Cesarean scar pregnancy: a systematic review of treatment studies


Objective: To study treatment modalities for cesarean scar pregnancies (CSPs), focusing on efficacy and complications in relation to study quality.

Design: Systematic review.

Setting: Not applicable.

Patient(s): A total of 2,037 women with CSP.

Intervention(s): Review of MEDLINE, EMBASE, and Cochrane Library to find studies including five or more women. Data were extracted on primary treatment modality/efficacy, complications, and future fertility. The level of evidence was categorized according to Oxford Centre for Evidence-based Medicine guidelines. Quality was assessed using The Cochrane Collaboration’s Risk of Bias Tools for Randomized Controlled Trials and the modified Delphi techniques for case series. Meta-analysis was impossible owing to multifarious treatments.

Main Outcome Measure(s): Successful first-line treatment. Complications were hysterectomy, laparotomy, bleeding >1,000 mL, or blood transfusion.

Result(s): Fifty-two studies were included: four randomized, controlled trials and 48 case series. Fifteen of the 52 analyzed studies were scored as high quality. Treatment modalities were condensed to 14 different approaches. Combining study quality, level of evidence, efficacy, and safety, five approaches for treating CSP are recommended, depending on availability, severity of patient symptoms, and surgical skills: [1] resection through a transvaginal approach, [2] laparoscopy, [3] uterine artery embolization in combination with dilatation and curettage and hysteroscopy, [4] uterine artery embolization in combination with dilatation and curettage, and [5] hysteroscopy.

Conclusion(s): This review recommends treatment options for CSP in clinical practice, based on efficacy and safety. The literature supports an interventional rather than medical approach. Present recommendations are primarily based on case series. Multicenter, well-designed studies are needed to draw definite conclusions on how to treat CSP. (Fertil Steril 2016;105:958–67. ©2016 by American Society for Reproductive Medicine.)

Key Words: Cesarean scar pregnancy, early pregnancy complications, ectopic pregnancy, hysteroscopy methotrexate

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The frequency of cesarean section (CS) is increasing worldwide (1, 2) (Supplemental Table 1, available online). In 2008, 15 countries worldwide had CS rates over 30%, with Brazil in front with a rate of 46% (3). In recent years there has been augmented focus on the complications seen in subsequent pregnancies, of which the more serious include uterine rupture, placenta accreta/percreta, postpartum hysterectomy, and ectopic pregnancy in a cesarean scar (cesarean scar pregnancy [CSP]) (4, 5). Cesarean scar pregnancy is characterized by an empty uterus and cervical canal, a gestational sac (GS) located in the anterior uterine wall with diminished myometrium between the sac and the bladder, and a discontinuity in the anterior wall of the uterus adjacent to the GS (6). Cesarean scar pregnancy can cause severe maternal morbidity.
and mortality (7, 8). Cesarean scar pregnancy was first described in 1978, and until 2001 only 19 cases were reported (9). Since then the frequency of reported cases has dramatically increased (10). It was recently estimated that 1 in 531 women with a cesarean scar will have a CSP and that 4.2% of ectopic pregnancies are CSP (11). During the last two decades ultrasonography and diagnostics have improved (12–14), and the techniques for uterine surgery have changed (8, 11). Today the uterus is often closed in one layer, compared with the previous two-layer technique (15, 16). All factors may play a role in the increasing prevalence of CSP (10, 14). Today, more than 30 CSP treatment regimens have been published, and the majority of recommendations are based on case series rather than randomized controlled trials (RCTs). This systematic review aimed to collect and condense published literature on CSP treatment. It is based on a predefined protocol and reports according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and MOOSE (Meta-analysis OfObservational Studies in Epidemiology) guidelines (17, 18). We present the largest number of CSP cases to date and evaluate the evidence level and study quality of eligible studies to address and recommend future treatment modalities. The lack of high-level evidence encouraged us to develop a one-page registration chart for CPS cases to be included in local and national guidelines to increase awareness, support coherent evaluation, and as an optimal basis for future treatment trials.

We aimed to investigate and define the most efficient and safe treatment for women with CSP.

MATERIALS AND METHODS

Sources

We searched MEDLINE, EMBASE, and the Cochrane Library for relevant articles from inception until June 2015 using the following search string combining MeSH key words: ((cesarean scar pregnancy OR (cesarean scar AND ectopic pregnancy) OR cesarean scar ectopic pregnancy OR (cesarean scar complications AND pregnancy) OR (previous cesarean scar AND pregnancy))) OR (cesarean scar pregnancy OR (cesarean scar AND ectopic pregnancy) OR cesarean scar ectopic pregnancy OR (cesarean scar complications AND pregnancy) OR (previous cesarean scar AND pregnancy)). Additional records were identified by reference lists in retrieved articles.

The search was primarily performed by K.B.P., E.H., and H.S.N., in collaboration with librarian Sussi Andersen. The retrieved articles were compared and discussed in plenum, and a dedicated EndNote database (version X7; Thomson Reuters) was established.

Study Selection

Eligible articles were published in peer-reviewed journals and written in English. Duplicates, articles in languages other than English, and articles in which title and abstract did not report on CSP treatment were excluded (PRISMA chart; Fig. 1). Full-text articles were screened (n = 198). Final inclusion or exclusion decisions were made after examination according to the following criteria: [1] studies with five or more women with CSP; [2] exclusion of background and review articles; [3] primary/first-line treatment and if necessary secondary treatment sufficiently described; and [4] treatment success and complications sufficiently described.

We chose an arbitrary threshold of five women in criteria 1 to reduce heterogeneity in extremely small reports and single cases. The study designs were divided in accordance with the Oxford Center for Evidence-based Medicine (19). All four authors extracted data regarding study design, efficacy, and complication rates in the 52 selected studies (Table 1 and Supplemental Table 2), and we divided treatment modalities into 14 categories (Table 2).

Study Outcomes

The success rate (as a percentage) was defined as the efficacy of first-line treatment. Major complications were defined as hysterectomy and/or hemorrhage ≥1,000 mL and/or blood transfusion (Table 1 and Supplemental Table 2).

Study Quality Assessment

All authors assessed selected articles for the level of evidence according to study design, on the basis of Oxford Centre for Evidence-based Medicine guidelines (19). Methodologic quality, including risk of bias in individual studies, was assessed in accordance with The Cochrane Collaboration’s Risk of Bias Tools for RCTs and a modified Delphi technique for case series (20–22).

Randomized, controlled trials (23–26) were assessed in relation to random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias such as selection bias.

Case studies (6, 27–74) were evaluated with regard to assessment of exposure, valid and reliable diagnostic procedures in relation to outcome of interest, and sufficient selection of cases.

Clinical Chart for CSP

The selected studies were also used to develop a clinical one-page chart for symptoms, treatment, and outcomes, to standardize the reporting with the aim of structured comparison and assessment in future studies (Supplemental Appendix 1, available online).

Statistics

Frequency statistics were calculated by Microsoft Office Excel 2010 (version 2.13.2).

Description of CSP Treatments

Medical treatment by systemic methotrexate. Systemic methotrexate (MTX) for CSP (single-dose 50 mg administered IM) is used in hemodynamically stable patients without pain, with a gestation age <8 weeks, myometrium thickness <2 mm between the pregnancy and the bladder, serum hCG <5,000 IU/L, GS ≤2.5 cm, and/or a fetus without heart action.
If the serum hCG does not decrease sufficiently additional MTX may be administered (26). Citrovorum rescue can be considered.

Medical treatment by systemic and local MTX. Local injection of MTX (up to 50 mg) can be performed transabdominally or transvaginally (40). A 20–22-G needle is used; both procedures are performed under local analgesia. Local injection of MTX results in a higher MTX concentration at the CSP and a more rapid termination of the pregnancy (42).

Treatment by needle aspiration and local MTX. General anesthesia is usually considered in relation to this procedure owing to needle size (16-G double-canal IVF needle). The gestational sac is aspirated transvaginally by ultrasound guidance (38).

Uterine curettage. A curette is inserted into the uterus through the dilated cervix. The curette is used to scrape the lining of the uterus and remove the pregnancy tissue. Uterine dilatation and curettage (D&C) can be performed blind or assisted by a perioperative transabdominal/transrectal ultrasound scan under general anesthesia (63).

Hysteroscopy. The procedure can be used for CSP with progression toward the uterine cavity or the bladder. The gestational sac is dissected free of the uterine wall through a natural entrance, and hemostasis can be achieved with electro-coagulation using a wire-loop or roller-ball. Hysteroscopy is a minimally invasive technique and is conducted under direct observation or abdominal ultrasound (51). A balloon catheter can be placed postoperatively for compression hemostasis and wound surface drainage (39).

Resection of CSP through a transvaginal approach. The bladder is dissected away through an incision in the anterior cervico-vaginal junction, and the CSP is identified in the anterior part of the lower uterine segment. The ectopic pregnancy tissue is removed through a transverse incision, and
suction curettage through the incision on the uterus can be performed. Finally, the myometrial and vaginal defects are repaired (56).

**Uterine artery embolization.** Interventional radiologists perform the procedure under local anesthesia. Catheterization of the uterine arteries is carried out through a transfemoral approach. If embolization is combined with a dose of MTX it is split between the two uterine arteries and infused via the arterial catheter (69). Finally, both uterine arteries are embolized with gelatin sponge particles (0.5–1.0 mm in diameter). Subsequently, postembolization angiography can be performed to validate the obstruction of the arteries. Gelatin sponge plugs can be replaced with polyvinyl alcohol (26).

**Laparoscopy.** This procedure is performed under general anesthesia and has been used in CSP with progression toward the bladder. The bladder is dissected free of the front of the uterus, and excision is performed of the uterine scar that contains the ectopic pregnancy, with subsequent repair of the defect in the uterus (39). A Frey catheter can be used for intrauterine drainage (39). To avoid heavy perioperative bleeding, bilateral ligation of the uterine arteries may be performed (71).

**High-intensity focused ultrasound.** The procedure can be performed with ablation alone or in combination with hysteroscopic D&C (44, 68). The initial procedure is performed under conscious sedation. A transducer produces the therapeutic energy required. Real-time ultrasound is used to target the area of the GS and monitor the response. Additional D&C is performed in general anesthesia.

**RESULTS**

Fifty-two studies out of 1,492 initially identified met our predefined criteria to be included in this systematic review, of which 4 were RCTs and 48 case series and with a total of 2,037 women diagnosed with CSP (Fig. 1, PRISMA flow chart). Accordingly, the vast majority of the studies had a low level of evidence (4). Chinese publications comprised 77% of the seven contributing countries. Details and assessments of the included studies are described in Table 1 and Supplemental Table 2. Success and complication rates are listed in Table 2. Contribution by country is listed in Supplemental Table 3.

**Treatment Modality 1: Expectant Management**

This treatment modality was described in five case series with 41 women (42, 47, 53, 55, 73). The efficacy was low (41.5%), and the complication rate was high (53.7%). The quality of the studies was assessed as medium and high (Table 2 and Supplemental Table 2).

**Treatment Modality 2: Systemic MTX**

This is the second most elaborated modality, reported for 339 women in 3 RCTs and 18 case series (23, 24, 26, 29, 31, 33, 36, 40–42, 47, 48, 50, 51, 53, 54, 60, 65, 70, 71, 75). Additional treatment was necessary in one-fourth of the cases, and severe complications were seen in 13%. The design the quality of the RCTs was only medium to low, primarily owing to suboptimal randomization and blinding procedures (Table 1).

**Treatment Modality 3: Needle Aspiration and MTX**

This modality was described in six studies of 148 women (32, 38, 40, 53, 54, 74); 71 women were from one study of medium quality (38). Major complications were present in 13.5%, and additional treatment was required in 15.5% (Table 2).

**Treatment Modality 4: Uterine Curettage (D&C)**

This treatment modality was described in 21 studies with a total of 243 women (29, 31, 33, 41–43, 45–47, 49, 51, 53, 55, 59–61, 63, 66, 69, 71, 75). All studies were case series, and the quality was assessed as primarily medium. Dilatation and curettage as treatment modality for CSP is characterized by a high complication rate of 21%, and additional treatment was needed in 52% of the cases.

**Treatment Modality 5: Hysteroscopy**

Hysteroscopy was described as primary treatment in 95 women reported in seven case series (29, 33, 39, 51, 52, 64, 76). Only 3.2% experienced major complications, but 17% needed additional treatment. The 11 women included in the Le et al. study (52) all received preoperative systemic MTX.

**Treatment Modality 6: Resection of CSP through a Transvaginal Approach**

This modality is a novel approach and was recently reported as primary treatment in 118 women in six studies (6, 30, 34, 52, 56, 58), of which 63% were high-quality cases. Twelve women had MTX preoperatively in one study (30). The complication rate was very low (0.9%); only one woman had a hysterectomy, and none of the remaining 117 women required additional treatment.

**Treatment Modality 7: Uterine Artery Embolization in Combination with D&C, without MTX**

Uterine artery embolization (UAE) combined with D&C was reported in 295 women distributed in two RCTs and five case series (24, 25, 33, 36, 37, 42, 46). The RCT by Qian et al. (25) was rated high quality (n = 33), and the remaining studies medium quality. Overall this treatment modality was efficient in relation to additional treatment needed (only 6.4%) and severe complications (3.4%, six hysterectomies and four bleeding episodes).

**Treatment Modality 8: UAE + D&C + Hysteroscopy**

Although only described in one recent RCT (n = 33) and one case series (n = 52) (25, 43), both studies were of high quality. Furthermore, the modality has a high success rate of 95.4% and a very low complication rate of 1.2% (one hysterectomy).
Treatment Modality 9: UAE in Combination D&C, with MTX

This was the most numerous treatment modality described, in 14 studies with a total of 427 women (one RCT and 13 case series) (26, 28, 33, 35, 41, 45, 46, 48, 49, 52, 54, 57, 66, 69). The majority of the cases were high quality (58.8%). All women received D&C in relation to the procedure, but additional treatment was needed in 31.4% because of treatment failure. Eight women experienced bleeding exceeding 1,000 mL, two required laparotomy, and two a hysterectomy (2.8%).

Treatment Modality 10: Local and Systemic MTX

Two case series (29, 42) described this treatment modality, primarily in the study by Timor-Tritsch et al. including 33 women of 34 in total. The quality assessment of this study was medium. Almost one-fourth of the women required additional treatment, and the complication rate was 2.3% (one hysterectomy).

Treatment Modality 11: Laparoscopy

Seven case series of 69 women described laparoscopy as first-line treatment (31, 39, 47, 52, 53, 62, 71). Two studies were assessed as high quality (n = 33) and the remaining five as medium (n = 36). The success rate was very high (97.1%), and there were no reported severe complications.

Treatment Modality 12: Repeated High-intensity Focused Ultrasound Ablation

This novel treatment modality was only described in one high-quality case series of 16 women (68). None of the women required additional treatment or reported severe complications.

Treatment Modality 13: Repeated High-intensity Focused Ultrasound + Hysteroscopic Suction Curettage

Similarly, this novel modality was described in another high-quality case series of 53 women (44), with a success rate of 100% and no complications.

TABLE 1

<table>
<thead>
<tr>
<th>Author, year (reference)</th>
<th>Study type</th>
<th>Inclusion period</th>
<th>n (±FHR)</th>
<th>Primary treatment</th>
<th>Gestational age (wk)</th>
<th>Success rate</th>
<th>Complications</th>
<th>Severe complication rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peng et al., 2015 (23)</td>
<td>RCT</td>
<td>2008–2013</td>
<td>104</td>
<td>Systemic MTX (50 mg/m²) (n = 52)</td>
<td>8.0 ± 3.2</td>
<td>35/52</td>
<td>UAE + D&amp;C (n = 17)</td>
<td>5.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Local MTX (50 mg/m²) (n = 52)</td>
<td>7.9 ± 2.9</td>
<td>36/52</td>
<td>Laparotomy due to bleeding (n = 3)</td>
<td>1.9</td>
</tr>
<tr>
<td>Zhuang et al., 2009 (24)</td>
<td>RCT</td>
<td>2003–2007</td>
<td>72</td>
<td>UAE + D&amp;C (n = 37)</td>
<td>7.3 ± 0.2</td>
<td>35/37</td>
<td>Iodoform meche (n = 1)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systemic MTX (50 mg/m²) + D&amp;C (n = 35)</td>
<td>7.4 ± 0.4</td>
<td>33/35</td>
<td>Hysterectomy (n = 2)</td>
<td>5.7</td>
</tr>
<tr>
<td>Qian et al., 2015 (25)</td>
<td>RCT</td>
<td>2008–2013</td>
<td>66 (+FHR 37)</td>
<td>UAE + D&amp;C (n = 33)</td>
<td>7.3±1.1</td>
<td>33/33</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UAE + D&amp;C + hysteroscopy (n = 33)</td>
<td>7.4±1.6</td>
<td>30/33</td>
<td>Hysterectomy (n = 1)</td>
<td>3</td>
</tr>
<tr>
<td>Li C et al., 2011 (26)</td>
<td>RCT</td>
<td>2002–2009</td>
<td>44 (+FHR 2)</td>
<td>Systemic MTX (50 mg/m²) (n = 13)</td>
<td>9.7 ± 2.5</td>
<td>10/13</td>
<td>Hysterectomy (n = 3)</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UAE with MTX (40 mg) and gelatin sponge + D&amp;C (n = 15)</td>
<td>9.8 ± 7.25</td>
<td>13/15</td>
<td>Severe bleeding 500–1,500 mL (n = 4)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>UAE with MTX (40 mg) and polyvinyl alcohol + D&amp;C (n = 16)</td>
<td>10.3 ± 1.8</td>
<td>16/16</td>
<td>Bleeding &lt;110 mL (n = 2)</td>
<td>0</td>
</tr>
</tbody>
</table>

Note: Success rate: No additional treatment needed. Severe complications: hysterectomy, laparotomy, bleeding >1,000 ml or blood transfusions. (1): Based on Oxford Centre for Evidence based medicine guidelines. (2): Quality was assessed using The Cochrane Collaboration’s Risk of Bias Tools for RCTs and the modified Delphi techniques for case series. FHR — fetal heart rate; GW — gestational weeks; TAS — transabdominal sonography; TVS — transvaginal sonography.

The consequences of the increasing prevalence of CSs in terms of CSP are escalating. Half of the reported CSP cases have been published within the last year, primarily from China. This bias in contribution by country is most likely explained by the high frequency of CS rates (two to four million per year) (3, 77). Combined with the large-scale tertiary hospitals in China, this induces the possibility to perform RCTs and cohort studies. Cesarean scar pregnancy is still a rare diagnosis, and the available literature regarding CSP is mostly observational or casuistic, with an unclear definition of the recruited populations. Treatment of CSP should be evidence based and focus on prevention of severe complications and conservation of fertility. This review is the first to collect, condense, evaluate, and recommend treatment options for CSP to clinical practice using existing guidelines and validated assessment tools for the reporting of systematic reviews (20–22). We have performed an extensive literature search and present the largest number of CSP cases to date. It was not possible to perform meta-analysis on the available data owing to the large proportion of different treatments. The treatment recommendations were based on quality assessment of the 52 studies which, despite validated tools, can be subjectively biased by the interpretation of the authors. A recent article from Timor-Tritsch and Monteagudo (78) identified 31 different primary treatment options in 751 women with CSP, whereas we chose to condense and simplify the treatment modalities into 14 approaches. This implies a risk of missing a possibly valid procedure. That the majority of included studies are case reports is the main limitation of the conclusions. Furthermore, only few of the studies described the localization of the CSP (i.e., endogenous [growth toward the uterine cavity] or exogenous [growth toward the myometrium and uterine serosal layer], the latter being more prone to cause uterine rupture and severe hemorrhage [79]). We found no consensus on treatment strategy in relation to CSP type or thickness of the myometrium between the bladder and gestational sac. Early detection by ultrasonography or MRI to determine the localization of the CSP is essential when deciding on the optimal approach. We recommend five treatment modalities. The following reflect these limitations in relation to each of the five suggested treatments. A similar discussion is available in the

<table>
<thead>
<tr>
<th>Fertility (menstruation, pregnancy, birth)</th>
<th>Author's comments and concerns</th>
<th>Conclusion of the present study</th>
<th>Level of evidence (1)</th>
<th>Author quality assessment (2)</th>
<th>Country of origin</th>
<th>Journal title, impact factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>No follow-up</td>
<td>Well-designed study, but relevant outcome data are missing. No follow-up.</td>
<td>Systemic and local MTX injections are equally effective.</td>
<td>1b</td>
<td>M</td>
<td>China</td>
<td>Therapeutics and Clinical Risk Management, 1.5</td>
</tr>
<tr>
<td>No follow-up</td>
<td>Randomization via sealed envelopes and a table. No blinding of patients and health care providers. No follow-up.</td>
<td>UAE followed by suction curettage seems to have more advantage than systemic MTX treatment and may be a priority option.</td>
<td>1b</td>
<td>M</td>
<td>China</td>
<td>American Journal of Obstetrics and Gynecology, 4.0</td>
</tr>
<tr>
<td>UAE/D&amp;C: Three pregnancies (two CS at 38 GW, one ongoing)</td>
<td>Computerized randomization. Well conducted study.</td>
<td>No significant difference between the two treatment regimens.</td>
<td>1b</td>
<td>H</td>
<td>China</td>
<td>Archives of Gynecology and Obstetrics, 1.4</td>
</tr>
<tr>
<td>No follow-up</td>
<td>Randomization via an open table. No blinding of patients and health care providers. No follow-up.</td>
<td>Arterial chemoembolization with MTX was more effective than systemic MTX treatment for termination of CSP.</td>
<td>1b</td>
<td>L</td>
<td>China</td>
<td>International Journal of Gynecology and Obstetrics, 1.6</td>
</tr>
</tbody>
</table>

### TABLE 2

**Treatment modalities.**

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Cases (n)</th>
<th>Success rate (%)</th>
<th>Severe complication rate (%)</th>
<th>Hysterectomy (n)</th>
<th>Bleeding &gt; 1,000 mL or blood transfusion (n)</th>
<th>Laparotomy (n)</th>
<th>H studies</th>
<th>M studies</th>
<th>L studies</th>
<th>H cases</th>
<th>M cases</th>
<th>L cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expectant management&lt;sup&gt;a&lt;/sup&gt;</td>
<td>41</td>
<td>41.5</td>
<td>53.7</td>
<td>17</td>
<td>5</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>0</td>
<td>20</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Systemic medical treatment MTX&lt;sup&gt;b&lt;/sup&gt;</td>
<td>339</td>
<td>75.2</td>
<td>13.0</td>
<td>10</td>
<td>25</td>
<td>9</td>
<td>2</td>
<td>14</td>
<td>5</td>
<td>20</td>
<td>240</td>
<td>79</td>
</tr>
<tr>
<td>Needle aspiration + MTX/KCl&lt;sup&gt;c&lt;/sup&gt;</td>
<td>148</td>
<td>84.5</td>
<td>13.5</td>
<td>9</td>
<td>9</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>16</td>
<td>82</td>
<td>50</td>
</tr>
<tr>
<td>Uterine curettage (D&amp;C)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>243</td>
<td>48.1</td>
<td>21.0</td>
<td>11</td>
<td>37</td>
<td>3</td>
<td>5</td>
<td>13</td>
<td>3</td>
<td>49</td>
<td>160</td>
<td>34</td>
</tr>
<tr>
<td>Hysteroscopy&lt;sup&gt;e&lt;/sup&gt;</td>
<td>95</td>
<td>83.2</td>
<td>3.2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>5</td>
<td>1</td>
<td>39</td>
<td>39</td>
<td>17</td>
</tr>
<tr>
<td>Resection of CSP through transvaginal approach&lt;sup&gt;f&lt;/sup&gt;</td>
<td>118</td>
<td>99.2</td>
<td>0.9</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>74</td>
<td>44</td>
<td>0</td>
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<tr>
<td>Selective UAE without MTX&lt;sup&gt;g&lt;/sup&gt;</td>
<td>295</td>
<td>93.6</td>
<td>3.4</td>
<td>6</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>6</td>
<td>0</td>
<td>33</td>
<td>262</td>
<td>0</td>
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<tr>
<td>UAE + D+C + Hysteroscopy&lt;sup&gt;h&lt;/sup&gt;</td>
<td>85</td>
<td>95.4</td>
<td>1.2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>85</td>
<td>0</td>
<td>0</td>
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<tr>
<td>UAE + MTX&lt;sup&gt;i&lt;/sup&gt;</td>
<td>427</td>
<td>68.6</td>
<td>2.8</td>
<td>2</td>
<td>8</td>
<td>2</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>251</td>
<td>99</td>
<td>77</td>
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<td>Local + systemic MTX&lt;sup&gt;j&lt;/sup&gt;</td>
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<td>76.5</td>
<td>2.3</td>
<td>1</td>
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<td>5</td>
<td>0</td>
<td>33</td>
<td>36</td>
<td>0</td>
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<tr>
<td>Laparoscopy&lt;sup&gt;k&lt;/sup&gt;</td>
<td>69</td>
<td>97.1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>5</td>
<td>0</td>
<td>33</td>
<td>36</td>
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</tr>
<tr>
<td>Local MTX&lt;sup&gt;l&lt;/sup&gt;</td>
<td>74</td>
<td>64.9</td>
<td>4.1</td>
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<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>74</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Repeated high-intensity focused ultrasound ablation&lt;sup&gt;m&lt;/sup&gt;</td>
<td>16</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>High-intensity focused ultrasound + hysteroscopic suction curettage&lt;sup&gt;n&lt;/sup&gt;</td>
<td>53</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>53</td>
<td>0</td>
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</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,037</strong></td>
<td><strong>59</strong></td>
<td><strong>88</strong></td>
<td><strong>21</strong></td>
<td><strong>63</strong></td>
<td><strong>14</strong></td>
<td><strong>689</strong></td>
<td><strong>1,091</strong></td>
<td><strong>257</strong></td>
<td></td>
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</tr>
</tbody>
</table>

Note: Success rate: no additional treatment needed. Severe complications: hysterecomy, laparotomy, bleeding >1,000 mL or blood transfusions. Quality assessed by The Cochrane Collaboration’s Risk of Bias Tools for RCTs and the modified Delphi techniques for case series. H = high quality; L = low quality; M = medium quality.

<sup>a</sup> References (42, 47, 53, 55, and 73).
<sup>b</sup> References (23, 24, 26, 29, 31, 33, 36, 40–42, 47, 48, 50, 51, 53, 54, 60, 65, 70, 71, and 75).
<sup>c</sup> References (32, 38, 40, 53, 54, and 74).
<sup>e</sup> References (29, 33, 39, 51, 52, 64, and 76).
<sup>f</sup> References (29, 33, 39, 52, 56, and 58).
<sup>g</sup> References (24, 25, 33, 36, 37, 42, and 46).
<sup>h</sup> References (25 and 43).
<sup>i</sup> References (26, 28, 33, 35, 41, 45, 46, 48, 49, 52, 54, 57, 66, and 69).
<sup>j</sup> References (29 and 42).
<sup>k</sup> References (29 and 42).
<sup>l</sup> References (23, 59, and 67).
<sup>m</sup> Reference (68).
<sup>n</sup> Reference (44).

supplemental file on the treatments not recommended (Supplemental Appendix 2).

Resection of CSP through a transvaginal approach is a promising novel and efficient treatment with a low complication rate. It is only reported in case series, which enhances the risk of selection bias. The 23 women described by Wang et al. [6] apparently chose their own treatment, and the type of information was not described, which furthermore enhances the risk of bias. A major limitation of this modality is the dependence on specific surgical skills, which calls for centralization and could make the procedure less accessible. Equally does the severity of the diagnosis CSP support centralized and highly specialized treatment. Again, well-designed and adequately powered studies are needed to draw a final conclusion.

Laparoscopy as an image-guided minimal invasive technique is superior to laparotomy owing to the low risk of bleeding. Using laparoscopy, the bladder is dissected free in front of the uterus, and excision is performed of the CSP with subsequent repair of the defect in the uterus. Hence, the procedure is preferable in CSPs with progression toward the uterine serosal surface, thus this modality could be the treatment of choice in selected cases initially assessed by ultrasound. However, similar concerns apply for laparoscopy as for the transvaginal approach with regard to the need of specialized surgical skills.

Uterine artery embolization plus D&C and hysteroscopy as a treatment modality has only been described in two studies of 85 women, which may impair the validity of the results. Yet the two studies have been published within the last year, and the quality of the RCT and the case series was high. Furthermore, subsequent pregnancies in the follow-up period were thoroughly described, in contrast to the majority of publications on CSP. Dilatation and curettage as well as hysteroscopy are usually easily accessible, but UAE requires an interventional radiologist, which may limit the availability of the treatment.

Uterine artery embolization combined with D&C without MTX has a low risk of heavy bleeding and hysterectomy. A recent review by Timor-Tritsch and Monteagudo [78] reported relatively higher rates of less-severe complications: fever, mild pains from the abdomen or the pelvis—overall a complication rate of 46.9%. In our review only 5% of the patients required additional treatment such as repeated UAE, hysteroscopy, or laparotomy. Although UAE combined with D&C is found to have significantly better results compared with systemic MTX with D&C in an RCT [24], the quality of this study was medium owing to no sample size calculation, no possible blinding, and the patients were randomized via sealed envelopes. However, UAE was described as a safe and efficient method in 295 women in medium- to high-quality studies, which is still a considerable number in the relation to the rare diagnosis. Because UAE with D&C is almost as safe and efficient without hysteroscopy, it could be considered as first-line treatment, because the costs are considerably lower.

Hysteroscopy was described in seven studies ranging from 1 to 39 women [29, 31, 33, 39, 51, 52, 64]. This modality is appealing owing to the minimally invasive procedure, the limited discomfort for the women, and the increasing accessibility. No major complications occurred, although additional treatment was required in 17%. The quality of the studies varied substantially. The 2014 study by Wang G et al. [39] was of high quality, despite the fact the patients chose their own treatment in relation to risk and costs. The patient selection and subsequent clustering in the study from Yang et al. [51] with 23 women was inhomogeneous and not comparable. Because of the diverse quality of the studies and the low number of patients, the full potential of hysteroscopy is not fully explored at the present.

Repeated high-intensity focused ultrasound is a promising novel approach, but the published literature on the subject is still too insufficient for further recommendations. The remaining eight treatment modalities cannot be recommended on the basis of the combined approach of study outcome with evaluation of study quality and level of evidence. Further details are listed in Supplemental Appendix 2. In general, medical compared with surgical treatments have disadvantages in terms of slow resolution, persisting risk of uterine rupture and hemorrhage, need for additional treatment, and uncertainty for the women [59].

In conclusion, cesarean scar pregnancy is an increasing challenge worldwide. The most safe and efficient clinical approach to CSP is yet to be determined, but five approaches depending on availability, severity of patient symptoms, and surgical skills are recommended. The literature supports an interventional rather than medical approach.

We suggest a prospective, multicenter RCT aiming to evaluate and compare minimally invasive surgery with UAE and medical treatment with MTX. The study should involve organizations conducting high-quality studies of these uncommon disorders on a regional, national, and international basis, with the objective of improving the quality of care for women. To facilitate this, we developed a one-page registration chart to optimize future treatment trials. We are concerned that recommendations for treatment and management of CSP would otherwise continue to be based on case reports and cohort studies with a limited number of patients and varying validity.

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REFERENCES
ORIGINAL ARTICLE: EARLY PREGNANCY


