OBSTETRICS

First-trimester cesarean scar pregnancy: a comparative analysis of treatment options from the international registry

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BACKGROUND: A cesarean scar pregnancy is an iatrogenic consequence of a previous cesarean delivery. The gestational sac implants into a niche created by the incision of the previous cesarean delivery, and this carries a substantial risk for major maternal complications. The aim of this study was to report, analyze, and compare the effectiveness and safety of different treatments options for cesarean scar pregnancies managed in the first trimester through a registry.

OBJECTIVE: This study aimed to evaluated the ultrasound findings, disease behavior, and management of first-trimester cesarean scar pregnancies.

STUDY DESIGN: We created an international registry of cesarean scar pregnancy cases to study the ultrasound findings, disease behavior, and management of cesarean scar pregnancies. The Cesarean Scar Pregnancy Registry collects anonymized ultrasound and clinical data of individual patients with a cesarean scar pregnancy on a secure, digital information platform. Cases were uploaded by 31 participating centers across 19 countries. In this study, we only included live and failing cesarean scar pregnancies (with or without a positive fetal heart beat) that received active treatment (medical or surgical) before 12+6 weeks' gestation to evaluate the effectiveness and safety of the different management options. Patients managed expectantly were not included in this study and will be reported separately. Treatment was classified as successful if it led to a complete resolution of the pregnancy without the need for any additional medical interventions.

RESULTS: Between August 29, 2018, and February 28, 2023, we recorded 460 patients with cesarean scar pregnancies (281 live, 179 failing cesarean scar pregnancy) who fulfilled the inclusion criteria and were registered. A total of 270 of 460 (58.7%) patients were managed surgically, 123 of 460 (26.7%) patients underwent medical management, 46 of 460 (10%) patients underwent balloon management, and 21 of 460 (4.6%) patients received other, less frequently used treatment options. Suction evacuation was very effective with a success rate of 202 of 221 (91.5%; 95% confidence interval, 87.8—95.2), whereas systemic methotrexate was least effective with only 38 of 64 (59.4%; 95% confidence interval, 48.4—70.4) patients not requiring additional treatment. Overall, surgical treatment of cesarean scar pregnancies was successful in 236 of 258 (91.5%, 95% confidence interval, 88.4—94.5) patients and complications were observed in 24 of 258 patients (9.3%; 95% confidence interval, 6.6—11.9).

CONCLUSION: A cesarean scar pregnancy can be managed effectively in the first trimester of pregnancy in more than 90% of cases with either suction evacuation, balloon treatment, or surgical excision. The effectiveness of all treatment options decreases with advancing gestational age, and cesarean scar pregnancies should be treated as early as possible after confirmation of the diagnosis. Local medical treatment with potassium chloride or methotrexate is less efficient and has higher rates of complications than the other treatment options. Systemic methotrexate has a substantial risk of failing and a higher complication rate and should not be recommended as first-line treatment.

Key words: balloon treatment, complications, hemorrhage, hysterectomy, KCl, management, methotrexate, suction evacuation, surgical excision

Introduction

Cesarean scar pregnancies (CSPs) can develop as consequence of a previous cesarean delivery (CD) with implantation of the placenta in the niche created by the incision of the previous CD.[1] CSPs represent a rising clinical concern stemming from an increasing rate of CDs.[2] In recent years, nearly one-third of babies were delivered by CD in developed countries.[3] The true incidence of CSPs is not known but estimates range between 1 in 1800 to 1 in 2656 pregnancies.[4]

Because of placental implantation in the uterine defect with absent decidua and partial loss of the myometrium and distal uterine vascular network, CSPs are strongly associated with serious complications. Among these are severe hemorrhage, preterm labor, uterine rupture, and implantation disorders, referred to as placenta accreta spectrum.[5,6] Major hemorrhage, which can occur in all 3 trimesters, can lead to loss of fertility, hysterectomy, and even death.[7,8]

Further serious complications include uterine rupture, second-trimester morbidly adherent placenta, uterine rupture, severe hemorrhage, and preterm labor.

A systematic review showed complications rates as high as 44% mainly because of missed diagnoses or potentially inappropriate treatments that increase the risk for massive hemorrhage.[2]

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AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate the safety and efficacy of different approaches to first-trimester management of cesarean scar pregnancies.

Key findings

Suction evacuation, surgical excision, and balloon treatment are effective (>90%) in the treatment of cesarean scar pregnancies. First-line use of a single dose of methotrexate has a higher risk of failing and complications than other methods and should not be recommended.

What does this add to what is known?

This study was based on a large set of original data on 460 cesarean scar pregnancy cases and compared different management methods from more than 30 high- and low-volume centers worldwide.

CSPs can be best diagnosed by ultrasound between 5 and 9 weeks' gestation.[9] The diagnosis is primarily based on a transvaginal ultrasound.[9,10] Depending on the gestational age, some ultrasound signs are easier to detect than others, which poses an ongoing diagnostic dilemma.[11] Because of the rarity of CSPs, patients are counseled based on case series containing diverse procedures and techniques.[12] There is no national and/or international agreement on the management strategies, and there is a huge variety of different approaches for pregnancy interruption.[12,13] Although publications exist on the evaluation of different management options to treat CSPs, individual practitioners and institutions persist in using very different methods at their discretion. In short, treatments are mostly based on individual clinicians' experiences, expertise, and the resources available.

There is little evidence regarding the effectiveness and safety of various treatment methods. A recent systematic review, based on multiple, small, single-center case series showed that there were more than 30 methods of treating a CSP.[2] To study the diagnosis, the natural history, and the management of CSPs in more detail, a group of experts set up the international registry for CSP (www.csp-registry.com).[12] The aim of this study was to investigate the safety and effectiveness of different treatment options in the management of first-trimester CSPs up to 12+6 weeks' gestation based on data from the International CSP registry.

Materials and Methods

The CSP Registry is an international research platform for data on CSP formed by an international network of collaborators referred to as the CSP collaborative network.

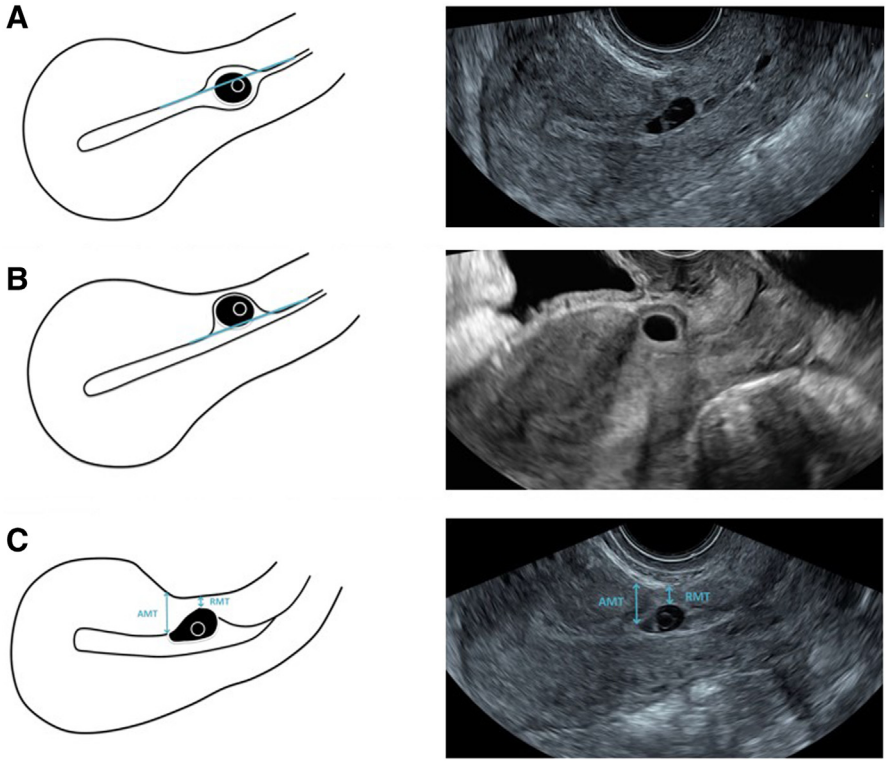
The project was approved by the National Health Service Health Research Authority and the Health and Care Research Wales (Integrated Research Application System project identifier, 246295). Ethical approval was further sought for each participating center according to local regulations. The registry was funded by unrestricted grants from the Voluntary Academic Society Basel (FAG), Basel, Switzerland and the Bangerter-Rhyner Foundation, Basel, Switzerland.

The CSP Registry was set up in 2018 to study the diagnosis, natural history, and management of CSP pregnancies. The registry contains structured, retrospective, individual coded data of patients with a CSP, including data on demographics, personal medical history, and previous pregnancies. Data on ultrasound findings, management, and the outcomes were also recorded. An anonymized panoramic ultrasound image showing the pregnancy, uterus, and endocervical canal in longitudinal section was uploaded for each case and reviewed by the board. Only coded, nonidentifiable data were recorded and stored in a secure database (Adjumed, Zurich, Switzerland). A sample of the collection form is provided in the Supplemental Material section.

A total of 9 public hospitals, 21 academic institutions, and 2 private clinics contributed to the registry until closure of data deposition. For this analysis, there were 31 clinics that contributed data among which there were 21 small-volume clinics that contributed <20 cases each (median, 9 cases; range, 1−19) and 10 large-volume clinics that each contributed ≥20 cases (median, 37 cases; range, 23−95 cases). The small-volume clinics contributed a total of 33.1% of the cases and the large-volume clinics contributed 66.9% of the cases that were analyzed for the purpose of this study.

In all centers, the examiners declared that they had a high level of experience and expertise in gynecologic ultrasound and additionally went through an onboarding process during which the important features of CSPs were discussed. A transvaginal ultrasound scan was performed to examine the location of the pregnancy and the presence of embryonic or fetal cardiac activity. We accepted the commonly used diagnostic criteria for a CSP based on the current literature, including a gestational sac located anteriorly at the level of the internal os covering the visible or presumed site of the previous lower uterine segment CD scar or niche and the presence of peritrophoblastic or periplacental vascularity on a color Doppler examination.[6,9,14] We have collected a number of different ultrasound variables for the population, including the gestational age, presence of a heartbeat, crown rump length (CRL), gestational sac diameter, placental location, presence of placental lacunae, residual myometrial thickness (RMT), adjacent myometrial thickness (AMT), subjective degree of vascularization, and type of CSP (details can be viewed in the Supplemental Material section). A CSP was defined as type 1 if >50% of the gestational sac protruded toward the uterine cavity or the cervical canal. A CSP was defined as type 2 when the placenta implanted into

FIGURE 1
CSP type 1 and CSP type 2



Schematic drawing and typical gray scale ultrasound images of CSP type I (**A**) and CSP type II (**B**) showing the measurements of AMT and RMT (**C**). CSP type 1 is when >50% of the gestational sac protrudes toward the uterine cavity or cervical canal. CSP is type 2 is when the protrusion of the gestational sac into the cavity is ≤50%. The residual myometrium thickness (RMT) is the measurement of the residual myometrium between the gestational sac and the serosa in a sagittal view. The adjacent myometrium thickness (AMT) is the measurement of the myometrium next to the gestational sac in a sagittal view.

AMT, adjacent myometrium thickness; *CSP*, cesarean scar pregnancy; *RMT*, residual myometrium thickness.

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a deficient or dehiscent scar and the protrusion of the gestational sac was ≤50%. The RMT is the measurement of the residual myometrium between the gestational sac and the serosa in a sagittal view. The AMT is the measurement of the myometrium next to the gestational sac in a sagittal view (Figure 1).

For the purpose of this study, we included all CSPs from the start of the registry until data download on the February 28, 2023. We included both live and failing CSPs (with or without a positive heartbeat) that underwent surgical, medical, or balloon catheter treatment before 12+6 weeks' gestation to evaluate the effectiveness and safety of the different methods used (Figure 2). Expectantly managed cases of CSP were excluded from this study. We collected data on the complications for each treatment method. Adverse events that occurred as a consequence of the procedures were considered as complications. The questionnaire contained queries about the treatment complications and maternal morbidity (including blood loss ≥1000 mL or the need for a transfusion, surgical injury, thrombotic event, sepsis, renal failure, cerebrovascular events, pulmonary edema, maternal death, and a free text box for clinics to add additional complications or morbidities). We collected data on the Clavien-Dindo grade II, III, and IV complications.[15] Blood loss >1000 mL was classified as grade II; retained products of conception (RPOC), bladder injury, and deep vein thrombosis were classified as grade III; and sepsis was classified as grade IV. Safety was defined as the inverse of the complication rate.

Effectiveness was defined as the success rate. Treatments were considered successful if the CSP resolved fully with no need for any additional medical or surgical intervention. We compared the ultrasound features of both live and failing CSPs.

Statistical analysis

All descriptive statistical analyses were performed in the Department of Biostatistics, University of Basel, Switzerland. The data are presented as counts and proportions for categorical data or the median and minimum and maximum for ordinal or metric data. *P* values were determined using the Mann-Whitney U test (for medians), and in the case of categorical variables, chi-squared or exact Fisher tests were used to determine *P* values depending on the variable numbers. All evaluations were done using R software, version 4.1.3 (R Core Team, Vienna, Austria).

Results

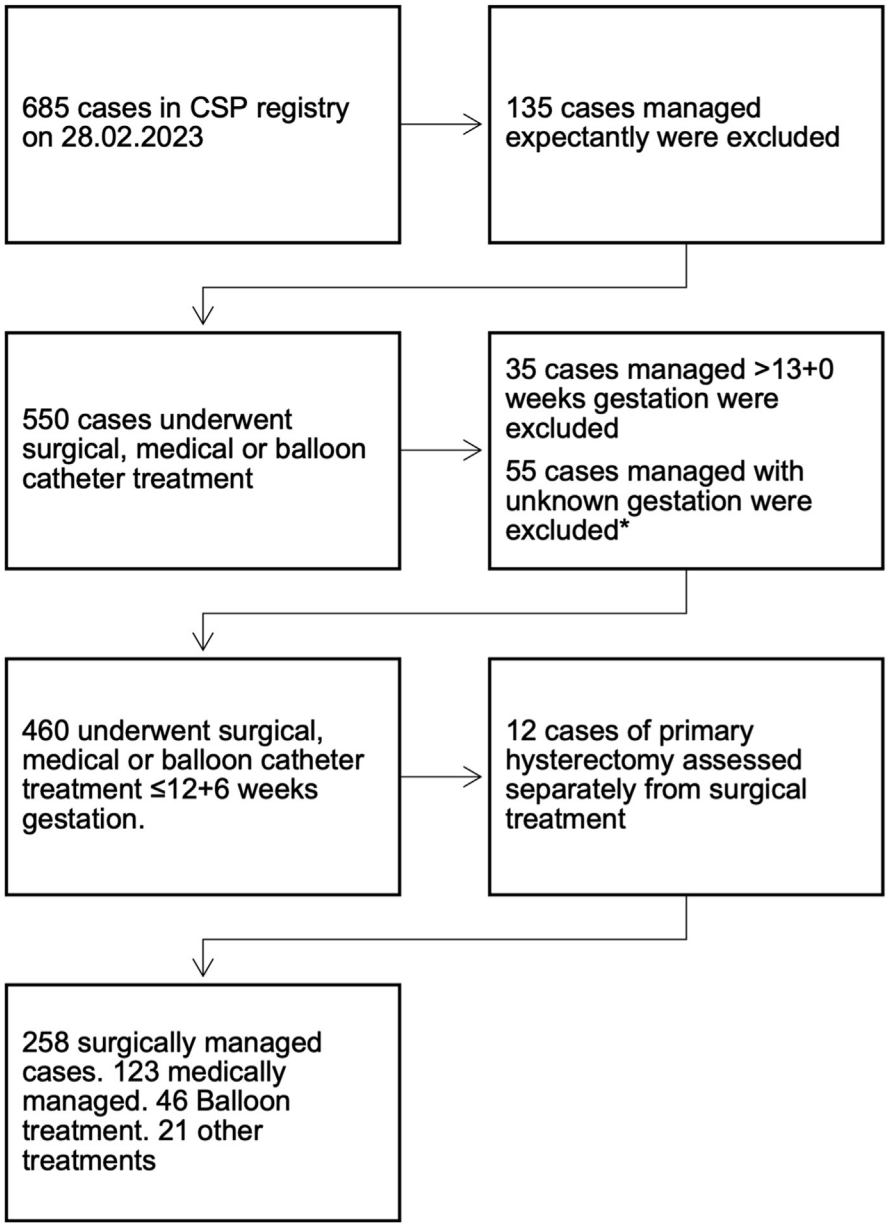
From the start of the CSP Registry in 2018 to data download on February 28, 2023, 460 cases of CSP (281 live, 179 failing CSP) were recorded that either underwent surgical, medical, or balloon catheter treatment before 12+6 weeks' gestation (Figure 2). A summary of the demographic and clinical data of the study population can be found in Table 1.

Ultrasound features of cesarean scar pregnancies

A comparison of the ultrasound features between live and failing CSPs can be found in Table 2. There were no differences in the AMT or RMT measurements between live and failed CSPs (*P*=.55 and *P*=.17, respectively) in our cohort.

The nature of the majority of both live and failing CSPs were type 2 based on the scan. The CRL measured slightly larger in live CSPs (*P*<.001). However, there was no difference in the mean gestational

FIGURE 2
Cases included in the study



Summary of the included cases. All cases that underwent expectant management or that were managed ≥13+0 weeks were excluded and only cases that underwent surgical, medical, or balloon catheter treatment at ≤12+6 weeks' gestation were included. *Asterisk* denotes cases in which no objective measurement of gestational age (ie, crown-rump length or gestational sac diameter) was possible were excluded because we could not accurately determine if they were ≤12+6 weeks' gestation.

CSP, cesarean scar pregnancy.

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sac diameter (*P*=.27). There was no statistically significant difference in the median gestational age between live CSPs and failing CSPs (*P*=.14).

Surgical management (including suction evacuation, surgical resection, or primary hysterectomy) was employed in 270 of 460 cases (58.7%), 123 of 460 cases (26.7%) underwent medical management, 46 of 460 cases (10%) were managed with a balloon catheter, and 21 of 460 cases (4.6%) were treated with other rarer management options, such as mifepristone or misoprostol or uterine artery embolization (UAE). A summary of the effectiveness and safety of the different treatment options is shown in Table 3.

Surgical management of cesarean scar pregnancies

The 270 cases that underwent surgical management included suction evacuation, surgical excision (via laparoscopy and laparotomy), and a primary hysterectomy for the CSP. A total of 20 patients underwent a hysterectomy, 12 of which were primary and 8 were secondary following failure of the initial treatment. The secondary hysterectomy cases were analyzed in the subgroups of their first-line treatments. To assess the overall effectiveness and safety of surgical treatment, we assessed the 12 cases of primary hysterectomy separately.

Overall, surgical treatment of CSP was successful in 236 of 258 cases (91.5%; 95% confidence interval [CI], 88.4−94.5) and complications were observed in 24 of 258 cases (9.3%; 95% CI, 6.6−11.9). The vast majority of cases had a single second-line treatment. There were 5 cases with multiple treatments, all of which were among patients with a blood loss >1000 mL.

The most frequently used surgical treatment for both live and failed CSPs was suction evacuation with or without ultrasound guidance. In 43 cases (15.3%), suction evacuation was combined with prophylactic placement of a temporary Shirodkar cerclage. Suction evacuation was the primary treatment of choice in 122 of 281 (43.4%) live CSPs and 99 of 179 (55.3%) failing CSPs. The presence of cardiac activity did not affect the effectiveness of this treatment with 10 of 111 (9.0%) live CSPs and 9 of 87 (10.3%) failing CSPs requiring additional treatment (*P*=.75). Additional treatments that were specified were laparotomy in 3 cases, repeat suction evacuation in 10 cases, emergency hysterectomy with a blood loss of 3500

mL in 1 case, systemic methotrexate in 3 cases, and balloon treatment and UAE in 1 case each. Two patients received a third-line treatment, namely 1 patient had a single balloon placement and UAE as hemostatic measures. Because these failed, a laparotomy and hysterectomy had to be performed. Overall, suction evacuation had relatively low complication rates (Table 3). Ten of 221 (4.5%) suction evacuation cases had a clinically significant blood loss (defined as loss of ≥1000 mL), 5 (5.0%) of those being among the 99 cases in the failing CSP group and 5 (4.1%) among the 122 live CSP cases between 7+0 and 12+4 weeks' gestation. Six of 221 (3.1%) cases had RPOC (tissue from the conception persisting after the pregnancy has ended), 1 case had deep vein thrombosis (0.5%), 1 case had sepsis (0.5%), and 1 case had a bladder injury (0.5%) at 11+5 weeks' gestation.

There were 37 cases of surgical excision of the CSP in our data set, which accounted for 13.7% of the surgical treatment cases; 19 of 37 (51.3%) cases were live CSPs and 18 of 37 (48.6%) cases were failing CSPs. Five (13.5%) were hysteroscopic resections, 15 (40.5%) were laparoscopic excisions, and 17 (45.9%) were laparotomies. Two cases were started as hysteroscopic resections and 1 case as a laparoscopic excision but were converted to a laparotomy and hysterectomy. The other cases did not require any additional treatment. The overall complication rate of surgical excision was 13.5% (Table 3). In terms of complications of surgical excisions, 2 cases (5.4%) had clinically significant blood loss (≥1000 mL). There was 1 case of maternal sepsis (2.7%), 1 case of Asherman syndrome (2.7%), and 1 case of broad ligament hematoma (2.7%).

We recorded 12 cases of primary hysterectomy for CSP in the first trimester of which 8 (66.7%) were between 10+0 and 12+6 weeks' gestation, 2 were at 7 weeks' gestation, 1 at 8 weeks' gestation, and another at 9 weeks' gestation. The 12 hysterectomies accounted for 4.4% of the first-choice surgical treatment for CSP. Six (50%) hysterectomies (all after 10+0 weeks' gestation) were performed in asymptomatic patients with an incidental finding of a CSP on a scan. The 6 symptomatic patients presented with heavy vaginal bleeding and abdominal pain. Three of the 12 (25%) cases were failed CSPs and 9 of 12 (75.0%) cases were live CSPs. The median maternal age was 37 (31–59) years and the median parity was 2.5. None of the 12 cases needed any additional treatment. However, there was a substantial number of complications, including clinically significant bleeding (≥1000 mL) in 5 of 12 cases (41.6%) and 4 (33%) bladder injuries.

TABLE 1
Demographics of the study population

Maternal demographics	Median (min–max) or n (%)	No.
Age (y)	35.0 (18.0–59.0)	460
Ethnicity		426
· White	241 (56.6%)	
· Middle Eastern	75 (17.6%)	
· Asian	36 (8.5%)	
· Afro-Caribbean	38 (8.9%)	
· Hispanic	20 (4.7%)	
· Mixed or other	16 (3.8%)	
BMI (kg/m^2)	26.7 (16.7–54.6)	291
Smoking		343
· Never or gave up before pregnancy	294 (85.7%)	
· Current	49 (14.3%)	
Parity	2 (1–11)	458
Conception		445
· Spontaneous	418 (93.9%)	
· Artificial conception with embryo placement · pIXWplacement placement	25 (5.6%)	
· Artificial conception with ovarian stimulation	2 (0.5%)	
Symptomatic at diagnosis	362 (65.8%)	458
· Vaginal bleeding	173 (37.8%)	
· Abdominal pain	29 (6.33%)	
· Incidental finding	185 (40.4%)	
· Combination of pain and bleeding	66 (14.4%)	
· Other symptoms	5 (1.1%)	
Number of previous CD	2 (1–8)	459

The data are presented as median (minimum–maximum) or number (percentage).

BMI, body mass index; *CD*, cesarean delivery.

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Medical treatment

A total of 123 CSPs were managed medically, including 59 patients who received a local gestational sac injection and 64 who received systemic methotrexate. The treatment was moderately efficient with a success rate of 82 of 123 (66.6%) and substantial complications in 16 of 123 (13.0%) cases.

Among 59 cases who received a local gestational sac injection of potassium

TABLE 2
Ultrasound findings of live and failing CSPs at diagnosis

Characteristics	Live CSP n=281	Failing CSP n=179	*P* value	No.
Gestational age at treatment (wk)	8+2 (3+6 to 12+6)	7+5 (5+2 to 12+6)	.14	457
CRL at diagnosis (mm)	7.0 (1.0–74.0)	4.0 (7.0–95.0)	<.001	331
Gestational sac diameter (mm)	18.0 (1.0–71.0)	17.0 (1.0–81.0)	.27	356
Site of implantation			.038	448
Type 1	104 (37.5%)	82 (48.0%)		
Type 2	173 (62.5%)	89 (52.0%)		
Residual myometrial thickness (mm)	2.8 (0.3–10.5)	3.00 (0.5–12.9)	.17	316
Adjacent myometrial thickness (mm)	13.0 (0.4–41.6)	13.0 (0.5–30.0)	.55	217
Enhanced myometrial vascularity in the area of the scar	149 (66.5%)	74 (52.9%)	.013	364

CSP was defined as type 1 if >50% of the gestational sac protruded toward the uterine cavity or cervical canal. CSP was defined as type 2 when the placenta implanted into a deficient or dehiscent scar and the protrusion of the gestational sac was ≤50%. Residual myometrium thickness is the measurement of the residual myometrium between the gestational sac and the serosa in a sagittal view. Adjacent myometrium thickness is the measurement of the myometrium next to the gestational sac in a sagittal view.

CRL, crown rump length; *CSP*, cesarean scar pregnancy.

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chloride (KCl) (15/59 cases) or methotrexate (44/59 cases), there were 7 (11.8%) cases for whom this was combined with systemic methotrexate. Of the 59 cases, 47 (79.6%) were live CSPs and 12 (20.4%) cases were failing CSPs. One-quarter (25.5%) of cases managed with gestational sac injection needed additional treatment (12/44 [27.2%] methotrexate cases and 3/15 [20.0%] KCl cases). Six of 59 cases (10.1%) underwent suction evacuation, 1 (1.6%) was treated with a balloon catheter, and 8 (13.5%) underwent UAE. In 2 cases, the suction evacuation was combined with UAE. Three of 59 (5.1%) cases had clinically significant hemorrhage (≥1000 mL), 1 (1.6%) was subsequently diagnosed with Asherman syndrome, and in 1 case (1.6%), it took >150 days for the human chorionic gonadotropin level to return to the prepregnancy level (median, 62 days; 11–155 days).

TABLE 3
Success rates and complications of different management options for CSP in the first trimester

Management strategy	Success rate (effectiveness) n (%) (95% CI)		Complication rate (safety) n (%) (95% CI)		Type of complication (n)
Suction evacuation	202/221	91.5% (87.8–95.2)	19/221	8.5% (5.9–11.2)	Hemorrhage[a] (10); RPOC (6); thrombosis (1); sepsis (1); bladder injury (1)
Surgical excision	34/37	91.8% (83.8–99.9)	5/37	13.5% (0–29.1)	Hemorrhage[a] (2); Sepsis (1); Asherman (1); broad ligament hematoma (1)
Balloon catheter treatment	42/46	91.3% (83.5–99.1)	4/46[b]	8.7% (2.4–14.9)	Hemorrhage[a] (2); EMV (2)
Local gestational sac injection	44/59	74.5% (64.1–85.1)	5/59	9.5% (1.6–15.4)	Hemorrhage[a] (3); Asherman (1); delayed resorption >150 d (1)
Systemic methotrexate	38/64	59.4% (48.4–70.4)	11/64	23.9% (8.5–25.9)	Hemorrhage[a] (3); methotrexate toxcicity (4); Sepsis (2), RPOC (1); GTN (1)
Primary hysterectomy	12/12	100%	9/12	75.0% (74.8-75.3)	Hemorrhage[a] (5); bladder injury (4)

Complication rate and additional treatment rate of the different treatment options. Details of the complications of each treatment method can be found in the results section.

CI, confidence interval; *CSP*, cesarean scar pregnancy; *EMV*, enhanced myometrial vascularity; *GTN*, gestational trophoblastic neoplasia; *RPOC*, retained products of conception.

[a] Hemorrhage refers to a blood loss >1000 mL; [b] Only 2 of 5 EMV cases that required treatment were included in the complication rate. Three of 5 EMV cases showed spontaneous resolution and were therefore not considered a complication. The other 2 complications were delayed hemorrhage after balloon treatment.

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We collected data on 64 cases treated with systemic methotrexate of which 33 (51.6%) were live CSPs and 31 (48.3%) were failing CSPs. Additional treatment was necessary in 30 of 64 (46.9%) cases. Five (7.8%) cases underwent surgical excision, 5 (7.8%) cases underwent suction evacuation, 2 (3.1%) cases ended in hysterectomy, 6 (9.3%) cases underwent UAE, and 8 (12.5%) cases had a second course of methotrexate. In 1 case, surgical excision was combined with UAE and in another case, suction evacuation was attempted first, followed by surgical excision. There were 2 (3.1%) cases of maternal sepsis, 1 case (1.5%) of gestational trophoblastic neoplasia, 3 (4.6%) cases of clinically significant hemorrhage (≥1000 mL), and 1 (1.5%) case of a prolonged inhomogeneous mass (RPOC) was reported. For 4 (6.2%) cases, methotrexate toxicity was reported.

Balloon catheter treatment

We collected data on 46 cases treated with a balloon catheter with 42 (91.3%) of those being live CSPs and the remaining 4 were failing CSPs. In 11 (23.9%) cases, the treatment was combined with systemic methotrexate. Overall, balloon management of CSPs had a high success rate with 4 of 46 (8.7%) cases requiring additional treatment. Two patients required an emergency hysterectomy for delayed hemorrhage within the first 28 days after removal of the balloon (1 at 22 days and 1 at 27 days). One (2.1%) patient required UAE for arteriovenous malformation and another required curettage. In 5 cases, a transiently increased blood flow within the uterine myometrium (enhanced myometrial vascularity [EMV]) was visible on follow-up scans, and for 2 cases, it was combined with an area of inhomogeneous mass (RPOC). In 3 of the 5 EMV cases, the EMV disappeared spontaneously, 1 required UAE because it turned out to be an arteriovenous malformation, and 1 was suspected to be RPOC and required surgical removal.

Large-volume vs small-volume cesarean scar pregnancy clinics

There was no statistically significant difference in the gestational age at treatment between small-volume clinics (median, 7.49 weeks; 5−12 weeks) and large-volume clinics (median, 7.49; range, 4−12 weeks; P=.44). There was a difference in the choice of first-line treatment between small- and large-volume clinics (P<.001) and also in terms of primary hysterectomy. Ten of 12 (83.3%) primary hysterectomies for CSP were done in small-volume clinics, whereas only 2 were done at advanced gestation (12 weeks) in large-volume clinics. Otherwise, both small- and large-volume clinics reported on suction evacuation (39.4% vs 57.6%), surgical excision (10.9% vs 7.6%,), local medical treatment (13.1% vs 14.1%), balloon catheter treatment (12.4% vs 10.1%), and systemic methotrexate (24.1% vs 10.6%). The effectiveness was lower in small-volume clinics when compared with high-volume clinics with 27 of 152 cases (17.7%; 95% CI, 12.1−23.4), compared with 40 of 308 cases (12.9%; 95% CI, 9.5−16.5), requiring second-line treatments (P<.001) because a substantially higher proportion of cases was managed with systemic methotrexate. There was also no statistically significant difference in the rate of complications with complications reported for 14 of 152 cases (9.2%; 95% CI, 5.2−13.2) in small-volume clinics and 30 of 308 cases (9.7%; 95% CI, 6.8−12.7) in large-volume clinics (P=.86).

Effectiveness and safety of treatment depending on gestational age

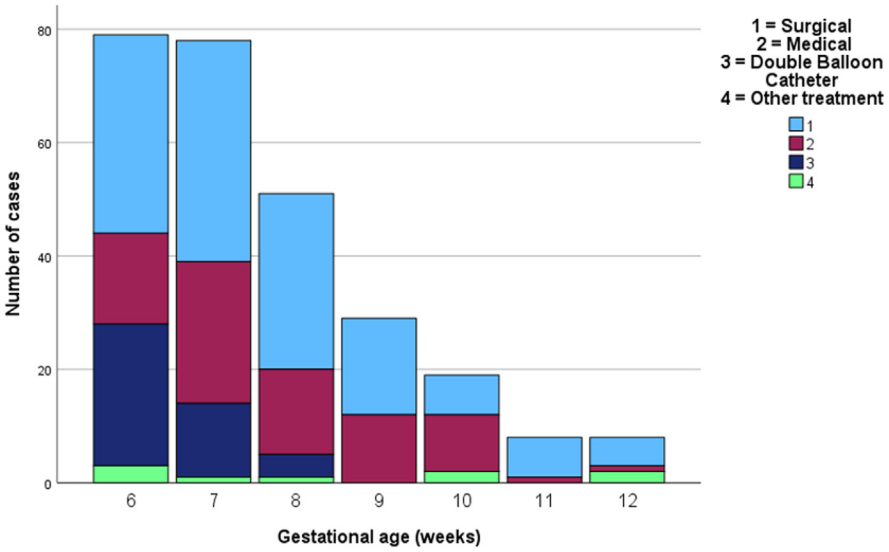
An overview of the treatments used at different gestational ages can be found in Figure 3. The percentage of cases that required additional treatment in relation to gestational age can be found in Figure 4. There was a negative correlation between the success of treatment and gestational age (P=.11; r, −0.156). There was also a moderate significant correlation between complications of treatment and gestational age (P<.01; r, 0.261) (Figure 5).

Comment

Principal findings

The results of this study showed that suction evacuation, surgical excision, and a double balloon catheter all have a high success rate in the treatment of first-trimester CSPs. The hysterectomy rates were higher among patients who

FIGURE 3
Number of cases treated at different gestational ages



Number of cases treated with medical treatment, surgical treatment, and double balloon at different gestational ages.

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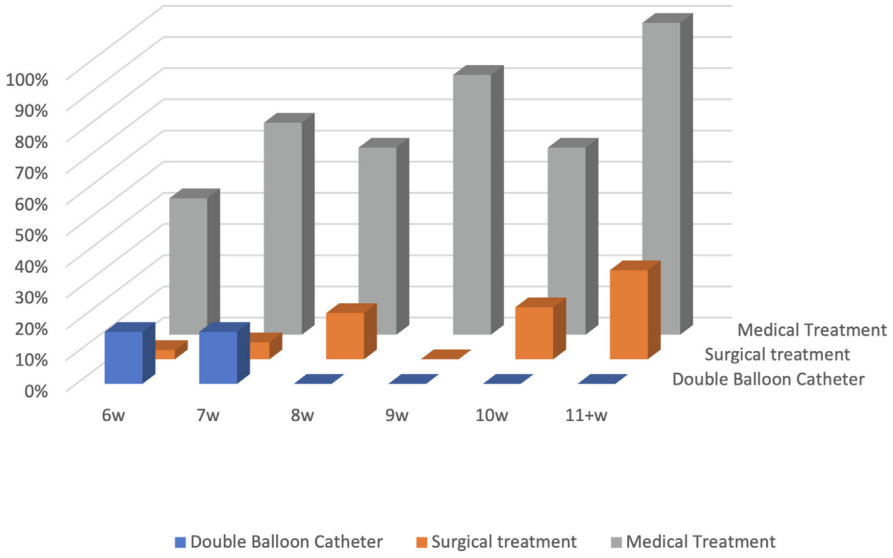
FIGURE 4
Need for additional treatment at different gestational ages in live CSP



Percentage of live CSP cases requiring additional treatment after different first-line management approaches by gestational age (effectiveness) for surgical, medical, and double balloon treatments.
CSP, cesarean scar pregnancy.
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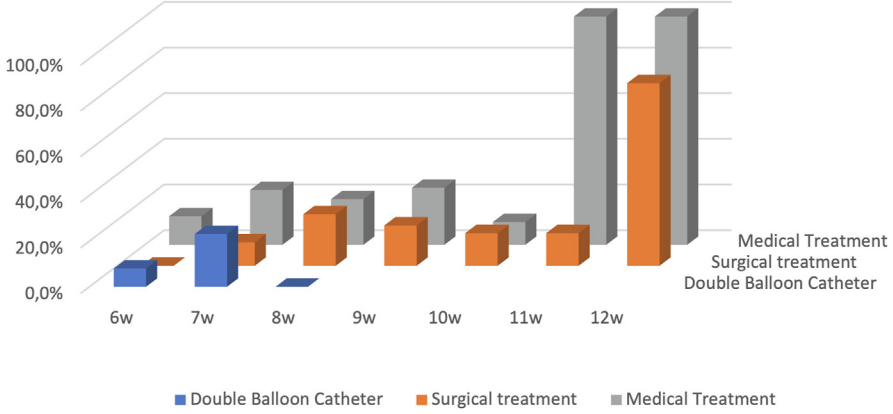
underwent surgical excision and treatment with a balloon catheter than among those who underwent suction evacuation. Although this may be a chance finding, bearing in mind that the overall number of hysterectomies was low, our findings indicate that close monitoring of the hysterectomy rates following different treatment options is needed. Local and systemic medical management were less effective than surgery, and a higher proportion of patients required additional treatment following medical management.

FIGURE 5
Safety of first-line treatments at different gestational ages in live CSPs



Percentage of cases of live CSPs with complications depending on the gestational age (safety) for surgical, medical, and double balloon treatments.
CSP, cesarean scar pregnancy.
Kaelin Agten. Cesarean scar pregnancy Registry: first trimester management. Am J Obstet Gynecol 2023.

Results in the context of what is known

Surgical management

Several smaller studies have investigated the effectiveness and safety of suction evacuation for CSP. Harb et al's[7] United Kingdom cohort study published in 2018 reported on the surgical and medical management of 92 patients with CSP. Comparable with our findings, their success rate for surgical management was 96% (54/56) with 5.6% of surgically managed cases requiring additional treatment. Our additional treatment rate was 8.5%. They reported a higher complication rate of 36% (20/56) in comparison with a rate of 9.6% (24/258) reported in our study.[7] Our complication rate was lower because we only included blood loss >1000 mL and major maternal morbidity in contrast with Harb et al[7] who included any bleeding complication regardless of the amount. Maymon et al[16] published a systematic review and meta-analysis of 22 studies involving 374 patients with CSP. The review reported a success rate of 92.2% for suction evacuation treatment and a low complication rate,[16] similar to the findings of this study. A previously published systematic review by Ilan Timor-Tritsch[2] based on smaller case series reported a complication rate for dilatation and curettage of 62.9%; this higher complication rate was attributed principally to bleeding complications. We suspect that there may also be publication bias based on overreporting of cases that had severe blood loss or other complications.

This same systematic review also reported higher complication rates following surgical excision of 28.6% (n=14),[17] although the details of the complications were not listed in the study to allow direct comparisons of the complications. Verberkt et al[18] used different surgical treatments depending on the type of CSP and they reported high success rates for both suction curettage and laparoscopic niche resection with a low complication rate.

Medical management

In the small United Kingdom cohort study, the success rate of medical treatment was 46% (7/15) and the complication rate was

9 of 15 cases (60%).[7] Our success rate, based on larger numbers, was slightly higher with 38 of 64 cases (59.3%) being sufficiently treated with medical management alone. Our complication rate was substantially lower, however, at 13% (16/123). The differences in success and complication rates can be partially explained by the fact that in the study by Harb et al, 14 of 15 patients received systemic methotrexate as the primary treatment and only 1 case underwent local gestational sac injection, whereas in our cohort, only 52% of cases (64/159) had systemic methotrexate and 48% (59/123) underwent a local gestational sac injection. If we compared their medical complication rate with our systemic methotrexate data then we would similarly report a substantially lower success rate and a higher complication rate. A recently published systematic review and meta-analysis of methotrexate treatment for CSPs that comprised 6 articles with a sample size of 600 individuals showed a success rate of 90.7% (95% CI, 86.7%−93.5%) and a complication rate of 9% (95% CI, 6.3%−12.8%), but reported a large heterogeneity among the studies.[19] We perceived that the small case numbers and failure to report the route of methotrexate administration in some of the studies and/or systematic review may account for the differences in the success and complication rates with the local route for methotrexate demonstrating the best effectiveness. In contrast, a previously published systematic review by Timor-Tritsch reported a complication rate of systemic methotrexate of 62.1% (n=87).[20]

Several studies have suggested that a local gestational sac injection is an effective treatment option for early first−trimester CSPs. Timor-Tritsch published on 19 cases treated with intragestational sac injections of methotrexate and systemic methotrexate, and none of the cases had any complications and all were successfully treated.[10]

Balloon catheter treatment

Timor-Tritsch et al[20] reported that the first 60 patients with CSP who underwent double balloon treatment with a success rate of 85% had complete resolution of CSP and no recurrence during the follow-up period. However, in our group, there were 2 emergency hysterectomies (4.3%). The procedure was well tolerated with no major complications reported. This was confirmed in a subsequent publication on 38 patients who underwent double balloon treatment and for whom a success rate of 98.8% was reported with only 1 patient requiring additional treatment because of incomplete resolution of CSP. A retrospective cohort study of type 1 CSPs (n=18) managed with double balloon treatment published by Kus et al[21] showed low morbidity and high treatment success. Our data support the findings of previous studies that double balloon treatment is an efficient treatment method for CSP, however, patients need close follow-up and we will continue to monitor its safety in the future.

More than 30 different treatment options have been described in the literature in the treatment of CSP, including combined treatments and different methods of local injections. However, the role of these techniques as first-line treatments seem to be limited because we only found 21 cases that were not treated using options we analyzed. For further analysis of these treatment options, more cases are needed.

Gestational age and risk of complications and additional treatment

Several studies have suggested that the risk for complications in the treatment of CSP is higher when the gestational age of the pregnancy is advanced. In a previous study of 15 patients, all those managed at gestational ages of <8 weeks had complete resolution of CSP, whereas those with gestational ages of ≥8 weeks had a higher risk for incomplete resolution. A recently published systematic review and meta-analysis of 36 studies (724 patients with CSP) reported that an overall adverse outcome complicated 5.9% (95% CI, 3.5−9.0) of CSP cases diagnosed at ≤9 weeks and 32.4% (95% CI, 15.7−51.8) of those diagnosed at >9 weeks.[22]

The increasing risk for complications with advancing gestational age in CSP is thought to be associated with several factors. First, the placenta tends to become more deeply implanted in the scar tissue as the pregnancy advances, which can increase the risk for bleeding and cause incomplete resolution during treatment. Second, the size of the gestational sac also increases with advancing gestational age, which can make it more difficult to completely evacuate the sac during treatment.[22]

Research implications

To further analyze the effectiveness and safety of individual treatments according to gestational week or for potential differences in effectiveness and safety between type I and type II CSP cases, further growth of the registry and collection of more cases is required.

Strength and limitations

The strength of our study is the unique study population that represent multiple centers around the world with advocacy for different treatment approaches, and each of the centers chose their preferred treatment. The results therefore are unbiased toward a specific treatment modality based on an individual clinician, center, or country bias, and the results can be considered generalizable. Furthermore, this study directly compared various treatments within a large patient population using primary data, thereby permitting clinicians to use these direct comparisons of effectiveness and complications when discussing options with their patients. The registry also allowed for the participation of a much larger number of centers than would be the case if this was a prospective study, which is required for the study of rare entities such as CSP.

This study has the limitations of data sets being dependent on accurate record keeping within each contributing center, which is the case for all retrospective and registry-based data collections. A registry allows international participation from centers that have an interest in the condition, which poses a risk for unrecognized early CSP or overreporting of complications in centers that rarely manage CSP.

Clinical implications and conclusions

CSP in the first trimester of pregnancy can be managed effectively in more than 90%

of cases with either suction evacuation, balloon treatment, or surgical excision. Surgical excision requires an experienced surgeon because of the risk for emergency hysterectomy, and patients who are treated with a double balloon catheter require close follow-up. The effectiveness of all treatment options decreased with advancing gestational age. CSP should be treated as early as possible after confirmation of the diagnosis. Local medical treatment with KCl or methotrexate is less efficient and has higher rates of complications than the other treatment options. Systemic methotrexate has a substantial risk for failing and a higher complication rate and should not be recommended as first-line treatment. ■

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Label	
Women's details	
Unique patient number	
Unique case number	
Year of birth (yyyy)	
Entry date (dd.mm.yyyy)	
Age: Admission Date minus 1 July of the year of birth (calculated)	
Ethnicity	[1] Caucasian [2] South Asian [3] East Asian [10] Middle Eastern [5] Afro-Caribbean[6] Hispanic[7] mixed, other
Smoking status	[1] Never [2] current [3] Gave up prior to pregnancy
Weight (kg)	
Height (cm)	
Body Mass Index (BMI) (calculated)	
Previous pregnancies	
Gravidity	
N° of completed pregnancies beyond 24 weeks	
N° of completed pregnancies beyond 24 weeks not recorded	True / False
N° of pregnancies that ended before than 24 weeks	
N° of pregnancies that ended before than 24 weeks not recorded	True / False
Previous caesarean sections	
Please specify the total number of previous caesarean sections	
Prior abnormally invasive placenta?	[1] yes [0] no
If yes	
Surgical management of abnormally invasive placenta (multiple answers possible)	[10] Vaginal delivery [12] Caesarean section[14] Gravid-hysterectomy[16] Triple-P Procedure [18] Leaving the placenta in situ[20] Methotrexate[22] Curettage[24] Balloon catheter occlusion[26] Embolization[88] unknown
Prior caesarean scar pregnancy?	[1] yes [0] no
Details of prior caesarean scar pregnancies	
Year of prior caesarean scar pregnancy (yyyy)	

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(continued)

Management of prior caesarean scar pregnancy	[10] Hysteroscopic excision [12] Hysteroscopy with transabdominal sonographic guidance and Mifepristone[14] Hysteroscopy and Vasopressin[16] Laparotomy and excision[18] Laparotomy with elective transabdominal hysterectomy[20] Laparatomy with hysteroscopy[22] Transabdominal sonographic guided local intragestational methotrexate injection[24] Transabdominal sonographic guided local intragestational KCL injection[26] Transabdominal sonographic guided local intragestational and intramuscular methotrexate[28] Transvaginal sonographic guided local intragestational methotrexate injection[30] Transvaginal sonographic guided local intragestational KCl injection[32] Transvaginal sonographic guided local intragestational and intramuscular methotrexate[34] Local intragestational injection of vasopressin[36] Uterine artery embolization alone[38] Uterine artery embolization and intramuscular methotrexate [40] Uterine artery embolization and intragestational methotrexate[42] D&C alone[44] D&C and intramuscular etoposide[46] D&C and Shirodkar cervical suture[48] D&C and uterine artery embolization [50] D&C and intramuscular methotrexate [52] Laparoscopic excision[54] Laparoscopy and hysteroscopy[56] Methotrexate intramuscular injection alone[58] Methotrexate intramuscular and hysteroscopy[60] Trichostatin[62] Transrectal ultrasound guided aspiration[64] Gravid-Hysterectomy[66] D&E alone[68] D&E and Shirodkar cervical suture[70] D&E and uterine artery embolization[80] single balloon treatment alone[81] single balloon and intramuscular Methotrexate[82] double balloon treatment alone[83] double balloon treatment and intramuscular Methotrexate[84] Misoprostol[85] Mifegyne/Misoprostol[88] other treatment
Further caesarean scar pregnancies	
Previous caesarean sections?	[1] yes [0] no
Please start with the first (oldest) cesarean section.	
Date of caesarean sections (dd.mm.yyyy)	
Date of previous caesarean sections unkown	True / False
Indication for caesarean section	[1] Breech presentation [2] Other malpresentations [3] Multiple pregnancy [4] Maternal medical conditions [5] Fetal compromise [6] Transmissible disease [7] Placenta praevia [8] Morbidly adherent placenta [9] Previous birth complication (ie, major shoulder dystocia, Previous 3rd/4th perineal tear) [10] Maternal request [11] Preterm Birth [12] Failure to progress in labour [13] Failed instrumental delivery [15] Previous uterine surgery macrosomia[14] Unknown
Type of incision	[1] Classical [2] Low transverse incision [3] unknown
Cervical dilation at time of CS (cm)	[1] 0-2cm [2] 3-6cm [3] 7cm and more [4] unknown
2- or 1- layer closure?	[1] 1 layer closure [2] 2 layer closure [0] unknown

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(continued)

Previous Medical History	
Any pre-existing medical problem?	[1] yes [0] no
If yes, please specify (multiple answers possible):	[1] Essential hypertension [2] Cardiac disease (congenital or acquired) [3] Renal disease [4] Endocrine disorders, for example, hypo or hyperthyroidism [5] Haematological disorders, for example, sickle cell disease, thrombophilia [6] Inflammatory disorders, e.v. inflammatory bowel disease [7] Psychiatric disorders [8] Epilepsy [9] Diabetes [10] Autoimmune disease [11] Cancer [12] HIV
Any previous uterine surgery (other than c-section)?	[1] yes [0] no
If yes:	
N° of Myomectomy	[0] 0 [1] 1 [2] 2 [3] 3 [4] 4 [5] 5 [6] 6 [7] 7 [8] 8 [9] 9 [10] 10 [88] unknown
N° of dilatation and curettage (D&C)/evacuation (D&E)	[0] 0 [1] 1 [2] 2 [3] 3 [4] 4 [5] 5 [6] 6 [7] 7 [8] 8 [9] 9 [10] 10 [88] unknown
N° of surgical termination of pregnancy	[0] 0 [1] 1 [2] 2 [3] 3 [4] 4 [5] 5 [6] 6 [7] 7 [8] 8 [9] 9 [10] 10 [88] unknown

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(continued)

N° of evacuation of retained products of conception (ERCP)	[0] 0 [1] 1 [2] 2 [3] 3 [4] 4 [5] 5 [6] 6 [7] 7 [8] 8 [9] 9 [10] 10 [88] unknown
N° of Endometrial ablation	[0] 0 [1] 1 [2] 2 [3] 3 [4] 4 [5] 5 [6] 6 [7] 7 [8] 8 [9] 9 [10] 10 [88] unknown
This pregnancy	
Last menstrual period (LMP) (dd.mm.yyyy)	
Last menstrual period unknown	True / False
Estimated Date of Delivery (EDD) (dd.mm.yyyy)	
Estimated Date of Delivery unknown	True / False
N° of embryos	[0] 0 [1] 1 [2] 2
If 2 embryos:	[1] Heterotopic CSP (one embryo in uterus, one in the scar) [2] both embryos in the scar
Clinical presentation at first visit (multiple answers possible)	[1] Vaginal bleeding [2] Abdominal pain [3] Haemorrhagic shock [4] Incidental finding [5] Other symptoms [8] Not recorded
Conception	[1] Spontaneous [2] Artificial conception with embryo placement [3] Artificial conception with hormones only [8] Not recorded
Gestational age at diagnostic scan (weeks/days)	
Crown-rump length (CRL) (mm) at diagnostic scan	
Crown-rump length at diagnostic scan not recorded	True / False
Gestational sac diameter (mm) at diagnostic scan	
Gestational sac diameter at diagnostic scan not recorded	True / False
Foetal heartbeat at diagnostic scan	[1] present [0] absent [8] not recorded

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Placenta lacunae	[1] yes [0] no [8] not recorded
Placenta location	[1] Anterior low, covering internal os [2] Posterior low, covering internal os
Placenta location not recorded	True / False
Site of implantation	[1] On the scar (Type 1) [2] In the niche (Type 2)
residual myometrium thickness (RMT) (mm)	
residual myometrium thickness (RMT) not recorded	True / False
adjacent myometrium thickness (AMT) (mm)	
adjacent myometrium thickness (AMT) not recorded	True / False
Subjective degree of vascularization	[1] normal [2] increased [8] not recorded
Distance lower throphoblastic margin to internal os (mm)	
Distance lower throphoblastic margin to internal os not recorded	
MRI performed?	[1] yes [0] no
Did MRI give more information than ultrasound alone?	[1] yes [0] no
Was the CSP terminated?	[1] yes [0] no
Termination of pregancy	[1] yes [0] no
If yes folllow here, if no follow line 101	
Gestational age at which pregnancy ended? (weeks/ days)	
Gestational age at which pregnancy ended not recorded	True / False
Method of 1st line medical/surgical management (multiple answers possible)	[10] Hysteroscopy [52] Laparoscopy[16] Laparotomy[23] Surgical excision of CSP[64] Hysterectomy[22] Local intragestational methotrexate injection[24] Local intragestational KCL injection[34] Local intragestational injection of vasopressin[42] D&C[50] D&C / suction [66] D&E[55] Suction evacuation [36] Uterine artery embolization[46] Shirodkar cervical suture[62] Transrectal ultrasound guided aspiration[56] Intramuscular methotrexate injection[80] Single balloon treatment[82] Double balloon treatment[84] Misoprostol[85] other treatment
2nd line medical/surgical management necessary?	[1] yes [0] no
Method of secondary surgical management (multiple answers possible)	[10] Hysteroscopy [52] Laparoscopy[16] Laparotomy[23] Surgical excision of CSP[64] Hysterectomy[22] Local intragestational methotrexate injection[24] Local intragestational KCL injection[34] Local intragestational injection of vasopressin[42] D&C[50] D&C / suction [66] D&E[55] Suction evacuation [36] Uterine artery embolization[46] Shirodkar cervical suture[62] Transrectal ultrasound guided aspiration[56] Intramuscular methotrexate injection[80] Single balloon treatment[82] Double balloon treatment[84] Misoprostol[85] other treatment

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(continued)

3rd line medical/surgical management necessary?	[1] yes [0] no
Method of 3rd line medical/surgical management (multiple answers possible)	[10] Hysteroscopy [52] Laparoscopy[16] Laparotomy[23] Surgical excision of CSP[64] Hysterectomy[22] Local intragestational methotrexate injection[24] Local intragestational KCL injection[34] Local intragestational injection of vasopressin[42] D&C[50] D&C / suction [66] D&E[55] Suction evacuation [36] Uterine artery embolization[46] Shirodkar cervical suture[62] Transrectal ultrasound guided aspiration[56] Intramuscular methotrexate injection[80] Single balloon treatment[82] Double balloon treatment[84] Misoprostol[85] other treatment
Medical/surgical complications?	[1] yes [0] no
Treatment complication	[5] blood loss of 300ml - 1000ml [10] blood loss requiring transfusion; greater than 1L[20] arteriovenous malformation[88] other[44] not recorded
Was follow-up ultrasound performed to document complete resorption of placenta?	[1] yes [0] no [8] not recorded
If yes to ultrasound, what was the date of complete resorption? (dd.mm.yyyy)	
Date of complete resorption not recorded	True / False
Peak bHCG value	
Peak bHCG value not recorded	True / False
Time from peak bHCG to 0 (in days)	
Time from peak bHCG to 0 not recorded	True / False
Outpatient or inpatient treatment	[1] outpatient [2] inpatient [8] not recorded
Planned treatment or emergency treatment	[1] planned [2] emergency
Is there a histopathology confirming an abnormally invasive placenta?	[1] yes [0] no
Major maternal morbidity?	[1] yes [0] no [8] not recorded
If major maternal medical complication, please choose:	[10] Renal failure [20] Thrombotic event[30] Septicaemia[40] Cerebrovascular accident [50] Pulmonary edema[60] Pulmonary aspiration [#hide#][70] Maternal death
Termination no follow line 102, if no follwo line 117	
Gestational age at which pregnancy ended? (weeks/ days)	
Did the woman have a miscarriage?	[1] yes [0] no
If yes follow here	
Surgical management necessary?	[1] yes [0] no

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(continued)

Method of surgical management (multiple answers possible)	[10] Hysteroscopy [52] Laparoscopy[16] Laparotomy[23] Surgical excision of CSP[22] Local intragestational methotrexate injection[64] Hysterectomy[24] Local intragestational KCL injection[34] Local intragestational injection of vasopressin[42] D&C [#hide#][50] D&C / suction [66] D&E [#hide#][55] Suction evacuation [#hide#][36] Uterine artery embolization[46] Shirodkar cervical suture[62] Transrectal ultrasound guided aspiration [56] Intramuscular methotrexate injection[80] Single balloon treatment [82] Double balloon treatment[84] Misoprostol[85] other treatment
Planned treatment or emergency treatment	[1] planned [2] emergency
Was abnormally invasive placenta suspected prior to delivery?	[1] yes [0] no
If yes, indicate which features were recorded (multiple answers possible)	[1] Placental lacunae [2] Loss of clear space [3] Disruption of bladder/myometrial interface [4] Placenta previa <2cm from internal os [5] Placenta thickness in lower segment >50mm [6] Myometrial thinning <1mm [7] Bridging vessels
Did the woman experience complications in pregnancy?	[1] yes [0] no
If yes, indicate any of the following (multiple answers possible)	[1] Antepartum haemorrhage [2] Retained placenta [3] Uterine rupture [4] Other
Was a hysterectomy performed?	[1] yes [0] no
Is there a histopathology confirming an abnormally invasive placenta?	[1] yes [0] no
Major maternal morbidity?	[1] yes [0] no
If major medical complication, please choose:	[10] Renal failure [20] Thrombotic event[30] Septicaemia[40] Cerebrovascular accident [50] Pulmonary edema[60] Pulmonary aspiration [#hide#][70] Maternal death
Miscarriage no follwo line 118	
What was the planned mode of delivery?	[1] Caesarean [2] vaginal
Neonatal outcome	[1] alive [2] neonatal death < 28 days [3] neonatal death > 29 days [8] not recorded
Planned treatment or emergency treatment	[1] planned [2] emergency
Was abnormally invasive placenta suspected prior to delivery?	[1] yes [0] no
If yes, indicate which features were recorded (multiple answers possible)	[1] Placental lacunae [2] Loss of clear space [3] Disruption of bladder/myometrial interface [4] Placenta previa <2cm from internal os [5] Placenta thickness in lower segment >50mm [6] Myometrial thinning <1mm [7] Bridging vessels

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(continued)

Did the woman experience complications in pregnancy?	[1] yes [0] no
If yes, indicate any of the following (multiple answers possible)	[1] Antepartum haemorrhage [2] Retained placenta [3] Uterine rupture [4] Other
Was a hysterectomy performed?	[1] yes [0] no
Is there a histopathology confirming an abnormally invasive placenta?	[1] yes [0] no
Major maternal morbidity?	[1] yes [0] no
If major medical complication, please choose:	[10] Renal failure [20] Thrombotic event[30] Septicaemia[40] Cerebrovascular accident [50] Pulmonary edema[60] Pulmonary aspiration[70] Maternal death

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