

Original Research

Cesarean Scar Pregnancy Treated by Systemic or Local Methotrexate Administration Followed by Hysteroscopic Removal: A Comparative Pilot Study

Giancarlo Garuti^{1,*}, Paola Francesca Sagrada², Lorenzo Sogaro¹, Serena Migliaccio¹, Marilena Farella¹, Marco Soligo¹

¹Obstetrics and Gynecology Department, Public Hospital of Lodi, 26900 Lodi, Italy

²Medical Oncology Department, Public Hospital of Lodi, 26900 Lodi, Italy

*Correspondence: giancarlo.garuti@tiscali.it (Giancarlo Garuti)

Academic Editor: Paolo Casadio

Submitted: 28 November 2022 Revised: 30 December 2022 Accepted: 9 January 2023 Published: 21 March 2023

Abstract

Background: Cesarean Scar Pregnancy (CSP) is a life-threatening condition following an ectopic implantation within the scar of a previous cesarean delivery and no guideline is shared about optimal treatment options. **Methods:** We present a retrospective study comparing the outcomes of patients with CSP diagnosed before the 10th week of gestation treated by systemic or local Methotrexate (MTX) for pregnancy termination, followed by hysteroscopic placental removal. After MTX administration, the weekly decrease-rate of beta Human Chorionic Gonadotropin subunit (β -HCG) was adopted as criterion to indicate a repeated MTX dose (less than 25% decline after 2 weeks) and to surgery timing (50% decline in two consecutive assessments). **Results:** Fourteen patients satisfied the inclusion criteria. Eight and six of them underwent systemic (group A) and local (group B) MTX administration, respectively. No significant difference was found in pre-treatment and intra-operative variables. Group B showed significantly accelerated times in weekly halving of β -HCG with respect to group A (p -value = 0.005). Accordingly, the elapsing time between MTX and surgery was found to be significantly longer in the group A than in the group B (p -value = 0.016). In group B no patient required further MTX administration whereas 3 out of 8 patients from group A required an additional MTX dose. In all patients hysteroscopic surgery resulted uneventful and no further treatment was required. **Conclusions:** When followed by hysteroscopic placental removal, systemic or local MTX administration resulted effective to treat CSP. Local MTX allows quicker trophoblastic demise, leading to significant anticipation of surgery with respect to systemic administration.

Keywords: cesarean scar pregnancy; ectopic pregnancy; hysteroscopy; methotrexate; outpatient hysteroscopy

1. Introduction

Cesarean Scar Pregnancy (CSP) is an uncommon ectopic pregnancy occurring in about 1 out of 500 women who underwent one or more cesarean deliveries. It is caused by a blastocyst implantation and placental growth within a cervical-isthmic uterine scar [1]. Based on Vial's classification, two clinical entities known as type 1 and 2 were recognized, depending on different implantation areas and pathways of placental development. In type 1, CSP implantation overlaps with the uterine scar and its growth pursues a cranial direction towards the endometrial cavity. In type 2 the placental development is ventrally-directed, growing within the cesarean scar niche towards the isthmic serous surface and bladder base. In both cases, life-threatening complications such as near-term previa/accreta or uterine rupture in the first months of pregnancy can be expected, respectively [2]. Due to these assumptions CSP termination is widely warranted to avoid maternal morbidity and to spare fertility. To improve the safety of management an early diagnosis of CSP based on established sonography criteria is of pivotal value [3]. No guideline for CSP treatment is cur-

rently shared and the choice among many proposed strategies are based on both individual clinical condition and single Institutional skills. Surgical excision by abdominal, laparoscopic, vaginal, hysteroscopic or curettage techniques, pregnancy termination by Methotrexate (MTX) administration, Uterine Artery Embolization (UAE), high-intensity ultrasound, intrauterine double-balloon insertion, as alone or combined treatments, summarized more than 30 procedures proposed to treat CSP [4]. MTX is an antimetabolite drug showing a competitive reversible binding with respect to natural dihydrofolates and acting as inhibitor of the dihydrofolate-reductase (DHFR), a key enzyme synthesizing the tetrahydrofolates needing for synthesis of purine and pyrimidine rings [5]. MTX has been widely used for pregnancy termination in patients with CSP, either by systemic or local administration [4–6]. This latter option of administration was found to improve the clinical results with respect to the systemic route, although about one third of patient required further treatments [4,7]. Sequential surgical removal of CSP terminated by MTX or UAE has shown a reduction of treatment failures and adverse outcomes [8,9].



First pioneered by Wang *et al.* [10] hysteroscopic removal of CSP was found safe and effective either as primary treatment or after MTX or UAE pregnancy termination [8,9,11]. Herein, we report a retrospective study conducted on two series of patients, comparing the clinical outcomes of systemic and local administration of MTX, followed by hysteroscopic placental removal to treat CSP.

2. Patients and Methods

The study was conducted at the Obstetrics and Gynecology Department of the public Hospital of Lodi (Italy) from January 2010 to August 2022. We selected all patients suffering from CSP that underwent a sequential treatment consisting of MTX administration followed by hysteroscopic pregnancy removal. The clinical data was retrieved from both the Institutional data-base and the first Author (GG) personal file collection of patients suffering from CSP admitted during the study period. The diagnosis of CSP was made accordingly with recognized Transvaginal Ultrasound (TVUS) and eco-color Doppler criteria; myometrial thickness of the uterine scar was not always reported and we did not consider this sonographic variable for CSP classification [2,3]. All therapeutic procedures were performed in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration with its amendments. Given the retrospective nature of the study, the lack of guidelines for CSP management and the urgency to start an effective therapy for pregnancy termination, formal Institutional Ethical Board approval was not applicable. However, before MTX administration an approval for the use of an off-label drug was obtained from the Local Health Authority whereas patient agreement was obtained by a signed informed consent and a tailored informative note. Until 2017, 50 mg/sqm MTX was administered through a systemic intramuscular route whereas subsequently, a local hysteroscopy-guided subchorionic MTX administration by 50 mg/sqm was used in an outpatient clinic setting, according to a previously described technique. Briefly, using a double flow 4mm to 5mm operative hysteroscope, we firstly gained the coelomic space of the gestational sac by opening the capsular decidua and the chorionic membrane. Thereafter, using a 17-gauge needle adaptable to the operative channel of hysteroscope, we injected MTX melted in 2 cc of saline within the subchorionic placental site under vision (Fig. 1) [12]. In all patients the serum level of Human Chorionic Gonadotropin beta-subunit (β -HCG) was measured before MTX administration and thereafter on a weekly basis, alongside physical examination and transvaginal ultrasound assessment. The trend of β -HCG decline after MTX administration addressed the management of every single patient. When β -HCG decreased less than 25% after 2 weeks from MTX, a second 50 mg/sqm of systemic MTX was administered. We scheduled the hysteroscopic removal of CSP when a halving of β -HCG, suggesting a substantial trophoblastic

demise, was found in at least two consecutive determinations [7,13]. In all patients the hysteroscopic removal of CSP was carried-out as an inpatient procedure under conscious sedation by the use of a 27-Fr resectoscope armed with a 2 to 4 mm bipolar loop set at 100 W power. Saline was used as the distending medium and it was delivered by an electronic irrigating-suction device set between 80 and 150 mm/Hg, modulated on the basis of intraoperative requirements. The deficit of saline was recorded at the end of each intervention. Due to the low consistency of the pregnant cervix, its instrumental dilatation was not always required; otherwise, a careful cervical dilatation using Hegar's dilators to 10 mm was used to gain uterine cavity. After the clearance of blood clots and tissue debris, we defined the endometrial landmarks and the boundary of uterine scar with respect to placental implantation site (Fig. 2a,b, Ref. [2]). A plane between villous trophoblast and basal decidua was developed by caudo-cranial directed mechanical cold separation of tissues in the anterior aspect of uterine wall. When required, coagulating and cutting currents were activated for selective bleeding control of placental vessels encountered during tissue separation and resection of bulky placental tissue or blood clots far from uterine wall, respectively. At the end of each procedure, we checked the uterine cavity in order to assess the completion of trophoblastic removal, the integrity of the uterine wall and the appropriateness of hemostasis. All collected tissues was sent for pathologic evaluation. After 2–3 hours from the end of intervention a venous blood sampling was obtained to assess hemoglobin levels. At discharge we planned a β -HCG determination and a clinical evaluation including TVUS assessment after the resumption of the first menstrual period.

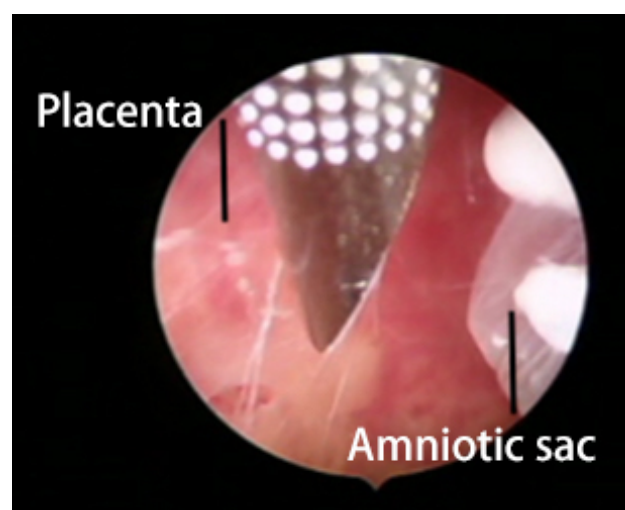


Fig. 1. Subchorionic hysteroscopically-guided local MTX administration. The tip of a 17-gauge needle is shown within the coelomic space of a CSP before the injection in the subchorionic space of placental ectopic implantation.

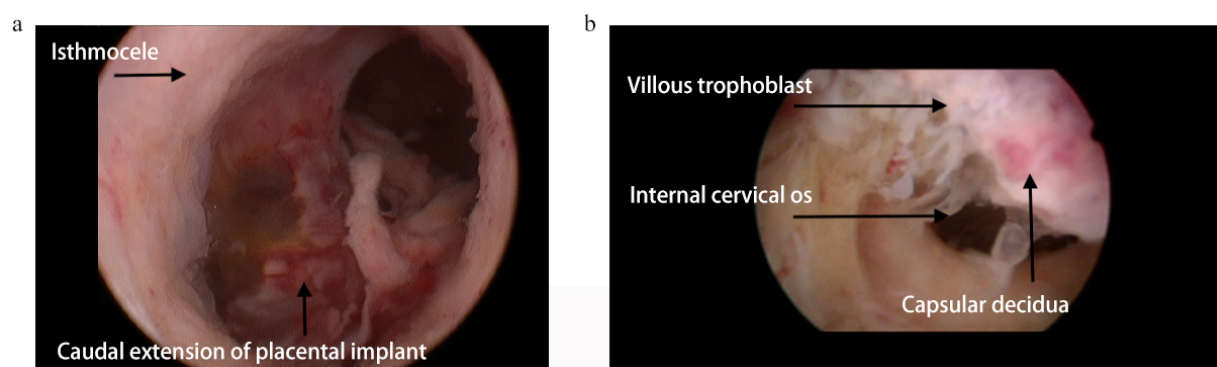


Fig. 2. Panoramic view of Type 1 and Type 2 CSP according to Vial's classification [2]. (a). Type 1 CSP is shown, partially involving the cranial boundary of the cesarean scar niche. (b). the placental implantation within the cesarean scar niche identifies a type 2 CSP.

Statistical Analysis

Parametric baseline characteristics were compared in both groups using two-tailed Fisher's exact test. Continuous variables such as patient age and gestational age, time from MTX administration to the defined drop in β -HCG levels, the times of hysteroscopic placental removal and the other continuous outcomes were compared using a two-tailed Wilcoxon rank sum test. Statistical significance was set with a p -value of <0.05 . Statistical analysis was carried out using statistical software R version 4.2.1 (R Core Team 2022. R Foundation for Statistical Computing, Vienna, Austria).

3. Results

During the study-period, 14 patients suffering from CSP were managed by primary MTX administration followed by hysteroscopy placental removal. Eight of them underwent systemic MTX whereas in six patients the MTX priming was accomplished through an outpatient hysteroscopy-guided subchorionic local injection. This latter procedure resulted uneventful and easy to accomplish, leading to the discharge of all patients within a few hours from intervention. The two groups were similar for all baseline characteristics, as shown in Table 1. In Fig. 3 we represented the basal β -HCG values and their mean (\pm SD) decrease over time after MTX administration in the two groups of patients. In 3 out of 8 patients (37.5%) treated by systemic MTX, a second administration was needed to obtain a significant decrease of β -HCG, whereas no patient who underwent local MTX required further treatment. One out of 3 patients needing additional MTX developed grade 2 oral mucositis according to Common Toxicity Criteria for adverse events. In all 8 patients admitted with a viable pregnancy, the embryonic heart beat disappeared after 7 days from MTX administration. In the follow-up period elapsed from MTX administration and hysteroscopy treatment all patients recorded a slight vaginal bleeding while weekly transvaginal sonography showed the persistence of gestational sac until hysteroscopy treatment. As shown in

Table 2, the two groups did not show any significant difference in operative times, preoperative or postoperative hemoglobin levels, blood loss and deficit of saline. A significant difference was found in the time elapsed between MTX administration and the detection of two consecutive weekly reductions of at least 50% in β -HCG levels (systemic group: mean 27.1 ± 6.9 days; local group: mean 16.3 ± 3.6 days, p -value = 0.005). Accordingly, the time inter-curred between MTX treatment and hysteroscopic surgery was found to be significantly longer in the systemic group (mean 33.4 ± 10.4 days) than in the locally treated group (mean 20.5 ± 5.0 days, p -value = 0.016). In all but one patient, an easy plane was developed by the cold action of the resectoscopic loop between the villous tissue and basal decidua (Fig. 4). In one case suffering from type 2 disease, firm tissue and thrombosed spiral vessels were found within the stromal tissue of the CSP niche requiring the activation of electrosurgical slicing for removal and suggesting the diagnosis of an abnormally adherent placenta (Fig. 5). At the end of surgery, the check of uterine cavity showed a full removal of placental tissue in all patients. No adverse peri-operative outcome was recorded and patients were discharged in the first post-operative day. In all cases, pathologic reports were consistent with villous tissue, often associated with hydropic aspects and detection of embryonic tissues. In all women normal clinical and ultrasonographic findings were found after the first post-surgery menstrual period, while at that time β -HCG levels decreased to the not pregnant levels.

4. Discussion

In this comparative report we found that MTX administration, followed by hysteroscopic pregnancy surgical removal, is safe and effective to treat CSP. Local MTX should be preferred, due to the significant quicker times of trophoblastic demise and surgical resolution with respect to the systemic route, without the need of additional drug's administration. MTX is an antimetabolite drug widely used to treat ectopic pregnancies, including CSP. Its effect is based

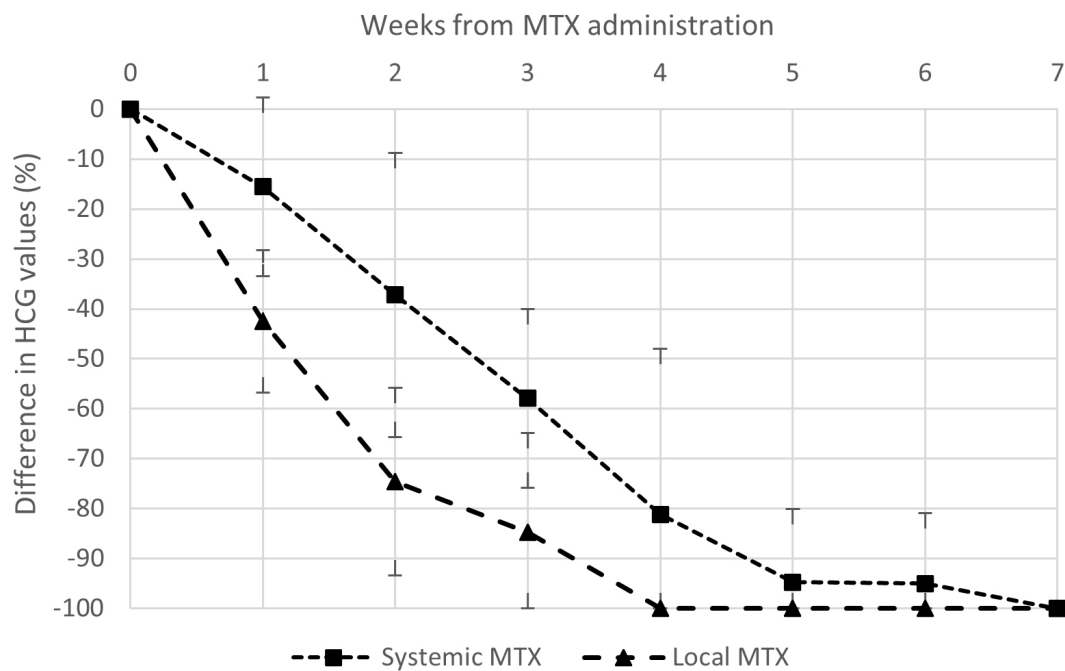


Fig. 3. Evolution in time of mean (\pm SD) HCG levels after administration of MTX systemically (short dashes, squares; $n = 8$) and locally (long dashes, triangles; $n = 6$); each value represents the difference (expressed in percent) in two consecutive HCG measurements, sampled 7 days apart. MTX, methotrexate; HCG, human chorionic gonadotropin; SD, standard deviation.

Table 1. Comparison between pre-operative clinical variables of 14 patients with CSP who underwent systemic and local MTX administration before hysteroscopic placental removal.

Parameter	Systemic MTX (n = 8)	Local MTX (n = 6)	p-value
Age (years), mean (range)	33.6 (22–44)	35.2 (28–42)	0.7461 [†]
Previous CD, %			
One previous CD	62.5%	50%	0.8831 [‡]
More than one previous CS	37.5%	50%	
Gestational age (days), mean (\pm SD)	48.9 (\pm 9.5)	52.5 (\pm 7.3)	0.5883 [†]
CSP type, %			
CSP type 1	25.0%	33.3%	1 [‡]
CSP type 2	75.0%	66.6%	
Viable pregnancy, %	50%	66.6%	0.6272 [‡]
Uterine bleeding, %	62.5%	33.3%	0.5920 [‡]

[†]Two tailed Wilcoxon rank sum test. [‡]Two tailed Fisher's exact test. CSP, cesarean scar pregnancy; MTX, methotrexate; CD, cesarean delivery; SD, standard deviation.

on the cytotoxic action of highly proliferating trophoblastic cells, allowing pregnancy termination [4,5,14]. The competitive and reversible nature of MTX binding to DHFR, a key enzyme in intracellular folate homeostasis, leads cell-drug concentration and exposure-time in target tissue as two main determinants of cytotoxicity [5]. The short half-life of MTX and the impaired blood supply to placental tissue implanted within a scarred uterine niche have been advocated to understand the low effectiveness of systemic MTX used as unique therapy to treat CSP [4,5,14,15]. By enhancing drug concentrations within the target tissue, local intra-gestational MTX administration through ultrasound-guided procedures improved the clinical results with respect

to systemic route. Nevertheless, even local MTX administration used as single therapy fails or leads to complications in about one third of patients, requiring further treatment measures [4,6,7]. A scheduled combined treatment, based firstly on pregnancy termination by MTX or UAE followed by timed placental surgical removal by controlled D&C or hysteroscopy, enhances the rate of successful procedures to more than 90% of cases [8,9,16,17]. Allowing the performance of an intervention under vision, hysteroscopy placental removal yielded safer results with respect to D&C by avoiding cervical-isthmic anatomy damage and permitting an effective electrosurgical control of bleeding [8,16,18]. In addition, there are few doubts that hysteroscopy pro-

Table 2. Comparison between operative variables in 14 patients suffering from CSP after systemic and local MTX administration who underwent subsequent hysteroscopic placental removal.

Outcome	Systemic MTX (n = 8)	Local MTX (n = 6)	p-value
Time from MTX administration to desired drop of β -HCG (days), mean (\pm SD)*	27.1 (\pm 6.9)	16.3 (\pm 3.6)	0.0056 [†]
Time from MTX administration to hysteroscopy (days), mean (\pm SD)	33.4 (\pm 10.4)	20.5 (\pm 5.0)	0.0164 [†]
Need for second dose of MTX, patients number	3	0	0.2088 [‡]
Operative time (min), mean (\pm SD)	26.3 (\pm 21.7)	23.5 (\pm 8.1)	0.7463 [†]
Hemoglobin levels (g/dL)			
Preoperative Hb, mean (\pm SD)	12.3 (\pm 1.0)	11.1 (\pm 1.0)	0.0526 [†]
Postoperative Hb, mean (\pm SD)	11.9 (\pm 1.2)	10.9 (\pm 1.1)	0.1743
Difference (postoperative – preoperative Hb), mean (\pm SD)	–0.48 (\pm 0.39)	–0.17 (\pm 0.27)	0.1542 [†]
Deficit of saline (mL), mean (\pm SD)	165 (\pm 159)	100.0 (\pm 71)	0.5582 [†]

*Desired drop in β -HCG levels is defined as two consecutive reductions of at least 50% at 7-days intervals. [†]Two tailed Wilcoxon rank sum test. [‡]Two tailed Fisher's exact test. HCG, human chorionic gonadotropin; MTX, methotrexate; SD, standard deviation; Hb, hemoglobin.

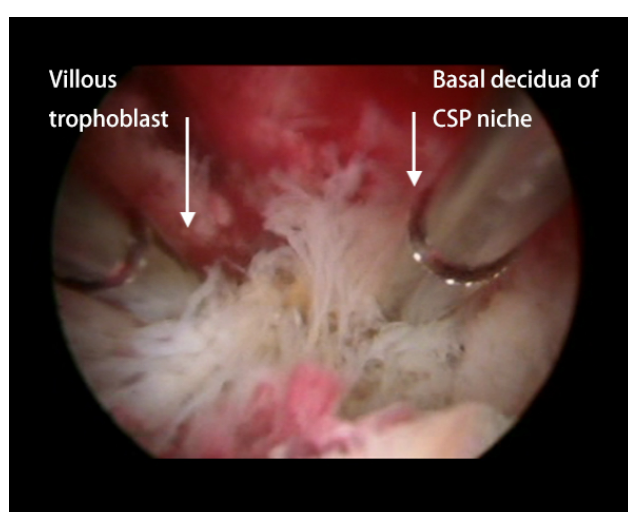


Fig. 4. Placental separation. The villous trophoblastic tissue (whitish tissue on the left) separation from basal decidua (pinkish tissue on the right) of CSP, using the cold mechanical action of resectoscopic loop is in progress.

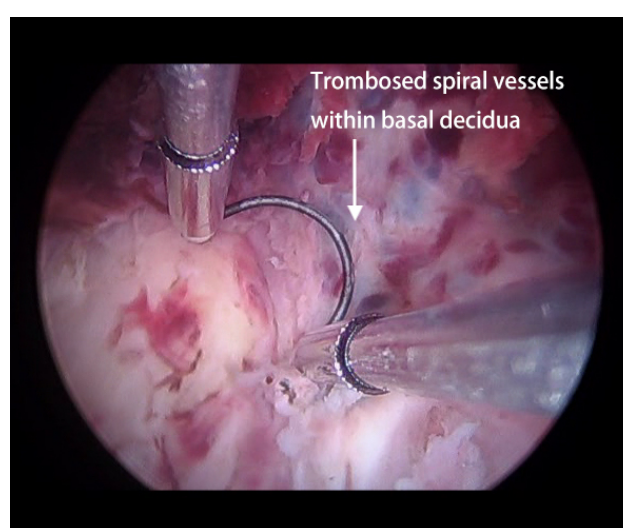


Fig. 5. The thrombosed spiral vessels within the niche of type 2 CSP appearing during placental separation below the basal decidua and the lack of an easy plane of separation suggest the diagnosis of concurrent adherent placenta.

vides better details about the anatomy of CSP, allowing a more careful placental separation, lowering operative times and medical costs with respect to major surgery such as vaginal, laparoscopic or laparotomic excisional procedures [1,4]. The safety and effectiveness of hysteroscopy used both as primary and combined treatment for CSP removal was largely demonstrated. In some hundreds of patients suffering from CSP reported in current literature, very few perioperative adverse outcomes and need of further therapy were recorded [8,13,16,18]. According to these findings the present study confirmed the safety and effectiveness of the resectoscopic treatment after MTX priming; in no case was a perioperative adverse outcome recorded and in no patient was further therapy required. Both systemic and local MTX administration resulted effective to obtain the embryo's demise; however, based on TVUS imaging we found in all patients the persistence of the ectopic gestational sac

until hysteroscopic removal, confirming the delayed times of CSP complete resolution after both systemic and local MTX administration [4,7,14,15]. In 2016 we first described a safe and effective hysteroscopy technique of local subchorionic MTX administration followed by resectoscopic placental removal and since then we have used that technique to manage all types of CSP [12]. We assumed an advantage of hysteroscopy with respect to sonography-guided MTX administration because of a more selective drive, accomplished under direct anatomic visualization, to the target tissue represented by the intervillous spaces of placental implantation site. To our knowledge, in current literature CSP termination by gestational sac local hysteroscopy-guided administration of embryocidal agents such as MTX and ethanol was experienced in only two patients, successfully treated by subsequent resectoscopic placental removal and D&C, respectively [19,20]. More recently, a case re-

port from Casadio *et al.* [21] described a successfully conservative procedure based on hysteroscopically-driven myometrial peri-gestational sac injection of MTX, followed by placental removal using a 6-mm truclear hysteroscopic morcellation system. This sequential technique to treat CSP appears conceptually very similar to that proposed in the present study.

Although this study is retrospective and carried-out on only a small series of patients, the present experience demonstrates the significant advantage of local with respect to systemic MTX to obtain a prompt decline of β -HCG levels, avoiding repeated drug administration with its associated adverse effects and significantly quickening the times of surgical removal. In current literature there is no study comparing the clinical outcomes of systemic and local MTX administration followed by surgical CSP removal although recent reports indicate that ultrasound-guided local MTX administration followed by D&C resulted safe and effective to treat CSP in more than 90% of cases [14,17]. MTX therapy and UAE appear equally effective to prime CSP before its surgical evacuation. With respect to UAE, which leads to a quick pregnancy termination following a sudden reduction of placental blood flow permitting an early CSP removal, MTX therapy needs more prolonged times for substantial trophoblastic demise, requiring more delayed times for the subsequent surgery [1,4,9,16]. Combined loco-regional uterine artery MTX injection followed by UAE have been also reliably proposed as single step therapy for the management of CSP [22]. Nevertheless, UAE demands the Institutional availability of interventional radiology skill, making it an expensive technique which may expose the patient to significant perioperative and long-term adverse outcomes such as acute vascular complications, pelvic pain, intrauterine adhesions and subsequent menstrual or obstetrics complaints [17]. Primary UAE followed by surgical evacuation should presumably be preferred with respect to MTX in patients suffering from CSP with a very high intraoperative hemorrhagic risk such as a type 2 CSP showing isthmic scarred myometrial thickness below 3 mm; however, at present no comparative clinical data is available on this topic [23].

5. Conclusions

The therapeutic management of CSP using MTX, firstly aimed at pregnancy termination and followed by timed hysteroscopic placental removal, is safe and effective, both by systemic or local administration. Nevertheless, local MTX administration led to significantly faster β -HCG decline and advanced times of surgical placental removal. When hysteroscopic skill and facilities are available, a selective subchorionic MTX administration under vision can be proposed as an alternative method, with respect to UAE or ultrasound-guided MTX priming, before surgical placental removal.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding Author on reasonable request.

Author Contributions

GG—Conceptualization and design of the study, senior surgeon accomplishing, describing and collecting data of all interventions; PFS—Conceptualization of MTX effects on CSP; LS—Analysis and interpretation of data; SM—Clinical management of patients by planning follow-up, ultrasonographic assistance; MF—Clinical management of patients by planning follow-up, ultrasonographic assistance; MS—Analysis and interpretation of data. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

All procedures were performed in accordance with the ethical standards of the national research committee and with the 1964 Helsinki Declaration with its amendments. Given the retrospective nature of the study, the lack of guidelines for CSP management and the urgency to start an effective therapy for pregnancy termination, formal Institutional Ethical Board approval was not applicable. Before MTX administration an approval for the use of an off-label drug was obtained from the Local Health Authority whereas patient agreement was obtained by a signed informed consent and a tailored informative note.

Acknowledgment

We thank Mrs Caroline Calnan, a native English speaker with expertise in medical papers, for the grammar and style revision of the manuscript.

Funding

This research received no external funding.

Conflict of Interest

The authors declare no conflict of interest. Giancarlo Garuti is serving as one of the Editorial Board members of this journal. We declare that Giancarlo Garuti 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 Paolo Casadio.

References

- [1] Gonzalez N, Tulandi T. Cesarean Scar Pregnancy: A Systematic Review. *Journal of Minimally Invasive Gynecology*. 2017; 24: 731–738.
- [2] Vial Y, Petignat P, Hohlfield P. Pregnancy in a cesarean scar. *Ultrasound in Obstetrics & Gynecology*. 2000; 16: 592–593.
- [3] Timor-Tritsch IE, Monteagudo A, Cali G, El Refaey H, Kaelin Agten A, Arslan AA. Easy sonographic differential diagnosis between intrauterine pregnancy and cesarean delivery scar preg-

- nancy in the early first trimester. *American Journal of Obstetrics and Gynecology*. 2016; 215: 225.e1–225.e7.
- [4] Maheux-Lacroix S, Li F, Bujold E, Nesbitt-Hawes E, Deans R, Abbott J. Cesarean Scar Pregnancies: A Systematic Review of Treatment Options. *Journal of Minimally Invasive Gynecology*. 2017; 24: 915–925.
 - [5] Stika CS. Methotrexate: the pharmacology behind medical treatment for ectopic pregnancy. *Clinical Obstetrics and Gynecology*. 2012; 55: 433–439.
 - [6] Cheung VYT. Local Methotrexate Injection as the First-line Treatment for Cesarean Scar Pregnancy: Review of the Literature. *Journal of Minimally Invasive Gynecology*. 2015; 22: 753–758.
 - [7] Cok T, Kalayci H, Ozdemir H, Haydardedeoglu B, Parlakgumus AH, Tarim E. Transvaginal ultrasound-guided local methotrexate administration as the first-line treatment for cesarean scar pregnancy: Follow-up of 18 cases. *The Journal of Obstetrics and Gynaecology Research*. 2015; 41: 803–808.
 - [8] Li Y, Xiao S, Wan Y, Xue M. Analysis of the efficacy of three treatment options for cesarean scar pregnancy management. *The Journal of Obstetrics and Gynaecology Research*. 2014; 40: 2146–2151.
 - [9] Gao L, Huang Z, Gao J, Mai H, Zhang Y, Wang X. Uterine artery embolization followed by dilation and curettage within 24 hours compared with systemic methotrexate for cesarean scar pregnancy. *International Journal of Gynaecology and Obstetrics*. 2014; 127: 147–151.
 - [10] Wang C, Yuen L, Chao A, Lee C, Yen C, Soong Y. Cesarean scar pregnancy successfully treated by operative hysteroscopy and suction curettage. *BJOG: An International Journal of Obstetrics and Gynaecology*. 2005; 112: 839–840.
 - [11] Deans R, Abbott J. Hysteroscopic management of cesarean scar ectopic pregnancy. *Fertility and Sterility*. 2010; 93: 1735–1740.
 - [12] Garuti G, Calabrese S, Quirino L, Di Mario M. Hysteroscopically-guided methotrexate administration, a new technique for termination of cesarean scar pregnancy. *Journal of Case Reports Imaging in Obstetrics and Gynecology*. 2016; 2: 1–6.
 - [13] Garuti G, Calabrese S, Baudino G, Reato C, Quirino L, Di Mario M. Hysteroscopic removal of cesarean scar pregnancy after primary therapy with methotrexate: a case series. *Clinical and Experimental Obstetrics and Gynecology*. 2017; 44: 856–861.
 - [14] Salari N, Kazeminia M, Shohaimi S, Nankali AA, Mohammadi M. Evaluation of treatment of previous cesarean scar pregnancy with methotrexate: a systematic review and meta-analysis. *Reproductive Biology and Endocrinology*. 2020; 18: 108.
 - [15] Timor-Tritsch IE, Monteagudo A. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. *American Journal of Obstetrics and Gynecology*. 2012; 207: 14–29.
 - [16] Qiu J, Fu Y, Xu J, Huang X, Yao G, Lu W. Analysis on clinical effects of dilation and curettage guided by ultrasonography versus hysteroscopy after uterine artery embolization in the treatment of cesarean scar pregnancy. *Therapeutics and Clinical Risk Management*. 2019; 15: 83–89.
 - [17] Tan K, Chen Y, Zeng W, Meng Y, Jiang L. Local Methotrexate Injection Followed by Dilation and Curettage for Cesarean Scar Pregnancy: A Prospective Non-randomized Study. *Frontiers in Medicine*. 2022; 8: 800610.
 - [18] Wu X, Xue X, Wu X, Lin R, Yuan Y, Wang Q, *et al.* Combined laparoscopy and hysteroscopy vs. uterine curettage in the uterine artery embolization-based management of cesarean scar pregnancy: a cohort study. *International Journal of Clinical and Experimental Medicine*. 2014; 7: 2793–2803.
 - [19] Di Spiezio Sardo A, Alviggi C, Zizolfi B, Spinelli M, De Rosa P, De Placido G, *et al.* Cervico-isthmic pregnancy successfully treated with bipolar resection following methotrexate administration: case report and literature review. *Reproductive Biomedicine Online*. 2013; 26: 99–103.
 - [20] Shao M, Hu M, Hu M. Conservative management of cesarean scar pregnancy by local injection of ethanol under hysteroscopic guidance. *International Journal of Gynaecology and Obstetrics*. 2013; 121: 281–282.
 - [21] Casadio P, Ambrosio M, Verrelli L, Salucci P, Arena A, Seracchioli R. Conservative cesarean scar pregnancy treatment: local methotrexate injection followed by hysteroscopic removal with hysteroscopic tissue removal system. *Fertility and Sterility*. 2021; 116: 1417–1419.
 - [22] Elmokadem AH, Abdel-Wahab RM, El-Zayadi AA, Elrakhawy MM. Uterine Artery Embolization and Methotrexate Infusion as Sole Management for Cesarean Scar and Cervical Ectopic Pregnancies: A Single-Center Experience and Literature Review. *Canadian Association of Radiologists Journal*. 2019; 70: 307–316.
 - [23] Family Planning Group, Chinese Medical Society of Obstetrics and Gynecology. Expert consensus on diagnosis and treatment of cesarean section scar pregnancy. *Chinese Journal of Obstetrics and Gynecology*. 2016; 51: 568–572.