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A retrospective comparison of systemic and local methotrexate therapy applied before uterine curettage in caesarean scar pregnancy

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Abstract

This study aimed to evaluate the results of patients who were treated with different treatment modalities due to cesarean scar pregnancy in terms of treatment success, development of complications, and additional treatment need. Patients underwent dilatation-curettage (D/C) only group 1 (n=22), systemic methotrexate was applied on the first and fourth day and D/C was applied on the seventh day, group 2 (n=27) and those who received intracavitary methotrexate on the first day and D/C on the seventh-day group 3 (n=33) to be divided into three groups. The demographic information of the patients, length of stay, response to treatment, complication rates, and whether there was any difference in factors associated with the development of complications were compared between the groups. When the patients were evaluated, it was seen that those in group 2 had a lower gestational week (p=0.011). In addition, it was observed that the patients in group 2 had a significantly longer hospital stay (p<0.001). When the effectiveness of the treatment methods in the groups was examined, no significant difference was found between the groups in terms of effectiveness (p=0.345). It was observed that pregnant women in group 2 developed more complications and this situation was evaluated as statistically significant (p=0.043). Although the duration of hospitalization and complication rates were less than the other two groups in patients using intracavitary methotrexate, this was not statistically significant (p>0.05). In our study, we observed that the possibility of complication development among the three methods was less in patients who underwent intracavitary methotrexate, but we could not statistically determine that this situation was significant. We also found that the use of systemic methotrexate is the most disadvantageous method in terms of both the length of stay and the development of complications.

Keywords: Caesarean scar pregnancy, systemic methotrexate, intracavitary methotrexate, dilatation/curettage

Introduction

Placement of the fertilized ovum outside the decidual layer of the uterus is defined as ectopic pregnancy (EP) and this is one of the most important complications of early pregnancy [1]. Although the true incidence of cesarean scar pregnancy (CSP) is still unknown, it is estimated that it is gradually increasing due to the increased number of Cesarean sections. It has been reported in recent studies that this rate is between 1/531 - 1/3000 births [2]. There are many reasons for reporting such different rates in studies. The gradual increase in the number of Cesarean sections and the misdiagnosis of some CSPs as cervical pregnancy can be considered among these reasons. Due to the development of transvaginal ultrasonography (TVUS), the incidence of diagnosing CSP has also increased. In addition, color Doppler imaging is important for accurate diagnosis of qualitative and quantitative vascularization in peripheral to the cesarean scar [2]. Demonstration of functional placental vascularization caused by increased blood flow with a peak systolic velocity (PSV) greater than 20 cm/sec and pulsatility index (PI) lower than 1 in color Doppler imaging is sufficient for the definitive diagnosis of CSP. Magnetic resonance imaging (MRI) is another recommended method for a diagnostic algorithm. MRI provides a more accurate measurement of the distance between the urinary bladder, myometrium, and gestational sac and better visualization of the uterine cavity and cervical canal [3]. If CSP is not diagnosed correctly and appropriate treatment is not administered, serious and life-threatening complications such as bleeding, uterine rupture, hysterectomy due to placental invasion anomalies in the following weeks, the need for intensive care due to massive blood loss and maternal mortality may occur [2].

Although there is no consensus on the optimal management of

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CSP, methotrexate (MTX) is used for various treatment strategies such as medical therapy, systemic and intracavitary medical therapy, uterine curettage, hysteroscopic resection, transvaginal resection of CSP, uterine artery embolization, and laparoscopy [4]. Few studies are comparing systemic and intracavitary use of MTX before uterine curettage. In a recent study comparing intracavitary and systemic MTX therapy, intracavitary MTX therapy is superior [5]. Another study conducted in 2015 showed that systemic MTX caused beta-human chorionic gonadotropin (β-HCG) to regress in a shorter time and earlier remission of the gestational sac [6]. Another study in 2018 showed that uterine curettage treatment provided satisfactory results for CSP therapy, MTX treatment before curettage did not provide additional benefit in intraoperative blood loss and remission of gestational tissue, and extended hospital stay [7]. These conflicting results of the data in the literature indicate that more studies are needed on this subject.

The objective of this study is to observe the difference between 3 different treatment modalities in patients with CSP diagnosis in our clinic and to compare the duration of hospitalization, treatment efficacy, and the complication rates of patients.

Materials and Methods

82 patients who were admitted to the Obstetrics & Gynecology Department from 01.01.2016 to 16.06.2020 were included in the study. The study was administered retrospectively by the Helsinki Declaration of 1975 after getting approval from the Local Committee of Ethics (dated 24.06.2020, Session No. 2020/12 and Decision No. 15).

In the study, the patients were divided into 3 groups including group 1 with only D/C (n=22), group 2 with intramuscular systemic MTX on days 1 and 4, and then D/C on day 7 (n=27), and group 3 with intracavitary MTX under ultrasonographic guidance on day 1 and then D/C on day 7 (n=33). Intramuscular systemic MTX of 1 mg/kg was administered to patients on days 1 and 4 while intracavitary MTX of 1 mg/kg was administered in the gestational sac of the patients on day 1 under ultrasonographic guidance after the sac content was aspirated and the injection site was verified. On day 7 following the first administration of MTX, D/C was performed for patients included in groups 2 and 3. These patients were invited and β-HCG and TVUS were performed.

According to electronic data and file scanning, maternal age (year), body mass index (BMI) (kg/m^2), gravidas (pieces), parities (pieces), weeks of gestation, presence and number of previous Cesarean sections, number of living children, number of abortions, number of dilatations/curettages (D/C), uterine surgery status other than Cesarean, residual myometrial thickness, preoperative, intraoperative and postoperative hematologic parameters [hemoglobin values (initial, lowest and last), β-HCG values (preoperative, postoperative)], period of menstrual resumption, time for negative US finding, presence of fetal heart rate (FHR) at the time of diagnosis, fetal crown-rump length measurement (CRL), presence of symptoms, need for replacement of intraoperative and postoperative blood and blood products (units), complications (bleeding, rupture), intensive care requirements, length of stay, additional treatment requirements (such as Foley catheter, hysterotomy) and surgical requirements were recorded, and the differences of these parameters between the groups were evaluated. The diagnosis was confirmed following a histopathological analysis of the postoperative biopsy material of patients with the diagnosis of CSP diagnosed using preoperative imaging methods.

SPSS 22 Windows (Statistical Package for the Social Sciences, Armonk, NY, USA) package program was used for data analysis. Compliance of the data to normal distribution was tested by the Shapiro-Wilk test and variance homogeneity was tested by the Levene test. Pearson Chi-Square and Fisher Exact tests were used to comparing categorical data and the Monte Carlo Simulation technique was used for testing. Using the ANOVA (ANOVA with Tukey HSD) test, multiple groups were compared. Pearson and Spearman correlation analyzes were used to evaluate factors associated with the development of morbidity. Quantitative data are expressed in tables as mean ± std (standard deviation) values. Categorical data were expressed as n (number) and percentages (%). A p-value less than 0.05 was considered significant.

Results

The average age of the patients included in the study (n=82) was found to be 31.98±6.06 years while BMI was 23.85±3.15 kg/m^2. It was observed that 20 of the patients (24.4%) had one cesarean section and the remaining 75.6% had a history of 2 or more Cesarean delivery. It was found that an average of 1.01±0.90 of the patients had a history of abortion. When considering the CSP status, it was seen that only 35.4% of the patients had FHR-positive pregnancy (Table 1).

Table 1. Demographics of the patients included in the study

Variables	(n=82)
Age (Year)	31.98±6.06
Gravida	4.14±1.36
Parity	2.24±0.83
BMI (kg/m2)	23.85±3.15
Smokers (n, %)	19 (23.2%)
Gestational age (week)	6.51±1.44
Gestational age	
<40 days	22 (26.8%)
40-70 days	51 (62.2%)
>70 days	3 (%)
Number of previous abortions	1.01±0.90
Number of living ones	2.18±0.87
FHB (positive n, %)	29 (35.4%)
Number of previous Cesarean sections	
1	20 (24.4%)
2	43 (52.4%)
3	17 (20.7%)
4	2 (2.4%)
Myometrial thickness	3.50±1.44

Data are expressed as mean ± standard deviation or number (%)
FHB: Fetal Heart Beat, BMI: Body Mass Index

It was found that high β-HCG levels (33598.92±26189.10 mlU/ml) of the patients at the time of the diagnosis became negative within an average of 18.09±7.37 days. It was observed that bleeding requiring blood transfusion occurred in 19.5% of the patients, 1 unit of erythrocyte suspension was replaced in 9 patients, 2 units in 4 patients, and 3 or more units in 3 patients during the treatment. Hemoglobin parameters of the patients at the time of the diagnosis were average 12.69±1.30 g/dl while 10.85±1.30 g/dl at the time of discharge (Table 2).

Table 2. Hematological and biochemical values, blood replacement requirements of the patients and blood products used

Variables	(n=82)
Number of patients in need of transfusion (n, %)	16 (19.5%)
Erythrocyte (in units)	0.37±1.03
Fresh Frozen Plasma (in units)	0.13±0.64
Initial Hb	12.69±1.30
Pre-discharge Hb	10.85±1.30
β-hCG level at the time of diagnosis	33598.92±26189.10
<10,000	31 (37.8%)
≥10,000	51 (62.2%)
Pre-D/C β-hCG level	8339.95±4519.10
Time for being negative of β-HCG level	18.09±7.37

Data are expressed as mean ± standard deviation or number (%)
β-HCG: Beta Human Chorionic Gonadotropin (mlU/ml), Hb: Hemoglobin (g/dl)

It was found that the average CSP time of the patients occurred an average of 31.26±16.43 months after the last Cesarean section. When considering the treatment modalities of patients with CSP, it was seen that D/C was chosen in 26.8% (n=22), systemic MTX and D/C in 32.9% (n=27), and intracavitary MTX and D/C in 40.3% (n=33) of the patients. However, it was found that in 34.1% (n=28) of the patients, none of the treatment modalities was adequate alone and additional treatment methods such as a Foley catheter (n=26, 31.7%) and hysterotomy (n=2, 2.4%) were required due to reasons such as bleeding (n=26) and uterus rupture (n=2). While the need for intensive care occurred in ten patients (12.2%), the average time of hospitalization was calculated as 3.90±1.30/day (Table 3).

While there was no statistically significant difference in the three treatment groups in terms of hemoglobin parameters (p=0.863, p=0.849 respectively), time for post-treatment negative β-HCG (p=0.586) and need for intensive care (p=0.244), it was observed that patients in the group 2 had statistically significant longer hospitalization time (p<0.001) (Table 4).

When considering the groups for the need for additional treatment after the primary treatment, it was seen that tamponade with Foley catheter was applied to 7 patients due to bleeding in patients with D/C only, and no additional treatment method was needed. The patients in group 2 were administered treatment in 2 phases. Accordingly, following routine systemic MTX on days 1 and 4, D/C was performed on day 7, however, upon observing bleeding after the second cycle of MTX in two of these patients, the D/C procedure had to be performed on day 5 of the treatment. After the first cycle of systemic MTX therapy, 1 patient experienced severe abdominal pain, nausea vomiting, and acute abdominal findings were observed during a physical examination and uterine rupture was diagnosed after a US imaging, and hysterotomy and CSP excision were performed. Another hysterotomy was performed upon observing a uterus rupture during the D/C procedure in one patient in this group. The treatment process of 23 patients other than these patients was completed and D/C procedures were performed. Upon observing bleeding in 14 patients after this procedure, Foley catheters were inserted, and hemostasis was ensured. Finally, after intracavitary administration of MTX, the D/C procedure was performed for 33 patients in group 3. After intracavitary administration of MTX, 1 of these patients developed minimal bleeding that did not impair hemodynamic stability, while no complication was observed in other patients. However, bleeding occurred in 6 patients during the D/C procedure and Foley catheters were inserted and hemostasis was ensured during the treatment Between the groups, a significant difference in favor of group 2 was observed in terms of occurrence of complications (p=0.043) (Table 5).

Table 3. Patients' treatment modalities and treatment-related parameters

Variables	(n=82)
Time between the last Cesarean section and the occurrence of SSG (months)	31.26±16.43
Treatment method	
D&C	22 (26.8%)
Systemic MTX+D/C	27 (32.9%)
Intracavitary MTX+D/C	33 (40.3%)
Need for additional therapy	28 (34.1%)
Additional treatment methods administered	
Foley Catheter	26 (31.7%)
Hysterotomy	2 (2.4%)
Day(s) of hospitalization	3.90±1.30
Number of patients in need of intensive care (n, %)	10 (12.2%)
Complications	28 (34.1%)

Data are expressed as mean ± standard deviation or number (%)
CS: Cesarean Section, D&C: Dilatation & Curettage, MTX: Methotrexate, CSP: Cesarean Scar Pregnancy

Between the groups, a significant difference in favor of group 2 was observed in terms of occurrence of complications (p= 0.043). Although the length of stay and complication rates of patients with intracavitary methotrexate were less than the other two groups, it was found that this was not statistically significant (p>0.05). When considering the factors associated with the development of complications, it was seen that gestational age of more than 70 days (r: 0.339, p=0.002), increased dimension of the sac (r: 0.296, p=0.007) increased crown-rump length of the fetal (r: 0.306, p=0.005) were associated with the development of complications (Table 6).

Table 4. Comparison of hematology and β-HCG changes, β-HCG change time after treatment and intensive care needs of the groups during treatment

Variables	Group 1 (n=22)	Group 2 (n=27)	Group 3 (n=33)	P
Initial Hb	13.00±1.57	12.77±1.40	12.60±1.25	0.863
Pre-discharge Hb	10.75±1.90	10.76±1.29	10.94±1.16	0.849
Time between the last Cesarean section and the occurrence of SSG (month)	27.68±18.50	31.81±19.30	33.21±17.89	0.469
β-HCG level at the time of diagnosis	16511.92±10749.72	33456.02±15967.29	38672.45±16189.10	0.008
Pre-D/C β-HCG level	-	8236.44±4627.47	8425.42±4429.31	0,840
Post-therapy time for being negative of β-HCG level (day)	17.59±5.67	17.25±4.86	19.12±9.76	0.586
Time of restarted menstruation (week)				
≤ 4	16 (72.7%)	20 (74.1%)	26 (78.8%)	
4-6	4 (18.2%)	4 (14.8%)	4 (12.1%)	0.891
> 6	2 (9.1%)	3 (11.1%)	3 (9.1%)	
Negative ultrasonographic finding time (week)				
≤ 2	17 (77.2%)	20 (74.1%)	24 (72.7%)	
2-4	4 (18.2%)	5 (18.5%)	7 (21.2%)	0.725
4-8	1 (4.6%)	2 (7.4%)	2 (6.1%)	
Requirement for intensive care hospitalization (hospitalized/non-hospitalized patients)	4/18	1/26	5/28	0.244
Day(s) of hospitalization	2.54±1.01	5.00±2.48	3.90±2.02	<0.001

Independent-Samples T test and Mann-Whitney U test were used to compare data. Values are expressed as mean ± standard deviation or number (n). Significant results are shown italic and bold
β-HCG: Beta HCG: Beta Human Chorionic Gonadotropin (mlU/ml), Hb: Hemoglobin (g/dl), Hb; Hemoglobin (g/dl), SSG: Cesarean Scar Pregnancy, ICU: Intensive Care Unit

Table 5. Comparison of complications according to treatment modalities

Complications	Unadjusted Hazard ratios	Group 1 (n=22)	Group 2 (n=27)	Group 3 (n=33)	P
D/C-associated Complication	**Hemorrhage**	7	10	6	0.043
	Uterus rupture	0	1	0	
MTX-associated complication	**Hemorrhage**	0	2	1	
	Uterus rupture	0	1	0	

Independent-Samples T test and Mann-Whitney U test were used to compare data
Values are expressed as mean ± standard deviation or number (n). Significant results are shown italic and bold

Table 6. Factors associated with maternal surgical complications

	Complications	
	R	p
β-HCG (Ref: ≥30000)	0.279*	0.011
Pregnancy time (Ref: ≥70 days)	0.339**	0.002
Body Mass Index	0.317**	0.004
Crown-to-rump length	0.306**	0.005
Pouch size	0.296**	0.007

*Correlation is significant at the 0.05 level (2-tailed)
**Correlation is significant at the 0.01 level (2-tailed)

Discussion

CSP is a rare Cesarean complication that occurs after implantation into the previous Cesarean incision line. This is associated with severe maternal morbidity and mortality due to diagnostic difficulties and uncertainty regarding optimal treatment once identified. Despite the recent studies reporting live birth because of wait-and-see practices, the current recommendation of the American Fetomaternal Medicine Association is the termination of pregnancy because it is associated with serious complications such as bleeding, uterine rupture, placental invasion anomalies (accreta, increata, percreata), permanent fertility loss and maternal mortality [4]. Medical, minimally invasive, and surgical treatment methods have been recommended for the treatment of the disease and studies have been conducted on this subject. These are generally retrospective studies with a limited number of patients, especially published over the last 10 years [5-7].

Although different numbers have been reported about the frequency of symptoms in different studies in the literature, it has

been reported that the most important symptom seen in patients with CSP is vaginal bleeding after amenorrhea [8]. In a recent study, it has been found that the most common symptom (68.1%) was vaginal bleeding after amenorrhea, only amenorrhea has been observed in 20.8% of patients, and abdominal pain concomitant to vaginal bleeding in the remaining patients [9]. Kim et al reported that 53.4% (n=31) of the patients have been determined incidentally during routine evaluation, 27 of the patients were symptomatic and the most common clinical presentation was vaginal bleeding 36.2% (n=21) in a study they evaluated 58 CSP patients treated in different treatment modalities [5]. We evaluated 82 patients in our study and the most common symptom was bleeding after amenorrhea. (n=51 (62.2%)). While 18 (21.9%) patients were asymptomatic, the remaining patients had complaints of abdominal pain and vaginal bleeding. We found that the clinical presentations of the patients were similar to the literature.

Many different alternatives for the treatment of the disease, from wait-and-see approaches to open or laparoscopic surgical treatments, have been described in the literature [7-9]. A limited number of randomized controlled studies compare treatment approaches [8]. We used three different treatment modalities for the treatment of patients in our study and evaluated their efficacy, additional treatment requirements, complication rates, the clinical course of the patients, and success rates. The use of the D/C procedure in CSP treatment is still up to date since it was first reported in the late seventies [4]. However, in cases where the CSP sac is located above the scar, it has been reported that the success rates may be low with the application of the D/C procedure alone due to the problem of reaching the CSP sac using a curette [9]. A recent study has shown that adding treatment protocols such as uterine artery embolization or MTX therapy to the D/C procedure will increase success rates [10]. In a recent study, Orhan et al treated 31 CSP cases with different treatment modalities and shared their results. They reported that pregnancy has been successfully terminated in all treatment modalities, but recurrent CSP developed in 3 of the patients who underwent D/C [11]. There are 21 case series in the literature involving a total of 243 patients for whom only D/C treatment was used for CSP treatment, but there are no randomized controlled trials (RCTs) evaluating the treatment. When the results of these studies on treatment modality are reviewed, it is seen that the method has 48% efficiency and a 21% complication rate [4]. In a study conducted by Polat et al in 2015, 19 out of 26 patients treated for CSP underwent vacuum aspiration as a first-line treatment, and six of them required a Foley balloon catheter for hemostasis because of vaginal bleeding. When the treatment method was evaluated in terms of effectiveness, they reported a success rate of 84.2% (n = 16) [12]. This method can have low success rates in cases where the cervical canal is long, and implantation is localized in far proximal segments. A US imaging was performed while performing the D/C procedure and it was confirmed that the gestational sac was aspirated in our study. While this increased our success rates, it has also helped to reduce the complication rates by preventing unnecessary tissue manipulations. In our study, we observed that while treatment was successful in all patients with this method, bleeding occurred in 7 patients. On the other hand, intracavitary or systemic MTX injection is one of the most used conservative approaches in the treatment of CSP [13,14]. However, it has been reported that the success rates of medical treatments alone are relatively low (approximately 37.5-80.9%), the resolution time of the pregnancy material extends from two months to one year [13], an additional treatment modality such as D/C is required in a large proportion of cases such as 29.8% [6], and complications such as unforeseen bleeding may occur in 17.5% of patients after methotrexate injection [15]. According to the CSP report of the Maternal-Fetal Medicine Association published in May 2020, there are 18 case series and 3 RCTs including 339 patients in total in the literature reporting the use of systemic MTX therapy alone. According to these studies, the efficiency of the method was 75%, while the complication rate was 13% [4]. In the same report, it has been reported that the efficiency of the method was 64.9% and the complication rate was 4.1% in 2 case series including 74 patients in total and 1 RCT in which local MTX treatment was used alone without combining it with any method. In our study, we found the complication rate in all three groups as 34.1%. The complication rate of patients who underwent D/C on the seventh day after intracavitary MTX administration was found to be 21.2%. This shows that patients who were administered intracavitary MTX had fewer complications compared to other groups. The success rate for all patients treated in this group is 100%. Complication rates after local MTX administration have been reported as 4.1% in the literature [4], and we determined the complication rate in our study to be 3%, and it was found to be like the literature. We found that the remaining 6 (18.2%) bleeding complications were secondary to the D/C procedure. The complication rates in patients who underwent D/C alone are 21% in the literature, and we determined the post-D/C complication rates less than in the literature. In our study, we saw the highest complication rates in group 2 patients to whom we administered systemic MTX and combined D/C. Although the treatment success in this group is also 100%, we observed that this method is more disadvantageous due to the highest complication rates. When we evaluated the methods in terms of success, we observed that there was no significant difference between them ($p>0.05$). The fact that patients were most susceptible to complications is the D/C stage among all methods and that the intracavitary methotrexate method has the least complication rate without decreasing success rates compared to other methods caught our attention especially in our study. We consider that the high complication rates during the D/C procedure are because the curetted part of the uterus is thinner than normal myometrial tissue and its contraction ability is lower.

Normalization of serum β-HCG levels is one of the most important indicators of treatment success in CSP treatment [6]. In our study, we observed that β-HCG levels regressed to normal levels in all patients within the first 4 weeks after the D/C procedure. This was significantly shorter than medical therapy alone. Like our study, it has been reported in the literature that β-HCG level regresses to normal levels within 4 weeks at the latest [15]. Pre-treatment β-HCG level is 43.887 mIU/mL (19.852 ± 74.552) and post-MTX β-HCG level is 8446 mIU/mL (5097 ± 9904) in the same study [15]. In our study, we found the β-HCG level as 33598.92±26189.10 mlU/ml at the time of the diagnosis and the post-MTX β-HCG level regressed to 8339.95±4519.10 mlU/ml, as like the literature. In our study, we only could not evaluate the results, complication rates, and treatment efficacy of the use of intracavitary and systemic MTX. As the limiting factor of our study, we consider the inability to evaluate this situation.

Conclusion

In a conclusion, we found that the D/C procedure has the most complication potential among primary treatment applications. For this reason, we consider that clinicians should behave more carefully, especially in the D/C stage. Among the treatment modalities used in our study, we observed that the treatment method causing the most frequent complications was the systemic MTX + D/C group and that the treatment method causing the least complication was local MTX + D/C treatment.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The ethics committee decision was obtained from the Ethics Committee of Kahramanmaras Sutcu Imam University with Session No. 2020/12, Decision No. 15 on 24.06.2020.

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