TITLE: CAESAREAN SCAR PREGNANCY IN THE UK: A NATIONAL COHORT STUDY

RUNNING TITLE: Caesarean scar pregnancy

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ABSTRACT

Objective: To estimate the incidence of caesarean scar pregnancy (CSP) and to describe the management outcomes associated with this condition

Design: A national cohort study using the UK Early Pregnancy Surveillance Service (UKEPSS).

Setting: 86 participating Early Pregnancy Units.

Population: All women diagnosed in the participating units with CSP between November 2013 and January 2015.

Methods: Cohort study of women identified through the UKEPSS monthly mailing system

Main Outcome Measures: Incidence, clinical outcomes and complications.

Results: 102 cases of CSP were reported, with an estimated incidence of 1.5 per 10,000 (95% CI 1.1 – 1.9) maternities.

Full outcome data were available for 92 women. Management was expectant in 21/92 (23%), medical in 15/92 (16%), and surgical in 56/92 (61%). The success rates of expectant, medical, and surgical management were 43% (9/21), 46% (7/15) and 96% (54/56) respectively. The complication rates were 15/21 (71%) with expectant, 9/15 (60%) with medical and 20/56 (36%) with surgical management. Discharge from care (median number of days) was 82 days (range 37-174) with expectant, 21 days (range 10-31) with medical, and 11 days (range 4-49) with surgical management.

Conclusions: Surgical management appears to be associated with a high success rate, low complication rate and short post-treatment follow up.

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Keywords: Caesarean, Ectopic, 'Caesarean Scar Pregnancy', 'Placenta accreta'; cohort study

Tweetable abstract: Surgery for CSP appears to be successful, with low complication rates and short post-treatment follow up

INTRODUCTION

A caesarean scar pregnancy (CSP) is a pregnancy which is partially or completely surrounded by myometrium and fibrous tissue of the scar of the prior lower uterine segment. The term CSP is usually used to describe first trimester pregnancies at the level of the internal os with evidence of myometrial involvement. It is generally becoming accepted that CSP is a precursor of abnormally adherent placenta in the second and third trimester of pregnancy.(1) Some authors have proposed that the term CSP should be used in the first trimester, early placenta accreta in the second and morbidly adherent placenta in the third trimester of pregnancy.(2)

The incidence of CSP is estimated to range from 1/1800 –1/2500 of all caesarean deliveries performed.(3-6) The number of reported cases has increased over recent years, possibly reflecting the rising number of caesareans performed and the more widespread use of transvaginal ultrasonography leading to the diagnosis being suspected in more cases.(7-11)

The exact cause of CSP is not well understood. Previous caesarean delivery, previous uterine surgery, multiparity, advanced maternal age and smoking are some of the predisposing factors that have been proposed in the literature. (15;16) Studies have shown that the risk of the caesarean scar healing poorly increases with the number of previous caesarean operations.(17) It has been suggested that after many caesareans deliveries the scar surface is increased, and the anterior uterine wall may be deficient due to fibrosis, poor vascularity, and impaired healing. Consequently the likelihood of implantation into such a scar is increased.(3)

The three main treatment options are expectant, medical or surgical. Women are counseled about the potential risk and benefits of the different options and are given

the choice to either continue with their pregnancy, to watch and wait or to terminate the pregnancy should it be ongoing.

There is currently limited knowledge about the risk factors for caesarean scar pregnancy, presenting features, diagnostic criteria and management options. (12) Furthermore, there is no agreement on the best management of caesarean scar pregnancies. This was highlighted by the recent RCOG/AEPU Green-top Guideline(13), which prioritised the need for research on the optimal management of caesarean scar pregnancy.

No population-wide studies of caesarean scar pregnancy have been previously undertaken. The aim of this study was to use the UK Early Pregnancy Surveillance Service (UKEPSS) platform to identify all women in the UK that were diagnosed with caesarean scar pregnancy. This study describes the cases, diagnosis, management and clinical outcomes.

METHODS

This was a national cohort study of women in the UK diagnosed with CSP conducted in 86 participating Early Pregnancy Units (EPU) from November 2013 to January 2015. A dedicated online data capture system was designed to facilitate data entry. Baseline data were recorded for age, ethnicity, smoking status at presentation, medical history, parity, and caesarean section history. A set of sonographic criteria was proposed in the study protocol by the study steering committee to aid the identification of CSP. This comprised the following four features; presence of gestational sac or placental tissue anteriorly at the level of the internal os; evidence of pregnancy invading into the myometrium; evidence of sustained peri-trophoblastic circulation on colour Doppler examination, characterised by high blood-flow velocity (over 20cm/sec) and low

impedance (PI<1) circulation, and negative sliding organ sign (inability to displace the gestational sac from its position using gentle pressure with a transvaginal probe).

The primary outcome was successful treatment following primary management. Success was defined as complete resolution of pregnancy without the need for further intervention following primary management. For instance, if a woman had surgical treatment as the primary management approach and on follow up she is found to have persistent products of conception for which further surgery is performed, this was considered as an additional intervention and failure of primary management. We also recorded complication rates and length of post-treatment follow up. The study outcomes were set by the UKEPSS CSP study steering committee. The UKEPSS general methodology and this study were approved by the North Wales Research Ethics Committee (REC reference 13/WA/0318). Funding was received from the Association of Early Pregnancy Units and Birmingham Women's and Children's Foundation NHS Trust R&D Springboard Fellowship for this study.

Data collection

Cases were identified on a national basis through the monthly e-mailing of UKEPSS reminders. Clinicians were asked to report any woman diagnosed with caesarean scar pregnancy. The UKEPSS methodology has been described in detail elsewhere.(14) All data collected were anonymous.

Statistical analysis

Incidence was calculated with 95% confidence intervals by using denominator data from the most recently available birth registration data as a proxy for the period between February 2014 and February 2015. Success and complication rates are provided for each treatment.

Patient involvement

This study question was prioritised by a nationally representative group of clinicians and patients as a joint UKEPSS initiative, which includes the Association of Early Pregnancy Units, the Miscarriage Association, the Ectopic Pregnancy Trust, the Early Pregnancy Clinical Studies Group, and was endorsed by the Royal College of Obstetricians and Gynaecologists. No patients were involved in setting the outcome measures, nor were they asked to advise on interpretation or writing up of results.

RESULTS

Incidence

Eighty-six hospitals with consultant-led EPU contributed data to UKEPSS during the study. A total of 102 cases were reported (Figure 1) through the UKEPSS platform between November 2013 and February 2015. We assessed the incidence of CSP over a 12 month period between 7th February 2014 and 6th February 2015. 58 cases of CSP were recorded during that period of time. The estimated number of maternities in the participating units was 390,361, giving an incidence of 1.5 per 10 000 maternities (95% CI, 1.1 – 1.9). Data outcomes were available for 92/102 (90%) of cases. Full treatment outcome data was available for 92 out of 102 (90%) reported cases, with a loss to follow up rate of 9.8%.

Diagnosis

The mean maternal age at presentation was 35 years (SD ± 4.7; range 23-45). The mean gestational age (by sonographic measurement) at presentation was 9 weeks (range 6 – 18). The most common symptom at presentation (Table 1) was vaginal bleeding (44/92, 48%), followed by vaginal bleeding and pain (21/92, 23%), pain (9/92, 10%) and the remaining women were asymptomatic (18/92, 20%). Of those that specified the severity of bleeding (n=30), 16 (53%) presented with bleeding reported

as less than a period, 6/30 (20%) with bleeding ‘like a period’, and 8 (27%) women bled ‘more than a period’.

Ultrasonography was performed in 85/85 (100%) of women where investigation was reported; 83 (98%) women had a transvaginal ultrasound scan, and 2 (2%) had a transabdominal ultrasound scan.

Table 2 shows the frequency of reporting of each of the sonographic criteria proposed in the study protocol. In 50/85 (59%) of cases all 4 features were present; in 17/85 (20%) 3 out of the 4 criteria were present; in 12/85 (14%) 2 of the 4 criteria were present and in 6/85 (7%) only 1 of the 4 criteria was present on scan.

Additional investigations

24 women had serial hCG measurements, 8 women had MRI assessment, 8 women had 3D ultrasonography, and 4 women had diagnostic laparoscopy. Hysteroscopy was used in one case as a combined surgical approach with laparoscopy. None of the cases were investigated by CT scan.

Outcomes

The treatment outcomes are presented in Table 3. Sixty one percent (56/92) of women presenting with CSP had surgical treatment as primary management of caesarean ectopic pregnancy. This was followed by expectant management (21/92, 23%) and medical management (15/92, 16%). There was no difference in the mean gestation in each group (8+4, 9+1 and 9 weeks for expectant, medical and surgical management respectively).

Expectant management

Twenty one (21/92, 23%) women opted for expectant management; the indication for expectant management was maternal request (10/21, 48%), uncertainty in diagnosis at presentation (5/21, 24%), and in 6/21 (29%) the reason was not reported.

Fetal cardiac activity was present in 9/21 (43%); of these, 2/9 (22%) pregnancies resolved spontaneously, 5/9 (56%) pregnancies progressed to livebirths, 1/9 (11%) required second line surgical treatment in the way of surgical evacuation of retained products of conception, and 1 woman (1/9, 11%) who had a heterotopic pregnancy and opted for expectant management presented at 17 weeks gestation in shock and underwent a hysterectomy for a ruptured uterus.

The remaining 12 cases were non-viable, of which; 5 resolved spontaneously following expectant management; 1 had second line medical treatment; and 6 had second line surgical treatment.

Medical management

Methotrexate was used in all (15/15, 100%) cases treated by medical management. In 14/15 women, methotrexate was given by the intramuscular route at a dose ranging from 50 – 110mg. In one case (1/15), methotrexate was administered directly into the gestational sac at a dose of 20mg. 2 women (2/15) had planned multi-dose methotrexate therapy; in the first case, a dose of 110mg IM was given with a further dose administered after 14 days, and in the second case 90 mg IM was administered on day 1 and on day 7.

Surgical management

Primary

Dilatation and curettage or suction curettage were the surgical approaches used in all women (56/56, 100%) who had planned primary surgical management. 52/56 (92%)

were performed under ultrasound guidance. In 46/56 (82%) cases additional haemostatic measures were used at the time of surgery, including misoprostol (38/46, 83%), syntometrine (26/44, 56%), Shirodkar suture (19/46, 41%), and Foley catheter (7/46, 15%) insertion.

One woman had an emergency admission with abdominal pain. A transvaginal scan suggested a viable CSP with possible breach of the scar. She underwent a diagnostic laparoscopy, which confirmed a scar pregnancy with uterine rupture. Due to uncontrollable haemorrhage a laparotomy and repair were performed.

Secondary

Other surgical approaches were used in three cases as second line treatment; two were emergency procedures, and one was planned surgery.

One woman presented with sepsis following medical management of CSP at 13 weeks. She was treated with 90mg of methotrexate followed by a repeat dose one week later. She had persistent vaginal spotting and a scan showed a gestational sac with an embryo and absent fetal heart. She presented 6 weeks later with signs of sepsis. An ultrasound scan showed a fluid area around the site of the scar pregnancy. A laparotomy was performed which revealed abscess formation at the site of the scar pregnancy which was excised.

Another woman had a heterotopic pregnancy and opted for expectant management. She presented at 17/40 with shock and at laparotomy was found to have intraabdominal bleeding secondary to a ruptured uterus which was not possible to repair. She lost 3500ml blood and underwent a hysterectomy.

One woman was initially misdiagnosed as having an anembryonic pregnancy and had medical management of miscarriage. She underwent planned secondary surgical

management with a combined laparoscopic and hysteroscopic approach. A balloon was inserted and bilateral uterine artery embolisation was performed.

Treatment success

The success rates of expectant, medical, and surgical management were 43%, 47% and 96% respectively.

Complications

The rates of complications for expectant, medical and surgical management were 15/21 (71%), 9/15 (60%) and 20/56 (36%) respectively.

Bleeding

10/21 (48%) of women who had expectant management had bleeding. 4/15 (27%) of cases managed medically and 19/56 (34%) of women who underwent surgical management were reported to have bleeding as a complication.

Uterine artery embolisation (UAE) was performed in 3 cases. Two cases were initially misdiagnosed as failed pregnancies; one was treated with medical management of miscarriage and due to a persistent mass on scan found in the CS scar, a surgical approach with combined laparoscopy and hysteroscopy was taken and bilateral UAE was performed. The other had an emergency suction curettage and suffered a 2.5L blood loss, which was managed with 2 units of blood transfusion, UAE, and foley catheter insertion. The third case opted for expectant management and underwent an elective CS at 33 weeks, with subsequent major PPH, managed by bilateral UAE and necessitating caesarean hysterectomy.

Retained products of conception (RPOC)

The rate of RPOC following expectant, medical and surgical management was 7/21 (33%), 9/15 (60%) and 2/56 (3.7%) respectively.

Infection

Infection was reported in 3 cases (3/92, 3%), of which 2 (2/21, 10%) were in women who had expectant management, and 1 (1/15, 7%) was following medical treatment.

Collapse

Nineteen percent (4/21) of women who had expectant management suffered a collapse. There was one case (1/56, 2%) of collapse in the surgical group, and none in the medical group.

Uterine scar rupture

There were two cases of uterine scar rupture; one (1/21, 5%) occurred following expectant management. The other (1/56, 2%) was an emergency presentation with scar rupture in a woman complaining of vaginal bleeding and pain; scar rupture was the indication for surgical management.

Hysterectomy

Four women underwent an emergency hysterectomy, all of whom had expectant management (4/21, 19%).

Placenta accreta

There were three cases of placenta accreta, all in women who opted for expectant management (3/21, 14%).

Live births

Five (5/21, 24%) live births resulted from women who opted for expectant management (Table S1). Three women had planned caesarean deliveries from 36 weeks gestation, and two women presented with sepsis and underwent pre-term emergency caesarean deliveries. Three (3/5, 60%) pregnancies were complicated by placenta accreta; all 3 required emergency hysterectomy (3/5, 60%) and 2 women (2/5, 40%) suffered major obstetric haemorrhage.

Follow-up

The median length of follow-up for expectant management was 82 days (range 37-174); 21 days (range 10 –31) for medical management; and 11 days (range 4-49) following surgical management.

DISCUSSION

Main findings

This study demonstrates the rarity of CSP, estimating the incidence in the UK to be 1.5 per 10,000 maternities overall. This equates to one case every 2 years in a unit delivering 5000 women.

CSP was diagnosed as early as 6 weeks to as late as 18 weeks in our study. The most common presenting symptom is light painless vaginal bleeding (47%). Transvaginal ultrasonography is the first line diagnostic tool for CSP. The study found that, in the UK, surgical management is used more often than expectant or medical treatment and appears to be associated with a high success rate, low complication rate and short post-treatment follow up.

Strengths and limitations

This is the first population-wide study of CSP to be performed in the UK. Data were reported to our study from 86 units across the UK. They include women from various

demographics who presented to their local hospitals and were diagnosed and managed according to local protocols. As such, the study reflects a broad representation of national practice. Our incidence estimates appear to be lower than those quoted in previous studies (3,6), however these estimates were based on a small number of cases in tertiary referral centres. The true prevalence of CSP is likely to be higher as some cases will end in the first trimester, either by miscarriage or termination, and go unreported and undiagnosed. (13)

There is currently no consensus on the diagnostic criteria for CSP. The criteria proposed in the UKEPSS study (provided in the methods section) has been previously published (3,14). Other published criteria include those proposed by Timor-Tritsch et al. (7), which consider the following ultrasound features diagnostic; an endometrial and endocervical canal devoid of a pregnancy; a placenta and/or gestational sac embedded in the hysterotomy scar; in early gestations, a triangular gestational sac that fills the niche of the scar; a thin (1–3 mm) or absent myometrial layer between the gestational sac and bladder; the presence of an embryonic/fetal pole and/or a yolk sac with or without heart activity; the presence of a prominent and at times rich vascular pattern at or in the area of a cesarean delivery scar; in the presence of positive human chorionic gonadotropin (hCG) levels.

The absence of a gold standard test for diagnosis is a key limitation. Current diagnostic criteria have not been validated and are derived from descriptive case series. In our study, 60% of submitted cases reported on all 4 sonographic features proposed in the UKEPSS study protocol. Doppler assessment for evidence of sustained peritrophoblastic circulation was used in 70% of cases. In the remaining 30%, Doppler assessment was either not performed or not reported, and this is of concern. Doppler assessment may help reduce false positive diagnosis. Reporting centres were invited to submit ultrasound images for review by an expert panel to confirm diagnosis,

however, few centres provided their images. It is therefore possible that false positive cases may have been reported to our study. To minimise the risk of false-positive diagnosis, the RCOG/AEPU Green-top Guideline(13) has recommended that all non-emergency cases of suspected scar pregnancy are referred to a regional centre to confirm the diagnosis.

Interpretation

Timor-Tritsch et al. (2) provide evidence that the histological appearance of first-trimester scar pregnancy resembles that of abnormally adherent placenta in the second trimester of pregnancy. This supports the long-held view that scar pregnancy may indeed be a precursor of placenta previa/accreta. There is a possibility that cases with a better outcome remain undiagnosed or unreported. Screening for scar pregnancy is considered controversial due to uncertainty regarding natural history, compliance and accuracy of diagnosis when ultrasound scans are carried out in centres with variable level of expertise. However, it needs further evaluation through a screening study for women with previous CS especially for those with multiple CS where the prevalence of the disease is higher.

Transcervical surgical evacuation performed under ultrasound guidance was the primary surgical approach in our study. Ultrasound guidance is believed to be vital to facilitate safe successful evacuation of the placental tissue, with less risk of perforation and reduced surgical time.(18)

Traditionally methotrexate was a popular treatment due to the concerns about bleeding with surgical treatment.(19) Greater blood loss with surgical management is not unexpected due to the location of the CSP within the myometrial defect which has impaired contractility. In 82% of cases where a primary surgical approach was taken, additional haemostatic measures were used at the time of surgery, including

misoprostol, syntometrine, insertion of Shirodkar suture and Foley catheter. The method of insertion of a Shirodkar cervical suture has been previously described in the literature. (24) The effectiveness of a Shirodkar suture in securing haemostasis may be explained by a more effective tamponade of the implantation site achieved by the blood clot that forms within the scar defect. Bleeding into the uterine defect when the cervix is occluded by the suture ensures an even distribution of pressure on the defective myometrium. The use of oxytocic drugs induce strong contractions of the uterine fundus which further increase the pressure on the blood vessels at the implantation site and prevent retrograde bleeding into the abdominal cavity through the Fallopian tubes.

Methotrexate was administered in all women undergoing medical management in our study. Less than half of medically managed CSP were treated successfully with methotrexate, which is consistent with other study findings(20). Women wishing to have medical treatment should be informed of the high risk of failure (54%), and the likely need for further treatment with surgical management. This is because one of the main complications of medical management is retained products of conception (60% in our study).

The main difficulty in counselling women diagnosed with asymptomatic scar pregnancy is our lack of understanding of the natural history of the condition and our inability to predict the likely outcome. In cases of diagnostic uncertainty, conservative management may be considered in the first instance. Ross et al. (21) suggest that when a wanted pregnancy is found to be implanted in or on a CS scar very early in gestation, it may be preferable to wait until the placenta has begun to develop and the cord and its insertion site are visible before making a definitive diagnosis and recommending intervention.

In our study, women who had expectant management had a 19% risk of hysterectomy; however where the CSP was viable, the risk of hysterectomy increased to 44%. 3/5 (60%) women who had a live birth suffered severe complications including; massive obstetric haemorrhage, need for blood transfusion, caesarean hysterectomy, and in one case cardiac arrest. Two women (2/5, 40%) presented with sepsis; sepsis can complicate these pregnancies given the close proximity of the placenta to the vagina making it susceptible to ascending infections. These findings are in keeping with published studies, which consistently show that women with live CSP can have severe outcomes (3;7;9;15;19;22). There is a widely held view that given these risks, an active approach to treatment is justified.(23)

Conclusion

Ultrasound guided surgical evacuation is a successful treatment with rapid resolution of pregnancy. Expectant management is associated with a high risk of morbidity, including the risk of hysterectomy due to morbidly adherent placenta.

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Disclosure of interests

None declared.

Contribution to Authorship

HH designed the study, coded and interpreted the data and wrote the manuscript. MK designed the study and contributed to the writing of the manuscript. AT and IDG analysed the data and contributed to the writing of the manuscript. CB, CO, MS, RF,

AH, PL, EE, MM, EM, JZ, FD, RS and JR designed the study, contributed data, and critically reviewed the manuscript. TB, AC and DJ designed the study, interpreted the data and contributed to the writing of the manuscript.

Details of Ethics Approval

The UKEPSS general methodology and this study were approved by the North Wales Research Ethics Committee (REC reference 13/WA/0318) on 23/09/2013.

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