Cesarean scar pregnancy: a systematic review of treatment studies

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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

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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 Of Observational 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 $\geq$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 $\leq$2.5 cm, and/or a fetus without heart action