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Cesarean scar pregnancy managed with local and systemic methotrexate: A single center case series

Amir Naeh[a,b,*], Alon Shrim[a,b], Einat Shalom-Paz[a,b], Michal Amir[a,b], Mordechai Hallak[a,b], Ilan Bruchim[a,b]

[a] Department of Obstetrics and Gynecology, Hillel Yaffe Medical Center, Hadera, Israel
[b] The Rappaport Faculty of Medicine, The Technion Institute of Technology, Haifa, Israel

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ABSTRACT

Objective: To report the efficacy of combined systemic and local methotrexate treatment for cesarean scar pregnancy and review data from selected, similar case series.
Study design: A retrospective case series of 12 patients with cesarean scar pregnancy treated in a university hospital between 2014 and 2018. The intervention was combined treatment of systemic and local methotrexate.
Results: Twelve patients were treated with combined systemic and local methotrexate. Clinical characteristics, clinical course and treatment efficacy were evaluated. Mean gestational age at diagnosis was 7.5 weeks (range 5.9–9.1). βhCG levels at diagnosis ranged from 1581 to 345,427 U/L with a mean of 77,795 U/L. All 12 patients were successfully treated without surgical intervention and with no significant side-effects. Mean hospitalization duration was 9 days (5.8–12.6) and mean time to normalization of βhCG levels was 98 days (63–132).
Conclusions: Treatment of cesarean scar pregnancy with a combination of systemic and local methotrexate was effective and safe. Although the treatment course tends to be longer than with other modalities, this protocol offers excellent success rates, with fertility preservation and few complications.

Introduction

Cesarean scar pregnancy (CSP) is a rare form of ectopic pregnancy. However, in recent years its incidence is rising, probably due to increasing rates of cesarean deliveries and improved availability and accuracy of early pregnancy ultrasound [1]. CSP occurs in 1 in 500 pregnancies among patients who previously underwent cesarean delivery and accounts for 4% of ectopic pregnancies [2].

In CSP, the blastocyst implants on the cesarean scar. This is followed by pathological invasion of the placenta to the myometrium or the scar tissue and formation of early morbidly adherent placenta [3]. Untreated, the placental invasion may cause life threatening complications, including uterine rupture with severe hemorrhage [4]. Hence, early diagnosis and treatment are extremely important

Treatment options for CSP include medical and surgical modalities, such as dilatation and curettage (D&C), laparoscopic or hysteroscopic resection of gestational mass, uterine artery embolization and hysterectomy [5–7]. Local mechanical treatment with a double-balloon catheter has also been suggested for CSP [8]. Combined and sequential treatments have been described. The current literature is mostly based on case reports or case series and there is no consensus regarding optimal treatment. Despite known complications, some patients elect to continue their pregnancy. However, this is associated with the risk of morbidly adherent placenta and often, consequent hysterectomy [9].

Methotrexate (MTX), administered systemically, locally, or both, is commonly used for treating tubal and non-tubal ectopic pregnancies.

In recent years, our department's protocol for CSP treatment includes local and systemic injection of methotrexate. In this study we describe our experience with 12 consecutive cases of CSP treated with combined systemic and local MTX. We also conducted a literature review to assess the success rate of CSP treatment with local MTX and the added efficacy of combining local and systemic MTX.

Abbreviations: CSP, Cesarean scar pregnancy.

* Corresponding author.
E-mail address: amir_naeh@outlook.com (A. Naeh).

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Material and methods

This retrospective case series included all patients diagnosed with CSP who were admitted to our Obstetrics and Gynecology department from 2014 to 2018.

Diagnosis of CSP was based on the following transvaginal sonographic criteria [7,10,11]:

1 An empty uterine cavity with a clearly demonstrated endometrium and empty cervical canal.
2 The presence of a gestational sac, with or without fetal cardiac activity, embedded and surrounded by the myometrium, in the anterior part of the uterine isthmus.
3 A thin (1–3 mm) or absent myometrial layer between the gestational sac and the bladder.
4 Peritrophoblastic flow surrounding the CSP appearing on Doppler flow sonography.
5 Negative "sliding sign" (inability to displace the gestational sac from its position using gentle pressure with a transvaginal probe).

Ultrasound exams were performed by an experienced operator at our ultrasound unit, using Voluson E8 or E10 ultrasound (GE Healthcare, Chicago, IL).

All patients were hospitalized at the initiation of therapy. Baseline serum beta chorionic gonadotrophin (βhCG) levels were measured, as well as complete blood count, liver and renal function tests, and coagulation tests. Gestational age was determined according to the last menstrual period, sac dimension and first trimester crown-to-rump length measurements.

A detailed discussion with the patient ensued, describing the risks of persistent CSP, including morbidly adherent placenta, uterine rupture and significant hemorrhage. Treatment options were discussed, including local and systemic treatment with MTX, surgical treatments and the option of continuing the pregnancy, with advantages and limitations of each treatment. All patients received detailed information regarding MTX treatment, including local transvaginal and systemic injection and possible side effects and complications, with the possibility of treatment failure and eventual hysterectomy. Informed consent was received before treatment.

The procedure was performed in the operating room, with the patient under general anesthesia, to prevent patient movement during injection and to prepare for potential serious bleeding and possible surgical intervention. Patients were placed in lithotomy position and the vagina was prepared with povidone-iodine solution. A 17 G, double-lumen oocyte pick-up needle (Ovum aspiration needle double-lumen, Cook Medical, Australia) was attached to a transvaginal probe and introduced into the gestational sac via the vaginal fornix. Under transvaginal ultrasound (TVS) guidance, the gestational sac was punctured and aspirated with the needle.

If fetal cardiac activity was present, a KCl solution (14.9% concentration, 1 ml diluted in 10 ml saline), was injected to the gestational sac prior to its aspiration, usually 1–2 ml until cessation of fetal pulse. The total dose of MTX was calculated by 50 mg x body surface area, with 50% of the dose given locally and 50% systemically.

After aspiration of the amniotic sac, MTX was instilled slowly into the gestational sac using the second lumen of the needle. Following the procedure, an equal dose of MTX was given intramuscularly (IM).

Inpatient surveillance included physical examinations, serial serum βhCG levels and TVS scans. The day of the procedure was defined as day 1. Serum βhCG levels were obtained on days 4 and 7. A decline of 15% or greater in βhCG levels was regarded as treatment success. Patients were discharged and continued outpatient follow-up with weekly βhCG levels. In cases of insufficient βhCG decline, the patient received additional doses of systemic MTX.

Patients with an extremely large gestational mass were initially classified as high-risk patients. Therefore, they were given additional doses of MTX in an alternating protocol with leucovorin (IM MTX1 mg on days 1,3,5,7 and leucovorin 0.1 mg on days 2,4,6,8).

Table 1
Patient characteristics and clinical parameters.

Case	Age (yr)	No. previous CS	GA (weeks)	Fetal pole	FCA?	Initial βhCG levels (U/L)	Local MTX dose (mg)	Systemic MTX dose (mg)	KCl inj.	Further treatment	Total MTX dose (mg)	Inpatient (days)	Time to βhCG normalization (days)
1	39	3	10	+	+	48,518	40	40	+	None	80	8	149
2	34	2	9	+	–	30,795	60	60	–	Alternating MTX/ leucovorin	480	15	53
3	28	4	6	+	+	127,327	N	75	+	Additional single MTX IM	175	11	129
4	34	4	6	+	+	24,663	40	40	+	Additional single MTX IM	160	12	98
5	37	3	7	–	–	13,668	40	40	–	Alternating MTX/ leucovorin	320	10	60
6	33	3	8	+	+	92,404	50	50	–	Alternating MTX/ leucovorin	400	9	N/A
7	27	3	6	+	+	38,862	40	40	+	Alternating MTX/ leucovorin	320	9	76
8	37	2	7	+	+	1581	40	40	+	None	80	3	N/A
9	34	4	9	+	+	345,427	50	50	+	Additional double MTX IM	300	7	107
10	37	2	10	+	+	187,390	50	50	+	Alternating MTX/ leucovorin	400	12	133
11	34	2	6	+	+	20,315	40	40	+	None	80	11	118
12	40	2	6	+	+	2598	41	41	–	None	82	4	56

Ethical approval

The study was approved by the Institutional Review Board on 28/11/2017, number 0073-17-HYMC).

Results

Clinical details of the patients are summarized in Table 1. All patients had undergone at least 2 cesarean sections. Gestational age at diagnosis was 6 to 10 weeks. βhCG levels at the time of diagnosis ranged from 1581 U/L to 345,427 U/L, with a mean of 77,795 U/L.

On the day of the procedure, patients were treated with local and systemic MTX according to the described protocol. One patient presented with leukopenia (3000 leukocytes) and therefore received systemic MTX only when her leukocyte counts normalized.

In 10 of the 12 patients, fetal cardiac activity was demonstrated; 8 were treated with KCl injections in addition to MTX. KCl was not administered to 2 patients, despite fetal cardiac activity, due to technical difficulties.

All patients were followed according to the protocol. Four patients did not need additional treatment, 2 received an additional single dose of IM MTX on day 7, due to rising βhCG levels. Five patients were initially defined as high-risk due to a large gestational mass, were treated with a protocol of alternating MTX (4 doses) with leucovorin, and did not require additional treatment.

Following discharge, all patients were followed in our outpatient ectopic pregnancy clinic. βhCG levels of one of the low-risk patients plateaued during follow-up. She was readmitted and treated with two additional doses of systemic MTX (i.e. 3 doses overall), as well as with a double balloon catheter and responded well.

The mean hospitalization duration was 9 days (5.8–12.6). Most patients had no side-effects from MTX. One patient developed a rash and elevated liver enzyme and another developed aphthous stomatitis. Both were managed expectantly and improved spontaneously.

All patients responded well to the treatment protocol and no additional surgical procedures were required. Levels of βhCG normalized in a mean of 98 days (63–132). Fig. 1 demonstrates decline in βhCG levels. Resolution of the sonographic findings took up to 9 months.

Discussion

In this case series, patients with CSP were treated with combined systemic and local MTX. All patients responded well to the treatment protocol and no surgical interventions were required.

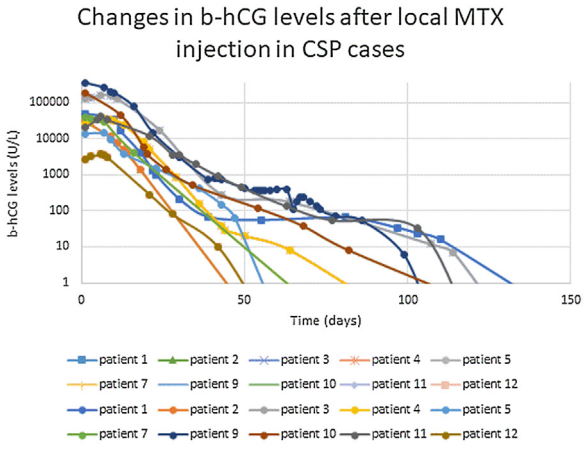

Fig. 1. Changes in βhCG levels after local MTX injection in CSP cases.

The incidence and diagnosis of CSP are rapidly rising, mainly due to higher rates of cesarean sections and increased use of ultrasound in early gestation. Early diagnosis and treatment of CSP is critical to increasing the success rate of treatment and to avoid complications [12].

Various modalities have been suggested for managing CSP, with no consensus regarding the optimal treatment method. Options include local and/or systemic medical treatment with MTX, uterine artery embolization and surgical procedures such as D&C, laparoscopic or hysteroscopic resection of gestational mass, and hysterectomy [6,7]. Local mechanical treatment with a double-balloon catheter has also been suggested for CSP [8]. Combined and sequential treatments have been described. Systemic reviews demonstrated success rates of 62%–65% for medical treatment and a 77% success rate for combined local and systemic MTX. Surgical treatment was described with a success rate of 83%, but with 18% complication rate compared to 7% for medical treatment [5,6]. In a recent national cohort study in the UK, surgical treatment was described with a success rate of 96%, but with 36% complication rate [13].

In an expert review from 2012, Timor-Trisch and Monteagudo demonstrated that of all treatment modalities for CSP, local MTX had the lowest complication rate of 9.6%, in comparison to 62% for D&C or systemic MTX injection, and that this modality was recommended as first line treatment for CSP [12]. Several subsequent case series and reviews demonstrated high efficacy and safety for local MTX treatment [14–16].Treatment with local MTX also offers preservation of fertility, which is an important advantage, as most patients with CSP are of reproductive age.

This study adds to the literature the following:

First, we describe our case series, with a high success rate for the combined treatment protocol. We also treated patients with relatively large CSP, including one with a very large uterine mass and a 10-week embryo with βhCG 345,427 U/L. To the best of our knowledge, this is the CSP with the highest βhCG level successfully treated with local MTX reported.

Second, we conducted a literature search for large case series of CSP treated with local MTX. Series with at least 6 cases were included for a total of 165 cases (including the current report). Patient characteristics and outcomes are summarized in Table 2. Overall, local MTX treatment modality has a very high success rate of 94%, with failure defined as need for surgical intervention.

Third, we examined the added efficacy of combining local and systemic MTX. As described above, our protocol combines local and systemic MTX treatment, simultaneously. Our experience shows that this protocol yields excellent results. As shown in previous articles, local combined with systemic MTX increases success rates [7]. Systematic reviews by Maheux-Lacroix et al. and Petersen et al. reported that adding systemic MTX to local treatment improved success rates from 62% to 77% and from 65% to 75%, respectively [5,6]. Systemic MTX has potential complications, such as nausea, stomatitis and bone marrow depression [5]. In our series, all patients were treated successfully, without major complications. In order to examine the added efficacy of combining local and systemic MTX, we reviewed the literature and divided case series into 2 groups: initial treatment with local MTX only as compared to initial treatment with local plus systemic MTX. The results are shown in Table 3. The combined treatment showed a trend for higher success rate (97% vs. 91%, P = 0.18). Data regarding side-effects of medical treatment are missing, but no major complications were reported.

Although treatment with MTX is efficient, physicians need to consider that it usually takes longer for βhCG levels to completely resolve and even longer for resolution of sonographic findings as compared to surgical intervention. In our series, complete

Table 2
Summary of large case series for treatment of cesarean scar pregnancies (CSP) with local MTX.

Reference	Total CSP cases	Cases treated with transvaginal MTX	Patient age (years)	Gestational age (weeks)	βhCG levels (U/L)	Overall success rate
Ko et al [21]	22	10	34.9 ± 4.8	6.7 + 1.6	50,666	8/10 = 80%
Yin et al [22]	34	22	28.5 ± 3.9	9 + 5.9	40,154	21/22 = 95%
Cok et al [23]	18	18	33.7 ± 3.4	6.2 + 1	12,699	15/18 = 83%
Uludag et al [15]	44	17	32.7 ± 5.2	6.4 + 0.9	27,970	17/17 = 100%
Timor-Tritsch et al [24]	60	33	NA	NA	NA	31/33 = 94%
Yamaguchi et al [20]	8	8	32.3 ± 4.1	8.0 + 1.3	45,823	8/8 = 100%
Seow et al [25]	11	11	33.8 ± 4.0	6.3 + 0.7	20,520	11/11 = 100%
Zhu et al [26]	68	28	31.2 ± 2.2	6.6 + 0.8	26,426	28/28 = 100%
Jurkovic et al [11]	18	6	39.4 ± 3.8	6.6 + 1.5	36,388	4/6 = 67%
Current study	12	12	34.5 ± 3.9	7.5 ± 1.6	77,795	12/12 = 100%

Table 3
Comparison between initial treatment with only local MTX and initial treatment with local + systemic MTX for CSP cases.

Cases initially treated with transvaginal MTX only		Cases initially treated with transvaginal + systemic MTX	
Reference	Success rate	Reference	Success rate
Ko et al [21]	8 of 10	Timor-Tritsch et al [24]	31 of 33
Yin et al [22]	21 of 22	Zhu et al [22]	28 of 28
Cok et al [23]	15 of 18	Current study	12 of 12
Uludag et al [15]	17 of 17	Total	71/73 = 97%
Yamaguchi et al [20]	8 of 8		
Seow et al [25]	11 of 11		
Jurkovic et al [11]	4 of 6		
Total	84/92 = 91%		

resolution took up to 9 months, with a mean of 168 days. Accordingly, both the patient and the medical team should be patient and the treatment duration should be discussed with the patients.

It is worth noting that βhCG levels can initially increase following treatment with MTX. However, this does not necessarily mean treatment failure. In our study, βhCG levels of 5 patients increased following initial treatment. However, levels declined steadily after 7 days without additional therapy. Similarly, with tubal pregnancies, βhCG levels might initially increase following treatment with MTX, due to trophoblast breakdown [17,18]. The same phenomenon probably occurs with CSP. Based on the results of current and previous reports [15], we suggest that the decision to administer additional MTX should be based on the dynamics of βhCG levels between days 4 and 7 of treatment, and not on βhCG level on day 4 of treatment.

Reproductive capacity after CSP is a main concern. Unfortunately, we do not have information regarding future pregnancies of patients in this series. Previous reviews have reported successful pregnancies after local MTX treatment, usually with elective cesarean sections, but with a higher rate of subsequent CSP and pregnancy complications [2,19,20].

Upon diagnosis of CSP, the possibility of preserving the pregnancy needs to be addressed. Although acceptable in some cases, this option yields a high rate of pregnancy complications [9]. In a recent systematic review, Jayaram et al. demonstrated that expectant management of CSP resulted in a live birth rate of 73%, but with 70% of cases requiring hysterectomy [4]. Risks including placenta accrete and increta, significant bleeding, uterine rupture, hysterectomy, and even maternal death, should all be discussed with the patient.

A limitation of this study is the small number of patients, due to the rare incidence of CSP. We did not have information regarding future pregnancies of patients in this series.

In conclusion, we suggest that combination of local and systemic MTX treatment should be considered the preferred treatment modality in clinically stable patients with CSP. This treatment offers excellent success rates, with low prevalence of complications and the possibility of fertility preservation. Moreover, it seems that this combined treatment might have an added efficacy compared with local MTX only, without significant side-effects. High-risk cases with large gestational masses may require a treatment regimen with multiple systemic MTX doses. As the incidence of these pregnancies is increasing, we suggest and are currently planning, multi-institutional studies that will compare different treatment modalities and suggest the optimal therapy.

Conflict of interest

The authors have no conflict of interest in relation to this work.

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