Hysteroscopy Newsletter

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$E_{ditorial \ tea}^{\rm HYSTEROSCOPY} M$

Dear global friends following in love with hysteroscopy,

When Morris first described isthmocele in 1995 nobody would have thought that today isthmocele would be a hot topic in the endoscopic world.

It is important to emphasize that not all isthmoceles cause symptoms, infertility or pregnancy complication; and multiple techniques have been used for symptomatic isthmocele treatment.

The hysteroscopic repair appears to be the most popular and less invasive treatment to discuss with patients as the first choice. However, there is a trending opinion that isthmocele could be associated with a risk of uterine perforation and bladder injury when residual myometrial thickness (RMT) is less than 2–3 mm and several surgeons recommend laparoscopic or vaginal approach.

These reference values were established arbitrarily because no single case of uterine niche wall perforation and bladder injury has been reported yet independently from the size of RMT in the lecture.

Since the removal of the local inflamed tissue may contribute to the improvement of symptoms, only hysteroscopic approach is suitable for visual confirmation, assessment and ablation. Therefore, resection should be performed not only of the fibrotic tissue underneath the isthmocele but also of the inflamed tissue placed around the niche and on the opposite site (the so-called channel-like 360° endocervical ablation).

Even if the ideal surgical treatment in symptomatic and infertile women with isthmocele remains to be elucidated, the channel-like 360° endocervical ablation using a miniresectoscope, appears to be a safe and feasible method when performed by surgeon with great knowledge of instrumentations and technologies.

In our future professional lives, we shouldn't forget isthmocele any time that a patient with a previous cesarean section complains about abnormal uterine bleeding, pelvic pain, dysmenorrhea and secondary infertility.

Furthermore, our passion to continuously stay on top of what is current in endoscopy leads to change our approaches and helps to find the optimal surgical treatment for isthmocele.

Never stop learning and improving!

Mario Franchini

If you are interested in sharing your cases or have a hysteroscopy image that you consider unique and want to share, send it to hysteronews@gmail.com

Istmocele: overview

Luis Alonso Pacheco / Ana Merino Marquez. Centro Gutenberg. Spain

Hysteroscopy Newsletter Vol 7 Issue 3

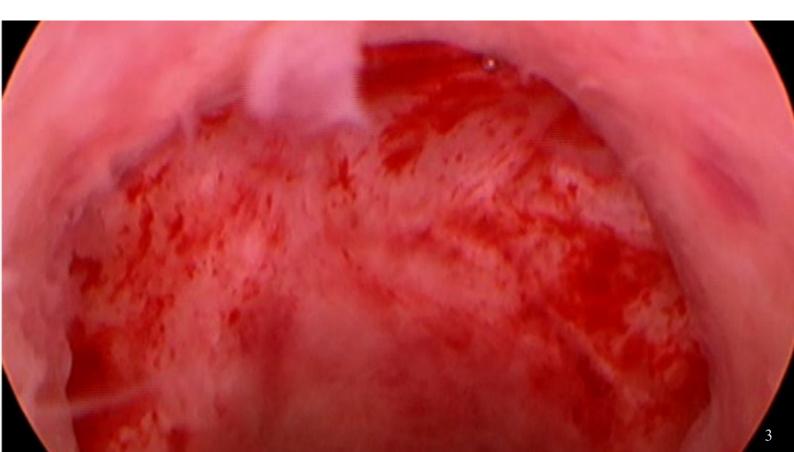
The cesarean section rate is alarmingly increasing in recent years in developed countries, this has been associated with an increase in the economic expense derived from the surgical intervention and on the other hand the appearance of new problems derived from the cesarean section itself, which may be both obstetric and gynecological in nature.

The most frequently documented in the literature are poor obstetric consequences in subsequent pregnancies after cesarean section, being well recognized the correlation between a previous cesarean section and the risk of developing placenta previa, placental accreta, implantation of pregnancy at the level of the cesarean scar and uterine rupture. Among future gynecological problems described in patients undergoing cesarean section are abnormal uterine bleeding, dyspareunia and abdominal pain.

When performing a pelvic ultrasound in patients with history of cesarean section, it is frequent to

find a hypoecogenic area, generally triangular with the vertex directed towards the bladder of different sizes, at the level of the previous caesarean section scar. This ultrasound image, defined as an "Isthmocele". It is a uterine wall sac-like structure located in the lower uterine wall, just in the area of the scar of a previous cesarean section.

The importance of the isthmocele lies, on the one hand, in its correlation to abnormal uterine bleeding that is usually post-menstrual, and on the other hand in its relationship with secondary infertility. Regarding to the abnormal bleeding, the main cause is that the isthmocele acts as a reservoir that hinders the flow of the menstrual blood; In addition, there is minimal "in situ" blood production derived from the increase in local vascularization at the level of the base of the isthmocele and local alteration of uterine contractility. Regarding the correlation with secondary infertility, the persistence of menstrual flow at the cervical level has a negative impact on sperm transport as well as implantation.



Several mechanisms to explain the isthmocele formation are considered. One is the difference in thickness between the anterior and posterior segments of the hysterotomy, another the different types of suture material used to close the hysterotomy. It seems that the more ischemic areas are created, the greater the possibility of developing an isthmocele, this leads to consider whether the use of 2 layers closure technique of the hysterotomy increases the risk of isthmocele formation.

The diagnosis of isthmocele is based on clinical signs and complementary tests such as hysterosonography ultrasound, and/or hysteroscopy. The ultrasound shows the presence of an hypoecogenic area, generally of triangular shape, located at the isthmic level with the vertex of it directed towards the bladder (3). This isthmocele is echographically more evident if ultrasound is performed during the postmenstrual phase, since blood accumulation facilitates the visualization as an ecogenic area. The measures that are usually carried out in this ecogenic area, are the ones to measure their area, following the formula (base x height / 2), classifying the





istmoceles according to the result in 3 degrees, grade 1 when the area is less than 15 mm², Grade 2 between 16 and 24 mm² and grade 3 when it is greater than 25 mm².

Hysterosonography enhance visualization of the isthmocele even when there is no blood accumulation inside of it. Hysteroscopy is the "Gold Standard" technique for the diagnosis of isthmocele. Hysteroscopy allows direct visualization of the anterior and posterior borders of the isthmocele that some authors define as an anterior and a posterior arch, the isthmocele is actually the area contained between these two arches.

There are several proposed treatments aimed at resolving the symptomatology associated with the isthmocele, especially bleeding and secondary infertility. The use of hormonal treatment has shown a decrease in the duration of postmenstrual bleeding and an improvement with respect to the associated symptomatology, although they do not eliminate the symptoms and have been less effective than surgical treatment. Some experts prefer to the laparoscopic (4) and even transvaginal route for the surgical treatment of the scar dehiscence of a previous cesarean section.

The hysteroscopic repair of a cesarean scar is frequently referred as Isthmoplasty. The surgical technique first described by Fernandez in 1996 at the 25th annual meeting of the AAGL (5), consists of remodeling the sac "flattening" the area of the isthmocele from the lower arch to the external cervical os. The surgical procedure must be performed extremely carefully and very superficially, taking into account that the dome of the isthmocele is in close contact with the bladder and the lateral areas of the defect with the uterine arteries (1). In addition to carrying out the resection of the fibrotic tissue, Fabres favors the treatment of the tissue at the base of the defect by means of the local fulguration of the dilated vessels as well as the inflammatory tissue, responsible for the "in situ" blood production.

The latest studies show that the surgical treatment of the isthmocele eliminates the symptoms of postmenstrual spotting in the vast majority of patients, it is also important to note that after surgery, some patients restore their fertility, obtaining in these patients pregnancy in the first 6-12 months after surgical correction (6).

CONCLUSIONS

The surgical treatment of isthmocele aims to avoid retention of menstrual blood at the level of the defect, eliminating post-menstrual spotting pattern and its consequences. The hysteroscopic approach is a symptomatic treatment, while laparoscopic or vaginal treatment aims to repair the defect, so are considered a restorative treatment. As a general rule, it is accepted that in cases in which the residual myometrium thickness at the level of the isthmocele is greater than 3 mm, the hysteroscopic approach is an adequate and safe option. However, if the endometrial thickness at this level is less than 3 mm, the laparoscopic approach should be preferred because of the risk of uterine perforation and allows to restore the uterine wall at that level. (7)

After surgical treatment, a new questions arise, such as whether a spontaneous vaginal delivery is safe after the completion of the isthmoplasty. The recommendation of the Global Congress of Hysteroscopy Research Committee is the to perform an elective cesarean section no later than week 38 of gestation due to the risk of uterine rupture (7)

It is important to bear in mind that post-menstrual bleeding in patients with a previous caesarean section may be related to the presence of an isthmocele and that they can also cause secondary infertility. It is also important to remember that the only treatment of this condition is surgical and that hormonal treatments do not solve the problem.



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Isthmocele: Definition, Prevalence And Main Risk Factors

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The defect caused by the cesarean section scar, also called isthmocele, niche, diverticulum, or pouch, was first described by Poidevin in 1961 as a wedge-shaped defect in the uterine wall. Due to the variety of names, this defect has been internationally known as Isthmocele, which gives a better idea of the anatomical defect described. (one)

Isthmocele can be defined as a hypoechoic area within the myometrium of the lower uterine segment, reflecting a disruption of the myometrium at the uterine scar site from a previous caesarean section. The isthmocele was defined as an anechoic defect at least 2.0 mm deep at the scar site (Fig. 1). It was defined as a large defect if the ratio between the thickness of the myometrial residue (MTR) and the thickness of the myometrium adjacent to the defect (MTA) is <0.50 (Fig. 1) (3)



Bij de Vaate et al, defined the isthmocele as an anechoic area at the site of the cesarean section with a depth of at least 1 mm. Isthmoceles can be asymptomatic. However, in many cases, they can lead to several gynecological symptoms, such as abnormal uterine bleeding, dysmenorrhea, chronic pelvic pain, dysmenorrhea, and infertility. Figure 2 outlines the different shapes of the isthmocele on transvaginal ultrasound, which allows its classification: Triangle, Semicircle, Rectangle, Circle, drop and inclusion cyst. (3)

The objective of this review is to give a general, broad overview of the current literature, describing each aspect of this condition, analyzing in depth its risk factors, diagnosis and medical-surgical management.

PREVALENCE

Cesarean section is one of the most common surgical procedures. However, its percentage has increased dramatically in most developed countries in recent decades, which has given rise to great concern. According to the latest data from 150 countries, caesarean section rates range from 6 to 27.2%.

The World Health Organization (WHO) states that the optimal rate of Cesarean section is around 15%. Cesarean incisions generally heal without consequences, but there is always the possibility of complications.

Recently, the increasing rate of caesarean sections has increased interest given the long-term morbidity of cesarean section defect or



Isthmocele. Moreover, 6% of all ectopic pregnancies have been evidenced in women with at least one previous caesarean section. However, the incidence of isthmocele correlates with the number of previous caesarean sections.

The estimated incidence of Isthmocele is:

-1 in 1688 pregnancies

-1 in 3000 general obstetric population

 –1 in 2000 of all previous caesarean sections (González N., J MinInvGynecol; 2017)

The prevalence of isthmocele is difficult to quantify, the reported prevalence in patients with a history of caesarean section ranges from 56% to 84%. Isthmocele can be observed when they are assessed by SHG between 6 and 12 months after the cesarean.

The prevalence varies depending on the detection method, the criteria used to define the isthmocele and the study population. It ranges between 24 and 70% with transvaginal ultrasound, and between 56 and 84% with Sonohysterography (SHG). Different risk factors associated with the presentation of isthmocele have been described, mainly the number of previous caesarean sections, location of the scar, labor before cesarean section, position of the uterus, among others. (4)

RISK FACTORS

The risk factors for the formation of an isthmocele depend on both the surgical technique and the patient.

Factors related to surgical technique.

Very low uterine incisions are reported to be an independent risk factor for the development of isthmocele. A higher prevalence of caesarean scar defects has been observed among patients with a C-section performed during active labor with cervical effacement. Vikhareva Osser et al, described a greater development of isthmocele when the cervical dilation was > 5 cm or the duration of labor greater than 5 hours. In addition, an isthmocele was observed in the upper two-thirds of the cervix in women with elective caesarean sections, while, in the case of caesarean sections performed after cervical

dilation, the niche was found in the lower part of the cervical canal.



One explanation for this phenomenon could be that the lower incisions are made through cervical tissue, which contains mucus-producing glands, and could negatively interfere with the wound healing process. Another probable factor is the closure technique, that is, double layer versus single layer closure. These techniques vary between countries and have changed over the years. For example, in some European countries, such as Belgium and the Netherlands, the single hysterotomy closure technique is the most widely performed, while in the United Kingdom, double layer closure is the recommended technique. A review in 2014 by Roberge et al, found no difference in the development of scar defects between the techniques used. (5)

Recent research has shown that the incidence of scar formation in caesarean section scar and niche depth were independent of the hysterotomy closure technique used. In a recent meta-analysis, Di Spiezio Sardo et al, reported that women who underwent single layer closure had a similar incidence of uterine scar defects, as did women who underwent double layer closure. Ceci et al, however, observed that patients with hysterotomy with a single-layer continuous locked suture compared to the interrupted single-layer suture group showed a statistically larger defect area on ultrasound and hysteroscopy evaluation, probably due to an ischemic effect on uterine tissue. The hypothesis could be that the deeper muscle layer does not close, leading to a disrupted myometrium and the development of an isthmocele. However, due to lack of data, a specific surgical technique for uterine closure cannot yet be recommended. (6)

Another hypothesis proposed is the surgery itself. Surgery is known to lead to the development of adhesions, and many factors can influence this process, including inflammation, tissue ischemia, tissue manipulation, and inadequate hemostasis. The formation of adhesions between the caesarean section scar and the abdominal wall can be a cause of the development of isthmocele. Vervoort et al, hypothesized that retraction of scar tissue could pull the uterine scar towards the abdominal wall, inducing the development of isthmocele. (7.8)

Patient factors

Patient factors may play a role in isthmocele formation and healing process of the caesarean section, due to individual differences. Some studies have observed the association between the development of scar defects and patient factors, such as retroflexed uterus, multiple cesarean incisions, body mass index (BMI) and hypertension, but its mechanism of action remains unclear. (9)

Among factors related to myometrial defects caused by previous caesarean sections, a history of curettage, adenomyosis, IVF, metroplasties, myomectomies, and manual placental extractions are the most comon. (5.10) Probably influences individual genetic predisposition along with other unknown causes.

The above mentioned or some additional factors could be the key to this phenomenon, but additional studies are required to answer this question.

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Isthmocele. Diagnosis and differential diagnosis

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INTRODUCTION

In recent years, the rate of caesarean sections has increased dramatically, especially in developed countries where the rates have reached alarming rates. (1) The World Health Organization (WHO) recommends a caesarean section rate of 10-15%, however, in South America and other Latin American countries the percentages have reached more than 40% and in North America more than 30% (2, 3). This high incidence of caesarean section has had a parallel effect on obstetric costs due to the nature of the surgical intervention.

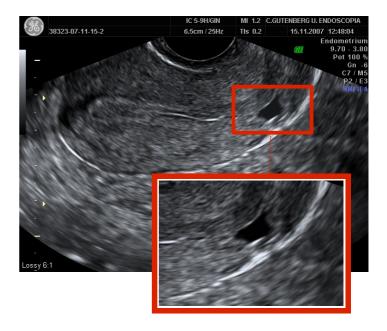
As a consequence of the increase in surgery, there has been an increase in the known dangerous sequelae of uterine surgery, including placenta previa, abnormal placental implantation including the accrete spectrum, and uterine rupture. Other known consequences of caesarean section are that patients experience more frequent abnormal uterine bleeding, dyspareunia, and abdominal pain believed to be related to caesarean section.

A very common consequence of cesarean section can be seen on ultrasound. The images occasionally reveal a hypoechoic area at the level of the cesarean section scar known as an "isthmocele." The area is of variable size, triangular, with the apex directed towards the bladder just in the area of the previous cesarean section scar.

This chapter is especially directed to the discussion on the diagnosis and differential diagnoses of this late complication of cesarean section.

DEFINITION

Isthmocele is a condition that has gained a lot of attention in recent years, especially with the increase in the practice of caesarean sections. This pathology has been described as a scarring defect after a previous cesarean section that occurs at the isthmic level of the uterus. (4) After a cesarean section, the myometrium at the site of the uterine scar should heal and reform as an unbroken muscle layer. However, in approximately 24-56% of caesarean sections, the incision does not heal well, consequently, it does not close completely and causes a defect in the healing of the caesarean section incision. (5)



Although the term "isthmocele" has been adopted more frequently in recent years, it does not necessarily define this condition because the defect may appear on the anterior wall of the lower uterine segment, depending on the location of the incision of the previous cesarean section and not necessarily at the level of the "uterine isthmus". (6) There is no universal definition, and other terms used in the literature to describe this condition include niche, diverticulum, bursa, poor caesarean section scar, and scar defect.

Like the lack of a definitive term, there is also difficulty in how to diagnose an isthmocele.

DIAGNOSIS

CLINICAL SIGNS AND SYMPTOMS

Diagnosis begins with the clinical presentation of the patient and history taking and physical examination. Complications from cesarean section that occur long after the surgery itself are very important. In a literature review, the symptoms related to the presence of an isthmocele are abnormal uterine bleeding, typically postmenstrual, chronic pelvic pain, heavy menstrual bleeding, dysmenorrhea, dyspareunia, and secondary infertility.

The most frequently reported symptom is abnormal uterine bleeding, postmenstrual spotting, with an incidence of 53%, followed by chronic pelvic pain (39.6%) and dyspareunia (18.3%). (12) Postmenstrual bleeding can last from 2 to 12 days and is usually dark spotting. Morris (13) was the first to describe the correlation between postmenstrual bleeding and the presence of an anatomical defect and histological change in the scar from a previous cesarean section.



Abnormal postmenstrual bleeding is estimated to occur in 1 in 3 women with a niche in the scar. (13) A direct correlation has also been found with the size of the defect and the amount and duration of bleeding. (8) Retroverted uteri are particularly susceptible to postmenstrual bleeding. Three factors are postulated to contribute to producing the postmenstrual bleeding seen in patients with isthmocele. The first one is the interruption of the continuity of the endometrium due to the uneven layers of the myometrium that create a type of pocket or "niche." The accumulation of blood in the scar pocket and then discharge during the days menstruation. (11) Second, following the myometrium at the level of the scar contains fibrotic tissue which interrupts the normal contractility of the muscle, and prevents the discharge of blood accumulated within the isthmocele. Finally, changes have been found at the cellular level in the area of the scar. Morris, in his pathological study of cesarean section scars, found free erythrocytes, leading to hypothesize the possibility that blood can be formed in situ and also cause breakthrough bleeding. (8)

The infertility reported in relation to isthmocele is proposed that it could be due to the blood and retained endometrial remains cause that disturbance in the cervical mucus, inflammation, and alter the transport and guality of sperm which interfere with implantation. (14-16) In addition, the presence of blood increases the production of cervical mucus, altering the implantation and transport of sperm. In several studies, the prevalence of isthmocele has been estimated between 7% to 69%, a very large range, perhaps due to the lack of a fully accepted definition. (12, 17)

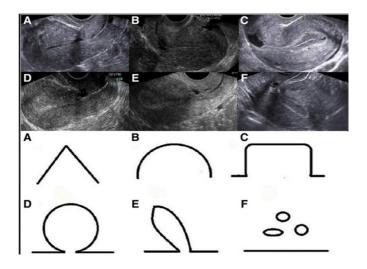
Therefore, in the absence of abnormal postmenstrual bleeding, the index of suspicion for an isthmocele, especially in women with multiple previous cesarean sections, has to remain high.

IMAGING STUDY

ULTRASOUND

As previously mentioned, there is currently no consensus or definitive test to diagnose isthmocele. Apart from the clinical presentation of the patient, the diagnosis is based mainly on complementary tests. Transvaginal ultrasound is the most commonly used method for diagnosis. Ultrasound usually shows the presence of an econegative area, generally triangular in shape, located at the isthmic level with the apex of it directed towards the bladder. (7) Figure 1 demonstrates various shapes of isthmocele seen by ultrasound in the study by Park et al. already described and published by other studies as well: triangular (Fig 1a), semicircular (Fig 1b), rectangular (Fig 1c), circular (Fig 1d), gout (Fig 1e), and inclusion cysts (Fig 1f). (18, 19) Measurements derived from ultrasound are illustrated in figure 2. These measurements, made in a sagittal plane, are the thickness of the remaining myometer (Fig 2A), the depth of the isthmocele (Fig 2B), the width of the isthmocele (Fig 2C), the cervical thickness (Fig 2D), the distance between the fundus of the uterus and the isthmocele (Fig 2E), and the distance from the isthmocele to the cervix (Fig 2F). (19)

The prevalence of isthmocele in the evaluation of a patient with a history of previous cesarean section when performed with conventional 2D ultrasound is 24%. (20) The use of 3D ultrasound can also help providing additional information and various planes of the defect. The best time to do the ultrasound is in the immediate postmenstrual phase (early proliferative phase of the menstrual cycle), giving the opportunity for the menstrual blood to accumulate within the isthmocele, and facilitate the visualization as an econegative area. Ultrasound is also suggested during the late proliferative phase of the menstrual cycle. In this period, the cervical mucus can fill the niche and also make it easier to diagnose the isthmocele.

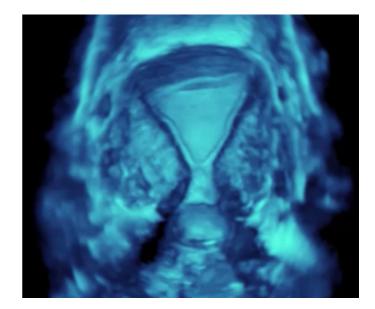


HYSTEROSALPINGOGRAPHY

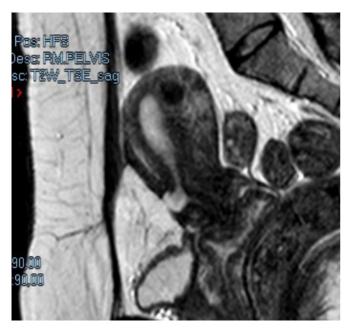
Isthmocele can be seen by hysterosalpingography as a diverticulum or a linear defect in the lower portion of the uterine cavity in approximately 60% of patients with history of cesarean section who undergo this procedure. (21, 22) In a study of 148 patients, 48 of them had a scar defect seen by hysterosalpingography and the most common appearances were a small rounded focal defect (65%) and a linear defect (35%). (23) The limitation of this diagnostic method is the inability to measure the thickness of the myometrium, restricting the isthmocele classification to only its size. It is important to note that the measurement of the thickness of the myometrium has an important clinical significance due to its correlation to dehiscence, which can increase the risk of uterine rupture. Therefore, it can be inferred that the presence of an isthmocele seen by hysterosalpingography, without being able to measure the thickness of the myometrium, limits its clinical meaning.

SONOHISTEROGRAPHY

Another diagnostic method is saline or gel infusion sonohysterography. This method allows the isthmocele to be seen at any time durin the menstrual cycle, including at a time during the menstrual cycle when there is no accumulation of blood in the niche. The fluid or gel infused causes the uterus to expand and increases the visualization of the defect. More isthmoceles are diagnosed with sonohysterography than with traditional ultrasound. (24) In a study by Langsjo et al of 371 patients, sonohysterography proved to be a superior method for the diagnosis of isthmocele. In fact, 50% of the defects diagnosed with sonohysterography remained undiagnosed with transvaginal ultrasound. In their conclusion, they suggest that, at the slightest suspicion of an isthmocele, or if it is necessary to completely exclude the presence of an isthmocele, the preferred study should be sonohysterography. (25)



The advantage of using sonohysterography, compared to hysterosalpingography, is that it also allows the evaluation of the thickness of the myometrium, therefore, it also allows the classification of the isthmocele based not only on its size. Naji et al, in their review of the literature, proposed to evaluate the isthmocele in different planes including the transverse and sagittal, and to evaluate the size, depth, and thickness of the residual myometrium surrounding the isthmocele to better evaluate the defect. (26) To achieve this, transvaginal ultrasound and sonohysterography equally useful. The disadvantage of are sonohysterography is that, although it may be higher in the menstrual phase where there is no blood accumulated in the defect, it may be lower during the post-menstrual period when menstrual bleeding obstructs the defect and prevents fluid from filling the isthmocele, perhaps producing a false negative test. (6)



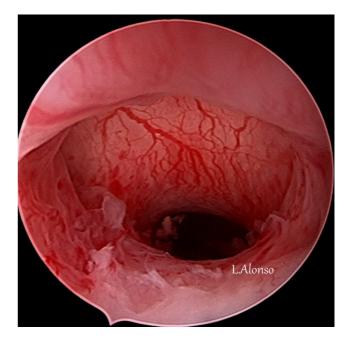
MAGNETIC RESONANCE IMAGING

Magnetic Resonance Imaging (MRI) can also detect myometrial defects in the lower uterine segment and can be used as a complementary method in the study of isthmocele. The image can assess the size of the defect, the thickness of the residual myometrium, and also to some extent, the contents within the defect. It is used to visualize the different layers of the uterus. MRI can also evaluate the pelvic area surrounding the defect and can be helpful in planning the surgical approach. (6) However, it is expensive and not universally available which limits its use. Additionally, a study found that to measure the thickness of the myometrium, transvaginal ultrasound is similar to MRI, indicating that the use of MRI is only beneficial to evaluate the area around the defect when planning its surgical management. (27)

HYSTEROSCOPY

The next diagnostic method is hysteroscopy, which has recently become popular as a diagnostic method because it allows direct visualization of the defect and also its immediate correction Hysteroscopy allows visualization of the anterior and posterior borders of the isthmocele, and has been described as the area, or the dome, contained between arches. two (7)The endometrium within the cavity has been described as congested tissue, perhaps in various stages of inflammation and neovascularization that may have a tendency to bleed on contact. (28) In addition, hysteroscopy provides a clear image of the uterine cavity and demonstrates the defect in more detail, including the presence of rim valves, enhancing blood accumulation. (6)

One of the greatest advantages of hysteroscopy is its use to exclude other causes of abnormal uterine bleeding such as endometrial polyps, submucosal fibroids, and endometrial hyperplasia. The weakness of hysteroscopy is that, like sonohysterography, it cannot measure the thickness of the residual myometrium.



LAPAROSCOPY

The last method to diagnose isthmocele is diagnostic laparoscopy. Laparoscopy can evaluate the outer surface of the defect and can be used in conjunction with hysteroscopy, then implementing the principle of "diaphanoscopy" to better identify the defect. The idea is to have two light sources, one from the hysteroscope, inside the uterine cavity outlining the defect from inside, and the other by laparoscopy inside the abdomen, outlining the defect from outside simultaneously. (22, 29) Similar to hysteroscopy, the superiority of laparoscopy over other methods is that it allows both diagnosis and treatment of isthmocele.

DIFFERENTIAL DIAGNOSIS

Based on the previously mentioned clinical characteristics, the presence of isthmocele should be ruled out in patients with a history of cesarean section who present complaining of postmenstrual bleeding, pelvic pain, dysmenorrhea or pain during sexual intercourse.

Among possible differential diagnoses we can highlight:

- 1. Adenomyosis
- 2. Retained Products of Conception (RPOC)
- 3. Chronic endometritis
- 4. Endometrial polyps
- 5. Endometrial Hyperplasia/Cancer
- 6. Presence of foreign body

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Cesarean scar defect and infertility: What do we know about it?

Thomas Moscovitz. Brasil

Hysteroscopy Newsletter Vol 7 Issue 3

INTRODUCTION

A Cesarean Scar Defect (CSD) or istmocele is a niche formally defined by the European Niche Taskforce as an indentation of the uterine myometrium of at least 2 mm at the site of the Caesarean scar, assessed by transvaginal ultrasound (Picture 1) (Jordans et al., 2019).



Spotting can be occurred in 30% of women with a niche after Caesarean section (van der Voet et al., 2014a; Bij de Vaate et al., 2014b).

Besides the gynaecological symptoms, niches may theoretically speaking impair a subsequent fertility. A niche can reduce the changes of embryo implantation and lead to miscarriages (Hemminki, 1986; Hemminki, 1996; Naji et al., 2013).

Caesarean may reduce the probability of pregnancy in 10% on average, compared with a previous vaginal delivery according a metaanalysis (Gurol-Urganci et al., 2013).

Several explanations for this scenario from placental bed disruption (Murphy et al., 2002) to psychosocial effects (Oral e Elter, 2007).

Various therapies were proposed over the last years to improve the reproductive results related to CSD (van der Voet et al., 2014b; Nikkels et al., 2017; Vervoort et al., 2018a; Vissers et al., 2020). In spite of the beneficial outcomes from surgical intervention on reproductive outcomes in relation to expectante management, that does not mean that it's a better route, as there are no clear randomized controlled trials. (Vitale et al., 2020).

Thus, what we intend to answer is if CSD may lead to secondary infertility and what the routes are.

Based on the medical literature available, we can find six hypothesis to explain how CSD (picture 2 and 3) may lead to a secondary infertility, being four of them related to detrimental environment for sperm penetration and implantation. Physical barrier for embryo transfer and implantation and Psychogenic causes that reduce the likelihood of pregnancy are the other two hypothesis (Visser et al., 2020).

HYPOTHESIS

1-DETRIMENTAL ENVIRONMENT FOR SPERM PENETRATION AND IMPLANTATION

1.1 Niche-related accumulation of intrauterine fluid impairing implantation

The accumulation of intracavitary fluid related to the niche may impair embryo implantation, aligned with negative effect of intrauterine fluid in women with hydrosalpinx (Mansour et al., 1991; Sharara e McClamrock, 1997; Sharara e Prough, 1999; Levi et al., 2001; Akman et al., 2005; Strandell et al., 2001). However, the impact has not yet been studied (Vervoort et al., 2018b).

A retrospective study showed a detrimental effect of a Caesarean section on implantation. In this study with 1317 women with one previous cesarean or vaginal delivery undergoing IVF/ICSI treatment, live birth rates were lower in women with a previous Caesarean section at 15.9% versus 23.3% for women with a previous vaginal delivery, which indicates that implentation is particularly more difficult after a caesarean.

In theory, intrauterine accumulation of either blood or fluid may cause a hostile environment for implantatio. That accumulation of blood may lead to degradation of haemoglobin in the uterine cavity, resulting in a higher iron exposure, which is known to be embryotoxic (Van Langendonckt et al., 2002; Lousse et al., 2009).

Besides that, unkown embryotoxicity factors could also be present in the intrauterine fluid related to isthmocele.

In addition to the possible embryotoxicity effect, the intrauterine fluid could prevent mechanically the implantation of the embryo.

In a cohort study of 159 women with isthmocele and underwent a laparoscopic repair pregnancy rates were promissing. Out of 40.2% pacientes who did not get pregnant with FIV, 52% conceived naturally two years after surgery repair (Vissers et al., 2020). Two other cohort studies Two other cohort studies on laparoscopic niche repair in 22 and 38 subfertile patients reported high pregnancy rates (55.6% and 44.0%, respectively) in most patients after more than 1-year follow-up (Tanimura et al., 2015; Donnez et al., 2017).

Two other cohort studies studies on laparoscopic niche repair in subfertile patients,

reported high pregnancy rates, 55.6% and 44.0% (Tanimura et al., 2015; Donnez et al., 2017).

These studies indicate that the niche and related intrauterine fluid may play an important intermediate role in subfertility after Caesarean section (Vervoort et al., 2018b).

Nevertheless the beneficial effect of laparoscopic niche resection on reproductive outcomes needs to be proven in randomized controlled trial.

Several studies have shown better pregnancy rates after isthmocele repair, achieving 100% (Table 1)

In conclusion, accumulation of fluid is seen in approximately 42% of patients with CSD (Vissers et al., 2020). This blood collected in a niche may prevent mechanically the implentation and/or be embryotoxic. However, further studies are needed to assess the effect of intrauterine fluid related to CSD and its potential embryotoxic effect on an embryo implentation, as well as the effect of a CSD surgery repair on the fertility outcomes.

1.2 Immunobiology and/ or increased inflammation when a niche is present

In a cohort prospective study with 380 women, it was assessed by ultrasound the site of implentation in women after Caesarean section. The conclusion was that the site of the implentation is affected by the presence of isthmocele and that implantation near to or in the niche resulted in miscarriage in seven out of eight pregnancies (Naji et al., 2013).

Author	Type of study	Patients	Follow-up (months)	Control group	Pregnancy	Outcome
Gubbini et al.[1]	Prospective	9	12-24	None	7	7 ECS
Fabres et al. [5]	Retrospective	32	Not applicable	Not applicable	Not known	Not applicable
Van Horenbeeck et al. [6]	Case-report	1	Not known	Not applicable	1	1 preterm delivery
Fabres et al. [7]	Prospective	11	12-24	None	9	5 ECS; unknown in
Gubbini et al. [11**]	Prospective	41	12-24	None	41	37 ECS; 4 abortions
Donnez et al. [29]	prospective	3	Not indicated	None	1	1 ECS
Fernandez et al. [30]	Prospective	4	12-24	None	2	Not known
Kawakami et al. [31]	Retrospective	13	Not applicable	Not applicable	Not known	Not applicable
Xu et al. [32]	Prospective	1	12	None	0	Not known

ECS, elective cesarean section.

Differences in angiogenesis or inflammatory response of the endometrium influenced by regeneration of the niche may play a role in this results.

The most significant alteration at the CSD is the lower number of leucocytes and vascularization than in the endometrium of the uterus without isthmocele (Ben-Nagi et al., 2009).

1.3 Contractility of the uterus altered by fibrosis or interruption of the myometrial layer at the site of the niche

In this hypothesis the implantation is impaired after Caesarean section due to uncoordinated or impaired uterine contractions.

The non-pregnant uterus shows myometrial contractile activity throughout the menstrual cycle. These contractions originate in the subendometrial myometrium and are controlled by steroids. During the menstrual cycle, wavelike activity patterns of the uterus with adequate wave patterns appear to be related to successful reproduction in natural cycles and assisted reproduction (Bulletti e de Ziegler, 2006). During the follicular phase contractile waves from fundus to cervix are seen and disappear after ovulation or after hCG administration. This pattern is reversed in the luteal phase. (Abramowicz e Archer, 1990; Lyons et al., 1991; van Gestel et al., 2003; Sammali et al., 2019).

In the isthmocele there is a myometrial discontinuity which can lead to a lower uterine muscle contrativity around the scar and the accumulation of fluid in the deffect. (Thurmond et al., 1999).

It is possible that in women with CSD uncoordinated or impaired uterine contractions occour during the menstrual cycle, which could lead to a lower implantation rate.

1.4 Accumulation of mucus and old blood in the niche, which may impair sperm penetration

Several isthomoceles present nabothian cysts, which produce mucus, mainly in low locations. The mucus accumulation in the niche may impair penetration of sperm cells and thus infertility. The presence of blood in the cervix may cause impaired sperm-mucus interaction for immunological reasons. In the cervical mucus of CSD patients absence of forward-progressing spermatozoa was noticed. (Glazener e Hull, 1987; Check e Spirito, 1995; Steures et al., 2007).

2- PHYSICAL BARRIER FOR EMBRYO TRANSFER AND IMPLANTATION

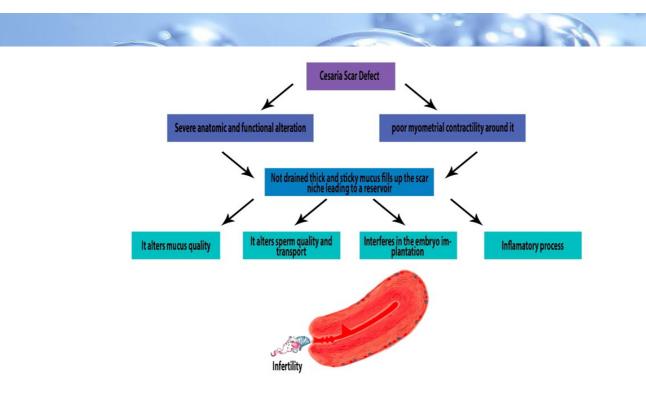
2.1- A large niche in combination with a strongly retroflexed uterus impairs accessibility for an eventual embryo transfer due to a distorted anatomy

Sometimes a niche in combination with a strongly retroflexed uterus or with various branches may hamper the insertion of an insemination or embryo transfer catheter, even under ultrasound guidance. In these cases, a laparoscopic resection to restore the anatomy for embryo transfer could be considered (Vervoort et al., 2018b).

A meta-analysis reported a low clinical pregnancy rate following a difficult embryo transfer (RR 0,75; IC de 95% 0,66-0,86) (Phillips et al., 2013).

A large CSD presence lead to extensive manipulation of the catheter to enter the uterine cavity. Such manipulations contribute to uterine irritation, which leads to a negative effect on embryo implantation, which is responsible for 30% of all IVF failures (Cohen, 1998).





Embryo transfer in women with a history of a prior Caesarean section, took longer and was more likely to have blood or mucus in the catheter compared to women with prior vaginal delivery in two studies (Alvero et al., 2003; Patounakis et al., 2016). Blood in the catheter is one of the criteria for a difficult transfer, which may lead to a lower pregnancy rate (Tomas et al., 2002)

In a recent study with CSD patients in which a retroversion was corrected by laparoscopy, 71.42% got pregnant (Vervoort et al., 2018b).

3-PSYCHOGENIC CAUSES THAT REDUCE THE LIKELIHOOD OF PREGNANCY

3.1- Gynaecological symptoms CSD associated may interfere in sexual relations

Approximately 30% of women with CSD experience postmenstrual spotting which may occour at any phase of the menstrual cycle (Osser et al., 2009; Bij de Vaate et al., 2011). This spotting makes these women feel insecure and gives them a sense of uncleanliness, frequently associated with shame and failure, which affects their sexual behaviour and arousal (Stegwee et al., 2020).

A recent prospective cohort study (n =146) showed that laparoscopic niche resection improved the quality of life, physicaly and mentaly, and those may affect sexual behaviour (Stegwee et al., 2020).

SUMMARY

Several mechanisms have been postulated to explain a CSD secondary infertility despite of the limited evidences. Therefore further research is needed o confirm them.

There is patient subgroup with CSD who present infertility and within this there a subgroup which benefits from hystoroscopic correction. However, randomized studies with a large number of patient are needed to answer:

"Cesarean Scar Defect and infertility: What do we know about it?"

Isthmocele surgery

Luis Alonso. Centro Gutenberg. Spain

Hysteroscopy Newsletter Vol 7 Issue 3

INTRODUCTION

The hysteroscopic isthmocele surgical correction technique was first presented in 1996 by E. Fernández, C. Fernández and C. Fabres at the 25th annual AAGL congress in 1994. Since that first presentation, the technique has been modified over the years, although it has continued to maintain its original essence.

The modifications that have emerged have been the result of a better understanding of the pathophysiology of isthmocele and have been aimed at improving the symptoms related to the scarring defect of the previous cesarean section.

In this review we will address the current surgical techniques and the different proposed approaches, in addition, we will describe the technique as it is conceived today and how it has evolved since its first presentation 23 years ago.

Secuelas tardías de la Cesárea

Por Eduardo García-Triviño Director de la Maternidad Provincial de Jaén (1)

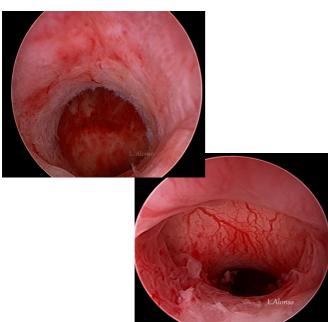
Señores:

Sería obvio razonar sobre el hecho de que en la Obstetricia actual, y salvo la distocia del Período basal, la Cesárea ha desplazado a la Tokurgia clásico o, al menos, ha relegado sus operaciones al orden de lo excepcional. Son los índices de mortalidad y de morti-natalidad, con sus ínfimos valores actuales, los que basamentan este criterio que es universal. Como universal es el deseo de restringir operaciones y la convicción de que ello será posible cuando un mejor conocimiento de la fisiopatología de la Distocia Funcional (fuente de muchas indicaciones de cesárea), y una Farmacología más efectiva de dicha disfunción, estén logrados. Ya está dando sus frutos en esa ruia la Conducción Médica del parto (que encauza muchas disrritmias primarias) y que tuviera sus precursores en Kreis y Schikele, en Es-

trasburgo, hace ya 40 años, cuando afirmaban que la medicación analgésica y espasmolítica era la mejor medicación occitócica del Periodo dilatante. Pero aún queda mucho camino por recorrer hasta controlar del todo el "motor del parto". En tanto, habrá que seguir considerando a la Cesárea como operación de muchas indicaciones, incluso, de liberales indicaciones, dada su seguridad actual.

Por la liberalidad de las indicaciones de la Cesárea, por su frecuente uso, la Cesárea sigue siendo motivo de preocupación para el Obstetra. Ciertamente que ya no nos preocupa la mortalidad, que pertenece a época rebasada. Los perfeccionamientos de la técnica de la operación, de la técnica quirúrgica general, del advenimiento de los antibióticos, nos permiten hoy afirmar que una mujer cesareada sin más problemas que su distocia,

 Conferencia en el Curso de Actualizaciones Médico-Quirúrgicas. Seminario Médico. Curso 1967-68.



Hysteroscopic view of the isthmocele

HISTORY OF ISTHMOCELE SURGERY

In 1968 during a conference in a medico-surgical update course, Dr. Garcia Triviño, medical director of the Maternal Hospital of Jaen presented his knowledge on what he named a late sequela of cesarean section. During it, he spoke of pathological healing, consisting of a myometrial continuity defect at the isthmic level and which was diagnosed by performing hysterosalpingogram performed 4 months after the cesarean section. Those women who had it underwent the test again at 12 months, to see if the defect had healed. In those cases in which the defect persisted, an elective cesarean section was recommended in case of a subsequent pregnancy.

As we have already commented in the introduction, the first existing reference on surgical remodeling of the scar defect dates from 1996, just one year after Morris described the correlation between the healing defect and the presence of menorrhagia, abdominal pain, dyspareunia and dysmenorrhea, which has been termed by many as the cesarean scar syndrome or Morris syndrome [1]

This first published work is due to Dr. Emilio Fernández and was presented as a communication at the 25th congress of the AAGL. This first series consisted of 20 patients, of whom hysteroscopic surgery was performed in 7 of them. The technique they used was the resection of the ring of fibrous tissue located in the lower part of the cesarean section scar. Of all the operated patients, four also suffered from secondary infertility; after the intervention, two of these patients spontaneously conceived. This first publication concluded that hysteroscopic resection of this fibrous ring improved postmenstrual bleeding in these patients [2].

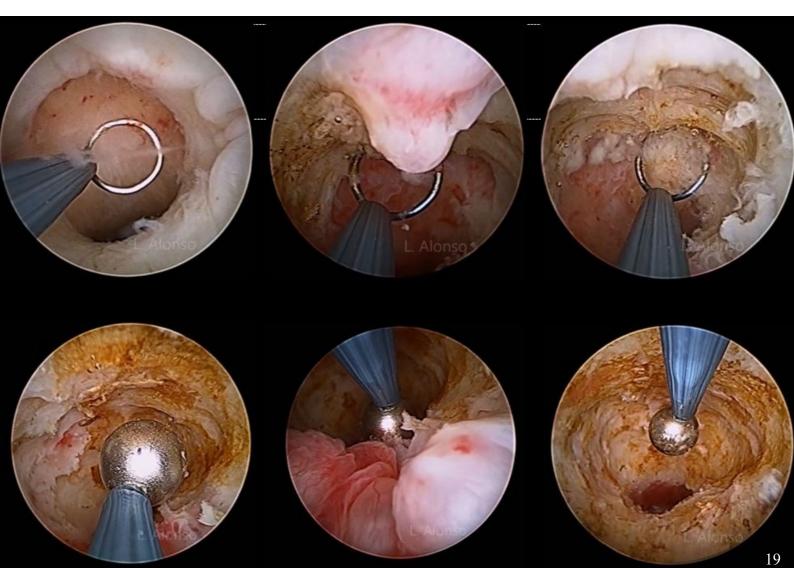


Cecilia Fabre

Giampietro Gubbini

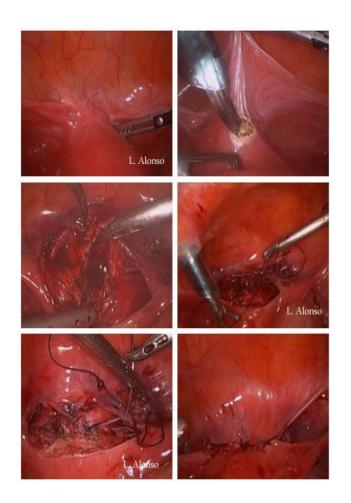
This postmenstrual bleeding that was produced by the existence of retained blood at the level of the scar, could be responsible for secondary infertility by interfering with the quality of cervical mucus.

It was not until 2005 when Dr. Cecilia Fabre from the Las Condes Clinic in Santiago de Chile



published her first work in which 24 patients with postmenstrual bleeding were included and in which the presence of any other intrauterine pathology as the cause had been ruled out. In these patients, a resection of the fibrous tissue located at the lower level of the scar was performed, as well as the fulguration of the endometrial glands and the blood vessels located at the bottom of the isthmocele.

Several years later, Dr. Giampietro Gubbini published his first series of 26 patients in which he performed resection of both the proximal and distal fibrous ring, completely flattening the healing defect and also performing an electrofulguration of the base with a rolling ball [3]. Years later, Gubbini himself proposed 360° carrying out а electrofulguration by means of which the aim was to destroy both the congestive tissue at the bottom isthmocele and the of the surrounding inflammatory tissue. This inflammatory tissue is usually located on the posterior aspect of the cervical canal and appears as a consequence of the irritation produced by the hematic accumulation located in the isthmocele.



The first reference to the combined laparoscopic and vaginal approach dates from 2005 and was presented by Petra Klemm [4]. In this study, they corrected the defect using both routes in three patients in which the bladder was dissected laparoscopically and the isthmocele was sutured vaginally. This is the first reference that exists of a reparative or corrective technique for isthmocele. Reparative techniques are those in which the existing healing defect is corrected and sutured, restoring the normal anatomy of the uterine isthmus.

Finally, it was Donnez who described the technique using exclusively the laparoscopic approach for isthmocele correction [5]. It is also a reparative technique that aims to achieve the integrity of the anterior wall of the uterine segment by re-suturing the defect related to a defective healing of the anterior cesarean section.

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Extensive Hysteroscopic Isthmoplasty: Channel-like 360° Isthmocele Treatment

Giampietro Gubbini, Mario Franchini, Pasquale Florio & Paolo Casadio. Italia

Hysteroscopy Newsletter Vol 7 Issue 3

Multiple approaches have been recently described for isthmocele treatment. such as medical therapies with oral contraceptives and medicated IUD (1) or reconstructive surgery laparoscopic robotic-assisted including and laparoscop-ic repair (2) vaginal repair (3) and resectoscopic correction such as channel-like hysteroscopic resection, proposed by Fabres and Gubbini (4-5)

Since all these procedures excise or ablate the fibrotic tissue of isthmocele, suggesting that the removal of the local inflamed tissue may contribute to the improvement of specific symptoms such as postmenstrual spotting and dark red or brown discharge, pelvic pain, or dull sensation after menstruation or infertility. (6-7-8)

Therefore, only for symptomatic women, a repair is a valid option. Moreover, because available data are limited, the correct choice between reconstructive surgery including laparoscopic and vaginal repair hysteroscopic isthmoplasty can be concluded yet.(9-10)

Hysteroscopic channel-like treatment is performed, after the bladder is filled with methylene blue solution, with small variations among surgeons, by resecting, with monopolar or bipolar loop, the fibrotic tissue of the inferior/ proximal rim of the niche (closest to the external cervical os) proposed by Fabres [4) or with superior/ distal edge of the defect (closest to the uterine cavity) proposed by Gubbini (5) usually using a 26 or 27 Fr resectoscope The procedure is ended, using a rollerball or loop electrode, with coagulation of fragile vessels of niche celling or superficial coagulation of entire isthmocele surface. (11)

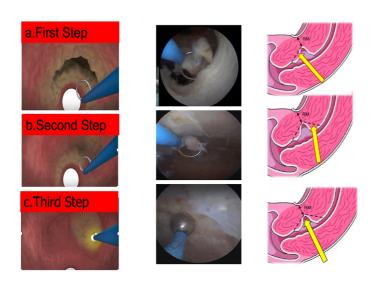
The hysteroscopic isthmoplasty, flattening the isthmocele area, restores a channel shape of the cervical canal and improves menstrual drainage reducing blood accumulation in the niche and reflux into the uterine cavity and increases the thickness of the residual myometrium and decreases the isthmocele volume (12-13).

One of the recent advents in hysteroscopic isthmocele treatment has been the introduction on the market of small diameter resectoscope (SDR) (14).

The SDR allows the surgeon to perform standard maneuvers of resectoscopic CSD repair with the advantages of miniaturized instrumentation. Thanks to small diameter the surgeon can introduce SDR under direct visualization with vaginoscopic approach without the complications related to cervical dilation and with a significant reduction in surgical time spent when compared to 26 Fr resectoscope use. Moreover, isthmoplasty with SDR is associated with reduced amount of distension medium used and of the fluid absorbed during the procedure (15).

Recently, the classic technique of channel-like hysteroscopic resection of the fibrotic tissue underneath the isthmocele has been improved by the resection of inflamed tissue placed around the niche and on the opposite site of cervical canal walls called 360° endocervical ablation (16)

Isthmocele is localized with vaginoscopic approach; a high-frequency 90° angled circular loop electrode and pure cutting current of 100 W is used to resect the fibrotic and inflamed tissue all around the proximal rim of the niche (step 1) and distal (step 2) part of the niche. A highfrequency angled ball electrode is used to obtain focused vaporization (thermal damage less than 1 mm) of all residual inflamed tissue still present on the niche surface (step 3). The procedure is ended by controlling any bleeding of the endocervical vessels by reducing the inflow and pressure of the distending medium and by



focused coagulation (thermal damage less than 3 mm) with a ball electrode (step 4).

-- The first aim of the resection of inflamed tissue of the opposite walls of cervical canal, is to reestablish a really channel shape of the cervical canal restoring the normal flow of menstrual blood through the cervix

--The second aim of the resection of the inferior and superior edges of the isthmocele is to better define the area of the niche usually more richly to treat

--The third aim of the 360° endocervical resection of all residual inflamed tissue is to facilitate the reepithelialization of the cervical canal walls by a physiological endocervical para epithelium improved by association with antibiotic treatment. This complete re-epithelization of all cervical walls cannot be archived with laparoscopic and vaginal repair limited to excise only fibrotic tissue defect

--The fourth aim of 360° endocervical resection with a new cuboid epithelium is to prevent cervical adherence to reduce the risk of scar pregnancy and to improve endometrial receptivity reducing chronic endometritis.

-- The fifth aim: Several surgeons recommend laparoscopic or vaginal approach when the residual myometrium thickness (RMT) is less than 2-3 mm but no cutoff for the correct choice between hysteroscopy or laparoscopy and vaginal approach can be concluded because available data are limited (17-18). Furthermore, no single

case of uterine niche wall perforation and bladder injury has been reported yet independently from the size of RMT in the lecture and the size of resectoscope.

Superficial coagulation of vessels				
Fourth Step				
Focused electro- cauterization with rollerball of bleeding cervical vessais				

Since cervical dilation modifies the anatomy of isthmocele, the use of SDR results to be the first choice when RMT is less than 2-3 mm because the isthmoplasty is performed in real anatomy of cervical channel without any modifications induced by dilation. The choice of miniaturized technology combined with an appropriate surgical strategy expands the indications of the resectoscopic isthmoplasty without increasing the risks related to the procedure.

In conclusion, hysteroscopic isthmoplaty appears to be effective for symptom relief and fertility improvement and easy to manage in day surgery model of care with low morbidity.

Therefore, the hysteroscopic repair appears to be the most popular and less invasive treatment to discuss with patients as the first choice. The ideal surgical treatment in symptomatic and infertile women with isthmocele remains to be elucidated and further prospective case-control studies are necessary to confirm the effectiveness of CSD repair (19).

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Cesarean Scar Ectopic Pregnancy

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INTRODUCTION

Cesarean Scar Ectopic Pregnancy (CSEP) is defined as a gestational sac that implants within the defect in the myometrium or isthmocele (Fig. 1-2), generated at the hysterotomy site produced as a result of a previous cesarean section. (1)

The CSEP is usually partially or completely surrounded by myometrium and fibrous scar tissue.



The prevalence of isthmocele in women with a previous cesarean section reaches 84% and the majority is asymptomatic. The correlation between isthmocele and CSEP is unknown. (2)

Although in one publication the CSEP has reached a prevalence of 1/500 (3) it is estimated that it varies between 1/1800 and 1/2500 of all deliveries by cesarean section (1,4-6). CSEP represents between 4% and 6% of all ectopic pregnancies.

The first published case of CSEP is from 1978 and from 1978 to 2001 only a total of 19 cases were published. (7)

The number of reported cases has been increasing in recent years, possibly due to the

increase in cesarean sections rate associated with the fact that ultrasound specialists begin to look for the isthmocele defect in their scans. The Canadian Institute of Health reported an increase in CSEP rates in Canada from 23.7% in 2003 to 27.5% in 2014. (8-9)

Despite this, knowledge about risk factors, diagnostic criteria and even therapeutic options is still limited. There is no consensus on which is the best therapeutic approach and medical evidence continues to be limited. The most common treatment options are, expectant management, medical treatment and surgical approach, the latter two can be used in combination.

25% of the patients are asymptomatic at the time of diagnosis. When symptomatic it may present with bleeding and / or pain. If treatment is delayed, CSEP could progress to a placenta accreta or even uterine rupture. Due to the depth of this type of gestation within the fibrous tissue of the scar, the treatment represents a great challenge and in case of failure it could result in hemorrhage and even requiring hysterectomy.

ETIOLOGY

The origin of CSEP is believed to be due to invasion of the myometrium by the gestational sac that occurs through microscopic dehiscence or a scar defect due to decreased vascularization of the uterine segment together with fibrosis and incomplete healing. This mechanism is similar to that proposed for intramural pregnancy, where dehiscence is secondarv to uterine manipulation/trauma such as curettage, myomectomy, metroplasty, or manual delivery of the placenta. (10)

These defects in the cesarean section scar are detectable by transvaginal ultrasound years after delivery, the size and depth can be measured by sonohysterography. In non-pregnant women, a triangular shape is seen in the ultrasound in the incision area with a liquid content. The number of cesarean sections represents a risk factor for CSEP, since after several procedures the surface of the scar increases and the vascularization on the anterior wall decreases, as well as the increase in fibrosis.

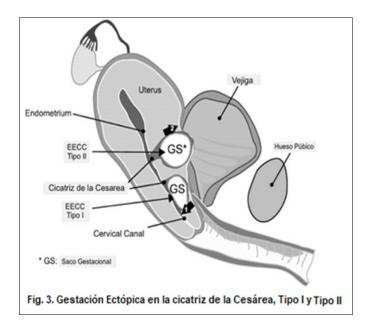
As a matter of fact, 72% of the patients with CSEP reported by Jurkovic et al had a history of 2 or more cesarean sections. (4) However, In a systematic review including 75 women, it was found that 39 (52%) had only one previous cesarean section, 27 (36%) had 2, and 9 (12%) had more than two, stating that the number of cesarean sections had no impact. (10) Other factors that were analyzed and found to have no effect on risk are the type of suture used and the hysterotomy closure technique.

TYPES OF CSEP

There are 2 types of CSEP (Fig. 2) depending on the depth of implantation. (11)

Type I or Endogenic: presents a progression towards the cervico-isthmic area or the uterine cavity. It can result in a viable pregnancy, but with a high risk of bleeding in the placental implantation area.

Type 2 or Exogenic: CSEP with deep invasion into the bladder or abdominal cavity. This type of CSEP can be complicated by uterine rupture and bleeding early in pregnancy.



DIAGNOSIS

The mean age of presentation is 32 (+/- 3) and the mean gestational age at presentation is 7 +/- 2.5 weeks.

Given the serious consequences of this pathology, early diagnosis and management is imperative. The symptoms of CSEP are nonspecific. (12). In a systematic review, 107 of the 751 cases of CSSE were not diagnosed. (4)

The most frequent symptoms are:

1. Vaginal bleeding, ranging from spotting to heavy bleeding

2. Low abdominal pain

Sonographic diagnostic criteria for CSEP include (In a patient with a positive pregnancy test): (7)

1. An empty endometrial cavity and endocervical canal

2. A gestational sac in the area of the CS scar

3. Thin or absent myometrial tissue between the bladder and the gestational sac

4. Presence of vessels in the hysterotomy CS scar area

The differential diagnosis includes cervical pregnancy and abortion in the course of an endocavitary gestation.

On Doppler, the gestational sac located in the cesarean scar defect is visualized, surrounded by vascular flows that are characterized by high flow (> 20 cm / s) and low impedance (pulsatility index <1). Using 3D color Doppler it is possible to quantify the changes in the uterine neovascularization that surrounds the CSEP. This technique is especially useful to monitor the response to medical treatment.

In cases where ultrasound and Doppler are not conclusive, it is possible to use Magnetic Resonance Imaging (MRI). MRI has the same sensitivity as ultrasound for the diagnosis of CSEP, but is better in evaluating the implantation in the scar. A T2 MRI and sagittal section best identify the scar defect, trophoblastic tissue and myometrium separately.

TREATMENT

Given the limited number of published studies with large series, there is no consensus regarding the best treatment for CSEP. Treatments vary from watchful waiting, medical treatment, local treatment, or surgical approach.

The best results is obtained with early treatment and with the use of more than one therapeutic strategy simultaneously. The objectives are, on the one hand, to preserve fertility and, on the other, to avoid situations that threaten the life of the patient, such as massive bleeding or uterine rupture.

Expectant Management

This option is associated with high morbidity, with a complication rate of more than 50%, which includes hysterectomy, uterine rupture, future infertility, and significant bleeding. Results are best in cases without a fetal heartbeat at the time of diagnosis. (13)

It should not be recommended as the first line of treatment and always inform the patient of the potential consequences of expectant management.

Medical treatment

Medical treatment can be with local (intragestational) or systemic (intramuscular) medication. The most widely used drug is Methotrexate (MTX) since is the recommended treatment of ectopic pregnancy.

Other alternative medications that have been used include hyperosmolar glucose, potassium chloride, gefitinib, ethanol, vasopressin, and mifepristone, although it is important to know that there is very little information on the use of all of these other alternatives. (13-14)

All these drugs can be administered alone or in combination, whether or not they are guided by ultrasound.

The use of drugs as the first line of treatment for CSEP is associated with a high failure rate (44% -91%) and will frequently require surgical intervention. (13)

The criteria for the use of medical treatment are:

- 1. Less than 8 weeks of gestational age
- 2. Absence of fetal heartbeat
- 3. Hemodynamically stable
- 4. $\beta\text{-hCG}$ less than 10,000 mIU / mL

5. Distance between the myometrium and the bladder> 2mm

Despite the accumulated experience in these treatments, there is lack of good quality randomized trials which makes it difficult to compare the different medical treatment options.

Methotrexate

This medication can be administered locally, systematic, alone or in combination with a surgical approach. If the CSSE does not resolve with the initial treatment with MTX, then the option of adding another drug or surgery should be considered.

Timor et al. published multiple studies addressing the use of MTX and in 2012 published a retrospective series of 26 cases in which MTX was administered within the gestational sac, just outside the sac and intramuscularly. Globally they achieved complete resolution in 19 cases, however, this required between 22 and 177 days. (15)

More recent systematic reviews have shown similar success rates (50% -66%) with moderate increase if more than 1 dose is administered.

Simultaneous administration of MTX locally and systemically does not improve results compared to multidose regimens. (4) The need to also use another type of approach is common when using MTX.

The factors that are associated with an increase in the success rates with the use of MTX are:

1. Distance between myometrium and bladder greater than 2 mm

2. Low levels of β -hCG (<5,000 mIU / mL)

We must not forget that MTX is also associated with adverse effects such as hair loss, pneumonitis, bone marrow depression, among others. In severe rare cases, liver failure and fibrosis can occur. The accumulation of MTX byproducts in erythrocytes, adipose tissue and in the liver can persist for weeks to months after the initial administration, the patient should be informed of this potential accumulation of MTX and monitored. (16-17)

Non-invasive treatments

Uterine Arteries Embolization (UAE)

UAE is a selective bilateral catheterization of the uterine arteries followed by the injection of Polyvinyl Alcohol or Tris-Vicril Gelatin particles into the vessels with the aim of completely obstructing the blood flow within them. Although it is possible to achieve a pregnancy after this procedure, it is not recommended for women who desire future fertility.

The use of this technique is reserved for cases prior to performing a curettage of the CSEP to minimize bleeding, especially in those cases in which the trophoblast penetrates deeply into the myometrium. This option alone should never be used as a first line therapeutic option but as an adjunctive treatment.

Lain et al. published a series of 12 cases successfully treated by a combination of MTX and UAE. (18) In a review of 239 cases that were treated with UAE followed by curettage, a success rate of 99.16% was achieved with an overall complication rate of 10.4% (19).

High Intensity Focused Ultrasound (HiFu)

HiFu ablation alone or in combination with blind curettage for the treatment of CSSE of less than 9 weeks gestation was reported in 3 studies. The overall success rate was 93% with a 4% risk of bleeding and a 0% risk of hysterectomy. The most frequent adverse effect was pain in 18% of the cases. (13)

Surgical Treatment

When choosing the surgical approach, the skill of the surgeon, the desire of future fertility, and the clinical course must be taken into account. The absence of quality studies makes it difficult to provide advice based on medical evidence. Minimally invasive approaches have improved significantly in recent years, making them safer. However, it is important to explain to the patient all the risks associated with the surgical approach such as infection, bleeding, thrombotic complications, pain, anesthetic complications, and potential mortality.

1. Dilation and Curettage (D&C)

D&C was used in the past as the preferred approach, resulting in major complications such as massive hemorrhage occasionally needing hysterectomy.

Currently there is no justification for an aggressive procedure without direct visualization of the uterine cavity. Currently there is emerging evidence that favors the use of hysteroscopy with direct visualization over blind D&C for the management of CSSE.

2. Excision of the CSEP

There are different studies that describe the excision of the CSEP and surrounding scar tissue by laparoscopic hysterotomy. This approach was studied in CSEP type 2 (extrauterine growth towards the bladder and abdominal wall). There are 2 systematic reviews that reported a 97% success rate with a rapid resolution of β -hCG without complications (13,21)

In addition, other positive long-term outcomes were seen including a higher rate of subsequent pregnancies and a reduction in CSEP recurrences when compared to other hysterotomy routes (laparotomy or transvaginal).

Given that this route allows direct visualization of the pregnancy, allowing minimally invasive excision of the scar, it should be one of the firstline approaches for the treatment of CSEP. (21) On the other hand, the skill level required to perform this procedure laparoscopic or robotassisted is high.

The procedure is performed initially by separating the bladder from the lower uterine segment. To minimize blood loss, a dilution of vasopressin is injected into the myometrium over the pregnancy. (22)

3. Vaginal Route or Colpotomy

The vaginal approach to CSEP uses similar technique to that of vaginal hysterectomy where an anterior colpotomy is performed to access the pregnancy followed by excision of the same and a repair of the scar defect. (13) This procedure is used less frequently compared to abdominal or laparoscopic hysterotomy. (14)

Morbidity from the vaginal route has been shown to be minimal with a success rate greater than 90%. (13,14,21)

4. Hysteroscopy

Hysteroscopy has been used to treat CSEP either as a single treatment or in combination with adjuvant drugs. Multiple variants have been described for the use of hysteroscopy that were reviewed in different studies, including hysteroscopic excision of the gestational sac, aspiration of the gestational sac after medical treatment, and injection of MTX or ethanol into the gestational sac. (13,14,21)

At present, few series have been published on the treatment of CSEP only by hysteroscopy. (26)

In a review, among 95 cases treated by hysteroscopy, major complications were found in 3.2% of cases and 17% required another intervention. (27)

Yang et al. reported a cohort of 39 cases of CSEP excision under ultrasound guide. 36 patients were treated pre-surgically with Mifepristone and in another 3 the combination of MTX and UAE. (28) No difference was found between type I and type II CSEP in relation to the amount of bleeding, the follow-up time until the β -hCG became negative. However, the absorption time of the gestational tissue was significantly longer in type II (72.2 vs 29.9 days).

Hysteroscopy could be used as a first-line approach especially for type II CSEP. (29)

Hysteroscopy allows good visualization of the gestational sac, the surrounding vessels, and the uterine wall. It can be performed using a resectoscope, preferably bipolar. Although the separation of the gestational sac is carried out without the use of energy, in case of bleeding it will

be used for electrocoagulation of the bleeding vessels. In certain cases, an intrauterine balloon will have to be left to control bleeding.

In certain cases in which ultrasound does not show excessive vascularization, it can be performed with a bipolar mini-resectoscope or with an operative hysterosocpe provided with a working channel. The technique is based on the separation of the gestational sac using the hysterosocpic grasper. If bleeding occur then it could be coagulated with bipolar energy or even diode laser.

These procedures for excision of the CSEP should always be performed by expert hysteroscopists. (26,28,29) Factors associated with better success rates are low parity, fewer previous cesarean sections, and early gestational age at the time of the procedure. (14)

A 2016 review of the American Society for Reproductive Medicine (ASRM) on different methods for the treatment of CSEP reported that hysteroscopy can be used by direct visualization or under ultrasound guide. (21)

These complications include fluid overload, uterine perforation, infection, and need for hospital admission. Although rare, the patient should be counseled about this potential complications before proceeding.

SUMMARY

In conclusion, despite the fact that there is still no consensus regarding the ideal treatment for CSEP, it is accepted that the treatment must consider the hemodynamic conditions of the patient, the location of the gestational sac by ultrasound, the gestational age, the desire for future fertility, the level of compliance of the patient and the experience of the surgeon.

A type II level of evidence supports any minimally invasive approach that allows both removal of the pregnancy and correction of the scar defect, either transvaginally or laparoscopically. These techniques have shown a high success rate with minimal complications. We emphasize that the lack of evidence requires to perform well designed randomized controlled trial to better evaluate treatment options.

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