



Review Article

Local Methotrexate Injection as the First-line Treatment for Cesarean Scar Pregnancy: Review of the Literature

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ABSTRACT The objective of this study was to determine the outcome of using ultrasound-guided local methotrexate injection as the first-line treatment of cesarean scar pregnancy (CSP). A literature review was performed on all eligible reports using this modality as the first-line treatment of CSP. Relevant publications were obtained from the PubMed electronic database from inception to December 2014. Ninety-six cases from 95 women reported in 17 articles were reviewed. The success rate was 73.9% after a single local methotrexate injection. An accumulated success rate of 88.5% could be achieved after additional local or intramuscular methotrexate administration. Eleven cases (11.5%) failed methotrexate treatment and required surgical interventions. Except for women with serum human chorionic gonadotropin levels higher than 100 000 IU/L, ultrasound-guided local methotrexate injection could be considered as a first-line treatment modality for CSP. *Journal of Minimally Invasive Gynecology* (2015) ■, ■–■ © 2015 AAGL. All rights reserved.

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Although cesarean scar pregnancy (CSP) has been considered a rare form of ectopic pregnancy, its incidence has been increasing in recent years because of an increased rate of cesarean delivery and the increasing availability of early pregnancy ultrasound [1,2]. CSP can lead to life-threatening consequences such as uterine scar rupture and hemorrhage. However, at present, there is still no consensus on the preferred mode of treatment because the evidence in the literature is based mostly on case reports or series due to the relative rarity of cases.

Methotrexate, administered systemically, locally, or both, is a commonly used medical treatment for tubal and nontubal ectopic pregnancies [1,3]. In recent years, our unit has been using local methotrexate as the primary treatment of CSP [2]. Specifically, local methotrexate is given transabdo-

minally or transvaginally under ultrasound guidance by injection of 25 mg (1 mg/kg body weight before 2012) of methotrexate in the gestational sac or mass. The amniotic sac, if present, is aspirated to mechanically disrupt the pregnancy and to avoid excessive intralesional pressure after methotrexate injection. Additionally, potassium chloride (14.9 g/100 mL) may be given at the discretion of the physician if the embryonic cardiac pulsation is present at a dose of 1 to 2 mL until the cessation of pulsation is evident. However, it is still not conclusive with regard to the efficacy and prognosis of using this treatment modality in treating CSP.

Because it is impractical to perform a randomized controlled study to evaluate the efficacy of this treatment modality, we have to rely on the available literature as a guide. Therefore, I conducted a literature review to determine the outcome of using ultrasound-guided local methotrexate injection as the first-line treatment of CSP.

Methods

A review of the literature published in English was obtained from the PubMed electronic database from inception

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to December 2014, using the search words “cesarean scar,” “caesarean scar” or “uterine scar,” “ectopic pregnancy” or “pregnancy,” and “methotrexate,” supplemented by additional articles obtained from reference lists. The abstracts of the articles and, if needed, the full text were reviewed. Only those reports using ultrasound-guided local methotrexate (with or without potassium chloride) injection as the first-line treatment of CSP, without the additional or prior use of any intervention, including systemic methotrexate, with relevant outcome data were included in the review. At the end of the search, 96 cases from 17 articles were reviewed.

The following data were retrieved from the eligible articles: patient age, gestational age at time of treatment, number of previous cesarean deliveries, the presence or absence embryonic cardiac activity, size of gestational sac or mass, serum human chorionic gonadotropin (hCG) level before methotrexate injection, definition of treatment failure, success of treatment and the need for further treatment, resolution time of hCG level, and information on subsequent pregnancy. Corresponding authors from articles in which only statistical data were available were contacted by e-mail to ask for individual case information.

Statistical analysis was performed using the χ^2 test, Fisher exact test, Mann-Whitney test, Student's *t* test, and Kruskal-Wallis test whenever appropriate. A $p < .05$ was considered statistically significant.

Results

Ninety-six cases from 95 women reported in 17 articles were reviewed [2–18]. Among these articles, 7 were retrospective reviews [2,4–7,10,15], 5 case reports [11,13,14,17,18], 3 case series [3,8,16], 1 letter to the editor [12], and 1 short communication [9]. Of the 3 articles in which only statistical data were provided [2,4,6], additional case information was obtained from the corresponding authors of 2 articles through e-mail requests [2,4]. Table 1 summarizes the case characteristics and the outcomes compiled from the articles.

From the available data, the mean age of patients was 33.9 ± 4.4 years ($n = 73$), and the mean gestational age at the time of treatment was 6.8 ± 1.3 weeks (range, 4.5–12 weeks; $n = 72$). Thirty-four women (45.9%, $n = 74$) had more than 1 previous cesarean delivery. The median interval between the last cesarean delivery and the CSP was 4 years (range, .5–13 years; $n = 43$). The median serum hCG level before treatment was 24 080 IU/L (range, 587–205 321 IU/L; $n = 72$). Embryonic cardiac activity was present in 49 of 72 women (68.1%). Of the 96 cases, only in 21, 20, and 3 cases were the crown–rump length, mean sac diameter, and gestational mass size, respectively, reported.

Seventy-one of the 96 cases (73.9%) were successfully treated after a single local methotrexate injection. The addition of potassium chloride with methotrexate in 11 cases did not improve the success [2,14,16,17]. Fourteen cases

achieved resolution after additional local or intramuscular methotrexate administration, giving an accumulated success rate of 88.5%. The reasons for additional doses of methotrexate given were re-elevation or inadequate decrease of hCG levels in all cases [4,5,7,14] and evidence of large venous sinuses seen around the gestational sac sonographically in 1 case [14]. Eleven cases had failed methotrexate treatment and required surgical interventions, including dilatation and curettage or evacuation (3 cases), hysteroscopy (1), uterine artery embolization \pm dilatation and curettage (3), and laparotomy \pm hysteroscopy (4). Eight of 11 cases had intervention because of significant hemorrhage, which was described to be persistent because of injection in 2 cases [2], to occur at 14 and 102 days after injection in 2 cases [8,18], and because details were not reported in 4 cases [5,16]. Three cases had intervention because of persistent sonographic abnormalities (2 with persistent ectopic mass and 1 with evidence of incomplete abortion).

Table 2 compares the characteristics of the following subgroups: success after a single injection of local methotrexate (group 1, $n = 71$), success after additional dose(s) of local or intramuscular methotrexate (group 2, $n = 14$), and unsuccessful with the need for surgical intervention (group 3, $n = 11$). Patient's age, gestational age at treatment, number of previous cesarean deliveries, and sonographic visualization of embryonic cardiac activity had no impact on the success rate of single local or multiple methotrexate injections of CSP. However, patients with serum hCG levels higher than 100 000 IU/L were more likely to require surgical intervention (odds ratio, 40.7; $p = .002$). For patients with hCG levels between 30 000 and 100 000 IU/L, a scatter plot illustrating treatment outcomes at different hCG levels within this range is shown in Figure 1. When considering that additional methotrexate injection was part of the methotrexate treatment regimen and comparing these groups (groups 1 and 2) with the unsuccessful group (group 3), there was no difference in success rate with regard to all clinical variables listed in Table 3, except when the serum hCG level before treatment was $>100\ 000$ IU/L.

Table 2 shows the median duration for serum hCG to return to normal level. Duration required for complete resolution of the gestational mass was reported in 12 cases, and the median time for that to occur was 5 months (range, 1.5–17). Two women had unresolved mass at 4.5 and 5 months when these cases were reported [15], and 1 woman got pregnant at 7 months with persistent residual lesion on ultrasound [2].

Table 4 summarizes the subsequent pregnancy information available in 10 of 96 cases. Six women (60%) had normal term delivery and 1 woman (10%) had recurrent CSP.

Discussion

Various treatment modalities have been used in the treatment of CSP [2,19]. Based on this review, the success rate of a single local methotrexate injection was 73.9% and the accumulated success rate after additional methotrexate

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