

# The Effectiveness of Combined Local and Systemic Methotrexate Treatment in Cesarean Scar Pregnancy Weeks 8 to 14

Xuyen Van<sup>1</sup>, Thuong Bui<sup>2</sup>, Hoang The Dinh<sup>3\*</sup>, Thong Van<sup>4</sup>, Anh Tran<sup>5</sup>

<sup>1</sup>Department of Obstetric and Gynecology, Tu Du Maternal Hospital, <sup>2</sup>Department of Obstetric and Gynecology, University of Medicine and Pharmacy, <sup>3</sup>Department of Obstetric and Gynecology, School of Medicine, Vietnam National University, <sup>4</sup>Department of Obstetric and Gynecology, TWG Hospital, Long An, <sup>5</sup>Department of Obstetric and Gynecology, My Duc Hospital, Ho Chi Minh City, Vietnam

## Abstract

**Objectives:** This study aims to identify the success rate and correlated factors of combined local and systemic methotrexate (MTX) injection treatment in cesarean scar pregnancy (CSP).

**Materials and Methods:** The combined local and systemic MTX administration has been used for CSP weeks 8–14 at Tu Du Maternal Hospital; however, its effectiveness and correlated factors have not been closely investigated. This is a retrospective case series of 123 CSP patients between 8 and 14 weeks of gestation who were treated at Tu Du Hospital from the year 2016 to 2020.

**Results:** The success rate, uterine-sparing rate, and side effects of MTX treatment are 50.4%, 95%, and 17.2%, respectively. The factors related to treatment failure with statistical significance included gestational age (odds ratio [OR] = 3.99), residual myometrial thickness >3 mm (OR = 0.37), and postprocedure gestational sac diameter (OR = 1.09).

**Conclusion:** Combined local and systemic MTX injection is minimally invasive and effective in CSP weeks 8–14. Therefore, it should be utilized routinely.

**Keywords:** Cesarean scar pregnancy, methotrexate, residual myometrial thickness

## INTRODUCTION

The rate of cesarean scar pregnancy (CSP) is a rising trend, in correlation with the increasing prevalence of cesarean delivery. At Tu Du Maternal Hospital, a tertiary teaching hospital in South Vietnam, we have recorded an exponentially increase in the number of CSP in recent years. In 2011, there were 192 cases of CSP recorded at Tu Du. The number increased to 875 cases in 2014. It continued to rise to 1380 cases in 2017, 1431 cases in 2018, and 1561 cases in 2019.<sup>[1]</sup> The increasing incidence of CSP leads to increased cases of CSP after 8 weeks, creating many clinical challenges, and elevated risk for severe complications due

to large gestational sac volume and rich blood supplies to the structure.

Methotrexate (MTX), a folate antagonist, is the first-line treatment for ectopic pregnancy.<sup>[2,3]</sup> Therefore, many studies have used MTX in patients with CSP.<sup>[4,5]</sup> Since the gestational sac in CSP is surrounded by fibrous scar tissue, systemic MTX injection may not be as effective as local MTX injection. Many studies have reported good results with the use of ultrasound-guided local MTX injection (25 mg MTX injected directly into fetal heart plus 25 mg MTX injected into the placenta) in combination with 25 mg MTX intramuscular

### Article History:

Submitted: 06-Feb-2023

Revised: 20-Mar-2023

Accepted: 31-Mar-2023

Published: 10-Aug-2023

### Access this article online

#### Quick Response Code:



Website:  
<https://journals.lww.com/gmit>

DOI:  
10.4103/gmit.gmit\_135\_22

**Address for correspondence:** Dr. Hoang The Dinh,  
School of Medicine, Vietnam National University, Ho Chi Minh City, Vietnam.  
E-mail: dthoang@medvnu.edu.vn

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

**For reprints contact:** WKHLRPMedknow\_reprints@wolterskluwer.com

**How to cite this article:** Van X, Bui T, Dinh HT, Van T, Tran A. The effectiveness of combined local and systemic methotrexate treatment in cesarean scar pregnancy weeks 8 to 14. *Gynecol Minim Invasive Ther* 2023;12:170-4.



**Figure 1:** Surgical instruments for local and systemic MTX injection procedure. MTX: Methotrexate

injection. These authors have recorded a success rate ranging from 50% to 76% in the treatment of CSP with combined local and systemic MTX injections.<sup>[6-8]</sup> In a report from Society for Maternal-Fetal Medicine (SMFM), the success rate of local MTX treatment for CSP is 73.9%. When two doses of local MTX or the combination of one local and one systemic injection are used, the success rate increases to 88.3%.<sup>[9]</sup> SMFM also emphasizes the high level of  $\beta$ hCG >100.000 mIU/mL as a strong risk factor for treatment failure. From those studies, we took one step further to investigate a series of CSP cases at Tu Du Hospital to identify the effectiveness of combined local and systemic MTX injection in the treatment of CSP weeks 8–14 in the Vietnamese population.

## MATERIALS AND METHODS

This is a retrospective case series of 123 women between 8 and 14 weeks gestational age admitted to Tu Du Hospital with diagnosed CSP from the year 2016 to 2020. They are treated by 25 mg MTX injected directly into fetal heart plus 25 mg MTX injected into the placenta in combination with 25 mg MTX intramuscular injection.

### Ethics

Our study was approved by the Ethics in Biomedical Research Committee of University of Medicine and Pharmacy at Ho Chi Minh City. No: 556/ĐHYD-HĐĐĐ May 28<sup>th</sup>, 2019. The study received consent from all patients to use their data.

### Study designs

#### Selection of participants

Clinically stable patients diagnosed with CSP through ultrasound based on standard criteria:

- Empty uterine cavity
- Empty endocervical canal
- Discontinuity of anterior uterine wall on sagittal view when ultrasound waves cross gestational sac

- Gestational sac with or without fetal pole and fetal heart activity (depending on postmenstrual age) embedded at site of cesarean scar
- Thin or absent layer of myometrium between the bladder and gestational sac
- Gestational age between 8 and 14 weeks estimated by crown-rump length according to Hadlock formula.

#### Description of participants

- Patients health status not suitable for medical intervention: significant illnesses, diabetes mellitus type II with complications, chronic hypertension with end-organ damage, thyroid disorders, asthma, and cirrhosis
- Patients with contraindications to MTX treatment such as: heart diseases, renal dysfunction, active tuberculosis, gastric and duodenal ulcers, acute hepatitis, and intolerance to MTX
- Patients with deficient medical records.

#### Technical information

##### Method

This is a retrospective study.

##### Sample size

Patients who met the inclusion requirements were selected from all of the hospital admission for CSP weeks 8–14 and discharged in the period from January 1, 2016, to January 1, 2020.

##### Procedure

Step 1: Screening and listing patient sample

We screen for patients with diagnosis of CSP weeks 8–14 from the hospital database. Next, those patients were listed chronologically according to their hospital admission year from 2016 to 2020. We proceeded to study their medical records.

Step 2: Collecting patient data

We identified patient records which met the study criteria and recorded their data into our data collecting Table 1. We collected all data about the patients from their hospital admission to their discharge, including serum  $\beta$ hCG records and outpatient ultrasound (every 2–4 weeks).

Step 3: Input and cleaning of data

We excluded patient records that did not met the study criteria or lacked information. We processed the data and finished our study [Figure 1].

##### Evaluation standard

Successful treatment is defined as normalization of serum  $\beta$ hCG (<5 UI) and regression of ultrasonographic findings without surgical intervention after the treatment of combined local and systemic MTX injection.

Unsuccessful treatment includes:

- Patient experienced serious side effects of MTX heavy uterine bleeding and gestational sac increased in size

**Table 1: Demographic information and clinical parameters of patients with cesarean scar pregnancy (n=123)**

Parameters	Frequency, n (%)
Age (years)	
<35	66 (53.7)
≥35	57 (46.3)
Number of past C-sections	
1	51 (41.5)
≥2	72 (58.5)
Clinical symptoms	
No symptom	48 (39.0)
Only abdominal pain	14 (11.4)
Only uterine bleeding	37 (30.1)
Abdominal pain and uterine bleeding	24 (19.5)
Gestational age (weeks)	
8–≤9	74 (60.2)
9–≤10	22 (17.9)
10–≤11	16 (13.0)
11–≤12	7 (5.7)
12–≤13	3 (2.4)
13–≤14	1 (0.8)
Presence of fetal heart activity	
No	0
Yes	123 (100)
Residual myometrium (mm)	
≤3	114 (92.7)
>3	9 (7.3)
Color Doppler flow at CS site	
No flow	5 (4.1)
Minimal flow	15 (12.2)
Moderate flow	64 (52)
High flow	39 (31.7)
Largest diameter of gestational sac (cm)	
≤5	84 (68.3)
>5	39 (31.7)
Serum β hCG (mIU/mL)	
≤100,000	35 (28.5)
>100,000	88 (71.5)

CSP: Cesarean scar pregnancy, CS: Cesarean scar

more than 7 cm (or more than 5 cm and patient requests surgical intervention after counseling)

- Patient must turn to surgical intervention (either planned or emergency), including laparoscopic, vaginal, or abdominal surgery.

### Analyzing and data administration

We stored and analyzed the data using the software SPSS 22.0 (IBM SPSS). We interpreted and described all variables, analyzed the results using linear correlation and analysis of variance. A confidence interval of 95% was used.

## RESULTS

In the period from 1/2016 to 1/2020, there were 5290 patients admitted with diagnosis of CSP. Most patients were diagnosed

before gestational week 8. There were 577 CSP patients who were between 8 and 14 weeks pregnancy, in which, 358 patients were indicated for MTX administration. We recorded 123 patients with CSP weeks 8–14 who underwent MTX treatment and met our study criteria. Among those patients, 62 (62/123, 50.4%) were treated successfully by MTX administration alone; 61 (61/123, 49.6%) required other medical interventions (54 required operations, 7 successful D and C). All 123 patients abided by their follow-up schedules with completed medical records fitting the time line of our study.

One hundred and two (82.9%) patients experienced no side effects of MTX treatment. Some patients experienced common side effects of MTX such as bleeding (1.6%), fever (2.6%), and elevated liver enzymes (13%).

In the 54 cases that required surgical interventions, 33 cases failed to respond to adjuvant treatment, including one additional intramuscular dose of 50 mg MTX injection in 30 (55.6%) cases and D and C in 3 (5.6%) cases. Surgical interventions consist of open surgery (68.5%) and laparoscopic surgery (31.5%). The uterus was reserved in 48 (88.9%) cases. Six (11.1%) cases had to proceed to hysterectomy. The decision for hysterectomy was made during the operation (one case was due to excessive bleeding and five cases because of significant pelvic adhesion).

Variances with statistical significance include gestational age at treatment time, residual myometrial thickness, and gestational sac diameter after MTX injection. In detail, failure rate increases with increasing gestational age, with one extra week increasing failure rate four folds (OR = 3.99,  $P < 0.05$ ). Residual myometrial thickness >3 mm decreases failure rate to 67.2% (OR = 0.368,  $P < 0.005$ ). Larger gestational sac diameter after MTX injection increases the chance for treatment failure, with 1 mm increases in diameter increases failure rate to 1.09 fold (OR = 1.088,  $P < 0.05$ ). Other variances such as patient’s age, parity, previous cesarean surgery, clinical symptoms, serum βhCG, and ultrasound image are not statistically significant ( $P > 0.05$ ).

## DISCUSSION

### About the treatment result

In the total 123 cases reviewed, 62 cases were successfully treated with only MTX injection (50.4%). The success rate is lower than the value 76.5% reported by Katherine in her two meta-analysis studies on 34 CSP cases. The discrepancy can be due to the larger gestational age in our study (9.3 weeks vs. 6.8 weeks), leading to difference in the size of gestational sac, blood supply, or serum βhCG. In addition, the two studies by Katherine have limited sample size and are not as consistent in methodology as our study.<sup>[6,10,11]</sup> In SMFM guidelines, the success rate of MTX injection is very high, 73.9% for local MTX

injection and 88.3% for combined systemic and local MTX injection, with emphasis on the serum  $\beta$ hCG  $>100.000$  mUI/mL as the most influential variable for treatment failure. With high success rate, combined systemic and local MTX injection is recommended as first-line treatment for CSP by SMFM.<sup>[9]</sup>

In the review by Glenn *et al.*,<sup>[12]</sup> the success rate of combined systemic and local MTX injection ranged from 50% to 60%. Six reports from Cok on 18 CSP cases show the success rate of 61.1%, which is similar to our result.<sup>[7]</sup> Meanwhile, in the report on 58 CSP cases by Kim shows a lower success rate compared to ours (41.3% vs. 50.4%), although the mean gestation age in our study is much higher (9.3 weeks vs. 6.5 weeks). Therefore, the success rate of the combined systemic and local MTX injection depends on different variables: patient age, race, number of previous CS, serum  $\beta$ hCG, gestational sac dimensions, and presence of fetal heart activity.

The relatively low success rate in our study is probably due to older gestational age, increased blood supply, and much larger gestational sac dimensions compared to other studies. In addition, in many cases, surgical intervention was indicated because patients could not follow-up for serum  $\beta$ hCG evaluation, even though the gestational sacs in those cases were only 5–7 cm. Due to the requirement for long-term follow-up, geographical and financial inconvenience, many patients prefer surgical intervention for faster treatment course.

Variables that influence the outcome of treatment are proven in multiple studies. Serum  $\beta$ hCG  $<100.000$ , residual myometrial thickness  $>2$  mm, gestational diameter  $<5$  cm, and CSP type I according to vial classification are elements that positively predict a successful treatment.<sup>[7,9,12-14]</sup> After analysis, we conclude that high gestational age (OR = 4.0), and large gestational sac diameter 1 week after treatment (OR = 1) is contributing elements to failure rate. Meanwhile, greater residual myometrial thickness increases the success rate (OR = 0.368,  $P < 0.05$ ). Our results are in agreement with those of Wang, where gestational sac  $>5$  cm is the risk factor for treatment failure.<sup>[15]</sup> Report from Shao also shows similar result, in which residual myometrial thickness  $>2$  mm is a positive predictor for treatment success.<sup>[11]</sup> As stated above, with increased gestational sac volume and gestational age, the myometrium at the scar site is stretched more. Fibrous scar hinders the action of MTX on the gestational sac. The stretched myometrium increases the chance of uterine abruption at scar site, which leads to hemorrhage. In addition, the gestational sac tends to transiently increase in size after MTX injection as it undergoes degeneration. Thick overlying myometrium at scar site shows that the muscle structure is well kept with little fibrous scar. The reserved blood vessels can carry MTX

from the system to the gestational sac. The thick residual myometrium also means that the uterus can contract well to control blood loss at placental attachment site. In 123 patients treated with MTX, only 6 (4%) patients need hysterectomy. Surgical method is opened abdominal surgery (68.5%) and laparoscopy (31.5%), in the total of 54 cases. Since the majority of patients are in their reproductive ages, with most of them under 35 years old, being able to preserve the uterus is extremely important to both physical and mental health of patients. The uterine preservation rate is 88.9%. There are six patients who have to proceed to hysterectomy, making up 11.1% in 54 cases of treatment failure. Our percentage of hysterectomy is much lower compared to other studies. In report by T. Tritsch over the year 2012, 2015, and 2019, the percentage is 15%, 19%, and 10.8%, respectively.<sup>[10,16,17]</sup>

Surgery to excise CSP is a complex procedure with high risk of complications. Most cases that require surgery have angiogenesis at the scaring site, which increases chance of hemorrhage and need for blood transfusion.<sup>[1]</sup> In fact, 19 or 35.2% of our patients require blood transfusion. Hemorrhage also increases the risk of postop infection. In our study, there are two patients that have postop infection, making up 3.7% of cases that need surgery. Our rate of blood transfusion is higher because our surgical team tried to preserve the uterus and repair the scar to prevent future CSP. These efforts lead to longer surgical time and higher rate of blood transfusion.

Surgery on patients with previous surgical history carries the risk of damage to surrounding organs because of adhesion. In case of CSP, the thin myometrium at the scaring site increases the risk of damage to the bladder. In our study, there are four cases with damage to surrounding organs such as the bowels or bladder, making up 7.4% the total of cases with surgical intervention. The percentage of surgical complications in our study is relatively low considering that this is a complicated procedure. This can be contributed to the action of MTX which helps reduce the level of angiogenesis and the invasion of the gestational sac into the myometrium and bladder. In four cases with damage to surrounding organs, multidiscipline specialists were contacted for counseling. There is no reoperation and no mortality in our study.

### Side effects of methotrexate treatment

Treatment with MTX can have adverse effects from nonserious to life-threatening such as: hair loss, skin darkening, oral ulcers, diarrhea, decreased immunity that leads to pneumonia, bone marrow suppression, anemia, hemorrhage, acute liver failure, cirrhosis, and acute kidney failure.<sup>[12]</sup> The side effects encountered in our study include petechiae/purpura (1.6%), fever (2.6%), and elevated liver enzymes (13%). We did not record other side effects such as oral ulcers, diarrhea, elevated urea/creatinine, or

thrombocytopenia. In our hospital, we administer a total dosage of 75 mg MTX. Therefore, the adverse effects are similar to those treated for ectopic pregnancy and much lower than in treatment for molar pregnancy. Presently, there is limited data on the adverse effects of treatment for CSP, and no study, other than this study, has had a systemic review.

### Time needed for involution of the gestational sac and serum $\beta$ hCG decomposition

Time needed for serum  $\beta$ hCG decomposition is, on the average,  $12.47 \pm 3.86$ , with minimum at 4 weeks and maximum at 23 weeks. About 43.5% of successful treatment has serum  $\beta$ hCG normalized in 8–12 weeks. The time for involution of the gestational sac is longer, on average  $17.9 \pm 4.47$ , with minimum 12 weeks and maximum 28 weeks. About 35.5% of successful treatment has complete involution in 12–16 weeks. In comparison, T. Tritsch and Peng report the decay time for serum  $\beta$ hCG after 7.5 weeks and 12.6 weeks. The time for gestational sac involution in Peng's study is 7.6 weeks.<sup>[17,18]</sup> The longer time for normalization of serum  $\beta$ hCG and involution of gestational sac in our study, which could be supposed by higher gestational age, larger gestational sac dimension, and higher initial serum  $\beta$ hCG, as a consequence, these variables lead to longer treatment time hypothetically.

### Updates and clinical applications

Our study offers a systemic view on treatment results of CSP gestational weeks 8–14 at Tu Du hospital from 2016 to 2020. Currently, very few studies focus on this range of gestational age.

In our study, we see that, with MTX-only treatment, the success rate is 50.4%. However, with additional treatment, the success rate increases to more than 90%. In successful cases, the time for involution of the gestational sac and normalization of serum  $\beta$ hCG is 12–18 weeks. We can consider using MTX to reduce the volume of the gestational sac before other treatment such as D and C or endoscopic surgery to elevate the success rate and reduce the waiting time for patients.

### Limitations

The study describes the success rate for MTX treatment of CSP 8–14 gestational weeks but does not compare MTX treatment to other available options.

### CONCLUSION

The success rate in treating CSP with combined systemic and local MTX administration is 50.4%, uterine reserved rate is 95%, and adverse effects 17.2%. Elements such as gestational age at treatment (OR = 3.99,  $P < 0.05$ ), residual myometrium thickness on ultrasound  $>3$  mm (OR = 0.368,  $P < 0.05$ ), and

gestational sac diameter after 1 week (OR = 1.088,  $P < 0.05$ ) influence the treatment success. We advise to use MTX as routine treatment for CSP weeks 8–14.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

- Vo TM, Dinh HT, Van TP, Nguyen CS. Value of crossover sign in anticipating under-8-week cesarean scar pregnancy treatment by foley insertion combined with suction curettage in Vietnam. *Gynecol Minim Invasive Ther* 2021;10:84-90.
- Tulpin L, Morel O, Malartic C, Barranger E. Conservative management of a Cesarean scar ectopic pregnancy: A case report. *Cases J* 2009;2:7794.
- Lipscomb GH, Stovall TG, Frank WL. Nonsurgical Treatment of Ectopic Pregnancy: Primary Care. *New England Journal of Medicine: Massachusetts Medical Society*; 2000. p. 1326.
- Maymon R, Halperin R, Mendlovic S, Schneider D, Herman A. Ectopic pregnancies in a Caesarean scar: Review of the medical approach to an iatrogenic complication. *Hum Reprod Update* 2004;10:515-23.
- Stovall TG, Ling FW, Gray LA. Single-dose methotrexate for treatment of ectopic pregnancy. *Obstet Gynecol Surv* 1991;77:754-7.
- Birch Petersen K, Hoffmann E, Ribbjerg Larsen C, Svarre Nielsen H. Cesarean scar pregnancy: A systematic review of treatment studies. *Fertil Steril* 2016;105:958-67.
- Gonzalez N, Tulandi T. Cesarean scar pregnancy: A systematic review. *J Minim Invasive Gynecol* 2017;24:731-8.
- Kim SY, Yoon SR, Kim MJ, Chung JH, Kim MY, Lee SW. Cesarean scar pregnancy; Diagnosis and management between 2003 and 2015 in a single center. *Taiwan J Obstet Gynecol* 2018;57:688-91.
- Society for Maternal-Fetal Medicine (SMFM) Electronic address: pubs@smfm.org, Miller R, Timor-Tritsch IE, Gyamfi-Bannerman C. Society for Maternal-Fetal Medicine (SMFM) Consult Series #49: Cesarean scar pregnancy. *Am J Obstet Gynecol* 2020;222:B2-14.
- Timor-Tritsch IE, Khatib N, Monteagudo A, Ramos J, Berg R, Kovács S. Cesarean scar pregnancies: Experience of 60 cases. *J Ultrasound Med* 2015;34:601-10.
- Shao MJ, Hu MX, Xu XJ, Zhang L, Hu M. Management of caesarean scar pregnancies using an intrauterine or abdominal approach based on the myometrial thickness between the gestational mass and the bladder wall. *Gynecol Obstet Invest* 2013;76:151-7.
- Glenn TL, Bembry J, Findley AD, Yaklic JL, Bhagavath B, Gagneux P, *et al.* Cesarean scar ectopic pregnancy: Current management strategies. *Obstet Gynecol Surv* 2018;73:293-302.
- Pędraszewski P, Właźlak E, Panek W, Surkont G. Cesarean scar pregnancy – A new challenge for obstetricians. *J Ultrason* 2018;18:56-62.
- Wang M, Yang Z, Li Y, Chen B, Wang J, Ma X, *et al.* Conservative management of cesarean scar pregnancies: A prospective randomized controlled trial at a single center. *Int J Clin Exp Med* 2015;8:18972-80.
- Wang S, Beejadhursing R, Ma X, Li Y. Management of Caesarean scar pregnancy with or without methotrexate before curettage: Human chorionic gonadotropin trends and patient outcomes. *BMC Pregnancy Childbirth* 2018;18:289.
- Timor-Tritsch IE, Monteagudo A, Cali G, D'Antonio F, Agten AK. Cesarean scar pregnancy: Patient counseling and management. *Obstet Gynecol Clin North Am* 2019;46:813-28.
- Timor-Tritsch IE, Monteagudo A, Santos R, Tsybmal T, Pineda G, Arslan AA. The diagnosis, treatment, and follow-up of cesarean scar pregnancy. *Am J Obstet Gynecol* 2012;207:44.e1-13.
- Dean R. Hysteroscopic management of cesarean scar ectopic syrgery of ectopic pregnancy. *J Minim Invasive Gynecol* 2009;16:432-6.