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Research Article

The Effect of Using Local Injection of Methotrexate in Management of Cesarean Scar Pregnancy in Minia University Maternity Hospital

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Abstract

Background; A cesarean scar pregnancy (CSP) is a rare and potentially life-threatening form of ectopic pregnancy. Therefore, the accurate and early diagnosis of CSP is very important for prognosis. Although MTX-based chemotherapy has been recognized as a relatively convenient and safe method of treatment, there have been no reports on the efficacy of local or systemic therapies for CSP, **Aim and objectives;** to determine the efficacy, acceptability and complication of using local injection of MTX in management of ceaserean scar pregnancy, **Subjects and methods:** This was a prospective study, was carried out on CSP patients treated at our Department of Obstetrics and Gynecology, Minia maternity and children university hospital, during the period of 2022 – 2023. A diagnosis of CSP relied on routine sonographic criteria. The protocol for treating CSP in our hospital was suction evacuation and chemotherapy with MTX, **Result**; there is a significant difference between success and failure treatment patients regarding initial β-hCG, **Conclusion;** single-dose local injection of MTX seems to be a safe, effective, and fertility-preserving treatment method for CSP treatment as a first-line treatment without surgical treatments. The presence of high β-HCG level at the beginning of treatment increase treatment failure. For this reason, local MTX can be applied as a safe and effective method in all technically applicable CSP cases,

Keyword: Cesarean scar pregnancy, B ultrasound-guided, Local methotrexate.

Introduction

Cesarean scar pregnancy (CSP) is defined as the implantation of a gestational sac within the scar of a previous cesarean surgery. If CSP is maintained, there are potentially higher risks that include uterine rupture, devastating hemorrhage, loss of subsequent fertility and even maternal mortality[1].

Therefore, the standard protocol for CSP management is to terminate the pregnancy. Nevertheless, while the optimal management of CSP remains unclear, there is a variety of therapeutic strategies are currently in use, such as medical treatment with systemic MTX, medical treatment with systemic and local MTX, uterine curettage, hysteroscopy, resection of CSP through a transvaginal approach, uterine artery embolization, laparoscopy, and high-intensity focused ultrasound[2]. Some complicated case may require combined application of several methods [3]

MTX is a folic acid antagonist that inhibits the enzyme dihydrofolate reductase, thereby interfering with DNA synthesis in rapidly dividing cells such as trophoblasts. The first usage of MTX in the treatment of ectopic pregnancy was reported by Tanaka et al.,, in an interstitial ectopic pregnancy in 1892 [4].

Some researchers have further suggested that local injection of MTX may be less effective in cases with higher serum hCG Concentrations [5]. The effects of local injection of MTX and whether it is ecommended are still unknown. The aim of this study was to evaluate the hCG

levels and outcomes in CSP patients treated with local injection of MTX to assess the efficacy of MTX.

This Prospective comparative controlled randomized clinical study will be conducted to determine the efficacy, acceptability and complication of using local injection of MTX in management of ceaserean scar pregnancy.

Patient and methods

This prospective study analyzed CSP patients treated at our Department of Obstetrics and Gynecology, Minia maternity and children university hospital, during the period of 2022 – 2023.

A diagnosis of CSP relied on routine sonographic criteria, including: Empty uterine cavity and cervical canal, a gestational sac located anteriorly at the level corresponding to the prior lower uterine segment of the cesarean section scar, evidence of functional trophoblastic/placental circulation on Doppler scans; and a negative sliding organs sign, which was defined as the inability to displace the gestational sac from its position at the level of the internal os.

Inclusion Criteria for study group: Patients who diagnosed with CSP, Patients of <12 weeks of gestation at diagnosis, no hepatic disorder and no DM, hemodynamic stable, no bleeding, no autoimmune disease and no history of cancer

Exclusion Criteria for groups: Patients who were unsuccessfully treated and then transferred to our hospital**,** patients of >12 weeks of gestation at diagnosis and patients with severe vaginal bleeding or hemodynamic changes

Methods: Data were collected through archived medical records

Complete history taking: Personal history including: Name, Age, marital state, address**,** menstrual history: including age of Menarche, menstrual disturbance, dysmenorrhea, related symptoms, history Parity**,** history of infertility**,** present history: of chronic diseases and medication, past history of HTN, DM, family history of similar condition or diabetes and history of allergy to any medication.

Examination: General examination: Vital signs (Blood pressure, Temperature, Heart rate, Respiratory rate), Signs of (Pallor, Cyanosis, Jaundice, and Lymph node enlargement) and **abdominal and local clinical examination.**

The protocol for treating CSP in our hospital: Suction evacuation **and** chemo-therapy with MTX

This study included women diagnosed with CSP and treated with a single dose of ultrasound-guided local MTX 50 mg/2 mL using transvaginal probe 7.5mhz, mindray 2200 plus model year 2019 (Unitrexate®, Korea United Pharm. Inc.) injection

A 22-G needle was inserted into the gestational sac with an adaptor under transvaginal ultrasound. The amniotic fluid and foetal tissues were aspirated and MTX (50 mg/2 ml) was slowly injected into the gestational sac.

Statistical Analysis:

All data were collected, tabulated and statistically analyzed using SPSS 22.0 for windows (SPSS Inc., Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean±SD (Standard deviation) for parametric and median and range for non-parametric data. Independent T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively. All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, $p < 0.001$ indicates highly significant difference while, $P > 0.05$ indicates non-significant difference.

Results

Table (1): Demographic characteristics among the studied patients

	Patients (n=30)
Age (years) Mean ± SD Range	 32.5 ± 3.77 25 – 40
BMI (kg/m^2) Mean ± SD	 28.43 ± 3.58
Residence	
Rural	13 (43.3%)
Urban	17 (56.7%)

This table shows that age ranged 25 – 40 years with mean BMI of 28.43 kg/m^2. 43.3% of the patients were rural and 56.7% were urban.

Table (2): Clinical characteristics among the studied patients

	Patients (n=30)
Gravidity Mean ± SD	 5.83±2.23
Parity Mean ± SD	 3.77±1.94

This table shows mean BMI was 5.83±2.23 and Mean parity was 3.77±1.94

Table (3): Comorbidities distribution of the studied patients

	Patients (n=30)
No comorbidities	27 (90%)
Hypothyroidism	1 (3.3%)
Rheumatoid arthritis	2 (6.7%)

This table shows that 2 patients had rheumatoid arthritis and one patient had hypothyroidism.

Table (4): Clinical presentation distribution among the studied patients

	Patients (n=30)	
	N	%
Fetal heartbeat	2	6.7%
Vaginal bleeding	18	60%
Abdominal pain	7	23.3%
Positive hypervascular signal	15	50%

This table shows that 60% presented with vaginal bleeding, 23.3% presented with abdominal pain, and 6.7% shows fetal heartbeat, meanwhile 50% showed positive hyper-vascular signal.

Table (5): Outcome distribution of the studied patients

	Patients (n=30)
Resolution time (days) Mean ± SD Range	 57.22±17.67 26–83
Outcome	
Success	27 (90%)
Failure	3 (10%)

This table shows that 90% of the patients were treated successfully with mean resolution time of 57.22±17.67 days.

Table (6): Sonographic findings among the studied patients according to outcome

	Success (n=27)	**Failure** (n=3)	t	**p**
Estimated GA (weeks) Mean ± SD	6.93±1.02	5.73±0.757	1.96	0.059
Gestational sac diameter (mm) Mean ± SD	16.23±6.24	8.87±5.66	1.95	0.061
Gestational sac position				
Type 1	20 (74.1%)	1 (33.3%)	2.13	0.144
Type 2	7 (25.9%)	2 (66.7%)		
Initial β-hCG (mIU/ml) Mean ± SD	25572.1±20871.6	83530.3±13751.2	**4.66**	**<0.001**

This table shows that there is a significant difference between success and failure treatment patients regarding initial β-hCG.

Table (7): History of dilatation and curettage distribution among the patients according to outcome

	Success n=27)	**Failure** (n=3)	χ^2	**P**
No	7 (25.9%)	0	**13**	**0.013**
1	7 (25.9%)	0		
2	8 (29.6%)	1 (33.3%)		
3	4 (14.8%)	0		
4	1 (3.7%)	2 (66.7%)		

This table shows that there is a significant difference between success and failure treatment regarding history of dilatation and curettage.

Discussion

Caesarean scar pregnancy (CSP) is a rare condition in which the implantation of the gestational sac takes place within the uterine scar of a previous caesarean section (CS). As a result, the gestation of a CSP is located within the area surrounded by the myometrium and fibromuscular tissue of the scar. The pathogenesis has not been delineated. However, the prominent theory is that impaired wound healing after previous trauma, such as after CS or myomectomy, creates a myometrial defect and a subsequent scar at which the blastocyst implants [6].

The most common CSP presentations are asymptomatic and discovered by ultrasonography, painless vaginal bleeding due to rupture towards the cavity or generalised abdominal pain caused by rupture through the uterine serosa. If the pregnancy continues within the uterus, the risk of placenta accreta or ruptured uterus is increased [7].

In this study we found that age ranged 25 – 40 years with mean BMI of 28.43 kg/m^2, 43.3% of the patients were rural and 56.7% were urban, mean Gravidity was 5.83±2.23, mean parity was 3.77±1.94 and mean estimated GA was 5.83±2.23 weeks.

Yamaguchi et al., [8] found that the mean age of the patient at the time of diagnosis was 32.3±4.1 years old (range, 25−38 years old). Three of the women had a history of uterine curettage. Two had experienced a single previous cesarean delivery, while five had undergone two previous cesarean deliveries. Five women had required emergency cesarean sections. The mean interval from the last cesarean section to the initial CSP therapy was 52.3±29.7 months (range, 6−108 113 months). All pregnancies were spontaneously conceived. The mean estimated gestational age at the time of the first injection was 8w0d±1w3d (range, 6w5d−10w5d).

In Cagli et al.,[9] study, 56 patients diagnosed with CSP were treated with local MTX. The mean age (SD) at the time of diagnosis was 34.2±5.5. The median number of previous cesarean sections was 2 (1–4), and the median time from the last cesarean to the first treatment for CSP was 7 (5–12) years.

Kotani et al.,[10] found that the mean age was 35.0±4.9 years, and the median gestational age at diagnosis was 7 (5–12) weeks.

Our results showed that mean initial β-hCG was 31367.9 ± 26764.7 mIU/ml and Mean time to normal β-hCG was 52.86 ± 22.49 days.
Cagli et al., [9] found that before treatment, the baseline median serum β-HCG level was 16 997 (113–233 835) mIU/mL and the mean time for patients' β-HCG normalization was 55.2± 41.0 days. The median time for the disappearance of the gestational sac was 28 (7–210) days.
Local MTX therapy was first performed by Godin et al.,[11] and they observed that the β-HCG level decreased to normal 82 days after the application. Ammar et al.,[12] found that the mean BHCG range was 41,771 at diagnosis and the values ranged from 1178 to 162,573.

In this study we demonstrated that 90% of the patients were treated successfully with mean resolution time of 57.22 ± 17.67 days.

In the study by Lewis et al.,[13] on 119 patients underwent medicinal therapy with MTX, 70% of patients received a single dose, and 11% received double dose, which rate of success was reported as 79%.

Lashin et al., [14] showed that methotrexate in a single or two doses could effectively treat ectopic pregnancy with fewer side effects providing that base line hCG level <5000 IU/L in hemodynamically stable young patients with no liver or kidney problems with a higher success rate.

Our results showed that there is no significant difference between success and failure treatment patients regarding age, BMI, gravidity, and parity. In this study we found that there is a significant difference between success and failure treatment patients regarding initial β-hCG.

Kotani et al., [10] found that the initial serum ß-hCG level in the success group was significantly lower than in the failure group (28,484 (804–262,611) mIU/ml vs. 81,418 (15,436–99,287) mIU/ml, p = 0.048).
Cheung et al., [15] found that patients with serum hCG levels higher than 100 000 IU/L were more likely to require surgical intervention (odds ratio, 40.7; p < .002).

Peng et al.,[16] found that the mean pretreatment serum β-hCG level of the cured group was 21,941±18,351 mIU/mL, which was much lower than that of the failed group (37,047± 30,864 mIU/mL) (P=0.038).

Lashin et al.,[14] showed that there are several factors which could predict success or failure of methotrexate therapy as; pretreatment level of β-hCG level of ≥5000 mIU/mL, a moderate to a huge amount of free fluid during transvaginal ultrasound, and a steady elevation in levels of β-hCG levels after two days of initiating medical therapy, while the rate of success rate was very high in patients with a pretreatment β-hCG levels between 1900 and 4999 mIU/mL.

In the study by Gamzu et al., [17], there was a 97% success in the treatment of β-hCG less than 2000 in comparison to 74% of success in the treatment of β-hCG higher than 2000.
In this thesis we cleared that there is a significant difference between success and failure treatment regarding history of dilatation and curettage.

Tan et al.,[18] demonstrated that the local intra-gestational sac methotrexate injection method combined with D&C has achieved a high success rate. Wang et al.,[19] analyzed the MTX with and without curettage and showed that both therapies could treat the majority of CSP patients successfully, but the combined therapy resulted in a shorter time of therapy and had a more favorable effect.
Another study by Jiang et al.,[20] included 45 patients showed that MTX administration followed by suction curettage with Foley tamponade was an effective treatment for CSP.

Conclusion

In conclusion, single-dose local injection of MTX seems to be a safe, effective, and fertility-preserving treatment method for CSP treatment as a first-line treatment without surgical treatments. The presence of high β-HCG level at the beginning of treatment increase treatment failure. For this reason, local MTX can be applied as a safe and effective method in all technically applicable CSP cases.

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