

The Applicability and Effectiveness of Saline Infusion Sonography Using Solid Embryo Transfer Catheter in the Diagnosis of Isthmocele in Patients with Secondary Infertility

Sekonder İnfertil Hastalarda İstmosel Tanısında Solid Embriyo Transfer Kateteri Kullanarak Salin İnfüzyon Sonografisinin Uygulanabilirliği ve Etkinliği

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ABSTRACT

Objectives: Isthmocele has been implicated as a causal factor in patients with secondary infertility. We aimed to investigate the diagnostic effect of saline infusion sonography using solid embryo transfer catheter in patients suffering from secondary infertility. **Materials and Methods:** Sixteen patients who applied for infertility evaluation at the Center for Human Reproduction and Infertility of Ankara University and were suspected to have isthmocele on standard vaginal ultrasonographic evaluation were enrolled in the study. All patients were then subjected to saline infusion sonographic evaluation to confirm the diagnosis and measure the base width and area of the isthmocele, and myometrial thickness if confirmed. **Results:** The mean age of the patients was 37.7±3.7, mean gravida was 2.7±1.4, and mean parity was 2.0±0.8. The mean procedure time was 4.1±1.1 min. Among the patients, 13 underwent one previous cesarean section, and three experienced two cesarean births. The mean duration of secondary infertility was 19.18 months. Apart from infertility, 10 patients (62.5%) suffered from intermenstrual bleeding, eight (50%) suffered from prolonged bleeding, and six suffered from mucous discharge (%37.5). The mean measured isthmocele base width was 5.6±1.6 and 10.1±2.4 mm (p<0.001), isthmocele area was 21.2±5.2 vs. 38.7±10.2 mm² (p<0.001), and residual myometrial thickness was 5.4±2.5 mm and 4.8±2.1 mm (p=0.49) before and following saline infusion sonography respectively. **Conclusions:** The contours and area of isthmocele and residual myometrial thickness can be more clearly depicted by saline infusion sonography, especially in patients with a suspicious diagnosis during routine transvaginal ultrasound examination. Saline infusion sonography using an embryo transfer catheter is a safe and easy procedure that may aid in the diagnosis of isthmocele and in tailoring the optimal treatment approach in patients suffering from secondary infertility.

Keywords: İsthmocele; cesarean scar defect; infertility; sonography

ÖZET

Amaç: İstmosel, sekonder infertilitesi olan hastalarda etiyolojik bir faktör olarak suçlanmıştır. Sekonder infertilitesi olan hastalarda solid embriyo transfer kateteri kullanılarak salin infüzyon sonografisinin tanısıl etkisini araştırmayı amaçladık. **Gereç ve Yöntem:** Çalışmaya Ankara Üniversitesi Üreme Sağlığı Teşhis ve Tedavi Merkezi'ne infertilite değerlendirmesi için başvuran ve standart transvajinal ultrasonografik değerlendirmede istmosel şüphesi bulunan 16 hasta alındı. Daha sonra tüm hastalar, teşhisi doğrulamak ve istmoselin taban genişliğini ve alanını ve doğrulanırsa myometrijal kalınlığı ölçmek için salin infüzyonu sonografik değerlendirmesine tabi tutuldu. **Bulgular:** Hastaların yaş ortalaması 37.7±3.7, ortalama gravida 2.7±1.4 ve ortalama parite 2.0±0.8 idi. Ortalama işlem süresi 4,1±1,1 dk idi. Hastalardan 13'üne daha önce bir sezaryen, üçünde iki sezaryen doğum hikayesi mevcuttu. Ortalama sekonder infertilite süresi 19.18 aydı. İnfertilite dışında 10 hastada (%62.5) intermenstrüel kanama, sekiz hastada (%50) uzamış menstrual kanama ve altı hastada (%37.5) mukus akıntısı mevcuttu. Ölçülen ortalama istmosel taban genişliği 5.6±1.6 ve 10.1±2.4 mm (p<0.001), istmosel alanı 21.2±5.2'ye karşılık 38.7±10.2 mm² (p<0.001) ve rezidüel myometrijal kalınlık 5.4±2.5 mm ve 4.8 idi. Sırasıyla salin infüzyon sonografisinden önce ve sonra 5.4±2.5 mm and 4.8±2.1 mm (p=0.49) idi. **Sonuç:** Özellikle rutin transvajinal ultrason muayenesi sırasında şüpheli tanı konulan hastalarda istmosel konturları, alanı ve rezidüel myometrijal kalınlık salin infüzyon sonografisi ile daha net olarak gösterilebilir. Embriyo transfer kateteri kullanılarak salin infüzyon sonografisi, istmosel teşhisine ve sekonder infertiliteye sahip hastalarda optimal tedavi yaklaşımını uyarlamaya yardımcı olabilecek güvenli ve kolay bir prosedürdür.

Anahtar Kelimeler: İstmosel; sezaryen skar defekti; infertilite; sonografi

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The incidence of cesarean section has continued to increase gradually worldwide over the last decades, and now accounts for almost 1 in 5 of all childbirths.¹ Worldwide cesarean section rates raised from around 7% in 1990 to 21 % today, which is even projected to continue rising in the following years. The cesarean rate is as high as 43% in Latin America and Caribbeans. Overuse of cesarean birth may have some gynecological consequences in the long term in addition to wasting human and financial resources. Thus, optimizing cesarean delivery use is a global concern and a challenge in public health.¹

In the year 1961, Poidevin first described a wedge-shaped defect using hysterosalpingography.² Monteagudo et al. defined the term “niche” in 2001, but the condition has also been termed a sacculation, isthmocele, a cesarean/postcesarean scar defect, scar pouch, and pouch-like diverticulum by various authors at the site of cesarean scar in the anterior wall of the lower uterine segment.^{3,4} In the year 2019, the “European Niche Taskforce” published a document using the term uterine niche; in which it was defined as an indentation at the site of the cesarean incision with a depth of at least 2 mm.⁵ According to Delphi consensus, the niche is subclassified as simple niche, simple niche with one branch, and complex niche.⁵

The presence of isthmocele has been widely linked to some gynecological disorders, including abnormal bleeding, pelvic pain, dyspareunia, and recently infertility. The incidence of isthmocele has been reported between 24-84% in various studies in women with previous cesarean sections. The results differ according to the number of previous cesarean section, whether the patient is symptomatic, and according to diagnostic tool use, such as ultrasonography, magnetic resonance imaging, hysterosalpingography of sonohysterography.

MATERIALS AND METHODS

Sixteen patients who applied to the Center for Human Reproduction and Infertility of Ankara University for secondary infertility evaluation between January 2020 and March 2022 were enrolled in the current study. This study was approved by the institutional review board and written informed consent was received. All enrolled patients had at least one previ-

ous cesarean section and were suspected to have isthmocele on vaginal ultrasonographic evaluation during initial infertility workup. Then all patients were subjected to saline infusion sonographic evaluation to confirm the diagnosis and measure the base width and area of the isthmocele, and residual myometrial thickness, if confirmed. Saline infusion sonography was performed in the infertility unit of Ankara University within 3 days following menstrual bleeding ends using a solid embryo transfer catheter (Wallace stylet, no 18, Cooper Surgical) (Figure 1). After vaginal povidone-iodine cleansing without anesthesia, all patients received 75 mg of intramuscular diclofenac sodium (Dicloron amp, Deva, Türkiye) 30 minutes prior to the procedure, and no antibiotics were used. All procedures were performed by two experienced operators (MS, BV). The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

Among the enrolled patients, 13 underwent one previous cesarean section, and three underwent two previous cesarean deliveries. The mean duration of secondary infertility was 19.1 months. Apart from infertility, 10 patients (62.5%) suffered from intermenstrual bleeding, eight (50%) suffered from prolonged bleeding and six suffered from mucous discharge (%37.5). The mean age of the patients was 37.7±3.7,

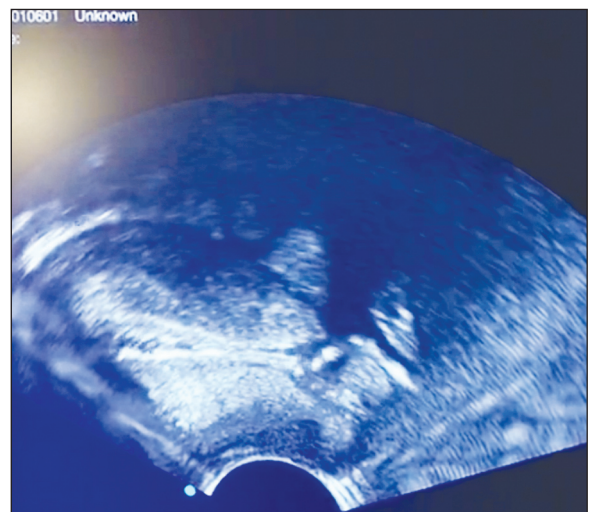


FIGURE 1: Saline infusion sonography with a solid embryo transfer catheter.

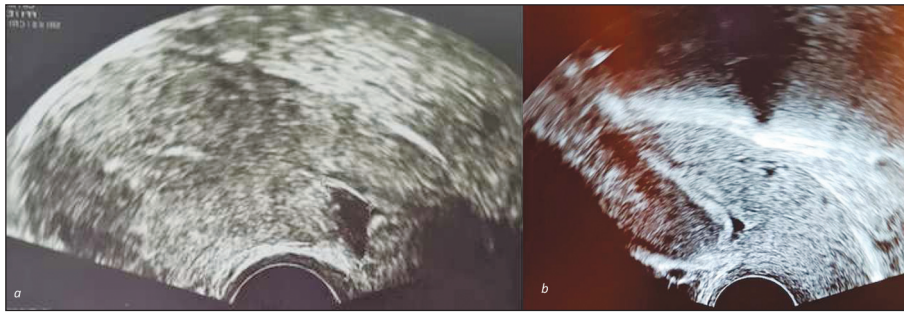


FIGURE 2: Imaging of isthmocele contours before (a) and following saline infusion sonography(b)

mean gravida was 2.7 ± 1.4 , and mean parity was 2.0 ± 0.8 . Excluding four patients with advanced maternal age as a causative factor for infertility, no other infertility factor was detected apart from isthmocele in the remaining 12 patients. The mean procedure time was 4.1 ± 1.1 min and all of the procedures could be performed in the first attempt. The procedure was well tolerated in all patients without needing an additional analgesic dose (Figure 2). The mean measured isthmocele base width was 5.6 ± 1.6 mm and 10.1 ± 2.4 mm ($p < 0.001$), isthmocele area was 21.2 ± 5.2 vs. 38.7 ± 10.2 mm² ($p < 0.001$), and the residual myometrial thickness was 5.4 ± 2.5 mm and 4.8 ± 2.1 mm ($p = 0.49$) before and following saline infusion sonography respectively (Table 1). Although statistically not significant, the isthmocele area was larger in three patients (24.8 vs. 19.6 mm²) who had two previous cesarean deliveries compared to those having one previous cesarean section.

DISCUSSION

In our study group, isthmocele base width, area, and residual myometrial thickness were all measured larger following saline infusion sonography. Saline infusion sonography using embryo transfer catheter is a safe, simple, and patient-friendly diagnostic tool with high accuracy of detecting isthmocele.

In the English literature, various terms were used for the definition including niche, sacculation, cesarean scar defect, uterine defect or isthmocele. Although various rates were given ranging between 24-84% according to the diagnostic modality used, this indentation is approximately observed in almost 60% of women after cesarean section and around 30% of these experience abnormal uterine bleeding and postmenstrual spotting which is characterized by brownish discharge at the end of the menstruation or blood staining between menstrual periods. There are different classifications for isthmocele. Conventionally, it is classified as “large” if the size of the defect involves $>50\%$ of the myometrial thickness. Some authors classified it as large when the residual myometrial thickness was <3 mm; however, others clinically classified them as large when associated with symptoms such as abnormal bleeding, pelvic pain, or infertility.⁶⁻⁸ It is also important to note that large defects are less frequent, with prevalence reported between 11-45% according to the definition used (depth of 50-80% of the myometrium, or residual myometrium ≤ 2.2 mm).⁷ In symptomatic women, the prevalence of uterine niche is higher compared to asymptomatic women.

TABLE 1: The mean isthmocele base width, isthmocele area, and the residual myometrial thickness before and following saline infusion sonography

	Pre-procedure (mean \pm SD)	Post-procedure (mean \pm SD)	p
Isthmocele base width (mm)	5.6 ± 1.6	10.1 ± 2.4	<0.001
Isthmocele area (mm ²)	21.2 ± 5.2	38.7 ± 10.2	<0.001
Residual myometrial thickness (mm)	5.4 ± 2.5	4.8 ± 2.1	0.49

The prevalence of isthmocele changes according to the time scale imaging procedure is performed and the imaging modality used.⁹ Some studies reported there might be differences in the measurement of isthmocele using saline contrast sonohysterography whether it is performed at 6-12 weeks or 12 months following cesarean section.¹⁰ In our study, we could not evaluate the accuracy of diagnostic evaluation according to time it was performed, since only four patients underwent saline sonohysterography within 20 months of cesarean section all of whom were of advanced maternal age. In addition to infertility, the leading symptom was intermittent bleeding followed by prolonged bleeding and mucous discharge in our study group. Of note five patients underwent hysterosalpingography for diagnostic evaluation of secondary infertility in the previous work-up; however, findings were unremarkable.

Another ongoing controversy hinges on the optimal time of niche measurement within the menstrual cycle period. While imaging during the mid-late follicular phase endometrial fluid accumulation due to increasing serum estradiol concentrations in the endometrial cavity may lead to technical difficulties, imaging during the luteal phase may compromise implantation. In the current study, all diagnostic evaluations were performed within three days as soon as menstruation ceases to overcome such technical shortcomings and rule out the possibility of an implanting pregnancy. We could have completed all of the procedures at the first attempt without any complication and without needing additional analgesic dose.

There has been a heavy debate on the risk factors for the development of isthmocele such as; lower uterine incision, emergent cesarean section especially performed after 5 cm of cervical dilatation, single layer locking sutures, infection formation between the uterus and abdominal wall, and hematoma formation, increased body mass index and diabetes mellitus.^{8,11,12} Some studies showed that single-layer closure resulted in thinner residual myometrium and increased incidence of large niches than double-layer closure. In our tertiary referral university hospital all uterine incisions are closed as a single layer locking suture using absorbable No:0 Vicryl (Ethicon Inc,

Somerville, NJ). Although statistically not significant, the only notable difference was that the isthmocele area was larger in three patients who had two previous cesarean births compared to those who underwent one cesarean section.

The increased incidence of infertility is proposed to be caused by impairment of sperm quality and embryo implantation due to the existence of blood products and mucus within the isthmocele pouch that may communicate with the endometrial cavity.¹³ Endometrial fluid accumulation is also observed more frequently in patients with isthmocele.¹⁴ In histopathological studies of isthmocele lymphocytic infiltration and capillary dilatation, foreign body giant cell reaction, fragmentation, and breakdown of the endometrium within the scar, iatrogenic adenomyosis, and polyp formation were observed.¹⁵ The epithelium lining the niche shows cystic dilatation, hybrid endocervical endometrial mucosa typical of the lower uterine segment with atypic and fibroblastic storm.¹⁶ It has been recently suggested that isthmocele volume, adjacent myometrial thickness, and residual myometrial thickness are associated with abnormal uterine bleeding. In our study, all six patients having isthmocele area >20mm² had intermenstrual bleeding, postmenstrual spotting, and mucous discharge. An optimal delineation of isthmocele contours along with the isthmocele area may aid a more appropriate classification of gynecological symptoms associated with the uterine niche.

Various diagnostic modalities have been proposed for the diagnosis of isthmocele, including hysterosalpingography, transvaginal ultrasonography, magnetic resonance imaging, and sonohysterography. It is suggested that the ratio between adjacent and residual myometrial thickness may be a critical marker possibly associated with clinical symptoms and in choosing the most appropriate surgical management. Existing treatment alternatives include medical treatment, levonorgestrel-releasing IUD, and hysteroscopic or laparoscopic isthmocele repair. For hysteroscopic resection to reduce the risk of bladder injury, various thresholds of residual myometrial thickness ranging from 2,5 to 4 mm have been proposed in order to reduce the risk of bladder injury.¹⁷ Some authors prefer laparoscopic approach when

residual myometrial thickness is below 2 mm to decrease complications. Therefore, it is of paramount importance to make an accurate measurement before scheduling the most appropriate surgical treatment.

CONCLUSION

Isthmocele contour, area, and residual myometrial thickness can accurately be depicted using this diagnostic modality to choose the most appropriate surgical treatment approach. In patients diagnosed with secondary infertility without having other definable risk factors, saline infusion sonography may aid in facilitating the diagnosis and tailoring the optimal treatment approach.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct con-

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Meltem Sönmezer, Murat Sönmezer; **Design:** Murat Sönmezer, Koray Görkem Saçıntı; **Control/Supervision:** Murat Sönmezer; **Data Collection and/or Processing:** Batuhan Aslan; **Analysis and/or Interpretation:** Bulut Varlı, Yavuz Emre Şükür; **Literature Review:** Meltem Sönmezer; **Writing the Article:** Meltem Sönmezer, Batuhan Aslan; **Critical Review:** Murat Sönmezer, Yavuz Emre Şükür; **References and Findings:** Murat Sönmezer.

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