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REVIEW ARTICLE

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Treatments for cesarean scar pregnancy: a systematic review and meta-analysis

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ABSTRACT

Objective: To report the outcome of cesarean scar pregnancy (CSP) undergoing treatment.

Methods: MEDLINE, Embase and CINAHL databases were searched. Inclusion criteria were women with CSP undergoing treatment. The primary outcome was successful treatment for CSP, defined as no need for additional medical or surgical strategies. Secondary outcomes were the type of additional treatment (surgical or medical), need for blood transfusion, emergency laparotomy, hysterectomy, post-treatment complications.

All these outcomes were explored in women undergoing single and compound treatments for CSP. Furthermore, we performed a separate sub-group analysis only including studies which reported on the outcomes of elective treatments. Random effects meta-analyses were used to analyze the data and results reported as pooled proportions or odd ratio (OR).

Results: 176 studies (13431 women with CSP undergoing treatment) were included.

Successful treatment after primary intervention was achieved in 86.2% (95% CI 82.3–89.7) of women with CSP undergoing treatment with ultrasound guided suction curettage, 72.4% (95% CI 64.8-79.3) with systemic MTX, 81.6% (95% CI 72.3–89.3) with local MTX, 83.9% (95% CI 66.7–95.6) with interventional radiology, 90.42% (95% CI 82.9–96.0) with hysteroscopy, 96.1% (95% CI (92.3–98.6) with laparoscopy and 92.6 with high intensity focused ultrasound (95% CI 78.2–99.6). Post-treatments complications were reported in 3.5% (95% CI 1.7–6.0) of women treated with systemic MTX, 5.9% (95% CI 0.8–15.1) with local MTX or KCl, 1.2% (95% CI 0.1–3.5) with interventional radiology, 1.4% (95% CI 0.4–2.9) with hysteroscopy, 5.5% (95% CI 0.4–25.7) with high intensity focused ultrasound and in none of the cases treated with ultrasound guided suction curettage.

When considering compound treatments, successful resolution of CSP was achieved in 91.9% (95% CI 88.0–95.10) of women treated with interventional radiology followed by curettage, 83.3% (95% CI 68.8–93.8) with systemic MTX and curettage, 79.4% (95% CI 56.3–95.2) with local MTX and curettage, 96.2% (95% CI 92.3–98.7) with curettage followed by single or double balloon insertion in the uterine cavity, 98.3% (95% CI 95.9–99.7) with high intensity focused ultrasound followed by curettage, 91.1% (95% CI 3.4–97.0) with interventional radiology followed by removal of CSP with hysteroscopy, 64.3% (95% CI 13.8–99.2) with interventional radiology and systemic MTX and in 95.5% (95% CI 92.9–97.5) with curettage and hysteroscopy.

When considering studies reporting a comparison between different treatments, there was no difference between systemic vs local MTX in the primary outcome. Curettage was associated with a higher chance of achieving a successful treatment.

Conclusions: A multitude of treatments for CSP have been reported in the published literature. All treatments described for CSP are apparently equally effective in treating this condition. The findings from this systematic review highlight the need for adopting a common definition and outcome reporting of CSP to better elucidate its natural history, estimate the magnitude of maternal complication after treatment and design appropriately powered RCT to elucidate the optimal treatment of CSP according to its ultrasound phenotype and gestational age at treatment, in terms of effective resolution of the condition and risk of post-intervention complications.

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Introduction

Cesarean scar pregnancy (CSP) is an iatrogenic complication of cesarean delivery (CD) characterized by the implantation of the gestational sac in the area of the prior CD scar [1–4].

Although the natural history of CSP has not been fully elucidated yet, a large proportion of CSPs develop abnormally and fail to progress beyond the early first trimester of pregnancy [5]. Conversely, when CSP continues through the second trimester, it develops into placenta accreta spectrum (PAS) disorders, for which CSP can be considered an early precursor [5]. Management options for women with CSP primarily depend on presenting symptoms [6,7]. Women with severe hemorrhage or/and haemodynamically unstable require immediate surgical intervention. Conversely, in hemodynamically stable patients, management options include termination of pregnancy (medical or surgical) or expectant management. The optimal management is unclear as there are insufficient numbers of reported cases on which to base a specific treatment recommendation. Although most women diagnosed with live CSP can progress through the second and third trimester of pregnancy there are no early ultrasound signs which could be used to predict reliably the risk adverse maternal outcomes later in pregnancy [8–11].

A multitude of different treatment options for CSP, from minimally invasive to surgical, have been described in the literature. Despite that, the optimal treatment for CSP has not been agreed upon yet. Small sample size of previously published studies, lack of differentiation between cases undergoing elective comparing to emergency treatment and heterogeneity in gestational age (GA) at treatment and type of CSP do not allow extrapolation of objective evidence to guide clinical practice.

In this context, we performed a systematic review and meta-analysis reporting the outcome of CSP undergoing various treatment modalities.

Methods

Protocol, eligibility criteria, information sources and search

This review was performed according to an *a priori* designed protocol recommended for systematic reviews and meta-analysis [12,13]. MEDLINE, Embase and CINAHL were searched electronically on the 1 February 2023 in line with current recommendations and reported as per PRISMA 2020 guidelines (https://pubmed.ncbi.nlm.nih.gov/33782057/), utilizing combinations of the relevant medical subject heading (MeSH) terms, keywords, and word variants for "caesarean scar pregnancy," "treatment," and "outcome" (Supplementary Table 1). The search and selection criteria were restricted to the English language. The reference lists of relevant articles and reviews were hand-searched for additional reports.

Study selection, data collection and data variables

Inclusion criteria were CSP undergoing treatment CSP was defined according to the recent Delphi consensus statement as a pregnancy with implantation in, or in close contact with, the niche [1]. However, there was no pre-defined diagnostic criteria for CSP before this consensus statement. Therefore, we included all studies which were describing the outcomes of treatment of CSP regardless of the criteria used.

The primary outcome was successful treatment of CSP, defined as no need for additional medical or surgical strategies, decline of serum hCG to pre-pregnancy level or physical resolution of the pregnancy. The secondary outcomes were:.

- Need for blood transfusion.
- Emergency laparotomy performed for hemodynamic instability, rupture of the CSP or hemoperitoneum.
- Hysterectomy.
- Post-treatment complications related to the primary medical or surgical treatment adopted, including post-treatments hemorrhage or uterine rupture.

All these outcomes were explored in women undergoing single and compound treatments for CSP. In view of the multitude of treatments options for CSP, we reported the occurrence of the explored outcomes for the following treatments:.

- Suction curettage under ultrasound guidance
- Compression of the CSP using single or double balloon catheter
- Systemic methotrexate (MTX)
- Local MTX
- Interventional radiology techniques, including embolization of the uterine arteries or the vessels perfusing the CSP.
- Resection of the CSP at hysteroscopy
- Resection of the CSP at laparoscopy
- High-intensity focused ultrasound, a new noninvasive technique, in which a wave energy ultrasound able to penetrate intact skin and generate a temperature of 60°–90° at the focal spot, inducing cellular death and vascular obliteration

- Systemic MTX + suction curettage
- Local MTX + curettage
- Curettage + balloon catheter
- Curettage + high-intensity focused ultrasound
- Interventional radiology + curettage
- Interventional radiology + hysteroscopy
- Interventional radiology + systemic MTX
- Curettage + hysteroscopy

All these outcomes were explored in the overall population of women undergoing surgery for CSP. Furthermore, we performed a separate subgroup analysis including only studies that specifically reported that intervention was performed in elective conditions.

Study selection and assessment of the risk of bias

Only full-text articles were considered eligible for inclusion; case reports, conference abstracts, and case series with <10 cases were also excluded to avoid publication bias.

Two independent investigators (AL, ST) selected studies in two stages. The abstracts of all potentially relevant papers were individually examined for suitability. Papers were only ruled out at this stage if they obviously did not meet the inclusion criteria. The remainder were obtained in full text and were independently assessed for content, data extraction and analysis. Disagreements between the two original reviewers were resolved by discussion with the third investigator (FDA). Full-text copies of those papers were obtained. Study characteristics and surgical outcomes were extracted using a predesigned data extraction protocol. If more than one study was published on the same cohort with identical endpoints, the report containing the most comprehensive information on the population was included to avoid overlapping populations.

The risk of bias for the included RCTs was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2). According to this tool, the risk of bias of each included study is judged according to five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in selection of the reported result. Although the RoB2 tool does not provide an overall risk of bias assessment, the overall risk of bias was considered low if four or more domains were rated as low risk (not counting 'other biases'), with at least one of them being sequence generation or allocation concealment, according to what was reported in previous systematic reviews of intervention.

The risk of bias for observational studies was performed The risk of bias in the observational studies was performed using the Newcastle-Ottawa Scale (NOS) for cohort studies [14]. According to NOS, each study is judged on three broad perspectives: selection of the study groups; comparability of the groups; and ascertainment of the outcome of interest. Assessment of the selection of a study includes the evaluation of the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure and the demonstration that the outcome of interest was not present at the start of the study. Assessment of the comparability of the study includes the evaluation of the comparability of cohorts based on the design or analysis. Finally, ascertainment of the outcome of interest includes the evaluation of the type of assessment of the outcome of interest, and length and adequacy of follow-up. According to NOS, a study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability. The conclusions of the meta-analysis on the primary outcome were assessed using the GRADE approach by the first author, who was familiar with GRADE (GRADEpro, Version 20, 2014, McMaster University, Hamilton, Ontario, Canada). A second author verified the ratings; any disagreements were reconciled after discussion. The pooled analysis of the primary outcome was assessed in relation to the quality of the evidence scored in the 5 domains specified within GRADE: limitations in study design and/or execution (risk of bias), inconsistency of results, indirectness of evidence, imprecision of results, and publication bias [15].

Statistical analysis

Random effects model of proportions was used to analyze the data. Furthermore, for studies reporting a comparison of different interventions, we performed pooled odd ratios (OR). Statistical heterogeneity was assessed with the Cochran's Q-test and the I^2 statistic (the proportion of variation in study estimates because of heterogeneity rather than sampling error). A value of 0% indicates no observed heterogeneity, whereas I^2 values of ≥ 50% indicate a substantial level of heterogeneity. Fixed effect model was used when I^2 values were <50%; conversely a random effect model was used when I^2 values were ≥ 50%. Tests for funnel plot asymmetry were not used when the total number of publications included for each outcome was less than ten. In this case, the power of the tests is too low to distinguish chance from real asymmetry [16].

Analyses were conducted using the StatsDirect software version 2.7.9 (StatsDirect, Ltd, Altrincham, Cheshire, United Kingdom).

Results

Study selection and characteristics

3081 articles were identified, 184 were assessed with respect to their eligibility for inclusion and 176[17–193] studies were included in the systematic review (Table 1, Figure 1, Supplementary Table 2). These 176 studies included (after removing the studies including overlapped cases) 13431 women with CSP undergoing treatment pregnant. Of these studies, four were RCTs, while the remaining were observational series.

The results of the quality assessment of the included studies using RoB2 tool and NOS are presented in Supplementary Tables 3 and 4. The major limitations of these studies were lack of consistency of CSP definition, heterogeneity of outcome definition and assessment and lack of stratification according to gestational age at diagnosis, maternal conditions and ultrasound clinical phenotypes of CSP.

Synthesis of the results

All women with CSP receiving a single treatment

Resolution of the CSP after the primary intervention was achieved in 86.2% (95% CI 82.3–89.7) of women with CSP undergoing treatment with suction curettage under ultrasound guidance, 72.4% (95% CI 64.8–79.3) with systemic MTX, 81.6% (95% CI 72.3–89.3) with local MTX or KCl, 83.9% (95% CI 66.7–95.6) with interventional radiology, 90.4% (95% CI 82.9-96.0) with hysteroscopy, 96.1% (95% CI 92.3–98.6) with laparoscopy and 92.6 with high intensity focused ultrasound (95% CI 78.2–99.6). Conversely, additional medical or surgical treatments were required in 16.62% (95% CI 4.6–34.3) of women with CSP undergoing treatment with ultrasound guided suction curettage, 27.6% (95% CI 20.7–35.2) with systemic MTX, 18.4% (95% CI 10.7–27.8) with local MTX or KCl, 16.1% (95% CI4.4–33.3) with interventional radiology, 9.6% (95% CI 4.1–17.1) with hysteroscopy, 3.9% (95% CI 1.4-7.4) with laparoscopy, 7.4% (95% CI 0.4–21.8) with high-intensity focused ultrasound. (Table 2).

Hysterectomy, mainly for uncontrolled bleeding after the primary treatment, was required in 1.1% (95% CI 0.2–2.5) of women treated with ultrasound guided curettage, 4.2% (95% CI 1.8–7.5) with systemic MTX, 2.4% (95% CI 0.5–5.8) with local MTX or KCl, 0.5% (95% CI 0.03–1.0) with interventional radiology, 0.8% (95% CI 0.2–1.9) with hysteroscopy and in none of the women treated with laparoscopy and high-intensity focus ultrasound (Table 4).

Finally, post-treatments complications were reported in 3.5% (95% CI 1.7–6.0) of women treated with systemic MTX, 5.9% (95% CI 0.8–15.1) with local MTX or KCl, 1.2% (95% CI 0.1–3.5) with interventional radiology, 1.4% (95% CI 0.4–2.9) with hysteroscopy, 5.5% (95% CI 0.4–25.7) with high intensity focus ultrasound and in none of the cases treated with laparoscopy and ultrasound guided suction curettage.

When considering combined treatments, successful resolution of CSP was achieved in 91.9% (95% CI 88.0–95.1) of women treated with interventional radiology followed by curettage, 83.3% (95% CI 68.8–93.8) with systemic MTX and curettage, 79.4% (95% CI 56.3–95.2) with local MTX and curettage, 96.2% (95% CI 92.3–98.7) with curettage followed by single or double balloon insertion in the uterine cavity, 98.3% (95% CI 95.9-99.7) with high intensity focused ultrasound followed by curettage, 91.1% (95% CI 3.4–97.0) with interventional radiology followed by removal of CSP with hysteroscopy, 64.3% (95% CI 13.8–99.2) with interventional radiology and systemic MTX and in 95.5% (95% CI 92.9–97.5) with curettage and hysteroscopy. Post-treatment complications occurred in 13.9% (95% CI 7.0-22.7) of cases treated with interventional radiology and curettage, 15.7% (95% CI 2.7–36.8) with systemic MTX and curettage, 12.7% (95% CI 1.6–32.2) with local MTX and curettage, 13.9% (95% CI 0.6–45.3) with high-intensity focused ultrasound and curettage, 16.6% (95% CI 1.8–42.0) with interventional radiology and hysteroscopy and in none of the cases treated with curettage and balloon and curettage and hysteroscopy.

CSP undergoing elective treatment

A successful treatment of CSP was achieved in 68.04% (95% CI 45.1–87.2) of women treated with curettage, 72.4% (95% CI 57.9–84.8) with systemic MTX, 86.3% (95% CI 74.8–94.7) with local MTX or KCl, 47.5% (95% CI 10.5–86.3) of women treated with interventional radiology, 93.9% (95% CI 86.9–98.4) with hysteroscopy, 88.8% (95% CI 70.1–99.0) with high-intensity focused ultrasound, and in all cases treated with laparoscopy (Table 3). Hysterectomy was required in 1.70% (95% CI 0.1–5.0) of women treated with ultrasound guided curettage, 5.8% (95% CI 0.5–16.2) with systemic MTX, 0.9% (95% CI 0.1–2.4) with local MTX or KCl, 1.04% (95% CI 0.2–2.6) with hysteroscopy and in none of the cases of women treated with interventional radiology, laparoscopy or high-intensity focused ultrasound.

Table 1. General characteristics of the studies included in the present systematic review.

First author	Year	Country	Study design	period	Gestational age at intervention	Type of intervention	Stratification according to GA at intervention or maternal sympotms	Cases (n)
Cao [17]	2022	China	Retrospective	2017–2019	7.79 ± 1.26	H/S + D&C vs only D&C	0	80
Karahasanoglu [18]	2022	Turkey	Retrospective	2009–2013	6.2 ± 3.9	D&C + Foley balloon	0	13
Zhou [19]	2022	China	Retrospective	2009–2018	7.86 ± 2.1	ultrasound guided vacuum aspiration after local injection of lauromacrogol v s ultrasound-guided vacuum aspiration after UAE vs transabdominal resection or hysteroscopy combined with laparoscopic resection	0	160
Zhu [20]	2022	China	prospective	2020–2021	8.62 ± 3.1	MTX + curettage vs MTX + UAE	0	142
Yu [21]	2022	China	prospective	2019–2021	8	MTX + curettage VS UACE + curettage	0	86
Gu [22]	2022	China	Retrospective	2011–2015	7.41 ± 3.11	UAE + ultrasound guided D&C	0	54
Liu [23]	2022	China	Retrospective	2014–2020	8.11 ± 0.81	HIFU + USg D&C	0	153
Tan [24]	2022	China	prospective	2018–2020	7.74 ± 1.43	local MTX injection + D&C vs UAE + D&C	0	77
Yin [25]	2022	China	Retrospective	2017–2019	6.86	C shape HIFU + USgD&C vs I shape HIFU + USgD&C	0	91
Yu [26]	2022	China	Retrospective	2015–2021	7.25 ± 1.25	mifepristone followed by D&C or hysteroscopy vs MTX followed by D&C or hysteroscopy vs MTX + mifepristone followed by D&C or hysteroscopy or laparotomy	1	66
Kus [27]	2022	USA	Retrospective	2018–2022	6	cervical double balloon catheter	0	18
Fu [28]	2022	China	Retrospective	2013–2018	Ns	laparoscopy vs laparotomy	1	278
Chen [29]	2022	Taiwan	Retrospective	2010–2019	6.2 ± 1.1	UAE + curettage	0	53
Peng [30]	2022	China	Retrospective	2017–2021	6.81	HIFU + USg suction curettage	0	153
Shao [31]	2022	China	Retrospective	2013–2018	8.06 ± 2.09	direct hysteroscopy vs UAE + hysteroscopy vs systemic MTX + hysteroscopy	0	276
Yu SS [26]	2022	China	Retrospective	2015–2021	7.25 ± 1.25	mifepristone + embryo removal vs MTX + embryo removal vs MTX/ mifepristone + embrio removal	0	66
Su [32]	2022	China	Retrospective	2017–2020	6.9 ± 1.85	internal iliac artery temporary occlusion + hysteroscopy vs bilateral UAE + hysteroscopy	0	32
Wu [33]	2022	China	Retrospective	2015–2021	6.0–9.0	MTX + curettage vs curettage	1	31
Xiang [34]	2022	China	Retrospective	2012–2019	8.08 ± 2.53	suction curettage vs laparoscopic resection with repair	0	237
Cagli [35]	2022	Turkey	Retrospective	2012–2022	7.2	local transvaginal UsG MTX	0	56
Zheng [36]	2022	China	Retrospective	2013—2020	6.46 ± 0.92	UACE + D&C with or without UsG	0	48
Failla [37]	2022	Italia	Retrospective	20121–2020	5.0–13.0	UAE vs UAE + MTX	0	33
Mu [38]	2022	China	Retrospective	Ns	7.18 ± 1.18	HIFU + curettage	0	41
Toh [39]	2022	Australia	Retrospective	2005–2020	6.4–7.3	MTX im vs MTX intra-sac vs MTX im + intrasacvs suction D&C vs laparoscopically guided D&C + MTX vs laparotomy	0	38
Velipasaoglu [40]	2022	Turkey	Retrospective	2015–2022	6.28–6.8	USg suction curettage + foley balloon tamponade	0	31
Lin [41]	2021	China	Retrospective	2014–2020	7.98 ± 2.51	curettage after UAE vs ultrasound guided hysteroscopic curettage vs laparoscopic cesarean scar resection)	0	55
Qin Tang [42]	2021	China	Retrospective	2013–2018	Ns	hysteroscopy + D&C vs systemic MTX followed by hysteroscopy + D&C vs UAE or laparoscopic ligation of the bilateral uterine arteries followed by hysteroscopy + D&C	0	439
Argawal [43]	2021	India	Prospective and Retrospective	2020	11.45	intracardiac KCl + systemic MTX vs systemic MTX vs UAE vs laparotomy	0	11
Bagli [44]	2021	Turkey	Retrospective	2015–2020	7.4 ± 1.34	suction curettage	0	36
Chen [45]	2021	China	Retrospective	2012–2018	7.79 ± 2.15	temporary ligation of the bilateral uterine arteries during laparoscopy + hysteroscopy vs hysteroscopy only	0	83
Levin [46]	2021	Israel	Retrospective	2011–2019	6.86 ± 1.75	single dose MTX vs multpile dose MTX	0	63
Melike [47]	2021	Turkey	Retrospective	2015–2019	6.6 ± 0.95	transabdominal USg suction curettage + Foley balloon	0	44
Mitsui [48]	2021	Japan	Retrospective	2006–2015	7.0	transabdominal hysterectomy vs medical treatments (systemic and/or local MTX or KCl + MTX) vs non medical treatments (D&C or UAE + D&C)	0	48

(*Continued*)

Table 1. Continued.

First author	Year	Country	Study design	period	Gestational age at intervention	Type of intervention	Stratification according to GA at intervention or maternal sympotms	Cases (n)
Mo [49]	2021	China	Retrospective	2005–2018	8.12 ± 1.47	D&C followed by: UAE + MTX vs UAE + surgery vs surgery	0	80
Mohapatra [50]	2021	India	Retrospective	20132020	8.6 ± 2.2	MTX only vs MTX + D&C vs wedge resection vs hysterectomy	0	22
Pyra [51]	2021	Poland	Retrospective	2013–2019	ns	UACE (Uterine Artery chemoembolization)	0	41
Shen [52]	2021	China	Retrospective	2016–2020	7.14	D&C vs UAE vs hysteroscopy + laparoscopy	0	71
Wang [53]	2021	China	Retrospective	2017–2019	7.07	pituitrin local injection followed by hysteroscopy or laparoscopy wedge resection vs UAE followed by hysteroscopy or laparoscopy wedge resection	0	49
Xu [54]	2021	China	Retrospective	2011–2018	7.23 ± 1.29	USg D&C vs laparoscopy monitored curettage vs laparoscopic resection	0	117
Yang [55]	2021	China	Retrospective	2016–2020	6.64 ± 0.61	traditional hysteroscopic-laparoscopic surgery vs modified hysteroscopic-laparoscopic surgery	0	31
Aslan [47]	2021	Turkey	Retrospective	2015–2019	6.6 ± 0.95	transabdominal uSg suction curettage + Foley balloon	0	42
Cao [56]	2021	Malaysia	Retrospective	2012—2017	7.1 ± 0.9	UAE + local MTX + hysteroscopy + curettage vs transvaginal removal and repair	0	87
De Braud [57]	2021	United Kingdom	Retrospective	2008–2019	6.6	transcervical suction curettage under ultrasound guidance	0	62
Wang [58]	2021	China	Retrospective	2014-2019	7.33 ± 1.56	UAE + curettage	0	314
Wu Y. [59]	2021	China	Prospective	2012–2016	8.88 ± 0.74	curettage vs transvaginal resection vs laparoscopic resection vs UAE + hysteroscopic curettage vs UAE + uterine curettage vs hysteroscopi curettage	0	135
Yu [60]	2021	China	prospective	2018–2020	6.82 ± 1.52	UAE + D&C at same time vs after12-72h	0	61
Zhang [61]	2020	China	Retrospective	2014–2017	7.79 ± 1.06	laparoscopy vs hysteroscopy	0	112
Fang [62]	2020	China	Retrospective	2010–2016	8.4 +-2.67	surgery (laparoscopy, hysteroscopy, hysteroscopy-laparoscopy) vs UAE vs HIFU treatments	1	154
Yuan [63]	2020	China	Retrospective	2017–2019	6.95 ± 0.98	focused ultrasound ablation surgery (FUAS) + suction curettage	0	52
Al Jaroudi [64]	2020	Saudi Arabia	Retrospective	2013–2019	5.5–13.6	systemic MTX vs intrasac MTX + systemic MTX vs intracardiac KCl + systemic MTX vs intrasac MTX vs UAE + systemic MTX vs laparotomy	0	25
Tan [65]	2020	China	Retrospective	2015–2017	7.09 ± 1.1	local MTX injection + D&C	0	31
Wu [66]	2020	China	Retrospective	2012–2016	8.92 ± 0.75	transvaginal resection vs laparoscopic resection vs UAE + hysteroscopic curettage vs UAE + hysteroscopic curettage vs UAE + uterine curettage vs hysteroscopic curettage	0	135
Drever [67]	2020	Australia	Retrospective	2013–2018	8.1	Systemic, intramuscolar, local MTX	0	28
Huang [68]	2020	China	Retrospective	2015–2019	7.12	hysteroscopy + laparoscopy (with reversible ligation of uterine artery) vs hysteroscopy vs curettage	0	173
Li [69]	2020	China	Retrospective	2013–2017	Ns	UAE + curettage	0	169
Lou [70]	2020	China	Retrospective	2013–2015	6.71 ± 1.2	MTX + UAE + curettage	0	53
Ou [71]	2020	China	Prospective	2016–2018	7.4 ± 0.15	UAE + curettage vs curettage alone	0	105
Qu [72]	2020	China	Retrospective	2013–2020	7.02	MTX + surgery vs USg curettage vs curettage + hysteroscopy	0	447
Roche [73]	2020	Australia	Retrospective	2009–2017	7.0	conservative vs medical (im MTX or intra-gestational sac MTX or misoprostol) vs surgical management (D&C or D&C + cervical cerclage or D&C + LPS or LPS excision or LPS hysterectomy or total abdominal hysterectomy or LPT + excision of CSP)	0	46
Yin [74]	2020	China	Retrospective	2016–2019	7.75 ± 2.14	Mifepristone or MTX + curettage vs UAE + curettage vs additional MTX + curettage vs LPT	0	49
Elmokadem [75]	2019	Egypt	Retrospective	2016–2018	7.45	UAE + intra-arterial MTX	0	11
Qiu [76]	2019	China	Retrospective	2013–2018	7.3 ± 1.34	UAE + D&C guided by ultrasonography vs UAE + hysteroscopy	0	62
Zhang [77]	2019	China	Retrospective	2015–2018	6.29	HIFU + USg D&C	0	23

(*Continued*)

Table 1. Continued.

First author	Year	Country	Study design	period	Gestational age at intervention	Type of intervention	Stratification according to GA at intervention or maternal sympotms	Cases (n)
Simsek [78]	2019	Turkey	Retrospective	2012–2019	6.3 (at diagnosis)	comparison of medical and surgical modalities of treatment	0	48
Fei [79]	2019	China	Retrospective	2008–2017	9.6 ± 0.97	comparison of fertility preservation treatments methods	0	204
Lu [80]	2019	China	Retrospective	2018–2019	7.24	transvaginal injection of absolute ethanol	0	26
Tanaka [81]	2019	Australia	Retrospective	2008–2017	6.9	high dose intravenous MTX infusion therapy	0	28
Cheng [82]	2019	China	Retrospective	2014–2017	7.31	UACE + D&C	0	65
Dior [83]	2019	Australia	Retrospective	2008–2016	6.6	systemic MTX treatment	1	13
Levin [84]	2019	Israel	Retrospective	2014–2017	6.5	systemic MTX vs systemic + intrasac MTX	0	37
Li [85]	2019	China	Retrospective	2007–2018	6.1 ± 0.8	USg local injection MTX	0	101
Stepniak [86]	2019	Poland	prospective	2015–2018	6.0–10.0	selective chemioembolization with MTX + suction curettage	0	22
Tahaoglu [87]	2019	Turkey	Retrospective	2015–2018	ns	D&C vs systemic MTX vs LPS CSP removal vs hysteroscopic CSP removal	0	21
Vo [88]	2019	Vietnam	Retrospective	2015–2016	<8.0	foley + D&C curettage	1	311
Xiao [89]	2019	China	Retrospective	2014–2017	ns	MTX + surgery vs UAE + surgery vs surgery	0	103
Li [90]	2018	China	Retrospective	2011–2015	7.79 ± 1.96	transvaginal surgery vs transcervical resection + MTX/mifepristone-combined treatment	0	54
Jabeen [91]	2018	UK	Retrospective	2012–2017	6	conservative management vs systemic MTX injection	1	26
Tumenjargal [92]	2018	Japan	Retrospective	2006–2017	6.27 ± 1.19	UAE followed by D&C	0	33
Sun QL [93]	2018	China	Retrospective	2012–2015	ns	UACE followed by evacuation	0	395
Sel [94]	2018	Turkey	Retrospective	2015–2018	ns (<8 wks)	vacuum extraction under ultrasound guidance	0	12
Le [95]	2018	China	Retrospective	2011–2016	Ns	USgD&C vs D&C with hysteroscopic guidance vs vaginal vs laparotomy vs laparoscopy	0	313
Kim [96]	2018	Korea	Retrospective	2003–2015	6.5 ± 1.1	MTX+-KCL vs D&C vs wedge resection vs hysteroscopy vs UAE vs hysterectomy	0	58
Fu [97]	2018	China	Retrospective	2013–2014	7.45 ± 1.96	MTX + UACE + curettage under hysteroscopy or ultrasonography or laparoscopic scar resection	0	189
Gao [98]	2018	China	Retrospective	2011–2015	7.84 ± 1.53	UAE + curettage vs intra-arterial MTX infusion + UAE + curettage	0	93
Guo [99]	2018	China	Retrospective	2012–2017	7.73 ± 1.31	UAE vs laparoscopic cesarean scar pregnancy debridement surgery	0	87
Hofgaard [100]	2018	Sweden	Retrospective	2018–2019	6.0 ± 13	surgical treatment with robot assisted LPS removal and simultaneous repair of the uterine defect	0	14
Giampaolino [101]	2018	Italy	Retrospective	2013–2017	6.0–13.0	EM vs HSC (Hysteroscopic resection of gestational tissue) vs MTXii + D&S vs UAE + D&S vs UAE + Surg	1	45
Karahasanoglu [18]	2018	Turkey	Retrospective	2009–2013	6.8	suction curettage + Foley balloon tamponade	0	13
Kim YR [102]	2018	Korea	Retrospective	2009–2015	6.35 ± 0.9	systemic MTX vs local MTX	0	41
Li Y [103]	2018	China	Retrospective	2006–2016	7.23 ± 1.74	UACE + curettage	0	383
Wang S. [104]	2018	China	Retrospective	2013–2015	7.28 ± 1.58	curettage vs MTX im + curettage vs MTX ev + curettage	0	107
Chiang [105]	2017	Taiwan	Retrospective	1994–2015	7.9 ± 0.35	primary hysterotomy vs primary evacuation with uterine curettage or hysteroscopy vs primary MTX	0	90
Washburn [106]	2017	USA	Retrospective	2000–2012	6.97	intra-sac KCl, systemic MTX, combination of systemic MTX and intrasac KCl, vaginal misoprostol ($n = 1$) vs primary surgical management: D&C, non-emergent hysterectomy, laparoscopic resection	0	23
Hong [107]	2017	China	Retrospective	2014–2016	7.33 ± 1.32	HIFU + suction curettage under hysteroscopy vs UAE + suction curettage under hysteroscopy	0	152
Chai [108]	2017	China	Retrospective	july 2016–december 2016	6.56	local lauromacrogol injection and aspiration	0	18
Chen [109]	2017	China	Retrospective	2014–2016	4.36 ± 0.44	transvaginal hysterotomy vs UAE + curettage	0	76

(*Continued*)

Table 1. Continued.

First author	Year	Country	Study design	period	Gestational age at intervention	Type of intervention	Stratification according to GA at intervention or maternal sympotms	Cases (n)
Fang [110]	2017	China	Retrospective	2010–2014	6.8 ± 1.02	USg D&C	0	82
Liu [111]	2017	China	Retrospective	2014–2016	7.84 ± 2.13	UAE + local MTX + D&C vs UAE + local MTX vs D&C	0	86
Ma [112]	2017	China	Retrospective	2012–2016	6.86	GS TAE + curettage vs PVA TAE + curettage	0	35
Ozcan [113]	2017	Turkey	Retrospective	2011–2016	5.0–14.0	USg D&C vs abdominal hysterotomy	0	50
Pan [114]	2017	China	Retrospective	2012–2015	Ns	hysteroscopic surgery	0	44
Wu [115]	2017	China	Retrospective	2014–2015	ns	ultrasound-guided suction curettage + cook cervical ripening balloon	0	15
Uludag [116]]	2016	Turkey	Retrospective	2000–2015	5.9 ± 0.9	local MTX injection vs systemic MTX	0	44
Li [117]	2016	China	RCT	2010–2014	ns	UACE (Uterine Artery chemoembolization) + D&C	0	144
Feng [118]	2016	China	Retrospective	2010–2012	8.34 ± 3.7	uterine curettage +- prophylactic UAE or MTX	0	30
Liu [119]	2016	China	Retrospective	2013–2015	7.19 ± 2.0	USg D&C	0	51
Liu W [120]	2016	China	Retrospective	2005–2013	8.15 ± 2.5	UAE + curettage vs systemic MTX + curettage	0	64
Li Y [121]	2016	China	Retrospective	2009–2014	7.89	MTX + D&C vs UAE + D&C vs laparotomic excision vs UAE + laparotomic excision	0	52
Ozdamar [122]	2016	Turkey	Retrospective	2008–2014	7.18 ± 1.17	USg suction curettage alone vs USg suction curettage + additional therapeutic tools (systemic MTX or intracavitary MTX or intracavitary ethanol instillation)	0	33
Xiao [123]	2016	China	Retrospective	2012–2014	7.16 ± 1.19	HIFU vs UAE + MTX intra-arterial + uterine curettage	0	76
Yang [124]	2016	China	prospective	2006–2011	ns	systemic MTX vs UAE	0	131
Zhu [125]	2016	China	Retrospective	2014	8.27 ± 2.32	HIFU + curettage vs UAE + curettage	0	122
Jurkovic [126]	2016	United Kingdom	Retrospective	1997–2014	7.57	US guided suction curettage +/- cervical suture or Foley ballon	Not performed	191
Zhu [127]	2015	China	Retrospective	2014	6.81 ± 0.71	HIFU + suction curettage	0	53
Du [128]	2015	China	Retrospective case-control	2006–2012	8.3 ± 2.09	UAE + suction curettage	0	175
Liu [129]	2015	China	RCT	2008–2013	7.76 ± 5.18	MTX local vs MTX systemic	0	104
Polat [130]	2015	Turkey	Retrospective	2005–2014	7.89	suction curettage vs MTX vs hysterectomy as first line treatment	1	26
Qian [131]	2015	China	prospective	2008–2013	7.38 ± 1.33	UAE before D&C vs UAE before operative hysteroscopy + curettage	0	66
Timor tritsh [132]	2015	USA	Prospective	2009–2014	7.93 ± 0.34	MTX intralesional injection/ expectant management	0	60
Michaels [133]	2015	USA	Retrospective	2000–2012	6.8 ± 1.6	systemic MTX + KCl vs intrasac KCl vs D&C vs expectant management vs hysterectomy vs laparoscopy vs systemic MTX vs misoprostolo + D&C	0	34
Qi [134]	2015	China	Retrospective case-series	2009–2013	7.3 ± 1.88	UAE + local MTX before curettage vs UAE before curettage	0	40
Peng [135]	2015	China	Retrospective	2012–2013	6.0–11.6	US guided evacuation and Foley balloon compression of the lower uterine segment	0	23
Wang [136]	2015	China	RCT	2008–2014	7.23 ± 0.38	UAE + MTX vs USg MTX	0	45
Huang [137]	2015	China	Retrospective	2009–2014	6.01 ± 0.9	UAE + MTX + uterine curettage	0	31
Ko [138]	2015	China	Retrospective	2004–2013	6.7	expectant management vs intramuscular MTX vs intralesional MTX vs intralesional MTX + KCl vs transvaginal aspiration vs USg suction evacuation vs laparotomy	0	22
Peng [129]	2015	China	RCT	2008–2013	7.95 ± 3.02	local MTX injection vs systemic MTX injection	0	104
Timor-Tristsch [139]	2015	USA	Retrospective	2013–2014	5.0–12.2	local + IM MTX followed by Foley catheter	0	16
Sun [140]	2015	China	Retrospective	2008–2012	6.45 ± 2.55	LPT surgery vs UAE + MTX	0	29
Wu [141]	2015	China	Retrospective	2009–2013	Ns	transabdominal sonography-guided D&C	0	232
Zhang [142]	2015	China	Retrospective	2010–2012	8.57	transvaginal surgery	0	25
Cheng [143]	2014	Taiwan	Retrospective	2000–2012	6.8–7.0	primary suction curettage	0	48
Gao [144]	2014	China	Retrospective	2009–2012	7.0 ± 1	MTX + D&C vs UAE + D&C	0	119
Cok [145]	2014	Turkey	case report	2011–2014	6.3	US guided local MTX	0	18
Huanxiao [146]	2014	China	Retrospective	2009–2013	8.4 ± 2.3	primary transvaginal hysterotomy vs transvaginal hysterotomy after primary conservative treatment	0	40
Xiao [147]	2014	China	Prospective	2011–2012	6.9 ± 1.2	HIFU ablation	0	16
Kutuk [148]	2014	Turkey	Retrospective cohort	2010–2012	5.5	systemic multidose MTX	0	13

(*Continued*)

Table 1. Continued.

First author	Year	Country	Study design	period	Gestational age at intervention	Type of intervention	Stratification according to GA at intervention or maternal sympotms	Cases (n)
Weiling [149]	2014	China	Prospective	2009–2013	7.28 ± 1.0	suction curettage	0	21
Wang [150]	2014	China	Retrospective case-series	2002–2010	6.0–10.0	laparoscopic surgery	0	31
Wang [151]	2014	China	Retrospective	2009–2011	7.7 ± 2.2	Hysteroscopic surgery vs laparoscopic surgery	0	71
Wang [152]	2014	China	Retrospective	2008–2012	7.45 ± 2.5	lesion resection by transvaginal approach vs lesion resection by transabdominal approach	0	33
Li [153]	2014	China	Retrospective	2009–2013	7.71	primary transvaginal surgery vs any previous treatment + transvaginal surgery	0	49
Seveket [154]	2014	Turkey	Retrospective	2008–2012	7.33 ± 1.54	systemic MTX + suction curettage vs suction curettage only	0	25
He [155]	2014	China	Retrospective	2005–2010	ns	MTX + UAE + combined laparoscopy and hysteroscopy vs MTX + UAE + ultrasound guided curettage	0	58
LiY [156]	2014	China	Retrospective	2008–2011	9.62	uterine curettage by hysteroscopy under ultrasound monitoring vs MTX + hysteroscopy vs UAE + hysteroscopy	0	124
Wu [157]	2014	China	Prospective	2009–2010	2.0–8.0	intra-arterial MTX + UAE + combined laparoscopy and hysteroscopy vs intra-arterial MTX + UAE + curettage	0	58
Xiao [147]	2014	China	prospective	2011–2012	6.9 ± 1.24	ultrasound-guided HIFU ablation	0	16
Yang [124]	2014	China	prospective	2006–2011	ns	UAE vs MTX im injection	0	131
Yin [158]	2014	China	Retrospective	2000–2013	8.8 ± 5.0	USg gestational sac MTX injection vs local IM MTX vs UAE MTX perfusion	1	34
Zhang [159]	2013	China	Retrospective	2005–2011	5.0–8-0	UAE-MTX-SS-mifepristone before hystero-lap	0	10
Wang [160]	2013	China	Prospective	2007–2012	7.1–2.3	D&C + uterine artery embolization	0	128
Seow [161]	2013	China	Retrospective	2006–2011	5.3 – 7.6	transvaginal aspiration + local MTX	0	11
Le [162]	2013	China	prospective	2008–2012	Ns	UAE vs endoscopic CSEP + chemotherapy vs transvaginal surgical therapy	0	38
Lan [163]	2013	China	Retrospective	2004–2010	7 (5–14)	UACE (Uterine Artery chemoembolization) + D&C	0	79
An [164]	2013	China	Retrospective	2010–2012	6.0–12.0	MTX + UAE	0	23
Wang [165]	2013	China	Retrospective	2008–2011	8.09	laparoscopic treatment (LPS bilateral uterine artery ligation and resection of the scar or LPS bilateral uterine artery ligationand transvaginal resection)	0	11
Zhang [166]	2013	China	Retrospective	2005–2010	6.57	curettage + MTX vs curettage + UAE vs MTX systemic + mifepristone vs curettage vs curettage + MTX + UAE + lesion resection	0	17
Shao [167]	2013	China	Retrospective	2010–2013	<7 vs >7	embriokilling: UACE vs MTX + leucovorin (CF)	1	61
Zhang [168]	2012	China	Retrospective	2009–2011	4.7–13.4	BUACE + D&C/D&C + BUACE	0	19
Zhang [169]	2012	China	Retrospective	2009–2012	7.0–9.0	UAE + curettage	0	15
Wu [170]	2012	China	Retrospective	2000–2010	6.9±.5	UAE + MTX vs MTX + curettage	0	47
Wang [171]	2012	China	Retrospective	2011–2012	7.3–10.4	transvaginal hysterotomy + MTX injection	0	12
Shen [172]	2012	China	Retrospective	2008–2010	7.93 ± 0.34	UAE + local MTX vs primary suctione curettage + UAE	0	46
Li [173]	2012	China	Prospective	2008–2010	3.75 ± 1.27	MTX systemic + curettage + hysteroscopic surgery vs transvaginal aspiration + local MTX	0	68
Timor tritsh [174]	2012	USA	Retrospective	2009–2011	6.0–14.0	intragestational + systemic MTX vs without MTX (expectant management, balloon catheter, UAE)	0	26
Yin [175]	2011	China	Retrospective	2002–2008	5.8–10.1	UAEC + vacuum aspiration	0	13
Jiang [176]	2011	China	Prospective	2007–2009	7.17 ± 1.65	MTX + suction curettage + Foley tamponade	0	45
Lian [177]	2011	China	Retrospective	2005–2009	7.89 ± 3.02	Primary systemic MTX vs primary systemic MTX + UAE + local MTX	0	33
Li [178]	2011	China	Prospective	2002–2009	9.3 ± 2.5	systemic MTX vs chemoembolization + MTX + GA particles vs chemoembolization + MTX + PVA particles	0	44
Li [179]	2011	China	Retrospective	2004–2010	7.24	hysteroscopy +- laparoscopy (+-MTX or UAE before endoscopic treatment)	0	21
Yang [180]	2010	China	Retrospective	2003–2008	6.0–12.1	MTX systemic or D&C or MTX local + UAE	0	73
Fahg [181]	2009	China	Retrospective	2004–2008	7.4 ± 0.7	UAE before D&C vs MTX or trichosanthin injection before UAE and D&C	0	48

(*Continued*)

Table 1. Continued.

First author	Year	Country	Study design	period	Gestational age at intervention	Type of intervention	Stratification according to GA at intervention or maternal sympotms	Cases (n)
Zhuang [182]	2009	China	Prospective	2003–2007	7	MTX + suction curretage vs UAE + suction curettage	0	72
Yang [183]	2009	China	Retrospective	2006–2008	5.0–12.8	hysteroscopic surgery	0	39
Wang [184]	2009	China	Prospective	2000–2007	7.97 ± 2.4	MTX only vs MTX + D&C	0	71
Michener [185]	2009	Australia	Retrospective	2002–2007	7.9	MTX systemic vs hysterectomy vs suction curettage vs intrasac MTX	1	13
Wang [186]	2006	China	Prospective	1999–2004	8.4 ± 1.7	laparoscopic surgery + hysteroscopic surgery vs hysreroscopic surgery vs laparoscopic surgery	0	11
Jurkovic [187]	2003	UK	Retrospective	1998–2002	6.67	D&C +/- Foley catheter vs local MTX vs expectant management	1	17

D&C: Dilatation and curettage; HIFU: High focused intensity ultrasound; LPS: Laparoscopic; LPT: Laparotomy; MTX: methotrexate; UAE: Uterine artery embolization; Usg: Ultrasound guided; UACE: Uterine artery chemoembolization.

Finally, post-treatment complications occurred in 2.8% (95% CI 0.9–5.7) of women treated with systemic MTX, 3.4% (95% CI 1.1–6.9) with local MTX or KCl, 1.7 (95% CI 0.4–3.7) with hysteroscopy, 12.3% (95% CI 3.3–61.2) with high intensity focused ultrasound, and in none of the cases treated with interventional radiology or laparoscopy.

When considering combined treatments, a successful treatment of CSP was achieved in 93.5% (95% CI 90.5–95.9) of women treated with interventional radiology and curettage, 85.5% (95% CI 70.3–95.7) with systemic MTX and curettage, 62.8% (95% CI 18-4–96.7) with local MTX and curettage, 94.8% (95% CI 89.8-98.2) with balloon and curettage, 98.2% (95% CI 95.5–99.7) with high intensity focused ultrasound and curettage, 95.2% (95% CI 91.3–97.9) with interventional radiology and hysteroscopy, 96.8% (95% CI 92.1–99.5) with interventional radiology and systemic MTX and in 96.6% (95% CI 93.8–98.6) with curettage and hysteroscopy.

Comparison of various treatments

Computation of the comparisons between the different treatments was affected by the smaller number of included studies compared to the main analysis, lack of comparison for the most used treatments for CSP and heterogeneity in outcome assessment among the included studies. There was no difference in any of the observed outcomes when comparing systemic vs local MTX; conversely, curettage was associated with a higher chance of achieving a successful treatment (OR 0.22, 95% CI 0.07–0.64) and lower risk of requiring additional treatments (OR 4.57, 95% CI 1.6–13.3) compared to systemic MTX. Systemic MTX and curettage had a lower chance of achieving a successful treatment compared to interventional radiology and curettage (OR 0.28, 95% CI 0.09–0.84). Likewise, IR and curettage had a higher chance of achieving a successful treatment (OR 0.19, 95% CI 0.05–0.70) but also presented a higher risk of post-treatment complications (OR 0.18, 95% CI 0.006–0.52). A comparison between the different treatments for CSP is reported in Table 4.

Discussion

Summary of the key findings

The findings from this systematic review showed that a multitude of treatments for CSP have been reported in the published literature. Although a direct comparison could not be performed for all the different management options, all minimally invasive and invasive treatments showed apparently similar effectiveness in resolving the CSP. Suction curettage was associated with a higher chance of achieving a successful treatment and lower risk of requiring additional treatments. Systemic MTX was associated with a relatively lower chance of achieving a successful treatment without the need for additional measures to resolve the CSP. There was a large heterogeneity in inclusion criteria, GA at diagnosis, maternal conditions and CSP phenotypes among the published studies, thus making it difficult to summarize objective evidence to guide clinical practice. Treatments comparison was also difficult as only a small proportion of the included studies reported a comparison between the most commonly used treatments, and this made computation of the risk analysis difficult.

More importantly, the definition of CSP was not consistent among the included studies and no meaningful sub-group analysis according to factors impacting the outcome of CSP such as gestational age at presentation, severity of maternal symptoms, magnitude and extension of peri-trophoblastic vascularity

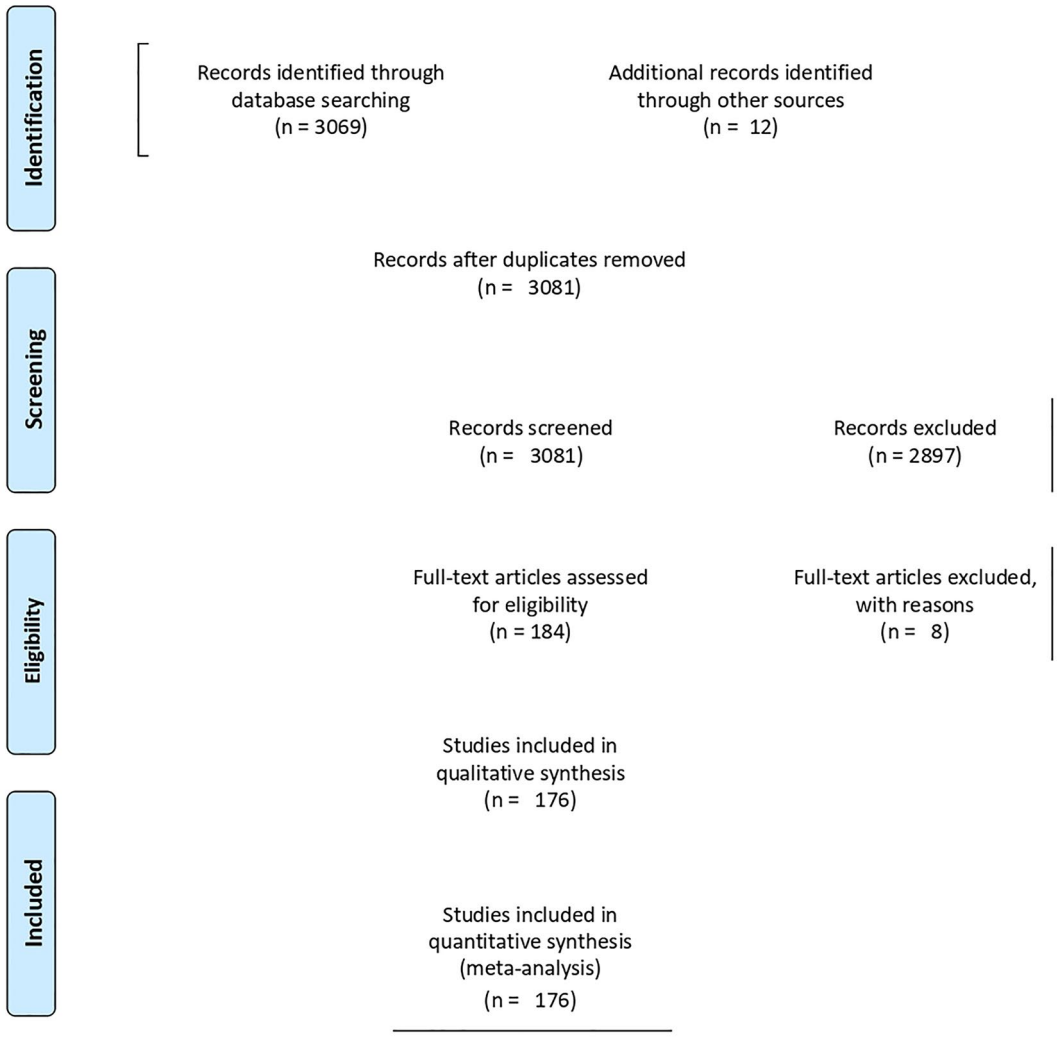

Figure 1. Systematic review flow chart.

could be performed. The findings from this review highlight the need for future studies aimed at exploring the influence of maternal and ultrasound characteristic in defining the outcome of CSP rather the type of treatment per se.

Comparison with other systematic reviews, strengths and limitations

This is, to the best of our knowledge, the largest systematic review and meta-analysis reporting the outcomes of women with CSP undergoing treatment.

A prior systematic review published in 2017 including 63 studies, reported the outcome of women undergoing treatment for CSP [188]. Another systematic review including 36 studies, reported the outcome in women with CSP treated before compared to after 9 weeks of gestations [189]. The authors reported that early treatment of CSP was associated with a lower risk of maternal complications and uterine rupture but did not report the occurrence of the explored outcomes according to each treatment option.

The main strengths of the present study include a thorough literature search, large sample size, multitude of outcomes explored and stratification of the analysis according to the type of intervention (overall vs elective) and inclusion of minimally invasive treatments, not reported in previously published systematic reviews. The primary limitations lie in the retrospective non-randomized design of most of the included studies, dissimilarity in the included populations and heterogeneity in outcome assessment and definition represent the main limitations of the present review. In particular, we could not stratify all the analyses according to the GA at treatment, presence of maternal co-morbidities, number of prior CD and CSP phenotype, as the large majority of the studies did not report aggregate data for this information, thus making a pooled analysis not feasible. Assessment of the potential publication bias may also be a limitation due

Table 2. Pooled proportions for the different outcomes observed in the present systematic review in women with CSP undergoing treatment.

Outcome	Studies	Women (n/N)	Pooled proportions	I^2 (%)
Single treatment				
Suction curettage under ultrasound guidance				
Successful treatment	8	268/324	86.20 (82.26–89.71)	91.9
Need for additional treatments	8	56/324	16.62 (4.57–34.27)	53.8
Need for transfusion	6	17/270	5.33 (1.72–10.76)	42.4
Emergency laparotomy	8	2/324	0.91 (0.17–2.22)0	0
Hysterectomy	8	1/324	1.07 (0.24–2.47)	0
Post-treatment complications	3	0/76	0 (0–72.9)	0
Systemic methotrexate				
Successful treatment	30	407/579	72.38 (64.84–79.33)	71.5
Need for additional treatments	30	171/479	27.62 (20.68–35.16)	71.5
Need for transfusion	15	21/291	5.28 (1.61–10.92)	67.3
Emergency laparotomy	18	15/295	4.73 (0.19–8.80)	46.5
Hysterectomy	18	12/295	4.18 (1.82–7.46)	29.4
Operative complications	16	8/272	3.54 (1.70–6.02)	0
Local methotrexate or KCL				
Successful treatment	16	380/456	81.56 (72.25–89.33)	78.6
Need for additional treatments	16	76/456	18.44 (10.67–27.75)	78.6
Need for transfusion	3	3/92	4.44 (0.39–12.55)	35.2
Need for laparotomy	16	14/375	3.07 (0.70–7.04)	61.9
Hysterectomy	16	12/375	2.40 (0.46–5.79)	57.6
Post-treatment complications	9	24/230	5.91 (0.84–15.11)	77.5
Interventional radiology				
Successful treatment	7	418/467	83.88 (66.73–95.60)	90
Need for additional treatments	7	49/467	16.12 (4.41–33.27)	90
Need for transfusion	6	6/464	2.58 (0.03–8.95)	80.5
Need for laparotomy	5	1/432	0.49 (0.03–0.95)	24.7
Hysterectomy	5	1/432	0.49 (0.03–0.95)	24.7
Operative complications	5	1/120	1.21 (0.09–3.46)	22.1
Hysteroscopy				
Successful treatment	16	444/498	90.42 (82.87–95.95)	81.5
Need for additional treatments	16	54/498	9.58 (4.05–17.13)	81.5
Need for transfusion	11	8/281	3.25 (1.525.61)	0
Emergency laparotomy	14	3/434	1.10 (0.34–2.29)	0
Hysterectomy	14	1/4340	0.80 (0.19–1.85)	0
Operative complications	11	3/336	1.36 (0.41–2.86)	0
Laparoscopy				
Successful treatment	16	398/422	96.07 (92.26–98.63)	56.8
Need for additional treatments	16	24/422	3.93 (1.37–7.74)	56.8
Need for transfusion	8	22/283	5.02 (0.66–13.13)	79
Emergency laparotomy	13	1/290	1.15 (0.25–2.67)	0
Hysterectomy	13	0/290	0 (0–2.34)	0
Operative complications	9	0/231	0 (0–2.39)	0
High intensity focused ultrasound				
Successful treatment	4	114/126	92.56 (78.17–99.56)	81.7
Need for additional treatments	4	12/126	7.44 (0.44–21.83)	81.7
Need for transfusion	4	0/126	0 (0–2.93)	0
Emergency laparotomy	4	3/126	2.60 (0.50–6.27)	7.8
Hysterectomy	4	0/126	0 (0–2.96)	0
Operative complications	4	17/126	5.45 (0.36–25.67)	90.8
Interventional radiology + curettage				
Successful treatment	49	2657/2923	91.92 (88.03–95.10)	91.5
Need for additional treatments	49	66/2923	8.08 (4.90–11.97)	91.5
Need for transfusion	24	36/1343	1.96 (0.84–3.54)	62.7
Emergency laparotomy	42	30/2520	1.39 (0.82–2.11)	37.8
Hysterectomy	42	23/2520	1.10 (0.65–1.67)	24.7
Operative complications	34	414/2027	13.88 (6.96–22.68)	96.2
Systemic methotrexate + curettage				
Successful treatment	13	275/341	83.25 (68.76–93.84)	89.9
Need for additional treatments	13	66/341	16.75 (6.13–31.24)	89.9
Need for transfusion	10	9/290	2.98 (0.59–7.13)	61.2
Emergency laparotomy	13	11/341	3.53 (1.22–6.97)	50
Hysterectomy	13	10/341	3.11 81.03–6.25)	46.2
Operative complications	11	47/316	15.73 (2.68–36.75)	94.7
Local methotrexate + curettage				
Successful treatment	6	118/145	79.39 (56.27–95.24)	88.7
Need for additional treatments	6	27/145	20.61 (4.76–43.73)	88.7
Need for transfusion	4	2/125	1.99 (0.30–5.12)	0
Emergency laparotomy	6	1/145	1.29 (0.11–3.72)	0
Hysterectomy	6	0/145	0 (0–3.08)	0
Operative complications	4	16/121	12.70 (1.55–32.24)	84.9

(*Continued*)

Table 2. Continued.

Outcome	Studies	Women (n/N)	Pooled proportions	I^2 (%)
Curettage + balloon				
Successful treatment	8	480/514	96.18 (92.33–98.73)	56.5
Need for additional treatments	8	34/514	3.82 (1.27–7.67)	56.5
Need for transfusion	5	5/441	2.32 (0.007–7.59)	75.4
Emergency laparotomy	8	0/514	0 (0–0.91)	0 (0–0.91)
Hysterectomy	8	0/514	0 (0–0.91)	0 (0–0.91)
Operative complications	4	0/370	0 (0–0.85)	0
High intensity focused ultrasound + curettage				
Successful treatment	8	585/595	98.33 (95.87–99.70)	67.8
Need for additional treatments	8	10/595	1.67 (0.30–4.13)	67.8
Need for transfusion	8	19/595	2.64 (3.29–7.06)	84.2
Emergency laparotomy	8	1/595	0.49 (0.088–1.20)	0
Hysterectomy	8	0/595	0 (0–0.90)	0
Operative complications	5	51/266	13.86 (0.60–45.33)	97.2
Interventional radiology + hysteroscopy				
Successful treatment	6	252/282	91.14 (83.40–96.97)	73.3
Need for additional treatments	6	30/282	8.58 (3.03–16.60)	73.3
Need for transfusion	6	0/282	0 (0–1.58)	0
Emergency laparotomy	6	0/282	0 (0–1.58)	0
Hysterectomy	6	0/282	0 (0–1.58)	0
Operative complications	5	74/271	16.60 (1.78–42.06)	95.3
Interventional radiology + systemic methotrexate				
Successful treatment	3	80/95	64.27 (13.80–99.17)	93.6
Need for additional treatments	3	15/95	35.73 (0.83–86.20)	93.6
Need for transfusion	3	0/95	0 (0–3.02)	0
Emergency laparotomy	3	4/95	6.71 (0.51–31.46)	81.8
Hysterectomy	3	0/95	0 (0–3.02)	0
Operative complications	3	12/95	16.57 (3.71–73.71)	95
Curettage + hysteroscopy				
Successful treatment	5	668/703	95.52 (92.94–97.54)	40.5
Need for additional treatments	5	35/703	4.48 (2.46–7.06)	40.5
Need for transfusion	5	14/703	1.67 (0.56–3.37)	39.4
Emergency laparotomy	5	0/703	0 (0–0.54)	0
Hysterectomy	5	0/703	0 (0–0.54)	0
Operative complications	5	0/703	0 (0–0.54)	0

to the nature of the outcomes evaluated (outcome rates, with the left-side limited to a value of zero).

Clinical and research implications

Prenatal counseling of women with CSP is challenging as its natural history is unpredictable [4,6]. The management options for women with live CSP include continuation or termination of pregnancy. In cases where the parents opted for termination, it is yet to be ascertained the optimal strategy to resolve CSP.

Treatments options for CSP include minimally invasive treatments, including suction curettage, local injection of MTX or KCL in the gestational sac or balloon catheter compression of the CSP, either in isolation or combined with other systemic treatments such as MTX or interventional radiology or major surgery such as CSP resection by laparoscopy or laparotomy. The rationale of minimally invasive treatments is to resolve the CSP without the need of major surgery.

The main issue in defining the outcome and an optimal therapeutic strategy for CSP is its definition which largely differ among the published studies. Some authors differentiate between CSPs located on the 'well-healed' cesarean delivery and those implanted in the dehiscent scar, while others used the level of invasion of the gestational sac and the remaining myometrial thickness to diagnose CSP and determine its severity. A recent consensus Delphi reported that CSP should be defined as a pregnancy with implantation in, or in close contact with, the niche [8]. The authors also reported that a CSP can occur only when a niche is present and not in relation to a healed cesarean delivery scar. Like PAS, CSP is not a unique condition but encompasses a heterogeneous group of abnormalities whose severity depends upon the relationship between the size and shape of the niche, residual myometrial thickness, peri-trophoblastic vascularity, and the size and the location of the gestational sac. Unfortunately, it was not possible to perform a pooled data synthesis reporting the outcome of CSP according to the ultrasound phenotype. This heterogeneity in CSP definition highlights the need to adopt a standardized diagnostic criteria and uniform approach to ultrasound assessment in the future studies on CSP in order to provide more objective evidence on its natural history.

Outcome definition in CSP represents another challenge. Studies on CSP treatment differ in the definition of primary outcome. Deciding on the most appropriate outcome of CSP is not easy. Severe events

Table 3. Pooled proportions for the different outcomes observed in the present systematic review in women with CSP undergoing elective treatment.

Outcome	Studies	Women (n/N)	Pooled proportions	I^2 (%)
Suction curettage under ultrasound guidance				
Successful treatment	4	136/156	68.04 (45.05–87.15)87.9	87.9
Need for additional treatments	4	52/156	31.96 (12.85–54.95)	87.9
Need for transfusion	2	6/41	4.22 (0.13–18.94)	83.5
Emergency laparotomy	4	2/156	1.70 (0.13–4.96)	27.4
Hysterectomy	4	0/156	0 (0–2.4)	0
Post-treatment complications	–	–	–	–
Systemic methotrexate				
Successful treatment	10	76/266	72.38 (57.89–84.80)	82.7
Need for additional treatments	10	90/266	27.62 (15.20–42.11)	82.7
Need for transfusion	4	0/64	0 (0–5.50)	0
Emergency laparotomy	6	8/131	8.85 (0.50–25.83)	84.2
Hysterectomy	6	7/131	5.80 (0.52–16.21)	70.6
Operative complications			2.81 (0.93–5.66)	0
Local methotrexate or KCL				
Successful treatment	8	295/344	86.29 (74.75–94.70)	86
Need for additional treatments	8	49/344	13.71 (5.30–25.25)	86
Need for transfusion	3	1/91	2.05 (0.18–5.91)	0
Need for laparotomy	3	3/270	1.33 (0.24–3.26)	3
Hysterectomy	3	1/270	0.93 (0.14–2.41)	3
Post-treatment complications	4	4/147	3.37 (1.09–6.86)	0
Interventional radiology				
Successful treatment	3	61/150	47.54 (10.50–86.29)	96.3
Need for additional treatments	3	89/150	52.46 (13.71–89.50)	96.3
Post-treatment hemorrhage	2	0/73	0 (0–3.8)	0
Need for laparotomy	2	0/73	0 (0–3.8)	0
Hysterectomy	2	0/73	0 (0–3.8)	0
Operative complications	2	0/73	0 (0–3.8)	0
Hysteroscopy				
Successful treatment	7	243/262	93.94 (86.89–98.40)	71.8
Need for additional treatments	7	19/262	6.06 (1.61–13.11)	71.8
Need for transfusion	7	8/262	3.10 (1.08–6.10)	24.9
Emergency laparotomy	7	2/262	1.04 (0.18–2.61)	0
Hysterectomy	7	2/262	1.04 (0.18–2.61)	0
Operative complications	7	8/262	1.67 (0.43–3.71)	8.7
Laparoscopy				
Successful treatment	4	102/102	100 (96.48–100)	0
Need for additional treatments	4	0/102	0 (0–3.52)	0
Need for transfusion	4	1/102	1.81 (0.15–5.25)	0
Emergency laparotomy	4	0/102	0 (0–3.52)	0
Hysterectomy	4	0/102	0 (0–3.52)	0
Operative complications	4	0/102	0 (0–3.52)	0
High intensity focused ultrasound				
Successful treatment	3	83/95	88.83 (70.05–98.95)	80.1
Need for additional treatments	3	12/95	11.17 (1.05–29.95)	80.1
Need for transfusion	3	0/95	0 (0–3.39)	0
Emergency laparotomy	3	0/95	0 (0–3.39)	0
Hysterectomy	3	0/95	0 (0–3.39)	0
Operative complications	3	25/95	12.30 (3.27–61.22)	96.2
Interventional radiology + curettage				
Successful treatment	29	1276/1348	93.47 (90.50–95.92)	71.9
Need for additional treatments	29	72/1348	6.53 (4.08–9.50)1	71.9
Need for transfusion	15	4/469	1.10 (0.36–2.23)	0
Emergency laparotomy	27	7/1263	0.75 (0.35–1.30)	0
Hysterectomy	27	1/1263	0.48 (0.17–0.93)	0
Operative complications	18	179/951	15.31 (6.75–26.52)	
Systemic methotrexate + curettage				
Successful treatment	5	131/153	85.53 (70.33–95.66)	74.2
Need for additional treatments	5	22/153	14.66 (4.37–29.67)	74.2
Need for transfusion	5	2/153	2.07 (0.10–6.44)	36.7
Emergency laparotomy	5	6/153	4.26 (0.30–12.50)	63.4
Hysterectomy	5	4/153	2.63 (0.16–7.80)	45.4
Operative complications		0/153	0 (0–2.49)	0
Local methotrexate + curettage				
Successful treatment	3	75/115	62.83 (18.37–96.68)	96.3
Need for additional treatments	3	40/115	37.17 (3.32–81.63)	96.3
Need for transfusion	3	3/115	3.04 (0.47–7.73)	27
Emergency laparotomy	3	0/115	0 (0–2.85)	0
Hysterectomy	3	0/115	0 (0–2.85)	0
Operative complications	3	10/115	7.71 (0.37–23.15)	82.9
Curettage + balloon				
Successful treatment	5	421/455	94.83 (89.81–98.23)	60.5

(*Continued*)

Table 3. Continued.

Outcome	Studies	Women (n/N)	Pooled proportions	I^2 (%)
Need for additional treatments	5	34/455	5.17 (1.77–10.19)	60.5
Need for transfusion	5	2/455	0.83 (0.012.89)	45.1
Emergency laparotomy	5	0/455	0 (0–0.82)	0
Hysterectomy	5	0/455	0 (0–0.82)	0
Operative complications	5	0/455	0 (0–0.82)	0
High intensity focused ultrasound + curettage				
Successful treatment	8	552/562	98.17 (95.52–99.66)	67.1
Need for additional treatments	8	10/562	1.83 (0.34–4.48)	67.1
Need for transfusion	6	0/386	0 (0–1.18)	0
Emergency laparotomy	8	1/562	0 (00.94)	0
Hysterectomy	8	0/562	0.51 (0.091–1.26)	0
Operative complications	5	45/241	12.59 (0.73–41.35)	96.3
Interventional radiology + hysteroscopy				
Successful treatment	4	153/160	95.16 (91.33–97.92)	0
Need for additional treatments	4	7/160	4.84 (2.08–8.67)	0
Need for transfusion	4	0/160	0 (0–2.20)	0
Emergency laparotomy	4	0/160	0 (0–2.20)	0
Hysterectomy	4	0/160	0 (0–2.20)	0
Operative complications	4	44/160	24.61 (18.31–31.52)	91.2
Interventional radiology + systemic methotrexate				
Successful treatment	2	81/83	96.81 (92.09–99.47)	0
Need for additional treatments	2	2/83	3.19 (0.53–7.99)	0
Need for transfusion	2	0/83	0 (0–3.14)	0
Emergency laparotomy	2	0/83	0 (0–3.14)	0
Hysterectomy	2	0/83	0 (03.14)	0
Operative complications	2	0/83	0 (0–3.14)	0
Curettage + hysteroscopy				
Successful treatment	2	291/301	96.62 (93.78–98.63)	22.1
Need for additional treatments	2	10/301	3.38 (1.37–6.22)	22.1
Need for transfusion	2	4/301	1.22 (0.08–3.67)	44
Emergency laparotomy	2	0/301	0 (0–0.92)	0
Hysterectomy	2	0/301	0 (0–0.92)	0
Operative complications	–	–	–	–

Table 4. Pooled odd ratio for the different outcomes observed in the present systematic review in women with CS.

Outcome	Studies	Women (n/N)	Pooled proportions	I^2 (%)	*p*-value
Systemic vs local MTX					
Successful treatment	7	128/170 vs 146/187	0.88 (0.47.1.65)	16.9	0.688
Need for additional treatments	7	42/170 vs 41/187	1.15 (0.60–2.24)	21.9	0.666
Need for transfusion	4	0/108 vs 0/106	–	–	–
Emergency laparotomy	5	0/116 vs 0/128	–	–	–
Hysterectomy	5	0/116 vs 0/128	–	–	–
Post-treatment complications	5	6/160 vs 4/158	1.39 (0.39–4.97)	0	0.613
Systemic MTX vs curettage					
Successful treatment	9	42/74 vs 65/79	0.22 (0.07–0.64)	0	0.006
Need for additional treatments	9	32/74 vs 14/79	4.57 (1.57–13.27)	0	0.005
Need for transfusion	7	0/67 vs 4/67	0.16 (0.01-2.30)	0	0.178
Emergency laparotomy	7	1/67 vs 4/58	0.077 (0.007–0.81)	0	0.033
Hysterectomy	7	1/67 vs 4/58	0.077 (0.007–0.81)	0	0.033
Operative complications	7	3/65 vs 6/71	1.41 (0.08–25.17)	48.9	0.842
Curettage vs local MTX					
Successful treatment	3	35/44 vs 18/24	1.33 (0.26–6.90)	0	0.923
Need for additional treatments	3	9/44 vs 6/24	0.69 (0.12–3.85)	2	0.976
Need for transfusion	2	0/42 vs 2/17	0.04 (0.003–0.61)	0	0.004
Emergency laparotomy	2	1/42 vs 0/17	0.49 (0.02–13.47)	0	0.676
Hysterectomy	2	0/42 vs 0/17	–	–	–
Post-treatment complications	2	0/42 vs 0/17	–	–	–
systemic MTX + curettage vs IR + curettage					
Successful treatment	7	123/144 vs 214/226	0.28 (0.09–0.84)	35.4	0.023
Need for additional treatments	7	21/144 vs 12/226	3.50 (1.20–10.21)	33.8	0.021
Post-treatment hemorrhage	7	8/144 vs 0/226	16.13 (2.17–119.74)	65.9	<0.001
Need for laparotomy	7	16/144 vs 1/226	8.01 (1.18–54.24)	50.7	0.033
Hysterectomy	7	9/144 vs 1/226	4.71 (1.33–16.64)	44.3	0.009
Operative complications	7	43/144 vs 28/226	3.92 (2.24–6.86)	74.2	<0.001
Local MTX + curettage vs IR + curettage					
Successful treatment	2	70/84 vs 76/79	0.19 (0.05–0.70)	0	0.013
Need for additional treatments	2	14/84 vs 3/79	5.23 (1.42–19.24)	0	0.013
Need for transfusion	2	2/84 vs 0/79	4.62 (0.21–99.48)	0	0.383
Emergency laparotomy	2	0/84 vs 0/79	–	–	–
Hysterectomy	2	0/84 vs 0/79	–	–	–
Operative complications	2	7/84 vs 19/79	0.18 (0.06–0.52)	0	0.002

associated with CSP such as uterine rupture are anecdotally reported in the literature while others such as the magnitude of blood loss, need for additional emergency treatments or post-surgical complications depends upon several factors such as surgeon's skill, timing at diagnosis and type of intervention. When assessing studies on outcome of treatment of live CSP, gestational age at the time of intervention should also be considered as interventions early in pregnancy tend to be associated with a reduced risk of hemorrhagic complications and less need for emergency intervention. In this scenario, a consensus statement on outcome reporting in CSP is also needed in order to provide a more comprehensive figure on the actual burden of maternal complications following a given treatment. Gestational age at intervention also affects the choice of the treatment [189]. Some treatment options, such as balloon compression or hysteroscopy, are technically more feasible and effective in the very early stages of pregnancy and the figures reported in the present systematic review for some of the interventions explored may have been the results of their higher efficacy when performed in early pregnancy rather than their actual effectiveness in resolving the disease per se.

Conclusions

All the reported treatment options for CSP showed a high effectiveness in resolving this condition. However, there was large heterogeneity as regard as definition of CSP, gestational age at treatment and outcome definition among the different studies, thus making extrapolation of an objective evidence of the optimal treatment of CSP difficult. The findings from this systematic review highlight the need for adopting a common nomenclature of staging of women with CSP in order to better elucidate its natural history and to plan appropriate trials which compare the different treatment option.

In view of the high heterogeneity in the clinical presentation of CSP, these RCTs should consider CSP phenotype and GA at intervention in order to provide robust evidence on how to treat CSP.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

What are the novel findings of this work?

A multitude of treatments for CSP have been reported in the published literature. All treatments described for CSP are apparently equally effective in treating this condition, although there was a high heterogeneity in the included studies as regard as gestational age at treatment, maternal co-morbidities and indication for treatment.

What are the clinical implications of this work?

The findings from this systematic review highlight the need for adopting a common definition and outcome reporting of CSP to better elucidate its natural history, estimate the magnitude of maternal complication after treatment and design appropriately powered RCT to elucidate the optimal treatment of CSP according to its ultrasound phenotype and gestational age at treatment, in terms of effective resolution of the condition and risk of post-intervention complications.

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Data available on request due to privacy restrictions.

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