

# Caesareans Section Scar Ectopic Pregnancy: An Emerging Challenge

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**Abstract:**

Caesarean scar ectopic pregnancy (CSEP) is an uncommon form of ectopic pregnancy. This review defines types of CSEP, discusses pathophysiology, clinical presentation and diagnosis and compares common treatment options and outcomes. The pathophysiology is not yet fully understood. One third of patient are asymptomatic. In symptomatic patients vaginal bleeding and pelvic pain which is usually misdiagnosed as threatened or missed abortion. The main principles of treatment for CSEP are early diagnose, quick management, and maintain reproductive function as much as possible. Up to date; no consensus or guidelines for the treatment and management of CSEP. Management of CSEP depends on the clinical presentation and gestational age. Significant controversy exists regarding management, for this reason, several factors should be considered including age of the patient, myometrial thickness, clinical symptoms, hemodynamic status, fertility preservation.

**Keywords: caesarean scar ectopic pregnancy, risk factors, clinical presentation, complications, management, outcome of CSEP**

**Introduction:**

Ectopic pregnancy is defined as the presence of pregnancy outside the uterine cavity. It is estimated that more than 90% of ectopic pregnancies occur in the fallopian tube. Other rare locations of ectopic pregnancy; cervix, intramural, ovaries, abdomen or hysterotomy or caesarean scar [1]. Generally; ectopic pregnancy accounts for 1 to 2 percent of obstetrics population [2].

Caesarean scar ectopic pregnancy (CSEP) is defined as the embryo implanting within the myometrial tissue that corresponds to the site of a previous lower segment caesarean section scar.

The purpose of this review to define types of CSEP, incidence of CSEP, discusses pathophysiology, clinical presentation and diagnosis, and compare treatment options and outcomes. A review of the literature using the keywords; caesarean scar ectopic pregnancy, risk factors, clinical presentation, complications, management, outcome of CSEP and conducted the search in Medline, EMBASE, and Cochrane Database of systematic reviews.

**Historic background:**

In the year 1978, Larsen and Solomon reported the first case of CSEP [3]. The case was managed as incomplete abortion and developed persistent haemorrhage as a result of major vessel bleeding in a previous scar. Since then until the year 2002 only 19 cases have been published in the English literature[4]. Following this, several case series and studies have been published including management options and outcome of CSEP.

**Incidence:**

It doesn't seem that the number of caesarean deliveries lead to increase in the incidence. The estimated incidence is 1: 1800 to 1: 2216 pregnancies (0.05–0.04%) and accounting for 6.1% of ectopic pregnancy in women with previous caesarean sections (CS) [5]. A recent data indicates that the incidence of CSEP is 1:3000 among general obstetric population and in the range of 1:2500 to 1:8000 for all caesarean deliveries [6, 7].

However, with increase awareness among obstetricians and high index of suspicion, the detection and diagnosis of SCEP is increasing.

### **Pathophysiology:**

The pathophysiology is not yet fully understood. The most accepted theory is that the blastocyst invades into the myometrium through a microscopic defect, which may be the consequence of trauma resulted from a previous CS or any prior uterine surgery [8]. In a random population of women with CS scar, the prevalence of this defect is 84% [9]. Roeder et al. studied the histopathology of CS scar wound healing, different thicknesses of the myometrium along the scar with elastosis and adenomyosis were found [10]. It seems that impaired healing of the CS wound may predisposes to the development of CSEP [11]. Ash et al. postulated that when the interval between CS and a subsequent pregnancy is short, the probability of having CSEP and placenta accrete is increased [12]. Timor-Tritsch et al. believe that placenta accreta share a similar histology and pathogenesis of CSEP, he postulated that implantation occurs where there defect of healing process so that trophoblastic tissue invades the myometrium and the surrounding scar tissue [13]. On the other hand, in a study by Flystra, he found that CSEP and placenta accreta are different disease entities. CSEP invade the myometrium and separated from endometrial cavity, while placenta accreta invade the myometrium and completely located in the endometrial cavity [14]. Some researchers suggested that CSEP is even more aggressive than

placenta accreta because CSEP invade the myometrium in the first trimester leading to massive bleeding and uterine rupture in early pregnancy [4, 5].

### **Types of CSEP:**

According to Vial et al. two different types of CSEP are identified: endogenic and the exogenic. Type 1 (endogenic type) it develops in the myometrium and surrounding scar and grows toward the uterine cavity. Type 2 (exogenic type) It develops in the myometrium and surrounding scar and progresses exophytically toward the uterine serosa, bladder and abdominal cavity [14]. In the endogenic type of CSEP a viable pregnancy may reach term with a high risk of bleeding at the placental site, while the exogenic type carries high risk of bleeding and uterine rupture early in pregnancy [15].

### **Etiology:**

Several risk factors have postulated to be a risk factor for CSEP. Apart from CS scar as a known risk factor [7]. Several factors that lead to increase the CSEP in the scar like poor wound healing, inadequate or single layer closure, uterine retroflexion, history of multiple CS with deficient scar, postoperative infections, decreased immunity, diabetes and collagen disease [16, 17]. Also, short interval between CS and subsequent pregnancy can be a risk factor for CSEP [10, 12, 18]. CSEP has been reported in myomectomy scar as well [19]. Other risk factors like adenomyosis, previous dilation and curettage, manual removal of the placenta, in vitro fertilization, previous history of abnormally adherent placenta, metroplasty and hysteroscopy [4, 20-22].

### **Clinical picture:**

About on third of patients are asymptomatic at diagnosis [23]. In symptomatic patients, vaginal bleeding and pelvic pain in the first trimester are usually misdiagnosed as threatened or missed abortion. This misdiagnosis could result in life-threatening hemorrhage, disseminated intravascular coagulation, shock, uterine rupture, and even death [24].

Generally; vaginal bleeding is the most common presenting symptom [13]. In a study includes 92 cases; vaginal bleeding alone was found in 48% followed by vaginal bleeding and abdominal pain in 23% of patients, Pain alone was found in 10% while 20% were asymptomatic [25].

### **Diagnosis:**

Obstetrician should have high index of suspicion when dealing with women with previous scar. Women with previous CS should have a transvaginal ultrasound (TVU) in the first trimester to exclude CSEP [15]. High accuracy rate in the diagnosis of CSEP can be achieved by combined transabdominal (TAU) and TVU approach [26]. Maymon et al. found that combined approach of both TAU and TVU reduce the risk of a false diagnosis. TAU allows visualization of myometrial thickness, size and location of gestational sac and its relation to the urinary bladder [27]. A sensitivity of 84.6% can be achieved by TAU for detection of CSEP in first trimester [28]. Doppler assessment may help reduce false positive diagnosis.

The majority of CSEP are diagnosed in the first trimester. From a recent systematic review, diagnosis of CSEP was confirmed at  $7.2 \pm 1.1$  weeks [26]. In a study included 92 cases, diagnosis was confirmed at mean gestational age of 9 weeks [25].

CSEP can be misdiagnosed as an early pregnancy, cervical or an inevitable abortion. However; diagnosis of an early CSEP can be very challenging. Delayed diagnosis can lead to massive haemorrhage and uterine rupture [26].

### **Criteria for the diagnosis of CSEP:**

Empty uterus and cervical canal with clearly visible endometrium. Gestational sac or placental tissue present in the anterior wall of the cervical isthmus surrounded by scar tissue of CS.

Diminished myometrium or absent between the bladder and gestational sac with or without fetal pole with positive or absent cardiac activity. Doppler with High velocity with low impedance blood flow of vascular flow around the gestational sac, the “ring of fire” sign.

Absent “sliding sign”, an additional confirmatory test as suggested by some investigators, a pressure on the cervix by vaginal probe, the gestational sac will slide against the endocervical canal in cases of miscarriage [30].

Magnetic resonance imaging (MRI) is a helpful tool when TVU and Doppler sonography are inconclusive, when uterine anatomy is distorted by a large fibroid or if the pregnancy has advanced [31]. MRI provides better pelvic soft tissue evaluation and relationship of CSEP to bladder and adjacent pelvic organs, thereby aids in the decision of management.

### **Treatment:**

The main principles of treatment for CSEP are early diagnose, quick management, and maintain reproductive function as much as possible. Up to date; no consensus or guidelines for the treatment and management of CSEP due to limited no of cases and reports. Currently, there is no standard management option for CSEP and no first-line treatment.

Treatment options depends on gestational age and presentation, the main aim is removing the gestational sac, preventing hemorrhage and preservation of future fertility.

### **Expectant management:**

For cases with a non-viable CSEP, expectant management might be an option. Ouyang et al. reported 100% success rate among 5 patients with a non-viable CSEP with expectant management [32]. Preservation of CSEP with viable fetus is a challenge. Although several case reports on successful term pregnancy of CSEP have been reported, but expectant management is not without complications [33, 34]. Kim et al. reported live births of 2 viable babies at 37.3 weeks of heterotopic CSEP with expectant management; however, the patient had severe postpartum haemorrhage secondary to placenta accreta which was controlled by excision of the anterior lower uterine segment and bilateral uterine artery ligation [34]. A recent systematic review on expectant management included 11 reports, a total of 44 patients with CSEP with positive fetal heart included. Live births in 73% of patients were achieved, 25% of them before 34 weeks. Seventy percent of patients required hysterectomy to control bleeding. Twelve patients out of 44 pregnancy lost secondary to complications before 24 weeks [35].

In a recent meta-analysis on expectant management of CSEP of 17 studies including 52 patients with CSEP with positive fetal heart. Forty patients progressed to third trimester, 39.2% experienced severe bleeding, 74.8% had abnormally adherent placenta, 69.7% found to have placenta percreta. 9.9% of patients had uterine rupture during the first or second trimester and 15.2% of patients needed hysterectomy [36].

In view of high rate of morbidity associated with this condition, termination of pregnancy could be the only therapeutic option offered for women with CSEP. It is still not clear that if the



thickness of anterior uterine wall at the gestational sac implantation with viable fetus can determine the decision to allow for expectant management [36-38].

### **Methotrexate (MTX):**

It acts by Inhibiting dihydrofolate reductase as a folic acid antagonist, which interferes with DNA synthesis in embryonic cells resulting in inhibiting embryonic development. The most common medical treatment is administration of methotrexate (MTX). It can be administered as systemic or local in haemodynamic stable patients with CSEP.

The most popular treatment using MTX is local administration into the gestational sac because of the rapid response and minimal side-effect. Local MTX is believed to be superior to systemic MTX because of fast drop of  $\beta$ -hCG titer after local MTX injection. local MTX injection is rapidly absorbed at a high concentration into the gestational sac and the placental tissues leading to necrosis of the trophoblastic tissue [39]. However, conflicting results are reported in the literature. Peng et al. found that success with local MTX injection of 50 mg/m<sup>2</sup> can be achieved if  $\beta$ -hCG levels <20,000 mIU/mL and gestational sac less than 3 cm in diameter. It can be given either transabdominal or transvaginal into gestational sac as a single dose, if needed a second dose can be given a week later [40]. In a review by Cheung, a success rate of 73.9 % was achieved by local MTX injection alone, additional local or intramuscular MTX, 88.5% success rate was achieved [41]. On the other hand, Kim et al. treated 26 cases of CSEP with local injection of MTX and 15 cases with systemic intramuscular of MTX, the success rate of local MTX was 93.7% while systemic MTX was 73.3% (P<0.05) [42]. Wang et al. reported 76.2% success rate and 19% hysterectomy rates in CSEP who were treated with systemic MTX alone [43]. However, Lian et al. in a study included 21 patients with CSEP

treated with systemic MTX. Failure rate of systemic MTX was observed in 12 patients, they required uterine artery embolization (UAE) and local MTX as an additional treatment [44].

To answer the question, which is more superior? A randomized trial by Peng et al. including 104 patients with CSEP, both local and systemic MTX administration were compared. The cure rates were (69.2% vs. 67.3%) for local and systemic treatment, respectively. Patient received systemic MTX experienced prolonged time for  $\beta$ -hCG titer remission and resolution of CSEP mass [40]. Surprisingly, in a systematic review by Kanat-Pektas et al. they found that MTX systemic administration was successful in only 8.7% of cases of CSEP with hysterectomy rate of 4% [45]. Complication rate with systemic MTX according to some reports reached up to 62.1% [46].

The possible explanation is that the effect on placenta and embryo cardiac activity is delayed or no effect when MTX is given systemic. Due to its short half life and limited exposure of trophoblast to MTX when given systemic, the concentration in trophoblastic tissue is blocked by fibrous tissue surrounding the gestational sac [22, 44]. Generally, due to low efficacy, more side effects and fertility loss with systemic MTX, it should not be given as a first medical choice when fertility preservation is needed.

Although local MTX is the most commonly used medical treatment, other less commonly used agents such as potassium chloride, mifepristone, ethanol and hyperosmolar glucose have been reported in the literature [47-50]. Persistent bleeding after medical treatment requires further intervention even though  $\beta$ -hCG may be undetectable.

**Combined treatment:**

Several combined treatments modality have been reported in literature as a treatment or to rescue patients from bleeding or when failure of medical treatment anticipated. A recent review showed that 63% complications rate when D&C is used as a first line treatment for CSEP. Complications reported like massive bleeding, blood transfusion, hysterectomy and loss of fertility [43]. MTX and Dilatation and Curettage (D&C) is commonly used if gestational sac dose not disappear, or bleeding occurs during treatment. Peng et al. enrolled 104 patients and randomized to receive systemic MTX treatment vs. local MTX into gestational sac. 71 out of 104 patients (66.4%) responded well, overall cure rate (69.2% vs. 67.3%) with local MTX and systemic MTX respectively, 39 patients did not require further treatment and 32 patients required additional D&C. The remaining 33 patients did not respond to MTX therapy and underwent uterine artery embolization (UAE) followed by D&C [51].

Wang et al. in a study included 107 patients with CSEP, 46 patients received MTX before D&C and 47 patients did not receive MTX and were treated by D&C alone, they found comparable outcomes, but shorter hospital stay was noted for patients who did not receive MTX [43]. In analysis of 3 combinations modalities, Li et al. in a study included 124 CSEP patients, 37 patients underwent hysteroscopic curettage under sonography guidance, 28 patients were treated with methotrexate and hysteroscopy and 59 patients underwent UAE and hysteroscopy. UAE followed by hysteroscopy was found to be the safest and most efficient method. Patients treated by hysteroscopy alone have the shortest length of hospital stay and the lower cost, but high blood loss and slow recovery was noted. They suggested that Patients with a low level of  $\beta$ -hCG, hysteroscopy under sonographic guidance or MTX and hysteroscopy is an option [52]. Several combination therapy in the literature, each method has various levels of success and

depends on patient presentation, in order of frequency; MTX+D&C, Mifepristone/D&D/UAE followed by hysteroscopy, UAE before D&C, UAE+ local MTX [43, 44].

### **Uterine artery embolization (UAE):**

The use of UAE without removal the gestational sac results in gradual decrease of  $\beta$ -hCG levels and irregular vaginal bleeding, so it is considered as an adjuvant treatment in CSEP to minimize bleeding [44, 53-55]. UAE minimize haemorrhage by blocking uterine perfusion temporarily, It has been used before or after curettage and D&C [56]. Qiao et al. In a recent meta-analysis included 725 patients treated with MTX+D&C, UAE followed by D&C. Patients treated with UAE followed by D&C had less time for  $\beta$ -hCG normalization (16.7 days) and less time of hospital stay (15 days). In addition, patients who underwent UAE had less blood loss and no side effects of MTX when compared with those treated with MTX plus D&C [57]. It seems that UAE followed by D&C has more advantage and may be a priority option for treatment of patient with CSEP with bleeding. UAE can lead to loss of fertility due to impairment of blood flow in the uterine arteries. UAE should be considered as a treatment option in cases with heavy bleeding or when high vascularity detected by doppler [53].

### **Hysteroscopy:**

Using hysteroscopy with direct visualization of the gestational sac; trophoblastic tissue can be removed precisely without injuring the endometrium. Coagulation of the vascular bed at the implantation site can be done directly to prevent profuse bleeding [55, 58].

Depending on the expertise in hysteroscopy, a loop electrode can be used to separate the products of conception from the uterine wall. If bleeding occurs, it can be controlled by

electrocoagulation or using an intrauterine Foley balloon [15]. If the myometrium  $< 3\text{mm}$ , caution should be considered during hysteroscopic resection, it is better to perform hysteroscopy under laparoscopic guidance due to significant risk of perforation of the uterus and injury to the bladder during the procedure [59]. Qiu et al. managed 62 patients with CSEP, 39 patients managed by UAE with D&C guided by sonography and 23 patients managed with UAE with hysteroscopy. They found that complications, blood loss intraoperatively and hospital stay were significantly lower in hysteroscopy group compared with D&C guided by sonography. Moreover, hysteroscopy group had less complications [57]. Pan et al. successfully managed 44 cases with CSEP using hysteroscopy, in two cases hysteroscopy under laparoscopic guidance, three cases required UAE due to massive hemorrhage before and four cases were treated by mifepristone 200 mg for 3 days and MTX 25 mg for 2 days, then underwent successful hysteroscopy [59]. According to expert opinion hysteroscopy is considered as an optimal approach for type 1 CSEP [46].

**Wedge resection:**

Occasionally uterine rupture may occur with CSEP. When rupture is confirmed or suspected, wedge excision is mandatory. This can be done by conventional hysterotomy to remove the CSEP and scar repair [27, 53]. Nevertheless, this approach is associated with a lot of complications as well. Complications associated with this approach include large surgical wounds, long hospital stay, long recovery time and postoperative adhesions. Furthermore; increase risk of placenta previa and accrete [4, 60].

**Transvaginal resection:**

Transvaginal approach for exogenous type 2 CSEP is an option. The key point of this procedures is that first, the bladder is separated from the lower uterine segment to avoid injury to the bladder and ureters. the gestational product will be completely removed, and the uterine scar tissue is sutured in a continuous 0 absorbable sutures [61]. The post-op recovery using transvaginal approach is rapid. However, this procedure with a narrow operative field, require good experience with transvaginal surgery [61, 63]. The  $\beta$ -hCG normalization rate is like that of the abdominal approach [61].

### **Laparoscopy:**

Laparoscopy is suitable option for type II CSEP, in which villi are growing towards bladder and abdominal cavity in hemodynamically stable patients. Laparoscopy can be used with hysteroscopy for treatment of type I CSEP if myometrium is < 3 mm, the main advantage is removal of the CSEP mass at the time of the surgery and reduced time of patient follow-up. So far, several case reports have been published in the literature [64-66]. However, this approach requires good expertise in endoscopic surgery [15].

### **High-intensity focused ultrasound (HIFU):**

It acts by converting focused acoustic energy into thermal energy at target tissue, UIFU have been successfully used in ablation of uterine fibroids and adenomyosis [67, 68]. So far, several researches used HIFU in management of CSEP with or without supplement treatment with promising results [69, 70]. Xau et al. managed 76 patients with HIFU, then underwent suction curettage under hysteroscopic guidance, 46 patients with UAE followed by suction curettage under hysteroscopic guidance. The pain score was lower, and the adverse effects were

fewer in the HIFU group. However, longer time for the normalization of  $\beta$ -HCG level and longer time for vaginal bleeding [71]. Similar results obtained by Hang et al. [72].

**Conclusion:**

CSEP is a challenging life-threatening condition for the gynecologist. Once CSEP is diagnosed, immediate termination is required to prevent massive hemorrhage, uterine rupture and other severe complications. Significant controversy exists regarding management. For this reason, several factors should be considered including age of the patient, myometrial thickness, clinical symptoms, hemodynamic status, fertility preservation. Therapeutic option should be an individualized to treat the CSEP. Generally, any treatment option has advantages and disadvantages, more favorable outcome can be achieved by combination of several methods.

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