



Ultrasound-guided local injection of methotrexate and systemic intramuscular methotrexate in the treatment of cesarean scar pregnancy

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Objective

To assess the efficacy and safety of ultrasound-guided intragestational injection of methotrexate (MTX) and systemic intramuscular MTX in the management of cesarean scar pregnancies.

Methods

This was a retrospective case-control study that included women diagnosed with cesarean scar pregnancy at CHA Bundang Medical Center unit between 2009 and 2015. The 26 cases were managed with local injection of MTX under ultrasound guidance and 15 cases were treated with systemic intramuscular of MTX. After the procedure, serial follow-up sonographic examination and serum beta-human chorionic gonadotropin (β -hCG) measurement were performed.

Results

The mean initial β -hCG level was 20,610.73 mIU/mL and ranged from 263.00–71,316.50 mIU/mL. Mean gestational age was 6.3 weeks and ranged from 4.8 to 8.5 weeks. The majority of ectopic cases were treated successfully and follow-up β -hCG level declined abruptly following the first dose of MTX. The rate of success of local MTX treatment was significantly higher than that of systemic MTX treatment. It was 93.75% vs. 73.33%, respectively ($P < 0.05$).

Conclusion

Ultrasound-guided intragestational injection of MTX is an effective method for the management of cesarean scar pregnancies and is associated with minimal side effects and high treatment success.

Keywords: Cesarean scar pregnancy; Ultrasonography; Guideline; Methotrexate

Introduction

A cesarean scar pregnancy (CSP) is a rare and potentially life-threatening form of ectopic pregnancy in which the embryo implants in an iatrogenic cesarean scar [1]. Therefore, the accurate and early diagnosis of CSP is very important for prognosis. In recent years, the measurement of serum beta-human chorionic gonadotropin (β -hCG) has become easier and the use of ultrasound imaging has permitted earlier and more accurate diagnosis of CSP, thereby facilitating the successful preservation of the uterus without causing maternal complications [2].

CSP may be managed conservatively with intragestational methotrexate (MTX) injection, systemic MTX administration,

or both; surgical evacuation with or without balloon catheter; and uterine artery embolization [3]. Although MTX-based

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chemotherapy has been recognized as a relatively convenient and safe method of treatment, there have been no reports on the efficacy of local or systemic therapies for CSP. Given the low incidence of CSP, few studies have evaluated the success rate of MTX treatment and the risk factors for predicting treatment failure.

The aim of the present study was to compare the clinical therapeutic effectiveness and safety of local MTX treatment in CSP vs. systemic MTX treatment.

Materials and methods

This was a retrospective, case-control study conducted in the Department of Obstetrics and Gynecology of CHA Bundang Medical Center. Women who visited the hospital for treatment of CSP between January 1, 2009 and February 12, 2015, were consecutively enrolled in the study. CSP was diagnosed by patient history, clinical manifestations, β -hCG titer, and standard ultrasonography criteria.

Eight patients with rupture of the gestational sac requiring immediate surgical treatment were excluded from the cases of 49 patients diagnosed with CSP. Forty-one women with CSP were divided into 2 treatment groups: those receiving systemic MTX intramuscular administration (systemic MTX group, n=15) and those receiving local MTX injection in CSP treatment (local MTX group, n=26).

1. Diagnosis and treatment

The diagnosis standard of transvaginal ultrasound (ATL 5000; Philips Medical Systems, Bothell, WA, USA) and β -hCG level were used for diagnosis and follow-up.

The diagnostic criteria of transvaginal ultrasound were as follows: 1) an empty uterine cavity, with a clearly demonstrated endometrium; 2) an empty cervical canal; and 3) a gestational sac, with or without fetal cardiac activity, was located in the anterior part of the uterine isthmus, embedded in and surrounded by the myometrium and the fibrous tissue of the scar, and separated from the endometrial cavity or fallopian tube [4].

All of the 15 patients in the systemic MTX group received (50 mg/m² body surface area) intramuscular MTX administration. Ultrasonography imaging and serum β -hCG were performed on day 7 after MTX administration. Treatment failure was defined as a reduction in serum β -hCG titer by <15% or an

increase in serum β -hCG titer from pre-therapy levels these patients received additional treatment.

The 26 patients in the local MTX group received an injection of MTX (50 mg/m² body surface area) directly into the CSP. All patients were retrospectively followed up with ultrasonography and serial β -hCG measurements.

The following clinical characteristics were evaluated: maternal age, parity, gestational age, previous cesarean deliveries, previous dilatation and evacuation, mean gestational distance, initial serum β -hCG and time to resolution of β -hCG less than 5 mIU/mL.

2. Statistical analysis

Data were collected and evaluated for parametric and non-parametric analysis. Mean \pm standard deviation is presented for continuous and ordinal data, whereas categorical data are presented as the absolute count and percentage. Statistical analysis was performed with the SPSS package (SPSS, Chicago, IL, USA). Statistical significance was calculated using the χ^2 test and the *t*-test for differences in continuous variables. Odds ratios and their 95% confidence interval were computed. *P*<0.05 was considered statistically significant.

Results

The clinical characteristics of pregnancies are shown in Table 1. A total of 41 cases were enrolled in the study. The mean age of the patients was 34.6 years (range 25–42 years). The mean abortion history was 1.68 times and the mean cesarean section was 1.36 times. The mean quantitative serum β -hCG at the time of initial diagnosis was 20,610.73 mIU/mL (range 263–71,316.50 mIU/mL) and the mean gestational age was 6.6 weeks (range 4.6–8.4 weeks). All patients were hemodynamically stable and had an unruptured ectopic pregnancy.

The local MTX treatment involved an injection of MTX (25 mg/mL solution) directly into the CSP lesion. The injection was administered transvaginally under continuous ultrasound guidance using a 20-gauge needle. Anesthesia was not performed and the procedure was performed on the outpatient department. Ultrasonography was performed for approximately 10 minutes after the injection to confirm that the procedure was complete.

After local and systemic administration of MTX, patients were followed up with regular ultrasound and serum β -hCG

levels. Follow-up consisted of weekly outpatient clinical assessment and measurements of serum β -hCG levels. Once β -hCG levels declined to <25 IU/L, an ultrasound examination was performed to assess the size of the retained products of conception. Ultrasound examinations were then arranged on a monthly until it was confirmed that all pregnancy tissue had been spontaneously expelled or absorbed.

The comparison of demographic data of the 2 groups according to treatment method is shown in Table 1. The mean time to normalization of β -hCG was 56.4 days and 41 days in the local and systemic treatment groups, respectively (Table 1). There were no statistically significant differences between groups with respect to maternal age, parity, previous caesarean deliveries, and previous dilatation and evacuation; however, gestational age was significantly higher in the local MTX treatment than in systemic MTX treatment. And the 2 groups did not differ with respect to gestational age at the start of treatment. Furthermore, the success rate of treatment was significantly higher in the local MTX treatment compared to the systemic MTX treatment was 93.75% vs. 73.33%, respectively.

There are reports between the local MTX group and the systemic MTX group with respect to maternal age, previous abortion, initial β -hCG, result of treatment, and resolution time to normal β -hCG (Tables 2 and 3).

Local MTX administration resulted in normalization of β -hCG at a dose significantly lower than that of systemic intramuscular administration. In other words, after local MTX treatment, serum β -hCG levels declined rapidly over days and then more gradually, without additional elevation of serum

β -hCG. In contrast, after systemic MTX treatment, serum β -hCG levels increased for the first 2 days, and then gradually declined with a mean resolution time of 41 days (Figs. 1 and 2). In addition, local MTX treatment was more effective than systemic therapy and the former treatment was associated with a minimal side effect profile.

There were no cases of adverse events following local MTX treatment. In the systemic MTX treatment, 2 patients experienced gastrointestinal complaints such as nausea and vomiting. However, more severe adverse effects such as leukopenia, thrombocytopenia, liver toxicity, and hair loss were not observed in either group. No patients treated with local MTX injection were admitted to the hospital, but the average length of hospital stay was 10 days in the systemic MTX treatment.

In comparison, there were no side-effects in the group of women who received local therapy suggesting that local MTX injection treatment appears to be more successful and better tolerated by patients and may be used as the first-line therapy.

Discussion

The incidence of CSP is rapidly rising because of the increased use of ultrasound in early gestation and the rising rate of cesarean section delivery [5]. Between 2009 and 2012, only 6 patients were detected or referred to our department for treatment of CSP, whereas the remainder of the patients enrolled in this study were referred to us during last 3 years (2012–2015) thereby supporting previous evidence that there has been a trend toward an increased CSP incidence.

Table 1. Demographic data of the 2 subgroups according to treatment method

Characteristics	Cesarean section scar pregnancies (n=41)	Local injection (n=26)	Systemic injection (n=15)	P-value
Age (yr)	34.6±4.5 (25–42)	34.8±4.3	34.2±5.0	0.696
History of D&C	1.68±1.17 (0–4)	1.77±1.27	1.53±0.99	0.541
History of C/S	1.37±0.76 (0–3)	1.42±0.86	1.27±0.59	0.536
Gestational age (wk)	6.35±0.90 (4.9–8.6)	6.63±0.95	5.86±0.55	0.002
MGD (mm)	14.90±6.82 (4.8–35.5)	15.65±6.90	13.58±6.64	0.355
Initial serum β -hCG concentration (mIU/mL)	20,610.73±19,335.00 (263.0–71,616.5)	24,539.17±21,445.10	13,801.44±12,982.30	0.087
Time to normal β -hCG (day)	51.70±21.00 (16–100)	56.40±21.60	41.00±15.88	0.051
Rate of successful treatment	36/41 (87)	25/26 (93.75)	11/15 (73.33)	0.041

Data are shown as mean±standard deviation (range) or number (%).

D&C, dilatation and curettage; C/S, cesarean section; MGD, mean gestational sac diameter; β -hCG, beta-human chorionic gonadotropin.

Table 2. Characteristics of the 26 pregnancies treated with local methotrexate injection

Patients	Age (yr)	History of D&C	History of C/S	EGA (wk)	MGD (mm)	Initial β -hCG	Local injection	Result	Resolution time (day)
1	33	2	2	8.1	8.4	2,924.8	MTX 50 mg	Success	26
2	32	4	2	5.4	5.8	5,121.2	MTX 50 mg	Failure	D&E
3	33	2	1	5.2	5.4	5,539.0	MTX 50 mg	Success	45
4	36	0	1	7.1	16.0	6,948.5	MTX 50 mg	Success	45
5	31	1	1	6.2	8.5	12,303.1	MTX 50 mg	Success	40
6	29	0	1	5.5	11.7	20,386.2	MTX 50 mg	Success	69
7	41	3	1	5.5	21.9	66,765.0	MTX 50 mg	Success	80
8	36	3	1	7.5	17.1	15,807.0	MTX 50 mg	Success	50
9	40	4	2	6.5	11.1	21,245.0	MTX 50 mg	Success	65
10	38	1	2	7.0	16.3	13,473.0	MTX 50 mg	Success	34
11	37	3	1	6.4	18.0	30,951.0	MTX 50 mg	Success	40
12	38	1	2	6.2	11.5	16,684.0	MTX 50 mg	Success	80
13	30	0	0	6.6	19.1	2,208.7	MTX 50 mg	Success	54
14	38	2	0	4.6	13.1	4,748.8	MTX 50 mg	Success	35
15	38	3	1	6.2	8.8	12,003.1	MTX 50 mg	Success	27
16	34	2	0	6.3	10.7	7,747.9	MTX 50 mg	Success	83
17	29	0	3	5.6	8.0	21,225.9	MTX 50 mg	Success	50
18	41	2	1	8.4	35.5	71,316.5	MTX 50 mg	Success	76
19	28	1	1	6.2	13.0	6,448.6	MTX 50 mg	Success	16
20	38	1	2	6.2	20.0	23,712.0	MTX 50 mg	Success	80
21	26	1	1	8.4	16.1	63,133.0	MTX 50 mg	Success	40
22	30	0	1	8.0	20.0	21,361.0	MTX 50 mg	Success	60
23	38	2	3	6.6	23.9	42,076.0	MTX 50 mg	Success	100
24	36	2	3	6.1	24.0	54,418.0	MTX 50 mg	Success	70
25	38	4	2	6.5	22.2	31,540.0	MTX 50 mg	Success	75
26	38	2	2	6.4	20.9	57,931.0	MTX 50 mg	Success	71

D&C, dilatation and curettage; C/S, cesarean section; EGA, estimated gestational age; MGD, mean gestational sac diameter; β -hCG, beta-human chorionic gonadotropin; MTX, methotrexate.

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 are preferable over surgical treatments. Therefore, a variety of treatment modalities have been proposed and studied [6].

Local and systemic MTX treatment are the 2 most widely used modes of treatment of CSP. Local intragestational MTX injection is one of the most popular treatments for CSP because of the prompt response and minimal side-effect profile such as leukopenia, thrombocytopenia and liver toxicity. However, studies evaluating the outcome of local MTX injection have reached conflicting results. Seow et al. [7] treated 11 women with non-ruptured CSP and reported that 6 patients

required additional systemic MTX administration. The authors reported that treatment success depended on β -hCG levels (<20,000 mIU/mL) and suggested that administration of additional systemic intramuscular MTX reduced rupture in patients whose β -hCG levels continued to rise the day after local MTX injection. Cheung [8] reviewed the existing literature on CSP treatment 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%.

In contrast, Hafner et al. [9] reported that local therapy was successful in all 5 cases (100%), whereas 4 out of 5 (80%) women receiving systemic intramuscular MTX were cured. Significant side-effects were noted in 2 women following systemic therapy. In comparison, there were no side-effects in

Table 3. Characteristics of the 15 pregnancies treated with systemic intramuscular methotrexate injection

Patients	Age (yr)	History of D&C	History of C/S	EGA (wk)	MGD (mm)	Initial β -hCG	Systemic injection times	Result	Resolution time (day)
1	25	2	1	5.3	4.8	17,800.7	3	Success	57
2	35	2	1	6.0	24.0	34,686.8	2	Success	30
3	37	2	1	6.2	9.0	9,965.7	1	Failure	D&E
4	38	3	2	5.3	16.6	43,144.0	1	Failure	D&E
5	31	1	2	6.1	6.4	1,894.0	4	Success	20
6	30	1	1	5.1	8.4	3,576.0	5	Success	50
7	38	1	1	6.4	14.3	3,455.0	2	Success	22
8	37	0	2	6.4	16.7	29,543.0	4	Failure	D&E
9	37	0	1	6.5	28.5	263.0	2	Failure	UAE
10	28	3	2	5.6	16.5	17,752.0	4	Success	68
11	36	1	2	5.0	10.8	7,861.0	4	Success	30
12	40	3	1	5.6	18.5	16,648.0	4	Success	40
13	32	1	1	5.1	11.0	10,081.0	3	Success	40
14	28	1	1	6.0	10.5	8,750.0	4	Success	60
15	42	2	0	5.5	7.7	1,601.4	4	Success	34

D&C, dilatation and curettage; C/S, cesarean section; EGA, estimated gestational age; MGD, mean gestational sac diameter; β -hCG, beta-human chorionic gonadotropin; UAE, uterine artery embolization.

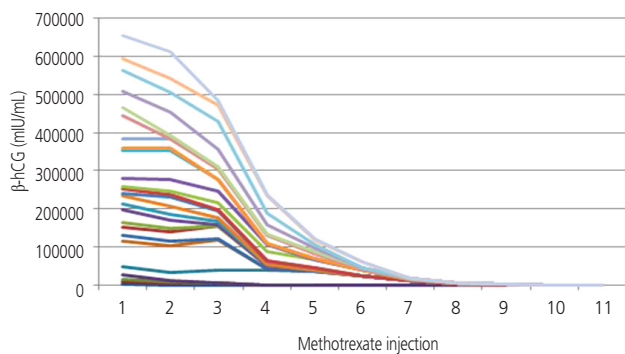


Fig. 1. Beta-human chorionic gonadotropin (β -hCG) levels (mIU/mL) after local methotrexate (MTX) injection.

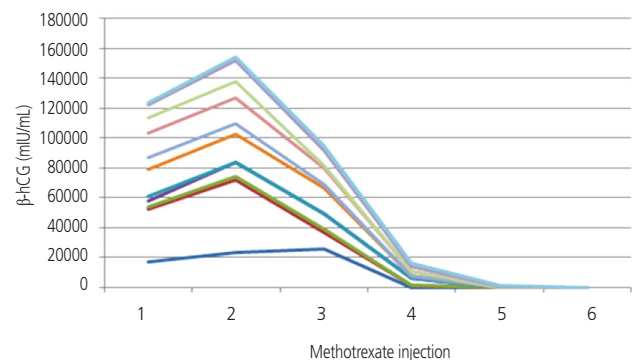


Fig. 2. Beta-human chorionic gonadotropin (β -hCG) levels (mIU/mL) after systemic methotrexate (MTX) injection.

the group of women who received local therapy. Suggesting that local administration appears to be more successful and better tolerated by patients and may be used as the first-line therapy.

In this study, although the initial β -hCG was significantly higher in the local MTX treatment. The success rate of the latter group was higher than that of the systemic MTX treatment. As explained in previous studies [7-9], comparing 2 treatments showed conflicting results elevation and/or limited decrease of β -hCG after local injection suggests treatment failure, and patients received additional treatment. However,

our data showed that serum β -hCG levels after local injection declined rapidly over days and then more gradually without additional therapy. In contrast, after administration of systemic intramuscular MTX, serum β -hCG levels increased for the first 2 days, and then gradually declined with additional therapy. This phenomenon may be due to the fact that disruption of the chorionic sac may exacerbate the initial cytotoxic lysis of the trophoblast, and lead to a prompt increase of β -hCG following systemic MTX treatment [10]. Alternatively, the steady decline of β -hCG levels following local MTX injection may be because local MTX injection is rapidly absorbed into not only

the gestational sac but also into the adjacent placental tissues at a sufficiently high concentration to promote necrosis of the placental trophoblast [11].

It is believed that CSP is more likely to be successful in the local MTX treatment because not only it is surrounded by fibrous scar tissue rather than the normal myometrium [12]. But also blockage of the uterus circulation and accumulation of MTX inside the intragestational sac [13]. In this respect, local intragestational MTX injection is one of the most useful treatments for CSP because of the prompt response and no side-effect profile. In addition, the recent development of assisted reproductive technology is increasing the number of combined pregnancies, which is also a method of treatment, although it is not yet established. However, it is thought that local MTX injection treatment may be a better choice for postoperative improvement prognosis and better outcomes than systemic MTX treatment for cesarean section scar pregnancy in combined normal intrauterine pregnancy, in light of adverse effects of MTX on intrauterine pregnancy.

There were some limitations of this study. This was retrospective observational study, and the 2 treatment groups were not equally matched for treatment. The data shown include patients with older gestational age, larger MGD size, and higher initial β -hCG levels in the local MTX treatment. Additionally, the rate of success was higher in the local MTX treatment and this was statistically significant ($P=0.041$). A large study sample should be enrolled in future studies for more meaningful results. Furthermore, it is necessary to carry out further studies through a large prospective randomized trial.

In conclusion, in this study, both local and systemic MTX treatment were effective in the treatment of CSP with total success. Local MTX treatment has a higher success rate compared to systemic MTX treatment. According to our results, the local MTX treatment would be the superior option to systemic MTX treatment for the therapy of hemodynamically stable patients with CSP who desire to become pregnant in the future.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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