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CAESAREAN SCAR PREGNANY: DIAGNOSIS, NATURAL HISTORY AND TREATMENT

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ABSTRACT

Purpose of review: This review aims at summarizing the latest evidence on diagnosis, natural history and management of caesarean scar pregnancy (CSP).

Recent findings: CSP can result in maternal morbidity from major haemorrhage, uterine rupture, placenta accreta spectrum disorders and hysterectomy. Classification of the CSP types, presence of fetal heart activity, gestational age and residual myometrial thickness seem to influence rates of ongoing pregnancy, subsequent development of placenta accreta with expectant management, as well as success and complication rates associated with various methods of pregnancy termination. Expectant management may be appropriate in certain good prognosis cases such as absent fetal heart activity or when the myometrial layer at the implantation site is relatively thick. Surgical treatments are typically associated with higher success rates, but also seem to result in severe haemorrhage more frequently than medical treatments, which have higher failure rates. Although other treatment modalities are available, in general, the size and quality of evidence to guide care provision in CSP is very poor.

Summary: CSP can be associated with severe maternal morbidity, but can also lead to a livebirth. There is currently a lack of good-quality evidence to predict the outcome of CSP and provide informed and evidence-based care.

KEYS WORDS: Caesarean scar pregnancy, Placenta accreta, Natural history, Management

BULLET POINTS:

- A recent Delphi procedure defined a standardised approach to diagnose and describe a CSP using transvaginal ultrasound, as well as a new classification into 3 types.
- The natural history and optimal management of CSP are not well established, which limits the ability to provide informed and evidence-based care.
- CSP can result in maternal morbidity from major haemorrhage, uterine rupture, placenta accreta spectrum disorders and Caesarean hysterectomy.
- Classification of the CSP types, fetal heart activity, gestational age and residual myometrial thickness influence rates of ongoing pregnancy, subsequent development of placenta accreta as well as success and complication rates associated with various methods of pregnancy termination.
- The potential seriousness of maternal complications could justify systematic early pregnancy ultrasound evaluation of the implantation site in any woman who has previously undergone Caesarean section.

INTRODUCTION

Caesarean scar pregnancy (CSP) is a rare complication of early pregnancy resulting from implantation of the conceptus in the uterine scar resulting from a previous Caesarean section (CS). CSP is associated with a significant risk of maternal morbidity and mortality and represents a clinical challenge with a lack of consensus or guidance to aid with subsequent management. In this review, we will discuss the latest evidence on diagnosis, natural history and management of CSP, as well as the gaps which limit our ability to provide informed and evidence-based care.

CLINICAL DEFINITION

A CSP is defined by the implantation of the gestational sac in the lower uterine pole at the site of a previous CS scar. A recent Delphi procedure defined CSP as a pregnancy implanted in or close to a uterine niche - an indentation of at least 2 mm at the site of the CS scar in a non-pregnant uterus (1, 2). It is considered that a CSP cannot develop in a properly healed uterine scar (2). The uterine cavity in early pregnancy also appears empty in a CSP, a finding which some clinicians have taken mean that a CSP is an ectopic pregnancy. However, as opposed to ectopic pregnancy, a CSP will expand and fill the uterine cavity with advancing gestation and can result in a livebirth if the pregnancy is left to continue (3, 4).

PATHOGENESIS

A CSP develops when the blastocyst implants on a previous CS scar, where the decidua is thinner or absent compared to the normal uterine wall. It has been demonstrated that CSP and Placenta Accreta Spectrum (PAS) disorders share a common histology with the observation of placental villi in the myometrium without the interposition of a decidual layer, suggesting that CSP is a precursor of PAS (5). The traditional hypothesis for PAS development is that the absence of decidua at the level of the CS scar allows a deeper invasion of the trophoblast into the myometrium, but another less popular hypothesis is that PAS development may be secondary to CS scar dehiscence, that would let the trophoblast reach deeper into the myometrium (6, 7).

EPIDEMIOLOGY

The incidence of CSP is increasing due to higher rate of CS deliveries, improvement in imaging diagnostic tools and higher awareness of the condition among physicians (4). However, the precise incidence of CSP remains unknown and experts agree that CSP is probably an underdiagnosed condition (3, 4). Estimates of CSP incidence from single centres range from 1 in 2,600 births to 1 in 1,800 pregnancies from early pregnancy assessment units (EPU) and 1 in 531 at CS birth. Of note, a recent national UK cohort study reported a lower incidence of 1.5 in 10,000 maternities attending an EPU (8-11).

NATURAL HISTORY

The natural history of CSP is unclear. The rate of spontaneous miscarriage is higher in CSPs than in intrauterine pregnancies, with a study reporting on 54 cases of CSP with only 34% being viable at the time of diagnosis between 6 and 11-weeks' gestation (12). In a larger retrospective cohort of 232 CSPs from 2 tertiary referral hospitals, 53% were viable at diagnosis (13). Only very small observational studies on viable CSPs that were left to continue beyond the first trimester are published and suggest an increased risk of severe haemorrhage, uterine rupture, preterm birth and Caesarean hysterectomy (14, 15). In 2018, a systematic review on the expectant management of CSPs reported on 52 cases of viable CSPs, where 40 pregnancies (77%) led to a livebirth (16). The other 12 pregnancies (23%) ended before the third trimester, including 13% of uncomplicated miscarriage. Among the 40 women who reached the third trimester, 40% suffered from severe haemorrhage, 6% experienced uterine rupture and 75% were diagnosed with PAS at birth (16).

RISK FACTORS

A previous history of one or more CS is the only known risk factor for developing a CSP (3). In a review of 75 CSP cases, 50% of women only had one previous CS delivery, suggesting that the number of previous CS does not have a major impact on the risk of developing a CSP (17). The latter assertion is supported by other studies that failed to show an association between number of CS and CSP prevalence (18). However, the indication of the CS could have an impact on the risk of developing a CSP, with several authors reporting an increased risk after a CS for breech presentation (17, 18). This increased risk could concern all elective CS deliveries, where the level of the incision and/or the thickness of the lower inferior segment differ from emergency or in labour CS (4, 17, 19). The proposed biological mechanism is that elective Caesarean deliveries are undertaken in a poorly developed lower uterine segment that may lead to faulty healing and, consequently, uterine niche formation predisposing to CSP (17). A case-control study of 291 CSP patients compared to 317 controls with at least one previous CS suggested that a short interval <2 years after the last CS was an independent risk factor for developing a CSP (20). The potential impact of the hysterotomy closure technique on the subsequent risk of CSP is unknown (4). However recent reviews have shown that double-layer unlocked sutures were associated with a higher residual myometrium thickness (RMT) than single-layer locked sutures (21-23) and that the prevalence of uterine niches was higher when the decidua was excluded from the suture (21).

CLINICAL PRESENTATION

A CSP is typically diagnosed in the first trimester and women can either be asymptomatic or present with vaginal bleeding, abdominal pain or a combination of both. In a recent report of 62 viable CSPs from a single centre, 26% of women were asymptomatic, 23% presented with vaginal bleeding, 12% with abdominal pain and 39% with a combination of both (24). In a retrospective cohort of 232 CSPs, 24.5% of women were asymptomatic, 48.5% presented with vaginal bleeding, 9% with abdominal pain and 18% with a combination of both (13). Given this data, it is possible that a quarter of women who remain asymptomatic with CSP may go undiagnosed in the first trimester.

DIAGNOSIS

Transvaginal ultrasound is the gold standard for the diagnosis of CSP with a combination of grayscale and colour Doppler imaging. Diagnosis between 6- and 7-weeks' gestation is optimal because expansion of the CSP into the uterine cavity with advancing gestation might preclude ease of diagnosis (2, 3). The sonographic criteria for diagnosing a CSP (Figure 1) are (1) a gestational sac (GS) implanted in the lower uterine segment and in the location of a previous CS scar (2) an empty uterine cavity and cervical canal (3) a thin or absent myometrial layer between the GS and the anterior uterine wall or the bladder (4) a rich blood flow around the GS using the colour Doppler modality (3, 4, 9). Based on a recently published Delphi consensus, the CSP evaluation should include the measurements of both the residual myometrial thickness (RMT) and the adjacent myometrial thickness (AMT) in the sagittal plane (2). They recommend the use of colour Doppler to assess the vascular pattern of the CSP in relation to the niche, the cervix and the uterine arteries and to diagnose an enhanced myometrial vascularity, which is thought to be associated with a high risk of bleeding. There is a lack of data about the additional value of three-dimensional ultrasound and Magnetic Resonance Imaging (MRI) to diagnose a CSP and these 2 modalities are not recommended by the Delphi consensus, particularly because their use may delay time to diagnosis (2-4). The differential diagnosis of CSP includes cervical pregnancy and an inevitable (ongoing) miscarriage. In a cervical pregnancy, the GS lies below the internal cervical OS. In an inevitable miscarriage there is no blood flow around the GS and it is possible to elicit the sliding sign - the GS moves on applying pressure to the uterus with the vaginal probe (9). There is a recommendation to refer complex cases for a second opinion in order to ensure a timely diagnosis (4).

CLASSIFICATION

There are 2 types of CSP: Type 1 or 'on the scar' - when the GS is implanted on a healed scar and Type 2 or 'in the niche' - when the GS is implanted on a poorly healed scar (25). The niche is defined outside pregnancy as a defect at the level of a previous CS scar represented by an

indentation of the myometrium with a minimal depth of 2mm - ideally on gel or saline contrast sonography (1). In the Type 1 CSP, more than 50% of the GS protrudes into the uterine cavity, whereas in the Type 2 CSP, less than 50% of the GS protrudes into the uterine cavity (Figure 2). A new Delphi consensus classifies CSPs into 3 categories based on the position of the GS in relation to 2 imaginary lines, the uterine cavity line between the endometrium and myometrium and the serosal line at the outer border of the myometrium (Figure 3) (2).

MANAGEMENT

Expectant management

Expectant management has been described for both non-viable and viable CSP. The Society for Maternal-Fetal Medicine (SMFM) considers expectant management to be a reasonable option for early non-viable CSPs providing that serial assessments of maternal symptoms, ultrasound signs and beta-human chorionic gonadotropin (βhCG) levels are undertaken to confirm resolution of the CSP (4). However, the SMFM warns that the spontaneous resolution of the CSP can take several months and that there is a risk of developing a uterine arteriovenous malformation (AVM), which may cause heavy vaginal bleeding. In a review of 69 pregnancies that were managed expectantly, 70% of non-viable CSPs had an uncomplicated miscarriage, while the remaining 30% required subsequent medical or surgical treatment mainly for severe bleeding (22%), but reassuringly, none of the women needed a hysterectomy (16). The Society for Maternal-Fetal Medicine (SMFM) recommends against expectant management of viable CSPs (4). In a review of 69 viable CSP cases managed expectantly, the livebirth rate was 77% (16). However, in the 52 cases that reached the third trimester, 40% of women presented with severe bleeding, 10% experienced uterine rupture and the majority (75%) were diagnosed with PAS at delivery. Expectant management of CSP can lead to a livebirth in the majority of cases, but at some considerable maternal morbidity. Therefore, counselling for viable CSP poses an ethical dilemma, as there is only limited scientific evidence about outcome (26).

Termination of pregnancy

The optimal management of CSP remains unknown. Due to the risk of significant maternal morbidity, most experts recommend early termination of pregnancy (TOP) for viable CSP, to be conducted in a referral centre (4, 27). There is no consensus about the preferred option for TOP with surgical (dilatation and curettage, hysteroscopy, laparoscopy, laparotomy, and transvaginal resection), medical (systemic or intra-gestational methotrexate injection and intra-gestational potassium chloride injection) and minimally invasive (double balloon catheter, uterine artery embolization) treatment modalities described alone or in combination in the literature. The data about these treatment modalities predominantly comes from case series

of moderate to weak quality, with a limited number of randomized controlled trials (RCT) comparing different therapeutic approaches (4, 28, 29). There are several factors to be considered about the preferred therapeutic approach including pregnancy viability, gestational age, physician's experience and institutional resources (4). The optimal treatment should have a high efficacy, a low rate of major complications (severe haemorrhage, blood transfusion, hysterectomy) and, whenever possible, preserve future fertility.

The largest review comparing treatment modalities to date includes 3,127 cases (29). The overall success rate of medical approaches was 62% with a 10% rate of complications (7% for haemorrhage ≥500ml and 3% for hysterectomy), whereas the overall success rate of surgical approaches was 83% with a 20% rate of complications (18% of haemorrhage ≥500ml and 2% of hysterectomy) (Table 1). The main reason for secondary treatment was insufficient βhCG decrease for medical approaches versus haemorrhage for surgical approaches. Medical therapies were only used for hemodynamically stable women and the authors concluded that they were associated with a higher need for secondary treatment and a longer time to obtain the resolution of the CSP (45 versus 24 days). The combination of UAE with D&C was associated with a higher success rate and a lower risk of haemorrhage, but the authors remain cautious about the impact of UAE on future fertility.

In 2018, a national UK cohort study reported on the management of 92 CSP cases (10). The success rate of surgical management by ultrasound-guided D&C was 2-times higher (96%) than that of medical management by systemic Methotrexate or expectant management (46 and 43% respectively) for a complication rate of 36%, that was about 2-times lower than that of medical and expectant management (60 and 71% respectively). Notably, additional haemostatic measures such as oxytocics, cervical suture and Foley catheter were used in 80% of cases managed by D&C. The time to obtain the resolution of the CSP was also shorter after surgical management (median of 11 days) compared to 21 and 82 days for medical and expectant management, respectively. For viable CSPs terminated by D&C, the gestational age (GA) at treatment is a predictive factor for the risk of severe bleeding and/or the need for transfusion, with one third of women requiring blood transfusion after 9 weeks versus none before 9 weeks' gestation in a cohort of 62 women (24). Monteagudo *et al.* published 48 cases treated by double balloon tamponade before 10 weeks' gestation (30, 31). One out the 48 patients required a hysterectomy for severe bleeding, which corresponds to an overall 98% success rate for this new minimally invasive technique.

The SMFM strongly recommends against the use of systemic Methotrexate (MTX) alone for pregnancy termination, although they recognize that the evidence is of low- to moderate-

quality. They propose immediate pregnancy termination by either surgical management using transvaginal/laparoscopic resection or ultrasound-guided vacuum aspiration or by medical management with local MTX, but these were classed as weak recommendations based on low-quality evidence (4).

PROGNOSTIC FACTORS

Fetal heart activity

The presence of fetal heart (FH) activity at diagnosis seems to be associated with a poorer prognosis. In a review of 69 CSP cases that were expectantly managed, a spontaneous uncomplicated miscarriage occurred in 13% of cases with FH versus 69% of cases without FH activity. About 15% of women with a viable CSP required a hysterectomy for bleeding or uterine rupture in the first or second trimesters, whereas no hysterectomy was necessary for the non-viable CSPs (16).

Gestational age (GA)

In a recent review of 724 cases, the risks of adverse outcome including severe haemorrhage, need for blood transfusion, uterine rupture and emergency hysterectomy were higher for CSPs diagnosed after 9 weeks' gestation (30%) as compared to those diagnosed at or before 9 weeks (6%) (32). Given these findings, early diagnosis and immediate treatment of CSP are justified and it has been suggested that early pregnancy localization should be offered to all women with a previous CS, and physicians should be directed to exclude CSP in these women (2, 4, 32).

Beta-human chorionic gonadotrophin (βhCG) levels

The impact of βhCG levels appears to be similar to gestational age. In one study of 104 CSP cases randomised to local versus systemic Methotrexate demonstrating similar treatment efficacy (70%), the mean pre-treatment serum βhCG level was significantly lower in the cured group versus failed group (33).

Type of CSP and residual myometrial thickness (RMT)

In a cohort of 17 patients managed expectantly, the outcome was better for Type 1 CSPs (n=6) with no antenatal complication, one hysterectomy (17%) and 5 CS at a median GA of 38 weeks. In the group of patients with a Type 2 CSP (n=11), all patients were treated by hysterectomy, including one hysterectomy for severe bleeding at 20 weeks, and the remaining 10 cases managed by Caesarean hysterectomy at 32-34 weeks. CSP cases with a RMT ≥4mm in the first trimester were associated with a good prognosis, as opposed to those with RMT ≤2mm, that were all associated with PAS and delivery by Caesarean hysterectomy (25). The

authors suggested that Type 1 CSPs with a RMT ≥4mm may be good candidates for expectant management.

RISK OF RECURRENCE

Two recent literature reviews suggest that the risk of recurrence could be as high as 20% (34, 35). The SMFM recommends to prescribe effective contraception to women with a history of CSP (4). There is a paucity of data about risk factors for recurrent CSP and the potential impact of mode of treatment of the previous CSP on recurrence risk (34). There is insufficient data on which to base advice on the optimal pregnancy interval to minimise risk of recurrence or whether surgical repair of the CS scar confers any benefit (4).

INTERNATIONAL CSP REGISTRY

The International CSP Registry (www.CSP-registry.com) is an international online database that collects anonymised data on diagnosis, disease behaviour and management of CSPs to fill the evidence gaps for this serious disorder. Data from the CSP registry will be used to improve outcomes in CSP cases by informing clinical management and enabling future multicentre collaborative work.

CONCLUSION

Caesarean scar pregnancy is a rare complication of early pregnancy, which can result in maternal morbidity from major haemorrhage, uterine rupture, placenta accreta spectrum disorders and Caesarean hysterectomy. The seriousness of maternal complications could justify systematic early pregnancy ultrasound evaluation of the implantation site in any woman who has previously undergone Caesarean section. Classification of the CSP types, fetal heart activity, gestational age and residual myometrial thickness influence rates of ongoing pregnancy, subsequent development of placenta accreta as well as success and complication rates associated with various methods of pregnancy termination. Although not recommended, expectant management may be appropriate in certain good prognosis cases, such as when the CSP is non-viable or with Type 1 CSP where the RMT is ≥4mm. Surgical treatments are typically associated with higher success rates, but also result in severe haemorrhage more frequently than medical treatments, which have higher failure rates. Although other treatment modalities are available, in general, the size and quality of evidence to guide care provision in CSP is very poor.

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CONFLICTS OF INTEREST

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The authors use the Delphi method to develop a standardized sonographic evaluation and reporting system for CSP in the first trimester.

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A systematic review of 36 studies of CSP showing that management <9weeks' gestation is associated with a significantly lower risk of maternal complications, supporting a policy of universal screening for CSP in women with prior Caesarean birth.

TABLE AND FIGURE LEGENDS

Table. Review of CSP management options showing type of management, number of studies, cases included, efficacy and rates of haemorrhage and hysterectomy. Adapted from Maheux-Lacroix *et al*. (29).

Figure 1. Sonographic criteria for the diagnosis of CSP showing a gestational sac implanted in the lower uterine segment in the location of a previous CS scar (A) and an empty uterine cavity and cervical canal as well as a thin or absent myometrial layer between the gestational sac and the anterior uterine wall or the bladder (B). Adapted from Timor-Tritsch *et al*. (3).

Figure 2. Type 1 CSP implanted “on the scar”. Image of a well-healed, non-deficient Caesarean scar (a). Grey scale ultrasound of the placenta implanted “on the scar” (b). Type 2 CSP implanted “in the niche”. Image of a dehiscent Caesarean scar or “niche” (c). Grey scale ultrasound of the placenta implanted “in the niche” (d). Adapted from Kaelin *et al.* (25).

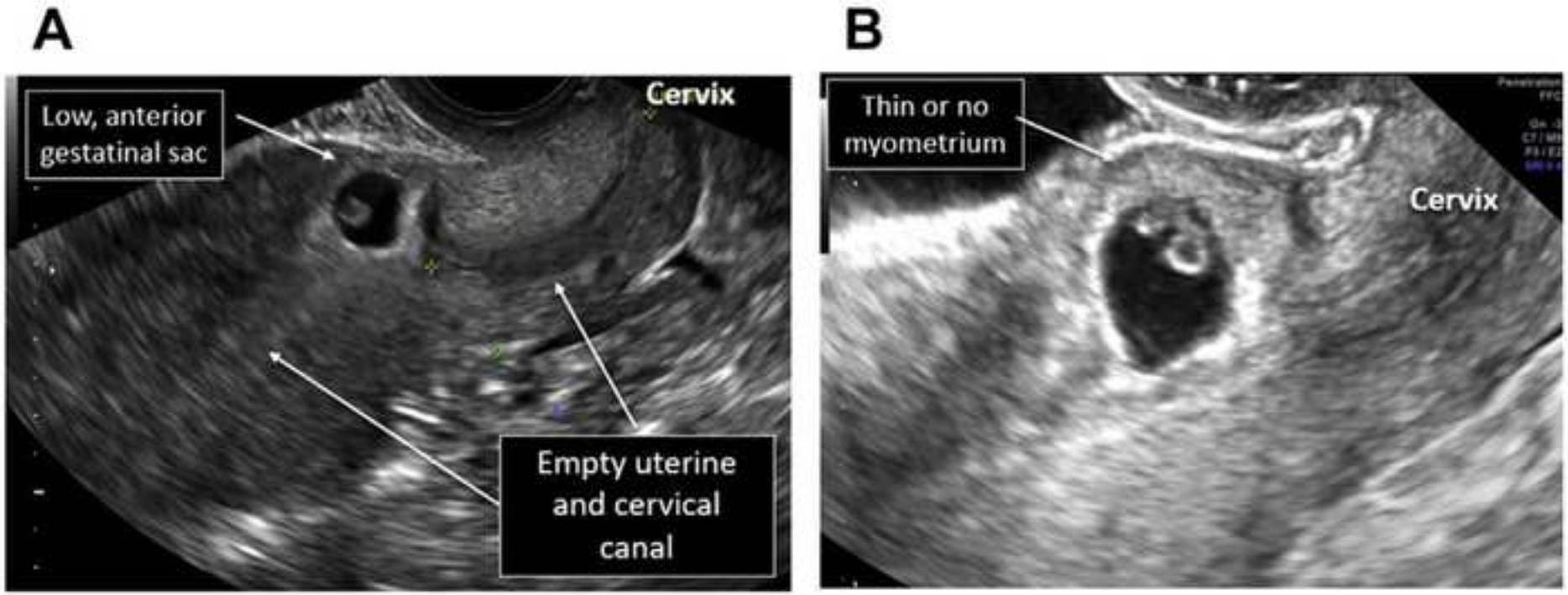
Figure 3. Schematic (a, c, e) and ultrasound (b, d, f) pictures of the 3 types of CSP based on the position of the gestational sac (GS) in relation to 2 lines, the ‘uterine cavity line’ (UCL) and/or the ‘serosal line’ (SL), a Delphi consensus, adapted from Jordans *et al. (2)* (1) the largest part of the GS crosses the UCL (a,b); (2) the majority of the GS is inside the myometrium and does not cross the UCL or the SL (c,d); and (3) the GS crosses the SL; the pregnancy is only covered by a thin layer of myometrium/peritoneum and protrudes towards the bladder or the broad ligament (e,f).

Table

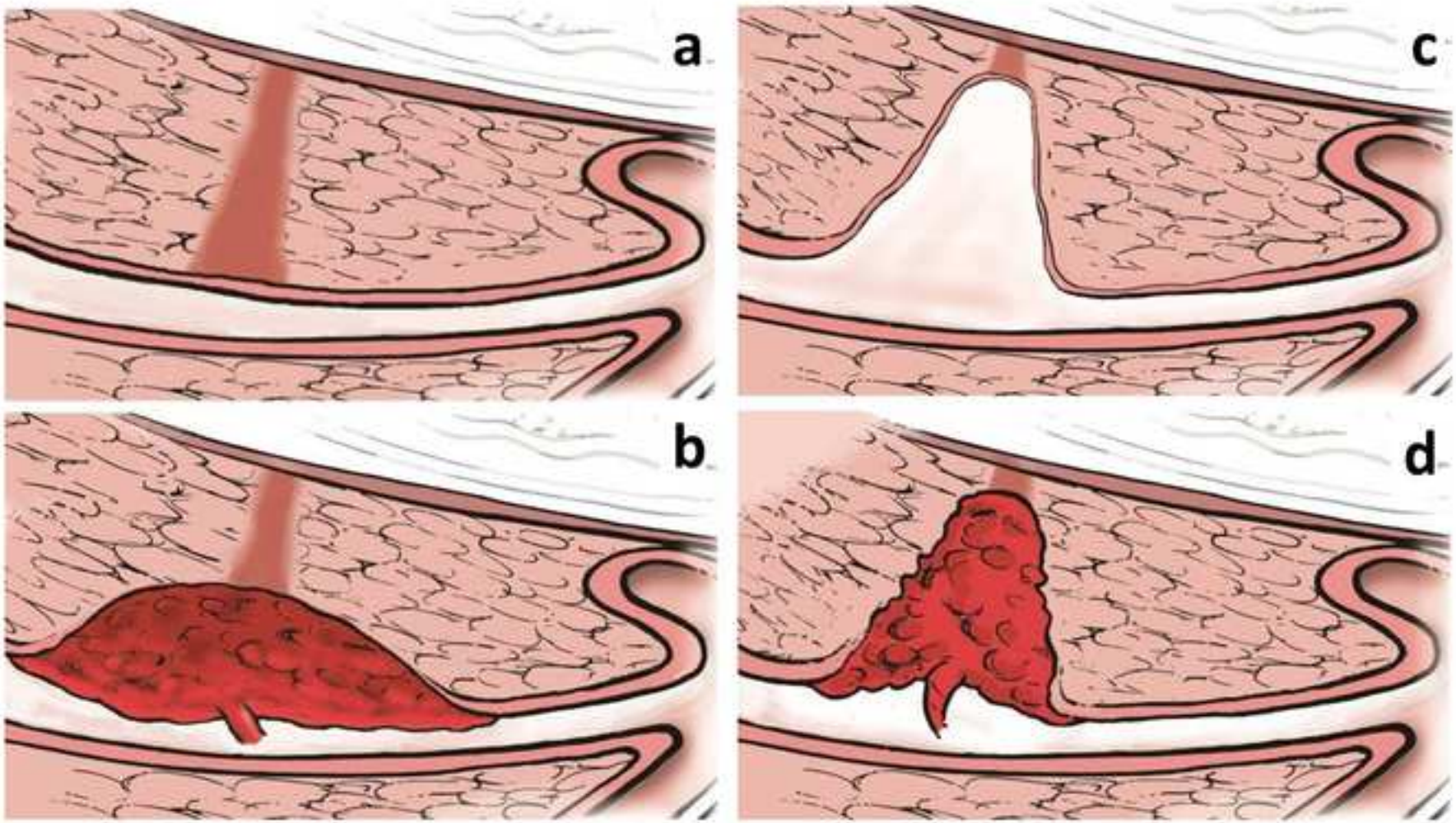
Table. Review of Caesarean Scar Pregnancy (CSP) management options showing type of management, number of studies, cases included, efficacy and rates of haemorrhage and hysterectomy (adapted from Maheux-Lacroix *et al*. (29)).

Treatment modalities	Studies (n)	Cases (n)	Success[a] (%)	Hemorrhage[b] (%)	Hysterectomy (%)
Expectant management					
Viable CSP[c]	17	52	77% livebirths	12.9* - 39.2**	15.2* - 60.6**
Non-viable CSP[c]	17	17	/	22.2	0
Medical					
Systemic MTX[d]	16	202	56	6	3
Local MTX/KCl[d]	12	137	60	4	2.2
Systemic + local MTX[d]	9	106	77	11	3.8
Surgical					
D&C[d]	25	645	76	28	2.5
Hysteroscopic resection[d]	8	117	88	3	1.7
Vaginal excision[d]	5	151	99	1	0.7
Laparoscopic excision[d]	6	62	97	0	0
Open excision[d]	4	23	96	4	0
Minimally invasive					
UAE[d]	5	113	81	5	4.4
Double balloon[e]	2	48	98	2.1	2.1
Combination					
Medical + D&C[d]	12	243	80	17	6.2
UAE + D&C[d]	14	595	93	4	1.2

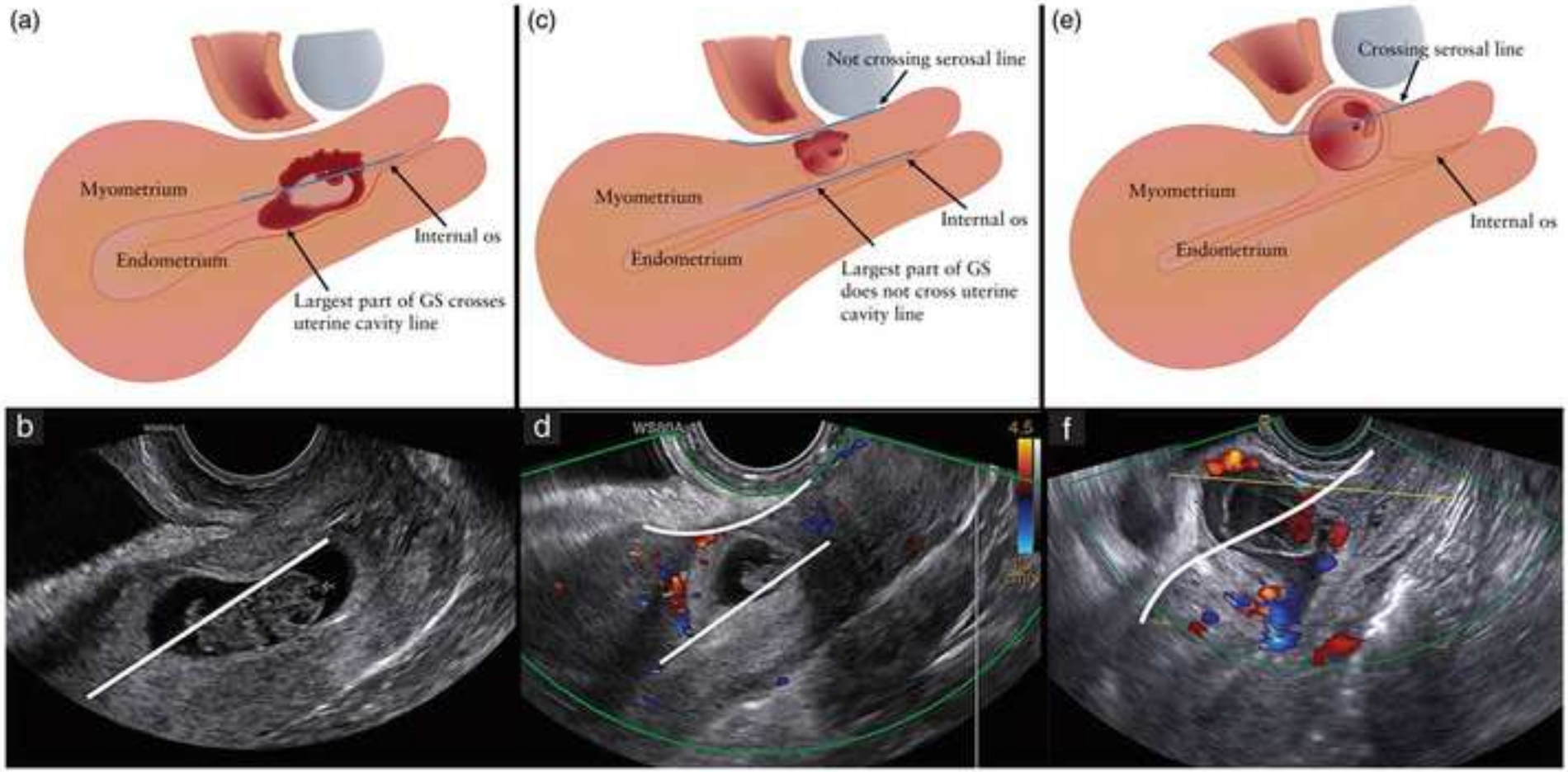
Figure


A
Low, anterior gestatinal sac
Cervix
Empty uterine and cervical canal
B
Thin or no myometrium
Cervix

Figure



Figure


(a)
Myometrium
Endometrium
Internal os
Largest part of GS crosses uterine cavity line
(c)
Not crossing serosal line
Myometrium
Endometrium
Internal os
Largest part of GS does not cross uterine cavity line
(e)
Crossing serosal line
Myometrium
Endometrium
Internal os
b
d
f

Supplemental Data File (.doc, .tif, pdf, etc.)