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Outcome of cesarean scar pregnancy treated with local methotrexate injection

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ABSTRACT

Local injection of methotrexate (MTX) has been widely used for caesarean scar pregnancy (CSP), but the optimal candidate remains undetermined. The aim of this study is to determine the risk factors associated with treatment failure among patients who received a single dose of local MTX.

This is a retrospective cohort study. Clinical information was compared between treatment success vs. failure groups. Risk factors related to treatment failure were also investigated with multivariate analysis.

Of 47 patients diagnosed with CSP, 30 received local MTX injection. The initial serum ß- human chorionic gonadotropin (hCG) level in the failure group was significantly higher than in the success group ($p = 0.048$), and the cut-off value was 47,000 mIU/ml. The rate of type 2 position of the gestational sac in the failure group was significantly higher than in the treatment success group ($p = 0.031$). A high initial serum ß-hCG level (≥ 47,000 mIU/ml) was identified as the independent risk factor for treatment failure (adjusted odds ratio = 21.9; 95% confidence interval = 1.3–383.1).

Type 2 gestational sac position and a higher level of ß-hCG at diagnosis appear to be associated with poor outcomes after local injection of a single dose of MTX.

Keywords: gestational sac, human chorionic gonadotropin, transvaginal ultrasound

Abbreviations and acronyms:
AUC: area under the curve
CI: confidence interval
CSP: caesarean scar pregnancy
hCG: human chorionic gonadotropin
MTX: methotrexate
OR: odds ratio
ROC: receiver operating characteristic

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INTRODUCTION

The rising frequency of caesarean section rates worldwide has been associated with an increased occurrence of serious complications in subsequent pregnancies, including uterine rupture and placenta accreta.[1] Caesarean scar pregnancy (CSP), the development of a gestational sac in a previous caesarean scar, is one of those complications. CSP is a rare type of ectopic pregnancy, but can be life-threatening. The precise prevalence of CSP is unknown, but the incidence of CSP among normal pregnancies is reportedly 0.05–0.06%,[2] and 0.15% among pregnancies with a previous history of caesarean section.[3]

More than 30 different treatment options have been reported for CSP, including expectant management, medical treatment, uterine artery embolization, surgical intervention, and combination approaches.[4] However, the optimal first-line regimen remains unknown. Recent reviews recommend a minimally invasive method that removes both gestational sac and caesarean scar transvaginally or laparoscopically, rather than medical treatment,[4-6] but randomized controlled trials with a large population to support that recommendation are lacking. Additionally, it should be a concern that availability of equipment and specific surgical skills for these interventions remain limited in some middle-income countries, including Vietnam.

For medical treatment, local or systemic injection of methotrexate (MTX) has been widely used. A single-dose local MTX injection is easily performed using techniques and equipment for ovum collection during in vitro fertilization, without high cost or specialized methods. Local injection is thought to be more effective than systemic injection, with minimal side effects,[7-9] but remains controversial.[10] Medical treatment as the first-line approach is often thought to need additional surgical treatment and several protocols for selection of candidates for medical treatment have been suggested[4]; these are based on gestational weeks, presence of fetal cardiac activity, hemodynamic state, and serum ß-hCG level, among others. It has also been reported that there are 2 types of CSP. In one, the gestational sac grows inward (endogenous, type 1), while the other grows outward toward the bladder and abdominal wall (exogenous, type 2).[11] Type 2 cases are thought to be at high risk of uterine rupture, but the management options based on these types of CSP have not been established.[4] Thus, a guideline for selection of the best candidates for local MTX injection based on characteristics including CSP type is needed, to establish safer and more effective treatment algorithms. Such a guideline would reduce the rate and costs of surgery and treatment for embolism and would be desirable for use in centers with limited resources.

This study aimed to determine the risk factors associated with treatment failure among CSP patients who received local MTX injection with aspiration.

MATERIALS AND METHODS

Study design

This retrospective cohort study included 30 women diagnosed with CSP and treated with a single dose of ultrasound-guided local MTX 50 mg/2 mL (Unitrexate®, Korea United Pharm. Inc.) injection between April 2015 and July 2017 at the Hue Central Hospital, a tertiary hospital in Vietnam. Patients of >12 weeks of gestation at diagnosis, and those with severe vaginal bleeding or hemodynamic changes were excluded.

Gestational age was determined according to the first day of the last menstrual period, sac dimension, or crown-rump length. The gestational sac position was assessed, and diagnosed as type 1 or type 2 using transvaginal ultrasound examination at diagnosis during the first trimester.[11] The initial level of serum β-human chorionic gonadotropin (hCG) was also measured before treatment. Serum ß-hCG levels were measured on the fourth and seventh days and subsequently once a week until the level was below 5 mIU/mL. Ultrasound examination for subtrophoblastic blood flow was also performed weekly. Coagulation, liver, and renal function tests and complete blood counts were also examined before treatment.

Women with CSP were divided into treatment success vs. failure groups; more than 15% reduction in serum ß-hCG level and disappearance of subtrophoblastic blood flow were regarded as treatment success, with treatment failure defined as need for additional intervention for subsequent haemorrhage or increasing serum ß-hCG level after local MTX injection.

Diagnosis of CSP

Transvaginal ultrasound for diagnosis of CSP was performed, with consultation by 2 expert sonographers in all cases, using the following criteria, as defined in previous reports[1,12,13]:

1. Empty uterine cavity and closed empty cervical canal.
2. Placenta and/or gestational sac embedded in the caesarean section scar.
3. Thin (1–3 mm) or absent myometrial layer between the gestational sac and the bladder.
4. Presence of embryonic/foetal pole and/or yolk sac with or without heart activity.
5. Presence of a prominent and at times rich vascular pattern at or in the area of a caesarean section scar in the presence of a positive pregnancy test.
6. Negative ‘sliding organs sign’.

Protocol of Therapy

Transvaginal ultrasound was performed to assess the gestational sac and the presence of a foetal pole. A 22-G needle was inserted into the gestational sac with an adaptor under transvaginal ultrasound. The amniotic fluid and foetal tissues were aspirated and MTX (50 mg/2 ml) was slowly injected into the gestational sac.

Statistical analysis

Statistical analysis was performed using SPSS 24 software. Normally and non-normally distributed variables were presented as mean ± SD and median (minimum - maximum) and compared using Student’s *t*-test and the Mann-Whitney U-test, respectively. Categorical data were presented as absolute value with percentage and compared with Fisher’s exact test, as appropriate. Based on a receiver operating characteristic (ROC) curve and a corresponding area under the curve (AUC), a cut-off value was determined as the point where Youden’s index is at maximum. The crude odds ratio (OR) and adjusted OR with the 95% confidence interval (CI) were calculated using unconditional logistic and multiple logistic regression models, respectively. Statistical significance was considered as $p < 0.05$.

RESULTS

During the study period, 47 women were diagnosed with CSP. Of these, 17 were excluded from the present study population: 14 had successful removal of the gestational sac with uterine preservation and 3 required partial hysterectomy because of unsuccessful preservation surgery. Thirty women who were treated with a single intragestational MTX injection were included in

this study.

The clinical characteristics are shown in Table 1. The mean age was 35.0 ± 4.9 years, and the median gestational age at diagnosis was 7 (5–12) weeks. Before treatment with MTX, vaginal bleeding and lower abdominal pain were reported by 19/30 (63.3%) and 7/30 (23.3%) patients, respectively. The median (minimum - maximum) serum ß-hCG level was 33,628 (804–262,611) mIU/ml. The treatment failure rate was 16.7% (5/30), and subsequent intervention included curettage (n = 1) and hysterectomy (n = 4). None of the 5 failure cases had complications, but a continued increase of serum ß-hCG levels, prolonged or increased hemorrhage, and enlargement of the mass were observed after local MTX injection. Patient age, number of previous caesarean sections, duration since the last caesarean section, percentage with the presence of a fetal heartbeat, presence of symptoms before treatment including vaginal bleeding and abdominal pain, and presence of a hypervascular signal around the gestational sac were not different between the success and failure groups. The frequency of type 1 gestational sac position (endogenous) in the treatment success group was significantly higher than in the treatment failure group (76.0% vs. 20.0%, p = 0.031). The initial serum ß-hCG level in the success group was significantly lower than in the failure group (28,484 (804–262,611) mIU/ml vs. 81,418 (15,436–99,287) mIU/ml, p = 0.048). The cut-off value for the initial serum ß-hCG level for prediction of treatment success or failure of local MTX injection was analysed with ROC curves (Fig. 1, AUC = 0.784), and was determined as 47,000 mIU/ml (80.0% sensitivity, 80.0% specificity). [Fig. 1]

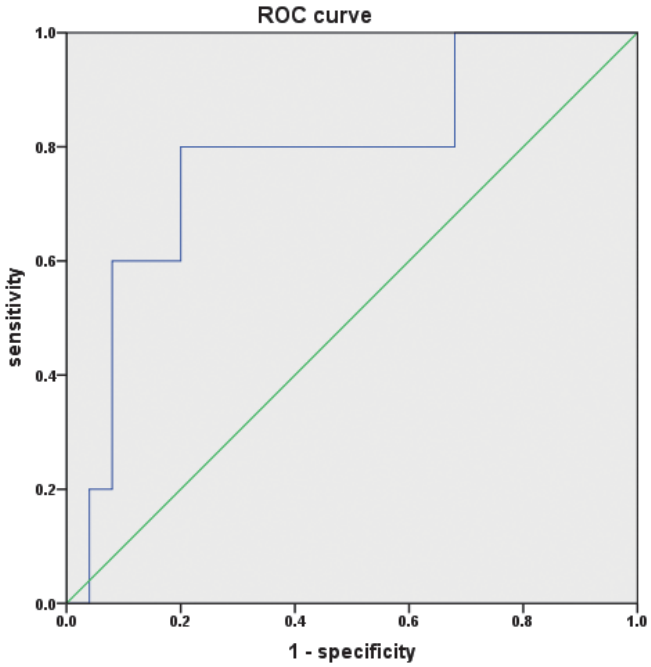

Fig. 1 ROC curve of initial serum ß-hCG level for prediction of treatment failure of local MTX injection The AUC was calculated as 0.784.

Table 1 Comparison of clinical characteristics between treatment success and failure group

Related factors	Total (n=30)	Success (n=25)	Failure (n=5)	*p* value
Age (years)*	35.0 ± 4.9	35.0 ± 4.8	35.0 ± 5.7	1.00
Number of previous CS				
1	16 (53.3)	14 (56.0)	2 (40.0)	0.43
2	14 (46.7)	11 (44.0)	3 (60.0)	
Duration from the last CS (years)*	2.7 ± 0.5	2.8 ± 0.5	2.6 ± 0.5	0.39
Gestational age (weeks)**	7 (5–12)	7 (5–12)	7 (6–8)	0.35
Fetal heart beat				
present	1 (3.3)	1 (4.0)	0 (0.0)	0.83
absent	29 (96.7)	24 (96.0)	5 (100.0)	
Vaginal bleeding				
present	19 (63.3)	16 (64.0)	3 (60.0)	0.62
absent	11 (36.7)	9 (36.0)	2 (40.0)	
Abdominal pain				
present	7 (23.3)	5 (20.0)	3 (60.0)	0.33
absent	23 (76.7)	20 (80.0)	2 (40.0)	
Gestational sac position				
Type 1 (endogenic)	20 (66.7)	19 (76.0)	1(20.0)	0.031
Type 2 (exogenous)	10 (33.3)	6 (24.0)	4 (80.0)	
Initial ß-hCG level (mIU/mL)**	33628 (804–262611)	28484 (804–262611)	81418 (15436–99287)	0.048
Hyper-vascular signal				
positive	16 (53.3)	13 (52.0)	3 (60.0)	0.57
negative	14 (46.7)	12 (48.0)	2 (40.0)	
Total	**30 (100.0)**	**25 (83.3)**	**5 (16.7)**	

CS: Caesarean section, hCG: human chorionic gonadotropin.
Normally and non-normally distributed variables were presented as mean ± SD and median (minimum - maximum) and compared using *Student's *t*-test and **Mann-Whitney *U*-test, respectively. Categorical data were presented as absolute value (%) and compared using Fisher's exact test.

The factors associated with the outcomes of CSP using local injection of MTX were evaluated with univariate analysis (Table 2). Type 2 position and a high initial serum ß-hCG level (≥47,000 mIU/ml) were significant risk factors for failure of local MTX injection [crude OR (95% CI) = 12.7 (1.2–136.3) and 16.0 (1.5–176.5), respectively].

On multiple logistic regression analysis, only high initial serum ß-hCG level (≥47,000 mIU/ml) was associated with a significantly high risk of failure of local MTX injection [adjusted OR (95% CI) = 21.9 (1.3–383.1)] (Table 3). Type 2 position showed a trend as a high-risk factor, but this was not significant [adjusted OR (95% CI) = 17.6 (1.0–313.5)].

Table 2 Factors related with the outcomes of Caesarean scar pregnancy with local methotrexate injection.

Related factors	Success n (%)	Failure n (%)	OR (95% CI)	*p* value*
Number of previous CS				
1	14 (56.0)	2 (40.0)		0.43
2	11 (44.0)	3 (60.0)	1.9 (0.3–13.5)	
Duration since the last CS				
< 2 years	5 (20.0)	2 (40.0)		0.33
≥ 2 years	20 (80.0)	3 (60.0)	0.38 (0.05–2.88)	
Gestational age				
< 7 weeks	12 (48.0)	1 (20.0)		0.26
≥ 7 weeks	13 (52.0)	4 (80.0)	3.7 (0.4–37.9)	
Abdominal pain				
Yes	5 (20.0)	2 (40.0)		0.33
No	20 (80.0)	3 (60.0)	0.38 (0.05–2.88)	
Gestational sac position				
Type 1 (endogenic)	19 (76.0)	1 (20.0)		0.03
Type 2 (exogenous)	6 (60.0)	4 (80.0)	12.7 (1.2–136.3)	
Hyper vascular signal				
Yes	13 (52.0)	3 (60.0)		0.57
No	12 (48.0)	2 (40.0)	1.4 (0.2–9.8)	
Initial ß-hCG level				
< 47,000 mIU/ml	20 (80.0)	1 (20.0)		0.02
≥ 47,000 mIU/ml	5 (20.0)	4 (80.0)	16.0 (1.5–176.5)	

CS, Cesarean section. hCG, human chorionic gonadotropin. OR, odds ratio. CI, confidence interval. OR and 95% CI were calculated by univariate analysis. *p values were calculated by Fisher's exact test.

Table 3 Risk factors related to treatment failure

Risk factors	*p* value	Adjusted OR*	95% CI
Gestational sac position	0.05		
Type 1 (endogenic)		1.0	
Type 2 (exogenous)		17.6	1.0–313.5
Initial ß-hCG level (mIU/mL)	0.04		
< 47,000		1.0	
≥ 47,000		21.9	1.3–383.1

CS, Cesarean section. hCG, human chorionic gonadotropin. OR, odds ratio. CI, confidence interval. *Adjusted for variables including duration since the last CS, gestational age, abdominal pain, gestational sac position, and initial ß-hCG level, and those p values were < 0.4 by univariate analysis.

DISCUSSION

The present study demonstrated that type 2 gestational sac position at diagnosis and a high initial ß-hCG level were significantly more frequent in the treatment failure group after a single dose of local MTX injection for CSP. These results suggested that local MTX injection should be used for CSP patients with type 1 gestational sac position or a low serum ß-hCG level as optimal management. According to multivariate logistic regression analysis, a high initial serum ß-hCG level was the only independent risk factor for treatment failure of local MTX injection.

The success rate of local MTX injection in this study reached approximately 83%, which was comparable to that in previous reports, ranging from 54–94%.[4,7,14] All patients in this study only received a single dose of MTX, although the success rate is known to increase with multiple doses of MTX.[4] Thus, the success rate in this study might be considered high. The median gestational age of this study population was 7 (5–12) weeks, with 1 at 10 weeks and another at 12 weeks, but the others (28/30, 93.3%) were diagnosed before 9 weeks. The earlier diagnosis might have led to the favorable outcome in this study, as previously suggested.[4]

There were no significant differences in clinical characteristics between the success and failure groups, including age, number of previous caesarean section, duration since last caesarean section, gestational age at diagnosis, presence of vaginal bleeding or abdominal pain before treatment, and presence of a hyper-vascular signal. In this study population, all but one case showed absence of a fetal heart beat, and the gestational age at diagnosis in all cases was <13 weeks. Thus, the outcome should be interpreted as applicable to patients diagnosed before 13 weeks and without a fetal heartbeat. On the other hand, the presence of vaginal bleeding, abdominal pain, and a hypervascular signal was observed in 64.0%, 20.0%, and 52.0% of patients, respectively, in the treatment success group. These factors did not seem to be related to treatment failure.

A previous report described similar results with regard to the gestational sac position. In 2 treatment options including local and systemic MTX injection, with or without uterine artery embolization, type 2 CSP position was an independent risk factor for failed management (OR 15.54, 95% CI 1.25–193.36),[14] similar to the finding in the present study. However, that study also reported that the level of ß-hCG before treatment was not significantly different between the treatment success and failure groups. In the present study, the cut-off value of ß-hCG was 47,000 mIU/mL and the median (minimum - maximum) serum ß-hCG level was 33,628 (804–262,611) mIU/ml. In the previous study, all but 1 case had a ß-hCG level ≤50,000 mIU/mL,[14] which would lead to this inconsistency. A systematic review recommended a ß-hCG level of <5,000–12,000 mIU/mL before treatment as the selection criterion in a candidate for medical treatment.[4] Evaluation of the initial ß-hCG level seems useful for treatment decision-making, although the cut-off value remains undetermined.

Considering these results, it is important to assess pregnant women with a previous history of more than 1 caesarean section at 7 to 9 weeks of gestation by ultrasound. The evaluation of CSP type according to gestational sac position and serum ß-hCG level would then be helpful in selecting promising candidates for local MTX injection. An interventional approach should be used as first-line treatment in patients with type 2 CSP or a high level of serum ß-hCG. We also speculated that the diagnosis of CSP at an earlier gestational age would be important for success of local MTX injection because of the association with a low ß-hCG level. However, diagnosis based on symptoms would be difficult, because approximately 20% of patients in this study were asymptomatic (data not shown); this percentage was similar to that in a previous report.[13] Moreover, symptoms of vaginal bleeding and lower abdominal pain could lead to misdiagnosis of miscarriage and inadequate treatment such as curettage, which could be dangerous. Therefore, routine examination using transvaginal ultrasound might be recommended for pregnant women

with a previous history of caesarean section. Actually, asymptomatic patients in this study were diagnosed during routine examinations. Transvaginal ultrasound could provide useful information on the type of CSP according to gestational sac position.

The present study had several limitations. First, this was a retrospective study. Patients who received a local injection of MTX were clinically selected, which might affect the success rate and odds ratio of risk factors. Patients at <13 weeks of gestation without severe vaginal bleeding or hemodynamic changes were selected for treatment with local MTX injection. In addition, other cases that were treated surgically were not included in this study, although such cases might have greater risk than those in this study. The selection criteria may have resulted in bias. A second limitation is that this was a single-center study with a small sample size, although it was comparable to that in previous reports,[10,14] because of the low incidence of CSP. The cut-off value of serum ß-hCG might be different in a larger population. Actually, the cut-off value in this study seemed high compared with previous studies. Thus, the cut-off value for serum ß-hCG should be determined in a larger study population.

CONCLUSION

Type 2 gestational sac position and elevated level of ß-hCG at diagnosis appear to be related to poor outcomes after local injection of a single dose of MTX. This suggests that detection of CSP at a low ß-hCG level would be associated with successful outcomes. During the first trimester, transvaginal ultrasound examination for patients with a previous history of caesarean section might be helpful for earlier detection, and would also be useful to diagnose CSP type. Before selection of first-line treatment with local injection of MTX, evaluation of the type of CSP and the level of ß-hCG should be considered. First-line management of selected patients with local MTX injection seems appropriate in countries with limited resources to avoid unnecessary intervention and reduce costs, although further investigation is required.

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STATEMENT OF ETHICS

Informed and written consent was obtained from all participants. The study protocol has been approved by the ethics committees at Hue University of Medicine and Pharmacy (H2015/182) and Nagoya University Hospital (2015–0153).

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1) Timor-Tritsch IE, Monteagudo A, Santos R, Tsymbal T, Pineda G, Arslan AA. The diagnosis, treatment, and follow-up of cesarean scar pregnancy. *Am J Obstet Gynecol*. 2012;207(1):44 e41–13.
2) Rotas MA, Haberman S, Levgur M. Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. *Obstet Gynecol*. 2006;107(6):1373–1381.
3) Seow KM, Huang LW, Lin YH, Lin MY, Tsai YL, Hwang JL. Cesarean scar pregnancy: issues in management. *Ultrasound Obstet Gynecol*. 2004;23(3):247–253.
4) Glenn TL, Bembry J, Findley AD, et al. Cesarean scar ectopic pregnancy: current management strategies. *Obstet Gynecol Surv*. 2018;73(5):293–302.
5) Birch PK, Hoffmann E, Rifbjerg LC, Svarre NH. Cesarean scar pregnancy: a systematic review of treatment studies. *Fertil Steril*. 2016;105(4):958–967.
6) Kanat-Pektas M, Bodur S, Dundar O, Bakir VL. Systematic review: what is the best first-line approach for cesarean section ectopic pregnancy? *Taiwan J Obstet Gynecol*. 2016;55(2):263–269.
7) Hafner T, Aslam N, Ross JA, Zosmer N, Jurkovic D. The effectiveness of non-surgical management of early interstitial pregnancy: a report of ten cases and review of the literature. *Ultrasound Obstet Gynecol*. 1999;13(2):131–136.
8) Kim YR, Moon MJ. Ultrasound-guided local injection of methotrexate and systemic intramuscular methotrexate in the treatment of cesarean scar pregnancy. *Obstet Gynecol Sci*. 2018;61(1):147–153.
9) Uludag SZ, Kutuk MS, Ak M, et al. Comparison of systemic and local methotrexate treatments in cesarean scar pregnancies: time to change conventional treatment and follow-up protocols. *Eur J Obstet Gynecol Reprod Biol*. 2016;206:131–135.
10) Koch M, Schwab S, Meyer E, et al. Management of uterine ectopic pregnancy: local vs. systemic methotrexate. *Acta Obstet Gynecol Scand*. 2018;97(7):824–829.
11) Vial Y, Petignat P, Hohlfeld P. Pregnancy in a cesarean scar. *Ultrasound Obstet Gynecol*. 2000;16(6):592–593.
12) Ash A, Smith A, Maxwell D. Caesarean scar pregnancy. *BJOG*. 2007;114(3):253–263.
13) Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. First-trimester diagnosis and management of pregnancies implanted into the lower uterine segment Cesarean section scar. *Ultrasound Obstet Gynecol*. 2003;21(3):220–227.
14) Wang M, Yang Z, Li Y, et al. Conservative management of cesarean scar pregnancies: a prospective randomized controlled trial at a single center. *Int J Clin Exp Med*. 2015;8(10):18972–18980.