Definition and diagnosis of cesarean scar ectopic pregnancies

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Abstract:

Cesarean scar ectopic pregnancy is a rare type of ectopic pregnancy, where the pregnancy implants into a myometrial defect caused by a cesarean scar. Its incidence is predicted to increase given the global increase in cesarean deliveries. As most cesarean scar ectopic pregnancies present as failing pregnancies or patients chose termination of pregnancy, there is limited data on their natural history. However, early first trimester diagnosis is essential given the associated significant maternal morbidity. Transvaginal sonography is generally considered to be the optimal method for diagnosing cesarean scar ectopic pregnancy. There is no evidence that MRI adds to the diagnostic accuracy, and it is therefore not recommended for routine evaluation of cesarean scar ectopic pregnancy. There is no agreed reference standard for the diagnosis of cesarean scar ectopic pregnancy; therefore the validity of several proposed sonographic diagnostic criteria reported by different authors remains unknown. There are also various suggested classification systems for cesarean scar ectopic pregnancies, which divide them in differet types. However, the proposals are very heterogeneous and superiority of one classification system over another is yet to be established.

Key words:

cesarean scar ectopic, diagnosis, definition, classification.

A: Introduction

Cesarean scar ectopic pregnancy (CSEP) was first described in the literature by Larsen et al. in 1978 [1], but it was not until 1998 that it was recognised as a type of uterine ectopic pregnancy [2]. CSEPs are associated with severe maternal morbidity [3], and it is therefore important to increase awareness of this condition among clinicians and other care providers, such as sonographers working in early pregnancy units (EPUs) to enable timely diagnosis, good patient counselling and effective management.

Only a small number of cases of CSEPs were reported in the literature up to the early 2000s [4]. The first ultrasound diagnosis of a CSEP was reported in 1990 by Rempen and Albert [5]. At that time the cesarean birth (CB) rates were around 15-20% in the Western world but have increased further since [6]. A recent analysis of the latest available world data (2010-2018) from 154 countries covering 94.5% of world live births shows that 21.1% of pregnant women gave birth by CB [7]. It has been estimated that by 2030, 28.5% of people around the world will be delivered by CB with the greatest increase predicted to be in Eastern Asia. Thus, the incidence of CSEP will continue to rise, which highlights the need for clinicians being aware of these trends and developing skills necessary for early diagnosis and treatment of CSEP.

B: Definition

Consensus agreements on the definition and description of different types of ectopic pregnancies on ultrasound was lacking in the wider international gynaecological community until the European Society of Human Reproduction and Embryology (ESHRE) working group on Ectopic Pregnancy provided a comprehensive classification for ectopic pregnancies in 2020 [8]. Their recommendation is that cervical, cesarean scar, and intramural ectopic pregnancies

should be considered as distinct types of uterine ectopic pregnancies [8]. In patients who have had previous classical CBs, it is often difficult to determine whether the pregnancy is implanted into the cesarean scar defect (CSD), and these could be indistinguishable from an intramural pregnancy [8].

The ESHREE working group also defines CSEP as partial (Fig. 1) versus complete depending on whether the gestational sac is completely confined to the myometrium or whether there is a visible communication with the endometrial cavity [8]. Complete scar pregnancies are rare and result from the development of the gestational sac within CSD also called “niche” or “isthmocele”. The communication between a niche and the uterine cavity can be very narrow and sometimes impossible to visualise on ultrasound scan. As the gestational sac grows, the niche may expand towards the peritoneal cavity protruding into the broad ligament or towards the bladder (Fig. 2).

Pathophysiology

CSEP is a recognised clinical entity, which is defined by implantation of the pregnancy into a myometrial defect caused by dehiscence of a lower uterine segment (LUS) cesarean scar [9]. Therefore, CSEP can only occur when a niche is present and not in patients with a closed (non-defective) cesarean scar [9]. The pregnancy implants into the CSD and the absence of decidua at the scar site drives the trophoblast to grow into the myometrium. As there is a partial loss of myometrium and uterine vasculature (spiral and radial arteries) at the site of implantation, the pregnancy derives its blood supply from the deeper and larger arcuate and helicine arteries, exposing the trophoblast to high-pressure arterial vessels. This, in combination with

the loss of myometrium at the scar site, which impairs uterine contractibility, contributes to the excessive blood loss whenever the pregnancy is concluded.

Ectopic gestations are pregnancies that develop beyond the anatomical boundaries of the uterine cavity, which result in suboptimal conditions for growth and development of the pregnancy, causing significant maternal morbidity due to excessive haemorrhage. CSEPs share these basic pathophysiological characteristics with all other ectopic pregnancies, both uterine and extrauterine, and therefore should be classified as a true ectopic pregnancy.

Incidence

There is inevitably a delay between an increase in CB rates and related complications such as CSEP and placenta accreta syndrome (PAS) in subsequent pregnancies. In the UK where the CB rates have remained relatively stable, i.e. around 28% over the last decade, the incidence of CSEP was reported as 1.5 per 10,000 maternities [10]. Other studies have reported higher rates, ranging between one in 1800 to two in 2500 pregnancies, and as high as one in 531 pregnancies [11, 12]. This increase in incidence may partially be explained by a global increase in CBs, but also is likely due to the increased awareness of the condition and better diagnostic capabilities. It is of note that up to 2001 only 18 cases of CSEP had been published in the English medical literature but within the next two years this number increased to 43 [4, 13-18].

The true incidence of CSEP still remains unknown, not only due to their relative rarity, but also potentially due to misdiagnosis and the use of various defintions in the literature, which could

result in underreporting of cases. CSEPs may be misdiagnosed as normally sited pregnancies and may be managed successfully surgically with transcervical suction evacuation, without the correct diagnosis being made. A significant proportion of CSEPs are also likely to miscarry without any intervention and may therefore not present to healthcare providers [19]. Alternatively they may progress to viability with the pregnancy appearing to develop mainly within the uterine cavity. Furthermore, as early pregnancy scans to assess pregnancy implantation in women with cesarean scars are not currently routinely performed, underreporting is very likely.

Terminology

A wide variety of terms have been used in the literature to describe CSEP, starting with the first description as a 'pregnancy in a uterine scar sacculus' in 1978 [1]. Over the years terms used to describe CSEP have included cervico-isthmic pregnancy, intramural pregnancy and myometrial pregnancy [20-23]. The first reference to CSEP as an ectopic pregnancy in the literature was in 1997 [23], but more than twenty years later there remains a debate in the wider gynaecology community whether CSEP is truly an ectopic pregnancy or not [8, 24, 25]. One of the primary arguments against a CSEP being an ectopic gestation is it has the potential to continue as a viable pregnancy partially inside the uterine cavity [24]. However, there are various published case reports of many types of ectopic pregnancies that have progressed to a viable gestation [25], but what sets ectopic pregnancies apart from normally sited pregnancies is their potential for significant maternal morbidity and mortality because of their abnormal location, which CSEP has the potential for.

Risk factors

The optimal technique for uterine closure to prevent the development of a niche and subsequently a CSEP is unknown [3]. Several systematic reviews have reported that double layer-unlocked sutures results in a higher residual myometrial thickness (RMT) and therefore one could postulate that with a better uterine closure technique the risk of CSDs and consequent CSEP may be lower in the future [26-28]. In addition, one review showed that if decidua was sutured during uterine closure the prevalence of subsequent uterine niches was lower [26]. However, a recent large multi-centre randomized controlled trial comparing single-layer and double-layer unlocked closure found there was no significant difference in the prevalence of RMT and large niches between the two techniques [29].

There is conflicting evidence in the literature with regards to whether the number of prior CBs impacts the risk of developing a CSEP or not in subsequent pregnancies. A single centre experience of 18 cases of CSEP found that 72% of patients had undergone two or more CBs [13]. Similarly, a retrospective review of 20 cases of CSEP in another centre found 75% of patients had a history of multiple CBs, (> 2) [30]. However, both studies included very small numbers of cases. It has been hypothesised that the risk of developing a CSEP is increased by the repeated trauma to the LUS caused by multiple CBs. This prevents adequate scar healing, due to poor vascularity and fibrosis of the LUS myometrium. As a result, the surface area of the scar is increased, which in turn increases the chance of blastocyst implantation into the scar [13].

By contrast, a review of the literature, which identified 112 cases of CSEP, found that the majority of patients, 52% had a history of only one previous CB [31]. These findings have also

been confirmed in several other studies [32-35] and it has been suggested that rather than the number of CBs, the indication for CB may have a more significant impact on the risk of CSEP development, in particular elective CB for breech presentation could increase the risk of CSEP in subsequent pregnancies [31, 32, 36]. Breech CBs usually are performed as elective pre labour procedures with uterine incisions being made higher up in the anterior uterine wall compared to emergency CB. This high location of the scar closer to the centre of the uterine cavity may be responsible for the higher risk of scar implantation. Some have postulated that a cut in a thicker section of the anterior uterine wall may be a key factor facilitating scar implantation [31]. However, this is questionable as high scars tend to heal better. In addition, development of PAS is very rare after myomectomy, which usually involves the upper uterine segment and there have only been nine cases of pregnancies in myomectomy scars reported in the English medical literature so far [37, 38].

The largest published single centre retrospective case control study with 291 patients with CSEP identified several other possible risk factors for developing CSEP, including maternal age >35 years, gravidity of >5, history of >5 surgical terminations and an interval of less than two years between a CB and the subsequent pregnancy [39].

It has been suggested that a short interval of less than two years, between CB and a subsequent pregnancy increases the risk of developing a CSEP and morbidity [34, 40]. There is insufficient evidence currently to advise a minimal interval between a CSEP and future conception, but experts have advised waiting anywhere between 12- 24 months before trying to conceive after CSEP [41, 42]. The risk of recurrence of CSEP has been reported in several

studies and it ranged widely from as little as 3 - 6.3% [43-45] to as high as 20% in two recent systematic reviews [46, 47].

Overall, data on the risk factors have not been quantified in a high-quality study and there is a need to obtain more evidence-based data, as these are essential in the evaluation of the patient presenting with a CSEP. Similarly, it is important that a standardized definition for CSEP is employed not only in clinical practice, but also in the medical literature to ensure high quality studies with less heterogeneity, to enable a reliable comparison of study outcomes.

C: Diagnosis

A universally applicable reference standard for diagnosis of CSEP has not yet been agreed upon. Histological confirmation of abnormal trophoblast invasion, which is often used in cases of extrauterine ectopic pregnancies, would only be applicable in cases of CSEP treated by hysterectomy, which is only done in a minority of CSEPs. Surgical diagnosis is also not an appropriate reference standard, as one cannot directly visualise extension into the myometrium at surgery. Several surrogate reference standards are therefore employed, including heavy vaginal bleeding and uterine rupture, but they are not specific or easily quantifiable.

Accurate diagnosis, however, is important, as being able to determine the site of implantation and likely location of the definitive placenta helps with counselling of patients regarding their risk of developing complications later in pregnancy.

Several groups recommend that the optimal time for diagnosing CSEP is at six to seven weeks' gestation [9, 48]. Beyond this gestation, the pregnancy tends to expand into the uterine cavity and the diagnosis becomes more challenging. The type of CSEP may also vary with advancing gestation, as the gestational sac is likely to protrude increasingly more into the uterine cavity or into the cervical canal, which can make classification more difficult.

In a large retrospective observational cohort study including 232 women with CSEPs, 53% were diagnosed with a live CSEP at presentation [44], but around two-thirds of all CSEPs will eventually fail before 10 weeks' of gestation [49]. However, early diagnosis is important in reducing the risk of adverse maternal outcomes. A single centre cohort study of 62 patients with live CSEPs who underwent surgical treatment in the form of transcervical suction evacuation found that patients who were treated after 9 weeks' gestation had an increased risk of haemorrhage requiring blood transfusion compared to patients treated at less than 9 weeks' gestation [43]. Similarly, a review including 724 women with CSEP found that diagnosis followed by immediate treatment before 9 weeks' gestation led to significantly lower maternal complications, particularly uterine rupture, and massive haemorrhage, compared to diagnosis and treatment at 9 weeks' and later [50]. Given the increased risk of maternal morbidity with later diagnosis of CSEP, some authors have advocated early (5-7 weeks' gestation) ultrasound screening of all pregnant people with previous CBs [50]. However, early screening of all women with previous history of CB would require development of significant additional resources which would increase the cost of antenatal care. It is also uncertain whether women would comply with a screening programe which requires them to attend for an ultrasound scan as early as a week or two after missing a menstrual period. In addition, in

the absence of universally agreed diagnostic criteria and with poor understanding of natural history it is hard to see how an effective screeing program could be designed.

Clinical diagnosis

Patients diagnosed with CSEP often present in early pregnancy with vaginal bleeding and pelvic pain [10]. A review of 112 cases of CSEP found that the most common presenting symptom (38.6%) was painless vaginal bleeding [31]. Similarly, in a UK national cohort study of 92 cases of CSEP, painless vaginal bleeding was the most common indication for presentation (48%) [10]. However, a significant number of women, 16-37% are asymptomatic at presentation [10, 31, 43] and therefore clinicians should have a high index of suspicion for CSEP in any patient with a history of a previous CB. There is no role for serum human chorionic gonadotropin (hCG) in determining the location of CSEP or, in fact, of any type of ectopic pregnancy. However, serial hCG measurement may play a role in cases of CSEP which are managed conservatively.

Ultrasound diagnosis

Transvaginal two-dimensional (2-D) B-mode ultrasound examination is considered the best imaging method for the diagnosis of CSEP. Colour Doppler imaging (CDI) and three-dimensional (3-D) ultrasound may help by providing more information regarding the exact implantation site [10, 51]. A review of 112 cases of CSEP found that transvaginal sonography (TVS) has a high sensitivity of 84.6% (95% CI 0.763-0.905), with missed cases being diagnosed as cervical pregnancies and incomplete miscarriages [31]. Similarly, in a review of 751 cases of CSEP, approximately 13.6% were missed or misdiagnosed as normally sited or cervical pregnancies at the initial examination [52]. Diagnosis may not always be conclusive on the

initial scan, but if the patient is stable, they can be brought back after a short interval for a repeat scan or referred to an expert centre for a second opinion.

Ultrasound as the primary diagnostic imaging technique has also been advocated by the Society for Maternal-Fetal Medicine (SMFM), who published a set of ultrasound diagnostic criteria for CSEP in 2020, as outlined in Table 1 [3], but they did not give information on how to report the location of the gestational sac in relation to the cesarean scar.

Following the first ultrasound description of a CSEP [5], several authors have described various ultrasound signs, but diagnostic accuracy or superiority of one diagnostic protocol over another has not yet been established.

Direct diagnostic signs

The only ultrasound parameter that is a reliable diagnostic measure of CSEP is direct visualisation of implantation of the pregnancy into a CSD and extension beyond the endometrial-myometrial junction. This is facilitated by the visualization of the myometrial defect in a typical location anteriorly in the vicinity of the internal cervical os. The placenta has to be seen filling the defect. Herniation of the anterior uterine wall at the implantation site into the vesico-uterine pouch or into the broad ligament helps to increase diagnostic confidence.

Indirect diagnostic signs

Several other ultrasound morphological features have been suggested as useful signs to diagnose CSEP but most of these are indirect diagnostic measures, which either quantify the RMT or a degree of pregnancy protrusion into the uterine cavity.

In 2000 Vial et al proposed the first set of sonographic criteria for diagnosis of what today would be considered a complete or type 2 CSEP [53].

1. "Trophoblast"(placental tissue) mainly located between the bladder and the anterior uterine wall.
2. No fetal parts visible in the uterine cavity.
3. On sagittal view of the uterus running through the amniotic sac, a discontinuity in the anterior wall of the uterus should be demonstrated.

As the number of cases of CSEP has continued to increase, several authors have adapted these initial sonographic criteria. The Royal College of Obstetricians & Gynaecologists (RCOG) has proposed the following diagnostic sonographic [51].

1. Empty uterine cavity.
2. Gestational sac located anteriorly at the level of the internal cervical os embedded at the site of a previous LUS cesarean scar.
3. Thin or absent layer of myometrium between the gestational sac and the bladder.
4. Evidence of prominent utero-placental circulation on CDI, characterised by high-velocity and low impedance.
5. Empty endocervical canal.

Furthermore, in 2019 Timor-Tritsch et al described the following diagnostic criteria [48].

1. Empty uterine cavity with a closed, empty endocervical canal.
2. An early gestational sac and/or early placenta in close proximity of the cesarean scar.
3. Absent or thin myometrial layer between the gestational sac and the anterior uterine wall or the bladder wall.
4. Increased vascularity on CDI around the gestational sac.

However, all these criteria are only useful in very early pregnancy as they are not applicable to any pregnancy beyond 7 weeks' gestation. By that stage the pregnancy has reached a relatively large size and it cannot be contained within the myometrial defect. The enlarging pregnancy has to expand either into the uterine cavity or into the cervical canal or both. It is important to stress that pregnancies in close proximity to a cesarean scar, but not developing wihin it, or pregnancies overlying an intact, well healed LUS cesarean scar (referred to in the literature as pregnancies "on the scar") do not conform to the pathophysiological principles of an ectopic pregnancy, as they are still implanted within the anatomical confines of the uterine cavity and, as explained earlier, a CSEP has to be defined by implantation beyond the endometrial-myometrial junction.

More than forty years after CSEP was first described in the literature as a clinical entity, international experts reached a consensus on standardized sonographic diagnostic criteria for CSEP in the first trimester [9]. In addition to all the aforementioned criteria reported by other authors, this group recommended two new indirect sonographic measures which should be assessed, as they are associated with not only a higher risk of hemorrhage but are relevant when choosing the most appropriate form of treatment [9].

1. Measuring the RMT and the adjacent myometrial thickness in the sagittal plane.
2. CDI assessment to assess the vascular pattern of CSEP in relation to the cesarean scar niche, the cervix and uterine arteries to diagnose enhanced myometrial vascularity.

Although TVS examination is considered the primary diagnostic tool for CSEP, as it provides the highest resolution images, several groups propose it should be used in combination with transabdominal imaging to reduce the risk of false positive diagnoses [32]. Transabdominal scan with a full bladder provides a panoramic view of the uterus allowing accurate assessment of the measurement between the gestational sac and the bladder [32, 54] but may be impossible in patients with a high body mass index (BMI). Similarly, assessment in the midline sagittal view allows bulging or ballooning of the LUS to be identified and therefore can provide additional support to the diagnosis of CSEP [55, 56].

Does Doppler have a role in diagnosis?

CDI assessment has been reported as a useful tool to provide additional diagnostic information by showing increased peri-placental vascularity around the gestational sac, which helps to delineate the location of the placenta in relation to the cesarean scar and proximity to the bladder [13, 40]. It therefore helps to avoid false positives, by being able to differentiate between a CSEP and a low implanted pregnancy (Fig. 3a) or a cervical phase of miscarriage (Fig. 3b) [9]. As CSEP advances it can becomes more challenging to identify the internal cervical os. In these cases the visualisation of the uterine artery on color Doppler can be used as an anatomical landmark, as the artery reaches the uterus at the level of the internal cervical os. The location of the CSEP in relation to the uterine and arcuate arteries can be assessed on CDI examination in the transverse plane; this also allows the assessment of myometrial vascularity

and provides an indication as to the risk of significant haemorrhage with treatment, whether it be conservative or surgical [9]. The recent published consensus statement stipulates that quantitative CDI assessment and scores are not considered a mandatory part of assessment of CSEP, but can be used for research purposes [9]. However, we feel that CDI is essential for both diagnosis and assessing the risk of haemorrhage [43] and should be employed as a routine tool during sonographic assessment of CSEP.

Similarly, pulsed Doppler examination can be used to gather information on the flow pattern of utero-placental vasculature and its resistance (RI) and pulsatility indices (PI) [42]. Several papers have described the use of pulsed Doppler in assessing CSEP to increase the accuracy of the diagnosis [40, 42, 57, 58]. In centres where pulsed Doppler assessment is used one would expect high flow velocity waveforms (peak velocity >20cm/second) and low impedance flow velocity waveforms (PI <1) [13]. However, pulsed Doppler is not considered as part of the routine assessment of CSEPs, as there is limited published experience of its use, but may be of interest in research settings.

There is mounting evidence indicating that a CSEP can be a precursor to PAS [59]. The ultrasound markers with the strongest association with PAS are increased subplacental hypervascularity and intervillous placental lacunae [60], which are often used in the second half of pregnancy to screen for PAS. Various sonographic features, such as low RMT, size of the niche in early pregnancy, and the amount of placental tissue inside the scar have been proposed as useful indicators for the prediction of the development of PAS [61]. It is important to look for these features during the first trimester to provide women who are considering continuing with their pregnancies with personalized assessment of risks such as major

haemorrhage, preterm delivery, and cesarean hysterectomy. Placental lacunae appear as large and irregular spaces within the placenta filled with blood, which often displays turbulent flow pattern. They are strongly associated with CSEPs, with 44% of CSEPs in one study having placenta lacunae compared to none in matched controls, which included low lying normally sited pregnancies [60, 61]. The presence of placental lacunae has also been associated with increased risk of severe blood loss and need for blood transfusion in CSEPs undergoing surgical termination of pregnancy [43].

Role of other imaging modalities

Other imaging modalities have been used in an attempt to improve the accuracy of diagnosing CSEP, however there is limited published data to support their routine use.

Several case reports have described diagnosis of CSEP using 3-D TVS, and have suggested that the use of multiplanar views and surface rendering enables a more precise delineation between the gestational sac and its implantation area, allowing thin myometrium between the gestational sac and bladder to be more easily recognised [57, 62-64]. However, the 3-D image is only as good as the quality of the original 2-D image and therefore a diagnosis of CSEP should be made confidently using 2-D imaging alone. Furthermore, the negative 'sliding organs sign' defined as the inability to displace the gestational sac from its position at the level of the internal cervical os using gentle pressure applied by the transvaginal probe allows differentiation of CSEPs from actively miscarrying pregnancies on 2-D imaging [13].

Several groups have also described the use of contrast-enhanced ultrasound (CEUS) to further improve the diagnostic accuracy of CSEP, by using intravenous microbubble contrast to

enhance imaging of high-pressure microcirculations in CSEP [65-67]. The largest prospective study of 220 cases of CSEP found that the overall sensitivity was higher for CEUS compared to TVS assessment for not only detecting CSEPs but also distinguishing the type of CSEP (97.3% versus 88.2%), with a specificity of 96.6% versus 75.5% [65]. It is unknown if the microbubble contrast passes through the placenta and what impact this would have on the pregnancy. In view of these safety concerns it would be difficult to justify its use in potentially normally developing pregnancies. Furthermore, not only is CEUS more expensive and time consuming, but standard sonographic color Doppler assessment is usually sufficient, as CSEPs vascular supply tends to be very prominent. The reference standard used in this study to assess diagnostic accuracy were surgical and histopathological outcomes, which were of limited value given that the authors suggested the pregnancies were surgically terminated, rather than the patients undergoing hysterectomy.

MRI has also been considered as an adjunct to ultrasound assessment [30, 36, 40, 68-73] to provide more information about the exact implantation site. Both T1 -and T2- weighted images have been used to assess the depth of invasion and PAS [30, 74, 75]. One study with 35 cases of CSEP found that MRI was as accurate as TVS at diagnosing different types of CSEP, but TVS was found to be more sensitive at assessing gestational sac contents [73]. However, assessing scar implantation should be more sensitive with TVS as it provides a more dynamic view than MRI.

Overall MRI is more time-consuming, not always readily available and operator-dependent, with few radiologists with expertise in diagnosing the condition. MRI may also delay diagnosis with unknown benefit over ultrasound and therefore does not add value to the diagnosis of

CSEP, however it may have a role where ultrasound expertise is lacking or the findings are inconclusive [3, 9, 51].

D: Classification

There is no universally accepted or adopted method for classifying CSEPs, which is reflected in the heterogeneity of classification systems used in published studies [76]. The aim of these classification systems is to assess severity of the condition and therefore predict better maternal risks and provide more information regarding the prognosis and management options.

Vial et al., proposed one of the earliest classification systems in 2000, describing CSEPs as two types; firstly, implantation of the pregnancy on the cesarean scar with progression of the pregnancy into the uterine cavity and cervico-isthmic space; secondly deep implantation of the pregnancy into a CSD with progression towards the abdominal cavity and bladder resulting in increased risk of uterine rupture and bleeding [53]. This classification could be criticised, as a pregnancy that is normally sited within the uterine cavity but in close contact with an intact cesarean scar does not fulfil the criteria for an ectopic pregnancy.

The classification system has evolved since then, with type 1 or "on the scar" and type 2 or "in the niche" descriptions in the literature [48, 77]. In cases of "on the scar" pregnancies the

gestational sac is implanted completely or partially on top of a healed scar and the RMT between the gestational sac/placenta and the anterior uterine serosa or bladder is 2mm ≥ [77]. By contrast, in the other form of CSEP the gestational sac is implanted in a niche and the RMT between the pregnancy and bladder is usually <2mm [77]. However, the definition of an "on the scar" pregnancy does not fulfill the basic pathophysiological criteria of an ectopic pregnancy, and in essence describes a pregnancy that is low in the uterine cavity, but normally sited. Studies have shown that the pregnancy outcomes for "on the scar" pregnancies are similar to normally sited pregnancies, and significantly better than "in the niche" pregnancies, strengthening the argument that they should not be considered CSEPs [77] .

A type 1 CSEP is also labeled as an 'endogenic type', as more than 50% of the pregnancy protrudes into the uterine cavity, where as a type 2 CSEP is also known as an 'exogenic type', as less than 50% of the gestational sac protrudes into the uterine cavity [78, 79]. These definitions have significant weaknesses, as the volume of pregnancy protruding into the uterine cavity will change as the pregnancy progresses and has no demonstrable correlation with patient outcomes.

Another group has proposed a new classification for CSEPs according to the size of the CSD or protrusion of the niche containing the gestational sac towards the pelvis [76]. The study included 198 patients with CSEP were divided into three types according to the size of their CSD, which were measured by MRI, as type I (size of CSD ≤40 mm), type II (size of CSD 41mm -70 mm) and type III (size of CSD >70 mm), with increasing types resulting in use of more invasive treatment approaches [76]. Alternative classification systems have been proposed based on the RMT between the gestational sac and bladder, with a type 1 CSEP having a thin

RMT of <3mm, a type 2 CSEP having a thicker RMT of >2mm and a type 3 CSEP defined as a gestational sac deviation, which is reported as a gestational sac located partly on the cesarean scar [80]. This classification system further subdivides type 1 CSEP into type 1a, type 1b and type 1c, which have been defined as a CSEP within a LUS cesarean scar; a CSEP within a cesarean scar on the higher uterine segment; and 'a giant protruding mass' either on the lower or higher uterine segment, respectively [80]. These proposed classification systems rely on RMT and degree of gestational sac protrusion, which are both indirect mesasures of questionable value, as they both change significantly with increasing gestational age.

Another novel classification system for CSEPs was proposed in 2018 by Lin et al. who described four grades of CSEP [81]. A grade 1 CSEP was defined by less than 50% of the gestational sac implanting into the myometrium; in grade 2 more than 50% of the gestational sac was implanted in the myometrium; in grade 3 the gestational sac protruded into the pelvic cavity; and in grade 4 the gestational became an "amorphous tumour" with rich vascularity [81]. Again, this proposed classification system is based on assessing the volume of pregnancy protruding into the uterine cavity, which changes rapidly with advancing gestation.

Only a couple of published classification systems provide information on how to report the location of the gestational sac in relation to the cesarean scar, the uterine cavity and the myometrium. Cali et al., proposed a classification system that assesses the relationship between the gestational sac and the "endometrial line", which may help determine whether a CSEP will progress towards PAS [82]. They proposed a new sonographic sign, the "crossover sign", which in the sagittal view of the uterus is an imaginary straight line connecting the internal cervical os and the uterine fundus through the endometrium [82]. The superior–

inferior diameter of the gestational sac, perpendicular to the “endometrial line” was traced and CSEPs were categorized according to the relationship between the “endometrial line” and the superior-inferior diameter of the gestational sac into two groups [82]. In the first group at least two-thirds of the superior-inferior diameter of the gestational sac was above the “endometrial line”, towards the anterior uterine wall and in the second group less than two-thirds of the superior-inferior diameter of the gestational sac was above the “endometrial line” [82]. In the early days of ultrasound, ectopic pregnancy was diagnosed by the absence of conclusive signs of a normally sited pregnancy in a patient with a positive pregnancy test. However, as ultrasound practice has developed direct visualisation of the ectopic pregnancy has become the only acceptable criterion for diagnosis and may even be considered a reference standard. We are still in the early phase of developing meaningful criteria for CSEP and all described indirect diagnostic signs are of very limited value, as the changes in the size of the gestational sac as the pregnancy progresses will alter significantly the relationship between the gestational sac and the uterine cavity.

In an attempt to standardize sonographic evaluation of CSEPs a new classification system has been proposed by Delphi consensus in 2022 [9]. It classifies CSEP into three types based on the position of the gestational sac in relation to two imaginary lines, the “uterine cavity line” and the “serosal line” [9]. The former is a line drawn between the transition between the endometrium and the myometrium and the latter is a line drawn at the outer border of the myometrium [9]. According to these lines CSEPs can be classified as:

1. CSEP in which the largest part of the gestational sac crosses the “uterine cavity line” and therefore protrudes into the uterine cavity.
2. CSEP in which the largest part of the gestational sac is embedded in the myometrium and does not cross the “uterine cavity line” or “serosal line”.

3. CSEP in which the gestational sac crosses the “serosal line” and the pregnancy is covered by a thin layer of myometrium/visceral peritoneum and is protruding into the broad ligament or towards to the vesicouterine space.

However, this newer classification system also contains indirect diagnostic signs that suffer from the same temporospatial issues which alter as the pregnancy is progressing.

There are numerous classification systems for CSEP, some may be more difficult than others for clinicians who do not work in expert centres to apply in their clinical practice. None of these reporting systems have been properly validated and are mainly derived from descriptive case studies/series or expert opinion. In the absece of this essential information best practice would be to refer non-emergency cases of suspected CSEP to regional expert centres to confirm the diagnosis and advise on management [51].

Summary

CSEP is a condition with causes significant maternal morbidity and has a potential to cause fatalities, if not diagnosed accurately in early pregnancy and promptly treated. The incidence of CSEP is likely to increase further over time given the global increase in CBs in both low/middle and high-income countries. It is therefore essential that all clinicians working in EPUs always consider the possibility of CSEP in any patients with a history of previous CB. A standardized sonographic approach using TVS and CDI should be adopted to increase diagnostic accuracy of CSEP and improve maternal outcomes. There is an urgent need to develop a reference standard for diagnosis, which is not only universally applicable, but also

reproducible and not influenced by gestational age, to avoid misdiagnoses and inadvertent terminations of normally sited pregnancies.

Practice points:

- CSEP is defined by implantation of the pregnancy into a myometrial defect caused by dehiscence of a lower uterine segment cesarean scar. This is the only definition that should be used.
- The incidence of CSEPs will continue to increase as CB rates increase globally.
- Transvaginal sonography and colour Doppler assessment are the primary imaging technique used to diagnose CSEP and allow differentiation from cervical pregnancies and cervical phase of miscarriage.
- All women with a history of CB that undergo early pregnancy scan for any reason, should have a thorough assessment of the cesarean scar to assess for pregnancy implantation at this site.
- Regional EPUs with expertise in diagnosing and managing CSEPs should be developed. They should have sufficient throughput to maintain their sklls and provide training.
- Early diagnosis helps to reduce the risk of massive bleeding and other complications associated with advanced CSEPs.

Research Agenda:

- There is a need for prospective studies on the diagnosis of CSEP using standardized core sonographic diagnostic criteria and classification systems to ensure high quality studies with less heterogeneity.

- Models and risk scoring systems need to be developed and validated to help predict which CSEPs are likely to progress to viability and which are likely to result in increased maternal morbidity or PAS, therefore management can be targeted by individualised risk.
- The psychological impact of diagnosis of early pregnancy loss, particularly miscarriage, but also tubal ectopic pregnancies has been established in the literature, but there have been no studies published looking at the psychological burden of a diagnosis of CSEP, which is unique among ectopic pregnancies as management may require termination of a wanted, potentially viable pregnancy.

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Table 1. Diagnostic ultrasound criteria for CSEP proposed by the Society for Maternal-Fetal Medicine [3].

Diagnostic criteria
An empty uterine cavity and endocervix
Placenta, gestational sac, or both embedded in the hysterotomy scar
<8 weeks' gestation: triangular gestational sac that fills the scar niche
>8 weeks' gestation: rounded or oval gestational sac that fills the scar niche
A thin (1-3mm) or absent myometrial layer between the gestational sac and bladder
A prominent or rich vascular pattern at or in the area of a cesarean scar
An embryonic or fetal pole, yolk sac, or both with or without cardiac activity