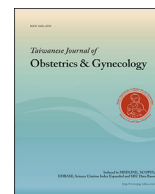




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Original Article

hCG values and gestational sac size as indicators of successful systemic methotrexate treatment in cesarean scar pregnancy



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ABSTRACT

Objective: To retrospectively investigate cesarean scar pregnancy (CSP) patients who received systemic methotrexate (MTX) and to clarify the criteria for administering systemic MTX to CSP patients.

Materials and methods: Fifteen CSP patients who were initially treated with systemic MTX (50 mg/m²/week) were included. Nine patients, who needed a uterine artery embolization (UAE) or a laparotomy, including a transabdominal hysterectomy (TAH), were defined as the unsuccessful MTX group. Six patients who did not require UAE or a laparotomy were defined as the successful MTX group. Furthermore, the hCG cut-off value and the GS cut-off size at the time of CSP diagnosis, which differentiated successful and unsuccessful patients, were defined. MTX success rates were investigated by combining the hCG and gestational sac (GS) size cut-off values.

Results: The hCG cut-off value was 17757.0 mIU/mL, and the GS cut-off size was 10.4 mm. In patients with hCG values less than 17757.0 mIU/mL, the MTX success rate was 75.0%. Fewer patients needed UAE or a laparotomy compared to patients with hCG values higher than 17757.0 mIU/mL ($P = 0.007$). In patients with a GS size less than 10.4 mm, the MTX success rate was 80.0%. Fewer patients among them needed UAE or a laparotomy compared to those among patients with a GS size greater than 10.4 mm ($P = 0.089$). In patients with hCG values and GS sizes lower than the cut-off values, the MTX success rate was 80.0%. Fewer patients among them needed UAE or a laparotomy compared to those among patients with hCG values and/or GS sizes higher than the cut-off values, respectively ($P = 0.010$).

Conclusion: Patients with hCG values less than 17757.0 mIU/mL and GS sizes less than 10.4 mm may have a greater chance of successful systemic MTX treatment when it is used as the first line of treatment for CSP.

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Introduction

In recent years, the frequency of cesarean section deliveries has increased along with the incidence of cesarean scar pregnancies (CSPs) [1,2]. It has been reported that CSP occurs in 0.15% of pregnancies, accounting for 6.1% of all ectopic pregnancies [3]. In the management of CSP, early diagnosis and prompt treatment are vital in the prevention of catastrophic maternal hemorrhage. However, it has also been reported that some CSPs can continue to full-term [4]. At present, there is no consensus regarding the treatment of CSP.

Many previous publications have discussed the medical treatment of CSP patients using methotrexate (MTX) [5–13]. In a randomized controlled trial reported by Peng et al. the therapeutic effects of systemic MTX and local MTX administration were examined [5]. The completion rate of treatment was 67.3% for the administration of systemic MTX and 69.2% for the administration of local MTX, and both routes were deemed effective [5]. However, as CSP can cause massive bleeding during the course of MTX treatment, some of the patients required uterine artery embolization (UAE) or a transabdominal hysterectomy (TAH) [14]. Further studies are required in order to clarify and enhance the effects of MTX in CSP patients. To increase the therapeutic effect of MTX, it is necessary to examine the effectiveness of systemic MTX for CSP and clarify the criteria for administering systemic MTX for CSP.

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Therefore, this study retrospectively investigated patients who received systemic MTX for CSP across multiple perinatal medical centers and compared CSP patients who were successfully and unsuccessfully treated with systemic MTX. This study aimed to clarify the criteria for administering systemic MTX for CSP.

Patients and methods

Fifteen patients who were diagnosed with CSP in early pregnancy and received systemic MTX (50 mg/m² per week) as the first treatment were included in this study. These patients were treated in 11 perinatal medical centers between January 2006 and December 2015. The criterion for a diagnosis of CSP included the absence of a gestational sac (GS) in the uterine cavity or cervical canal and the presence of a GS in the cesarean scar site in early pregnancy. Patients who were diagnosed with CSP in the early stages of pregnancy and received local MTX and potassium chloride (KCl) were excluded along with patients who selected surgery as the first treatment option. Systemic MTX was administered between one and seven times, based on the human chorionic gonadotropin (hCG) values. Indications of repeated MTX injection included a lack of extensive bleeding during the clinical course of CSP and a decrease in hCG values after systemic MTX administration. If there was massive bleeding during the clinical course of CSP and/or no decrease in hCG values after systemic MTX administration, the administration of these injections was stopped. Indications for UAE or laparotomy after systematic MTX administration included extensive bleeding, an increased risk of extensive bleeding, and/or no decrease in hCG levels. Patients who needed UAE or a laparotomy, including TAH, were defined as the unsuccessful systemic MTX group, and patients who did not need UAE or laparotomy were defined as the successful systemic MTX group. Age, number of pregnancies, number of deliveries, number of previous cesarean sections, number of gestational weeks at the diagnosis of CSP, hCG levels at the time of CSP, the size of the GS at the time of CSP diagnosis, the presence of a fetal heartbeat at the time of CSP diagnosis, and the presence of genital bleeding the time of CSP diagnosis were retrospectively compared between the two groups. Using a receiver operating characteristic (ROC) curve, the hCG cut-off value at CSP diagnosis and the size of the GS at CSP diagnosis were identified in the two groups. The patients were divided on the basis of the hCG cut-off value and the size of the GS at the time of CSP diagnosis. The success rates of systemic MTX were investigated by combining the hCG cut-off value and the cut-off size of the GS.

The Mann–Whitney U test and the Fisher's test were used for statistical analysis; $P < 0.05$ was considered to be significant.

GraphPad Prism 8.2.0 (GraphPad Software Inc., La Jolla, CA, USA) was used to perform the statistical analysis.

This study was conducted under the approval of the Ethics Committees of each institution. The requirement for informed consent was waived by the ethics committees because the information used in this retrospective study, including the research plans, had been previously published on the internet.

Results

The characteristics of patients who received medicinal therapies as the first treatment for CSP are shown in Table 1. At the time of CSP diagnosis, the median number of gestational weeks was six weeks (range, five–eight weeks), the median hCG value was 14491.2 mIU/mL (range, 2271.0–88502.8 mIU/mL), and the median size of the GS was 13.0 mm (range, 3.5–51.0 mm). Of the total 15 patients, five patients (33.3%) exhibited fetal heartbeats, 10 (66.7%) exhibited genital bleeding, and three (20.0%) received blood transfusions during the treatment. Of the total 15 patients, five (33.3%) were able to have future pregnancies (Table 1).

Of the 15 CSP patients who selected systemic MTX as their first treatment, treatment was unsuccessful in nine patients (60.0%) and successful in six patients (40.0%) (Table 1). The hCG value was significantly higher in the unsuccessful group than in the successful group (Table 1). There was no difference in the MTX dose between the unsuccessful group and the successful group (Table 1).

Using an ROC curve, the hCG cut-off value and size of the GS at CSP diagnosis were identified in the successful and unsuccessful patients. An hCG value of 17757.0 mIU/mL (area under curve [AUC]: 0.85, sensitivity: 77.8, specificity: 100.0) and a GS size of 10.4 mm (AUC: 0.74, sensitivity: 88.9, specificity: 66.7) were determined as cut-off values that differentiated successful from unsuccessful patients.

Of the eight patients with hCG values less than 17757.0 mIU/mL, six (75.0%) did not need UAE or a laparotomy, and only two patients (25.0%) needed UAE or a laparotomy. However, of the seven patients with hCG values of 17757.0 mIU/mL or higher, all patients needed UAE or a laparotomy. In the group with hCG values less than 17757.0 mIU/mL, significantly fewer patients needed UAE or a laparotomy compared to patients with hCG values of 17757.0 mIU/mL or higher ($P = 0.007$) (Fig. 1).

Among the five patients with a GS size less than 10.4 mm, four (80.0%) did not need UAE or a laparotomy, and only one (20.0%) needed UAE or a laparotomy. Among the 10 patients with a GS size of 10.4 mm or larger, two (20.0%) did not need UAE or a laparotomy, and eight (80.0%) did need UAE or a laparotomy. In the group with GS sizes less than 10.4 mm, fewer patients needed UAE or a

Table 1

Characteristics of 15 patients who chose systemic methotrexate as their first CSP treatment and a comparison of the characteristics in successful and unsuccessful patients treated with systemic MTX.

	All patients (n = 15)	Unsuccessful group (n = 9)	Successful group (n = 6)	P – value
Age (years) ^a	34.0 (27.0–44.0)	34.0 (32.0–42.0)	35.0 (27.0–44.0)	0.836
Number of pregnancies ^a	2.0 (1.0–5.0)	2.0 (1.0–5.0)	2.0 (2.0–4.0)	1.000
Number of deliveries ^a	2.0 (1.0–5.0)	2.0 (1.0–5.0)	1.5 (1.0–2.0)	0.461
Number of previous cesarean sections ^a	2.0 (1.0–5.0)	2.0 (1.0–5.0)	1.5 (1.0–2.0)	0.511
Gestational weeks at the diagnosis of CSP (weeks) ^a	6.0 (5.0–8.0)	6.0 (5.0–8.0)	5.5 (5.0–7.0)	0.605
hCG value at the diagnosis of CSP (mIU/ml) ^a	14491.2 (2271.0–88502.8)	25523.0 (3130.0–88502.8)	9195.0 (2271.0–14491.2)	0.026
GS size at the diagnosis of CSP (mm) ^a	13.0 (3.5–51.0)	16.0 (3.5–51.0)	10.0 (9.0–28.0)	0.143
MTX dose (mg)	150 (50–350)	100 (50–300)	150 (50–350)	0.195
Presence of fetal heartbeat	5 (33.3%)	4 (44.4%)	1 (16.6%)	0.287
Genital bleeding	10 (66.7%)	5 (55.6%)	5 (83.4%)	0.580
Blood transfusion	3 (20.3%)	3 (33.3%)	0 (0.0%)	0.229
Future pregnancies	5 (33.3%)	3 (33.3%)	2 (33.3%)	1.000

CSP, cesarean scar pregnancy; GS, gestational sac; MTX, methotrexate.

^a Data are presented as medians (range).

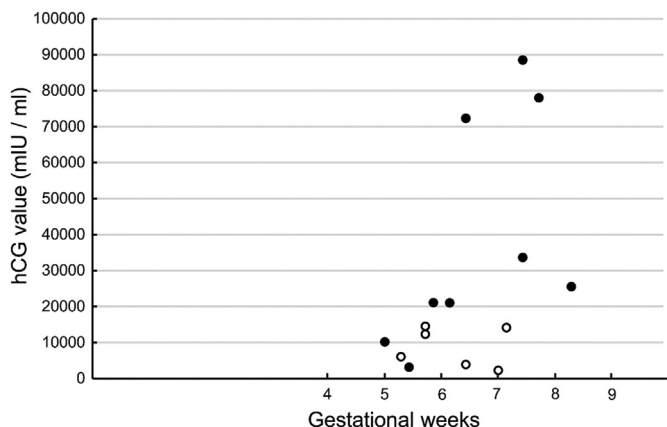


Fig. 1. hCG values at the time of CSP diagnosis in 15 patients. ○: Successful systemic MTX treatment patients. ●: Unsuccessful systemic MTX treatment patients. CSP, cesarean scar pregnancy; MTX, methotrexate.

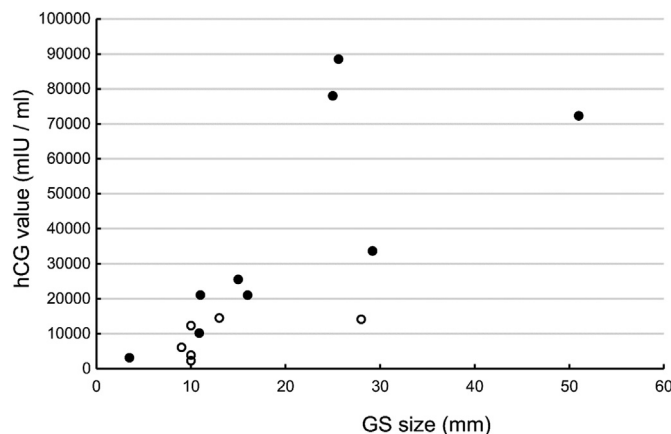


Fig. 3. hCG value and GS size at the time of CSP diagnosis in 15 patients. ○: Successful systemic MTX treatment patients. ●: Unsuccessful systemic MTX treatment patients. CSP, cesarean scar pregnancy; MTX, methotrexate.

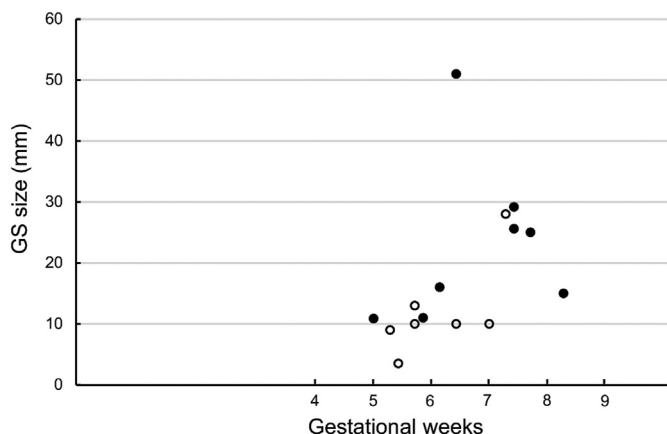


Fig. 2. GS size at the time of CSP diagnosis in 15 patients. ○: Successful systemic MTX treatment patients. ●: Unsuccessful systemic MTX treatment patients. CSP, cesarean scar pregnancy; MTX, methotrexate.

laparotomy than patients with GS sizes of 10.4 mm or larger ($P = 0.089$) (Fig. 2).

Among the five patients with hCG values less than 17757.0 mIU/mL and GS sizes less than 10.4 mm, four (80.0%) did not need UAE or a laparotomy, and only one (20.0%) needed UAE or a laparotomy. Among the seven patients with hCG values of 17757.0 mIU/mL or higher and GS sizes 10.4 mm or larger, all patients needed UAE or a laparotomy. Compared to the group with hCG values less than 17757.0 mIU/mL and GS sizes less than 10.4 mm, the number of patients who needed UAE or a laparotomy was significantly greater in the group with hCG values of 17757.0 mIU/mL or higher and/or GS sizes of 10.4 mm or higher ($P = 0.010$) (Fig. 3).

Discussion

The results of this study revealed that hCG values less than 17757.0 mIU/mL and GS sizes less than 10.4 mm are indications that MTX medical treatment is likely to successfully treat CSP patients.

There are cases in which UAE and/or TAH are required because of extensive bleeding and uterine rupture during the treatment for CSP. In a systematic review reported by Petersen et al. the success rate of dilatation and curettage (D&C) for treating CSP patients was 48.1%, and serious complications occurred in 21.0% of patients. The success rate of D&C or hysteroscopy after UAE has been reported as

95.4% and the serious complication rate reported as 1.2% [14]. The hemostatic effects of UAE are very important for controlling extensive bleeding, and UAE is considered to have therapeutic effects on CSP. However, a systematic review by Soro et al. reported that UAE affected the occurrence of implantation and placenta accrete [15]. Thus, UAE should not be used indiscriminately in CSP patients who desire future pregnancies. As an alternative, MTX has been used as one of the first treatment options for CSP patients.

In this study, the success rates of systemic MTX were 75.0% in patients with hCG values less than 17757.0 mIU/mL, 80.0% in patients with GS sizes less than 10.4 mm, and 80.0% in patients with both an hCG value less than 17757.0 mIU/mL and a GS size less than 10.4 mm. The success rates of these groups were equal to or higher than the success rates for systemic MTX reported in the systematic review reported by Petersen et al. [14]. In CSP patients with hCG values less than 17757.0 mIU/mL and CSP patients with GS sizes less than 10.4 mm, systemic MTX should be the first treatment choice for patients who wish to have future pregnancies. Additionally, the success rate of systemic MTX was 0.0% in patients with hCG values 17757.0 mIU/mL or higher, 20.0% in patients with GS sizes of 10.4 mm or larger, and 0.0% in patients with both an hCG value of 17757.0 mIU/mL or higher and a GS size of 10.4 mm or larger. The success rates in these groups were very low. It has been suggested that systemic MTX should not be recommended for CSP patients with hCG values of 17757.0 mIU/mL or higher and CSP patients with a GS size of 10.4 mm or larger. Interventional therapies, such as D&C or hysteroscopy after UAE, resection of a CSP through a transvaginal approach, and a laparoscopy, should be recommended instead [14].

This study was retrospective and used data from multiple perinatal medical centers; however, only 15 cases were included in this study. This presented a major limitation; thus, future prospective studies are necessary to determine criteria and management guidelines for MTX use in CSP.

In conclusion, when selecting systemic MTX as the first treatment in CSP patients, those with an hCG value less than 17757.0 mIU/mL and a GS size less than 10.4 mm are likely to achieve positive outcomes.

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Declaration of competing interest

None.

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