Review Article

Progress in diagnosis and treatment of cesarean scar pregnancy

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Abstract: Cesarean scar pregnancy (CSP) is a special ectopic pregnancy, and the incidence of the disease increases with the increase in cesarean section rate in recent years. Because CSP usually has massive bleeding and other risks, early diagnosis and early treatment is particularly important. Based on the status quo of diagnosis and treatment of CSP, this review summarizes the progress of current commonly used diagnostic technologies, treatment and their corresponding advantages and disadvantages. UAE is a classical treatment at present, but its main risk destroys ovarian function, causes intrauterine adhesions, which may affect re-fertility, so a more optimized treatment plan is worth exploring. The new treatments mentioned in this review (high-intensity focused ultrasound, lauromacrogol) have certain feasibility, which can be further extended and verified in future research.

Keyword: Cesarean scar pregnancy diagnosis treatment

Cesarean scar pregnancy (CSP) is a rare ectopic pregnancy in which the embryo implantation is located in the scar of the uterine incision of the original cesarean section, where it grows and develops [1]. Since Larsen first reported CSP in 1978, the disease has been gradually recognized [2]. Previous scholars reported that the incidence of this disease was 1/1800-1/2216, accounting for 6.1% of all ectopic pregnancies and 0.15% of pregnant women with cesarean section history [1, 3]. In China, the cesarean section rate is the highest in the world [4], in 2011 alone, the cesarean section rate reached 54.9% [5]. In recent years, with the opening of the two-child policy, the rise of cesarean section rate and the further improvement of diagnostic technology, the incidence of CSP shows a significant increasing trend.

If CSP patients cannot be effectively and timely treated, they may suffer from massive bleeding, placenta previa, placenta implantation, uterine rupture, even hysterectomy and life-threatening risks [6, 7]. Therefore, it is recommended to terminate the pregnancy immediately once the diagnosis is made. So far, there are no unified standards and guidelines for the diagnosis and treatment of CSP [8]. This article reviews and discusses the main diagnostic and therapeutic methods and their recent progress.

Diagnosis of CSP

The clinical manifestations of CSP are not typical. Even some patients have no obvious clinical manifestations before being diagnosed [9], and the clinical manifestations are mainly vaginal bleeding, lower abdominal pain and so on [10], which are not significantly different from the common clinical manifestations of threatened abortion, tubal pregnancy and other diseases. Therefore, its diagnosis is difficult and easy to be diagnosed as “inevitable abortion”, “cervical pregnancy”, “lower intrauterine pregnancy”, even “extrauterine pregnancy”, etc. [11]. Usually, the diagnosis depends on auxiliary examinations, especially imaging examinations.

Transvaginal doppler ultrasound

At present, transvaginal color doppler ultrasonography is the main diagnostic method of CSP [12, 13]. Rotas et al. reported that the conformance rate of ultrasonic diagnosis of CSP was
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86.4% [14]. Ash etc. put forward the diagnostic criteria for CSP: (1) an empty uterine cavity, without contact with the sac, (2) a clearly visible empty cervical canal, without contact with the sac, (3) presence of the gestation sac with or without a fetal pole with or without fetal cardiac activity (depending on the gestation age) in the anterior part of the uterine isthmus, (4) absence of or a defect in the myometrial tissue between the bladder and the sac [15]. With the progress of pregnancy, placenta implantation can be seen in some patients during the second and third trimesters of pregnancy, and even in some patients can penetrate the muscular layer [16]. Ultrasound is simple, inexpensive, noninvasive, has high sensitivity and is repeatable, so clinicians mainly rely on ultrasound examination to diagnose and select appropriate treatment. It can also be carried out in primary hospitals. All women with a positive pregnancy test and prior cesarean delivery should undergo an early transvaginal sonographic (TVS) assessment during the first trimester [10], particular attention should be paid to the position of the gestational sac and its relationship with the scar of the previous cesarean section, further examination is needed if necessary. Recently, some scholars have invented the position examination of the gestational sac center relative to the axis of uterus under ultrasound to differentiate the diagnosis of intrauterine pregnancy, this report shows that it can improve the sensitivity and specificity of CSP diagnosis (sensitivity 93%, specificity 98.9%) [17]. Ultrasound is not only used for CSP diagnosis, but also for guiding treatment and follow-up after treatment because it is noninvasive and repeatable. It has been accepted as the first-line imaging method for CSP [18].

Contrast-enhanced ultrasound (CEUS)

Although ultrasound is the preferred diagnostic method of CSP at present, it still has some defects that lead to misdiagnosis or missed diagnosis in some patients. For example, not all gestational sacs located in the isthmus after cesarean section are CSP, if the gestational sac is implanted in the posterior and bilateral walls of the lower uterine segment. After gestational sac enlargement, ultrasonography can show an image similar to CSP, which is difficult to differentiate by two-dimensional ultrasonography. In addition, color doppler ultrasound is greatly affected by objective factors, such as the sensitivity of the detection equipment, the regulation of the detectors, etc. Sometimes it cannot reflect the real blood flow, and sometimes it is difficult to correctly judge the relationship between the lower uterine segment gestational sac and the uterine myometrium, serosa. Therefore, many scholars have studied the clinical value of contrast-enhanced ultrasound in the diagnosis of CSP. After injection of contrast agent SonoVue (Bracco Imaging S.p.A., Milan, Italy), the enhancement of gestational sac and its relationship with surrounding tissues were observed. The results showed that contrast-enhanced ultrasound could clearly show the blood perfusion of micro-vessels, which provided a new method for the evaluation of CSP. Contrast-enhanced ultrasound can determine the location of gestational sac by contrast agent perfusion at the lesion, distinguish the implanted or necrotic tissue of gestational sac, observe the integrity of uterine serosal layer and muscular layer, identify the relationship between the lesion periphery and muscle wall, and to provide basis for rational clinical treatment [19, 20]. Moreover, CEUS has the advantages of lower cost, a safer contrast agent, real-time tracking contrast agent imaging and displaying gray-scale image and enhancement image at the same time compared with enhanced Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) [18].

Magnetic resonance imaging (MRI)

Although ultrasonography is the main diagnostic method of CSP, it is difficult to evaluate the lesion extent of uterine myometrium and parametrial tissue comprehensively [21]. Compared with ultrasonography, MRI can clearly show the lower uterine segment gestational sac through multiple directions and sequences, distinguish the relationship between uterine cavity, endometrium, cesarean scar and gestational sac, and determine the position of gestational sac and the thickness of the surrounding uterine myometrium. In particular, it has more obvious advantages in evaluating the degree of gestational sac infiltration into uterine myometrium. Therefore, for those cases which are difficult to diagnose by ultrasound, MRI can be performed to further clarify the diagnosis [22, 23].

Dynamic monitoring of human chorionic gonadotropin (hCG)

hCG is mainly used in the diagnosis of pregnancy, including intrauterine pregnancy, ecto-
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Hypoplastic pregnancy and gestational trophoblastic disease, and the increase of hCG is not specific for the diagnosis of CSP. But it can be used for preoperative evaluation of gestational sac activity and follow-up after treatment. If there is incomplete removal of gestational product or residual trophoblasts continue to grow after treatment, the decrease of serum hCG will be slow, have no decrease or even increase. So regular monitoring of blood hCG changes after surgery is of great significance in judging the therapeutic effect of surgery and giving supplementary treatment as soon as possible [24].

Types of CSP

Ghezzi F [25] believe that the classification of CSP is very important for the guidance of clinical treatment. There are two types of CSP that have been proposed [26]. Type I (endogenic type) is caused by implantation of the gestational sac on the scar with progression toward either the cervicoisthmic space or the uterine cavity. Type II (exogenous type) is caused by deep implantation into a previous CS defect with infiltrating growth into the uterine myometrium and bulging from the uterine serosal surface, which may result in uterine rupture and severe bleeding during the first trimester of pregnancy. Thus, correct typing has important guiding significance for follow-up treatment.

Treatment of CSP

Drug treatment

At present, the treatment of CSP with methotrexate (MTX) is generally accepted. MTX is a chemotherapeutic drug that inhibits DNA synthesis and cell division and has the ability to inhibit trophoblast cell growth [27]. Drug treatment is generally suitable for patients with willingness and no drug treatment contraindications, such as stable vital signs, no active vaginal bleeding. While the lower the hCG value, the smaller the gestational sac mass, the higher the success rate of drug treatment [28]. There are two ways to treat drugs. (1) Systemic MTX: the usual dose is 50 mg/m² intramuscular injection; (2) Local MTX: Local injection of MTX 25-50 mg/m² into gestational sac guided by ultrasound. Some authors have found the local MTX has better curative effect and fewer side effects [29]. However, patients treated with MTX alone may still have a high failure rate (the reported failure rate was 57% [30, 31]), so often combined with uterine curettage to treat CSP after MTX treatment to reduce embryonic activity, intraoperative bleeding, shortens the treatment time. Surgical treatment is still needed for massive bleeding in the course of treatment.

Uterine artery embolization (UAE)

Uterine artery embolization (UAE) is a kind of interventional operation, which uses embolic particles to inject into the uterine artery, induces platelet aggregation and thrombosis, obstructs uterine artery cavity without destroying the capillary network, so that uterine blood supply is significantly reduced. It is often used in the treatment of gynecological and obstetric hemorrhagic diseases with remarkable effect. UAE treatment has been reported for CSP for the first time since 2002 [25], more and more studies have confirmed the efficacy of UAE [32, 33]. In the treatment of CSP, UAE is mainly used for the pretreatment of preventing bleeding before removing the gestational sac at the scar site of the uterus and the emergency hemostasis treatment in the case of emergency massive hemorrhaging. It has been reported that UAE can be combined with MTX for uterine artery embolization and chemotherapy with has a high success rate (The success rate of 31 cases was 100%) [34]. However, some studies have found that there are relative risk factors for CSP in UAE treatment, and massive bleeding may still occur after UAE, especially at gestational weeks > 8 weeks or gestational sac diameter > 6 cm [35]. Therefore, a complete preoperative evaluation should be conducted before UAE treatment, and other treatments should be considered for patients with a higher risk of bleeding.

Of course, the side effects and complications after UAE treatment cannot be ignored. It mainly includes embolism of other body parts after operation, abdominal pain caused by uterine ischemia, intrauterine adhesions caused by endometrial ischemic necrosis, fever and allergy [36]. UAE has even been found to cause amenorrhea in 2% to 10% of patients postoperatively [37], as well as affect ovarian function and lead to ovarian insufficiency [38]. Therefore, UAE should be avoided as far as possible for young patients with reproductive requirements,
so as not to affect reproductive function due to intrauterine adhesion and ovarian insufficiency after operation.

**Surgical management**

Because some CSP patients may have a clear risk of massive hemorrhage before treatment, such as large gestational sac, thin myometrium in cesarean scar, or even they came to the hospital with a massive hemorrhage, some patients treated with drug alone have a longer period of gestational sac absorption or excretion after treatment. At this time, there are still risks of persistent vaginal bleeding, secondary infection and even massive hemorrhage. So some patients can be treated by surgery.

Surgical management should fully consider the size of gestational sac, the level of blood hCG, the thickness of myometrium in cesarean scar, the degree of protrusion of gestational sac to bladder, and whether the patient has reproductive requirements to determine the specific surgical plan.

**Suction curettage:** As the main treatment for terminating early pregnancy, suction curettage is also considered to be used in the treatment of CSP. It has the advantages of low cost, simple operation and less trauma, it can also retain the reproductive function of patients as most treatments, and ultrasound-guided operation is generally used. Although there are many reports about the successful treatment of CSP by suction curettage, it is not suitable for everyone. It is often used for early treatment of endogenous CSP (type I CSP), small gestational sac, low blood hCG value, and insufficient blood flow around the gestational sac [39, 40] its success rate is 91% in the report [39]. It needs to be prepared for the rescue of massive hemorrhage before the operation, including laparotomy or laparoscopic resection of scar gestational sac. It has been reported that the use of Foley catheter for immediate hemostasis by balloon compression in the lower uterine segment is effective if massive intraoperative bleeding occurs [41]. For most of the cesarean scar pregnancy parts the muscle layer is thinner, even defective or seriously destroyed, and the attachment part of the gestational sac is often rich in blood supply, so the risk of suction curettage is higher. Some literature reported that the incidence of complications of suction curettage is higher, such as uterine perforation, massive hemorrhage and so on [3, 42]. So now clinical suction curettage is mainly used for the next combined treatment after pretreatment to remove the gestational sac, shorten the treatment cycle, and reduce vaginal bleeding.

**Hysteroscopy:** Hysteroscopy has been widely used in the examination and treatment of uterine cavity and cervical diseases, is a minimally invasive operation. Compared with suction curettage, hysteroscopy has the greatest advantage of visualization. Operators can perform operations under direct vision and resect lesions accurately, so as to reduce the occurrence of complications such as uterine perforation and residual uterine cavity, and it can also use electric energy to complete the electrocoagulation hemostasis of bleeding points in uterine wounds. Therefore, it can be used for the treatment of CSP [43, 44], even for some exogenous CSP (type II CSP), but the reports recommended that the thickness of the myometrial layer in cesarean scar should be more than 3 mm [45]. In addition, due to the increase of in vitro fertilization-embryo transfer (IVF-ET), the incidence of intrauterine pregnancy complicated with scar pregnancy has also begun to increase. Due to the visual advantages of hysteroscopy, some cases have also reported that hysteroscopy is used to remove the gestational sac in the scar of the uterus and retain the gestational sac in the uterine cavity, so as to achieve a smooth delivery [46].

**Cesarean scar gestational product resection:** For exogenous CSP (type II CSP), the gestational sac grows into the myometrium, implants deeply, and even protrudes into the bladder. Especially for patients with thin myometrium of cesarean scar, the risk of uterine perforation, bladder injury, intraoperative uncontrollable bleeding and residual uterine cavity is higher when suction curettage and hysteroscopy are used. Some scholars suggest that hysteroscopy should not be performed on patients whose myometrium is less than 3 mm in cesarean scar [47], so it is recommended that the lesion be resected. Even if suction curettage or hysteroscopy is successful, the original thickness of cesarean scar myometrium remains unchanged, and there may still be cesarean scar diverticulum, resulting in prolongation of menstrual period in the future or re-pregnancy of
cesarean scar. Therefore, for such patients, sometimes need surgical excision of the pregnancy lesions to treat, the operation can completely remove cesarean scar gestational product, but also can repair cesarean scars, and reduce recurrence. Surgical approaches can be performed by laparotomy, laparoscopic or transvaginal.

Laparotomy is the most traditional surgical method, and some scholars once believed that laparotomy cesarean scar gestational product resection is the best choice for the treatment of CSP [26, 48]. It has the advantages of easy operation, rapid and thorough hemostasis, but it also has some disadvantages, such as trauma, slow recovery, long hospital stay, etc. Therefore, it is mostly used for conservative treatment failure, uncontrollable bleeding, uterine rupture and when the risk of using other methods is high.

Laparoscopy is a minimally invasive surgery, which has been widely used in surgery and gynecology. Lee [49] first reported a successful laparoscopic resection of CSP in 1999. Laparoscopic resection is characterized by less trauma, less bleeding, good visual field, a shorter hospital stay, and faster recovery times. It need an experienced and skilled gynecologic laparoscopists. The reports show that laparoscopic management of CSP can achieve good results [50-52], but the patient should be switched to laparotomy immediately when operating difficulties or uncontrolled bleeding occur intraoperatively. So bilateral uterine artery ligation can be performed in laparoscopic surgery to reduce intraoperative bleeding [51].

There are more and more reports on the treatment of CSP by transvaginal surgery [53-55]. These studies have shown that transvaginal surgery has a high success rate and fewer complications. It operates through women’s natural orifice without scars on the abdomen, faster recovery, and the equipment and instruments needed in the operation are also simple, even some basic hospitals can carry out the operation. For patients with vaginal inflammation or vaginal malformation, it is not advisable to undergo this surgical treatment. When the gestational sac is large and the blood flow is abundant, the transvaginal operation may slow hemostasis, or it is difficult to separate the adhesion from the lower uterine segment and abdominal wall or the bladder during the operation, then the transvaginal operation is not recommended, and laparoscopic or laparotomy surgical lesion resection is preferred.

If there is uncontrollable bleeding during the treatment of CSP, hysterectomy may ultimately be necessary to save lives [15].

New treatments

High-intensity focused ultrasound (HIFU)

High-intensity focused ultrasound (HIFU) is a new non-invasive treatment technology. It can transform the ultrasonic wave into the heat energy at the focal point, then the temperature of the heated area can rise rapidly to 60-90°C, which can cause coagulation necrosis of the target tissue [56]. The technology has been used to treat gynecological diseases such as uterine fibroids and adenomyosis [57, 58] and was approved by FDA in 2004 [59]. In 2014, researchers first reported the treatment of CSP with HIFU [60]. In this study, HIFU can be repeated many times for patients with a large gestational sac. Since then, more researchers have found that HIFU treatment of CSP is feasible [61-63]. It was found that the advantages of this treatment were non-invasive operation, good therapeutic effect, no radiation hazard, and compared with uterine artery embolization, it did not affect ovarian function. However, postoperative fever, lower abdominal pain and sacrococcygeal pain are common side effects, and more serious side effects are that inaccurate preoperative localization may damage surrounding tissues such as intestine, bladder and nerve tissue. In addition, the main limitation of HIFU is that the micro-vessels and capillaries with diameter less than 2 mm are damaged by HIFU [64]. For larger vessels, the temperature of local tissue will be taken away by abundant blood flow during HIFU ablation, so the therapeutic effect will be worse when the gestational sac is large and the blood supply is abundant, especially when the supply vessels are large.

Lauromacrogol

Lauromacrogol is a new foam sclerosant, which is widely used in clinic. Its advantages are low toxicity, low adverse reactions and high safety.
Early it was mainly used for the treatment of varicose vein of the lower extremities, oesophageal and gastric varices [65, 66]. Later, it has also been used for the treatment of gynecological diseases such as uterine fibroids [67]. The principle of its treatment is that the injection of lauromacrogol in the vascular side and lumen can damage the vascular endothelium, promote thrombosis, generate aseptic inflammation, promote fibrous tissue hyperplasia and adhesion, and eventually occlude the blood vessels. Zhang [20] first reported in 2015 that it is feasible to treat CSP with lauromacrogol. The procedure is multi-point injection of lauromacrogol in the muscle layer around the gestational sac under the guidance of ultrasound, especially in the location with obvious blood supply, so as to achieve the purpose of hardening, sealing local blood vessels and hemostasis. After operation, suction curettage was performed to remove the gestational sac in the uterine scar. It was found that the bleeding is significantly reduced and the effect is definite. Other researchers have reported successful use of lauromacrogol in the treatment of CSP in 2017 [68]. Compared with the traditional effective UAE treatment, this treatment has no obvious abdominal pain, shortened hospitalization time, significantly reduced treatment costs, and is easy to operate. Of course, at present, the number of samples of this treatment method is still small, and there is a lack of follow-up long-term follow-up case data, so its long-term complications, safety and other data can be further studied. Because lauromacrogol needs to be injected into the myometrium around the gestational sac for hemostasis, if the CSP patients with obvious exogenous type which the myometrium is thin in the uterine scar, or even with no continuous myometrium in this area should not be treated with this method, surgery is still recommended.

To sum up, there are many diagnosis and treatment methods of CSP, each with advantages and disadvantages, but there is still no clear standard for optimal treatment up to now. However, improper diagnosis or treatment may lead to serious consequences, so the treatment of such patients still needs to be paid attention to. Each patient should be treated individually according to the patient's condition, the medical conditions of the hospital, and the doctor's own diagnosis and treatment technology. A recent meta-analysis suggested that CSP with positive embryonic/fetal heart activity tends to have a higher risk and more serious complications, which are significantly different from CSP with no cardiac activity [69], so stratified treatment may be attempted. For the current effective treatment methods, especially the new technology, we need to further study and improve the treatment methods, and fully follow-up to evaluate the short-term and long-term complications after treatment, so as to improve the treatment success rate and reduce complications.

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Disclosure of conflict of interest

None.

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