

great role towards the realization of effective implementation of birth companions for all mothers during labor and delivery as recommended by WHO guidelines, as best evidence-based practice, across sub-Saharan settings.

AUTHOR CONTRIBUTIONS

KL, DB, and LBT contributed the conception and development of the study protocol. TK and KL contributed data collection and data analysis. AFS, LBT, KL, and DB contributed manuscript write-up. AFS edited the final manuscript. All authors critically revised the article for intellectual content. All authors reviewed the final manuscript and approved its submission for publication.

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The authors have no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are available on reasonable request from the primary author.

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Obstetrics

Isthmocele diagnosis: The optimal timing for detection

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The term isthmocele refers to an iatrogenic uterine defect at the site of the scar from a previous cesarean section or other isthmic tract

surgery. Uterine isthmocele affects up to 70% of women with a history of previous cesarean sections, and approximately one-third of

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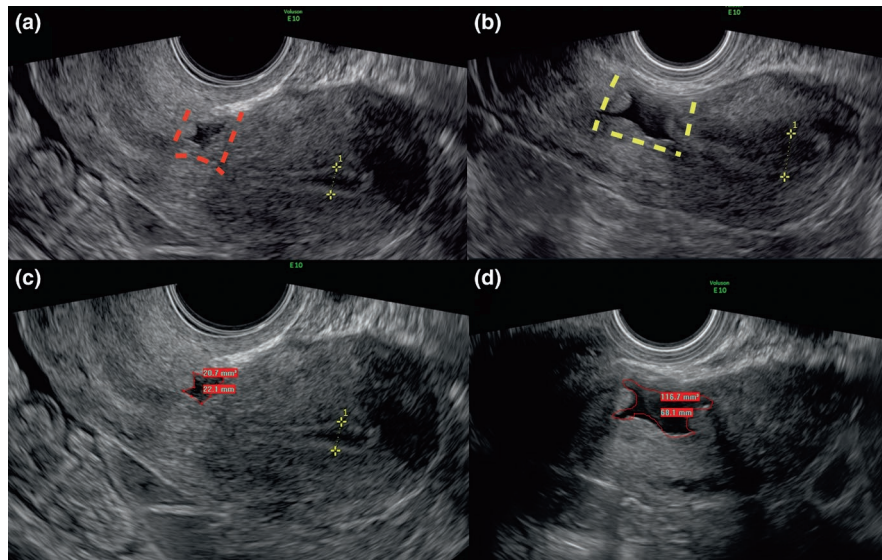


FIGURE 1 A two-dimensional (2D) transvaginal ultrasound showing uterus, cervix, endometrium and the isthmocele in (a) the proliferative phase and in (b) the secretive phase; same image with isthmocele area measurement in (c) the proliferative phase and in (d) the secretive phase.

them exhibit symptoms such as menstrual spotting, abnormal uterine bleeding, or abdominal pain.^{1,2}

Factors such as multiple cesarean sections, maternal obesity, diabetes, and retroverted uteri have been associated with the typical disruption of the myometrium at the scar.¹ Another potential causative factor is the closure technique of the hysterotomy, specifically, double- versus single-layer closure. A recent meta-analysis demonstrated that single-layer uterine closure had a similar incidence of isthmocele as double-layer closure 6–12 months after the cesarean section.³

Accurate diagnosis is crucial as isthmocele has been linked to various gynecologic and obstetric complications such as scar pregnancy, placenta accrete spectrum disorders, and uterine rupture in subsequent pregnancies.⁴ Additionally, women with a uterine niche may experience poorer fertility outcomes due to intrauterine fluid accumulation (mainly menstrual blood and mucus), which could lead to chronic endometrial inflammation and compromise embryo implantation.²

Transvaginal ultrasonography (TVU) is considered the primary diagnostic method. Isthmocele appears as a triangular anechoic indentation communicating with the endometrial cavity within the myometrium of the lower uterine segment. The exact timing for a diagnostic ultrasound has not been yet clearly defined, with several studies conducting diagnostic procedures during the follicular phase of the menstrual cycle.⁵ The size of the uterine niche has been shown to be different during the proliferative and secretory phases, highlighting the need to standardize the exact time of measurement.

Regarding surgical correction of the isthmocele, most authors claim that a residual myometrium ≥ 3 mm can be corrected by a resectoscopic approach, whereas if it is < 3 mm, laparoscopic treatment is recommended.

A precise ultrasound follow-up has been carried out to refine the diagnostic timing for isthmocele.

We analyzed the diagnostic path of eight patients aged between 31 and 39, referred to our center who were subsequently diagnosed with isthmocele. Seven of our patients were diagnosed after the first cesarean section, while the remaining one was diagnosed after the second cesarean section.

All patients underwent multiple TVU examinations throughout the menstrual cycle, conducted by a single operator (EB) using Voluson E10 (General Electric, Boston, MA). Isthmocele perimeters and area were measured offline in both proliferative and secretive phases of the cycle by the same operator (EB) twice and intraobserver reliability was calculated using Pearson correlation coefficient. Ethical Committee Approval from our department was obtained in line with local law (committee: Comitato Etico Area Vasta Emilia Nord).

Comparing the uterine images of all patients through the different phases, the visualization of the isthmocele appeared clearer when the TVU was performed in the secretive phase of menstruation (Figure 1b), compared to the proliferative phase (Figure 1a). Vascularization was clearly detected in two of the total cases.

Both the mean perimeters (31 ± 5.2 vs 40.7 ± 58.2 , $P=0.003$) and the mean areas (47.9 ± 12 vs 79.8 ± 36.4 , $P=0.010$) were larger in the secretive phase (Figure 1c,d). The mean delta between the two phases was 16.9 ± 13.8 and 39.2 ± 34.4 for perimeter and area, respectively, with a mean percentage increase of $32\% \pm 17.4\%$ for the perimeter and $41.1\% \pm 21.5\%$ for the area.

Intraobserver reliability was high for all measurements, in particular for perimeters in proliferative ($r=0.8795$, $P=0.004$) and secretive ($r=0.9614$, $P<0.001$) phases and similarly for areas in proliferative ($r=0.09001$, $P=0.002$) and secretive ($r=0.9943$, $P<0.001$) phases.

During the secretive phase TVU revealed a more defined isthmocele in borders, echogenicity, perimeters and areas. In the second half of the menstrual cycle, the endometrium was uniformly echogenic

due to mucus and glycogen in the endometrial cells. Moreover, the endometrial thickness and the enhancement of echoes allowed a better visualization of a uterine niche facilitating the isthmocele evaluation. Three patients underwent hysteroscopic treatment of uterine isthmocele and subsequently obtained spontaneous pregnancy.

Isthmocele is usually detected and characterized by two-dimensional (2D)-TVU, which is the first-line imaging approach in this diagnosis. Two recent consensus Delphi on criteria and methodology for imaging and measurements of isthmoceles in non-pregnant and early pregnancy were produced.^{6,7} Only one study⁸ reported on timing of visualization of isthmocele and concluded that the best time is during the bleeding episode. However, in this study, all TVU were performed during the follicular phase of the cycle and no comparison with secretive phase was carried out. In this case series, ultrasound images were analyzed across the different stages of the menstrual cycle for visualization of the isthmocele. The measurements were reliable and the diagnosis of isthmocele was more evident during the secretive endometrial phase.

AUTHOR CONTRIBUTIONS

Emma Bertucci: Acquired data, designed and drafted the manuscript, critically reviewed the manuscript for important intellectual content, approved the final version to be published, and agreed to be responsible for all aspects of the work. Filomena Giulia Sileo, Maria Longo, Giulia Tarozzi, Martina Benuzzi and Antonio La Marca: Contributed to the design and draft of the manuscript. They also agree to be responsible for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

Research data are not shared.

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