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Efficacy of Treatment of Cesarean Scar Ectopic Pregnancies with Alcohol Injection to the Gestational Sac and Dilatation Curettage with or without Systemic Methotrexate: A Case-Control Study

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ABSTRACT

Purpose: We aim to assess the effectiveness of treating cesarean scar ectopic pregnancies by injecting alcohol into the gestational sac (GS) and performing dilatation curettage with or without prior systemic methotrexate (MTX) administration.

Methods: A total of 37 patients were treated for cesarean scar pregnancy (CSP), 11 of which received systemic 75 mg MTX three days before local injection of 10% alcohol into the GS via 18G double lumen oocyte pick-up needle (Geotek, Ankara, Turkey) and 26 cases received local alcohol injection without prior MTX. Two or three days after the alcohol injection, the products of conception were removed again with a Karman cannula, and the β-hCG level was monitored weekly. After termination of CSP, the patients were followed up until they used contraception or delivered the following pregnancy.

Results: The MTX plus alcohol injection group and the alcohol injection alone group were compared. Significantly more women required Foley balloon tamponade 13 (50%), erythrocyte transfusion 13 (50%), and fresh frozen plasma infusion 9 (34.6%) in the local alcoholl injection alone group compared to the MTX plus alcohol group [n=1 (9.1%) p=0.01, n=1 (9.1%) p=0.01, n=0 p=0.02, respectively]. The mean resolution time of β-hCG was shorter in the MTX group [m=25±7.1 (18-48) and m=32.6±9.3 (22-58), p=0.01]; also; however, long hospitalization time was a disadvantage in this group. The recurrent CSP rate of 7.7% (n=2) was higher in the local alcohol injection alone group compared to nil in the MTX group. Cesarean niche surgery, abortion rate, and term pregnancy rates were similar in the two groups.

Conclusion: Although the efficacy of local alcohol injection alone is comparable to MTX plus alcohol injection, this group is at a disadvantage due to increased hemorrhage risk and the need for hemorrhage management. Local alcohol injection in combination with systemic MTX may be utilized as a good treatment option in patients.

Keywords: Cesarean scar pregnancy, methotrexate, alcohol, transvaginal ultrasound

INTRODUCTION

Cesarean scar pregnancies (CSPs) are a type of ectopic pregnancy located in a cesarean scar that has been experienced at least once before.[1,2] A gestational sac (GS) typically resides in the anterior uterine wall with a thinned myometrium between the sac and the bladder and an interruption in the anterior wall of the uterus next to the GS.[3] The prevalence of CSP has increased since the 2000s due to higher cesarean section rates,[4,5] changes in cesarean section techniques (one-layer technique, compared with the previous two-layer technique),[6] and improved ultrasound technologies for diagnosis.[7]

There are many ways to treat CSPs, as documented in the literature. These treatment modalities include expectant management, medical treatment by systemic methotrexate (MTX), medical treatment by systemic and local MTX, treatment by needle aspiration and local MTX, uterine curettage, hysteroscopy, resection of CSP through a transvaginal approach, uterine artery embolization (UAE), laparoscopy, and high-intensity focused ultrasound.[8-13] Various types of agents, such as potassium chloride (KCl), MTX, and vasopressin, have been experimented with for intragestational injection.[14-16] CSP can be a life-threatening condition if unrecognized and inadequately managed.

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Unfortunately, there is no definitive treatment with consensus in the literature.

In this study, we aim to assess the effectiveness of treating cesarean scar ectopic pregnancies by injecting alcohol into the GS and performing dilatation curettage two days apart.

METHODS

We conducted the study by retrospectively searching for patient data in the Consultant Clinic database from 2012 to 2020. Actually, all patients were followed up longitudinally between 2012-2020 in accordance with the principles outlined in the Declaration of Helsinki. Serum samples were collected at admission and during follow-up on the days specified.

During this study period, we did not aim to apply these methods on pregnancies older than ten weeks, and actually, no admissions later than ten weeks were observed in our clinic.

The diagnosis and management of CSP was conducted by the same perinatologist (EÇ). Voluson S8 5 MHz vaginal probe was used for the diagnosis of CSP. The diagnostic criteria were as follows: no content in the uterus and endocervical canal; identification of a GS and/or placenta in the area near the previous incision (hysterotomy scar or niche); a missing or slim layer of muscle tissue between the GS and the anterior uterine or bladder wall; and Doppler USG examination to determine rich peritrophoblastic blood flow around the GS.

The patients received 75 mg systemic MTX, three days before local alcohol injection if the gestational age was more than seven weeks or 49 days with positive fetal heart rate. A total of 37 patients were treated for CSP, 11 of which received systemic MTX before local injection of 10% alcohol into the GS via 18G double lumen oocyte pick-up needle (Geotek, Ankara, Turkey) under conscious sedation. Intravenous fentanyl 0.5-2 micrograms administered slowly in 25 microgram increments up to 75 micrograms were used for conscious sedation.[17] After vaginal disinfection with povidone-iodine, the needle was inserted through the anterior of the cervix between the uterus and the urinary bladder until puncturing the GS. The fluid inside the sac was aspirated first, and then 10% alcohol was injected instead of the fluid until the GS was fully dilated again. The patient was then followed up for two to three days, and the products of conception were removed again with a number 6 or seven Karman cannula (cervical dilation and manual vacuum aspiration: D&S) under conscious sedation and transabdominal ultrasound guidance. If bleeding is bright red and excessive, according to the managing perinatologist, Transamin 1 gr was administered, and/or Foley catheter size 16 was inserted into the uterine cavity; the Foley balloon was inflated with 3 mL of saline, and under transabdominal guidance, pulled back until the cesarean niche and then inflated up to 10-15 mL until the bleeding ceases. The balloon was kept in place for 24 hours and removed thereafter. All the procedures were performed in inpatient or outpatient settings according to the patient's preferences. Weekly β-hCG values were measured until the value dropped to non-pregnant reference values. The patients were followed up until the first spontaneous pregnancy after the termination of CSP. All women were then allowed to conceive spontaneously. All cases were followed until conception unless they decided to use contraception.

Statistical Analysis

Statistical analysis was used using the Statistical Program for Social Sciences (SPSS 20.0). Continuous variables between the two groups were compared using the Mann-Whitney U test. Categorical variables were compared using the chi-square test. A probability less than 0.05 was considered to be statistically significant. Continuous variables are presented in brackets as the mean and standard deviation of the mean and minimum-maximum values, and categorical variables are presented in brackets as numbers and percentages.

RESULTS

The mean age of the CSP patients was 34.2±4.2 (20-43) years, and the mean gestational age at diagnosis was 48.1±8.3 days. Twenty-two (59.5%) of the cases had one prior cesarean delivery, while 12 (32.4%) had two, and three cases (8.1%) had three cesarean deliveries before the scar pregnancy. The present CSP was achieved with intrauterine insemination in two (5.4%) and in vitro fertilization in four (10.8%) of the patients.

The distribution of selected variables and the outcome of the cases are presented in Table 1. The maternal age, gravida, parity, and number of prior cesarean deliveries were similar in the MTX plus alcohol injection group compared to the alcohol injection alone group. In accordance with selection criteria for inclusion in the MTX plus alcohol group, the mean gestational age 56±3.6 (52-61) and β-hCG at admission was higher 11605±5785 (4350-22748) compared to the alcohol injection alone group [m=44.3±3.7 (35-49), p<0.001; m=9043±5609 (1750-24857), p=0.03 respectively]. Significantly more women required Foley balloon tamponade 13 (50%), erythrocyte transfusion 13 (50%), fresh frozen plasma infusion 9 (34.6%) in the local alcohol injection group compared to MTX plus alcohol group [n=1 (9.1%) p=0.01, n=1 (9.1%) p=0.01, n=0 p=0.02 respectively]. Hospitalization time was longer in the systemic MTX plus local alcohol injection group, as most patients were hospitalized for MTX injection until local alcohol injection (Table 1). The mean resolution time of β-hCG to undetectable levels was shorter in the MTX plus local alcohol injection group compared to the local alcohol injection alone group [m=25±7.1 (18-48) and m=32.6±9.3 (22-58), p=0.01].

Follow-up of the patients and pregnancy outcome after resolution of CSP is presented in Table 2. Eleven cases had cesarean niche surgery, seven with laparoscopy, and four with laparotomy due to inability to conceive within a year or symptomatic menstrual spotting. Two cases had recurrent CSP in the Local Alcohol injection alone group compared to none in the MTX plus local alcohol injection group. A total of four (10.8%) patients had abortions, and fifteen patients (40.5%) had term pregnancies during follow-up. The distribution of pregnancy outcomes among the treatment groups was similar.

DISCUSSION

We found that local alcohol injection into the GS of the CSP by adding MTX in pregnancies more than seven completed weeks of pregnancy is effective. However, in our study, Foley balloon tamponade was needed to stop bleeding, and transfusion of erythrocyte suspension and fresh frozen plasma were more frequent in the local alcohol injection alone group.

Prenatal diagnosis of CSP is very important; it can be confused with missed/incomplete miscarriage or simply intrauterine pregnancies. This can be followed without intervention or with sharp curettage intervention, so it may cause complications such as heavy bleeding and uterine rupture.[18] Poor management of CSP can lead to severe life-threatening conditions such as hemorrhage, uterine rupture, hysterectomy, third-trimester bleeding, maternal death, and the occurrence of an abnormally invasive placenta.[19] There is no definitive consensus on the optimal CSP treatment modality and no guidelines on which patients should be treated and how. As a result, clinicians have experimented with various treatment modalities.

According to a systematic review, which evaluated 2,037 women in fifty-two studies, Treatment for CSPs should be interventional rather than medical. The review also recommended treatment options for CSP based on their efficacy and safety for clinical practice.[20]

Bağlı et al.[11] evaluated the efficacy of suction curettage (SC) as an effective treatment alternative for CSPs. Of 36 patients, 31 had favorable results with SC ± Foley balloon tamponade with a success rate of 86% (31/36). They reported that; this success is not related to the presence of an embryonic pole and fetal cardiac activity also, initial β-hCG levels, and a history of vaginal delivery. However, myometrial thickness was significantly depressed in the failed group (p=0.033).[11]

In some cases, researchers have attempted to use expectant management as a method of treatment for patients with a progressing pregnancy that eventually leads to a viable birth.[21] Silva et al.[22] published a systematic review including 47 studies on the expectant management of CSP. Miscarriage occurred in 20.1% of pregnancies, while 8.3% experienced fetal death. Only 25% of pregnancies lasted to term, while 41.8% were preterm, and 13.9% were born before 34 weeks. Also, In 52.6% of patients, a hysterectomy was performed. All cases had antenatal suspicion for placenta accreta spectrum and were later confirmed as placenta increta or percreta.[22]

It is widely known that MTX works by stopping the production of DNA at different points in the cell cycle. As a result, it causes

Table 1. Distribution of the selected clinical variables in cesarean scar ectopic pregnancies with respect to management groups

Variable	Systemic methotrexate plus local alcohol injection n=11	Local alcohol injection alone n=26	p-value
Maternal age (y)	34.1±2.6 (30-39)	34.3±4.8 (20-43)	0.56
Gravida	3.7±1.6 (2-7)	3.3±1.6 (2-10)	0.56
Parity	2.1±1.5 (1-5)	1.6±0.69 (1-3)	0.52
Prior cesarean delivery	1.4±0.68 (1-3)	1.5±0.64	0.83
Gestational age at admission (days)	56±3.6 (52-61)	44.3±3.7 (35-49)	<0.001**
Initial beta-hCG (IU/mL)	11605±5785 (4350-22748)	9043±5609 (1750-24857)	0.03**
Fetal cardiac activity	9 (81.8%)	16 (61.5%)	0.22
Transamin 1 gr	4 (36.4%)	13 (50%)	0.44
Foley baloon tamponade	1 (9.1%)	13 (50%)	0.01*
Any erythrocyte suspension	1 (9.1%)	13 (50%)	0.01*
Any fresh frozen plasma	0	9 (34.6%)	0.02*
Hospitalisation time (days)	7.7±5.4 (0-16)	3.3±3.1 (0-13)	0.01**
Resolution time(d)	25±7.1 (18-48)	32.6±9.3 (22-58)	0.01**

*: Statistically significant, chi-square test, p<0.05
**: Statistically significant, Mann-Whitney U test, p<0.05

Table 2. Follow-up of the patients and pregnancy outcome after resolution of cesarean scar pregnancy

Variable	Systemic methotrexate plus local alcohol injection n=11	Local alcohol injection alone n=26	p-value
Cesarean niche surgery	1 (9.1%)	10 (38.5%)	0.07
Future pregnancy outcome Contraceptive use Cesarean scar pregnacy Abortion Term pregancy	 5 (45.5%) 0 1 (9.1%) 5 (45.5%)	 11 (42.3%) 2 (7.7) 3 (11.5%) 10 (38.5%)	0.8

the death of cells that divide rapidly and trophoblast cells.[23] This particular mechanism makes MTX an effective treatment for a type of ectopic pregnancy known as CSP.

Heidar et al.[24] conducted a study on the effectiveness of systemic and/or local MTX treatment. The study evaluated four cases. A single dose of systemic MTX treatment was effective in two cases. However, in two other cases, the β-hCG level increased after a single dose of systemic MTX administration; for these cases, multiple doses of MTX were used; in addition to systemic administration, MTX was also injected into the GS. They emphasized that medical management alone can successfully treat CSP diagnosed at early gestation, with an additional injection into the sac required if primary treatment fails.[24]

Al-Jaroudi et al.[8] shared their experiences from a single center on various treatment options for CSP. These options included systemic MTX [n=14 (51.85%)]; intra-sac and systemic MTX [n=3 (11.1%)]; intra-cardiac KCl along with systemic MTX [n=2 (7.4%)]; expectant management [n=5 (18.51%)]; laparotomy wedge resection (n=1); UAE and systemic MTX (n=1). They find that first-line treatment success is 74.07% (n=20). They did not observe any side effects in the MTX group. No significant correlation was found between the time it took to resolve β-hCG and the chosen treatment methods (p=0.58).[8]

Bağlı et al.[11] retrospectively examined 36 patients with CSP treated solely by SC and found that a Foley catheter was needed in 23 patients (n=23/36, 63.8%). In our study, this rate was only 9.1% (n=1) in the group to which we added systemic MTX. Also, they reported that blood products were required in four patients (4/36, 11.1%) in their study, while only one patient (9.1%) received ERT and no fresh frozen plasma in the systemic MTX-added group of our study. In addition, they performed laparotomy on two patients due to hemodynamic instability, but it was not necessary for us. Adding systemic MTX to D&S treatment appears to reduce bleeding, treatment needs, and complication rates related to bleeding. Moreover, In a systematic review, Kanat-Pektas et al.[25] reported that the hysterectomy rates were higher in CSP cases treated with the D&S group than with the systemic MTX group (7.3% vs. 3.6%, respectively). Because MTX inhibits folic acid synthesis and new purines and pyrimidines, the synthesis of DNA and cell proliferation are destroyed. Tissues with high cell turnover, such as pregnancy products, are particularly prone to experiencing these effects, so MTX causes the death of trophoblasts. This death may cause thrombosis in the vessels feeding the product of conception, which may explain the lesser amount of bleeding if MTX is added to the treatment.

Heidar et al.[24] published four CSP patients who were treated with systemic MTX + local MTX/KCl. They didn't see any bleeding complications. Weeks later, they removed remnants of tissues by hysteroscopy.[24]

Giampaolino et al.[26] shared their experiences of 45 cases retrospectively. The patients were treated with five different approaches: Expectant management, Hysteroscopic resection, UAE + D&S, UAE and surgical laparotomic resection, systemic MTX + D&S. The group with the highest complication (profuse bleeding, hematoma, myometrial infarction), rate with a statistically significant difference was the UAE + D&S group (p≤0.001). No complications were observed in the MTX + D&S group.[26]

Like our study, bleeding-related complications were rare in the MTX + D&S group. A single dose of 50 mg MTX was administered, and after that, following 48 hours, the manual vacuum aspiration with a Karman cannula (D&S). This 48-hour period appears to be crucial for trophoblast death, leading to thrombosis. On the other hand, Huo et al.,[27] in their 11-year experience, declared that patients with a history of treatment for CSP using systemic or local and systemic MTX are more likely to develop persistent scar pregnancy and also have a higher risk of bleeding during subsequent surgery. However, they didn't combine the MTX treatment with the D&S, which could explain the disadvantages of MTX treatment.

Ge et al.[9] attempted to treat CSP using both intrachorial and systemic MTX applications, and they successfully treated 8 out of 11 patients (72.7%). However, our study showed a 100% treatment success rate. D&S was additionally required in two patients, and in one patient, UAE was needed.[9]

Although injecting MTX into the GS along with systemic MTX treatment seems like a reasonable approach to treating CSP, our study found that there were no observed side effects in patients who received systemic MTX in combination with local alcohol injection into the GS. In contrast, two patients experienced MTX side effects in that study, possibly due to an increase in the total MTX dose administered.[9]

In terms of hospitalization time, the systemic MTX plus local alcohol injection group seems to be more disadvantaged than the local alcohol injection alone group in our study (7.7±5.4 vs. 3.3±3.1, p=0.01, respectively). On the other hand, the resolution time is shorter than the local alcohol injection alone group (25±7.1 vs. 32.6±9.3, p=0.01, respectively). The use of MTX has been linked to a decrease in the time required for hCG remission and the disappearance of cesarean scar masses.[28]

Treatment choice for CSP is important not only in terms of bleeding complications but also in terms of how it affects the patient's fertility in the future. Unfortunately, very few studies in the literature have followed cases in terms of fertility outcomes.

Qian et al.,[29] 24h after UAE, compared D&S (n=33) and operative hysteroscopy (n=33) in the treatment of CSP, and they didn't find a significant difference in the intrauterine pregnancies after surgeries between the two groups (p=1.000) in the 12 months following. According to a report by Gundewar et al.,[30] three of four patients who desired to conceive were able to do so naturally after undergoing intra-sac KCl and MTX treatment. Likewise, in a study, among 13 cases treated with systemic MTX, three out of four patients who wanted to conceive were able to have a successful pregnancy.[31] Our study group that received systemic MTX showed similar results.

Qian et al.[29] found recurrent CSP was seen in one of 33 patients in the HS group, while none was in the D&S group. In a study of patients with CSP treated only with local MTX, 5 of 8 CSP cases desired subsequent pregnancies. Four healthy

pregnancies were observed, but one had recurrent CSP.[32] In our study, although the rate of recurrent CSP in patients who received local alcohol injection treatment was quite low (n=2/15), adding MTX to the treatment reduced recurrent CSP rates.

Insufficient literature data make it impossible to comment on subsequent pregnancy outcomes and recurrent CSP rates. However, our study is important because it includes subsequent pregnancy data for all treated CSP cases.

Although, in our study, there is no statistically significant difference between the groups, systemic MTX plus local alcohol injection group seems to be more advantageous in terms of future pregnancy outcomes like CSP, abortion, and term pregnancy. This may be due to the low number of patients in the systemic MTX plus local alcohol injection group.

Unfortunately, after the CSP treatment, there is insufficient data in the literature about abortion rates and the need for niche surgery, so it is impossible to comment on the effects of treatment options on these outcomes.

The literature widely discusses several factors that can affect the success of treatment methods used to treat CSP. These factors include the initial β-hCG level, fetal cardiac activity at the time of diagnosis, the location of scar pregnancy, and the thickness of the lower uterine segment myometrium. However, it is unknown which factors significantly impact the treatment's effectiveness, and there are no consensus cut-off values.

While our study's strength is that it follows our patients after CSP treatment and includes subsequent pregnancy data, the number of cases in our study is entirely satisfactory despite most publications on CSP treatment having limited case numbers.

Since not all treated patients plan pregnancy after treatment, it is pretty restrictive to comment on the effect of the treatment options on resulting in abortion or achieving term pregnancy. Although this is a limiting aspect of our study, it contains more data than many studies in the literature on this subject.

Subsequent pregnancy outcomes after treatment can be determined more clearly in larger case series in which systemic MTX is added to treatment.

CONCLUSION

In conclusion, adding systemic MTX to D&S treatment can reduce bleeding, bleeding-related treatment needs, and associated complication rates, which in turn helps lower treatment expenses.

Although MTX treatment can be effective, the fibrous tissue circumambient of the GS in systemic administration could limit exposure to the trophoblast.[33] Therefore, local administration of alcohol directly to the GS is necessary. Particularly in the later stages of pregnancy, combining a local injection of medication with aspiration is a more appropriate strategy.[34]

Local alcohol injection in combination with systemic MTX may be utilized as a good treatment option in patients where surgery is not a viable choice.

Ethics

Ethics Committee Approval: As the data was collected retrospectively, there is no requirement for approval from the ethics committee. All patients were followed up longitudinally between 2012-2020 in accordance with the principles outlined in the Declaration of Helsinki.

Informed Consent: Retrospectively study.

Authorship Contributions

Surgical and Medical Practices: B.A., Concept: H.Ş.S., Design: H.Ş.S., Data Collection or Processing: H.Ş.S., E.Y., N.A., B.A., Analysis or Interpretation: H.Ş.S., Literature Search: H.Ş.S., E.Y., N.A., Writing: H.Ş.S.

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