Figure 1B to 1D). Hysteroscopy imaging confirmed ultrasound findings

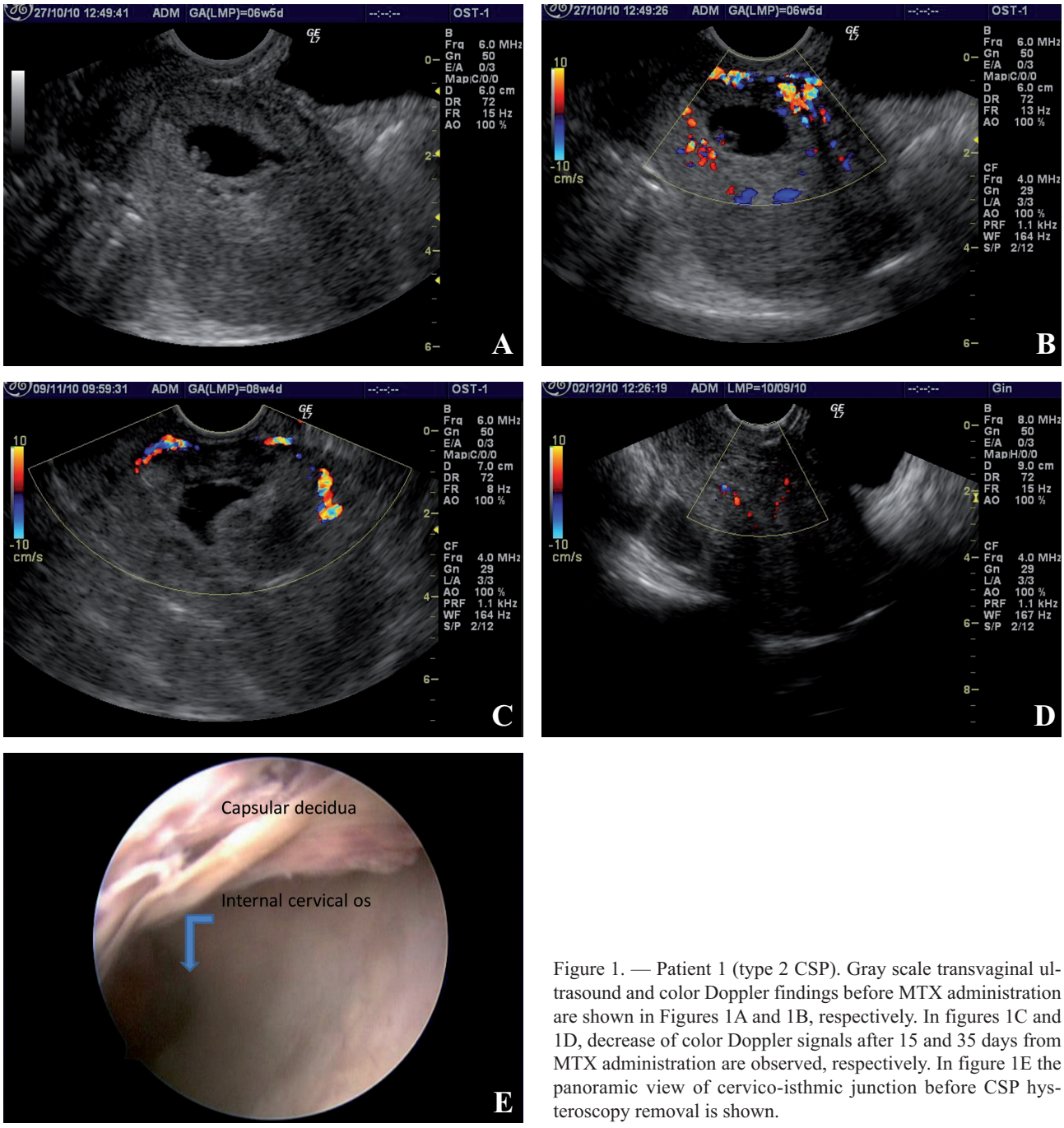


Figure 1. — Patient 1 (type 2 CSP). Gray scale transvaginal ultrasound and color Doppler findings before MTX administration are shown in Figures 1A and 1B, respectively. In figures 1C and 1D, decrease of color Doppler signals after 15 and 35 days from MTX administration are observed, respectively. In figure 1E the panoramic view of cervico-isthmic junction before CSP hysteroscopy removal is shown.

(Figures 1E and 2B); only in one patient, hysteroscopy found a posterior cervical wall placental implantation, mirroring the cesarean scar niche, instead of a type 1 CSP suspected by ultrasounds (Figure 3). Hysteroscopy removal of placental tissue resulted uneventful in all patients; a cleavage plane between villous tissue and basal decidua was generally maintained and easily developed by the cold-loop of resectoscope (Figure 4). During placenta separation, in few cases, focal adhesions of placenta to the underlying scar were found, showing thrombosed spiral vessels embedded in a firm fibrous tissue not cleavable by the cold loop (Figure 5). These areas of abnormally adherent placenta were cleared from adjacent separable tissues but were left in situ without attempting their electrosurgical resection. No patient had significant intraoperative blood loss and satisfactory hemostasis was obtained by minimal co-

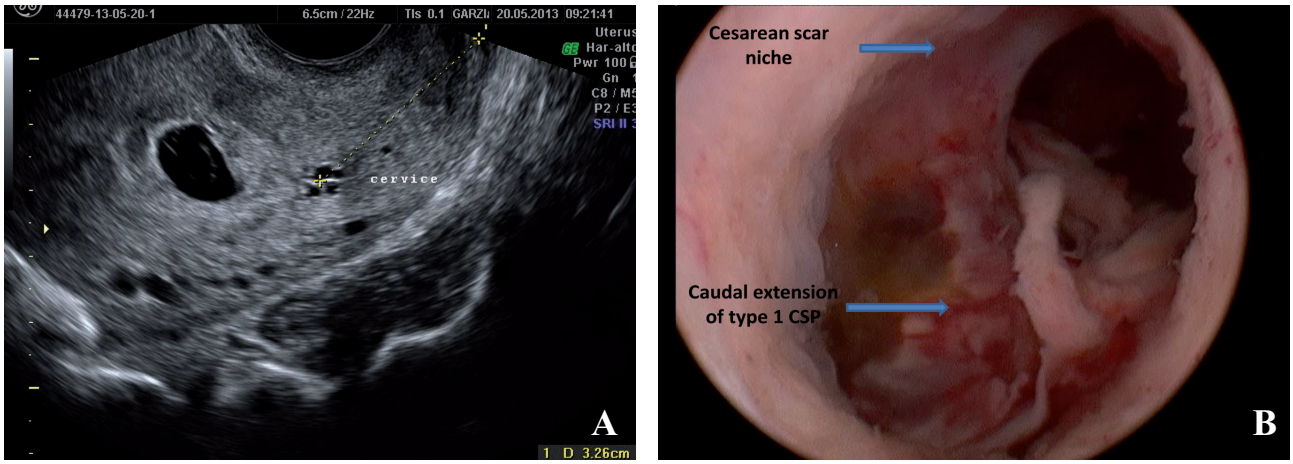


Figure 2. — Gray scale ultrasound (Figure 2A) and hysteroscopic findings (Figure 2B) of patient 7 are shown. Both ultrasound imaging and hysteroscopy show a placental implantation involving the cesarean scar, but a prevalent cranial placental growth towards isthmus and endometrial cavity is shown, consistent with a type 1 CSP.

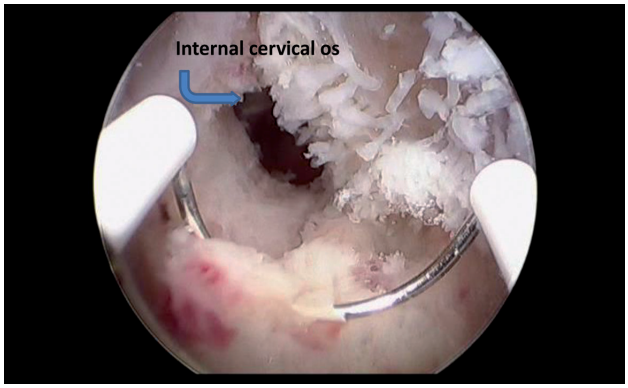


Figure 3. — Patient 8. Separation of hydropic trophoblastic villous tissue implanted in the posterior aspect of cervical wall is in progress.

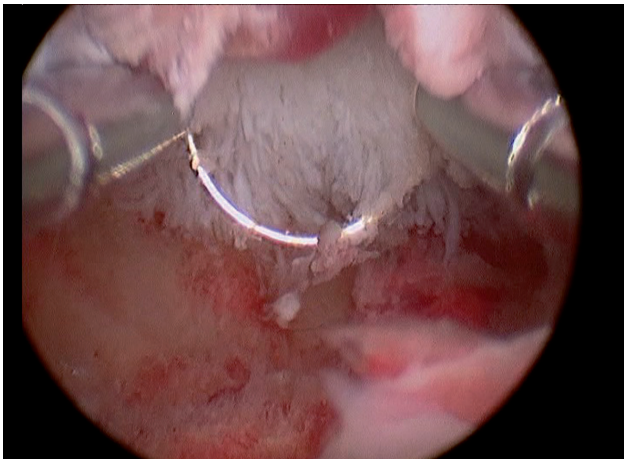

Figure 4. — Patient 5 (type 2 CSP). A cleavage plane between villous tissue and isthmic basal decidua is easily developed by the cold loop.

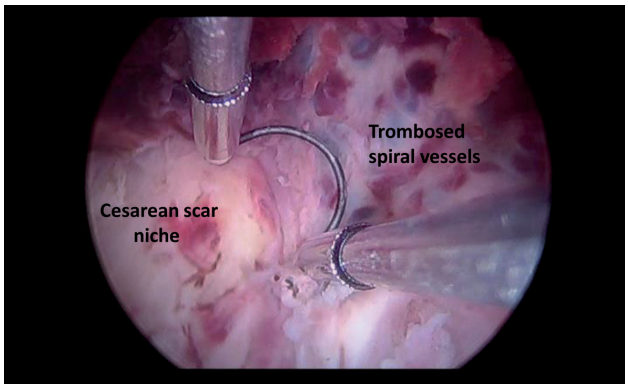


Figure 5. — Patient 6 (type 2 CSP). Clearance of placental tissue from the cesarean scar niche is in progress; a knot of thrombosed spiral vessels embedded within an adherent fibrous placental tissue, not cleavable bluntly from the underlying scarred uterine wall, is shown.

agulating needs. The mean operating time was 20.8 (range 7 to 50) minutes, the mean deficit of distending fluid was 81 (range 0 to 300) ml, and stable postoperative HGB levels were recorded with respect to preoperative findings. In all cases pathologic assessment found chorionic villi and embryonic tissues consistent with retained products of conception. Unremarkable postoperative recovery was reported and all patients were discharged within 48 hours from surgery. The first menses were resumed after a mean period of 35.5 (range 28 to 48) days after surgery. At that time, all patients showed β-hCG levels in the non-pregnant range and empty uterine cavities. No delayed complication was reported.

## Discussion

CSPs represent a clinical challenge, due to high risk of early or delayed obstetrics hemorrhage and lack of shared guidelines for their management [3]. Conservative therapy is based on surgical, interventional radiology, and pharmacologic measures, accomplished alone or combined [2, 3]. Primary surgery by D&C is generally discouraged, due to high complication-rate associated with such procedure [3, 10, 11], whereas more invasive surgical techniques as transvaginal, laparoscopic or laparotomic hysterotomies provided safer results [2, 14, 15]. MTX is a drug acting by a reversible inhibition of dihydrofolate reductase, a key enzyme in intracellular folate homoeostasis, essential in DNA and RNA precursors synthesis [21]. It has shown effectiveness in blocking trophoblast growth and it has been extensively used as primary therapy for CSP termination, either by systemic or local administration [2, 3, 5, 17]. Nevertheless, when used alone, systemic MTX therapy showed significant morbidity and slow pregnancy absorption [2, 3]. Local MTX administration under ultrasound guidance shows a better therapeutic index [5, 17], but even by this route, pregnancy absorption is often slow and failures as single therapy need additional treatments in 26%-39% of patients [17, 20]. The combined management of CSP resulted safer and more effective. The first measure is focused on pregnancy termination mainly obtained by MTX administration or by inducing an acute reduction of placental blood supply by UAE. Subsequently, an appropriate timing for pregnancy surgical removal is suggested [2, 16, 18, 22, 23]. Over the last two decades, hysteroscopy gained the role of reference technique to study the uterine cavity, replacing blind techniques for the diagnosis and treatment of all endometrial pathologies. In 2005, Wang *et al.* first described the hysteroscopy removal of CSP [24, 25]. Subsequently, the effectiveness of the technique in the CSP management was suggested in case series and case reports as primary therapy, in combined approaches after MTX administration, or after primary intervention failures [12, 13, 24-26]. A laparoscopy-assisted hysteroscopy removal was also suggested, as either single treatment [27] or following UAE [23]. Recently, in larger retrospective trials, resectoscopic removal was successfully experienced in 149 patients as primary therapy, after MTX pregnancy termination and after UAE [22, 23]. Based on the current literature, reporting until now about 250 patients suffering from CSP and treated by hysteroscopy, as unique or combined therapy, neither intraoperative complications were recorded nor further treatments were required. In the present experience, based on a consecutive series of patients, the effectiveness and safety of CSP hysteroscopy removal after MTX administration, was confirmed. Accordingly with color Doppler findings, showing a substantial decrease of peritrophoblastic blood flow after MTX, during hysteroscopy placental separation, no significant bleeding was found. In current literature, no hemorrhagic complications were reported even by primary hysteroscopy CSP removal [12, 24-26, 28]. Nevertheless, in a retrospective trial comparing patients managed by primary hysteroscopy and hysteroscopy accomplished after MTX or UAE, Li *et al.* reported that primary hysteroscopy led to the highest intraoperative blood losses [22]. In experienced hands, hysteroscopy allows the precise anatomy of placental implantation site, drives the selective removal of trophoblastic tissue, avoids perforative injuries to the scarred uterine wall, spares the health cervical and endometrial linings, and permits the accomplishment of a satisfactory hemostasis. Comparative trials between hysteroscopy and other surgical techniques suitable for CSP removal are currently not available. Only in one prospective trial, in a primary UAE-based management, Wu *et al.* found a significantly better clinical outcomes in patients undergoing hysteroscopy placental removal with respect to ultrasound-guided curettage [23]. With respect to other reliable surgical techniques such as laparotomic, laparoscopic or vaginal CSP excisions, hysteroscopy probably provides a better anatomical assessment of the placental implantation, a less invasive surgery, a shorter hospitalization, and lower medical costs.

## Conclusions

CSP termination with MTX followed by its hysteroscopy removal resulted in a safe and effective combined management when accomplished before nine weeks of pregnancy.

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