Caesarean Scar Pregnancy: Single Dose of Intrasac Ultrasound-Guided Methotrexate Injection Seems to be a Safe Option for Treatment

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Key words
ectopic pregnancy, cesarean scar pregnancy, transvaginal ultrasound, methotrexate, gynecology

Objective
The purpose of the study was to assess the efficacy of local ultrasound-guided methotrexate injection in patients with caesarean section scar pregnancy, to chart the course of beta-human chorionic gonadotropin levels (HCG) after treatment, and to see if HCG levels are correlated with clinical presentation.

Methods
Between May 2018 and January 2021, data were collected retrospectively from the Early Pregnancy Unit of a tertiary hospital.

Results
Our clinic assessed 20 patients; one disputed terminating the pregnancy and was not included in the research. The remaining 19 patients, with a median age of 34 years, received intragestational sac methotrexate injection under ultrasound guidance. 7w3d was the median gestational age. These women had one to four previous caesarean sections, with a mean of 1.60 ± 0.3. Patients with caesarean scar pregnancy most typically presented with spotting (42.1%), whereas 26.3% were asymptomatic. Except in cases of pain, the symptomatic women's HCG levels were lower than in the non-symptomatic women. The level of HCG in patients with pain was approximately double that of non-pain patients (p = 0.2557). In our series, intragestational sac methotrexate injection was effective in 17/19 women, or 94.7% (95% CI: 75.7-100%). HCG levels were undetectable in 97.6% ± 30 days on average (minimum: 42 days, maximum: 147 days).

Conclusion
Caesarean scar pregnancy is a rare possibly fatal condition with no consensus on the optimal treatment. An experienced Early Pregnancy Unit member performing local methotrexate injections under ultrasound guidance is a feasible and successful strategy in clinically stable patients.
Introduction

Caesarean scar pregnancy is a rare type of ectopic pregnancy that results from the implantation of a pregnancy on a previous caesarean section scar. It was first described in 1978 by Larsen and Solomon [1] and is now regarded as a severe “late complication” following a caesarean section birth.

The reported cases of caesarean scar pregnancy have increased over the last years in a parallel manner to a worldwide increase in the prevalence of caesarean section deliveries [2] and the widespread use of transvaginal ultrasound. The technical expertise acquired by clinicians and sonographers as well as the establishment of Early Pregnancy Units within Obstetric Healthcare systems has undoubtedly enhanced the awareness of this condition. Early recognition of this subtype of ectopic pregnancy is crucial and nowadays feasible, allowing termination of pregnancy on time and minimizing hazardous consequences such as uterine rupture with severe life-threatening bleeding.

Despite the above amelioration regarding the diagnosis of a caesarean scar pregnancy case, there is no agreement concerning the optimal treatment. This could be explained by the extremely low and sporadic incidence of these cases as well as the lack of randomized and controlled trials to compare the available treatment modalities [3]. To date, medical and surgical options, or a combination of both, have been proposed. All the suggested methods aim to eliminate catastrophic complications associated with caesarean scar pregnancy in order to preserve fertility and to avoid major hemorrhage, which may lead to hysterectomy.

In this study, we aim to assess the efficacy of intra-gestational methotrexate injection under ultrasound guidance as a method of choice to treat women with caesarean scar pregnancy.

Materials and Methods

Statistical analysis

In this single-center, retrospective study conducted between May 2018 and January 2021, we examined the efficacy of local ultrasound-guided intra-gestational methotrexate injection to treat caesarean scar pregnancies. Diagnosis of a caesarean scar pregnancy was established in our Early Pregnancy Unit by transvaginal ultrasound using the following imaging criteria [4, 5] (Fig. 1): a) an empty uterine cavity and endocervical canal, without contact with the sac,

b) the presence of a gestational sac with or without a fetal pole (with or without fetal cardiac activity) implanted in the lower anterior uterine segment at the site of a previous caesarean section scar,

c) thin or absent myometrium between the bladder and the sac,

d) negative ‘sliding organ sign’,

e) evidence of increased peritrophoblastic or periplacental vascularity on color Doppler examination.

Alternatively, Timor-Tritsch et al. [6], proposed an easy approach to estimate the risk of underlying caesarean scar pregnancy in three simple steps. First, based on the sagittal image of the uterus, they connect the external cervical os to uterine fundus via a longitudinal line. Second, they draw a line vertical to the first dividing it into two equal parts. The cross section of the two lines is the area of interest that could define the risk of caesarean scar pregnancy. If the gestational sac is located towards the uterine fundus, then it is suggestive of intrauterine pregnancy, whereas if it is located on the crossline area or towards the cervix, it is a caesarean scar pregnancy (Fig. 2).

Following diagnosis, patients were counselled and offered to terminate the ectopic pregnancy with ultrasound-guided methotrexate injection at the site of the implantation.

The procedure was performed in main operating rooms by an experienced member of the Early Pregnancy Unit team. Patients were placed in lithotomy position and general anesthesia was administered. Local disinfection of the vagina followed by catheterization of the bladder using a nelon catheter was the first step of the procedure. Then a punctured needle, attached to the ultrasound probe, was inserted into the gestational sac transvaginally. The fluid in the gestational sac was aspirated and 50 mg/m² of methotrexate was injected intracavitary (Fig. 3). Finally, a thorough check for any signs of active bleeding was performed. The patients recovered in the operating room and remained in the hospital for at least 24 hours.

During follow-up, HCG levels were used to assess the therapeutic effect of the methotrexate injection. A first HCG level check was performed on day four and then on day seven (on average) after the procedure along with transvaginal ultrasound. We carried out weekly blood tests until HCG concentrations returned to undetectable levels.

Data were collected in Microsoft Excel spreadsheets from the Early Pregnancy Unit records and then were imported into SAS for Windows 9.4 software platform (SAS Institute Inc., NC, U.S.A.) for statistical analysis. Descriptive values are expressed as median and 1st-3rd quartile range (Q1–Q3) and in some cases the mean ± standard deviation (SD) is reported to allow for possible future comparisons and meta-analyses. For the categorical data the frequency and the relevant percentages are reported. Comparison of the HCG levels during diagnosis and methotrexate injection was performed using the Wilcoxon ranked sum test since a paired test was required.
Twenty patients with cesarean scar pregnancy were treated in our clinic. One of them refused to terminate her pregnancy and therefore is not included in the subsequent analysis. The remaining 19 patients ranged in age from 18 to 39 years (median age = 34 years, Q1–Q3: 30–38 years). These women had a history of one to four previous cesarean sections (mean number of cesarean sections before diagnosis = 1.6 ± 0.9, 63.2 %: one cesarean section, 21.1 %: two cesarean sections, 10.5 %: three cesarean sections, and one woman had four cesarean sections). On average, the participating women had 3.6 ± 1.7 gestations (min: 1, max: 7.00, median: 3 Q1–Q3: 2–4.00) and the resulted parities were 1.7 ± 1.0 (min: 1, max: 4, median: 1 Q1–Q3: 1–2), leading to a success percentage of 47 % ± 10 %.

In 5 out of 19 cesarean scar pregnancy incidences (26.3 %), the patients did not report any symptoms at the time of diagnosis. From the remaining 14 symptomatic patients, 8 (42.1 % of all patients) reported spotting, 4 (21.1 %) had bleeding, and 3 (15.8 %) experienced pain (only one patient reported both spotting and pain).

The median gestational age at diagnosis was 7w3d (Q1–Q3: 6w1d – 8w5d). On the day of diagnosis, the median HCG level was 22365 mIU/ml (Q1–Q3: 5554–61645 mIU/ml) and on the day of the methotrexate injection, the median HCG level was 21,307 mIU/ml (Q1–Q3: 7217–63224 mIU/ml). No difference in the HCG levels between the day of diagnosis and the day of methotrexate injection was observed (p = 0.1094). Note that in 12 cases diagnosis and methotrexate injection occurred on the same day.

For two women (10.5 %) a complimentary intervention was required [the first: intramuscular (IM) additional methotrexate injection (50 mg/kg IM) and the second: laparotomy]. Table 1 shows the characteristics of the patients with cesarean scar pregnancy identified in our records. Note that one woman did not receive a methotrexate injection. This woman was consequently excluded from subsequent analysis. In one case the time for HCG standardization was not retrieved. Therefore, the data for this woman was only partially analyzed.

During the follow-up period, HCG levels dropped. On average, the time required for HCG levels to drop to undetectable levels was 97.6 ± 30.0 days (minimum: 42 days, maximum: 147 days, median: 94.5 Q1–Q3: 77–119 days). On average the drop rate was 375 ± 427 mIU/day (min: 18.5 mIU/day, max: 1343.7 mIU/day, median: 201.7 Q1–Q3: 68.7–451.6 mIU/day). However, note that HCG levels do not follow a linear drop pattern, since the drop rate is higher in the initial days and becomes lower in the following days. During the first month, HCG levels did not drop to zero for any woman. Within two months two women had HCG levels of zero. Levels normalized within three months in nine women (about 50 %) and within four months in 14 (75 %) women. It took more than four months for HCG to be undetectable in five women (about 25 %). In terms of efficacy, the method led to successful treatment in all cases. However, two women required additional interventions. Thus the method efficacy is 17/19 = 89.5 % (95 % CI: 75.7 %–100 %).

Subsequently and despite the fact that there is a rather limited set of data, we examined the data for a relationship between HCG levels and the various symptoms (Fig. 5). Actually, no statistically important difference in HCG (at methotrexate injection) was able to be confirmed among the patients grouped according to their symptoms. However, there is strong evidence that HCG levels may differ between individual groups. Table 2 shows the descriptive statistics of HCG levels during the injection of methotrexate in relation to the symptoms. Notably, in all cases with the exception of pain, HCG levels in patients with symptoms were lower compared to the group of women without symptoms. In women experiencing pain, the HCG level was almost double (72325.33 ± 62433 mIU/ml) compared to the women who did not experience pain (35506.63 ± 38358 mIU/ml) (p = 0.2557).
Discussion

Caesarean scar pregnancy is a rare form of ectopic pregnancy and even though a recent national cohort study from the United Kingdom (UK) reports an incidence of approximately 1.5 in 10,000 deliveries [3], other retrospective studies with a small number of cases from tertiary referral centers estimated that the prevalence of caesarean scar pregnancy may vary from 1:1800 to 1:2216 [7, 8]. Our hospital is a tertiary referral center with an Early Pregnancy Unit where many patients are referred from all over the country for diagnosis and further management. This paper presents our experience in 19 patients with caesarean scar pregnancy treated by injecting local methotrexate directly into the gestational sac between May 2018 and January 2021.

Early diagnosis of a scar ectopic pregnancy offers a wider range of management options with a higher success rate of conservative treatment options and chance of preserving fertility [9, 10]. It must be noted that ultrasound is the gold-standard imaging test for the diagnosis of caesarean scar pregnancy with a sensitivity of 86.4 % [11]. Missed or delayed diagnosis of caesarean scar pregnancy could have detrimental consequences for the pregnancy and the patient [12]. All caesarean scar pregnancies presented in this report were diagnosed by transvaginal ultrasound and the median gestational age at diagnosis was 7w3d.

Consistent with existing data, most women in our caesarean scar pregnancy series presented with painless spotting or painless vaginal bleeding [11]. Although this is a rather limited set of data, there is evidence that HCG levels were almost double in women that experienced pain compared to the women that did not. However, vaginal bleeding and abdominal pain is very common in early pregnancy and is not specific. According to our findings, women with a history of prior caesarean delivery who present with these symptoms in early pregnancy should be evaluated with clinical vigilance for caesarean scar pregnancy.

Advanced maternal age, multigravidity, induced abortions, short pregnancy interval from previous caesarean section, induced abortions after caesarean section, and retroverted uterus have all been described as possible predisposing factors for caesarean scar pregnancy [13]. However, little is known about the pathogenesis of this condition; the most accepted theory for the caesarean scar pregnancy is that delayed wound healing caused by prior trauma and poor vascularization in the lower uterine segment forms a microscopic dehiscent myometrial defect through which the blastocyst inserts into the myometrium [14]. These defects have been described as ‘niche’ and usually occur in women with a history of multiple caesarean sections [15]. In our series, 63.2 % had only one previous caesarean section, 21.1 % had two previous caesarean sections, 10.5 % had three previous caesarean sections, and one
A woman had four caesarean sections. Nonetheless, due to the small number of patients in our investigation, we could not detect a strong correlation between the number of previous caesarean sections and the probability of caesarean scar pregnancy.

It has also been suggested that caesarean scar pregnancy and morbidly adherent placenta spectrum disorders share the same microscopic features, thus the former is considered by many authors as the precursor to morbidly adherent placenta if the pregnancy progresses to the late 2nd or 3rd trimester [16]. The crossover sign (COS) has been suggested as a useful sonographic marker to ascertain the evolution of a caesarean scar pregnancy. It seems that when the ectopic sac is implanted within the previous caesarean section scar and more than two thirds above the endometrial line towards the anterior uterine wall (COS 1 group), the risk of placenta percreta is significantly higher compared to other locations of caesarean scar pregnancy [17].

Patient 8 in our case series opted to continue with the pregnancy due to personal beliefs. She was able to complete 34 weeks of pregnancy and presented with contractions and spotting. Total abdominal hysterectomy was performed because of placenta accrete. Post-operatively, she remained in intensive care unit (ICU) for five days and was transfused.

### Table 1  Summary table of patients with scar pregnancy.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>GP</th>
<th>Number of CS</th>
<th>HCG at presentation</th>
<th>GA at diagnosis</th>
<th>Time of HCG standardization (days)</th>
<th>Complications/interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>29</td>
<td>G3P1</td>
<td>1</td>
<td>25679</td>
<td>7w 1d</td>
<td>147</td>
<td>IM MTX</td>
</tr>
<tr>
<td>Patient 2</td>
<td>35</td>
<td>G3P1</td>
<td>1</td>
<td>34907</td>
<td>7w 4d</td>
<td>112</td>
<td>No</td>
</tr>
<tr>
<td>Patient 3</td>
<td>38</td>
<td>G3P1</td>
<td>1</td>
<td>16000</td>
<td>6w 3d</td>
<td>84</td>
<td>No</td>
</tr>
<tr>
<td>Patient 4</td>
<td>35</td>
<td>G3P1</td>
<td>1</td>
<td>22365</td>
<td>8w 3d</td>
<td>133</td>
<td>No</td>
</tr>
<tr>
<td>Patient 5</td>
<td>31</td>
<td>G4P2</td>
<td>2</td>
<td>61645</td>
<td>7w 6d</td>
<td>84</td>
<td>No</td>
</tr>
<tr>
<td>Patient 6</td>
<td>36</td>
<td>G4P2</td>
<td>1</td>
<td>101542</td>
<td>12w 5d</td>
<td>NA</td>
<td>Laparotomy</td>
</tr>
<tr>
<td>Patient 7</td>
<td>38</td>
<td>G4P2</td>
<td>2</td>
<td>122277</td>
<td>9w 0d</td>
<td>91</td>
<td>No</td>
</tr>
<tr>
<td>Patient 8 *</td>
<td>32</td>
<td>G3P2</td>
<td>2</td>
<td>16w 6d</td>
<td>Delivery + hysterectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 9</td>
<td>24</td>
<td>G2P1</td>
<td>1</td>
<td>5554</td>
<td>5w 2d</td>
<td>105</td>
<td>No</td>
</tr>
<tr>
<td>Patient 10</td>
<td>35</td>
<td>G5P3</td>
<td>3</td>
<td>33777</td>
<td>11w 5d</td>
<td>133</td>
<td>No</td>
</tr>
<tr>
<td>Patient 11</td>
<td>30</td>
<td>G3P1</td>
<td>1</td>
<td>26526</td>
<td>7w 4d</td>
<td>140</td>
<td>No</td>
</tr>
<tr>
<td>Patient 12</td>
<td>39</td>
<td>G3P1</td>
<td>1</td>
<td>2074</td>
<td>8w 5d</td>
<td>42</td>
<td>No</td>
</tr>
<tr>
<td>Patient 13</td>
<td>34</td>
<td>G2P1</td>
<td>1</td>
<td>139410</td>
<td>7w 0d</td>
<td>119</td>
<td>No</td>
</tr>
<tr>
<td>Patient 14</td>
<td>25</td>
<td>G7P3</td>
<td>2</td>
<td>10254</td>
<td>7w 3d</td>
<td>98</td>
<td>No</td>
</tr>
<tr>
<td>Patient 15</td>
<td>18</td>
<td>G2P1</td>
<td>1</td>
<td>7910</td>
<td>5w 5d</td>
<td>77</td>
<td>No</td>
</tr>
<tr>
<td>Patient 16</td>
<td>34</td>
<td>G2P1</td>
<td>1</td>
<td>15921</td>
<td>6w 1d</td>
<td>112</td>
<td>No</td>
</tr>
<tr>
<td>Patient 17</td>
<td>34</td>
<td>G3P2</td>
<td>2</td>
<td>78202</td>
<td>8w 5d</td>
<td>70</td>
<td>No</td>
</tr>
<tr>
<td>Patient 18</td>
<td>38</td>
<td>G2P1</td>
<td>1</td>
<td>507</td>
<td>5w 0d</td>
<td>49</td>
<td>No</td>
</tr>
<tr>
<td>Patient 19</td>
<td>31</td>
<td>G7P4</td>
<td>4</td>
<td>1811</td>
<td>5w 5d</td>
<td>77</td>
<td>No</td>
</tr>
<tr>
<td>Patient 20</td>
<td>39</td>
<td>G7P4</td>
<td>3</td>
<td>4138</td>
<td>6w 4d</td>
<td>84</td>
<td>No</td>
</tr>
</tbody>
</table>

GP: Gestations/Parities, CS: Caesarean Section, GA: Gestational Age, HCG: Human Chorionic Gonadotropin, NA: Not Available. *This woman was not included in data analysis because she has chosen to continue the pregnancy.

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**Fig. 5** Box and whisker plots of HCG levels during MTX injection and the various symptoms. Box limits show the Q1 and Q3 values, the line within the boxes indicates the median values, the diamond symbol corresponds to the mean values, and the whisker limits to the minimum and maximum values.
with six units of red blood cells (RBCs) and six units of fresh frozen plasma (FFPs). She recovered well and was discharged after 15 days.

The current evidence regarding the optimal management and proper counselling for caesarean scar pregnancies is sparse and derived from small retrospective series reflecting the need for further research in this field. Various treatment modalities for caesarean scar pregnancy have been described in the literature such as systemic or local methotrexate, intralesional potassium chloride injection, surgical resection, dilatation and curettage with or without hysteroscopy, uterine artery embolization and hysterectomy, bilateral uterine artery chemoembolization combined with dilation and curettage [18, 19]. Since this condition affects women of reproductive age, the treatment of choice should be tailored to preserve fertility. Expectant management is not usually recommended due to the risk of severe complications [7, 19, 20]. Methotrexate is the most widely used treatment modality. Ko et al. [21] reported an 80% success rate with the use of intralesional methotrexate with or without potassium chloride in their series. In the present study, 19 cases were treated with intragestational methotrexate and the efficacy of the method was 89.5%. Only 2 out of 19 patients required complimentary intervention. Of note, none of them experienced side effects associated with methotrexate administration.

Patient 1 received additional intramuscular methotrexate due to HCG levels reaching a plateau on day 21 and on day 28 (4857 mIU/ml and 4971 mIU/ml, respectively). It should be taken into account that she was the first patient treated with intragestational methotrexate in our department and the administration of intramuscular methotrexate could be explained by the lack of experience at the time regarding these cases.

Based on the allocation in our pool of data, patient 6 underwent laparotomy because of massive bleeding during the intrasac injection of methotrexate under ultrasound guidance. Neither bimanual pressure of the uterus nor uterine artery ligation managed to control the bleeding. Therefore, laparotomy was urgently performed, during which uterine rupture was observed at the site of the ectopic implantation on the previous caesarean section scar. The area was repaired with intermittent sutures. The patient was admitted to the ICU for 48 hours and was transfused with three units of RBCs. She remained at the hospital for three more days and then was discharged. Late referral to our unit due to delayed diagnosis of caesarean scar pregnancy (12w5d) as well as high levels of C-reactive protein preoperatively (67 mg/L) that were underestimated could possibly explain the massive bleeding that occurred during the intrasac methotrexate injection.

Overall, our data suggest that intragestational methotrexate under ultrasound guidance is a safe and effective approach for hemodynamically stable patients with caesarean scar pregnancy that wish to maintain their fertility. We observed very low complication rates with this procedure. However, it needs to be performed by an experienced gynecologist in a controlled environment suitable to deal with hemorrhagic complications. Women with caesarean scar pregnancy that undergo this procedure should be counselled about complications such as the risk of bleeding as well as the slow resolution of the pregnancy and the need for contraception until then.

On day four following the procedure, HCG levels increased in three patients (16%) on average by 5.8%. For the remaining 16 (84%) women, a decrease in HCG levels was observed, on average by

### Table 2 - HCG levels during MTX injection in relation to symptoms.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Positive for symptom</th>
<th>Negative for symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Minimum-maximum</td>
</tr>
<tr>
<td>N</td>
<td>14</td>
<td>38167 ± 4518</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>32344 ± 4160</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>18834 ± 2651</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>72225 ± 6243</td>
</tr>
<tr>
<td>Any</td>
<td>0.4416</td>
<td>906–139410</td>
</tr>
<tr>
<td>Spotting</td>
<td>0.5435</td>
<td>17923–61645</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>0.1937</td>
<td>7635.5 (45–43153)</td>
</tr>
<tr>
<td>Pain</td>
<td>0.2557</td>
<td>15291–139410</td>
</tr>
</tbody>
</table>

N: number of women in each group.
19.9% (min: 1.1%, max: 69.3%). Undetectable HCG levels were observed within an average of 97.6 days following the methotrexate injection, which is consistent with other study findings [21,22], although the disappearance of the “gestational sac” may occur later.

Fig. 6 (a–c).

Conclusion

Our study showed that the most prevalent symptom in caesarean scar pregnancy is vaginal bleeding but often patients are asymptomatic. Transvaginal ultrasound is crucial for timely diagnosis. Although to date, there is no universal agreement regarding the preferred method of choice for managing this rare form of ectopic pregnancy, we suggest that medical management using intragastational methotrexate under transvaginal ultrasound guidance appears to be an effective and safe approach in clinically stable women when performed by an experienced member of an Early Pregnancy Unit. However, this conclusion may be limited due to the retrospective nature of our study involving a small number of patients as well as the individual and often unpredictable progression of this condition.

Conflict of Interest

The authors declare that they have no conflict of interest.

References


