

Original Research

A Two-Step Hysteroscopic Management for Cesarean Scar Pregnancy: A Proposal Method

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Abstract

Background: Cesarean Scar Pregnancy (CSP) is a cause of severe maternal morbidity. Currently, no guideline for its management is shared. We assessed safety and effectiveness of Methotrexate (MTX) administration within the sub-chorionic space under hysteroscopic guidance, followed by resectoscopic placental removal. **Methods:** Five patients suffering from type 2 CSP underwent a sequential treatment based on hysteroscopic techniques. Pregnancy termination was firstly obtained by injection of 80 mg of MTX within the intervillous spaces of placental site. The intervention was performed in an office setting using a 16Fr hysteroscope. MTX was administered by a 17-gauge needle suitable for the operative channel of hysteroscope. Subsequently, based on the decline of Human Chorionic Gonadotropin β -subunit (β -HCG), we timed a placental removal using a 27-Fr resectoscope, under conscious sedation. **Results:** In all women a diagnosis of CSP was achieved between 6 and 8 gestational age weeks. Hysteroscopic MTX administration resulted easily, quickly, painlessly and uneventfully in all patients. A substantial decrease of β -HCG was obtained in all patients within 15 days from the MTX administration. After a mean time of 27 days from MTX a resectoscopic removal of CSP was carried-out without any recorded adverse outcome. After 30 days from surgery β -HCG returned to non-pregnant level and normal physical findings were found in all patients. **Conclusions:** Hysteroscopy-guided MTX sub-chorionic administration resulted safe and effective for CSP termination. It was followed by successful and uneventful resectoscopic placenta removal in all patients. When hysteroscopy facilities are available, this combined therapy can be an option to treat CSP.

Keywords: Cesarean Scar Pregnancy; hysteroscopy; ectopic pregnancy; Methotrexate

1. Introduction

Abnormal placental implantation can develop within the scar of cervico-isthmic uterine junction following a previous cesarean delivery. Cesarean Scar Pregnancy (CSP) is considered an ectopic pregnancy and it has been estimated that 1 out of 500 women carrying a cesarean scar can develop a CSP [1]. If untreated, CSP exposes the patient to life-threatening complications such as uterine rupture during the first months of pregnancy (type 2 CSP, showing placental growth toward the bladder and abdominal cavity) or the development of a placenta previa-accreta (type 1 CSP, showing placental growth from cervico-isthmic space to endometrial cavity) [2,3]. Early diagnosis and pregnancy termination represent the cornerstone of CSP management, aimed at sparing fertility and reducing maternal morbidity [4]. Established ultrasonographic criteria for an early diagnosis are available [2,5] but no consensus on the most cost-effective management of CSP is currently shared. More than 30 treatment regimens, based on medical therapy, high intensity ultrasound, intrauterine double balloon insertion, surgical removal, uterine artery embolization (UAE) alone or combined, have been proposed in the management of CSP [1,2,6,7]. The reversible inhibitor of dihydrofolate reductase (DHFR), Methotrexate (MTX), is

widely used as medical therapy for CSP termination, either by systemic or local administration [2,4,8]. Nevertheless, when used alone MTX shows significant morbidity and slow pregnancy absorption, frequently needing additional interventions [1,2,8,9]. Combined treatments, based on surgical removal of CSP following MTX administration or UAE showed an improvement of clinical outcomes [10,11]. More than 10 years ago, Wang *et al.* [12] firstly described a safe hysteroscopic management of CSP. Subsequently, the effectiveness of hysteroscopy to treat CSP was suggested both as primary therapy and following MTX administration or UAE [10,11,13,14]. Herein we propose a double-step technique based on hysteroscopically-driven subchorionic MTX administration followed by placental resectoscopic removal [15] and present the clinical outcome of a consecutive series of 5 patients suffering from type 2 CSP.

2. Materials and Methods

From January 2017 to January 2022 a consecutive series of 5 patients showing type 2 CSP were diagnosed in the first trimester of pregnancy at the Obstetrics and Gynecology Department of the Hospital of Lodi (Italy). All women underwent one or more previous cesarean deliver-



ies. The diagnosis of type 2 CSP was based on the following established transvaginal ultrasound criteria: (i) An empty endometrial cavity and an empty cervical canal. (ii) The gestational sac, containing an embryonic pole viable or not, was found deeply embedded within the uterine wall at the cervico-isthmic junction, bulging ventrally toward the bladder. (iii) A trans-vaginal eco Color-Doppler showing a high blood-flow with low impedance around the cervico-isthmic area [5]. Assuming that pregnancy termination was wished, we proposed local MTX administration to the patients, through office hysteroscopic guidance, followed by the resectoscopic removal of pregnancy. All patients signed a tailored consent and an informative chart displaying the potential hemorrhagic risks associated with the procedure. Pre-treatment serum level of β -HCG was obtained. All patients underwent sub-chorionic MTX administration in an outpatient clinic setting, without analgesia or anesthesia. By the vaginoscopic technique and saline as distending medium, we used a double-flow 5 mm operative hysteroscope to administer 80 mg of MTX melted in 2 cc of saline, through a 17-gauge needle suitable for the 5Fr operative channel (Figs. 1,2). Saline flow was delivered at working pressure set between 60 and 100 mm/Hg, by an electronic device. After the confirmation of pregnancy implantation within the uterine scar, we entered the coelomic space with a 5Fr hysteroscopic scissors, opening the capsular decidua and the chorionic membrane. MTX was then injected 2–3 mm deep into the chorionic membrane within the ventral implantation of the placenta into the intervillous spaces. The experienced pelvic discomfort was assessed by the submission of a 10-cm Visual Analog Scale (VAS) after the intervention. After a few hours of observation all women were discharged with a planned weekly clinical, sonographic and β -HCG serum level assessment. Resectoscopic removal of CSP was timed based on the drop in β -HCG showing at least a weekly halving, indicating the demise of trophoblastic viability. The removal of CSP was accomplished as inpatient procedure under conscious sedation using a 27Fr resectoscope with a 4 mm bipolar loop set at 100 W power. In some cases, due to the soft consistency of the cervix, we avoided cervical dilatation. Saline was used as distending medium at 80 mm/Hg initial working pressure but it was sometimes enhanced during intervention even to 120–130 mm/Hg, to optimize the visualization of surgical field. After the clearance of clots and tissue debris, the tubal ostia uterine landmarks were identified. By the outward progression of hysteroscope, the topography of placental implantation and its relationships with the cesarean scar niche and cervico-isthmic wall were assessed. After the development of a cleavage plane between the trophoblastic tissue and decidua, a separation was accomplished using the cold loop (Fig. 3). The use of cutting and coagulating currents was reserved to tissue slicing requirements or for bleeding control, respectively. All removed tissue specimens were sent for pathologic assess-

ment. At hospital discharge, we recommended to all the women a 30 days post-intervention reassessment of β -HCG and a physical examination with transvaginal sonography after the first menstrual period.

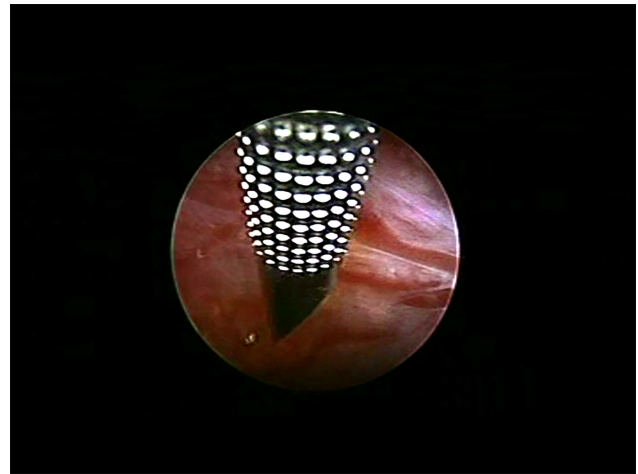


Fig. 1. The tip of the 17-gauge needle inserted in the operative channel of a 5-mm operative hysteroscope is shown within the coelomic space of a type 2 Cesarean Scar Pregnancy, before Methotrexate sub-chorionic administration.

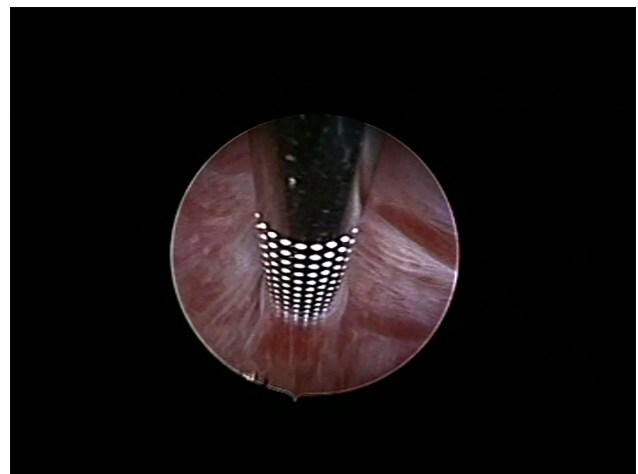


Fig. 2. Needle removal from sub-chorionic inter-villous placental space after Methotrexate administration.

3. Results

Clinical features of the 5 patients are summarized in Table 1. An early diagnosis of CSP, lasting from 6 to 8 weeks (mean gestational age 7.2 weeks), was carried-out in all women. Vaginal bleeding led to emergency obstetrics consultations in 3 patients whereas in 2 cases the diagnosis was suggested during the first obstetric office visit in asymptomatic women. A viable pregnancy at ultrasound

Table 1. Clinical features of 5 patients suffering from type 2 CSP who underwent Methotrexate sub-chorionic administration under hysteroscopy guidance.

Patients	Age	Obstetric history	Gestational age	Pregnancy viability	Symptoms	Basal β -HCG
1	28	2 CS	7 weeks	yes	none	55222
2	34	1 CS, 1 dilatation & curettage	8 weeks	yes	AUB	96000
3	42	2 CS	8 weeks	no	none	27000
4	36	1 CS, 1 Vaginal delivery	7 weeks	yes	AUB	18000
5	36	2 CS	6 weeks	no	AUB	12424

CS, Cesarean Section; AUB, Abnormal Uterine Bleeding.

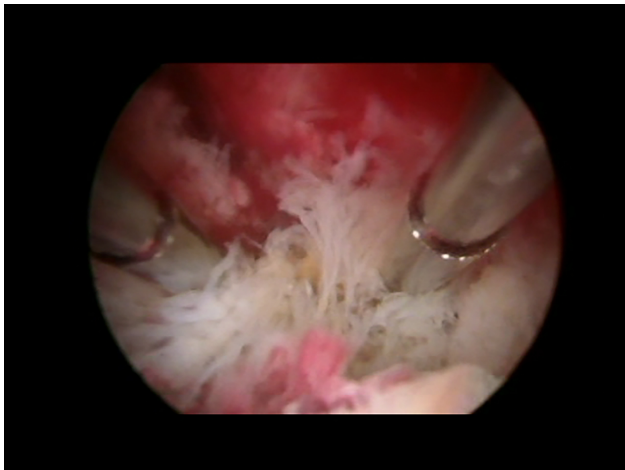


Fig. 3. Resectoscopic removal of CSP after hysteroscopic sub-chorionic administration of Methotrexate. The cleavage plane between the cervico-isthmus uterine niche (pinkish tissue) and villous trophoblast (blanching tissue) is developed by blunt loop separation.

was observed in 3 out of 5 patients. Hysteroscopy sub-chorionic administration of MTX was easily accomplished in all patients without any perioperative complication. The operating times were from 5 to 12 minutes (mean operating time of 8.4 minutes), the VAS score ranged from 1 cm to 3 cm (mean VAS score of 2.2 cm) and all patients were discharged after an uneventful 3–4 hours period of observation. During the weekly observational time, all patients recorded mild vaginal bleeding and in viable pregnancies the embryonic hearth activity disappeared within 7 days since MTX administration. In all cases, the sonography assessment found both the persistence of gestational sac and a progressive decrease in placental blood flow. As depicted in Fig. 4, a substantial drop of β -HCG serum level was observed within 14 days after MTX administration in all patients. Resectoscopic removal of CSP was planned between 23 and 40 days (mean time of 27 days) from MTX administration. In 3 patients a vaginoscopic uterine insertion of the 27Fr resectoscope resulted feasible while in 2 patients speculum vaginal insertion, cervical grasping and careful cervical dilatation were deemed necessary. The resectoscopic interventions for CSP removal lasted from 8 to 27 minutes (mean operating times 19.4 minutes). The

cutting current was mainly used to slice organized clots and bulky trophoblastic and decidua tissue within the gestational sac far from uterine walls to clear the surgical field, while a careful use of coagulating current was adopted to control bleedings from spiral and venous vessels encountered in the wall of uterine niche during trophoblastic separation. At the end of surgery, control of uterine cavity identified a cesarean scar niche that was free of trophoblastic tissue remnants without significant active bleeding in all patients. In no case was further intervention needed and the patients were discharged on the first postoperative day. In every case pathological report were consistent with villous trophoblastic tissue showing degenerative features such as necrosis and hydrops. The β -HCG serum level returned to the non-pregnant range at 30 days from intervention and normal physical examination as well as a normal transvaginal sonography were documented after the first menstrual period in all patients.

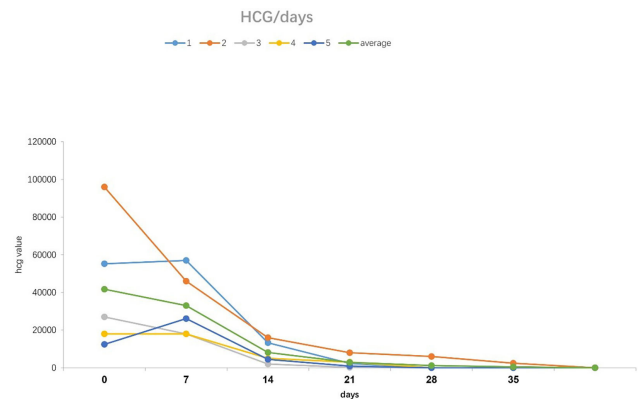


Fig. 4. The basal and weekly serum β -HCG assessment of 5 patients who underwent sub-chorionic Methotrexate administration is shown. The mean curve of β -HCG trend is shown as green line.

4. Discussion

An early diagnosis and an active management of CSP are recommended to preserve fertility and to prevent complications such as hemorrhage and uterine rupture [1,16]. Although no consensus is currently shared, single-step surgery such as vaginal, laparoscopic or laparotomic CSP

excision and combined treatments such as MTX administration or UAE followed by Dilatation and Curettage or hysteroscopy placental removal are suggested as the most effective treatment regimens [1,16,17]. MTX represents the drug most extensively adopted for conservative CSP treatment, either as single therapy or within therapeutic combined pathways [1,8,9,16,17]. The antiproliferative MTX toxicity is based on a reversible inhibition of DHFR, an enzyme playing a pivotal role in folate homeostasis that promotes the conversion of dihydrofolate to tetrahydrofolates. These latter are required to synthesize purine and pyrimidine rings, the precursors of DNA and RNA molecules. The reversibility of MTX binding to DHFR with respect to the natural dihydrofolate substrates, leads either drug concentration and time of cell exposure two relevant determinants of cytotoxicity [18]. The short half-life of MTX and the limited blood supply to scarred tissue around the CSP may justify the low effectiveness of systemic MTX administration [2,4,11,16,17]. Driving MTX administration directly within placental villous tissue may lead to greater concentration able to enhance the level of DHFR inhibition, potentially improving its therapeutic effectiveness. Ultrasound-guided MTX administration within the gestational sac of CSP has improved the clinical results with respect to systemic MTX, although in 26% to 39% of patient placental absorption takes a long time with frequent failures requiring further treatments [2,8,9,17]. The villous trophoblast of the ectopic implantation, leading to the placental differentiation within the scar niche, is the target tissue of MTX. The inhibition of placental growth represents the mainstay measure to reduce the risks of uterine wall rupture and hemorrhage. Miniaturized hysteroscopes enable an easy access within the gestational sac allowing a quite simple identification of the placental site implant [19]. Based on these assumptions we believed that the selective MTX administration under hysteroscopy vision in sub-chorionic space of placental implantation, may improve its cytotoxicity, enhancing the drug concentration within the intervillous spaces. In the consecutive series of patients presented here, the hysteroscopic approach enabled in all cases a clear CSP anatomy assessment, allowing MTX administration in the subchorionic villous spaces of the placental implantation within the uterine scar. With respect to hysteroscopy guidance, ultrasound techniques of intra-gestational sac MTX administration may be less selective in addressing drug administration, due to the possible difficulty in positioning the needle tip within the tissue target [2,9]. In experienced hands, hysteroscopy MTX administration can be accomplished as outpatient procedure and resulted as technically easy, quick, painless and safe. Its effectiveness in pregnancy termination was demonstrated by the early embryos demise, by the early increase of β -HCG (due to trophoblast cells necrosis) in some cases, followed by a quick and progressive decrease [9,20]. To the best of our knowledge, only two reports in current literature described hysteroscopy-guided embryocidal agent administration for the treatment of viable CSP.

In the first case report, after systemic MTX failure Di Spiezo Sardo A *et al.* [21] administered MTX in the gestational sac, obtaining the embryo's demise but observing an increase of β -HCG levels. In the second single case, Shao MJ *et al.* [22] injected 95% ethanol within the gestational sac under hysteroscopic guidance, resulting in a prompt fall in β -HCG serum level. Subsequently, uneventful bipolar resectoscopic and dilatation and curettage were used for CSP removal, respectively [21,22]. Wang *et al.* [12] firstly described the feasibility of CSP hysteroscopy treatment. The effectiveness and safety of hysteroscopy in the CSP management was later suggested in case series and case reports as a primary therapy method, as well as in combined approaches after MTX administration [2,10,13,14,16,23]. In larger retrospective studies, the hysteroscopic removal of CSP was found as safe and effective either as a primary therapy and following MTX or UAE pregnancy termination [10,24]. In the presented series, we confirmed the reliability and safety of hysteroscopic removal of CSP after MTX administration. According to color Doppler findings showing a decline of placental blood flow after MTX, during hysteroscopic separation of placenta, no significant bleeding was observed. In the available literature, no hemorrhagic complications were described even by primary hysteroscopic CSP removal [12–14]. However, in a retrospective study comparing patients treated with primary hysteroscopy and hysteroscopy accomplished after MTX or UAE, Li *et al.* [10] found that primary hysteroscopy led to higher blood loss, suggesting that postponing the placental removal after primary growth inhibition or de-vascularization may be safer. A careful hysteroscopic technique allows the precise anatomical assessment of placental implantation, drives the selective removal of trophoblastic tissue, avoids perforative injuries to the scarred uterine wall, spares the health cervical and endometrial linings and allows selective hemostasis. Until now, comparative trials between hysteroscopy and other surgical techniques used to treat CSP are not available. Isolated data are reported in a prospective study based on primary UAE management, demonstrating a better clinical outcome in patients undergoing hysteroscopic CSP removal with respect to ultrasound-guided curettage [24]. Compared with other major surgical techniques such as laparotomic, laparoscopic and vaginal CSP excisions, the hysteroscopic CSP removal provides a better assessment of the placental implantation, a less invasive surgical approach, shorter hospitalization times and lower medical costs. In this view a combined minimally invasive approach including a selective hysteroscopically-driven subchorionic MTX administration seems of interest. The major limitation of our report is represented by the small number of cases; the effectiveness and safety of the described management should be assessed in larger clinical trials.

5. Conclusions

We presented a case series of patients suffering from CSP and treated with a technique based on two sequential hysteroscopic steps. The first, aimed to terminate pregnancy, consisted of a selective MTX administration within the placental inter-villous spaces under hysteroscopic guidance. After appropriate timing, based on the evidence of trophoblastic demise, it was followed by a successful and uneventful resectoscopic placental removal. In well-established hysteroscopy context, this sequential minimally invasive approach can be considered an option for the treatment of CSP.

Author Contributions

GG designed the research study and wrote the manuscript. MS, BN and EB performed the research. VB and MC provided help and advice on the experiments. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Given the characteristic of the report, institutional review board approval was not required. All subjects gave their informed consent for inclusion before they participated in the study.

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Conflict of Interest

The authors declare no conflict of interest. GG is serving as one of the Editorial Board members of this journal. We declare that GG had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AT and MHD.

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