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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.

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.