A Consequence of Cesarean Delivery: First-Trimester Cesarean Scar Pregnancy

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Ilan E. Timor-Tritsch, Ana Monteagudo, and Terri-Ann Bennett

Introduction/Terminology

Before discussing epidemiology, the diagnostic issues and management of cesarean scar pregnancy (CSP) are important to touch upon. There are various terms and names used to define this entity and special form of early pregnancy which is often referred to as "cesarean ectopic pregnancy," "cesarean scar ectopic," or "cesarean delivery scar pregnancy." Other terms may also include the word "ectopic." Since the majority of reports use what we think is the correct and most fitting term for the disease, we have used "cesarean scar pregnancy" (in short CSP) in all of our writings. We, therefore, are consistent in this chapter, too.

In fact there are three main reasons to avoid using the term "ectopic." First, CSP is *well within the uterine cavity*. The placenta at times (but not always) is squeezed into the niche or dehiscence created by the cesarean delivery in the lower segment of the uterus or at the level of the internal os. If untreated, the gestational sac and the embryo/fetus will develop within the uterine cavity. Second, a CSP can lead to a live offspring as opposed to any kind of true ectopic pregnancy that rarely, if ever, results in a viable neonate. Last, treatments devised for true ectopic pregnancies and applied for a CSP may not work or may even cause complications.

Our analysis of 751 cases of CSP reviewed until 2012, found that almost a third (30 %) were misdiagnosed or diagnosed at a late gestational age, significantly contributing to a large number of treatment complications that could have been avoided by an early and correct diagnosis. Although an exact number cannot be quoted, it seems that, due to a higher awareness of the disease, among 1223 cases found in the literature published between 2012 and 2014, the number of misdiagnoses appeared to have dropped significantly.

I.E. Timor-Tritsch, MD (✉)
Department of Obsterics and Gynecology, NYU School of Medicine, 550 First Avenue, NBV-9N1, New York, NY 10016, USA
e-mail: ilan.timor@nyumc.org; josepc02@nyumc.org

A. Monteagudo, MD
Department of Obstetrics and Gynecology, NYU School of Medicine, 550 First Avenue, NBV-9N1, New York, NY 10016, USA
e-mail: ana.monteagudo@nyumc.org; josepc02@nyumc.org

T.-A. Bennett, BS, MD
Department of Obstetrics and Gynecology, New York University Medical Center, 351 E 82nd St., Apt 3RE, New York, NY 10028, USA
e-mail: terri-ann.bennett@nyumc.org

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Background

Due to the close and causal relationship between a previous CD and CSP we have to discuss the gradual but steady increasing rate of CD in the USA and the rest of the world. In the USA the rate of CD slowly increased from 5 % in 1970 to 32.9 % in 2009 [1]. Recent national statistics by the Centers for Disease Control and Prevention report a leveling off of CD rate, which in 2012 reached 32.8 % [2]. Rates ranging from 35 to 80 % were reported in other parts of the world [3], leading us to believe that the incidence of CSP is higher in those countries than in the USA.

Keeping in mind the causative connection between CD and its recognized consequences, such as the placenta previa and morbidly adherent placenta (MAP, placenta accreta and percreta) in the last decade, many Ob/Gyn practitioners became increasingly exposed to the clinical picture of MAP. Most have rarely, if ever, faced a patient with a first- or early second-trimester CSP. The learning process was traumatic resulting in misdiagnosed patients with CSP as "aborting gestations," "ectopic pregnancies," and "cervical pregnancies." Also, obstetricians were confronted with diagnostic and management dilemmas. When "traditional" treatments, such as D&C and systemic methotrexate (MTX) were employed, practitioners experienced severe and almost unmanageable vaginal bleeding that, at times, led to hysterectomy. If "low lying" pregnancies were left to continue, many resulted in second trimester uterine ruptures and profuse internal or vaginal bleeding causing loss of the pregnancy and requiring hysterectomy. Even in reviewing the literature, one could usually find reports of single or sporadic cases or a series of one to two dozen cases that would fit the clinical picture. It is clear, that it was impossible to learn from the numerous, previously used treatments, "tested" on few patients (sometimes only one). The published review compiling 751 patients diagnosed with CSP [4] may have helped to shed light on the various treatments and their complications; however, to date, there is no universally recognized treatment protocol adopted by professional societies. Our chapter will discuss the pathogenesis, diagnosis, counseling and management options to treat CSP based upon evidence in the literature as well as our own clinical experience.

What Is a Cesarean Scar Pregnancy?

Cesarean scar pregnancy develops if a blastocyst implants *on* the uterine scar or *in* the dehiscence (otherwise known as a "niche") resulting from repair of the uterine incision at the previous CD. Implantation of the fertilized oocyte in the faulty anterior uterine wall will give rise to the CSP.

Before engaging in the diagnosis of CSP we will devote a paragraph to discuss the two ways an incision made at the time of the CD heals and appears after it was repaired. Normally we expect that healing tissues generate a thick scar without leaving behind a defect. At times, a dehiscence or as it is usually referred a niche, with a certain depth and width marks the area of the previous CD and can be seen with or without a saline infusion sonohysterography [5]. The niche can be triangular or rectangular and can be filled with fluid (Fig. 17.1a). The size of the niche on a sagittal section of the uterus may be misleading; therefore, the area should always be looked at in the transverse plane on which the real size of the dehiscence can be appreciated (see Fig. 17.1b). This is logical, since most primary Cesarean incisions are performed from side-to-side, e.g., in the transverse plane. Bij deVaate et al. [6] published an extensive review analyzing 21 articles dealing with the prevalence, potential risk factors for development and symptoms related to the presence of uterine niches following CD. The prevalence of a niche after a CD was found to vary between 56 and 84 %. Several risk factors for development of niches were found: the technique of repair, location of the incision, wound healing, and probably the number of layers included in the closure as well as multiple CDs and uterine retroflexion. The dehiscence left behind by the previous CD may be extensive and reaches the anterior uterine wall or the area below the bladder in the shape of a fistulous connection between the uterine cavity and the abovementioned areas (see Fig. 17.1c, d).

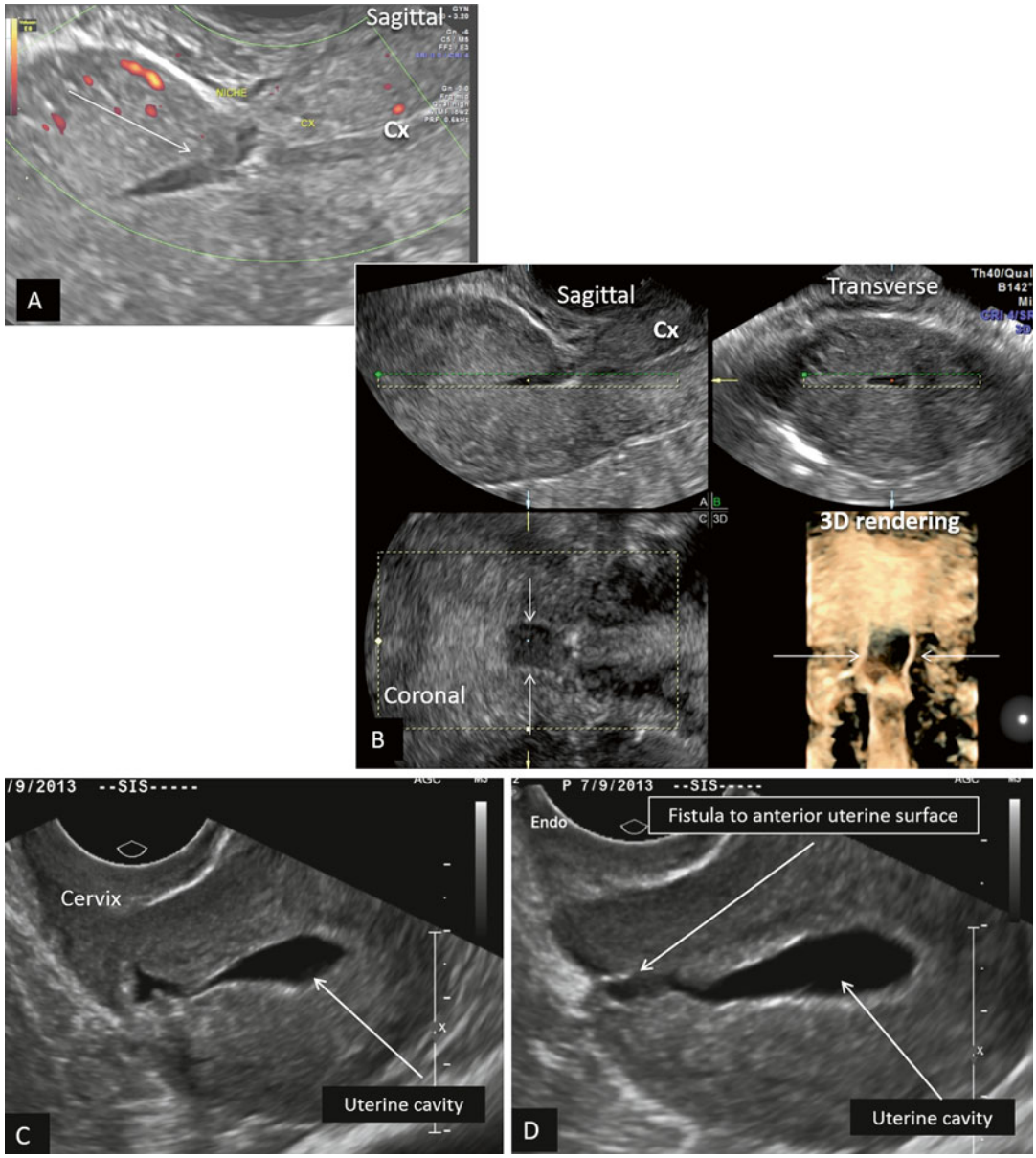

Fig. 17.1 Niche/defect left behind by the previous CD. (**a**) Sagittal image of the niche marked by an *arrow* (*Cx* cervix). (**b**) Three-dimensional orthogonal images of the uterus showing the niche (*arrows*). The width of the dehiscence should always be looked at on a transverse or coronal view since that is the real size of it. Unenhanced images. (**c**, **d**) At times, the niche/dehiscence extends all the way from the uterine cavity to the anterior surface of the uterus. Saline infusion sonographic images

At times, the niche is deep and wide (Fig. 17.2a), explaining the deep insertion of the tiny placenta with its rich blood supply (see Fig. 17.2b, c). Since the prevalence of niches is relatively high, it can be expected that the possibility of such deep implantation is realistic; therefore, a careful scrutiny of the small placenta and its vessels should be performed in all first-trimester diagnoses of CSP.

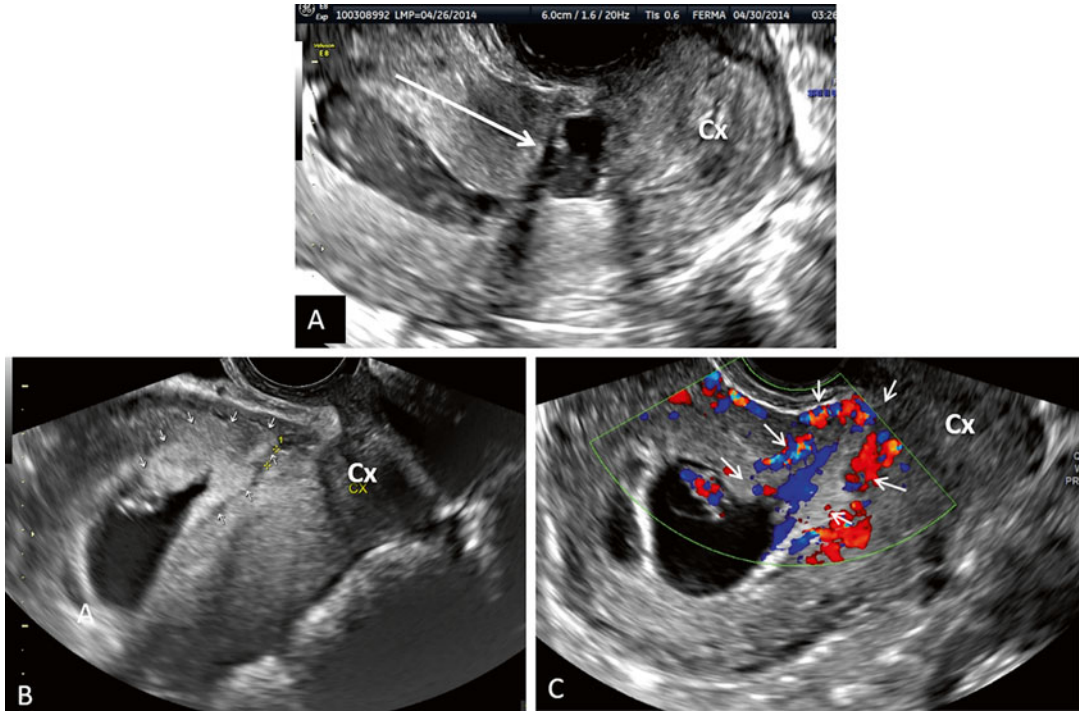

Fig. 17.2 Placental implantation into the niche of a previous CD. Sagittal images (*Cx* cervix). (**a**) Saline infusion sonohysterography of a uterus with a large niche. (**b**) Gray scale sagittal image of a CSP. Note the implantation of the placenta in the niche outlined by *small arrows*. (**c**) Color Doppler image of the same CSP demonstrating the invasion of the placenta (*outlined* by *small arrows*) with its blood vessels into the myometrium

Incidence/Risk Factor

Estimated incidence rates of CSP range between 1/1800 and 1/2500 of all CDs performed [7–10]. Seow et al. [11] states that CSP was seen in 0.15 % of all pregnancies with a history of a previous CD. The above numbers appear unrealistic; however, their true incidence is unknown due to the lack of population based statistics (registries).

The only risk factor for CSP is a previous CD. However, since we found about eight cases of recurrent CSP in the literature, including our own case with four recurrences [12], we have to consider a previous CSP as a rare but possible risk factor for this entity.

Pathogenesis of CSP

Later in this chapter, we will provide evidence that the histology of the tiny placental insertion or myometrial invasion of a CSP in the first trimester of the gestation is identical with the histologic findings of a MAP in the second and third trimester of pregnancy. The only scientifically proven fact is that, in both diseases (CSP and MAP), intervening fibrinoid layer between the myometrium and the cytotrophoblastic shell in the placenta is naturally present between the endometrium in normally attached placentae when thinned or missing. This fibrin layer (fibrinoid material) is known by the name of Nitabuch layer. Previous uterine surgery or uterine inter-

ventions lead to *thin or absent decidua basalis in scarred areas*, *as well as the abovementioned protective layer* of the lower uterine segment. In CSP and in MAP this membrane is missing and the placental villi attach themselves and penetrate between the myometrial fibers into the depth of the uterine wall.

Other theories, such as the role of a low oxygen tension at the area of the scar providing a stimulus to help the invading cytotrophoblast [13, 14], as well as the in vitro studies of Kliman et al. [15] with trophoblast and EM explants, showing a strong propensity for attaching to exposed extracellular matrix and then to endometrial epithelial cells, are the most frequently quoted. Both theories support the observation that the more CDs a patient has, the higher risk of placenta previa and a MAP.

Diagnosis of CSP

The two diagnostic modalities used are ultrasound and MRI; however, ultrasound is the best modality. Transvaginal sonography (TVS) presents an advantage over transabdominal ultrasound (TAS), since it has a higher resolution and can be placed in close proximity to the low, anterior gestational sac. MRI has been used for imaging and is expensive. In addition, it requires moving the patient to a radiology site. Also, MRI lacks the color Doppler flow that provides a high resolution image, which is important in establishing a correct diagnosis.

The diagnosis of CSP requires a high clinical index of suspicion. We reiterate, that every woman with a history of a previous CD and a positive pregnancy test, presenting in the first trimester of the pregnancy, should be considered a "rule out CSP" until proven otherwise. Stirnemann et al. [16, 17] published studies to lay the basics for such screening if proven significant. Until that time, this should be strongly considered, since there is no downside to that first early scan. Godin et al. [18], Vial et al. [19], and Seow et al. [20] published similar sonographic criteria they used to define a CSP; however, other authors used additional characteristics, relying mostly on single cases.

Our diagnostic criteria of CSP [4, 21] took in consideration a history of previous CD, a positive pregnancy test and the following sonographic criteria (Fig. 17.3):

- Endometrial and endocervical canal devoid of a gestational sac;
- Placenta and/or a gestational sac embedded on or in the hysterotomy scar/niche;
- In early gestations, a triangular gestational sac that fills a niche of the scar (Fig. 17.4);
- Thin or absent myometrial layer between the gestational sac and the bladder;
- The presence of a chorionic sac, with or without embryonic/fetal pole and/or yolk sac and with or without heart activity;
- The presence of a prominent and at times rich vascular pattern at or in the area of a CD scar. As a rule, detection of peri-trophoblastic blood flow, detected by the most sensitive Doppler settings around a low, anteriorly situated chorionic sac, in a patient with a previous CD, is a reliable sign of CSP.
- It is remarkable that, at very early stages of the pregnancy (4–5 weeks), the blood vessels tend to concentrate on the anterior side of the chorionic sac (Fig. 17.5) "marking" the site of the placental implantation.
- The usefulness of 3D ultrasound in the diagnosis is debated. However, it furnishes information regarding the exact location of the sac, its vascularity and volume, the latter two in a quantitative fashion (Fig. 17.6). We use the above measurements to follow the healing process of the treated cases or for the early warning signs of an impending arteriovenous malformation (AVM) developing at the treatment site.

If an AVM was suspected (at times, this may be the presenting sonographic picture), Doppler measurements of the blood velocity were measured and expressed by the peak systolic velocity (PSV) in cm/s. Velocities above 39 cm/s were considered for uterine artery embolization (UAE) by the interventional radiologist. This evaluation

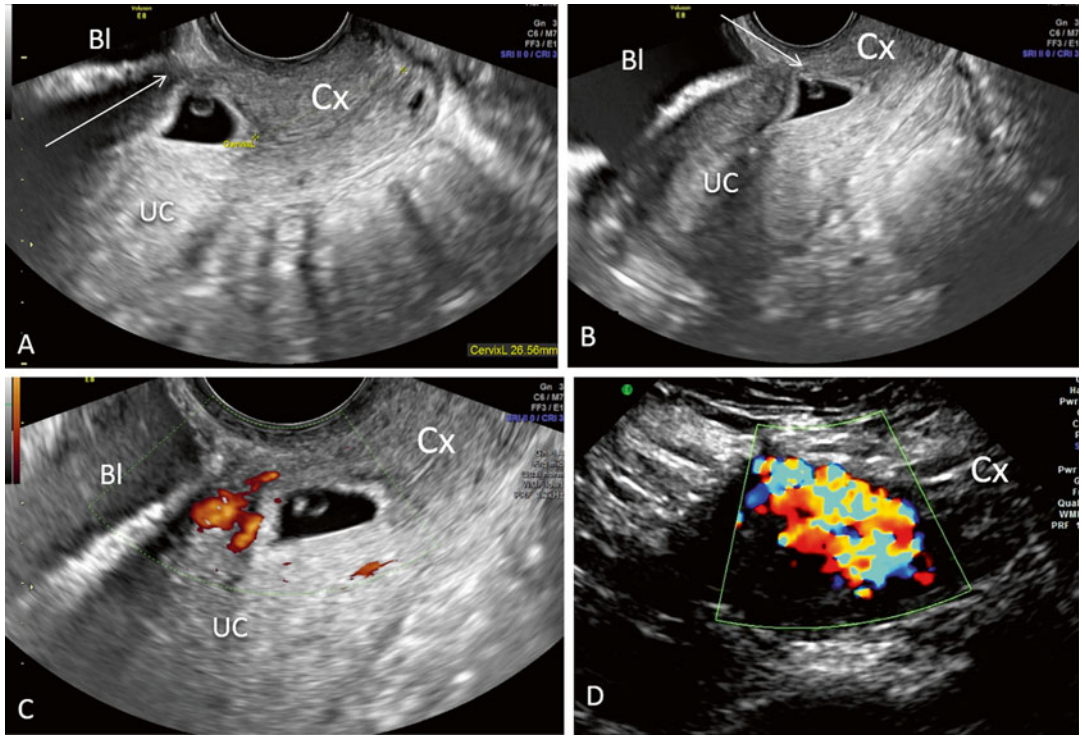

Fig. 17.3 Sonographic markers of CSP (*Cx* cervix, *Bl* bladder, *UC* uterine cavity). (**a**) Empty uterine cavity and cervical canal. Low anterior triangular gestational sac with yolk sac in close proximity to the bladder (*long arrow*). (**b**) Triangular gestational sac with close proximity to the bladder. (**c**) The developing vascularity between the sac and the bladder. (**d**) Arteriovenous malformation in a CSP that required UAE

is best done when the region of interest of the Doppler interrogation is constricted to the questionable area, using the appropriate pulse repetition frequency and filter settings.

These are pathological, high velocity, low resistance "short circuits" of the blood stream between an organ's arterial and venous supply. Ultrasound presents a valuable tool for the diagnosis of AVM and guideline for their treatment [22]. Although uncommon, they may cause dangerous hemorrhages due to disrupted blood vessels, after miscarriage or uterine instrumentation [23]. The acquired form, seen in CSP, is usually traumatic, resulting from prior dilation and curettage (D&C), therapeutic abortion, uterine surgery, or direct uterine trauma. Their incidence is about 1 % of CSPs. In our series of 60 CSPs five, patients had AVM [24].

Differential Diagnosis of CSP

There are two main differential diagnostic entities to consider: First, a *cervical pregnancy*, which is rare and has no history of prior CDs. Second, a *miscarriage in progress*, which can be seen in the cervical canal or close to the internal os and "on its way out" having no heart activity. Also, under pressure on the cervix with the vaginal probe, the sac will slide back-and-forth, while a true CSP will stay fixed. It should be noted that misdiagnosis has, at times, severe consequences. The proof is in the literature: 107 of the 751 cases of CSP reviewed (13.6 %) were missed or misdiagnosed leading to complications (e.g., hysterectomy and loss of fertility) [4]. Figure 17.7 demonstrates a simple method to distinguish between the two,

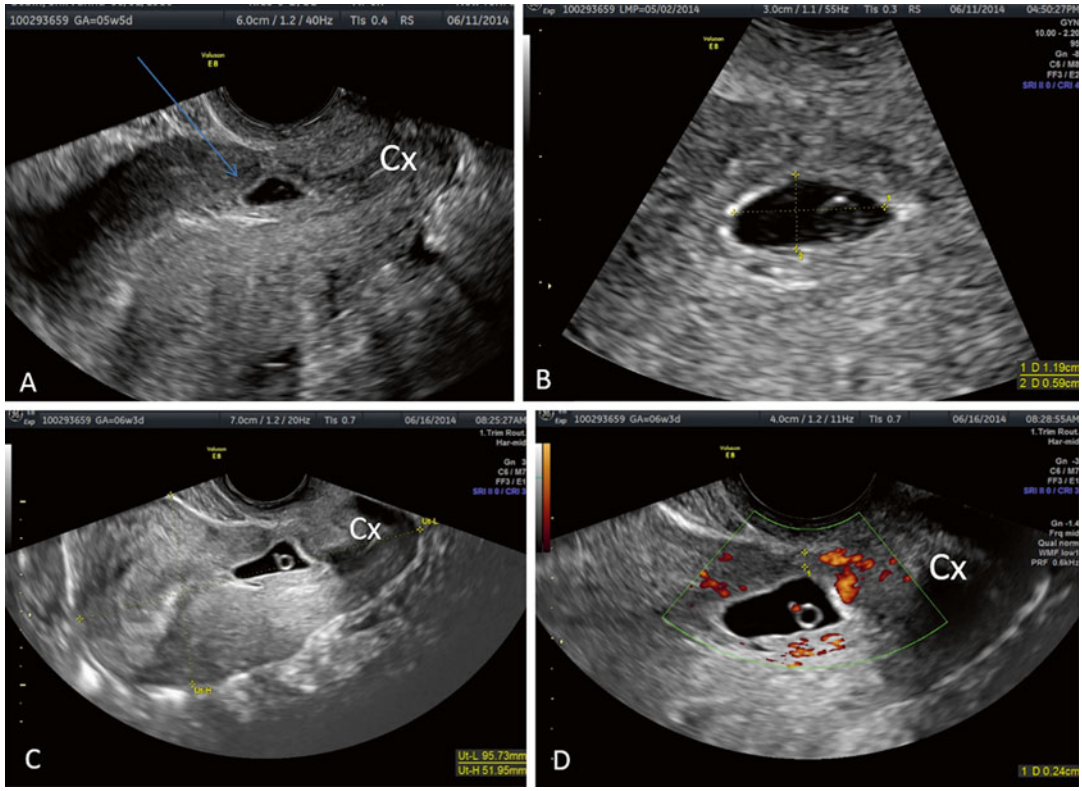

Fig. 17.4 Additional images of the shape of the early 4–6 week chorionic sac of the CSP (*Cx* cervix). (**a**) Flat sac. (**b**) Oval sac. (**c**) Triangular sac. (**d**) Square sac

abovementioned, differential diagnostic entities and a true CSP.

However, it is extremely important to realize that this simplified diagnostic aid is valid and reliable only while the gestational sac is small (e.g., 5–6 mm in diameter or 5–6 postmenstrual weeks) and remains "local," close to the niche or above the scar. In other words, the sac did not start to elongate and move/expand cranially to fill the uterine cavity. In this case, the sac will be found increasingly in the uterine cavity misleading the uninitiated observer to think that it is an intrauterine sac. In such cases one should shift the attention from the sac and concentrate upon the blood vessels of the tiny placenta, which stay in their original site of implantation, thereby holding the most important diagnostic feature of CSP: the true site of placental implantation. Figures 17.2, 17.3, 17.4, and 17.5 clearly demonstrate the abovementioned diagnostic principle.

Lately, clinicians and clinical researchers have started to pay attention to the exact location of placental implantation in the area of the scar/niche left behind by the previous CD. Vial et al. [19] suggested that there are two kinds of CSPs, based on depth of implantation. The question is whether a deeply implanted chorionic sac *in* a niche or dehiscence, close to the bladder with very thin or no visible myometrium (Fig. 17.8a, b) will result in a worse outcome than if inserted *on* top of a scar that has some thickness (see Fig. 17.8c, d). Comstock et al. [25] and personal communication with Cali G. refer to "on-the-scar implantations" as "low lying sacs" and assume that these are the CSPs that may proceed to third trimester giving rise to MAP. Deeply implanted in the niche, surrounded by myometrium and seldom reach term is a "true" scar pregnancy. We slightly differ about the latter form of CSP since we have witnessed the reaching delivery of a live offspring.

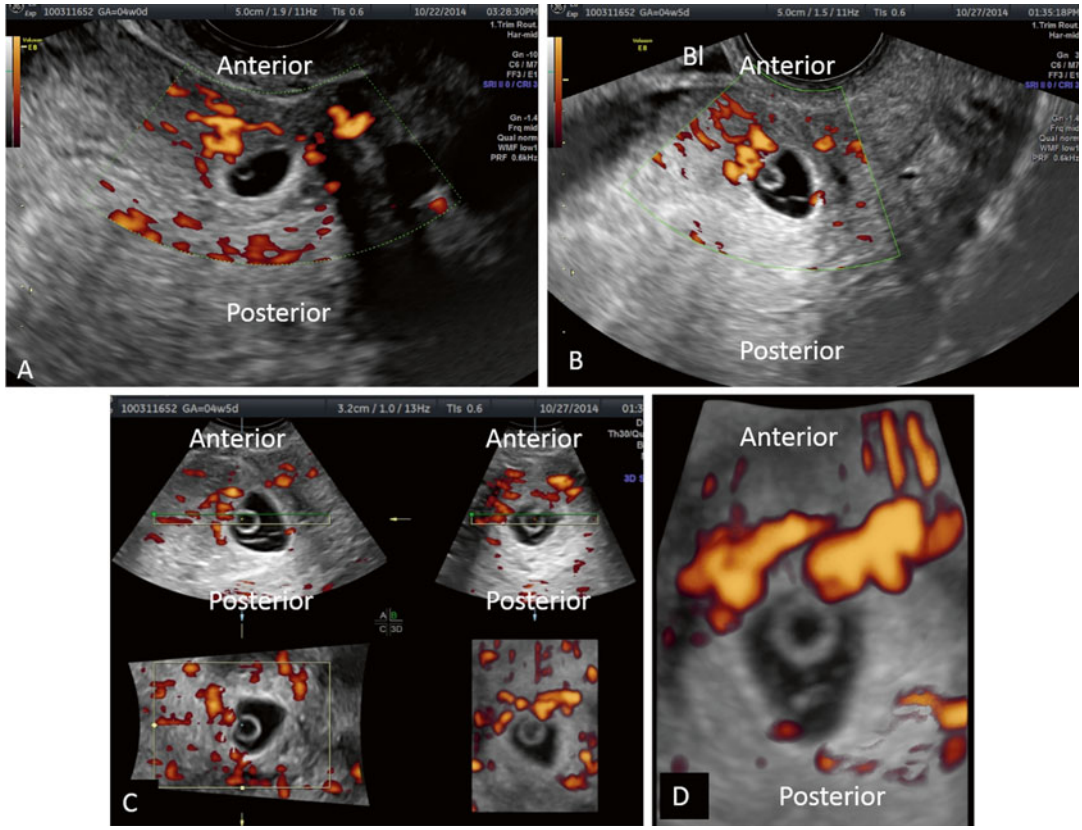

Fig. 17.5 The developing vascular grid of the early CSP. (**a**, **b**) 2D color Doppler of the vessels surrounding the chorionic sac. (**c**) Three-dimensional, orthogonal planes and 3D rendering (*lower right picture*) of the vascularity that starts to concentrate on the anterior side of the sac, the future site of the placenta. We suspect that the future placenta will invade the myometrium in the anterior direction. (**d**) Thick-slice 3D rendering of the sac with its vessels clearly more prominent anteriorly

Rac et al. [26] studied 39 patients, of which 14 had histologically confirmed MAP. The smallest myometrial thickness measurement was one of the variables associated with invasion. More research is needed before the gestational-sac-to-bladder distance (see Fig. 17.8) can become useful in counseling patients with CSP in the first trimester of pregnancy.

The Connection Between CSP and MAP

The connection or continuity between CSP and MAP has gradually become evident through clinical observation [27, 28]. We studied placental implantation in the early (second trimester) placenta accreta and in CSP, to find out if they represent different stages in the disease continuum leading to morbidly adherent placenta in the third trimester [29]. Two pathologists, blinded to the diagnosis, evaluated their histologic slides on the basis of these microscopic slides. They could not tell the difference between the two clinical entities and found that both had one thing in common: neither had intervening deciduas between the villi and the myometrium, consistent with the classic definition of morbidly adherent placenta. Therefore, our conclusion is that CSP and an early second trimester placenta accreta are histopathologically identical and represent different stages in the disease continuum leading to MAP in the third trimester.

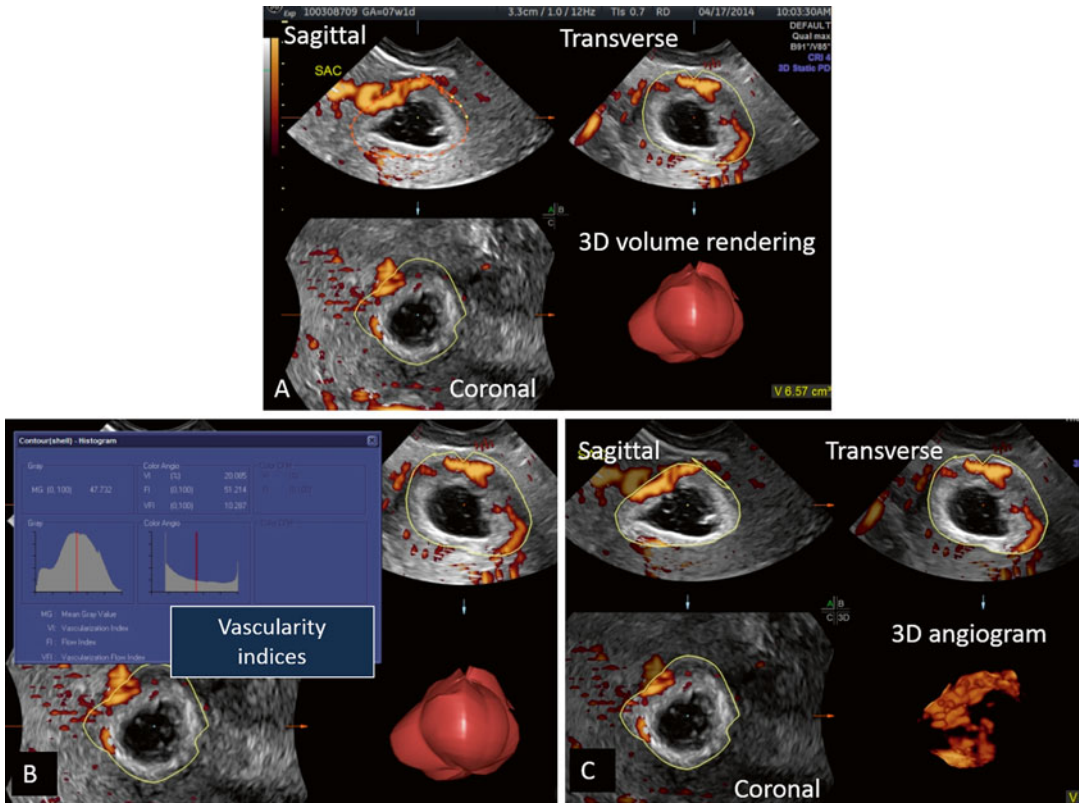

Fig. 17.6 The use of 3D ultrasound in the diagnosis and follow-up of treatment of CSP. (**a**) 3D orthogonal planes with power Doppler used in segmentation (marking the perimeter of the sac) to obtain the volume of it. (**b**) After the volume of the sac is obtained a special algorithm is applied to compute and display the quantitative vessel content of the above volume. (**c**) Visual display of the 3D vascular angiogram that can be used qualitatively for follow-up purposes after local injection of UAE treatments

The next logical question is whether, left untreated, a CSP would result in a live born offspring. We followed ten patients diagnosed with CSPs who opted to continue the pregnancy declining early termination [30]. The diagnosis of CSP was made before 10 weeks. All ten had sonographic signs of MAP by the second trimester. Nine of the ten patients delivered live born neonates, between 32 and 37 weeks. One patient had progressive intractable vaginal bleeding, leading to hysterectomy, at 20 weeks. The other nine patients underwent hysterectomy at the CD. Blood loss ranged from 300 to 6000 mL. Histopathological diagnoses of all placentae was: placenta percreta.

Above, we provided reliable data regarding two clinical issues: (1) CSP is a precursor of MAP, both sharing the same histopathology and (2) pregnancies diagnosed as CSP in the first trimester may proceed to deliver live offspring, risking premature delivery and loss of uterus and fertility. This data can be used to counsel patients with CSP, to make an evidence-based and informed choice between first-trimester termination of an early pregnancy or continuation, risking premature delivery and loss of uterus and fertility.

Map in the First Trimester

MAP can exist in the first trimester of pregnancy. For beginners, Comstock et al. [25] described seven patients after sonographic examination at 10 weeks or earlier with placenta accreta, increta,

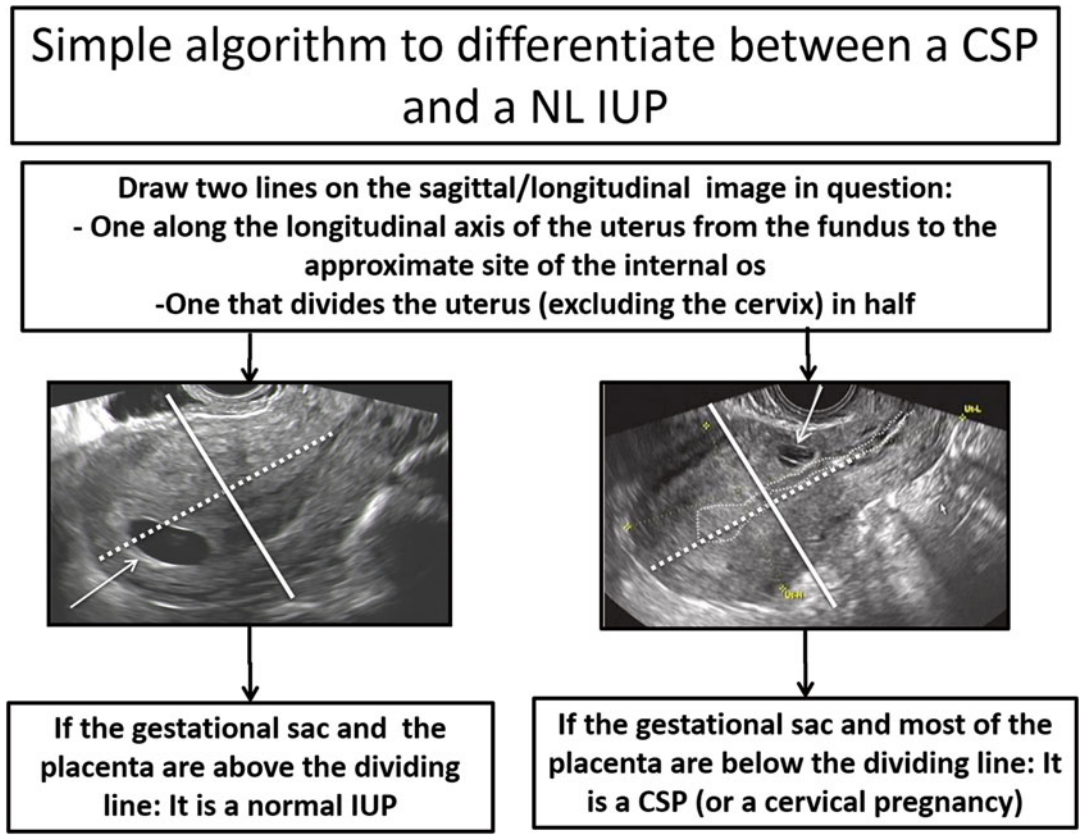

Fig. 17.7 The simple algorithm to differentiate between an IUP and a CSP (or cervical pregnancy)

percreta, not only by their clinical course but, more importantly, by pathologic examination of the uterus. In six, at the time of the early ultrasound, the chorionic sac was located in the lower uterine segment, in the scar area of the previous CD. Two patients underwent D&C, at which time severe bleeding led to hysterectomy. The remaining four had sonographic findings typical of placenta accreta during subsequent scans but delivered at term. The author's conclusion suggested that, in a patient with a previous CD, a chorionic sac detected by a 10 week or less ultrasound, located in the lower uterine segment, suggests the possibility of placenta accreta. A similar article was published by Ballas et al. [27].

Using our material, Fig. 17.9 depicts the early sonographic markers of a MAP: placenta previa, focal loss of the clear space and focally increased vascularity. The patient in this example delivered at 34 weeks and had placenta accreta. In ten patients, we reported [30] the early sonographic markers of MAP could be detected at the end of the first and beginning of the second trimester.

Counseling Patients with a First-Trimester CSP

Prior to treatment and after the reliable diagnosis of CSP, one has to determine if fetal heart beats are seen. If no yolk sac and/or no embryo and/or no heart beats are seen, re-scan every 2–3 days. If, after a week, no heart activity, no yolk sac and/or no embryo are detected, a sonography and biochemistry based follow-up should be planned. Only after this time should the gestation be

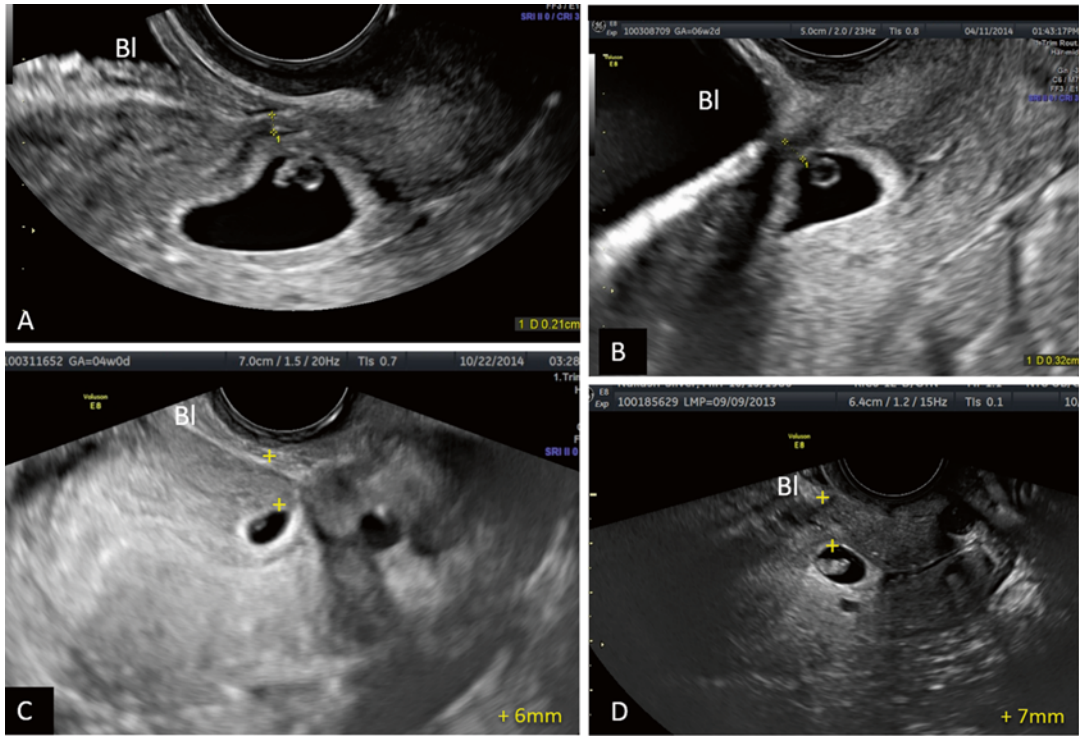

Fig. 17.8 The issue of distance between the anterior uterine surface and the gestational sac: "*in* the niche/scar" or "*on* the scar" (*Bl* bladder). (**a**, **b**) These two are examples of a close proximity of the sac to the bladder (2.1 mm and 3.2 mm, respectively). (**c**, **d**) Depicts two CSPs in which the sac is 6 and 7 mm remote from the bladder

considered live or a pregnancy failure and the serum hCG should be followed until nonpregnant levels are reached. Some management protocols call for systemic administration of MTX, even with the absence of heart beats for early drug effect. While such an approach is not contraindicated, the patient and the provider *must* be sure that under no circumstances is this a wanted pregnancy.

In the case of positive heart activity, counseling should enumerate the two main, clinical management options to reach a decision as early as possible. The two options before further growth of the gestation are: (1) termination or (2) continuation of the pregnancy. Our counseling of patients with a CSP diagnosed in the first trimester of pregnancy underwent a fundamental change. Several years ago we would counsel toward termination of the pregnancy without delay. Recent studies on the natural history of the CSP, with the possibility of reaching term or near term delivery of a live offspring, has changed our counseling. We provide the patient with evidence that this is possible and that the patient should understand that a placenta accreta at the CD may necessitate hysterectomy. Management in the above case should be based on the patient's age, number of previous CDs, desired number of children, and the expertise of the clinicians giving the care. If the patient decides to continue the pregnancy, bleeding precautions should be given. The management should be based upon serial ultrasounds, until a safe gestational age is reached. A multidisciplinary team should be involved in the delivery and blood products should be available, since ultrasound cannot predict the blood loss at surgery. Our general guidelines in counseling and managing the patient with a CSP are shown in Fig. 17.10.

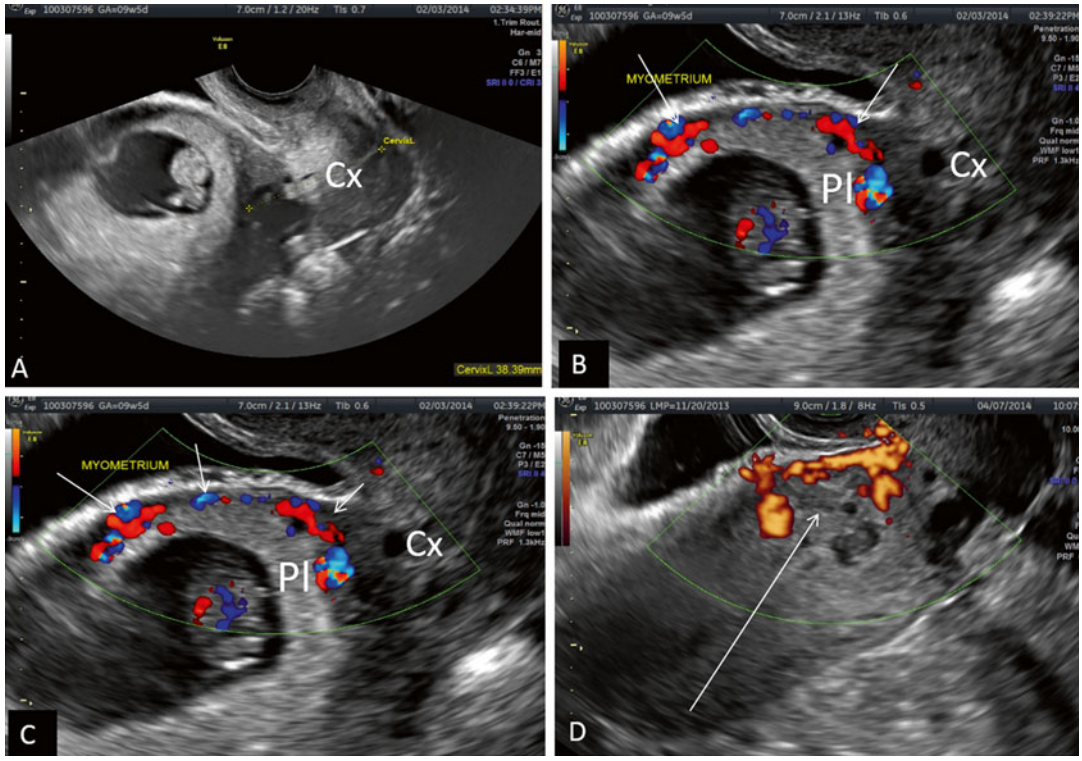

Fig. 17.9 CSP is a precursor of MAP. This is a 9 weeks and 5 days gestation (*Cx* cervix, *Pl* placenta). (**a**) Sagittal, gray scale image of a CSP with an anterior placenta previa. (**b**) Power Doppler reveals two areas of vessel proximity to the bladder with loss of the myometrium (*arrows*). (**c**) Another plane showing the same findings as in (**b**). (**d**) A more lateral section concentrates on an area with clear vessel invasion of the myometrium (*arrow*)

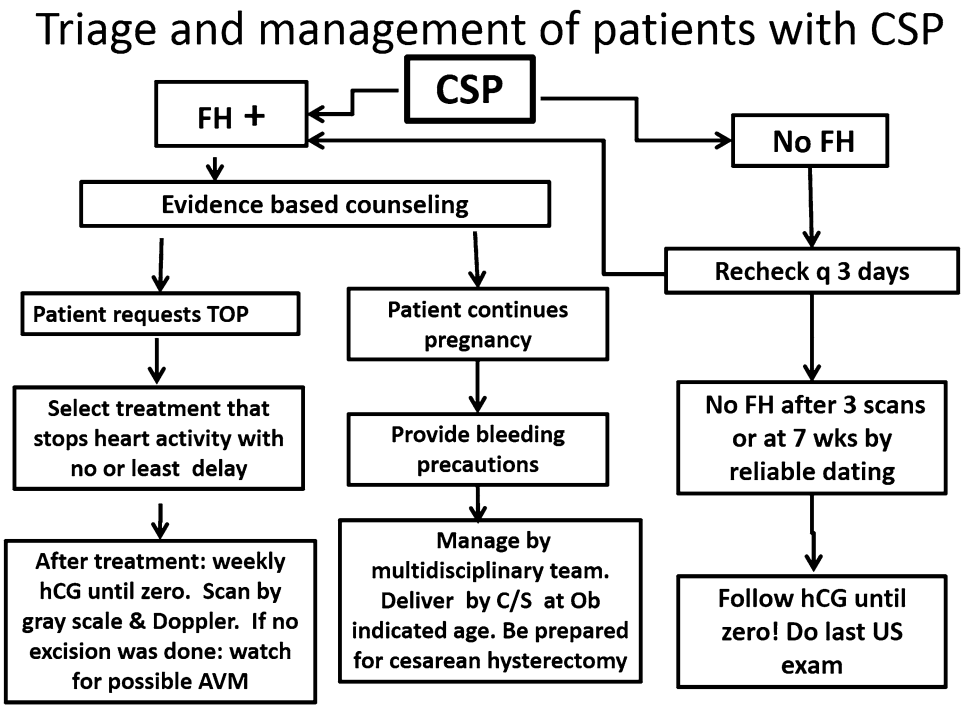

Fig. 17.10 Triage and management of CSP by the presence or absence of cardiac activity

Management of CSP

Treatment regimens and their combinations can be classified as one of the following:

1. Major Surgery (these require general anesthesia)
   (a) Laparotomy (hysterectomy or local excision)
   (b) Excision by laparoscopy, hysteroscopy or by transvaginal surgery
   (c) Dilatation of the cervix and sharp or blunt curetting
   (d) Suction aspiration without dilatation of the cervix
   (e) Excision performed by the vaginal route

   The last two can be guided by continuous, real-time ultrasound.

2. Minimally invasive surgery (does not involve general anesthesia)
   (a) Local injection of MTX or KCl
   (b) Vasopressin locally was also used
3. Systemic medication
   (a) Single or repeated doses of MTX and etoposide (some articles originating from China advocate intravenous use of MTX claiming reasonable success)
   (b) Uterine artery embolization (UAE)
4. Combination of the above treatments. A large number of articles report on combining treatments in a planned, simultaneous or sequential fashion. Treatments are also changed, mostly after the first-line therapy failed. As a matter of fact, it is rare to find a recently (2012–2014) published case or case series in which the patients were managed *only* by one single treatment agent or protocol.
5. Adjuvant measures. Most recently, Foley balloon placement and inflation to prevent and/or control bleeding, following local treatments such as aspiration, curettage and local injection.

It is beneficial for the patient with CSP to be referred to a facility that provides evidence-based care as well as experienced in managing cases, in response to developing emergency situations. Such centers should be able to provide operating rooms, interventional radiology procedures and have available immediately blood transfusion/blood products. The latter, since bleeding complications is typical of this dangerous clinical entity.

Treatment Options Available for CSP

Based upon the in-depth and available literature, analyzing the different aspects of CSP, in 2012 there were about 33 published treatment modalities with their results and complications [4]. No preferred treatment became apparent, however, of the 751 patients D&C (305), surgical excision (laparoscopic, hysteroscopic and transvaginal) (261), UAE (142), MTX (92), and local, intragestational sac injection (86) were the most used.

Between 2012 and 2014, no less than 1223 cases of CSP were published in about 61 peer-reviewed articles. Not surprising is the fact that Chinese authors contributed 91 % of the cases, describing their various and different treatment modalities/combinations of managing approximately 1115 patients. This is due to their large population and over 40 % CD rate. At least 36 primary or combination treatments were found; however, the number is not substantially different from the list of treatment approaches described in our review of 751 cases. No wonder one cannot draw a clear conclusion as to which treatment was the most effective, resulting in the least or no complications. This large number underlines the fact that, in 2015, there is no nationally/internationally agreed upon or suggested management protocol published with a set of guidelines to manage CSP or early first-trimester placenta accreta. While the distribution of the various treatments and their rates of use are found in the tables of our previous review [4], the somewhat different distribution of treatment choices are detailed in Table 17.1.

Despite several treatments for CSP our detailed discussion will be limited to the most used. A much more detailed analysis is found in our in-depth review [4], complete with their efficacy and complication rates. We now add the pertinent data resulting from the review of the 1223 cases published after 2012.

Table 17.1 Treatment options for CSP

Treatments: single or in combination	No. of patients	Percent of 1223 patients (%)
Dilatation and curettage	577	52.4
Uterine artery embolization	309	28.0
Methotrexate	236	21.4
Suction aspiration	81	12.0
Transvaginal excision	119	9.7
Laparoscopic excision	94	7.7
Hysteroscopic excision or guidance	63	5.2
Excision by laparotomy or straight TAH	15	1.2
High-frequency ultrasound	20	1.6

Suction Aspiration or D&C, Alone or in Combination

Based on our first review of treating 305 cases with D&C only or in combination with other means as a "first line" or a backup, therapy had a mean complication rate of about 62 % (range, 29–86 %) [4]. The main complication was unanticipated bleeding, forcing an emergency second or third-line treatment that, almost always, was surgical. At times, hysterectomy became necessary. This option requires general anesthesia.

There were some changes between the results of the two reviews. If D&C was used as a sole treatment, in 69 cases 24 (34.7 %) resulted in complication as opposed to first line or secondary treatment combined with other treatments. Only 52 of 413 (12.2 %) had complications. If UAE was combined with systemic MTX it caused 35 % complications, while combined with other means (e.g., suction evacuation or hysteroscopic excision among others), the rate was only 11.3 %.

As opposed to a spontaneous delivery or spontaneous abortion, where the uterine myometrial grid constricts the bleeding after placental separation, in CSP, the sharp curettage exposes vessels of the gestational sac leading to severe and sometimes unstoppable bleeding since there is less or no adequate muscle grid to contain the bleeding. A sharp curettage might injure the thin myometrium leading to bleeding or even perforation.

If D&C or suction aspiration is still the preferred treatment, blood and blood products as well as a Foley balloon catheter should be readily available [31]. Foley balloon catheters were successfully used to stop and tamponade possible bleeding [32, 33]. Cali et al. [34] successfully used the following sequential treatment approach in eight of their patients. At admission to the hospital, the patient undergoes UAE and, after 5 days, a gentle suction aspiration under continuous, real-time ultrasound is performed by immediate insertion and inflation of a Foley balloon catheter for bleeding prevention and control [31].

A number of recent articles advocate the safe and uncomplicated use of blunt sac aspiration; however, all were followed or preceded by other treatment methods [35]. Interestingly, no complications were seen in 81 suction aspirations in our review of the cases between 2012 and 2014. This probably is attributed to its blunt, as opposed to a sharp curetting at the time of D&C, therefore, less prone to disrupt blood vessels.

Uterine Artery Embolization, Alone or in Combination

This treatment requires general anesthesia. If used as a primary and only treatment, the complication rate among the 64 cases described in the review of 751 cases of CSP was 47 %. It is difficult to evaluate the real complication rates, due to partial or incomplete data in the published articles. In another 78 cases, UAE was used in combination with other treatments. It seems that UAE is not the best first-line treatment, if administered alone as a single agent therapy, since it allows the pregnancy, with its vascularity, to grow and increase. For this reason, Cali et al. [34] delayed

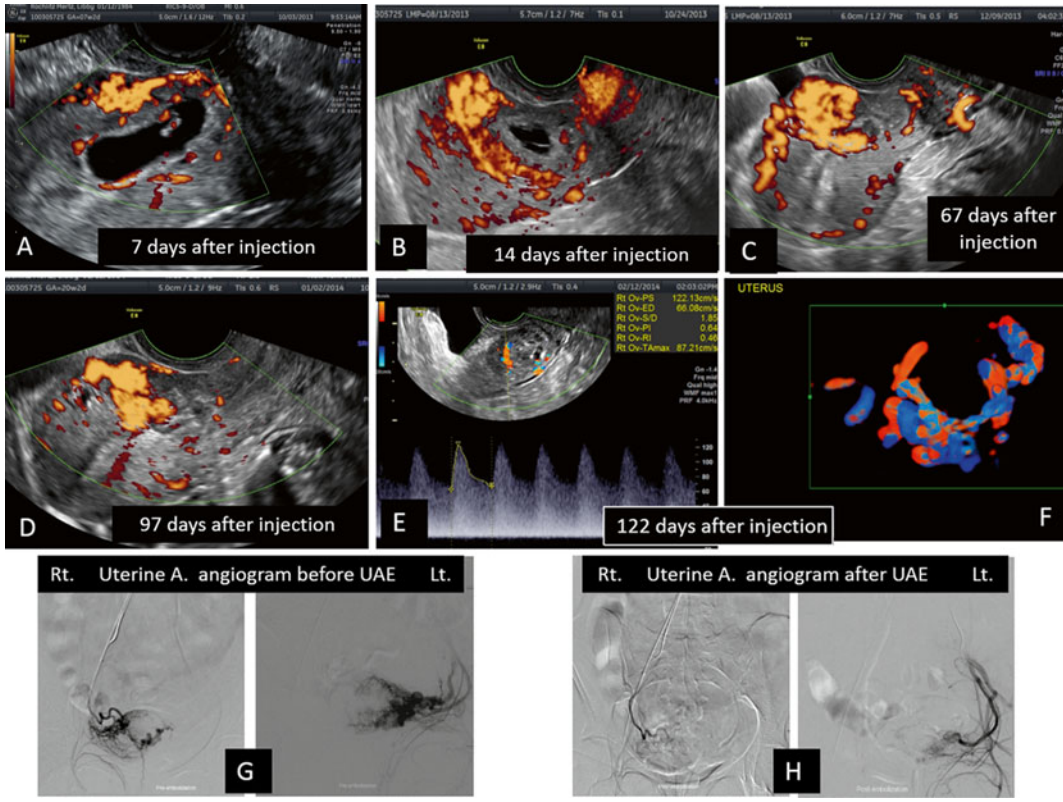

Fig. 17.11 Late development of an AVM after local intragestational injection of MTX injection with sonographic follow-up of the vascularization on days 7, 14, 67, 97, and 122 following the treatment (**a**–**f**). The patient refused an UAE after 4 weeks; however, the continuous vaginal spotting and slight bleeding finally led to the acceptance of the bilateral embolization of the uterine arteries, which was successful (**g**, **h**)

suction aspiration in their patients with CSP for 5 days after UAE. Uterine artery embolization works better combined with other noninvasive and invasive (suction aspiration) treatments [36–38]. In our 60 cases of CSP, UAE was used as a secondary treatment in four patients with persistent vaginal bleeding or developing AVM. Embolization failed to stop the bleeding in one of the patients with AVM, therefore, hysterectomy was performed [24].

If UAE fails, which may be the case, the clinician must contend with a larger gestation applying a secondary treatment. However, it is hard to evaluate its actual complication rates, since some articles have insufficient data to rely on. As stated previously, in our 60 cases of CSP, one of the patients required (and finally agreed to) AVM embolization to stop her continuing vaginal bleeding (as well as her high PSV on Doppler), 122 days after her initial local MTX injection (Fig. 17.11).

Updating this treatment approach with the review of 1223 patients published after 2012, UAE was used alone or in combination in 309 cases with a mean complication rate of 28 %, with its highest rate if combined with intra-arterial injection of MTX, at the time of the catheterization: 18 of 52 (34.6 %).

Excision by Hysteroscopy and/or Laparoscopy

Hysteroscopic and laparoscopic surgery require general anesthesia. The overall complication rate for 108 cases managed by hysteroscopy was

13.8 % [4]. However, no complications were noted if hysteroscopy was combined with transabdominal ultrasound guidance (nine cases were published). The rate of complications increased to 17 % if hysteroscopy was combined with mifepristone. In the hands of an experienced clinician, guided by transabdominal ultrasound, hysteroscopy may be a reasonable way of treatment for CSP [35, 39–45]. The use of an inflatable balloon catheter, after treatment with hysteroscopic excision, may prevent (or treat) possible bleeding from the operative site.

Laparoscopic surgery, alone or in combination, was used to excise the site of the scar pregnancy and repair the anterior uterine wall. Fifty four such cases were published up to 2012 in the reviewed literature, with complication rates between 20 and 30 % [4]. Since 2012, there were several other laparoscopically treated case reports [38, 46–50].

Robotic-assisted laparoscopic removal of CSP was also published [51]. We speculate that the complicated, time consuming and probably costly robotic surgery involving dedicated staff and its availability only in selected medical centers make the use of this operative approach to CSP questionable, since it can be replaced with several office based, simple and less involved treatments.

Methotrexate

One of the most frequently used therapies to treat CSP is undoubtedly methotrexate (MTX). Administered in single or multiple, successive doses, intramuscularly, injected locally into the gestational sac, as intravenous slow drip and finally injected into the umbilical artery at the time of a UAE. It was reported to be administered as a first line or a secondary or backup medication, as a single agent, and/or combined with any other conceivable treatment as an adjunct.

Systemic, "*first-line*," *single-dose MTX* is administered as an intramuscular, single injection. The usual protocols were 1 mg/kg of body weight or 50 mg/m^2 of body surface area. Its complication rate is 62.1 % due to a required second-line treatment, when the fetal heart beat fails to cease after several days [4]. Bodour et al. [52] challenged this result, which prompted a reevaluation of the reviewed material; however, after the more rigorous recounting of the cases, an even higher (66.1 %) complication rate was found [53].

The reason for this, we suspect, may be caused by its slow action and that the results may take days to be seen. We also suspect, that it may not be able to stop cardiac activity and placental invasion. During these several days (or entire week) the gestational sac, the embryo or fetus, and its vascularity continues to grow, forcing a secondary treatment that must be able to handle a larger gestation with more abundant vascularization. The slow action of systemic MTX treatment is echoed, among others, in the series of Yin et al. [54]. It is true that there are also proponents of the use of systemic MTX as a single agent; however, it is impossible to attribute the cessation of the heart activity to the effect of MTX, since at least 10 % of first-trimester intrauterine pregnancies undergo a spontaneous demise.

Based upon our recent review of 1223 cases of CSP, there were 236 cases in which MTX was administered as a single agent or in a combined fashion with other treatments, with a mean of 21.4 % complications. Methotrexate used alone (as single or multi-dose) lead to 38 % of the cases needing a secondary treatment [35, 55]. Combined with D&C (26 cases), another therapy with high complication rate, all needed a secondary treatment.

Systemic, *sequential*, *multidose use of MTX*. The injected amounts of MTX are similar to the dose for the single-dose regimen. However, two to three intramuscular injections (1 mg/kg of body weight or 50 mg/m^2 of surface area) are given at an interval of 2 or 3 days over the course of a week. In this case one should be aware of the cumulative, adverse effects of this drug on the liver and bone marrow, since the total amount is higher than in the single dose regimen. In fact, even multidose treatments have failed [56]. Some combine it with different doses of leucovorin, which protects against unwanted and adverse

systemic effects (termed "rescue" regimen). Several articles expressed their authors' confidence in support of systemic multidose MTX treatment [57].

It is difficult to assess the complication rate associated with the above approach because it was often used in conjunction with, or after "first-line" or even after "secondary" treatments [54]. It is clear that MTX can successfully be applied as an adjunct and combined with other mostly nonsurgical treatments. The drawback of both treatments is the long waiting time to observe their effect. If they fail to stop the heart and quickly lower the levels of hCG, a secondary treatment has to deal with a larger gestation and vascular supply.

Intra-arterial or intravenous MTX treatment. Adopted and used in China—a total of 193 patients were treated using intravenous or intra-arterial administration of MTX solution. The intra-arterial route is used at the time of UAE. Most intravascular treatments were combined with other methods such as suction aspiration laparoscopy, hysteroscopy and D&C. Li C et al. [58] treated 33 patients with CSP out of 13 patients treated with intravenous MTX. Three of the 13 required hysterectomy for profuse bleeding. Zhang Y et al. [59] has a series of 96 patients of which 33 had intravenous MTX treatment. Since most patients, however, were treated in combination with other methods, their outcome is unclear from the English abstract. Another method is to infuse MTX solution into the uterine artery at the time of UAE. An et al. [60] treated 22 patients with UAE and intra-arterial MTX infusion: 6 patients had severe hemorrhage, 12 had abdominal pain and 4 hysterectomies were necessary. As opposed to this Lan et al. [61] successfully used 50 mg MTX infused into the uterine artery at the time of UAE in 79 patients.

Excision by Hysteroscopic Guidance Alone or in Combination

In our first review [4], hysteroscopic excision was used alone or with other treatments in 113 cases, with a mean complication rate of 18.4 %, which is reasonably low in comparison to other treatment methods. General anesthesia is required for the procedure.

In the literature published after 2012, we found 63 cases managed by this method alone or combined, usually, with laparoscopy [46, 59, 62–65].

Excision by Laparoscopic Guidance

Mostly used as the sole, standalone treatment, since it provides a final solution removing the gestational sac and the tiny placenta. General anesthesia is required. Fifteen of the 49 cases (30.6 %) described in the literature published before 2013 involved complications, as opposed to the 94 cases published in or after 2012 [35, 38, 46, 47, 49, 50, 64, 65], which experienced only 7.7 % in complications when hysteroscopy and laparoscopy were combined. The small numbers may not allow meaningful evaluation of the latter two approaches.

Excision by Laparotomy

Only a handful of articles were published, about 15 patients undergoing excision of the gestational sac using this, relatively involved, surgery procedure, which is usually performed under general anesthesia [46, 65–67]. At times, elective laparotomy was the treatment of choice to perform hysterectomy or it was used as a solution to treat bleeding complications [60, 68–71]. Figure 17.12a depicts the closed suture line after the excision of a CSP while Fig. 17.12b shows the local results after 1 year.

Transvaginal Surgical Excision

Requires a skilled surgeon and used electively in 119 patients with a relatively low (mean 9.7 %) complication rate [72–75]. Li et al. [35] described this surgical approach, which elevates the bladder, excising the gestational sac after curetting and, finally, suturing the area. They managed

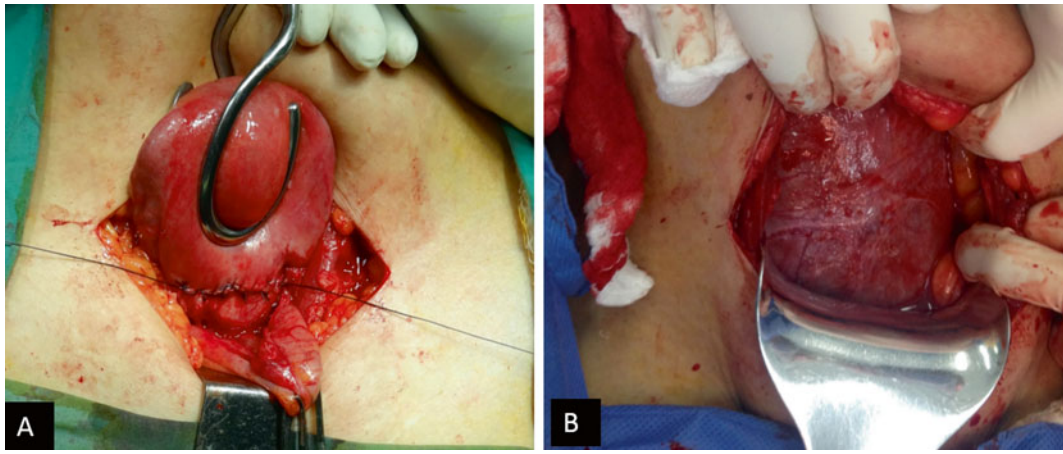

Fig. 17.12 Excision of a CSP sac and the resulting repair (**a**) as well as a follow-up picture 1 year after a previously performed excision and repair (**b**). Courtesy of Dr. Jose Palacios Jaraquemada, Argentina

49 cases, reporting that, despite 18 % minor complications, the procedure is easy and safe. Three patients had intrauterine pregnancies at 6 and 12 months postoperatively. One patient had a recurrent CSP and repeat transvaginal surgical excision. Another patient had an intrauterine pregnancy 5 months postoperatively, however, D&C was performed to prevent uterine rupture.

Intragestational-Sac Injection of Methotrexate or Potassium Chloride, with Continuous, Real-Time Ultrasound Guidance

No anesthesia required. This approach (Fig. 17.13) had the fewest and least-involved complications. In certain cases we completed the local injection by an immediate placement of a Foley balloon catheter that, after inflation with several ml of saline solution, can be kept in place for several days to prevent vaginal bleeding (Fig. 17.14a–f). Of the 83 cases, only 9 (10.8 %) involved complications. Cases performed with transabdominal sonography guidance had a slightly higher complication rate (15 %) than those using TVS guidance. Since 2012 several authors used this simple treatment in 53 patients.

Since the publication of our review, a handful of articles reported on the successful use of the local, intragestational sac injection of ethanol [64], MTX [56, 76–79] and KCl [55] in a total of 53 patients with a complication rate of 5.8 %. Yin et al. [54] treated 20 of 34 patients with CSP by local, transvaginal ultrasound-guided intragestational sac injection of MTX, without complications. Yamaguchi et al. [79] treated eight CSP cases, using intragestational injection of MTX, guided by TVS. Two of the patients needed additional local or systemic MTX injection. The time to the hCG normalization was a mean of 78.5 days (range, 42–166 days). Four of the five patients went on and had pregnancies after the treatment and had uneventful parturition, however, another CSP was diagnosed in one patient. Pang et al. [77] successfully treated three patients with local, intragestational MTX injection. Some providers prefer the use of KCl for all their local injections in all types of ectopic pregnancies including CSP [80]. KCl is exclusively used to inject heterotopic pregnancies to enable the normal development of the intrauterine gestation.

Local, intragestational sac injections render *final solution* by stopping the heart activity and it appears to be the most effective and simple intervention for first-trimester CSP between 6 and 8–9 weeks and can be performed by TAS or TVS guidance. This treatment may be even more relevant for patients desiring future fertility.

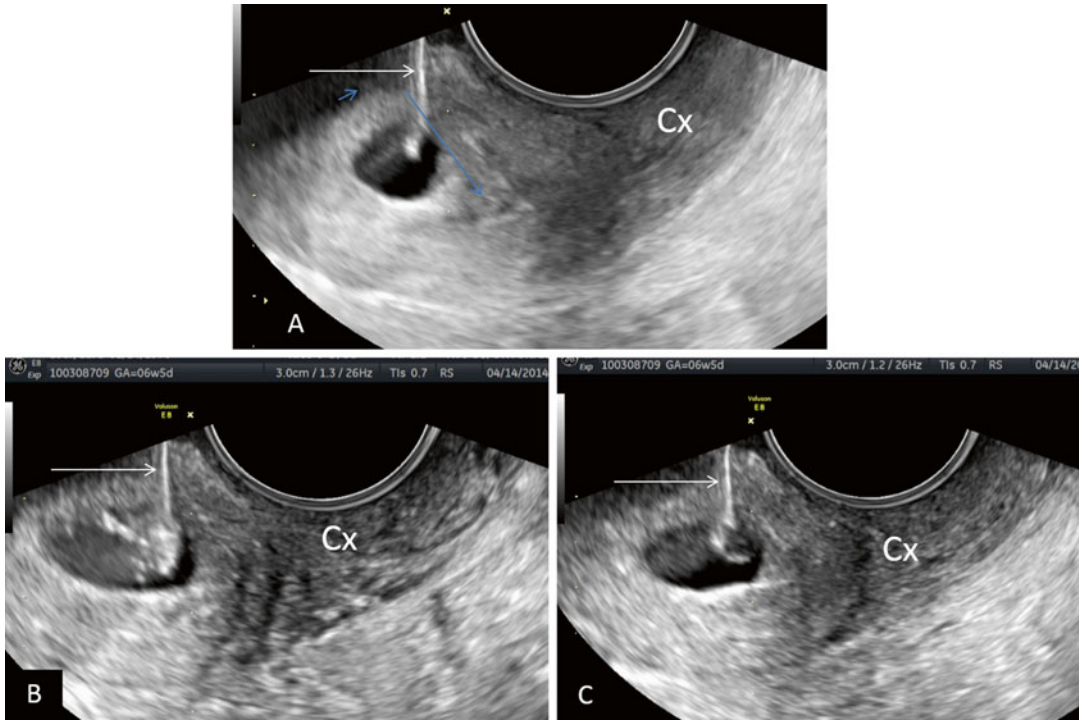

Fig. 17.13 Transvaginal ultrasound guided transvaginal, local injection of a CSP. The needle approach into the chorionic sac (**a**), insertion into the embryo (**b**) and targeting the yolk sac (**c**) trying to damage it with a rotation of the needle

Shirodkar Suture in the Treatment of CSP

Used by Jurkovic et al. [81], during the evacuation of a cesarean scar pregnancy, it is an effective method for securing hemostasis. In their view, it minimized the need for blood transfusion and ensured preservation of fertility.

Foley Balloon Catheters as an Adjuvant to Other Treatments to Prevent/Control Bleeding

A creative and, relatively new, approach to the treatment is inserting a Foley balloon catheter that is inflated at the site of the CSP, alike the Bakri balloon in cases of obstetrical hemorrhage [32, 82–84]. We used this approach as an adjuvant to treatments of CSP [31]. Even so, this approach is almost always used in a planned fashion, in conjunction with another treatment or as backup, if bleeding occurs (Fig. 17.15a–h). Catheters may be kept in place for as long as 3–4 days, according to the individual case, provided antibiotic coverage is prescribed. As stated above, this approach is almost always used in a preplanned case of a patient who restarted bleeding 23 days after local injection of MTX, with a relatively large gestation of 9 weeks 3 days. Inflating the balloon to 20 ml controlled bleeding (Fig. 17.16).

Recurrent CSP

Patients treated in the first trimester for CSP, should be informed that such a gestation may not happen again in a future pregnancy since the risk is about 1 % for reoccurrence. In the literature

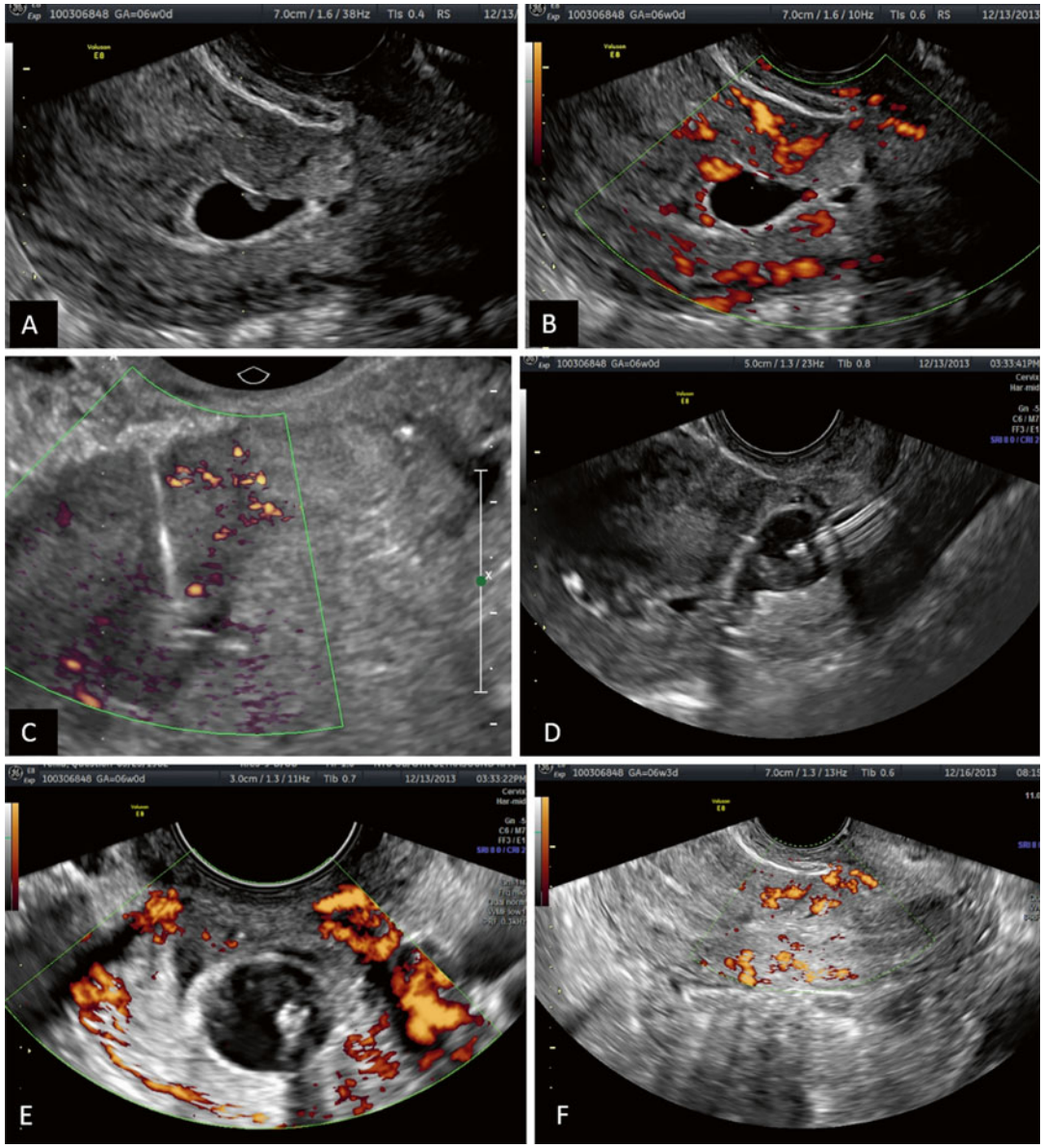

Fig. 17.14 Sequential images of treating a 5–6 week live CSP using local injection followed by insertion of a Foley balloon. (**a**) Sagittal image showing the gestational sac in an anterverted/anteflexed uterus. (**b**) The vascularization is evident. (**c**) The needle was inserted under transvaginal ultrasound guidance and MTX was injected. (**d**) The inflated balloon in situ creating pressure on the surrounding tissues. (**e**) Transverse image of the inflated balloon with barely detectable blood vessels. (**f**) The area 3 days later after removal of the balloon. Minimal vascularity was seen and the minimal vaginal bleeding stopped after 1 week

Fig. 17.15 (continued) MTX would suffice as treatment. (**b**) At 5 weeks 4 days embryonic heart beats were seen. (**c**) A transverse section demonstrates the anterior placenta with its vessels between the sac and the bladder. (**d**) 3D Doppler angiography clearly shows the rich vascular web below the bladder. (**e**, **f**) After local, intragestational injection of MTX a Foley balloon was inserted. The compressed sac is seen. (**g**, **h**) Two hours after balloon insertion diminished blood flow was observed around the sac by Doppler interrogation

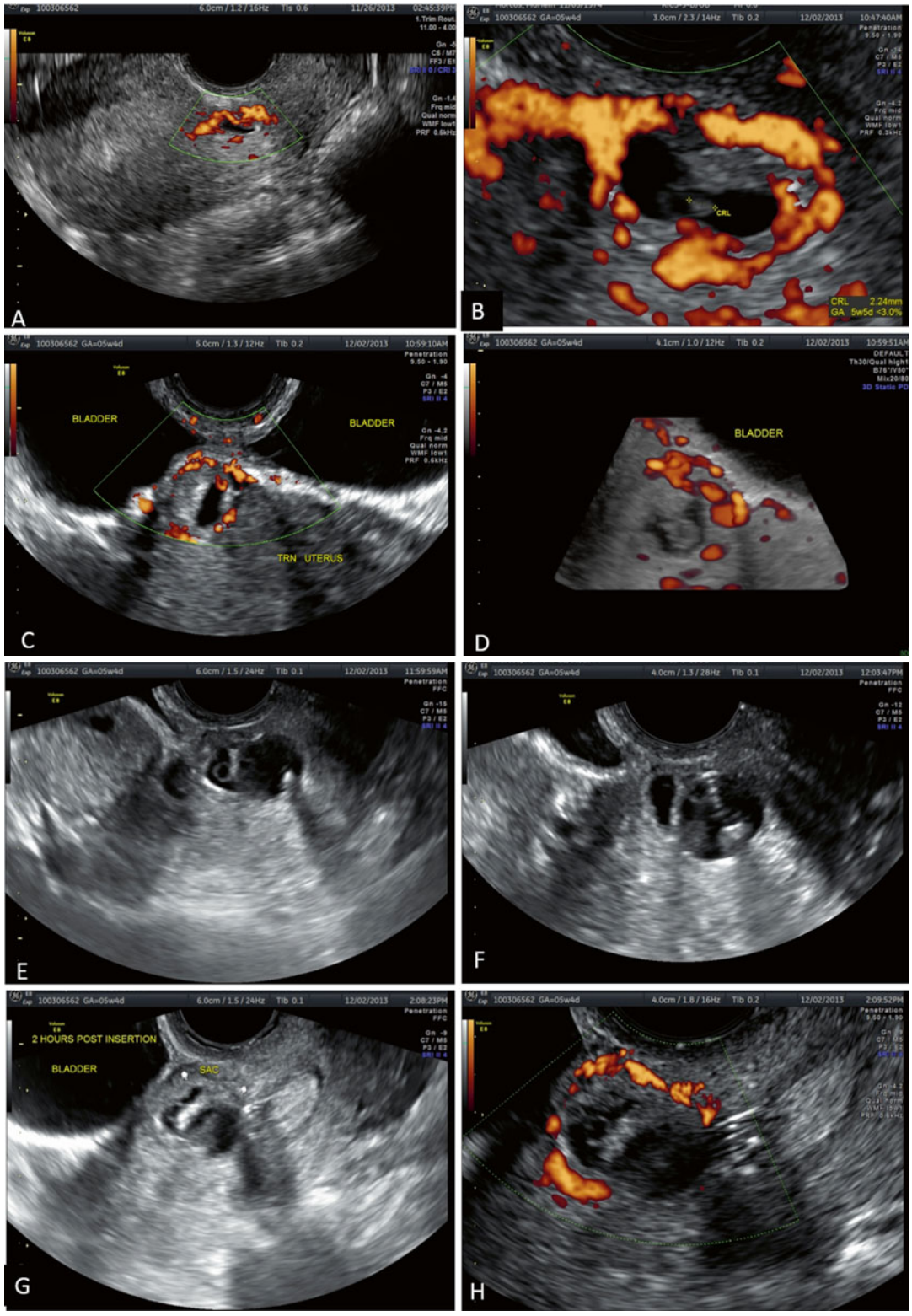

Fig. 17.15 Sequential, pictorial demonstration of the treatment of a 4 week 5 day CSP and use of a Foley balloon catheter. (**a**) The sagittal, power Doppler image at 4 weeks 5 days. The patient selected to wait if systemic

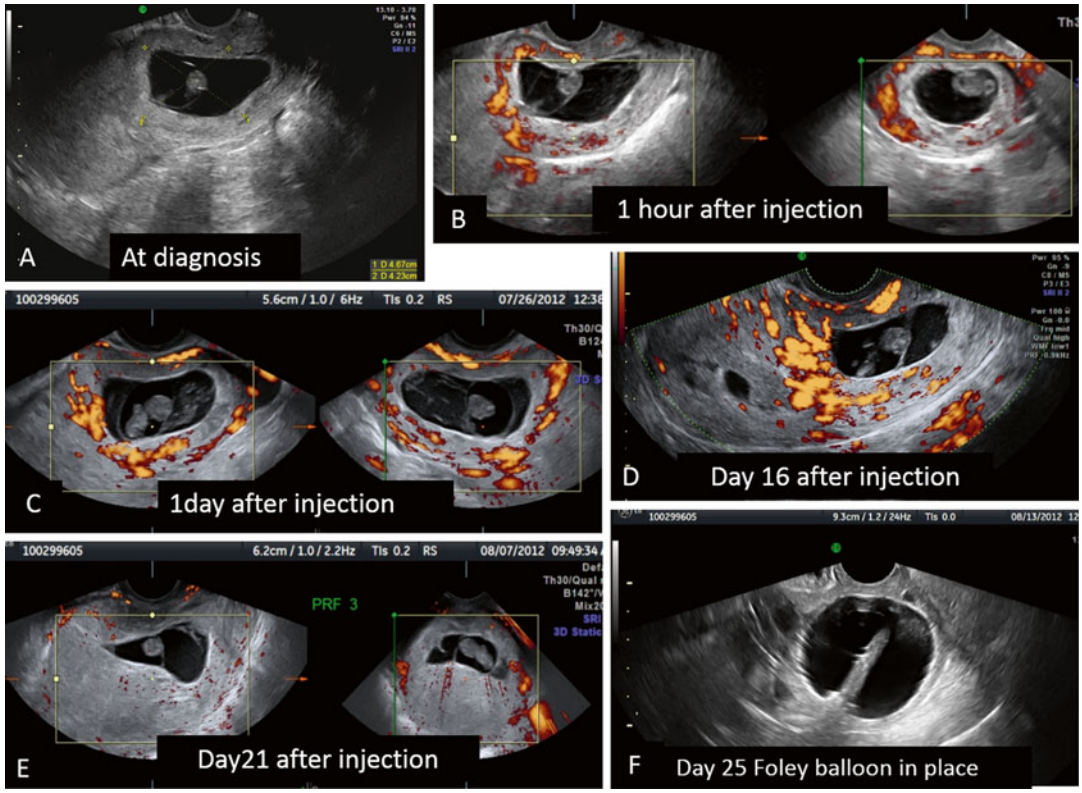

Fig. 17.16 The use of Foley balloon catheter in a patient with a relatively advanced CSP of 9+ weeks with a gestational sac of 4.4×4.3 cm treated by local intragestational injection of MTX and who started to bleed late, 25 days after treatment. (**a**–**e**) Sequential power Doppler ultrasound images from diagnosis and immediately after the local injection of MTX stopping the heart beats and throughout days 1, 16 and 21 after treatment. No vaginal bleeding was reported, however, no real decrease of the sac size occurred and the small embryo was still visible in the sac. (**f**) On day 25 after the initial treatment vaginal bleeding occurred, which was successfully treated by insertion of a Foley balloon catheter and inflated to about 4 cm diameter by about 20

reviewed through 2012, seven recurrent cases of CSP were described [4]. Gupta et al. [12] provided an additional case, with a patient who had four consecutive CSPs within 2 years. Please note, this patient became pregnant with the fifth CSP, decided to continue the pregnancy, and at the time of this writing, is 16 weeks pregnant.

Multifetal CSP

Rare but possible, two gestational sacs with two embryos can be present as a twin CSP (Fig. 17.17). There was also a triplet CSP published. Their treatment, so far, was to terminate the pregnancies.

Heterotopic CSP

Several heterotopic pregnancies were reported. In these cases the intrauterine pregnancy can result in live offspring (Fig. 17.18). Several articles reported heterotopic IUP and CSP. The best review, however, containing detailed information is by Ugurlucan et al. [85]. Heterotopic CSP after CS may occur especially when a pregnancy follows assisted reproductive technology. These pregnancies are usually managed by selective injection of the scar pregnancy by local intragestational injection of KCl and laparoscopic excision [86, 87]. Fortunately, most intrauterine pregnancies can be preserved after treatment.

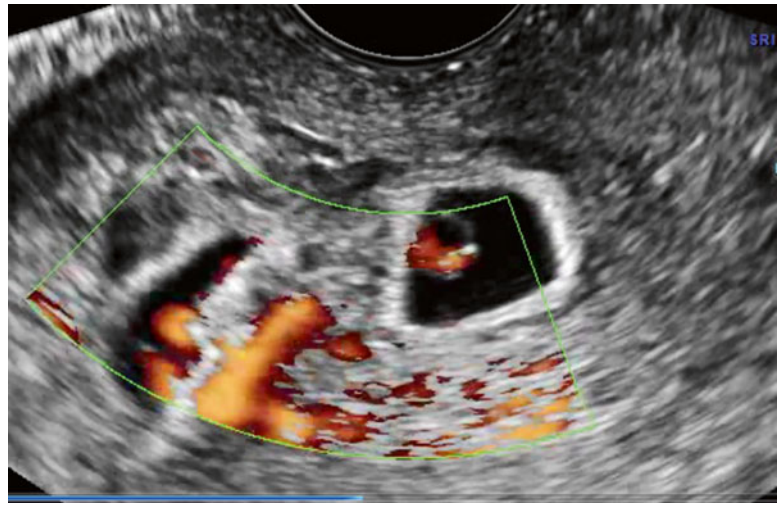

Fig. 17.17 Twin CSP in the scar with active heart activity in this 5 week 5 day pregnancy. Local, intragestational MTX was performed using one single needle insertion slightly adjusting the needle direction to reach both sacs

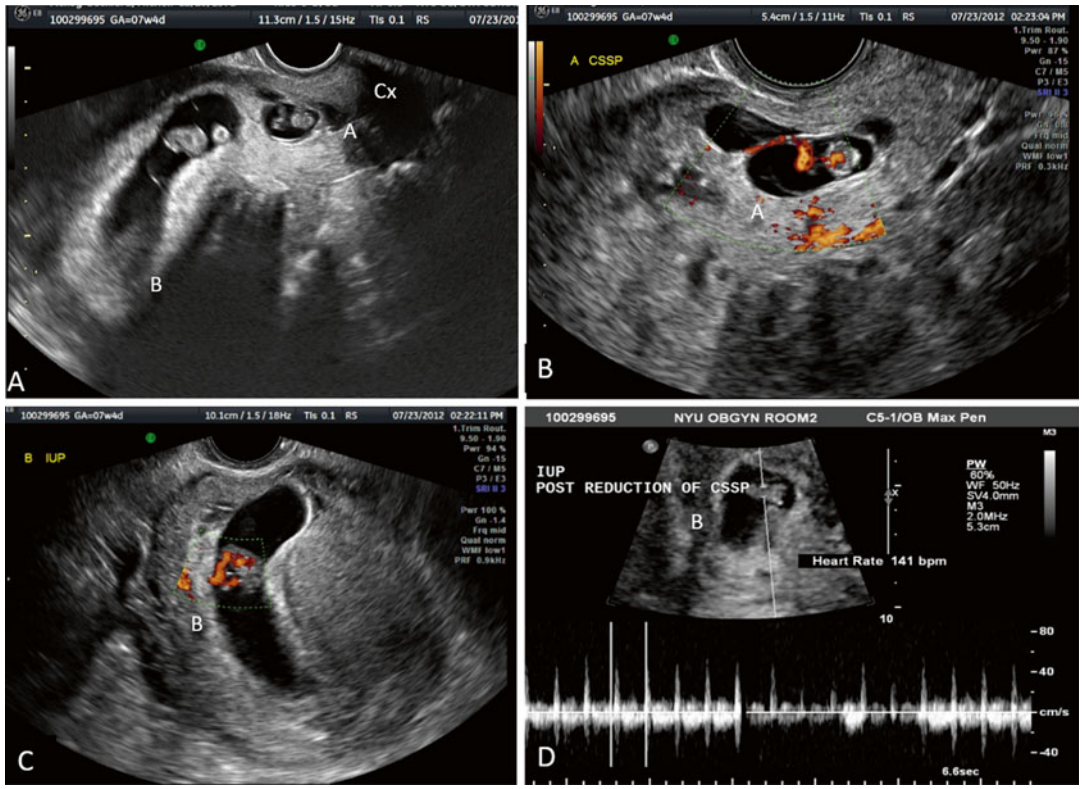

Fig. 17.18 Heterotopic CSP and IUP at 7 weeks and 4 days. (**a**) Panoramic, sagittal view of the two sacs. Both embryos were alive. The intrauterine sac (*B*) is filling the available space in the uterine cavity (*Cx* cervix). (**b**) Image of the embryo (*A*) in the lower anterior sac. (**c**) Image of the intrauterine embryo (*B*) in the upper sac. (**d**) Proof of the heart beats of the intrauterine embryo moments after the injection of the scar pregnancy. The patient delivered at term a healthy neonate

Summary

Cesarean scar pregnancy is *not* an ectopic pregnancy by definition. Contrary to *real* ectopic pregnancies, the CSP is in the uterine cavity and if not terminated (based upon the recently available literature) can result in a live offspring. CSP is a relatively rare but dangerous and complicated-ridden clinical entity, closely related to a consequence of CDs.

The best diagnostic tool for its detection, and at times for treatment, is transvaginal sonography. In addition transabdominal and color Doppler ultrasound provide satisfactory diagnostic information. The main differential diagnostic entities of a CSP are cervical pregnancy and a miscarriage in progress. Patients with CSP should be counseled based upon new, peer-reviewed evidence published in the latest literature. In addition, patients must be informed of the possible second- and third-trimester complications.

There is mounting evidence that every patient with previous CD should be screened for CSP, as soon as possible. Also, there has been evidence of first-trimester MAP. CSP and MAP share the same histologic picture, as CSP is a precursor of MAP. Most patients with a CSP diagnosed in the first trimester will by the third trimester have MAP. And almost all repeat CD will have hysterectomy.

There is no single best treatment approach to terminate CSP with positive heart activity. Therefore, the procedure with the least complications should be considered and performed without delay. Single-dose systemic MTX injection is a lengthy and usually ineffective first line therapy, delaying the final treatment. MTX, however, as an adjuvant to other treatments has a proven efficacy. Ultrasound guided local, intragestational sac injection of MTX/KCl is simple and has low complication rates. Sharp curetting of the CSP site can cause severe bleeding. Uterine artery embolization alone is less effective as a single, first line treatment but has proven useful as an adjunct to other therapies and in cases of emergency due to sustained vaginal bleeding. Insertion and inflation of a Foley balloon catheter is effective to prevent or treat bleeding from the site of a CSP, following local injection or endoscopic treatment of CSP. Attention should be given to the possibility of recurrent multifetal and heterotopic CSP.

Teaching Points

- Diagnose a cesarean scar pregnancy by the diagnostic criteria and differentiate it from cervical pregnancy and/or a spontaneous abortion.
- Realize that there is a common histologic basis of cesarean scar pregnancy and morbidly adherent placenta (accreta, increta and percreta).
- Construct a counseling and a management plan for the CSP taking into consideration patients' obstetrical goals and evidence based management.

References

1. Spong CY, Berghella V, Wenstrom KD, Mercer BM, Saade GR. Preventing the first cesarean delivery: summary of a joint Eunice Kennedy Shriver National Institute of Child Health and Human Development, Society for Maternal-Fetal Medicine, and American College of Obstetricians and Gynecologists Workshop. Obstet Gynecol. 2012;120(5):1181–93.
2. Hamilton BE, Hoyert DL, Martin JA, Strobino DM, Guyer B. Annual summary of vital statistics: 2010-2011. Pediatrics. 2013;131(3):548–58.
3. Arnold J. World Cesarean Rates: OECD Countries 2012. Available from: http://www.cesareanrates.com/blog/2012/12/8/world-cesarean-rates-oecd-countries.html
4. Timor-Tritsch IE, Monteagudo A. Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. Am J Obstet Gynecol. 2012;207(1):14–29.
5. Monteagudo A, Carreno C, Timor-Tritsch IE. Saline infusion sonohysterography in nonpregnant women with previous cesarean delivery: the "niche" in the scar. J Ultrasound Med. 2001;20(10):1105–15.
6. Bij de Vaate AJ, van der Voet LF, Naji O, Witmer M, Veersema S, Brolmann HA, et al. Prevalence, potential risk factors for development and symptoms related to the presence of uterine niches following Cesarean section: systematic review. Ultrasound Obstet Gynecol. 2014;43(4):372–82.
7. Jauniaux E, Jurkovic D. Placenta accreta: pathogenesis of a 20th century iatrogenic uterine disease. Placenta. 2012;33(4):244–51.

8. Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. Cesarean scar pregnancy. Ultrasound Obstet Gynecol. 2003;21(3):310.
9. Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. First-trimester diagnosis and management of pregnancies implanted into the lower uterine segment Cesarean section scar. Ultrasound Obstet Gynecol. 2003;21(3):220–7.
10. Rotas MA, Haberman S, Levgur M. Cesarean scar ectopic pregnancies: etiology, diagnosis, and management. Obstet Gynecol. 2006;107(6):1373–81.
11. Seow KM, Hwang JL, Tsai YL, Huang LW, Lin YH, Hsieh BC. Subsequent pregnancy outcome after conservative treatment of a previous cesarean scar pregnancy. Acta Obstet Gynecol Scand. 2004;83(12):1167–72.
12. Gupta S, Pineda G, Rubin S, Timor-Tritsch IE. Four consecutive recurrent cesarean scar pregnancies in a single patient. J Ultrasound Med. 2013;32(10):1878–80.
13. Norwitz ER. Defective implantation and placentation: laying the blueprint for pregnancy complications. Reprod Biomed Online. 2006;13(4):591–9.
14. Rosen T. Placenta accreta and cesarean scar pregnancy: overlooked costs of the rising cesarean section rate. Clin Perinatol. 2008;35(3):519–29. 3.
15. Kliman HJ, Feinberg RF, Haimowitz JE. Human trophoblast-endometrial interactions in an in vitro suspension culture system. Placenta. 1990;11(4): 349–67.
16. Stirnemann JJ, Chalouhi GE, Forner S, Saidji Y, Salomon LJ, Bernard JP, et al. First-trimester uterine scar assessment by transvaginal ultrasound. Am J Obstet Gynecol. 2011;205(6):551.e1–6.
17. Stirnemann JJ, Mousty E, Chalouhi G, Salomon LJ, Bernard JP, Ville Y. Screening for placenta accreta at 11-14 weeks of gestation. Am J Obstet Gynecol. 2011;205(6):547.e1–6.
18. Godin PA, Bassil S, Donnez J. An ectopic pregnancy developing in a previous caesarian section scar. Fertil Steril. 1997;67(2):398–400.
19. Vial Y, Petignat P, Hohlfeld P. Pregnancy in a cesarean scar. Ultrasound Obstet Gynecol. 2000;16(6):592–3.
20. Seow KM, Hwang JL, Tsai YL. Ultrasound diagnosis of a pregnancy in a Cesarean section scar. Ultrasound Obstet Gynecol. 2001;18(5):547–9.
21. Timor-Tritsch IE, Monteagudo A, Santos R, Tsymbal T, Pineda G, Arslan AA. The diagnosis, treatment, and follow-up of cesarean scar pregnancy. Am J Obstet Gynecol. 2012;207(1):44.e1–e13.
22. Timmerman D, Wauters J, Van Calenbergh S, Van Schoubroeck D, Maleux G, Van Den Bosch T, et al. Color Doppler imaging is a valuable tool for the diagnosis and management of uterine vascular malformations. Ultrasound Obstet Gynecol. 2003;21(6):570–7.
23. Polat P, Suma S, Kantarcy M, Alper F, Levent A. Color Doppler US in the evaluation of uterine vascular abnormalities. Radiographics. 2002;22(1):47–53.
24. Timor-Tritsch IE, Khatib N, Monteagudo A, Ramos J, Berg R, Kovacs S. Cesarean scar pregnancy (csp): experience of sixty cases. J Ultrasound Med. 2015;34(4):601–10.
25. Comstock CH, Lee W, Vettraino IM, Bronsteen RA. The early sonographic appearance of placenta accreta. J Ultrasound Med. 2003;22(1):19–23. quiz 4-6.
26. Rac M, Moschos E, Wells E, McIntire DD, Dashe JS, Twickler DM. Ultrasound (US) findings of placenta accreta in the first trimester. Ultrasound Obstet Gynecol. 2014;44 Suppl 1:62–180.
27. Ballas J, Pretorius D, Hull AD, Resnik R, Ramos GA. Identifying sonographic markers for placenta accreta in the first trimester. J Ultrasound Med. 2012;31(11):1835–41.
28. Sinha P, Mishra M. Caesarean scar pregnancy: a precursor of placenta percreta/accreta. J Obstet Gynaecol. 2012;32(7):621–3.
29. Timor-Tritsch IE, Monteagudo A, Cali G, Palacios-Jaraquemada JM, Maymon R, Arslan AA, et al. Cesarean scar pregnancy and early placenta accreta share common histology. Ultrasound Obstet Gynecol. 2014;43(4):383–95.
30. Timor-Tritsch IE, Monteagudo A, Cali G, Vintzileos A, Viscarello R, Al-Khan A, et al. Cesarean scar pregnancy is a precursor of morbidly adherent placenta. Ultrasound Obstet Gynecol. 2014;44(3):346–53.
31. Timor-Tritsch IE, Cali G, Monteagudo A, Khatib N, Berg R, Forlani F, et al. Foley balloon catheter to prevent or manage bleeding during treatment for cervical and cesarean scar pregnancy. Ultrasound in Obstet Gynecol 2015;46(1):118–23.
32. Jiang T, Liu G, Huang L, Ma H, Zhang S. Methotrexate therapy followed by suction curettage followed by Foley tamponade for caesarean scar pregnancy. Eur J Obstet Gynecol Reprod Biol. 2011;156(2):209–11.
33. Yu XL, Zhang N, Zuo WL. Cesarean scar pregnancy: an analysis of 100 cases. Zhonghua Yi Xue Za Zhi. 2011;91(45):3186–9.
34. Cali G, Giambanco L, Puccio G, Forlani F. Morbidly adherent placenta: evaluation of ultrasound diagnostic criteria and differentiation of placenta accreta from percreta. Ultrasound Obstet Gynecol. 2013;41(4):406–12.
35. Li JB, Kong LZ, Fan L, Fu J, Chen SQ, Yao SZ. Transvaginal surgical management of cesarean scar pregnancy: analysis of 49 cases from one tertiary care center. Eur J Obstet Gynecol Reprod Biol. 2014;182C:102–6.
36. Cao S, Zhu L, Jin L, Gao J, Chen C. Uterine artery embolization in cesarean scar pregnancy: safe and effective intervention. Chin Med J (Engl). 2014;127(12):2322–6.
37. Gao L, Huang Z, Gao J, Mai H, Zhang Y, Wang X. Uterine artery embolization followed by dilation and curettage within 24 hours compared with systemic methotrexate for cesarean scar pregnancy. Int J Gynaecol Obstet. 2014;127(2):147–51.
38. Wu X, Xue X, Wu X, Lin R, Yuan Y, Wang Q, et al. Combined laparoscopy and hysteroscopy vs. uterine curettage in the uterine artery embolization-based management of cesarean scar pregnancy: a cohort study. Int J Clin Exp Med. 2014;7(9):2793–803.

39. Chang Y, Kay N, Chen YH, Chen HS, Tsai EM. Resectoscopic treatment of ectopic pregnancy in previous cesarean delivery scar defect with vasopressin injection. Fertil Steril. 2011;96(2):e80–2.
40. Chao A, Wang TH, Wang CJ, Lee CL, Chao AS. Hysteroscopic management of cesarean scar pregnancy after unsuccessful methotrexate treatment. J Minim Invasive Gynecol. 2005;12(4):374–6.
41. Chen ZY, Zhang XM, Xu H, Zhang J, Huang XF. Management of cesarean scar pregnancy by hysteroscopy combined with uterine artery embolism. Zhonghua Fu Chan Ke Za Zhi. 2011;46(8):591–4.
42. Deans R, Abbott J. Hysteroscopic management of cesarean scar ectopic pregnancy. Fertil Steril. 2010;93(6):1735–40.
43. Gubbini G, Centini G, Nascetti D, Marra E, Moncini I, Bruni L, et al. Surgical hysteroscopic treatment of cesarean-induced isthmocele in restoring fertility: prospective study. J Minim Invasive Gynecol. 2011;18(2):234–7.
44. Ozkan S, Caliskan E, Ozeren S, Corakci A, Cakiroglu Y, Coskun E. Three-dimensional ultrasonographic diagnosis and hysteroscopic management of a viable cesarean scar ectopic pregnancy. J Obstet Gynaecol Res. 2007;33(6):873–7.
45. Robinson JK, Dayal MB, Gindoff P, Frankfurter D. A novel surgical treatment for cesarean scar pregnancy: laparoscopically assisted operative hysteroscopy. Fertil Steril. 2009;92(4):1497.e13–6.
46. Wang G, Liu X, Bi F, Yin L, Sa R, Wang D, et al. Evaluation of the efficacy of laparoscopic resection for the management of exogenous cesarean scar pregnancy. Fertil Steril. 2014;101(5):1501–7.
47. He Y, Wu X, Zhu Q, Wu X, Feng L, Wu X, et al. Combined laparoscopy and hysteroscopy vs. uterine curettage in the uterine artery embolization-based management of cesarean scar pregnancy: a retrospective cohort study. BMC Womens Health. 2014;14:116.
48. Hudecek R, Ivanova Z, Smerdova M, Pankova S, Krajcovicova R. Effect of GnRH analogues pretreatment on myomectomy outcomes in reproductive age women. Ceska Gynekol. 2012;77(2):109–17.
49. Jiang S, Zhao S. Laparoscopic surgery for ectopic pregnancy within a cesarean scar. Clin Exp Obstet Gynecol. 2013;40(3):440–4.
50. Wang YL, Weng SS, Huang WC, Su TH. Laparoscopic management of ectopic pregnancies in unusual locations. Taiwan J Obstet Gynecol. 2014;53(4):466–70.
51. Siedhoff MT, Schiff LD, Moulder JK, Toubia T, Ivester T. Robotic-assisted laparoscopic removal of cesarean scar ectopic and hysterotomy revision. Am J Obstet Gynecol. 2015;212:681.e1.
52. Bodur S, Gun I, Guido R. What is the role of primary methotrexate treatment in scar ectopic pregnancy? Am J Obstet Gynecol. 2014;210(4):379–80.
53. Timor-Tritsch I, Monteagudo A. Correction: unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review. Am J Obstet Gynecol. 2014;210(4):371–4.
54. Yin XH, Yang SZ, Wang ZQ, Jia HY, Shi M. Injection of MTX for the treatment of cesarean scar pregnancy: comparison between different methods. Int J Clin Exp Med. 2014;7(7):1867–72.
55. Uysal F, Uysal A. Spontaneous heterotopic cesarean scar pregnancy: conservative management by transvaginal sonographic guidance and successful pregnancy outcome. J Ultrasound Med. 2013;32(3):547–8.
56. Berhie SH, Molina RL, Davis MR, Anchan RM, Wang KC. Beware the scar: laparoscopic hysterectomy for 7-week cesarean delivery scar implantation pregnancy. Am J Obstet Gynecol. 2015;212:247.e1.
57. Kutuk MS, Uysal G, Dolanbay M, Ozgun MT. Successful medical treatment of cesarean scar ectopic pregnancies with systemic multidose methotrexate: single-center experience. J Obstet Gynaecol Res. 2014;40(6):1700–6.
58. Li C, Feng D, Jia C, Liu B, Zhan X. Transcatheter arterial chemoembolization versus systemic methotrexate for the management of cesarean scar pregnancy. Int J Gynaecol Obstet. 2011;113(3):178–82.
59. Zhang Y, Chen YS, Wang JJ, Lu ZY, Hua KQ. Analysis of 96 cases with cesarean scar pregnancy. Zhonghua Fu Chan Ke Za Zhi. 2010;45(9):664–8.
60. An X, Ming X, Li K, Wang J. The analysis of efficacy and failure factors of uterine artery methotrexate infusion and embolization in treatment of cesarean scar pregnancy. TheScientificWorldJournal. 2013;2013:213603.
61. Lan W, Hu D, Li Z, Wang L, Yang W, Hu S. Bilateral uterine artery chemoembolization combined with dilation and curettage for treatment of cesarean scar pregnancy: a method for preserving the uterus. J Obstet Gynaecol Res. 2013;39(6):1153–8.
62. Fylstra DL. Cervical pregnancy: 13 cases treated with suction curettage and balloon tamponade. Am J Obstet Gynecol. 2014;210(6):581.e1–5.
63. Mollo A, Alviggi C, Conforti A, Insabato L, De Placido G. Intact removal of spontaneous twin ectopic Caesarean scar pregnancy by office hysteroscopy: case report and literature review. Reprod Biomed Online. 2014;29(5):530–3.
64. Shao MJ, Hu MX, Xu XJ, Zhang L, Hu M. Management of caesarean scar pregnancies using an intrauterine or abdominal approach based on the myometrial thickness between the gestational mass and the bladder wall. Gynecol Obstet Invest. 2013;76(3):151–7.
65. Li Y, Xiang Y, Wan X, Feng F, Ren T. Clinical study on 39 cases with caesarean scar pregnancy with sonographic mass. Zhonghua Fu Chan Ke Za Zhi. 2014;49(1):10–3.
66. Abdelkader MA, Fouad R, Gebril AH, El Far MA, Elyassergi DF. Caesarean scar pregnancy: hysterotomy is rapid and safe management option. Arch Gynecol Obstet. 2014;290(2):381–3.
67. Kai K, Shimamoto K, Matsumoto H, Narahara H. Conservative surgical treatment for caesarean scar pregnancy. J Obstet Gynaecol. 2014;34(1):91–2.

68. Nankali A, Ataee M, Shahlazadeh H, Daeichin S. Surgical management of the cesarean scar ectopic pregnancy: a case report. Case Rep Obstet Gynecol. 2013;2013:525187.
69. Sorbi F, Sisti G, Pieralli A, Di Tommaso M, Livi L, Buccoliero AM, et al. Cervicoisthmic choriocarcinoma mimicking cesarean section scar ectopic pregnancy. J Res Med Sci. 2013;18(10):914–7.
70. Wozniak S, Pyra K, Kludka-Sternik M, Czuczwar P, Szkodziak P, Paszkowski T, et al. Uterine artery embolization using gelatin sponge particles performed due to massive vaginal bleeding caused by ectopic pregnancy within a cesarean scar: a case study. Ginekol Pol. 2013;84(11):966–9.
71. Zhang B, Jiang ZB, Huang MS, Guan SH, Zhu KS, Qian JS, et al. Uterine artery embolization combined with methotrexate in the treatment of cesarean scar pregnancy: results of a case series and review of the literature. J Vasc Interv Radiol. 2012;23(12):1582–8.
72. Shi J, Qin J, Wang W, Zhang H. Clinical study on 57 cases with caesarean scar pregnancy. Zhonghua Fu Chan Ke Za Zhi. 2014;49(1):18–21.
73. Wang DB, Chen YH, Zhang ZF, Chen P, Liu KR, Li Y, et al. Evaluation of the transvaginal resection of low-segment cesarean scar ectopic pregnancies. Fertil Steril. 2014;101(2):602–6.
74. Wang Z, Shan L, Xiong H. Transvaginal removal of ectopic pregnancy tissue and repair of uterine defect for cesarean scar pregnancy. Clin Exp Obstet Gynecol. 2013;40(4):546–7.
75. Le A, Shan L, Xiao T, Zhuo R, Xiong H, Wang Z. Transvaginal surgical treatment of cesarean scar ectopic pregnancy. Arch Gynecol Obstet. 2013;287(4):791–6.
76. Nguyen-Xuan HT, Lousquy R, Barranger E. Diagnosis, treatment, and follow-up of cesarean scar pregnancy. Gynecol Obstet Fertil. 2014;42(7-8):483–9.
77. Pang YP, Tan WC, Yong TT, Koh PK, Tan HK, Ho TH. Caesarean section scar pregnancy: a case series at a single tertiary centre. Singapore Med J. 2012;53(10):638–42.
78. Seow KM, Wang PH, Huang LW, Hwang JL. Transvaginal sono-guided aspiration of gestational sac concurrent with a local methotrexate injection for the treatment of unruptured cesarean scar pregnancy. Arch Gynecol Obstet. 2013;288(2):361–6.
79. Yamaguchi M, Honda R, Uchino K, Tashiro H, Ohba T, Katabuchi H. Transvaginal methotrexate injection for the treatment of cesarean scar pregnancy: efficacy and subsequent fecundity. J Minim Invasive Gynecol. 2014;21(5):877–83.
80. Doubilet PM, Benson CB, Frates MC, Ginsburg E. Sonographically guided minimally invasive treatment of unusual ectopic pregnancies. J Ultrasound Med. 2004;23(3):359–70.
81. Jurkovic D, Ben-Nagi J, Ofilli-Yebovi D, Sawyer E, Helmy S, Yazbek J. Efficacy of Shirodkar cervical suture in securing hemostasis following surgical evacuation of Cesarean scar ectopic pregnancy. Ultrasound Obstet Gynecol. 2007;30(1):95–100.
82. Atilgan R, Celik A, Boztosun A, Ilter E, Yalta T, Ozercan R. Evaluation of cervical cytological abnormalities in Turkish population. Indian J Pathol Microbiol. 2012;55(1):52–5.
83. Tsui KH, Lin LT, Yu KJ, Chen SF, Chang WH, Yu S, et al. Double-balloon cervical ripening catheter works well as an intrauterine balloon tamponade in post-abortion massive hemorrhage. Taiwan J Obstet Gynecol. 2012;51(3):426–9.
84. Shao HJ, Ma JT, Yang XE, Xu LP, Yang CL. Diagnosis and treatment of cesarean scar pregnancy. Zhonghua Yi Xue Za Zhi. 2010;90(37):2616–9.
85. Ugurlucan FG, Bastu E, Dogan M, Kalelioglu I, Alanya S, Has R. Management of cesarean heterotopic pregnancy with transvaginal ultrasound-guided potassium chloride injection and gestational sac aspiration, and review of the literature. J Minim Invasive Gynecol. 2012;19(5):671–3.
86. Demirel LC, Bodur H, Selam B, Lembet A, Ergin T. Laparoscopic management of heterotopic cesarean scar pregnancy with preservation of intrauterine gestation and delivery at term: case report. Fertil Steril. 2009;91(4):1293.e5–7.
87. Wang CJ, Tsai F, Chen C, Chao A. Hysteroscopic management of heterotopic cesarean scar pregnancy. Fertil Steril. 2010;94(4):1529.e15–8.