

Ultrasound-Guided Surgical Evacuation versus Combined Local and Systemic Methotrexate Injection for Management of Caesarean Scar Pregnancy

Randomized controlled Trial

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Abstract

Background: Caesarean scar pregnancy (CSP) is a rare form of ectopic pregnancy characterized by implantation of the gestational sac at the site of a previous cesarean section scar. Despite advances in early diagnosis, CSP remains associated with severe potential complications. Optimal management strategies remain controversial.

Objective: To compare the effectiveness, safety, and clinical outcomes of ultrasound-guided surgical evacuation versus combined local and systemic methotrexate (MTX) injection in the management of CSP.

Methods: This non-blinded randomized controlled trial was conducted at Minia Maternity University Hospital from January 2024 to June 2025. Fifty-six women with confirmed, unruptured CSP before 12 weeks of gestation were randomly allocated into two equal groups: Group A (n=28) underwent ultrasound-guided surgical evacuation, while Group B (n=28) received combined local and systemic MTX therapy. The primary outcome was treatment success. Secondary outcomes included blood loss, hospital stay, time to serum β -hCG normalization, and complications.

Results: Treatment success was higher in the surgical group than in the combined MTX group (92.9% vs. 67.9%, $p=0.040$). Hospital stay (2.2 ± 0.7 vs. 3.7 ± 1.3 days, $p<0.001$) and estimated blood loss (25.4 ± 25.8 vs. 204.7 ± 158.4 mL, $p<0.001$) were significantly lower in the MTX group. Conversely, time to β -hCG normalization was significantly shorter following surgery (36.9 ± 8.9 vs. 83.3 ± 16.7 days, $p<0.001$). Major complications did not differ significantly between groups.

Conclusion: Combined local and systemic Methotrexate injection seems to be a safe alternative to ultrasound-guided surgical evacuation for Caesarean Scar Pregnancy, offering comparable overall safety and minimal blood loss despite lower initial success and prolonged biochemical resolution.

Keywords: Caesarean scar pregnancy; methotrexate; ultrasound-guided evacuation; ectopic pregnancy; β -hCG; randomized controlled trial.

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Introduction

Caesarean scar pregnancy (CSP) is an uncommon form of ectopic pregnancy in which the gestational sac implants at the site of a previous caesarean section scar. Although CSP is rare, delayed or inappropriate management may result in severe maternal morbidity, including massive hemorrhage, uterine rupture, placenta accreta spectrum disorders, and, in severe cases, maternal mortality. Early diagnosis and appropriate treatment are therefore essential to minimize complications and preserve reproductive potential. [Ref: 16, 20, 21]

The incidence of CSP has increased in parallel with increasing caesarean delivery rates and the widespread use of early transvaginal ultrasonography. The reported incidence ranges from approximately 1 in 1800 to 1 in 2216 pregnancies, while CSP has been reported in approximately 6.1% of ectopic pregnancies among women with a previous Caesarean delivery. Transvaginal ultrasonography with color Doppler is the principal diagnostic modality.

Typical sonographic findings include an empty uterine cavity and cervical canal, an anteriorly located gestational sac at the level of the previous cesarean scar, evidence of trophoblastic vascularity, and a negative sliding-organ sign. CSP may present with different implantation patterns. The endogenic type grows toward the uterine cavity, whereas the exogenic type is deeply implanted within the scar and may expand toward the bladder or abdominal cavity. [Ref: 15, 17, 18]

Clinical presentation ranges from an asymptomatic early pregnancy to pelvic pain and significant vaginal bleeding. Because the clinical presentation may resemble miscarriage, cervical pregnancy, or other early pregnancy complications, accurate early ultrasonographic diagnosis is particularly important. [Ref: 8, 18]

Several treatment options have been proposed for CSP, including systemic or local methotrexate, combined medical treatment, uterine artery embolization, hysteroscopic resection, laparoscopic surgery, and ultrasound-guided surgical evacuation. However, there is no universally accepted treatment strategy, and treatment selection is generally individualized according to gestational age, serum β -hCG concentration, fetal cardiac activity, CSP morphology, residual myometrial thickness, hemodynamic status, and the patient's reproductive wishes. [Ref: 16, 20, 21]

Methotrexate provides a conservative approach aimed at terminating trophoblastic activity while preserving the uterus. Combined local and systemic administration may enhance treatment efficacy by providing a high local drug concentration together with systemic treatment. Nevertheless, medical management may require prolonged follow-up and may be associated with delayed resolution, treatment failure, or bleeding requiring additional intervention. [Ref: 2, 3, 5, 10]

Ultrasound-guided surgical evacuation provides immediate removal of gestational tissue and may result in more rapid β -hCG decline and resolution of the pregnancy. However, the procedure may be associated with bleeding, uterine perforation, and other surgical complications. [Ref: 1, 11, 22]

Despite the increasing number of reported treatment strategies, evidence directly comparing ultrasound-guided surgical evacuation with combined local and systemic MTX remains limited. Therefore, the present randomized controlled trial aimed to compare the effectiveness and safety of ultrasound-guided surgical evacuation with combined local and systemic MTX injection in women with cesarean scar pregnancy. [Ref: 11, 12, 13, 14]

Patients and Methods

Study Design and Setting: This was a non-blinded randomized controlled clinical trial conducted at the Department of Obstetrics and Gynecology, Minia Maternity University Hospital, Faculty of Medicine, Minia University, Egypt, from January 2024 to June 2025. The study protocol was reviewed and approved by the local institutional ethical review committee. Written informed consent was obtained from all participants before enrollment. The study was registered at clinicaltrials.gov (NCT07288307).

Selection Criteria: Inclusion criteria of the study were hemodynamically stable women with confirmed, undisturbed caesarean scar pregnancy, gestational age less than 12 weeks, and willingness to accept prolonged follow-up, repeated β -hCG measurements, and possible additional interventions including surgery or hysterectomy if required. While cases with gestational age greater than 12 weeks, hemodynamic instability, ruptured CSP, refusal of pregnancy termination, contraindications to methotrexate or anesthesia, or prior failed treatments referred from other centers were excluded.

Diagnosis of Cesarean Scar Pregnancy: CSP was diagnosed using transvaginal ultrasonography based on standard criteria: an empty uterine cavity and cervical canal, a gestational sac located anteriorly at the level of the previous lower uterine segment scar, functional trophoblastic circulation on color Doppler, and a negative sliding-organ sign. Residual myometrial thickness between the sac and the urinary bladder was routinely measured. [Ref: 15, 18]

Baseline Assessment: All participants underwent detailed history taking, physical examination, and baseline laboratory investigations including complete blood count, liver and kidney function tests, and coagulation profiles. Baseline ultrasound parameters recorded were gestational sac diameter, residual myometrial thickness, fetal cardiac activity, and subtrophoblastic vascularity.

Sample Size and Randomization: Sample size calculation using G*Power software (version 3.1.9.6) determined a requirement of 21 participants per group based on estimated success rates of 90% for surgery and 40% for MTX ($\alpha=0.05$, 80% power). This was adjusted to 28 participants per group (56 total) to accommodate a potential 10% dropout rate. Eligible participants were randomly allocated into two equal groups: Group A (Ultrasound-Guided Surgical Evacuation under spinal anesthesia) and Group B (Combined Local and Systemic MTX: 50 mg intra-gestational sac injection under ultrasound guidance plus 50 mg intramuscular injection).

Outcome Measures: The primary outcome was treatment success defined as complete resolution without additional intervention. Secondary outcomes included estimated blood loss, duration of hospital stay, time to serum β -hCG normalization, need for secondary interventions, and adverse effects or major complications.

Statistical Analysis: Data were analyzed using IBM SPSS Statistics version 27.0. Continuous variables were evaluated for normality using the Shapiro-Wilk test and expressed as mean $\pm$ SD or median (range). Categorical

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variables were expressed as frequencies and percentages. Group comparisons were conducted using independent t-tests, Mann-Whitney U tests, Chi-square tests, or Fisher's exact tests as appropriate. Multivariate logistic regression was applied to evaluate independent predictors of treatment success. A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics: A total of 56 women with CSP were included, with 28 participants randomly assigned to each group. The baseline demographic and clinical profile of participants across both study arms is presented in Table 1.

Characteristic	Surgery (n=28)	Combined MTX (n=28)	P-value
Age (years), mean ± SD	32.8 ± 3.9	32.5 ± 4.1	0.876
Gravidity, mean ± SD	3.9 ± 0.9	4.2 ± 1.03	0.297
Parity, mean ± SD	2.6 ± 1.1	2.9 ± 0.9	0.311
Previous CS, mean ± SD	1.7 ± 0.7	1.5 ± 0.9	0.297
Gestational age (weeks), mean ± SD	6.7 ± 0.8	7.03 ± 1.01	0.172
Fetal cardiac activity, n (%)	9 (32.1%)	10 (35.7%)	1.000

Table 1: Baseline Characteristics of the Study Population

Ultrasound and Laboratory Findings: The main sonographic and initial biochemical findings prior to intervention are outlined in Table 2.

Variable	Surgery (n=28)	Combined MTX (n=28)	P-value
Gestational sac diameter (mm), mean ± SD	17.6 ± 4.2	20.7 ± 4.9	0.015*
Residual myometrial thickness (mm), mean ± SD	3.8 ± 0.8	3.6 ± 0.9	0.358
Initial β-hCG (mIU/mL), median (range)	17,157 (6,564–38,676)	18,755.5 (7,172–71,452)	0.676

Table 2: Ultrasound and Laboratory Findings

Treatment Success and Operative Outcomes: Overall treatment success was significantly higher in the surgical evacuation group compared with the combined MTX group. Secondary management details and specific procedures required in cases of failure are detailed in Table 3.

Outcome	Surgery (n=28)	Combined MTX (n=28)	P-value
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Treatment success, n (%)	26 (92.9%)	19 (67.9%)	0.040*
No additional intervention, n (%)	26 (92.9%)	25 (89.3%)	0.285
Laparotomy for perforation repair, n (%)	1 (3.6%)	0	-
Blood transfusion + tamponade, n (%)	1 (3.6%)	0	-
Rescue suction evacuation, n (%)	0	2 (7.1%)	-
Emergency evacuation for bleeding, n (%)	0	1 (3.6%)	-

Table 3: Treatment Success and Additional Interventions

Recovery and Secondary Outcomes: Significant differences were observed regarding hospitalization time, resolution velocity, and blood loss. Duration to resolve β -hCG levels was significantly shorter following surgical intervention, whereas combined MTX demonstrated markedly lower blood loss and reduced hospital stay. Key clinical recovery parameters are summarized in Table 4.

Outcome	Surgery (n=28)	Combined MTX (n=28)	P-value
Hospital stay (days), mean $\pm$ SD	3.7 $\pm$ 1.3	2.2 $\pm$ 0.7	<0.001*
Time to β -hCG normalization (days), mean $\pm$ SD	36.9 $\pm$ 8.9	83.3 $\pm$ 16.7	<0.001*
Estimated blood loss (mL), mean $\pm$ SD	204.7 $\pm$ 158.4	25.4 $\pm$ 25.8	<0.001*

Table 4: Recovery and Secondary Outcomes

Complications: The frequency and nature of major adverse events did not differ significantly between the groups. Observed major complications are presented in Table 5.

Complication	Surgery (n=28)	Combined MTX (n=28)
Uterine perforation, n (%)	1 (3.6%)	0
Significant intraoperative bleeding, n (%)	1 (3.6%)	0

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Pelvic hematoma, n (%)	1 (3.6%)	0
Post-abortive hemorrhage, n (%)	0	1 (3.6%)
No major complication, n (%)	25 (89.3%)	27 (96.4%)

Table 5: Major Complications

Predictors of Success: Multivariate logistic regression identified primary treatment modality and CSP type as independent predictors of treatment success, with adjusted parameters displayed in Table 6.

Variable	Adjusted OR	95% CI	P-value
Surgery vs. MTX	4.86	1.05–22.48	0.043*
Type I vs. Type II CSP	4.33	1.08–17.32	0.038*
Gestational sac diameter	0.91	0.80–1.04	0.172
Initial β -hCG	0.88	0.62–1.24	0.456
Residual myometrial thickness	1.28	0.63–2.61	0.492
Fetal cardiac activity	0.58	0.15–2.21	0.425

Table 6: Multivariate Logistic Regression Analysis for Treatment Success

Discussion

This randomized trial evaluated ultrasound-guided surgical evacuation versus combined local and systemic MTX in women with stable CSP managed before 12 weeks of gestation. In summary, surgical evacuation yielded significantly higher success rates and faster β -hCG clearance, whereas combined MTX resulted in markedly lower blood loss and shorter hospitalization.

Our surgical success rate (92.9%) aligns with previous trials like Kadu et al. (93.3%) [11] and Bashir et al. [12], which confirmed superior immediate success with surgical approaches over medical therapy. Conversely, our success rate for combined MTX (67.9%) falls within the reported literature range, bounded by studies such as Toutain et al. (91.4%) [10], Nach et al. (100%) [3], and Van et al. (50.4%) [5]. These variances are largely attributable to variations in baseline β -hCG thresholds, sac vascularity, and inclusion of exogenic CSP types. Furthermore, studies by Yamaguchi et al. [4] and Huo et al. [7] highlighted that medical treatment failure often stems from higher initial β -hCG levels, whereas Hortu et al. [13] and Elsayed et al. [14] underscored that surgical intervention consistently provides a more definitive immediate resolution across different CSP subtypes.

The prolonged time to β -hCG resolution observed in our MTX group (~83 days vs ~37 days in surgery) is consistent with observations by Nach et al. (~98 days) [3] and Toutain et al. (~66 days) [10]. Additionally, clinical reports by Lin et al. [8], Cheng et al. [9], and Han et al. [19] observed similar delayed resolution kinetics and potential risks of secondary hemorrhage during conservative medical management. Conversely, the minimal blood loss associated with medical treatment in our series supports earlier findings by Mitsui et al. [2] and Hameed et al. [6], highlighting local and systemic MTX as a minimally invasive uterine-sparing option. Review findings by D'Antonio et al. [16], Alameddine et al. [20], and Piróg et al. [21] further reinforce that while surgical techniques provide rapid clearance, conservative protocols minimize operative trauma in carefully selected patients.

Points of strength of this study include its prospective randomized design, direct comparative evaluation of surgical and combined medical management, standardized diagnostic criteria, objective guidance using intraoperative

ultrasound, and rigorous assessment of both efficacy and safety outcomes. On the other hand, limitations were its single-center setting, relatively small sample size, non-blinded design, and lack of long-term follow-up regarding subsequent fertility and future pregnancy outcomes.

Conclusion

Local and systemic Methotrexate injection represents a safe and conservative alternative to surgical evacuation for managing Caesarean Scar Pregnancy. Although associated with a lower primary success rate and prolonged β -hCG resolution, its high safety profile and minimal blood loss can be weighed favorably against surgical risks in stable patients. Further large multicenter randomized controlled trials are needed to confirm these findings and evaluate long-term reproductive outcomes.

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