

## Isthmocele: Successful Surgical Management of an Under-Recognized Iatrogenic Cause of Secondary Infertility

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### Abstract

**Background:** The aim of our study was to assess the prevalence and the benefits of endoscopic surgical procedures to patients with secondary infertility.

**Design:** This is a retrospective hospital based study, in a private hospital with a major profile in assisted reproductive techniques and endoscopic surgery in Budapest, Hungary.

During the study period of between 1st January 2013 - 31st December 2016, patients presenting with secondary infertility after one or more caesarean section were evaluated, using the HyCoSy and diagnostic hysteroscopy. Within a group of 15 patients diagnosed with isthmocele who had surgical treatment, 80% (n=12/15) became pregnant within 24 months and delivered before 36 months of treatment. All the patients had hysteroscopy guided laparoscopic isthmoplasty, except one who had hysteroscopy procedure alone.

**Conclusion:** We therefore conclude, that the combined use of laparoscopy and hysteroscopy is an effective method for the accurate diagnosis and treatment of patients with isthmocele related infertility problems based on assessment of their reproductive performance after the surgery, even though larger studies maybe suitable to confirm the effectivity of the procedure.

**Keywords:** Caesarean section, Infertility, Caesarean section scar defect, Hysteroscopy, HyCoSy, Laparoscope

### Background

Infertility has been one of the major medical challenges for decades but measurable advances have been achieved recently with the sporadic development in medical sciences and with the introduction of assisted reproductive technology. However, the improvement in the reproductive medicine has invariably contributed to the upsurge in the rate of caesarean section [1,2]. Caesarean section, as an established tool in modern obstetrics, has improved the fetomaternal morbidity and mortality [1]. However, caesarean section has been assumed as the main causative factor of the isthmocele in some patients [3]. Referred to as niche or caesarean scar defect in various medical literature, is a reservoir similar to a U- or V-shaped pouch found on a previously scarred uterine anterior wall [4,5]. This gynaecological phenomenon, has been associated with various medical conditions such as suprapubic or lower abdominal pain various forms of bleeding disorders including postmenstrual bleeding disorder, chronic vaginal discharge, scar ectopic pregnancy, secondary infertility, dyspareunia etc [6]. It was first described by Poidevin in 1961 as a wedge observed during hysterosalpingography. Also observed by D Hugh Morris in 1995 when analysing uterine specimens of women who had hysterectomies [4,7]. Although, the disorder has been recognized for sometimes, literature about the surgical management of the defect has only recently been published [7]. However, actual incidence of the utero-peritoneal fistula, niche or isthmocele is underestimated, or unknown, and seems underdiagnosed, as the figures may be staggeringly high. Considering the fact that, the average caesarean section delivery rate has increased globally between  $\geq 25\%$ - $\geq 50\%$  depending on the centres and countries [2,8]. The reported incidences of isthmocele varies considerably by different some authors. Bij de Vaate AJ, et al. estimated the incidence to be between 24%-84%, C.B Wang, et al. reported 6.6%-69%. While, Florio, Tower and Frishman reported an incidence of 30%-52% and 19.4%-88% respectively [9,10]. This disparity could be due to lack of standardized criteria or definition of the defect, which could precisely

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describe the size, depth, and other characteristic values of the changes [10,11]. The other challenge is that, not all patients are symptomatic, and some of the symptoms are not specific with the defect, though all authors are of the opinion that isthmocele is an iatrogenic condition, and despite its close relationship with caesarean section, the true mechanism of occurrence is not well understood [12,13]. However, there are some hypothesis in support of the onset, like some deficiencies in the type of sutures, knotting lapses in between sutures, intra-post-operative infection delaying wound healing, closure techniques (single/double), the reason for the caesarean section, and type of the operations (emergency/elective). Other conditions, like patient's age, and other medical states that may inhibit quick wound healing, and the expertise of the surgeon may all have in some ways contributed to the formation of the scar [13,14]. Moreover, secondary infertility could be regarded as an unintended consequence of some of the symptoms of the isthmocele such as the postmenstrual and spotting bleeding, making the ecosystem of the vagina and the endometrial hostile to the sperm, and even directly impair negatively on implantation as a result of the fibrotic tissue formation, or due to the constant silent inflammatory process going on in the pouch [10,11]. Despite, the fact that isthmocele is no longer regarded uncommon, suspicion and regular evaluation during gynaecologic examination has not been done routinely. This present retrospective study reports on the fertility outcome of surgically corrected cases in women with secondary infertility as a result of isthmocele.

## Materials and Methods

The study was conceived and carried out at the Endoscopy department of Robert Károly Magán Hospital, Budapest, Hungary. The study protocol and data collection was approved by the Ethical committee of the Hospital.

Patients with secondary infertility and isthmocele seeking for assisted reproductive technique support were evaluated. During the period between 1st. January 2013- 31st. December 2016, 15 women were evaluated. Excluding criteria; includes, male factor causes of infertility, patients physical characteristics, and those with known disabling medical conditions of infertility (endocrine disorders, fibroid etc). All the patient underwent general infertility evaluation examination which included (sperm analysis, hormone profiles, general gynaecologic examinations, ultrasonographics evaluations, other laboratory investigations etc.) The patients were examined at the end of menstruation (or on the tenth day for patients with menstruation lasting >10 days) by transvaginal three-dimensional (3D) colour Doppler ultrasound (Phillips HD 11 device) using the combination of the HyCoSy ultrasound techniques. To evaluate the myometrium thickness. The choice of surgical procedure was based on the myometrium thickness, and the size of the isthmocele. Those with myometrium thickness of  $\geq 3\text{mm}$  were eligible for hysteroscopy management, while, those with  $< 3\text{mm}$  were eligible for both hysteroscopy and laparoscopic management. The volume (size) of the isthmocele was also calculated, measuring the hypo echoic triangular space in the lower part of the scar by the depth ( $D=\text{height}$ ) and width/base ( $W=$  (longitudinal spread) of the isthmocele. The depth of the hypo echoic triangle ( $D$ ) was defined as the distance between the surfaces of the endometrial/ endocervical layer of the posterior uterine wall to the tip of the hypo echoic triangle. The width ( $W$ ) was defined as the distance between the proximal

and distal parts of the myometrium of the anterior uterine wall measured at the surface of the endometrial/endocervix of the posterior uterine wall. With the combination of this formula ( $\text{Base! height}/2$ ). The resultant outcome is as follows: Those with isthmocele width (volume)  $\leq 15\text{mm}^2$  were group as grade 1; grade 2 was those with  $\geq 16\text{-}25\text{mm}^2$ ; and grade 3 is those with  $\geq 25\text{mm}^2$ . They consequently underwent a combined surgical treatment of hysteroscopy and laparoscopic repair. All the patients were evaluated during the surgical repair with hysteroscopy, while the repair was done with laparoscopic removal of the scarred tissues and sutured, except one who was treated hysteroscopically due to the size and thickness of the myometrial walls. Patients were followed up for about 24 months post-surgery.

## Surgical Procedure

Operation were done within 1 week after menstruation, under general anesthesia, and patients were placed in the Trendelenburg (head-down) position. After a careful inspection of the abdominal cavity is concluded, to rule out other pathologies that, could cause patient's problems. Ultrasonic scalpel was used to incise the peritoneal fold over the bladder, and the bladder was pushed down to 2 cm below the lower edge of the isthmocele with the help of duckbill pliers. Meanwhile, under the hysteroscopic examination, the operating surgeon identified the presence of isthmocele mucosal hyperplasia, which appeared partially white, to confirm the location and size of the isthmocele. While a surgical assistant was designated to used an intrauterine sound and the orange-red light source to locate the diseased area of the lower segment of the uterus. Electric coagulation hook was used to open the isthmocele laparoscopically. The uterine isthmocele is cut in full length, the wound trimmed, and 2-0 absorbable stich used to perform full thickness suture. The peritoneum covering the bladder is closed after the repair uterine walls, control ultrasound uterine wall integrity is performed 4 weeks postoperation.

## Result

The average age of the study subjects was  $37.0769 \pm 3.73$  years, however, 86.67% ( $n=13$ ) patients only had one caesarean section before, and 13.33% ( $n=2$ ) have had repeated caesarean section before in Table 1. Among the study subjects who underwent isthmoplasty 53.33% ( $n=8$ ) patients had grade 3 isthmocele, with a myometrium thickness of  $< 3\text{mm}$ , while 33.33% ( $n=5$ ) had grade 2 isthmocele, with a myometrium thickness of  $< 3\text{mm}$  (Table 2). Meanwhile out of the 15 patients who underwent this surgical treatment 11 patients (73.33%) became pregnant within the first 12 months, while one (6.67%) was pregnant within the first 24 months. However, 3 patients (20%) were lost to follow up after the second postoperative visit in Table 3. The remaining women who became pregnant were monitored closely in the institution to term. The average duration of years of infertility problems was  $3.625 \pm 1.408$  years in Figure 1A-1C. Interestingly, 58.33% ( $n=7/15$ ) became pregnant by IVF-ET, while 41.66% ( $n=5/15$ ) became pregnant spontaneously in Table 3. Majority of the patients had safe delivery at term by caesarean section as a result of the obstetrics history and other medical conditions of the patients, only one patient had miscarriage in the first trimester. No complication or uterine rupture was observed during the pregnancy or during the surgery.

Past obstetrics history	Frequency	Percent	Cum. Percent
No. of pregnancy			
1	3	20.00%	20.00%
2	6	40.00%	60.00%
3	3	20.00%	80.00%
4	2	13.30%	93.30%
5	1	6.67%	100.00%
No. of parity			
1	9	60.00%	60.00%
2	3	20.00%	80.00%
3	3	20.00%	100.00%
Abortion and C-section	1	6.67%	6.67%
Vaginal delivery and C-section	5	33.33%	40.00%
Caesarean section only	9	60.00%	100.00%
Previous mode of delivery			
1x Caesarean-section	13	86.67 %	86.67%
Duration of infertility			
≥2 year	9	60.00%	60.00%
≥4 years	5	33.33%	93.33%
≥6 years	1	6.67%	100.00%
Total	15	100.00%	100.00%

Table 1: Base line patient characteristics (n=15).

Myometrium thickness	Frequency	Percent	Cum. Percent	
≤3 mm	1	6.67%	6.67%	
≥3 mm	14	93.33%	100.00%	
Total	15	100.00%	100.00%	
Grade 1	≤15mm <sup>2</sup>	2	13.33%	13.33%
Grade 2	≥16-25mm <sup>2</sup>	5	33.33%	46.66%
Grade 3	≥25mm <sup>2</sup>	8	53.33%	100.00%

Table 2: Isthmocele characteristics at baseline and after surgery (N=15).

Duration between operation and pregnancy	Frequency	Percent	Cum. Percent
≥ 12 months	11	73.33%	73.33%
≤ 24 months	1	6.67%	79.96%
≥ 36 months (No pregnancy) lost to follow-up	3	20.00%	100.00%
Mode of pregnancy			
ART	7	58.33%	58.33%
Spontaneous	5	41.66%	100.00%
Total	12	100.00%	100.00%

Table 3: Fertility and pregnancy outcome (N=12/15).

## Discussion

The effect of caesarean section scar deficiency or niche (isthmocele) on fertility is becoming an area of concern in our current gynaecological practice. More incidences are being recorded due to the newer investigative procedures and the improvement in the ARTs [9,12,15]. The increase incidences of isthmocele could be credited to the increase rate of caesarean section in the past few decades [2]. Although fresher publication about this post caesarean section complication (isthmocele) is unfolding. However, the prevalence of this anatomical defect (isthmocele) discovered accidentally and the inconsistent manifestation of the symptom remains unclear [16,17]. Making this pathology questionable and has definitely influenced the hypothesis or theory behind the formation. Despite the different postulations existing in the literature presently, an absolute cause is still not clear. However, factors that could be considered to have played some roles in the development of the scar maybe, probably deficiencies in the surgical technique. Such as single layer interrupted sutures, which may not proffer proper alignment of the uterine tissue during the healing processes [14,17]. Other possibilities like the state of chronic inflammatory processes sometimes present during the healing period of any surgical intervention, therefore the fibrotic tissue reactions and the inflammatory process, may alter the arrangement of the myometrium fibres at the site of the uterine closure, and may possible create a discrepancy at the level of the incision [16,18]. Other possible risk factors are ongoing inflammatory process during and after surgery, poor wound healing due to immune compromised state or congenitally, in a very rare situation congenital uterine diverticulum has been observed, but usually accompanied by congenital renal dysplasia [19]. Subfertility (secondary infertility) as a result of isthmocele is still not very clear; considering the fact that, isthmocele is not noticed in every patient with previous SC. However, some school of thoughts are of the opinion that, the mechanism with which this may occur is as a result of accumulation of blood in this diverticulum like space, which may often alter the menstruation pattern, given rise to persistence postmenstrual bleeding. The post menstrual bleeding may result in negatively affecting the mucal quality in the cervix, obstruct the sperm transportation upstream, and may affect implantation due to the low grade chronic inflammatory activities in the uterus. With this, it could interfere with the embryo implantation, or abnormal implantation, as in a rare case of scar ectopic or placenta praevia



Figure 1A. Hysterectomy -longitudinal picture of uterus scar defect: Source(Publication from the internet [3].)  
 1B. Surgical picture of scar defect: Source from (Robert Károly Hospital, Budapest)  
 1C. Ultrasonographic picture of scar defect: Source from (Robert Károly Hospital, Budapest)

etc [3,20]. Other pathological abnormalities also associated with the isthmocele, are Postmenstrual Abnormal Uterine Bleeding (PAUB), Suprapubic/Lower Abdominal Pain (SPP/LAP), Chronic Vaginal Discharge (CVD), Dysmenorrhoea etc. However, in this study we evaluated patients presenting with secondary infertility who were subsequently diagnosis with isthmocele. The patients were followed up till 36 months after surgical management. During this treatment module some patient were exposed to ART treatment (IVF-ET), based on their fertility status before and after the surgical treatment. Although, all the patients were examined and evaluated by HyCoSy; a double-edge approach was applied during the surgery as the entire fifteen patients with sub fertility/infertility issues undergone hysteroscopy evaluation to ascertain the degree of damage and location of the isthmocele. All patients had laparoscopic isthmoplasty, except one case of hysteroscopy repair. Return of fertility after the hysteroscopy-laparoscopic isthmoplasty within the first 24 months was 80% (n=12/15), which was lower than the 90.2% recorded by Giampietro Gubbini, et al. but higher than the study reported by Tanimura S, et al 63.6%. The poor outcome, could be as a result of the heterogeneity of family and other medical history of the couples, some were offered ART, while others got pregnant spontaneously [10,21]. Eleven of the twelve women delivered healthy life babies, while one had a missed abortion. All the patients reported about great improvement, or even became symptomless on other comorbidities as a result of the isthmoplasty. Before the surgery, almost all the patients experienced inability to conceive even without any contraceptive means between 1-4 years after the caesarean section 93.3% (n=14/15), among the group, 13.3% (n=2/15) have had more than one caesarean section. Isthmocele size of greater than  $\geq 16\text{mm}^2$  was seen in 86.7% (n=13/15). This study has emphasized the strength and importance of the early diagnosis and management of isthmocele in our contemporary gynaecologic practice applying the combined approach of hysteroscopy with laparoscopy. The combined surgery minimizes some of the shortfalls of each approach singularly; as the hysteroscopy procedure is associated with higher rate of damage to organs like bladder, or further decrease the thickness of the myometrium at the site of isthmocele. Other uterine abnormalities, causing danger such as uterine perforation or placenta pathologic adhesions. Also, improper localization, size and site of isthmocele may hamper adequate repair with laparoscopic without the hysteroscopy guidance [5,10,22]. These procedures also, improve the efficacy of the fertility workup, as other pathologies independent of the isthmocele were also appreciated or detected, during the process and treated. Such conditions like; Chronic PID, intra-abdominal adhesions, fibroids, endometriosis, ovary cyst, endometrial polypus, uterine synechia or Ashermann syndrome could be managed, which may ultimately improve the chance of pregnancy. Although, more data and research will be required to ascertain to fully understanding of this phenomenon, but it is also clear, that fertility returns to almost everyone after the surgical repair of those with isthmocele, irrespective of the methods. However, the combined use of both endoscopic surgical techniques provides more options and satisfaction, with just few lapses like cost, and surgical time.

## Conclusion

General consensus is lacking as to when to investigate this phenomenon! From all indications, caesarean section is on the

increase; coupled with the different school of thoughts on the mode of uterine scar closure techniques, more of this defect is expected. Therefore, it may not be out of place to revisit the double uterine wall (wound) closure technique and a thorough ultrasound screening, most preferably with HYSCOY of woman on their first postnatal visit or at least after the return of first menstruation of the endometrial cavity. Such may improve early discovery, management and reduce medical cost on patients and the health system, also reducing patient's discomfort.

## Interests

The authors declare that, there are no competing interests regarding the publication of this paper.

## Contribution to Authorship

The article was conceived by EAA, FI, TI and RÁ, and they selected the articles and collected the data. Analysis of the data was performed by EAA, and FI. The first draft was written by EAA, and FI. While RÁ and SP supervised the article to the final draft.

## Ethics Approval

Ethical approval was sort for and given by the Róbert Károly Magán hospital ethical committee.

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## Abbreviations

CVD- Chronic Vaginal Discharge, PAUB- Postmenstrual Abnormal Uterine Bleeding, SPP/LAP- Suprapubic/Lower Abdominal Pain, HyCoSy- Hystero-Salpingo-Contrast Sonography, IVF-ET: In-Vitro Fertilization and Embryo Transfer, ARTs- Assisted Reproductive Techniques

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