OBSTETRICS

# Unforeseen consequences of the increasing rate of cesarean deliveries: early placenta accreta and cesarean scar pregnancy. A review

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This review concentrates on 2 consequences of cesarean deliveries that may occur in a subsequent pregnancy. They are the pathologically adherent placenta and the cesarean scar pregnancy. We explored their clinical and diagnostic as well as therapeutic similarities. We reviewed the literature concerning the occurrence of early placenta accreta and cesarean section scar pregnancy. The review resulted in several conclusions: (1) the diagnosis of placenta accreta and cesarean scar pregnancy is difficult; (2) transvaginal ultrasound seems to be the best diagnostic tool to establish the diagnosis; (3) an early and correct diagnosis may prevent some of their complications; (4) curettage and systemic methotrexate therapy and embolization as single treatments should be avoided if possible; and (5) in the case of cesarean scar pregnancy, local methotrexate- and hysteroscopic-directed procedures had the lowest complication rates.

**Key words:** cesarean section pregnancy, early pregnancy, ectopic pregnancy in the cesarean section, pregnancy, ultrasound

The cesarean delivery (CD) rate in the United States was 31.8% in 2007.[1] It is predicted that this rate may have been surpassed in 2009.[2] In 1970, the CD rate was 5.5%; it increased to 24.7% in 1988 and showed a trend toward a lower rate of 20.7% in 1996.[3-5] Between 2002 and 2006, another increase was noted to reach the rate of 30.5%.[6] Thus, from 1996 to 2007, the CD rate rose 53%, the highest reported in the United States.[1] A need to reduce the increasing trend of CD was recognized as early as 1974.[4,7-13] This trend toward an increasing rate of CD was seen also in other countries.[10,14,15]

## Unexpected consequences of a cesarean delivery

The classical long-term effects of a CD such as uterine rupture, placenta previa, pathologically adherent placenta in a subsequent pregnancy, ectopic pregnancy, infertility, and intraabdominal adhesions among others were duly described in the literature and in many textbooks.

## Pathologically adherent placenta at the site of a cesarean section scar in a subsequent pregnancy

The incidence of pathologically adherent placentae (accreta-increta and percreta) increases with the increasing number of CDs.[16-18]

Placenta accreta (PA) (we will use this term to refer to all 3 forms of pathologically adherent placentae [eg, such as accreta, increta and percreta]) was rare between 1930 and 1950, with a frequency of 1 in 30,000 deliveries. However, this frequency rose to 1/19,000 between 1950 and 1960. By 1980, the rate increased to 1/7,000. A 4-fold increase in frequency was noted between 1994 and 2002. Several investigators cite the frequency of 1/2000 to 1/2500 deliveries.[18,19] Others estimate the frequency to be as high as 3/1000 deliveries occurring in the last decade.[17,20]

This drastic change in the number of patients with a potential PA fundamentally changed the diagnostic approach as well as the obstetric (surgical) management of this pregnancy complication. Early and reliable diagnosis of PA, knowledge of its natural history, and the realization of the fact that most are implanted in the scar of the previous CD are slowly focusing attention to its first-trimester complications.[21]

A detailed discussion of sonographic and clinical aspects surrounding placenta accreta in the second half of pregnancy is not the focus of this review because it is available in textbooks as well as review articles.[18,22-25] The first purpose of this article is to review the consequences of placenta accreta in the first and early second trimester of pregnancy with an emphasis on a possible spontaneous rupture of the uterus and/or profuse bleeding because of implantation in the pregnancy in the hysterotomy scar of a previous cesarean delivery. Even though in this review we discuss placenta accreta occurring in the first and early second trimester (inclusive of 14-16 weeks) to underline the importance of recognizing the threat of a severe complication of placenta accreta before the third trimester and/or delivery, we included a handful of articles[26-34] describing disastrous outcomes in midpregnancy. In these cases, the clinical picture and outcomes matched or were very similar to those occurring in the first and early second trimester.

## Cesarean section scar pregnancy

Another less well-known and less studied consequence of CD is the cesarean section scar pregnancy (CSP), which, by

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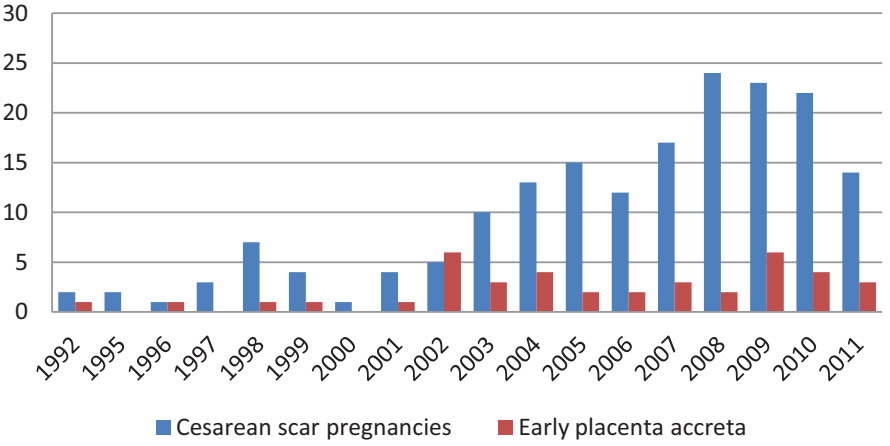
FIGURE 1
**Number of early placenta accreta and cesarean scar pregnancy articles based on their year of publication**

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definition, is not a classical ectopic pregnancy. The term CSP, scar pregnancy, or even the sporadically used term, isthmic pregnancy, refers to a gestational sac that has implanted in the scar or the niche of a previous cesarean delivery (Figure 1).

This serious consequence of the increasing rate of cesarean deliveries has consistently appeared in the literature in the last 10 years. CSP is fundamentally different from a cornual and tubal as well as a cervical pregnancy. Our second purpose of this article was to describe varying approaches in the diagnosis and management of the CSP along with its complications. We also provide support to demonstrate a possible link between the pathogenesis of PA and CSP.

Because the condition is relatively rare and has an unusually high complication rate, CSPs are likely to be published as single case reports or a case series containing few patients.

## Methodology of the review

To be able to draw practical clinical conclusions regarding the early placenta accreta (EPA) and CSP, an in-depth literature search was performed. We searched PubMed/Medline electronic databases for key words such as "pathologically adherent placenta," "placenta accreta," "placenta increta," "placenta percreta," "spontaneous uterine rupture," "first trimester," "second trimester," "cesarean scar pregnancy," "cesarean scar," "cesarean scar ectopic," "previous cesarean section scar," "first-trimester accreta," "scar implantation," "scar pregnancy," and "isthmic pregnancy." The articles obtained were cross-referenced by the "related articles" and "link" enabled by PubMed.

We also searched Embase, Web of Science, and BIOSIS and Scholar Google for additional search of the Internet. Additional references were also looked for in the respective reference lists of the citations cited in previous text. We reviewed original articles in English, French, German, Spanish, and Portuguese languages. In the case of other foreign languages (eg, Chinese, etc), we relied on the English abstract.

This review was focused not only on finding the possible causative and pathophysiologic link(s) between early placenta accreta and cesarean section scar pregnancy but also primarily on their clinical presentations, management approaches, and complications to provide the most focused answer.

The literature search yielded a total of 204 publications between 1972 and 2011. There were 49 articles related to early complications of PA and 176 articles dealing with CSP. These will be mentioned in detail in the following text in the article. Eleven review articles about PA provided information about the pathogenesis, incidence, diagnosis, and clinical behavior of first- and second-trimester PA. These were evaluated and referenced.[16,18,19,22-24,35-39] There were 6 review articles related to CSP[40-46] without case descriptions. There were numerous case reports with the subject of which were both PA and CSP at the end of which there was usually review of the literature. Most case series or case presentations expressed personal views based on either a few cases or a single case.

## Results of the literature review on early placenta accreta

Forty-two articles containing descriptions of 47 cases of PA detected and treated in the first and second trimesters were found. We included 2 cases at 27 and 28 weeks because their clinical courses and outcomes were identical to those in the first trimester. Table 1 contains detailed information about their history, previous CDs' gestational age at presentation, clinical presentation, treatment, and outcome. Nine patients did not have a history of CD (19%), 31 patients had 1 CD (66%), 6 patients had 2 (12.7%), and 1 patient had 3 previous cesarean sections.

In analyzing the published material, several observations can be made based on the 42 articles: 29 were published in or after the year 2000. This increasing number of publications reflects the increasing rate of CDs. Nine of the silent uterine ruptures occurred in patients without a history of previous CDs. Eleven cases had an elective dilation and curettage (D&C) followed by bleeding and hysterectomy. This fact raises questions about the difficult aspects of sonographic diagnosis of early PA and CSP.

Spontaneous rupture of the uterus was reported in 15 of the 47 cases (32%), most of them being silent ruptures and were followed by bleeding, shock, and hemoperitoneum leading to laparotomy, uterine artery embolization, or hysterectomy. Mean gestational age at rupture was 18.1 weeks (range, 6–28 weeks). Based on the case histories, it is reasonable to surmise that many other patients, whose reports did not specifi-

**TABLE 1**
**Cases of first- and early second-trimester placenta accreta**

| Author | Year | GA | Previous CS | Clinical presentation | Management | Outcome |
|---|---|---|---|---|---|---|
| Kinoshita et al[30] | 1996 | 25 wks | No | Rupture, bleeding | Laparotomy | Hysterectomy |
| Imseis et al[27] | 1998 | 26 wks | No | Acute pain, shock | Laparotomy | Hysterectomy |
| LeMaire et al[31] | 2001 | 16 wks | No | Acute abdomen, bleeding | Laparotomy | Hysterectomy |
| Shih et al[167] | 2002 | 8 wks,15 wks | No | Expectant | Elective laparotomy | Hysterectomy |
| Esmans et al[165] | 2004 | 14 wks | No | Rupture, shock | Laparotomy | Hysterectomy |
| Son et al[121] | 2007 | 8 wks | No | Shock, bleeding | Laparotomy | Hysterectomy |
| Medel et al[166] | 2010 | 18 wks | No | Shock, hemoperitoneum | Laparotomy | Hysterectomy |
| Helkjaer et al[176] | 1982 | 11 wks | ×1 | Bleeding | Laparotomy | Repair |
| Innes and Rosen[28] | 1985 | 18 wks | ×1 | Rupture, shock | Laparotomy | Hysterectomy |
| Veridiano et al[177] | 1986 | 16 wks | ×1 | Bleeding, D&C, severe bleeding | Laparotomy | Hysterectomy |
| Woolcott et al[178] | 1987 | 10 wks | ×1 | Torrential bleeding | Laparotomy | Hysterectomy, bladder injury |
| Haider[179] | 1990 | 10 wks | ×1 | D&C, bleeding | Laparotomy | Hysterectomy |
| Ecker et al[180] | 1992 | First trimester | | D&C, severe bleeding | Laparotomy | Hysterectomy |
| Marcus et al[124,181] | 1999 | 13 wks | ×2 | Cramping, spotting | UAE, D&C, laparotomy | Hysterectomy |
| Passini Junior et al[182] | 1996 | 14 wks | ×1 | Rupture | IM, MTX | Hysterectomy |
| Smith and Mueller[183] | 1996 | 14 wks | ×1 | Rupture, shock | Laparotomy | Hysterectomy |
| Gherman et al[184] | 1999 | 5 wks | ×1 | D&C, profuse bleeding | Laparoscopy, laparotomy | hysterectomy |
| Walter et al[83] | 1999 | 11 wks | ×1 | D&C, severe bleeding | A-VM, laparotomy | Hysterectomy |
| Hopker et al[185] | 2002 | 10 wks | ×1 | D&C, heavy bleeding | Laparotomy | Hysterectomy |
| Chen et al[186] | 2002 | 9 wks; 15 wks | ×1 | D&C, heavy bleeding | Transfusion, laparotomy | Hysterectomy |
| Baloul[26] | 2002 | 27 wks | ×1 | Rupture, bleeding | Laparotomy | Hysterectomy |
| Buetow[187] | 2002 | 8-9 wks | ×1 | Bleeding, pain | Laparotomy | Hysterectomy |
| Singh et al[188] | 2002 | 14 wks | ×2 | Fainting, bleeding | Laparotomy | Hysterectomy |
| Liu et al[125] | 2003 | 4 cases | ×1 | Severe bleeding × 4 D&C | 3 UAE embolization 1 laparotomy | 1 hysterectomy |
| Liang et al[127] | 2003 | 10 wks | ×2 | D&C, shock | Laparotomy | Hysterectomy |
| Kazandi[29] | 2003 | 27 wks | ×1 | Rupture shock | | |
| Topuz[34] | 2004 | 21 wks | ×1 | Acute abdomen | Laparotomy | Subtotal hysterectomy |
| Lichtenberg and Frederiksen[32] | 2004 | 21 wks | ×1 | Rupture, bleeding | Laparotomy | Hysterectomy |
| Coniglio and Dickinson[133] | 2004 | 8 wks | ×1 | Rupture, bleeding | Laparotomy repair | Repair resolved |
| Park et al[189] | 2005 | Early pregnancy | ×1 | Rupture bleeding, hemoperitoneum | Laparotomy | Hysterectomy |
| Honig et al[190] | 2005 | 15 wks | ×2 | Rupture | Laparotomy | Hysterectomy |
| Ismail and Toon[191] | 2007 | 6-7 wks | ×1 | Rupture | Mifepristone oral Methotrexate IM | Resolution |
| Dabulis and McGuirk[131] | 2007 | 9 wks | ×3 | Rupture, hemoperitoneum | Laparotomy | Hysterectomy |

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**TABLE 1**
**Cases of first- and early second-trimester placenta accreta** *(continued)*

| Author | Year | GA | Previous CS | Clinical presentation | Management | Outcome |
|---|---|---|---|---|---|---|
| Tanyi et al[73] | 2008 | 7 wks | ×1 | D&C, bleeding | Laparotomy | Hysterectomy |
| Papadakis and colleagues[192,193] | 2008 | First trimester | ×1 | D&C bleeding | Laparotomy | Hysterectomy |
| Roca et al[33] | 2009 | 28 wks | ×1 | Rupture, shock | Laparotomy | Hysterectomy |
| Soleymani et al[194] | 2009 | First trimester | No | D&C, severe bleeding | UAE | Resolved (no CD) |
| Yang et al[65] | 2009 | 12 wks | ×1 | Bleeding | UAE | Resolved |
| Takeda et al[47] | 2010 | 12 wks | ×1 | Severe bleeding 8 wks after D&C | UAE malformation, UAE laparotomy | Hysterectomy |
| Soliman and Babar[139] | 2010 | 14 wks | ×1 | Rupture bleeding | Laparotomy | Repair of lesion |
| Pont et al[195] | 2010 | 13 wks | ×1 | Rupture, hemoperitoneum | Laparotomy | Subtotal, hysterectomy |
| Hanif et al[196] | 2011 | 12 wks | ×2 | Rupture hemoperitoneum | Laparotomy | Hysterectomy |

*A-VM*, arterio venous malformations; *CS*, cesarean section; *D&C*, dilation and curettage; *GA*, gestation age; *IM*, intramuscular; *MTX*, methotrexate; *UAE*, uterine artery embolization.

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cally contain the words "rupture," "uterine rupture," or "silent rupture," may have had a ruptured uterus because "severe bleeding," "acute abdomen," "profuse bleeding," "shock," or "hemoperitoneum" were mentioned. Five patients (10.6%) had uterine artery embolizations. Thirty-seven patients (78.7%) had laparotomies and 35 (74.4%) had hysterectomies (78.7%). One patient had an arteriovenous malformation after the D&C with subsequent embolization requiring a hysterectomy.[47]

In 10 articles discussing patients with uterine ruptures in the first trimester who had previous cesarean sections, the clinical descriptions are identical for both the early PA and that of a CSP. These cases were counted in both series. Reading the case description, it is obvious that the rupture occurred due to and at the site of the CD scar. Striking similarities make these cases hard to classify as pure PA or, for that matter, pure cases of CSP. This may be another compelling reason to believe in the hypothesis of their common pathogenesis, at least in those with a history of previous CD.

## Results of the literature search on CSP

One question is whether the diagnostic entity of CSP is indeed new. Between 1990 and 1999, we found only 19 articles regarding the subject. Between 2000 and 2005, 48 articles were found, and 104 articles were published from 2006 to 2011 (Figure 1). This increase in publications is testament to the mounting awareness and attention now focused on the diagnostic challenges of this new disease.

We identified 751 CSP cases with sufficient clinical information to be evaluated for this review. We will review the diagnosis and treatment of this condition.

Undoubtedly and clearly, as a result of the mounting risk of the cesarean section delivery, the obstetrical and gynecologic community started to become aware of its unpredicted consequences. This increased awareness is reflected in the steadily increasing number of articles dealing with the problems. As mentioned before, Figure 1 shows the number of publications containing cases, case series, and reviews for the last 20 years. Their numbers steadily increased toward the year 2010. This increasing number of articles supports the fact that CSP is becoming another diagnostic and clinical entity in urgent need of a well-thought-out and applied standardized treatment protocol.

## The diagnosis of CSP

Our own experience with scanning 26 cases with CSP made us aware of the difficulty in the diagnosis.[48] Indeed, in at least 107 of the 751 cases[35,44,49-81] (13.6%), the diagnosis of CSP was missed. Reading carefully the entire text of case presentation in all reviewed articles, there were at least as many cases, if not more, in which the authors did not clearly report that the diagnosis was missed. However, indirectly, based on the description of the events ("heavy bleeding," "shock," "hemoperitoneum," etc) after D&C for "termination of an early pregnancy" or D&C for missed abortion, we suspected that in these cases there were some problems establishing the primary diagnosis. Because of the uncertainty of the diagnosis of CSP, these cases were not included in the 107 described in the previous text.

## Findings of arterio venous malformations (A-VM)

There were 8 cases with descriptions of A-VM detected in the placentae in the scar. Some of these were diagnosed prior to interventions; others were detected as a result of treatment (current study).[47,52,55,82,83] The primary management of 3 of these was by uterine artery embolization[52,82]; the other 5 were managed with hysterectomies. In our own series of 26 CSPs, we had 2 cases with A-VM.[48] The first of these 2 cases presented as a possible complication of a D&C procedure, whereas the second one presented to the emergency department with heavy vaginal bleeding and was

promptly treated with uterine artery embolization.

### Heterotopic locations, twin/triplet, and recurrent CSP

Heterotopic pregnancies involving a CSP with singleton or twin intrauterine gestations were reported in 11 articles.[84-94] The management of these cases will be discussed in the following text. Four twin cesarean section scar pregnancies were reported in 3 articles[53,83,95]: 1 single case of triplet CSP was reported.[88] Six cases with 1 single recurrent CSP;[83,89,96-98]; 2 unusual cases of 3 consecutive CSPs[99]; 1 molar pregnancy, and 1 case of an endometrioma[100] in the scar were also reported. Sepsis secondary to cesarean section scar diverticulum was also seen.[101]

### Future obstetric performance after CSP

Our ability to properly counsel women who did not have their uteri removed and desired to become pregnant again has to rely on the reported literature. We therefore reviewed the literature reporting on pregnancies after a successful treatment of a CSP. Sixty-four intrauterine pregnancies after CSP were reported.[38,70,76-78,81,82,86,87,98,102-107] We speculate that these cases (ie, pregnancies and deliveries after CSP) are underreported. We can only hypothesize that even though many patients who after treatment of CSP retain their ability to have another pregnancy may not want to do so. Another reason would be that practitioners do not see a successful pregnancy after a previous CSP as worthy of publication, just as few will report pregnancies after ectopic gestations. This issue requires a more in-depth study.

### The different treatment modalities used in managing CSP

Analyzing the different primary management protocols and approaches led us to our greatest surprise. There were no less than 31 primary approaches to treat the 751 CSPs. These are summarized in Table 2. The sporadic, mostly individual cases and their results were insufficient to enable to draw a clear conclusion as to which was the most effective management protocol leading to the least or no complications. The result of such a large variety of treatment approaches and their different combinations reported in relatively small case series left the community of obstetricians and gynecologists relatively unsure as to the best approach for treatment.

Importantly, without a wide review, it is almost impossible to assess which treatment had the most complications and therefore should be avoided. Based on reviewing the literature and observing treatment choice of most authors, we realized that gynecologic surgeons tended to do D&C, laparoscopy, and hysteroscopy as their preferred first-line approach. Obstetricians preferred injecting the chorionic sac and relied on the help of interventional radiology. Many times the choice of the patient to have a hysterectomy performed was granted. Few coun-

**TABLE 2**
**Primary treatment in 645 cases**

| | |
|---|---|
| 1. | Hysteroscopic excision |
| 2. | Hysteroscopy with transabdominal sonographic guidance |
| 3. | Hysteroscopy and mefipristone |
| 4. | Hysteroscopy and vasopressin |
| 5. | Laparotomy and excision |
| 6. | Laparotomy with elective transabdominal hysterectomy |
| 7. | Laparotomy with hysteroscopy |
| 8. | Transabdominal sonographic guided local intragestational methotrexate injection |
| 9. | Transabdominal sonographic guided local intragestational KCl injection |
| 10. | Transabdominal sonographic guided local intragestational and intramuscular methotrexate |
| 11. | Transvaginal sonographic guided local intragestational methotrexate injection |
| 12. | Transvaginal sonographic guided local intragestational KCl injection |
| 13. | Transvaginal sonographic guided local intragestational and intramuscular methotrexate |
| 14. | Local intragestational injection of vasopressin |
| 15. | Uterine artery embolization alone |
| 16. | Uterine artery embolization and intramuscular methotrexate |
| 17. | Uterine artery embolization and intragestational methotrexate |
| 18. | D&C alone |
| 19. | D&C and intramuscular etoposide |
| 20. | D&C and Shirodkar cervical suture |
| 21. | D&C and uterine artery embolization |
| 22. | D&C and intramuscular methotrexate |
| 23. | Laparoscopic excision |
| 24. | Laparoscopy and hysteroscopy |
| 25. | Methotrexate intramuscular injection alone |
| 26. | Methotrexate intramuscular and hysteroscopy |
| 27. | Expectant management |
| 28. | Trichostatin |
| 29. | Transrectal ultrasound guided aspiration |
| 30. | Hysterotomy by vaginal approach |
| 31. | Multiple combined treatments |

*D&C*, dilation and curettage; *KCl*, kalium chloride (potassium chloride).

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tries have a set of guidelines at hand when a patient has an early PA or a CSP. An overview of the individual treatment modalities including their references are detailed in Table 3.

## Treatment complications of CSP

Complications were defined as the immediate or delayed need for a secondary treatment. The most frequent reasons for the additional treatment involved blood loss defined by blood loss requiring transfusion; greater than 200 mL; heavy bleeding; shock; hemoperitoneum or surgical interventions such as laparoscopy, hysteroscopy, laparotomy, hysterectomy, or procedures reported as requiring general anesthesia; or embolization of the uterine arteries. If patients required more than 2 different, additional consecutive treatments short of major surgical intervention or embolization, the case was counted as a complication.

We compiled the number of times each treatment approach was used and listed the complications in each of the 31 treatment modalities (Table 3). There were a total of 331 cases with complications in the 751 CSPs (44.1%). Table 4 demonstrates the 3 first-line treatment approaches that, if used alone or in any combination, resulted in the largest number of complications. Treatments that featured uterine artery embolization or D&C alone, or in any "combination treatment," had complication rates (mean, 46.9; range, 0–80% and mean, 61.9%; range, 29.5–100, respectively). The reason is probably the fact that unlike the multilayered myometrium in the uterine body, which are able to contain bleeding at the placental site after its separation, the vessels exposed by curettage bleed because the scar tissue is unable to contract and contain the profuse bleeding.

Intramuscular methotrexate without any other treatment in combination had a 62.1% complication rate. Intramuscular methotrexate and D&C in combination had a complication rate of 86%. The only speculation we may offer to explain the failure of this primary noninvasive treatment approach is due to the slow action of the drug and its questionable ability to stop the cardiac activity and placental expansion. The expected result may take days. While waiting for the drug effect, the gestational sac, the embryo/fetus, and its vascularity are growing. In this case, a secondary treatment has to be directed toward a larger gestation with a richer vascularization; thus, the risk of complications may increase.

Table 4 contains the first-line treatment choices that, if used alone or in any combination, resulted in the lowest complication rate. Any treatment involving hysteroscopy had a relatively low complication rate (18.4%). The lowest complication rates were those using local, intragestational sac injection of methotrexate or KCl (KCl was used only for heterotopic CSP) under transabdominal and/or transvaginal real-time ultrasound guidance (8 of 81 cases: 9.6%). Our previous experience managing multifetal pregnancy reductions and various types of ectopic pregnancies using transvaginal ultrasound guided local intragestational injections[108-117] leads us to the belief that locally injecting methotrexate in cases of CSP is minimally invasive and leads to a rather quick resolution with fewer complications.

There were several treatments resulting in a very large or very small complication rate; however, these were single cases or case series with a very low number of patients. Although included in the tables, these treatments should not be considered as a guide for their use or to be considered as preferential first-line treatments until they are proven by evaluating their efficacy in a larger number of patients.

The management approach suggested by Jurkovic et al[118] deserves some discussion. This author used a Shirodkar cervical suture in arresting hemorrhage following D&C of 28 scar pregnancies. The suture was left untied until the end of the surgical procedure. In 22 women, the suture was tied to achieve hemostasis because they "bleed significantly during the evaluation of scar pregnancies." For the purpose of this review, these cases were counted as complications.

## Outcomes after treatments of CSP

Excluding 49 cases of uterine artery embolizations, 14 cases of laparotomies, and 3 elective hysterectomies, which were rendered as planned primary treatment approaches, there were emergency surgeries performed to treat complications. Thirty-six hysterectomies,[55,60,67,70,73,78,86,89,106,119-131] 40 laparotomies,[45,46,50-52,54,60,67-69,95,96,99,120,121,128-130,132-143] and 22 uterine artery embolizations[52,59,60,62,64,65,71,82,125,132,140,144-147] were performed, mostly to rescue patients from life-threatening hemorrhages. We were not able to assess the number of patients receiving general anesthesia, and because most therapeutic approaches (hysteroscopy, D&C, laparoscopy, embolization, etc) are usually performed under general anesthesia, one should also keep in perspective the risks general or regional anesthesia present.

## Does early intervention yield better outcome?

We wanted to know whether early detection and treatment of CSP would also result in a better outcome. Unfortunately, in only 184 of the 751 cases was the exact gestational age and other accurate, critical, and necessary data determining outcome available. We divided these 184 cases into the following: (1) good outcome if after the initial treatment (single or in combination), they did not have complications (heavy bleeding, embolization, emergency surgery) and (2) complications group, requiring emergency surgery or embolization. If elective laparotomy, embolization, or hysterectomy were chosen as the primary treatment of choice by either patient or provider and no complications followed, we decided to include these in the good outcome group because despite the major intervention, the problem was addressed promptly without endangering the patient.

Despite the complex evaluation of the data and the possibility that the sample may not be completely unbiased, statistical calculations were not performed. However, it seems that diagnosing and treating earlier rather than later shows a trend toward an improved outcome. The results are listed in Table 5.

## The true frequency of CSP may be underreported

Based on the number of cases in the literature, it appears that there is an

**TABLE 3**
**Primary treatment modalities of cesarean scar pregnancy and their complications**

| No. | Primary treatment approach | Cases, n | Complications, n | Complications, n | References |
|---|---|---|---|---|---|
| 1 | Hysteroscopic excision | 61 | 9 | 14.7 | 57,65,75,92,95,107,159,197,198 |
| 2 | Hysteroscopy with TAS guidance | 9 | 0 | 0 | 65,197 |
| 3 | Hysteroscopy and mifepristone | 36 | 6 | 16.7 | 65 |
| 4 | Hysteroscopy with vasopressin | 2 | 0 | 0 | 199 |
| 5 | Laparotomy and excision | 14 | 4 | 28.6 | 65,79,95,96,122,136,138,200-204 |
| 6 | Laparotomy with elective TAH | 3 | 0 | 0 | 70,123 |
| 7 | Laparotomy with hysteroscopy | 1 | 1 | 100 | 132 |
| 8 | TAS-guided local intragestational MTX injection | 9 | 1 | 11.1 | 77,102,104 |
| 9 | TAS guided local intragestational KCl injection | 3 | 0 | 0 | 92,104,205 |
| 10 | TAS-guided local intragestational and intramuscular MTX injection | 14 | 2 | 15.4 | 76,89,91,102,146,206-209 |
| 11 | TVS-guided local intragestational MTX injection | 32 | 4 | 12.5 | Current study and, 56,60,70,72,85,87,88,90,94,98,106,107,129,130,210-214 |
| 12 | TVS guided local intragestational KCl injection (heterotopics) | 5 | 0 | 0 | 62,87,90,93,94 |
| 13 | TVS-guided local intragestational and intramuscular MTX injection | 19 | 1 | 5.3 | Current study and, 60,145 |
| 14 | Local intragestational injection of vasopressin | 1 | 1 | 100 | 215 |
| 15 | UA embolization alone | 5 | 4 | 80 | 58,82,147,216,217 |
| 16 | UA embolization and intragestational MTX | 56 | 25 | 44.6 | 60,81,119,144,218 |
| 17 | UA embolization and local intragestational injection of MTX | 3 | 0 | 0 | 119,217,219 |
| 18 | D&C alone[a] | 97 | 61 | 62.9 | Current study and, 32,51,52,55,57-61,64,66,68-71,73,77,78,81,99,123,126,127,129,135,220-227 |
| 19 | D&C and intramuscular etoposide | 1 | 1 | 100 | 49 |
| 20 | D&C and Shirodkar cervical suture | 33 | 22 | 66.7 | 118 |
| 21 | D&C and UA embolization | 78 | 23 | 29.5 | 44,59,81 |
| 22 | D&C and intramuscular MTX | 54 | 43 | 86 | 81,120 |
| 23 | Laparoscopic excision | 49 | 15 | 30.6 | 45,46,50,63,68,74,84,95,99,137,197,224,228-233 |
| 24 | Laparoscopy and hysteroscopy | 5 | 1 | 20.0 | 74,95,102,197,234 |
| 25 | MTX intramuscular injection alone | 87 | 54 | 62.1 | 60,70,72,77,81,82,96,98,107,120,128,134,207,212,213,217,220,222,232,235-249 |
| 26 | MTX intramuscular and hysteroscopy | 5 | 5 | 100 | 57,105 |
| 27 | Expectant management | 11 | 6 | 54.5 | 45,46,76,129,141,146,217,250 |
| 28 | Trichostatin | 11 | 1 | 9.1 | 58 |
| 29 | Transrectal US-guided aspiration | 5 | 1 | 20 | 53 |
| 30 | Hysterotomy by vaginal approach | 1 | 0 | 0 | 251 |
| 31 | Combination of ≥3 treatment approaches[b] | 42 | 39 | 75.6 | 80,252 |

*D&C,* dilation and curettage; *KCl,* kalium chloride (potassium chloride); *MTX,* methotrexate; *TAH,* total abdominal hysterectomy; *TAS,* transabdominal sonography; *TVS,* transvaginal sonography; *UA,* uterine artery; *US,* ultrasound.

[a] Fourteen of the failed D&C cases received secondary treatment by embolization and intramuscular MTX; [b] Intramuscular methotrexate; 7 days later local methotrexate, another 7 days later followed by suction curettage, followed by intracervical inflation of a balloon catheter. Even though the failure rates were high, there were no major surgeries performed and all patients were successfully treated.

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**TABLE 4**
**First-line treatment choices for cesarean scar pregnancy with the most and the least complication rates**

| Treatment alone or in combination | Cases, n | Complications, n | % |
|---|---|---|---|
| MTX alone | 87 | 54 | 62.1 |
| D&C[a] | 305 | 189 | 61.9 |
| UA embolization[a] | 64 | 30 | 46.9 |
| Hysteroscopy[a] | 119 | 22 | 18.4 |
| Local intragestational injection of MTX/KCL (TAS or TVS guidance)[a] | 81 | 8 | 9.6 |

*D&C*, dilation and curettage; *KCl*, kalium chloride; *MTX*, methotrexate; *TAS*, transabdominal; *TVS*, transvaginal; *UA*, uterine artery.

[a] Alone or in any combination.

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underreporting of CSP. If in 2007 in the United States, there were 4,247,694 deliveries, the CS rate was 32.8%: this represents approximately 1,393,244 cesarean deliveries. Given the reported frequency varies between 1/2000 and 1/2500, it can be estimated that in the United States alone, there should have been 557-696 cesarean scar pregnancies that year. Yet our review of the literature published in the United States over the last 20 years reveals only 44 cases.

Authors from China have reported most of the cases documented in the literature (n = 483), and authors in the United Kingdom reported 107 cases. Correcting for the total population of each country seems an oversimplistic way to assess the frequency of the condition. However, that placing in perspective the relatively large number of case presentations by investigators from China, their birth and cesarean section rates provide a strong database to study the epidemiology of this condition. There are approximately 16 million infants born in China annually,[148] and the reported cesarean section rate is 48.9%.[149] If we apply the rate of CSP as being 1/2500 cesarean deliveries, there should be approximately 3130 CSP in China.

In reviewing the literature, we found signs of increasing interest for studying the hysterectomy scar or niche.[150-156] These articles attempted to raise questions as to how to predict, diagnose, and possibly treat pregnancies that implant in or in the vicinity of these scars. There are also indications that some authors have recognized the need for early diagnosis of pathologically adherent placentae (accreta and/or scar pregnancy). This would enable early counseling and intervention, preventing complications or loss of the uterus.

**TABLE 5**
**Clinical outcome of patients with CSP as a function of gestational age at first treatment**

| | Gestational age, wks | | | | |
|---|---|---|---|---|---|
| Outcome[a] | 5-6 | 7 | 8 | 9 | 10-15 |
| No complications | 51 | 35 | 14 | 4 | 4 |
| Complications | 12 | 16 | 26 | 6 | 16 |

*CSP*, cesarean section scar pregnancy.

[a] Number of cases.

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## Is it possible to prevent CSP?

Several articles raised the question of preventing a CSP in a future pregnancy by surgical repair of the uterine dehiscence (niche) in patients with previous cesarean deliveries while not pregnant. Ben Nagi et al[99] reported on a successful surgical repair of a CD scar; however, the patient had a subsequent chemical pregnancy and 2 additional despite normal intrauterine implantations of the gestational sac. Donnez and colleagues[157-159] performed hysteroscopic repair of the uterine scar in 3 patients. One in 3 patients of Donnez and colleagues became pregnant and had an uneventful pregnancy.[157] Klemm et al[160] used laparoscopic-assisted vaginal repair of the scar dehiscence in 5 patients with previous cesarean scar niches. Yalcinkaya et al[161] performed robotic-assisted laparoscopic repair of cesarean delivery scars in 2 patients who conceived 3 and 11 months after surgery. Their outcomes were not reported. More research is necessary before making recommendations for such surgical treatment to prevent CSP.

Whether any specific surgical technique such as single- or double-layer closure of the incision can minimize or avoid a pathologically adherent placenta or a CSP is still an open question. We did not find any pertinent reference that could have answered this frequently asked question. There are numerous articles devoted to the different incision closure techniques. Most are summarized in a Cochrane Database report reviewing 30 studies.[162] None of them, however, was designed to address whether the type of surgical technique can present early PA and CSP.

## Are there similarities in the pathogenesis of EPA and CSP?

One of the yet-unanswered questions is whether there is a causative connection between CSP and a later developing PA. It would appear that both have the same pathogenesis. In both cases the placenta implants and invades the myometrium (in the case of placenta accreta) and the scar tissue (in CSP). Because the numbers of both PA and CSP occurrence are steadily increasing, one must consider the relationship between the previously

mentioned and the similarly increasing rate of cesarean deliveries. The invasion of the placenta in a subsequent pregnancy almost always occurs at the site of the previous hysterotomy and its scar.[16,17,19,35] There is a linear increase in the incidence of PA with the number of repeat CDs.[16-18] This fact also reinforces our original theory that there is a common underlying causal relationship between PA and CSP.

By definition, if the placenta attaches abnormally and penetrates to various depths into the underlying myometrium, the term, pathologically or morbidly adherent placenta, is used. The degree of myometrial penetration defines the descriptive terminology used. Accreta is identified when the villi penetrate through the decidual baseline to the level of the myometrium. Increta is diagnosed by the pathologist when villi penetrate into the depths of the myometrium. If the placenta invades the entire thickness of the myometrium and invades the peritoneum or the bladder wall, the term percreta is used. Because even the best imaging technology in the most competent hands cannot provide a histologically accurate diagnosis of the degree of invasion, the term placenta accreta (PA) is used to refer to all of the previously mentioned degrees of adherent placentae.

This abnormal adherence of the placenta found usually, but not exclusively, at the site of the scar tissue resulting from a surgical intervention leads to increased risk of bleeding upon attempted delivery of the placenta. Less well known is the danger of a spontaneous rupture of the uterus not only near term but also during the first and second trimesters. This danger of spontaneous rupture of the uterus occurs usually in scarred uteri (after cesarean deliveries, curettages, and myomectomies).

Studies were conducted to evaluate the biochemical behavior of the scarring process in previous CD scar tissues.[163,164] One of the studies[163] found that in the scarred lower uterine segment, there was a reduction of pan-transforming factor-beta 3. There was also a reduction of connective tissue growth factor and a slight increase in vascular and endothelial growth factor and tumor necrosis factor. Even though these studies found altered biochemical processes in the lower uterine segment, at the uterine scar, such processes may only partly explain some of the early-late first- and early second-trimester uterine ruptures because a consideration has to be given to the already thin tissue layers made weaker by the invading trophoblast. This weakening of the already thin hysterectomy scar is probably a plausible explanation of the rupture and bleeding. A pathologically adherent placenta may weaken the walls of even an unscarred uterus, leading to its rupture, serious hemoperitoneum, and shock leading to hysterectomy.[27,30,31,121,165-167] We hypothesize that, together with the steep increase of cesarean deliveries in the last 20 years, there will be an increasing number of articles attesting to the parallel increase of pregnancies with early detection of PA and its serious complications.

Cesarean section scar pregnancy is an iatrogenic entity. The pathophysiology of placental implantation in PA and CSP appears to be similar. There is one exception, as stated before: that PA may occur in an unscarred uterus, whereas CSP refers only to implantation of the gestational sac in the scar of the previous cesarean section(s). Transvaginal ultrasound using saline infusion sonography has visualized the existence of a clearly visible space that was created at the incision site.[151] We used the term, niche, emphasizing the shape and sonographic image of the filling defect created after the healing process[151] (Figure 2, A).

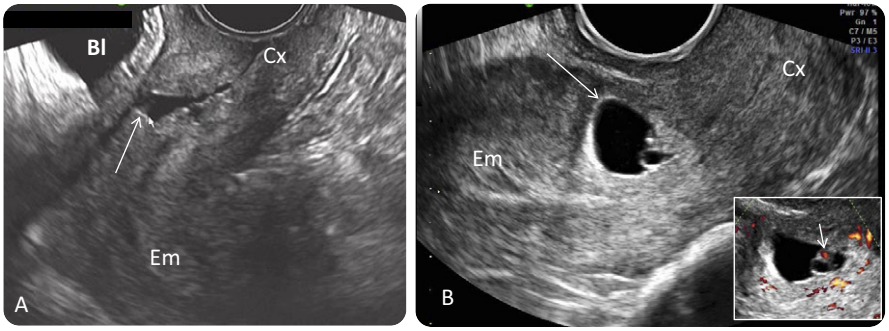
Several articles have described the scars left by cesarean deliveries without making a clear connection between the niche and CSP.[142,150,152-156,168,169] At times a triangular or even a rectangular niche may be evident on plain, unenhanced transvaginal ultrasound or during saline infusion sonohysterography. The implications of the defect created by the hysterotomy may be emphasized by a case of a uteroperitoneal fistula between the niche and the abdominal cavity, which was reported as a consequence of the CDs.[170]

High-resolution ultrasound imaging of a very early CSP clearly indicates the chorionic sac in the depth of the niche (Figure 2, B), providing further support for the pathogenesis of the adherent and penetrating villi resulting in this entity.[40,133] A review of the literature indicates that there are no satisfactory explanations for the cause and pathophysiology of this entity. It seems that such hypothesis are repeated in subsequent articles in the absence of histopathologic support or compelling evidence. The fact that placental villi transverse past the Nitabuch layer of the decidua and into the scar can indeed explain the pathophysiology. Rosen[38] reviewed the subject of the PA and CSP, discussing some of the theories behind their pathophysiology. In vitro work demonstrated a role of a low oxygen tension that seems to be an important prerequisite for the invading cytotrophoblast to proliferate regulating placental growth and its architecture.[171] The scar tissue into which the placenta implants may provide that exact environment of low oxygen tension stimulating the cytotrophoblast to deeply invade the scarred area.[172]

Opposing views may offer a different explanation as to the implantation into the scar. In vitro studies with trophoblast and endometrial explants have shown that a trophoblast has a stronger propensity for attaching to exposed extracellular matrix than endometrial epithelial cells.[173] This may explain why blastocysts have a preference to exposed scar tissue, which is denuded of epithelial cells. This theory may explain the observation that the higher the rate of previous CD is, the higher the risk of early PA and CSP, both because of areas of denuded scar tissue exposed to the blastocyst.

The same basic idea of a facilitated implantation of a fertilized egg on to an area of the uterine cavity was considered in 2 articles dealing with local injury of the endometrium, inducing an inflammatory response that prompted implantation.[174,175] It is indisputable that the absolute number of CSPs increased concomitantly with the increase in cesarean deliveries. Reviewing the literature, it seemed to us, that, in addition to the increase in cesarean deliveries and the resulting increase in the cases of pathologically implanted placentae and CSP there may be a significant underreporting of these cases.

FIGURE 2
**The niche at the CD site and a CSP**




**A,** Sonographic image of a niche (*arrow*) at the site of the hysterotomy performed at the cesarean delivery. **B,** Sonographic image of a CSP at 6 postmenstrual weeks and 3 days (*arrow*) showing the yolk sac and above it the embryonic pole. Note its triangular shape adjusted to the shape of the niche into which it is wedged. *Inlay* shows that the color Doppler highlights the site of cardiac activity.

*CD,* cesarean delivery; *CSP,* cesarean section scar pregnancy; *Cx,* cervix; *EM,* endometrium of the uterine cavity.

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## Conclusions

In studying the literature of PA and CSP, their missed diagnoses, lack of evidence-based treatment approaches, and serious but preventable complications, our review of the cases involving EPA and CSP resulted in the following observations:

1. The diagnosis of early PA and/or CSP is difficult. These were often misdiagnosed as low intrauterine pregnancies, cervical pregnancy, or a miscarriage in progress.
2. The best diagnostic tool appeared to be high-frequency transvaginal ultrasound, although transabdominal ultrasound and magnetic resonance imaging were also mentioned as additional means of arriving at the diagnosis.
3. An earlier correct diagnosis led to a better outcome. This was true even if treatment modalities with slightly higher complication rates were used in very early gestation.
4. Both entities, EPA and CSP, are fraught with significant complications partly because of their misdiagnosis and partly as a result of different treatment regimens. It is clear from the literature that there is no consensus regarding treatment of EPA and CSP. Because the occurrence rate is increasing, it may be time to standardize the therapeutic approach to this clinically significant entity.
5. If possible, D&C should be avoided because it can lead to profuse bleeding, additional secondary backup procedures, general anesthesia, blood transfusion, and in many instances laparotomy and loss of the uterus. If D&C is still the preferred treatment of choice, blood products can be readily available at the site. As a palliative measure, a balloon catheter should be inserted in the cervix (possibly under transabdominal ultrasound guidance) and inflated to minimize blood loss.
6. Systemic methotrexate as a single treatment of choice should be avoided. The argument is: waiting days for its effect to stop the heart beats, which may not happen. It also led to the additional growth of the embryo/fetus as well as the vascularization of the sac and wastes precious time because a subsequent, second-line treatment approach with a possibly higher complication rate may endanger the patient.
7. Uterine artery embolization as a primary treatment in a seemingly uncomplicated case of EPA or CSP should be used sparingly or not at all. Waiting for its effect to stop or slow the bleeding could delay a more effective primary treatment that may avoid hysterectomy. Clearly its use as a rescue procedure in the case of significant bleeding or an A-VM is undisputed.
8. Transvaginal- or transabdominal-guided local and ultrasound-directed methotrexate injection with or without additional intramuscular methotrexate administration as well as surgical excision by hysteroscopic guidance carried the lowest complication rate.
9. Early recognition of CSP and early PA starts with patient education. At the time of discharging women from the hospital after a CD, the patient should be advised that in a future pregnancy, an early visit to the obstetrician for a transvaginal ultrasound is of importance.

Based on the literature, the present review is the most extensive and comprehensive account of the early PA and the CSP.

Even though it is practically impossible to review this literature in the form of a classical metaanalysis, a well-thought-out treatment protocol may emerge on the basis of this evidence-based review. ■

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