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# Comparison of systemic and local methotrexate treatments in cesarean scar pregnancies: time to change conventional treatment and follow-up protocols

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ABSTRACT

*Objective:* The aim of this study was to compare the use of systemic and local methotrexate in the treatment of cesarean scar pregnancy.
*Study design:* In this retrospective cohort study, we collected the data of 44 patients with cesarean scar pregnancy. The patients were grouped according to treatment modality: Group 1, local methotrexate injection (n = 17) and Group 2, systemic methotrexate (n = 27). The groups were compared with respect to side effects, recovery time, reproductive outcome, and treatment cost.
*Results:* The mean gestational age at diagnosis (6.4 ± 0.93 vs. 5.4 ± 0.80 weeks, p = 0.001), pretreatment serum β-human chorionic gonadotrophin level [27,970 (11,010–39,421) vs. 7606 (4725–16,996) mIU/mL, p = 0.001], and lesion size (2.74 ± 1.36 and 1.28 ± 0.55 cm, p = 0.001) were higher in Group 1. All patients were cured by primary therapy without additional surgery. The mean times for β-human chorionic gonadotrophin normalization, the uterine-mass disappearance, were significantly shorter in Group 1 than in Group 2 (6.17 ± 1.55 vs. 8.11 ± 2.0 weeks, p = 0.001 and 10.47 ± 4.14 vs. 13.40 ± 4.44 weeks, p = 0.002, respectively). The cost of treatment was similar between groups (281.133 ± 112.123 $ vs. 551.134 ± 131.792 $, p = 0.76). The total pregnancy rates were not different between groups (5/16, 31.4% vs. 6/11, 54.6%, p = 0.301). One recurrent cesarean scar pregnancy occurred after systemic methotrexate. Oral ulcers, the most common side effect, were seen in seven patients in Group 2.
*Conclusion:* Even though treatment success and reproductive outcomes are similar, local methotrexate is superior to systemic methotrexate with regard to recovery time, side effects, and treatment costs, even in patients with unfavorable pretreatment prognostic predictors.
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## Introduction

Cesarean scar pregnancy (CSP) is a rare type of ectopic pregnancy seen in 1:531 pregnant women with a history of one or more cesarean sections (CSs). In parallel with the increased CS rate and widespread use of ultrasound (US) in early pregnancy, the incidence of CSP has increased worldwide [1,2]. Although the exact cause and mechanism are poorly understood, implantation of the blastocyst into the myometrium through a microtubular tract between the CS scar and the endometrial canal has been suggested [3,4]. This abnormal implantation of the embryo within the myometrium and fibrous tissues in a previous scar can lead to uterine rupture, adherent placenta, and uncontrolled hemorrhage, which leads to hysterectomy and permanent loss of fertility, or even maternal death [5–8]. Early and accurate diagnosis and timely management are very important to reduce life-threatening complications and preserve fertility. Despite the myriad of clinical report and nearly 30 different therapeutic approaches, there is still no consensus on the treatment of CSP [9].

Methotrexate (MTX) is an antimetabolite drug that has been used in the treatment of molar and ectopic pregnancies including CSP [10,11]. MTX-based therapies alone or in combination with different methods have been used in CSP with varying success rates [12,13]. Although MTX is considered a safe and effective therapy, the optimal dose, route, and protocol of its use are yet to be determined in CSP [5,12]. In this study, we present our experience with 44 CSP patients in a single tertiary referral center, and

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compare the local and systemic administration of MTX in CSP treatment.

## Materials and methods

This retrospective cohort study included all CSP patients admitted to Erciyes University, Faculty of Medicine, Department of Obstetrics and Gynecology, between January 2000 and July 2015. Ethics approval was obtained from the instructional review board of Erciyes University School of Medicine. Forty-seven cases were identified during this period. CSP was diagnosed when the following transvaginal sonographic criteria were fulfilled: (1) an empty uterine cavity with a clearly demonstrated endometrium; (2) the gestational sac visualized as a "double ring" sign in the anterior part of the isthmic part of the uterus; (3) the presence of the gestational sac with or without fetal cardiac activity embedded and surrounded by the myometrium; (4) a thin (1–3 mm) or absent myometrial layer between the gestational sac and the bladder; and (5) peritrophoblastic flow surrounding the CSP, appearing on Doppler flow sonography [5,14].

Baseline serum beta chorionic gonadotrophin (β-hCG) levels were noted. Blood tests for liver and renal functions and complete blood count were requested. Gestational age was determined according to the last menstrual period. Both sac dimension and crown-to-rump length were used to determine gestational age when patients could not remember their last menstrual period.

*Acording to our instutitional protocol*; after counseling about the risk of uterine rupture and hemorrhage, the side effects of MTX and the possibility of treatment failure, management in the form of systemic or intragestational MTX was offered.

All of the patients were hospitalized at the beginning of therapy. Systemic multidose protocol included administration of four 1 mg/kg doses of MTX, alternated with 0.1 mg/kg of leukoverin injected intramuscularly. Additional doses were given every other day when the βhCG level plateaued or did not decrease to 50% of the baseline level.

For local MTX injection, after an overnight fasting, intravenous anesthesia without endotracheal intubation was applied. The patient was placed in a lithotomy position, and the vagina was cleared with 10% povidone-iodine solution. Cephalosporin was administered intravenously at a dose of 2 mg, for prophylaxis. The gestational sac was punctured and aspirated using a transvaginal US guide and 16 G, oocyte pick-up double-lumen aspiration needle (Swemed Med, Follicle Aspiration Needle, 1.5 × 350 mm, double-lumen, tubing, Vitrolife). After aspiration, 50 mg MTX was instilled slowly into the gestational sac. The day after injection, Color Doppler US imaging was performed to confirm the absence of fetal cardiac activity, and serum β-hCG tests were checked. If fetal cardiac activity was detected, patients were kept on the inpatient ward, and cardiac activity was checked every day for 2 days. Seven days after the treatment, a 15% or greater drop in serum β-hCG level was regarded as response to treatment, and the β-hCG level was monitored weekly until the level was below 5 mIU/mL.

Complete sonographic resolution of the CSP was defined as the absence of the gestational sac, hyperechogenic chorionic rim, and any other echo densities under the CS scar, along with a regular endometrial line in the lower uterine segment on transvaginal US. Resolution of the gestational sac was monitored weekly with transvaginal US.

SPSS 22.0 software was used to perform statistical analyses. Shapiro–Wilk test and histogram were used to ensure the normality of the data. For statistical analysis of the data, the Student's *t*-test, Mann–Whitney U test, and chi-square tests were used, and a *P*-value $<0.05$ was considered statistically significant.

## Results

Our electronic database retrieved 1489 patients with the diagnosis of ectopic pregnancy in the study period. The distribution of type of ectopic pregnancies was 1420 tubal ectopic pregnancies (95.3%), 47 CSP (3.1%); 11 cervical (0.7%); 8 cornual (0.5%); 2 ovarian (0.1%); and 1 abdominal (0.06%). Of 47 CSP patients, 3 were lost to follow-up, and 44 with CSP were analyzed in the study. Further, 17 patients were treated with local intragestational injection of MTX (Group 1), and 27 patients were treated with systemic multidose MTX (Group 2). The mean maternal age was 31.7 ± 4.6 years, and the main gestational age was 5.8 ± 0.9 weeks. The mean number of previous CSs in the study population was 1.56 ± 0.58. The average interval between current the CSP and the previous CS was 39.18 ± 14.6 months.

The mean maternal age (32.76 ± 5.25 and 31.07 ± 4.17 years, p = 0.243), number of previous CSs (1.4 ± 0.51 and 1.6 ± 0.62 p = 0.387), and average time interval between the current CSP and the previous CS (39.05 ± 12.69 and 39.25 ± 15.96 months, p = 0.965) were similar between the groups. The mean gestational age at diagnosis (6.4 ± 0.93 and 5.4 ± 0.80 weeks, p = 0.001), mean pretreatment serum β-hCG level [27,970 (11,010–39,421) mIU/mL and 7606 (4725–16,996), mIU/mL p = 0.001], and mean lesion size (2.74 ± 1.36 and 1.28 ± 0.55 cm p = 0.001) were significantly higher in Group 1 than in Group 2. Average MTX dose was significantly higher in Group 2 than in Group 1 [5.72 ± 1.91 (2–9) and 1 p = 0.001]. All of the patients in the local MTX group (Group 1) had fetal cardiac activity, and 10/27 patients in the systemic group (Group 2) had fetal cardiac activity. All fetal heart activity disappeared within 48 h after local MTX injection, and no additional local MTX injection was applied. The comparison of demographic and clinical data between the two groups is shown in Table 1.

Patients in both groups did not need any additional surgical procedure, and the overall cure rate in both groups was 100%. The mean β-hCG remission time (6.17 ± 1.55 vs. 8.11 ± 2.0 weeks, p = 0.001), uterine-mass disappearance time (10.47 ± 4.14 vs.

**Table 1**
Comparison of demographic and pretreatment clinical parameters between the two groups.

| | Local injection (mean ± SD) | Systemic administration (mean ± SD) | *P*-Value |
|---|---|---|---|
| Age (years) | 32.76 ± 5.25 | 31.07 ± 4.17 | 0.243 |
| BMI (kg/m$^2$) | 25.83 ± 2.16 | 25.77 ± 4.85 | 0.933 |
| Gravida | 3.17 ± 0.80 | 2.96 ± 0.89 | 0.430 |
| Parity | 1.52 ± 0.51 | 1.70 ± 0.72 | 0.393 |
| Cesarean section | 1.4 ± 0.51 | 1.6 ± 0.62 | 0.387 |
| Gest age (weeks) | 6.4 ± 0.93 | 5.4 ± 0.80 | 0.001 |
| Pretreatment serum β-hCG level (mIU/mL) | 27970 (11,010–39,421) | 7606 (4725–16,996) | 0.001 |
| Gestational sac size (cm) | 2.74 ± 1.36 | 1.28 ± 0.55 | 0.0001 |
| Average MTX dose | 5.72 ± 1.91 (2–9) | 1 | 0.0001 |
| Interval between current CSP and last CS (months) | 39.05 ± 12.69 | 39.25 ± 15.96 | 0.965 |
| Positive heart beat | 17/17 (%100) | 10/27 (37%) | 0.0001 |

BMI: Body Mass Index; MTX: Methotraxate; CSP: cesarean scar pregnancy.

**Table 2**
Clinical and reproductive outcomes of local injection and systemic administration of MTX.

| | Local injection n = 17 | Systemic administration n = 27 | *P*-Value |
|---|---|---|---|
| Time for serum β-hCG remission (weeks) | 6.17 ± 1.55 | 8.11 ± 2.0 | 0.001 |
| Time for uterine-mass disappearance (weeks) | 10.47 ± 4.14 | 13.40 ± 4.44 | 0.002 |
| Hospitalization time (days) | 7.05 ± 2.77 | 11.96 ± 4.02 | 0.0001 |
| Cost of treatment ($) | 281.133 ± 112.123 | 551.134 ± 131.792 | 0.76 |
| Overall cure rate (%) | %100 | %100 | 1 |
| Clinical pregnancy rate | 6/11 (54.6%) | 5/16 (31.4%) | 0.301 |
| Interval from CSP to subsequent pregnancy (month) | 12.16 ± 2.85 | 14.2 ± 3.89 | 0.344 |
| Recurrent CSP rate | 0/17 (0%) | 1/27 (6.3%) | 1 |
| Live-birth rate | 4/11 (36.4%) | 3/17 (18.8%) | 0.438 |

CSP: cesarean scar pregnancy.

13.40 ± 4.44 weeks, p = 0.002), and hospitalization duration (7.05 ± 2.77 vs. 11.96 ± 4.02 days, p = 0.0001) were significantly shorter in Group 1 compared with Group 2. No statistically significant difference was detected between groups with regard to cost of treatment (281.133 ± 112.123 $ vs. 551.134 ± 131.792 $, p = 0.76). Seven patients had oral ulceration in Group 2, and all responded to local symptomatic treatment. No treatment cancellation or switch occurred. No side effects were reported in Group 1.

In the study population, total clinical pregnancy and take-home baby rates after the treatments were 40.7%, and 25.9%, respectively. Moreover, 11 of 17 women who wished to get pregnant in Group 1 conceived (54.6%), and four healthy babies (36.4%) were born at term without complication. Two pregnancies culminated with spontaneous abortion at 6 and 8 weeks, respectively. In Group 2, 16 of 27 women wished to get pregnant, and three had live, healthy births (18.8%). One pregnancy was lost at 6 weeks by spontaneous abortion. There was only one case of recurrent CSP in the study group, which was seen 12 months after a CSP treated with systemic MTX (Group 2). The median interval from CSP to subsequent pregnancy was similar between groups (12.16 ± 2.85 vs. 14.2 ± 3.89 months, p = 0.344). The treatment and reproductive outcomes are outlined in Table 2.

All patients responded to medical theraphy and no additional surgical procedures required.

## Discussion

The incidence of CSP is rapidly rising because of the increased use of US in early gestation and the rising rate of CS delivery [9,13]. The distribution of our cases with respect to time showed that only six patients were detected or referred to our department between 2000 and 2009. In contrast, we diagnosed and treated 38 patients with CSP during last 6 years (2010–2015) which supports previous findings showing a trend toward increased CSP incidence [5,9].

Because most women with CSP are of reproductive age and want to remain fertile, treatment should be purposed to eliminate the CSP while retaining the woman's fertility. In this context, medical or minimally invasive treatments appear preferable over radical treatments. Therefore, a variety of treatment modalities has been proposed and studied. Review of the whole spectrum of treatment is beyond the scope of this study; however, the interested reader can refer to the review papers [9,12,14,15].

Local intragestational MTX injection is one of the most popular treatments of CSP because of the prompt response and favorable side-effects profile. However, studies evaluating the outcome of local MTX injection have reached conflicting results. Seow et al. [1] treated 11 women with non-ruptured CSP and reported that six patients needed additional systemic MTX administration. They reported that treatment success depended on β-hCG levels (<20.000 mIU/mL) and suggested that administration of additional systemic MTX reduced rupture in patients whose β-hCG levels continued to rise the day after MTX injection. Peng et al. [16] compared local and systemic MTX injection prospectively and reported a 69.2% cure rate in a local injection group. Similarly, Cok et al. [17] reported a 61.1% success rate with local MTX injection, and 7 of 11 patients required additional treatment. Ko et al. [18] evaluated the success rate of local MTX injection with or without potassium chloride. They reported an 80% success rate even in "viable" pregnancies. Lian et al. [19] assessed the effectiveness of the step-wise treatment of CSP with single dose 50 mg systemic MTX followed by uterine artery embolization plus local MTX injection if the baseline β-hCG levels did not decrease to 50% of the initial level. They achieved a 57.1% success rate with systemic MTX, and the remaining patients were treated with UAE and local MTX injection. Cheung et al. [20] reviewed the existing literature regarding treatment of CSP and showed that local MTX injection had a 73.9% success rate. They also demonstrated that the addition of local or intramuscular MTX increased the cure rate to 88.5%.

As explained in the previous discussion, the addition of adjuvant or back-up therapies and the variation in the definitions of terms such as *success* and *cure* in the studies complicate the evaluation and comparison of the effect of local MTX treatment. In some studies [1,16,17], elevation and/or limited decrease of β-hCG after local injection were accepted as treatment failure, and led to additional treatment. Our data showed that β-hCG levels after local injection plateaued or increased in eleven patients, and levels declined steadily after 7 days without additional therapy. It was known that β-hCG levels increased immediately after administration of systemic MTX and plateaued nearly 5 days after the treatment of tubal ectopic pregnancies because of the breakdown of trophoblast [21–23]. Most probably, the same phenomenon may explain the increase in β-hCG levels in CSP. In addition, disruption of the chorionic sac by the needle may exacerbate the initial cytotoxic lysis of the trophoblast, and lead to a prompt increase of β-hCG. Therefore, assuming the increased/plateaued β-hCG levels after local MTX seems to increase the reported treatment failure, and the additional back-up invasive treatment rate. Based on our data and previous studies [17,24], we strongly recommend that decision to administer additional therapy after local MTX should not be made based on the increased β-hCG levels within a week of treatment. With expectant therapy, steady decline of β-hCG levels would be the most probable outcome.

The treatment of CSP with systemic MTX treatment raises several concerns. A very recent review [12] demonstrated that almost every fifth woman (19%) treated with this modality had a major complication, and 99% needed additional surgery with D&C. However, contrary to previous data, our results showed a complete cure rate in all patients. In our systemic MTX protocol, unlike others [16,19], the drug was administrated in at least four doses, which were alternated with folic acid. In addition, we use criteria that were more strict (50% reduction of β-hCG levels from baseline) for defining "response." In theory, MTX has slow action

that may take many days to cause trophoblastic cytolysis. In addition, the short half-life of MTX and the fibrous tissue around the CSP make absorption of MTX into the sac and embryo more difficult [25,26]. Because of these setbacks, trophoblastic cells in the CSP may recover after a single dose, or widely separated multiple doses, of MTX administration. In fact, a small decrease of β-hCG levels after each systemic MTX administration seems not to reflect the actual therapeutic response, and may explain the late β-HCG elevations and treatment failure seen in previous reports using systemic MTX protocols that were less intense [16,19,27,28].

Systemic and local MTX are the two most widely used modes of treatment for CSP. Previous studies comparing two treatments showed conflicting results because of study design, additional treatment, definition of response, and cure. The most striking result of our study was that both methods had a complete response and cure rate as defined by declining β-hCG levels. Because this was a retrospective study, the two treatment groups were not equally matched for pretreatment β-hCG levels, gestational age, and cardiac activity, and the local MTX group (Group 1) had an unfavorable pretreatment prognostic indicator. However, despite higher initial β-hCG levels, higher rate of positive heart activity (17/17, 100% vs. 10/27, 37%) bigger sac size ($2.74 \pm 1.36$ vs. $1.28 \pm 0.55$), and older gestational age ($6.4 \pm 0.93$ vs. $5.4 \pm 0.80$), time to β-hCG and sonographic resolutions were significantly shorter in the local MTX group (Group 1). Additionally, duration of hospitalization and cost of the treatment was lower in the local MTX group (Group 1), but the former did not reach statistical significance ($p = 0.76$).

Reproductive outcome after CSP is main concern for the patients and caring physicians. Under natural conditions, 75% of women trying to conceive at age 30 years will have a conception ending in a live birth within 1 year; 66% at age 35 years; and 44% at age 40 years [29]. The data regarding reproductive performance after CSP were scarce and limited. Maymon et al. reported a 44% pregnancy rate, 75% live-birth rate, and 25% recurrent CSP rate in their series containing 18 patients treated with systemic or local MTX injection [30]. Michener and Dickonson [31] followed thirteen patients after CSP and reported a 31% pregnancy and a 100% live-birth rate n patients treated either with systemic or local MTX injection. Ben Nagi et al. [32] showed that 21 of 24 women who wanted to get pregnant achieved pregnancy (88%), with a 42% live-birth rate. In their literature review, Maymon et al. [30] analyzed 90 cases, and reported a 58% pregnancy and 11% recurrent CSP rate. It is important to keep in mind that the reproductive performance of the couples is affected by a variety of factors, such as age, ovarian reserve, coital frequency, and pelvic pathologies. Because the aforementioned studies are mostly retrospective and did not consider those factors, the reproductive outcomes differed significantly. In addition, follow-up periods were not standard in these studies and usually were not reported. In the present study, clinical pregnancy and live-birth rates were similar to those found in previous studies (40.7% and 25.9%, respectively) and were not statistically different among treatment groups.

In conclusion, in the study, both local and systemic MTX treatments were effective in the treatment of CSP with total success. Local MTX has more a favorable side effects, recovery-time, and treatment-cost profile, even in patients with advanced gestational age. According to our results, conventional treatment and follow-up protocols of local and systemic MTX should be revised.

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