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Systematic Review on Cesarean Scar Pregnancy (CSP) Diagnosis, Treatment and Management

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Abstract

Introduction

Cesarean scar pregnancy (CSP) is a rare but increasingly recognized complication where an embryo implants on the cesarean section scar. The incidence of CSP is rising in parallel with increasing global cesarean rates, posing significant health risks such as severe bleeding and uterine rupture. Early and accurate identification using criteria like the gestational sac's position within the scar and specific ultrasound features is crucial for preventing severe outcomes.

Aim of the Study

To evaluate the diagnostic criteria and various treatment strategies for CSP, assessing their effectiveness and challenges.

Materials and Methods

A review of the literature collected in the PubMed database was performed to gather information found under the key words cesarean scar pregnancy," “ectopic pregnancy,” "CSP treatment," "uterine artery embolization," "methotrexate," "hysteroscopy," "dilation and curettage," and "chemoembolization."

Summary

The review discusses various treatment strategies, including methotrexate administration, UAE, and surgical options like hysteroscopy and laparoscopy, highlighting their effectiveness and associated challenges. It emphasizes the importance of tailoring treatments to individual patient conditions, with newer methods like chemoembolization showing promise in minimizing complications. The findings underscore the need for a personalized treatment approach,

considering patient-specific factors and health goals. Further research is needed to refine these strategies and improve outcomes for those affected by CSP.

Keywords: Cesarean scar pregnancy (CSP), Methotrexate (MTX), Ectopic Pregnancy, Cesarean cut, CSP treatment.

Introduction

Ectopic pregnancies appear in around 2% of pregnancies, this pregnancies are the leading cause of maternal mortality, account for 9% mortality related with pregnancy the first trimester[1]. Pregnancy of unknown location is a term used to describe a clinical scenario, when woman presents with a positive urine pregnancy [2]. Cesarean scar pregnancy (CSP) is a rare and unique form of ectopic pregnancy where the embryo implants into the scar tissue of a previous cesarean section. Several mechanisms contribute to this abnormal implantation [3].

Types of CSP:
A type I CSP is partially located in the scar and presents a myometrial thickness of >3 mm. A type II CSP is characterized as partially located in the area of the scar and has a myometrial thickness of ≤3 m. A CSP is considered type III when completely located within the area of the scar and having a myometrial thickness of ≤3 mm [4].
One key factor is the invasion of the myometrium by extra villous trophoblastic cells, facilitated by the disrupted microtubular connections between the scar tissue and the normal myometrium. The scar tissue itself undergoes various pathological processes, including apoptosis, elastosis, inflammation, and a decrease in smooth muscle density, leading to myofiber disarray. These changes create a conducive environment for deeper trophoblastic invasion, potentially reaching myometrial vessels. Additionally, the hypoxic environment within the scarred myometrium further stimulates trophoblastic cell invasion, increasing the risk of complications such as placenta accreta spectrum (PAS) disorders.[4]
CSP can lead to severe complications, including uterine rupture, hemorrhage, and adverse effects on future fertility. The incidence of CSP is estimated to range from 1 in 1,000 to 1 in

2,500 pregnancies, correlating with the increasing number of cesarean deliveries and advancements in imaging technologies that facilitate earlier and more accurate diagnosis [5]. As the global cesarean section rate has risen from approximately 6% in 1990 to 21% in 2015, and is projected to reach 29% by 2030, the prevalence of CSP is expected to increase accordingly [6].

The rise in cesarean deliveries, coupled with enhanced imaging capabilities, has led to more frequent and earlier identification of CSP. This presents an evolving challenge for the medical community, necessitating comprehensive understanding and tailored treatment approaches to mitigate risks and improve outcomes for affected women.

Clinical Presentation and Diagnosis

CSP often presents clinically with vaginal bleeding and abdominal pain, though it can also be asymptomatic and detected incidentally during routine ultrasounds. Diagnosis is typically confirmed by using transvaginal ultrasound.

Criteria for diagnosing CSP by ultrasound include:

- Visible empty uterine cavity
- Detection of the placenta and/or gestational sac existing in the cesarean scar
- Triangular gestational sac in the niche of the scar, usually seen before 7 weeks
- A thin (1-3 mm) or absent myometrial layer between the gestational sac and the bladder
- A closed cervix and empty endocervical canal
- The appearance of an embryonic/fetal pole and/or yolk sac with or without cardiac activity
- A prominent and at times rich vascular pattern at or around the chorionic sac and the placenta.

In this review, cases of CSP diagnosed early (≤9 weeks of gestation) were compared with those diagnosed later (>9 weeks). The review found that early diagnosis was associated with lower risks of adverse maternal outcomes, including hemorrhage, blood transfusion, emergency hysterectomy, and uterine rupture. Conversely, approximately 30% of women diagnosed with CSP after 9 weeks experienced significant complications [7, 27].

Treatment Modalities

Risk factors for conservative treatment failure of CSP:

In this meta-analysis of the risk factors for conservative treatment failure of CSP. This analysis included 7 studies. The results has shown, that more than 2 cesarean sections, mass type CSP, serum β-hCG value <20,000 U/L, and pregnancy more than 3 years from the last cesarean section were risk factors for the failure of conservative treatment of CSP. Patients with the this risk factors should be examined and informed of the possibility of conservative treatment failure in a proper time [25].

Zhang et al. invastigated total 20 case − control studies including 3101 CSP patients, where bleeding group had 573 patients and the control group had 2528 patients. The study found that several factors may increase the risk of significant bleeding during the treatment of cesarean scar pregnancy (CSP), including multiple pregnancies, a large gestational sac, an advanced gestational age, elevated serum β-HCG levels, a rich blood supply to the pregnancy sac, and a thin myometrial layer[26].

Description of CSP Treatments:

Systemic methotrexate- MTX for CSP (single-dose 50 mg) is used in hemodynamically stable patients without pain, with a gestation age <8 weeks, myometrium thickness <2 mm between the pregnancy and the bladder, serum hCG <5,000 IU/L, GS %2.5 cm, and/or a fetus without heart action.

Systemic and local MTX- including systematic MTX and local injection MTX(50 mg, transabdominally or transvaginally). This method increase concentration of MTX in CSP and lead to faster termination of the pregnancy).

Needle aspiration and local MTX- in this method the gestational sac is aspirated transvaginally by ultrasound guidance, usually in general anesthesia.

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

Hysteroscopy- The gestational sac is dissected free of the uterine wall through a natural entrance, and hemostasis can be achieved with electro-coagulation using a wire-loop or rollerball. Resection of CSP through a transvaginal approach [8].

Uterine artery embolization- embolization of uterine arteries by interventional radiologists. The procedure is performed under local anesthesia. Catheterization of the uterine arteries is perform through a transfemoral approach [9].

Laparoscopy- This procedure is conducted under general anesthesia and is utilized for cesarean scar pregnancies (CSP) progressing toward the bladder. The bladder is separated from the front of the uterus, and the uterine scar containing the ectopic pregnancy is excised, followed by the repair of the uterine defect. An intrauterine drainage catheter, such as a Frey catheter, may be used. To prevent excessive perioperative bleeding, bilateral ligation of the uterine arteries may be performed.

High-intensity focused ultrasound- The procedure can be performed using ablation alone or in combination with hysteroscopic D&C. Initially, it is done under conscious sedation, where a transducer generates the necessary therapeutic energy. Real-time ultrasound guides the targeting of the gestational sac (GS) and monitors the response. Additional D&C is carried out under general anesthesia [7].

STUDY 1: In this systematic review took part sixty-nine woman with CSP: fifty-five of them with embryonic/fetal heart activity and seventeen without embryonic/fetal heart activity. Serious vaginal bleeding in the first trimester of pregnancy occurred in 12,9% in the group with embryonic/fetal heart activity and 22.2% without embryonic/fetal heart. Remaining clinical symptoms occurred in 37,3% in the group with embryonic/fetal heart activity(20% of all cases including surgical or medical intervention, 13% with CSP suffered from uncomplicated miscarriage and didn't require any extra intervention, 20% woman suffered from miscarriage required treatment, in 9,9% cases during first or second trimester of pregnancy experienced uterine rupture- hysterectomy was required in 15,2% of those cases.)in comparison to the group without embryonic/fetal heart activity, 36,4% of them occurred on other clinical symptoms(26% of all cases including surgical or medical intervention, 69,1% with CSP suffered from uncomplicated miscarriage and 31% woman suffered from miscarriage required surgical treatment or medical intervention during or directly after miscarriage, 13,4% women experienced uterine rupture in first trimester, there were no cases about hysterectomy or

maternal death in first trimester in this systematic review). This systematic review noticed that women suffered from CSP with positive embryonic/fetal cardiac activity had a high risk of serious bleeding and clinical symptoms requiring surgical or medical intervention during the first trimester of pregnancy [5].

Uterine Artery Embolization (UAE)

Cesarean scar ectopic pregnancy is increasingly treated by uterine artery embolization in China. Uterine artery embolization (UAE) is an adjunctive treatment used for managing Cesarean Scar Pregnancy (CSP). This procedure is particularly effective in minimizing bleeding, especially when the trophoblastic tissue is deeply embedded in the myometrium [10].

STUDY 1: The meta-analysis reviewed data from 2,655 CSP patients treated with UAE as a first-line treatment. The results indicated that UAE was a successful method, achieving β-hCG normalization in an average of 30.3 days, with a mean intraprocedural blood loss of 41.9 mL, a success rate of 93.4%, and a severe complication rate of 1.2%. Due to the specific characteristics of the healthcare system in China, these findings might have limited applicability to patient care in other countries [9].

STUDY 2: Additionally, another study by Qiao et al.[11] supported these findings, concluding that UAE combined with dilation and curettage had a shorter β-hCG normalization period compared to the alternative method of methotrexate (MTX) combined with dilation and curettage.

STUDY 3: The use of UAE may carry risks similar to those seen in treatments for uterine myomas, such as decreased ovarian reserve, intrauterine growth restriction, premature delivery, placental abruption, or placenta accreta [10].

Methotrexate (MTX)

MTX is another key treatment option for CSP, used both systemically and locally. It acts by inhibiting cell division, particularly affecting the rapidly dividing trophoblastic cells, thereby reducing β-hCG levels.10 MTX is especially effective in hemodynamically stable patients with low β-hCG levels. When combined with UAE or D&C, MTX has been shown to accelerate β-hCG normalization and shorten hospital stays [12].

STUDY 1: The study results indicate a significant reduction in the mean level of β-hCG following the intervention with the mean level 28,744.98±4425.1 mIU/ml prior to intervention and mean β-hCG level 23,836.78±4533.123,836.78±4533.1 mIU/ml afterwards. In the current

systematic review and meta-analysis, methotrexate (MTX) resulted in more than a 15% reduction (17%) in β-hCG levels, indicating it as a successful pharmaceutical treatment for cesarean scar pregnancy (CSP). The findings showed a success rate of 90%, with an average hospital stay of 11.7 ± 1.2 days. The success rate for using MTX in treating ectopic pregnancies varies widely, ranging from approximately 71% to 100% and is lesser when the the level of β-hCG is high at the baseline.

According to the study we can consider MTX treatment of CSP as effective, safe(rate of complications was 9%) and low-cost method. Also this treatment method allows patients to preserve their fertility potential in future in comparison to the other treatment methods [10].

Complications of treatment with MTX including medical problems such as: hair loss, skin darkening, oral ulcers, diarrhea, decreased immunity [12].

STUDY 2: Both systemic and local MTX treatments can be effective for CSP, with systemic MTX showing slightly quicker β-hCG remission and mass resolution. However, systemic MTX may be limited by its half-life and fibrous tissue barriers, potentially requiring additional treatments. This method has shown effectiveness, especially in cases with serum β-hCG levels below 12,000 mIU/mL, absence of embryonic cardiac activity, and gestational age under 8 weeks [8].

Local MTX offers a more targeted approach, though its success can vary based on the specifics of the treatment protocol as MTX treatment showed a 61.1% success rate, with 22.2% of cases requiring additional MTX doses and 16.7% necessitating surgical intervention. A randomized trial comparing local and systemic MTX administration in 104 CSP patients found similar cure rates (69.2% for local vs. 67.3% for systemic treatment). However, systemic MTX was associated with faster β-hCG remission and cesarean scar mass disappearance [13].

The choice between systemic and local MTX should consider factors such as β-hCG levels, gestational age, and the characteristics of the cesarean scar mass.
Further research is necessary to refine protocols and optimize outcomes for CSP patients [14].

Surgical Interventions

Surgical options for CSP include hysteroscopy, D&C, laparoscopy, and laparotomy.

Hysteroscopy is a minimally invasive surgical procedure used for diagnosing and treating certain types of ectopic pregnancies, including cesarean scar pregnancy (CSP). It involves the use of a hysteroscope to visualize the inside of the uterus and perform surgical interventions. Hysteroscopy offers clear visualization of the gestational sac, surrounding blood vessels, and uterine wall. During the procedure, a resectoscope is used with glycine 1.5% as a distending medium. The products of conception are carefully detached from the uterine wall using a loop electrode without electrical current, which helps minimize tissue damage [15].

If bleeding occurs, it can be managed through electrocoagulation or by inserting an intrauterine Foley balloon. This method is associated with a quick recovery time, a short follow-up period, and a rapid decline in β-hCG levels to normal. It also helps maintain the normal structure of the uterine cavity. However, it is crucial that the procedure be performed by a skilled hysteroscopist to avoid complications. Regular follow-up with repeated β-hCG measurements is essential to ensure the complete resolution of the pregnancy [16,17].

It has been shown to have higher success rates and fewer complications compared to ultrasound-guided D&C.

STUDY 1: involving 39 cases of CSP removal using hysteroscopy under ultrasound guidance, 36 patients received mifepristone preoperatively, while 3 were treated with methotrexate and uterine artery embolization. There were no differences in the amount of bleeding during the procedure or in the time required to reach undetectable β-hCG levels between type I and type II CSP. D&C involves scraping the uterine lining to remove pregnancy tissue and is often guided by ultrasound to ensure complete removal. Laparoscopy and laparotomy are more invasive and typically reserved for cases with significant complications or when other methods are contraindicated [18].

STUDY 2: In this non blinded, randomized clinical trial conducted at a single center in Italy they focus on the differences in the success rate between hysteroscopic resection and ultrasound-guided dilation and evacuation for the treatment of cesarean scar ectopic pregnancy. In this study took part only women with singleton gestations at <8 weeks and 6 days of gestation. They expected women to have cesarean scar ectopic pregnancy who had a heartbeat

detected in the embryo and chose to terminate the pregnancy. Researchers divided 54 women for two groups. Women in first group were supposed to undergo hysteroscopic resection while women in the second group were expected to have ultrasound-guided dilation and evacuation. Both groups received methotrexate injections to help terminate the pregnancy, first dose at the baseline (day 1) and second dose on day 3, a third dose on day 5 if needed. Third dose of methotrexate was needed by 10 women: 3 in the dilation and evacuation group and 7 in the hysteroscopic resection group. Study has shown that hysteroscopic resection is better than ultrasound-guided dilation and evacuation with success rate 100% vs 81,5% [19].

Additionally, in the other systematic review of treatment studies they demonstrated that D&C was associated with a risk of hemorrhage of 28%, and a risk of hysterectomy of 3% while when it comes to hysteroscopic resection the risk of hemorrhage was ≤ 4%, and the risk of hysterectomy was ≤ 2%. [8].

Chemoembolization

Chemoembolization is one of the newest methods, and at the same time advanced technique used to treat CSP. This procedure involves the administration of a chemotherapeutic agent, typically methotrexate, directly into the uterine arteries supplying the gestational tissue. This is followed by the injection of embolic agents, such as polyvinyl alcohol particles or Gelfoam, to block these arteries, cutting off the blood supply to the area. This approach ensures targeted drug delivery and reduces systemic toxicity, providing high success rates (83%-99%) with minimal complications.

Chemoembolization for CSP is indicated in cases where there is a live or viable embryo implanted in the cesarean scar, the gestational age is less than 12 weeks, and there are no severe maternal symptoms like heavy vaginal bleeding or hemodynamic instability. This procedure is particularly considered when other treatments, such as methotrexate injections or dilation and curettage (D&C), are either not effective or contraindicated.

Many authors have described successful chemoembolization procedures despite the presence of fetal heart activity, so it is not a contraindication to the procedure [20].

Here are the procedure details: The procedure is performed under local anesthesia, with access typically obtained via the femoral artery. Real-time imaging, known as angiography, is used to map the uterine vasculature and identify the arteries supplying blood to the gestational tissue.

Methotrexate is then administered directly into the uterine arteries. Following the chemotherapy infusion, embolic agents are injected to block blood flow, creating ischemia in the targeted tissue [21].

The other studies show that:

Stępniak et al. found that 90% of women treated with chemoembolization followed by suction curettage were successfully treated. However, one patient experienced abnormal bleeding, and another required repeated embolization due to rich vascularization from the ovarian artery [22].

Pyra et al. reported a success rate of 83% among 41 patients, while a larger retrospective study showed a 99% success rate in 383 patients. Factors like gestational mass size, presence of a fetal heartbeat, and type of CSP influenced treatment efficacy. Chemoembolization was more effective compared to methotrexate and curettage, offering better outcomes in blood loss, hospitalization duration, and normalization of β-HCG levels [20].

Possible complications include uterine cramping, nausea, and, in rare cases, hemorrhage or the need for a hysterectomy. The procedure may impact ovarian reserve and future fertility, especially if repeated embolizations are required or if occlusion of utero-ovarian anastomoses occurs.

Chemoembolization is an effective and promising treatment for managing Cesarean Scar Pregnancy (CSP), with a high success rate and a generally favorable safety profile. However, it's important to consider each patient's specific circumstances, such as their fertility goals and potential complications, when selecting this treatment. Further studies are necessary to comprehensively understand the long-term impacts on fertility and the potential for CSP to recur [21].

High-intensity Focused Ultrasound Compared with Uterine Artery Embolization in Cesarean Section Pregnancy:

STUDY 1: In the meta-analysis, Liu Y. et al. compared the efficacy and safety of UAE and HIFU (High-intensity Focused Ultrasound). According to this analysis, HIFU has shown satisfactory treatment success, including similar intraoperative blood loss,, menstruation recovery, and slower normalization of beta-HCG levels, but potentially shorter hospitalization time, fewer adverse events, and lower treatment costs comparing to UAE. Therefore, HIFU is an effective, safe, and economical treatment for patients with CSP [23].

STUDY 2:In this meta-analysis participated 715 patients divided into two groups: 388 patients in the HIFU group and 327 patients in the UAE group. Conclusions from these meta-analyses are as follows: patients from the HIFU group had lower risk of blood loss, duration of the hospital stay was shorter, there was a lower risk of adverse effects, but the time of normalization beta-HCG was longer than in UAE group. These meta-analyses showed that HIFU group appears to have more beneficial effects than the UAE treatment [24].

Reproductive outcome after cesarean scar pregnancy

Meta-analysis of Morlando including eighteen studies (300 women) stated the reproductive outcome after a prior CSP; among women trying to conceive, 70.6% successfully became pregnant. In women with an intrauterine pregnancy following a prior cesarean scar pregnancy (CSP), the rate of uterine rupture was 1.5%. Overall, 67.0% of the cases had an uncomplicated pregnancy. Miscarriage and preterm birth complicated 16.2% and 8.9% of women undergoing surgical management, compared to 14.7% and 15.2% of those undergoing non-surgical management. Additionally, 2.7% of pregnancies managed surgically and 10.6% of those managed non-surgically for the prior CSP experienced PAS disorders in the subsequent pregnancy [30].

Physiotherapy

Weerasinghe et al. stated that incorporating face-to-face physiotherapy training and education into standard pre-operative care for elective CS can significantly enhance the post-natal quality of life. The study involved 54 women scheduled for elective cesarean sections (CS). These participants were divided into two groups: the intervention group, which received a 10-minute face-to-face physiotherapy session before surgery, including structured education and exercise guidelines, and the control group, which received standard nursing care.

The results indicated that the intervention group experienced significantly higher post-natal quality of life scores in areas such as physical function, role limitations due to physical health, energy/fatigue, and pain compared to the control group. re-operative physiotherapy appears to

be an effective intervention for improving post-operative outcomes. It helps in reducing post-operative pain, the need for additional pain medications, discomfort during the return to functional activities, and the duration of hospital stays. This intervention supports better recovery outcomes for mothers after cesarean sections by enhancing physical functioning and overall post-operative recovery [28, 29].

Outcomes and Complications

The success of CSP treatment depends on factors such as the gestational age at diagnosis, the presence of fetal heart activity, and the patient's overall health. Early diagnosis, ideally at or before 9 weeks of gestation, is crucial for reducing the risk of severe maternal outcomes, including hemorrhage, emergency hysterectomy, and uterine rupture. While treatments like UAE and MTX are generally effective, they are not without risks, such as decreased ovarian reserve and potential complications in future pregnancies.The choice of treatment should be individualized, considering the patient's stability, gestational age, and reproductive goals. Comprehensive management strategies, including close follow-up care, are essential to optimize patient outcomes.

Conclusions

Managing CSP requires a multidisciplinary approach due to its complexity and the high risk of complications. While treatments such as UAE, MTX, and various surgical interventions have proven effective, there is no universal consensus on the best approach. Treatment plans should be individualized based on clinical presentation and patient preferences. There is a critical need for further research to develop standardized treatment protocols and improve clinical outcomes for patients with CSP.

Disclosure

Author's contribution

Conceptualization: Marcelina Teresa Marzec and Weronika Zofia Marzec; Methodology: Aleksandra Łakoma; Software: Aleksandra Wydra-Rojek; Check: Paulina Wasiewicz- Ciach and Katarzyna Kutyła; Formal analysis: Anna Marszałek and Piotr Kuczyński; Investigation: Maciej Choiński and Wojciech Jan Mokot; Resources: Piotr Kuczyński; Data curation: Aleksandra Łakoma; Writing - rough preparation: Marcelina Teresa Marzec and Weronika Zofia Marzec; Writing - review and editing: Aleksandra Wydra-Rojek and Paulina Wasiewicz-Ciach; Visualization: Wojciech Jan Mokot; Supervision: Maciej Choiński; Project administration: Katarzyna Kutyła and Anna Marszałek; Receiving funding - no specific funding. All authors have read and agreed with the published version of the manuscript.

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