IMAGING

The uterine junctional zone: a 3-dimensional ultrasound study of patients with endometriosis

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OBJECTIVE: The uterine junctional zone (JZ) alterations are correlated with adenomyosis. An accurate evaluation of the JZ may be obtained by 3-dimensional transvaginal sonography (TVS). The aim of the present prospective study was to assess the value of detectable alterations by 3-dimensional TVS of the JZ in patients with pelvic endometriosis (diagnosed by laparoscopy and histologic condition) and to compare these findings with those of women without pelvic endometriosis.

STUDY DESIGN: Eighty-two patients who were scheduled for laparoscopy had undergone previous surgery and 2- and 3-dimensional TVS. Uterine multiplanar sections that were obtained by 3-dimensional TVS were used to evaluate JZ features. During laparoscopy, an accurate staging of pelvic endometriosis was performed. JZ thickness and JZ alterations were correlated with stage of endometriosis.

RESULTS: Of the 82 patients, 59 patients had endometriosis at laparoscopy and histology. The maximum thickness of JZ in patients with endometriosis was significantly greater than in patients without endometriosis (6.5 $\pm$ 1.9 mm vs 4.8 $\pm$ 1.0 mm; $P < .001$). The features of JZ appeared similar at different stages, whereas they are statistically different if correlated with patients without endometriosis.

CONCLUSION: JZ thickness and its alterations are different in patients with endometriosis compared with those women without endometriosis and are not correlated with American Society of Reproductive Medicine staging methods. Because these JZ ultrasound features are associated mostly with adenomyosis, a correlation between endometriosis and JZ hyperplasia and adenomyosis could be hypothesized. Noninvasive evaluation of the JZ may be useful in the identification of those women who are affected by endometriosis also in early stage of the disease when there are no other sonographic signs of pelvic endometriosis.

Key words: 3-dimensional transvaginal sonography, adenomyosis, endometriosis, junctional zone

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The junctional zone (JZ), also known as the endometrial-myometrial junction or inner myometrium, is the transitional zone that is located between the endometrium and the outer myometrium. Unlike most human tissues with a mucosa, the endometrium does not contain a submucosal layer that usually exists to protect against mucosal invasion into adjacent tissue.[1,2]

It has been observed that, in the nonpregnant uterus, highly specialized contraction waves originate exclusively from the JZ and participate in the regulation of diverse reproductive events, such as sperm transport, embryo implantation, and hemostasis during menstruation.[3-6] Conversely, growing evidence suggests that disruption of the normal JZ architecture that is associated with hyperplasia (that seems to precede adenomyosis) and adenomyosis inevitably alters the coordinated peristaltic activity of the inner myometrium.[7-11]

The JZ thickness increases with age between 20 and 50 years.[12] Kunz et al[8] reported a gradual increase in diameter of the posterior JZ myometrium starting in the third decade of life, which is accelerated markedly in women >34 years old and found that the posterior JZ thickness was invariably higher in patients with endometriosis, yet the age-dependent increase paralleled that of women without endometriosis.

Dysfunctional and hyperperistalsis may affect sperm transport and implantation, which contributes to infertility.[6,8,13-15] They have also been linked to dysmenorrhea and menorrhagia and may play a role in the pathogenesis of endometriosis by facilitating retrograde menstruation and implantation of viable endometrial cells into the abdominal cavity.[6,16,17] Pelvic endometriosis,

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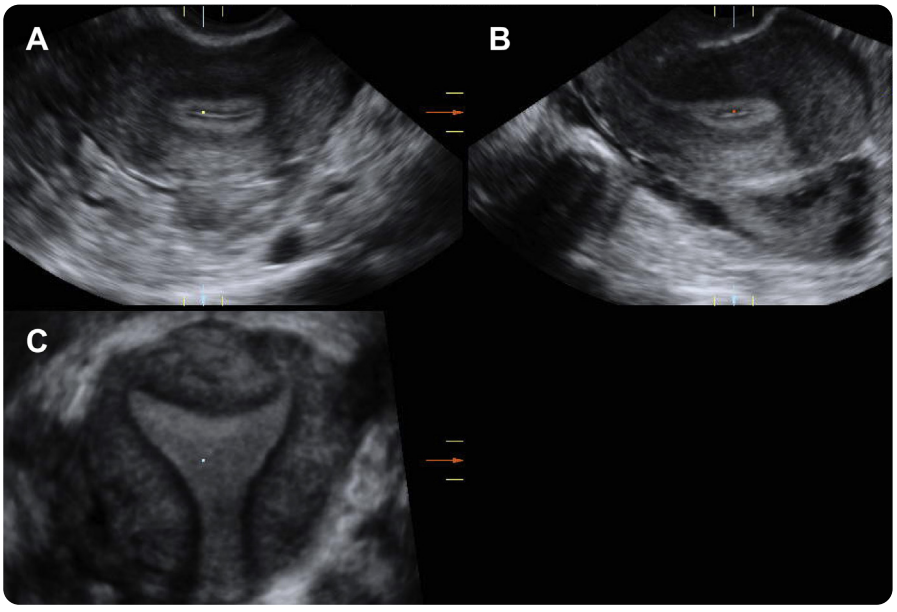
FIGURE 1
Three-dimensional multiplanar ultrasound imaging of a normal uterus



Multiplanar view of the uterus with the endometrium (hyperechoic in the center); the inner myometrium or junctional zone (hypoechoic halo around the endometrium); and the outer myometrium. **A,** longitudinal, **B,** transverse, and **C,** coronal section. Note the clearer view of the hypoechoic junctional zone on the coronal section.

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especially in severe stages, also is associated strongly with JZ thickening.[18-21] Therefore, the evaluation of JZ and its alterations by noninvasive imaging seems very important especially in patients with endometriosis.

Reinhold et al[22] demonstrated that a JZ thickness that measures >12 mm is highly predictive of adenomyosis and that an increased thickness of the posterior JZ of the uterus on magnetic resonance imaging (MRI) that is correlated with invasion of the basal endometrium into the inner myometrium has been proposed for the diagnosis of diffuse adenomyosis.[8,23,24]

It has been shown that 3-dimensional reconstruction of uterine anatomy in the coronal plane provides a new and different view of the JZ.[2,25-27]

With 3-dimensional transvaginal sonography (TVS) coronal and multiplanar views of the uterine cavity, it is possible to assess the lateral and fundal aspects of the JZ, which are impossible to see clearly on standard 2-dimensional imaging. We showed in a previous study that 3-dimensional TVS evaluation of JZ is more accurate than conventional 2-dimensional to detect adenomyosis.[26]

The aim of this prospective study was to assess the 3-dimensional TVS detectable uterine morphologic alterations of the JZ in patients affected by pelvic endometriosis that had been diagnosed by laparoscopy and histologic evaluation and to compare these findings with patients without pelvic endometriosis. Furthermore JZ 3-dimensional TVS features were correlated with the laparoscopic stage[28] of pelvic endometriosis.

Materials and Methods

Eighty-two premenopausal patients who were scheduled for laparoscopy in 2 university units (Gynecology Department, Ospedale Generale S. Giovanni Calibita 'Fatebenefratelli' Italy and Department of Obstetrics and Gynecology, University of Connecticut, New Britain, CT) from March 2010 to January 2012 were included in this prospective study.

Institutional review board approval for this study was obtained before study initiation in both University hospitals. Informed patient consent was not required because in all cases patients were submitted to TVS and because we did not discuss the subsequent medical or surgical treatment at the time of the TVS.

Inclusion criteria consisted of premenopausal women who had benign pelvic disease that was diagnosed by ultrasound imaging and required laparoscopy. Patients with clear signs of pelvic endometriosis (ie, endometriomas or deep nodules) were considered in this study. We included patients with suspected endometriosis, based on the presence of chronic pelvic pain and dysmenorrhea and without any TVS evidences of pelvic disease, who were scheduled to go to diagnostic laparoscopy. Exclusion criteria consisted of ongoing pregnancy, menopausal status, reproductive tract cancer, gonadotropin-releasing hormone analogue therapy, or any other hormonal. Patients with endometrial disease and polyps and with fibroid tumors that affected the JZ were excluded (ie, those patients with submucous fibroid tumors and with intramural fibroid tumors >3 cm). Hormonal therapies and fibroid tumors can affect measurement accuracy of JZ.

Of the 82 patients who were included in this study, 59 women had endometriosis; 22 women had ovarian endometriosis, and 28 women had posterior deep infiltrating endometriosis, which was associated to anterior bladder endometriosis in 1 case. Indications for laparoscopy were chronic pelvic pain or a suspected endometriosis at ultrasound examination (68 patients) and the presence of benign adnexal lesions (14 patients: 4 subserous leiomyomas, 7 dermoid cysts, 2 hydrosalpinxes, 1 mucinous cystadenoma).

All included patients underwent 2-dimensional, 3-dimensional, and power Doppler TVS examination during the secretory phase of the cycle within 2 months before surgery.

Ultrasound evaluation

Ultrasound imaging was performed an E8 or E6 ultrasound machine (GE Healthcare, Zipf, Austria).

A transvaginal scan of the pelvic organs was performed with a multifrequency 3-dimensional volume endovaginal probe (2.8-10 MHz).

During 2-dimensional TVS examination, an accurate evaluation and measurements of the pelvic organs were performed. In particular, the uterus, endometrium, and adnexa were evaluated for any abnormalities that were described accurately. The presence of myometrial lesions (myomas and signs of adenomyosis) was described and measured.

Finally, in the case of pelvic endometriosis, the extent of disease (ovaries, fallopian tubes, rectum, sigmoid, bladder, uterosacral ligaments, rectovaginal septum, vagina) was assessed by TVS.

Then 3-dimensional TVS was performed to acquire the volume of the uterus to obtain the coronal view. Two to 4 static volumes of the uterus in gray scale were obtained from the sagittal plane and from the transverse plane.

The sonographic volume acquisition technique was standardized according to the following criteria: frequency 6-9 MHz, magnification of the uterus up to one-half of the screen; sweep angle of 120 degrees; sweep velocity adjusted from medium to maximum quality; and 3-dimensional box size exceeding the uterus by 1 cm on each side.

The coronal view reconstruction technique was standardized according to the following criteria: straight or curved line (omni-view or rendering mode) along the endometrial stripe on the sagittal and transverse view (Figure 1); the multiplanar view was manipulated until a satisfactory coronal view image was obtained of the uterine external profile and the cavity with the visualization bilaterally of the interstitial portion of the fallopian tube; volume contrast imaging (VCI) was applied on a multiplanar view at 2- to 4-mm slice thickness with volume rendering mixed light surface and gradient light. After acquisitions, ultrasound volumes were stored on the hard drive of the machine and subsequently retrieved for offline analysis.

On the coronal view, the JZ appeared as a hypoechoic zone around the endometrium; with VCI modality with 2- to 4-mm slices, it was possible to view it clearly in all planes of the multiplanar view (Figure 1). Disruption and infiltration of the hypoechoic JZ by means of the hyperechoic endometrial tissues was described, and JZ thickness was measured as the diameter from the basal endometrium to the internal layer of the outer myometrium (Figures 2 and 3).

On the multiplanar planes with VCI modality we evaluated (1) the minimal thickness of the JZ (JZmin); the maximal JZ thickness (JZmax); the maximal myometrium thickness at the side of JZmax, and the presence of alterations in the JZ.

These sonographic features obtained on 3-dimensional multiplanar view and VCI modality were defined in the following manner[26]: JZmax and JZmin diameter as the greatest and lowest thickness measured of the JZ, on coronal section or longitudinal section at any level of the uterus (fundus, anterior, posterior, and lateral walls); maximal myometrium thickness as the diameter from the basal endometrium to uterine serosa that was measured at the same level of JZmax thickness; alteration of the JZ as distortion and infiltration of the hypoechoic inner myometrium by hyperechoic endometrial tissue or ill-defined JZ[26] (Figures 3 and 4).

FIGURE 2
Three-dimensional ultrasound imaging of a normal uterus in the coronal plane

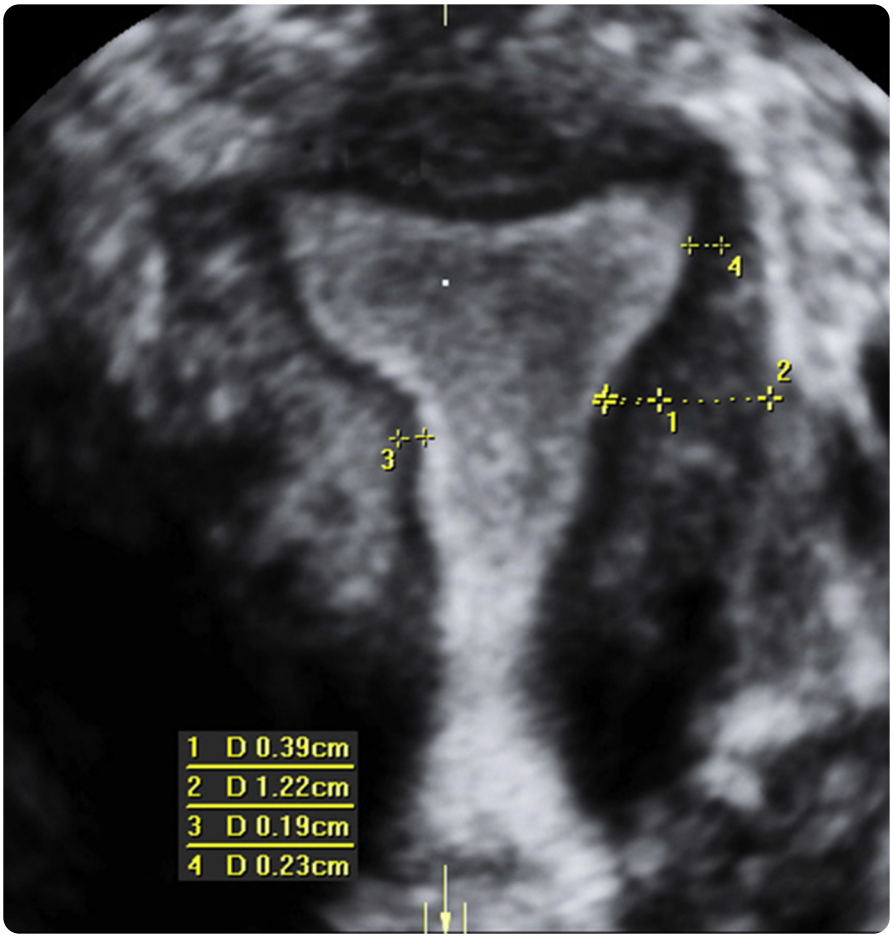

Image shows the measurements of maximum (*caliper 1*) and minimum (*caliper 3* and *4*) thickness of junctional zone and the myometrial thickness (*caliper 2*).

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FIGURE 3
Three-dimensional ultrasound imaging of a uterus in the coronal plane

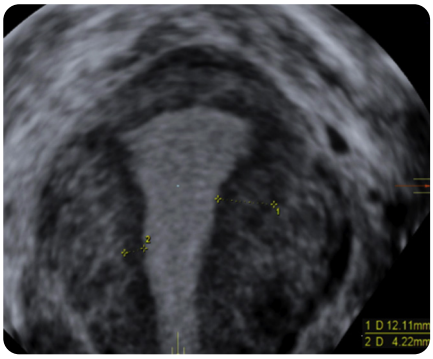

Image shows the measurements of maximum (*caliper 1*) and minimum (*caliper 2*) thickness of junctional zone. Note that the junctional zone appears thicker at the lateral wall (maximal diameter, >12mm).

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JZmax/total myometrial maximum thickness and JZmax−JZmin (JZ difference) were calculated. We considered the difference between maximum and minimum JZ thickness because it is less influenced by age and menstrual cycle.[24]

JZ measurements were performed only on 3-dimensional multiplanar view and VCI modality, which allows a clear visualization of the JZ.

All the scans were performed by 2 expert sonographers (C.E. and D.L.) with >10 years practice. Two-dimensional and 3-dimensional ultrasound evaluations were performed during the same examination period and by the same operator. No intra- and inter-observer variability was tested in this study. Ultrasound digital and photographic images were saved and stored on a USB drive for subsequent retrieval.

FIGURE 4
Three-dimensional ultrasound imaging in the coronal plane

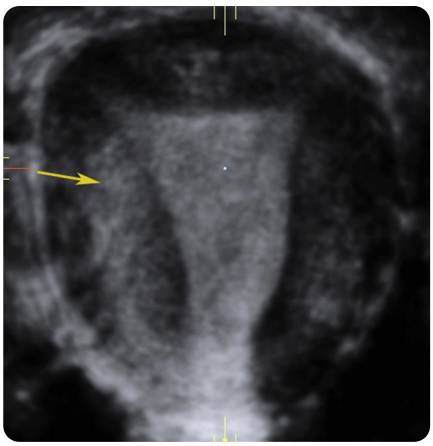

Image shows an alteration of the junctional zone that appears infiltrated laterally (*arrow*); moreover, the uterine cavity is distorted with asymmetric myometrial walls.

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Laparoscopy

All the patients underwent laparoscopy in a manner appropriate for their clinical condition.

Laparoscopy was performed with a 10-mm laparoscope a 0 degrees (Karl Storz, Tuttlingen, Germany) that was introduced through an umbilical incision- two 5-mm trocars were introduced suprapubically as accessory instruments. As a first step, the pelvis, abdomen, and external surface of the ovary were inspected for possible evidence of endometriotic lesions. All suspected endometriotic lesions were removed and sent for histologic evaluation. Diagnosis of endometriosis was based on visualization and radical resection of all tissues with endometriotic involvement followed by histologic confirmation. In the presence of pelvic endometriosis, the disease was staged according to the American Society of Reproductive Medicine classification method.[28] If necessary, adhesiolysis was performed. When present, superficial endometriosis was treated with bipolar coagulation. Endometriotic cysts were removed with a stripping technique. Deep endometriosis was removed, if necessary, according to patients' symptoms. In infertile patients, chromopertubation was performed. Hemostasis was achieved by bipolar coagulation.

Statistical analysis

After laparoscopy and histologic evaluation, the patients were divided into groups as patients with and without endometriosis (Table 1). In patients with pelvic endometriosis, JZ findings were compared with the findings of those patients without endometriosis.

Descriptive analysis was achieved with proportions.

Statistical analysis was performed with the use of the Student t test for mean and SD.

Proportions were compared with the use of the χ^2 test or Fisher exact test, as appropriate. A probability value of $< .05$ was considered statistically significant.

Results

The mean age (± SD) of all the 82 patients who were included in this study was 33.9 ± 4.6 years (range, 20−42 years); the mean parity was 0.54 ± 1.3 (median, 0; range, 0−4), and the mean gravidity was 0.83 ± 1.2 (median, 0; range, 0−5). Of all 82 patients, 59 women had pelvic endometriosis at laparoscopy and histologic evaluation; test results for 23 women did not show endometriosis.

We did not observe statistically significant differences in the mean age in the 2 groups that were considered in this study; mean parity and gravidity were also not significantly different in patients with and without endometriosis (Table 1).

With analysis of the different features of the JZ, the patients with endometriosis showed a clear difference in the features of JZ in contrast to the patients without endometriosis (Table 2); only the mean JZmin thickness was not different.

No significant difference in mean age was observed among patients in different endometriosis stages and in those without endometriosis. We have to underline that, in our group of patients, the mean age was 33.9 ± 4.6 years, which means that it probably could be different in another age study group (Table 3). The features of JZ appeared similar at different American Society of Reproductive Medicine stages, whereas they are statistically different when correlated with patients without endometriosis. In fact, there was an increased thickness of the JZ in patients with mild-to-minimum endometriosis (stage 1-2) and also in an advanced stage (stage 4) when compared with women without

endometriosis (Table 3). JZmax thickness seems to be the most significant parameter to differentiate stage 1-2 (difficult to diagnose by ultrasound imaging) from patients without endometriosis. JZ infiltration and ratio between JZmax and myometrial thickness seems to be important features in case of advanced disease.

COMMENT

The JZ, if altered, is correlated with adenomyosis and seems to be involved in the process that determines pelvic endometriosis.[17,19,21,29-31] The aim of our study was to evaluate the JZ ultrasound features in patients with endometriosis. We tried to detect a correlation between endometriosis and adenomyosis in the case of JZ modifications.

The present study showed, in patients with endometriosis, a significantly higher JZ thickening and higher percentage of alterations compared with those without endometriosis. In a previous article, we showed that these 3-dimensional ultrasound JZ alterations are associated with adenomyosis.[26] These study results demonstrated an association of uterine adenomyosis and pelvic endometriosis. Structural and functional characteristics of the endometrium and myometrial JZ in women with adenomyosis and endometriosis provide increasing evidence that they frequently are associated; both are characterized by an aberrant function of the JZ and may be an important factor of infertility.

Tocci et al[32] have proposed that the "endometrial-subendometrial myometrium unit (or JZ) disruption disease" should be considered to be a new entity that is distinguished from adenomyosis. This condition is expressed mainly by a pathologic thickening or abnormality of the JZ. Other studies suggest that smooth muscle proliferation and hyperplasia in the JZ may precede the outgrowth of endometrial cells and adenomyosis.[1,33-35] The term *JZ hyperplasia* was coined to define partial or diffuse thickening of the JZ; it does not necessarily indicate the presence of adenomyosis but that disruption of JZ architecture may constitute the primary event in the development of adenomyosis and infertility by altering uterus peristalsis.[6,35-37]

It seems that endometriosis, JZ abnormalities, and adenomyosis could represent phenotypes of a similar endomyometrial dysfunction syndrome rather than different diseases. The histologic diagnosis of endometriosis is based on a simple biopsy specimen that is obtained at the time of laparoscopy or laparotomy, although the diagnosis of adenomyosis traditionally has required a specimen after

TABLE 1
Study population characteristics of 82 patients with and without endometriosis

Variable	Endometriosis	
	Yes (59 patients)	No (23 patients)
Age, y[a]	34.2 ± 4.4[b]	33.3 ± 5.3
Parity[a]	0.4 ± 0.9[b]	0.8 ± 1.2
Gravidity[a]	0.7 ± 1.2[b]	1.0 ± 1.3
American Society of Reproductive Medicine staging method,[28] n (%)[c]		
Stage 1-2	13 (22.0)	
Stage 3	15 (25.4)	
Stage 4	31 (52.5)	
Endometrioma, n (%)[c]	22 (37.3)	
Deep infiltrating endometriosis, n (%)[c]	28 (47.5)	

[a] Data are given as mean ± SD; [b] P = no significant difference; [c] $P < .05$.

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TABLE 2
Three-dimensional TVS features of the JZ in patients with and without endometriosis

Variable	Endometriosis	
	Yes (59 patients)	No (23 patients)
Age, y[a]	34.2 ± 4.4	33.3 ± 5.3
Three-dimensional TVS of the JZ		
Maximum thickness, mm[a]	6.5 ± 1.9[b]	4.8 ± 1.0
Minimum thickness, mm[a]	2.6 ± 0.7	2.3 ± 0.5
Maximum − minimum mm[a]	3.9 ± 1.8[b]	2.5 ± 0.9
Maximum/myometrium thickness, %[a]	37.3 ± 10.5[b]	29.5 ± 5.6
Infiltration, n (%)	23 (38.9)[b]	4.4 (1)
Maximum ≥6 mm, n (%)	38 (64.4)[b]	26.1 (6)
Maximum − minimum ≥4 mm, n (%)	31 (38.2)[b]	17.4 (4)
Maximum/myometrium percentage ≥50%, n (%)	11 (18.6)[b]	0

JZ, junctional zone; *TVS*, transvaginal sonography.

[a] Data are given as mean ± SD; [b] $P < .05$.

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TABLE 3
Three-dimensional TVS features of the JZ in patients with endometriosis, according to stage

Variable	Endometriosis, according to American Society of Reproductive Medicine stage			No endometriosis (23 patients)
	1-2 (13 patients)	3 (15 patients)	4 (31 patients)	
Age, y[a]	34.2 ± 4.2	32.5 ± 5.2	34.3 ± 4.3	33.3 ± 5.4
Three-dimensional TVS of the JZ				
Maximum thickness, mm[a]	5.9 ± 1.8	6.8 ± 2.5	6.5 ± 1.8	4.8 ± 1.0[b]
Minimum thickness, mm[a]	2.3 ± 0.7	2.6 ± 0.8	2.6 ± 0.6	2.3 ± 0.5
Maximum − minimum, mm[a]	3.5 ± 1.2	4.4 ± 2.7	3.7 ± 1.3	2.5 ± 0.9[b]
Maximum/myometrium thickness, %[a]	33.9 ± 9.5	37.8 ± 10.2	38.3 ± 11.5	29.5 ± 5.6[b]
Infiltration, n (%)	3 (23.1)	6 (40.0)	14 (45.2)	1 (4.4)[b]
Maximum ≥6 mm, n (%)	9 (69.2)	10 (66.7)	19 (61.3)	6 (26.1)[b]
Maximum − minimum ≥4 mm, n (%)	8 (61.5)	8 (53.3)	15 (48.4)	4 (17.4)[b]
Maximum/myometrium percentage ≥50%, n (%)	1 (7.7)	3 (20.0)	7 (22.5)	0

JZ, junctional zone; *TVS*; transvaginal sonography.

[a] Data are given as mean ± SD; [b] $P < .05$, no endometriosis vs all American Society of Reproductive Medicine stages.[28]

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an hysterectomy.[10] From a clinical point of view, endometriosis is diagnosed possibly even in its early stage in younger women, because of the diagnostic/operative laparoscopy carried out in infertile/pain patients. Adenomyosis is a late histologic diagnosis that is obtained in older women who have submitted to hysterectomy because their symptoms of heavy menstrual bleeding and/or pain and can be suspected in young patients by imaging (TVS; MRI). Consequently, there is still a need of an earlier diagnosis of adenomyosis and JZ abnormalities. Three-dimensional TVS represents an accurate diagnostic tool that can easily and repeatedly be performed in young patients to evaluate JZ features.

When comparing different stages of pelvic endometriosis, we observed that there are no significant differences in terms of JZ thickening between lower and advanced stages. These results are in contradiction with the paper of Larsen et al,[21] who studied patients with endometriosis by means of MRI and showed that JZ-difference (JZmax − JZmin) was higher in women with American Fertility Society stage IV, compared with stages I-III. However, also in the study by Larsen et al, JZmax is not statistically different in the 4 American Fertility Society stages, which is similar to our findings. Larsen et al also observed, in presence of rectovaginal endometriosis, that the JZ depth infiltration is not correlated with extension and infiltration of the disease. Nevertheless, he showed also a clear correlation of JZ alterations to endometriosis and adenomyosis.[21]

Also, our results suggest that endometriosis and JZ alterations could be part (cause or effect) of the same disease. It is difficult, however, to demonstrate whether JZ thickening could be the first injury and the cause of endometriosis, as some studies suggest.[6,17]

JZ alteration in a minimal stage of endometriosis, at which time ultrasound imaging does not reveal particular features of the disease, could be a sign to diagnose minimal endometriosis, which at present is difficult to diagnose by ultrasound imaging. We can conclude that 3-dimensional TVS may be useful in the identification of those women who are affected by minimal and mild endometriosis when there are no other sonographic signs of the disease.

Finally although the link between endometriosis, JZ hyperplasia, and adenomyosis has been puzzling, the role of the myometrial JZ appears to be associated with several pathologically and clinically recognizable features. Therefore, the presence of endometriosis, JZ alterations, or adenomyosis should alert the physician to the possible presence of disease. Although the reason that they occur together has not yet been discovered, they could create a set of reproductive and obstetric disorders.[10] As a consequence, these features can justify the introduction of an accurate 3-dimensional evaluation of the JZ in patients with pelvic endometriosis, infertility, or chronic pelvic pain. ■

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