

Could the uterine junctional zone be used to identify early-stage endometriosis in women?

“An accurate evaluation of junctional zone and its potential modifications can provide important information for patients with endometriosis and/or infertility or chronic pelvic pain.”

Keywords: junctional zone • stage I–II endometriosis • transvaginal sonography

Although the correlation between endometriosis, junctional zone (JZ) hyperplasia and adenomyosis is still debated, the correlation among JZ and different etiological and clinical aspects is, today, well recognized. Starting from that, clinicians must consider in their own practice all the potential modifications of the JZ because the described could be correlated with reproductive or obstetrics disorders [1]. The accurate and analytical evaluation, case by case, of the JZ is one of the most crucial points in the flowchart of infertile patients and also endometriotic patients. An accurate evaluation of JZ and its potential modifications can provide important information for patients with endometriosis and/or infertility or chronic pelvic pain. We know that adenomyosis is a common gynecologic disease characterized by the migration of endometrial glands and stroma from the basal layer of endometrium into the myometrium, and could be associated with smooth muscle hyperplasia.

The first author that mentioned adenomyosis and its histopathological features was Rokitansky in 1860 describing the invasion of stroma and endometrial glands inside the myometrium with different levels of invasion up to the serosa [2].

A common pathogenesis for adenomyosis and endometriosis has been hypothesized, and it is argued that endometrial stroma being in direct contact with the underlying myometrium allows communication and

interaction, thus facilitating endometrial invagination or invasion of a structurally weakened myometrium during periods of regeneration, healing and re-epithelization. Dislocation of basal endometrium may also result in endometriosis through retrograde menstruation [3]. Pelvic endometriosis and uterine adenomyosis are variants of the same disease, which involves the dislocation of basal endometrium and results from a dysfunction and disease primarily at the level of the JZ [4]. Pelvic endometriosis, especially in its severe stages, is also strongly associated with JZ thickening [5–8]. Therefore, the evaluation of JZ and its alterations by noninvasive imaging are very important, especially in patients with endometriosis.

Adenomyosis is also defined as the chronic disruption of the boundary between the basal layer of the endometrium and the myometrium, known as the JZ, with the hallmark pathologic finding of endometrial glands and stroma within the myometrium [9].

Both parts of the JZ (endometrium and subendometrial myometrium) have a common embryological origin from the paramesonephric ducts and show cyclical changes during the menstrual cycle, whereas the outer myometrium is of nonparamesonephric mesenchymal origin [10]. The etiology of adenomyosis is not known, but there are recent interesting theories that consider adenomyosis as an expression of pathological endomyometrial JZ, trying to explain, in this



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way, the association of adenomyosis with subfertility and endometriosis.

Even if in many cases adenomyosis appears to be asymptomatic, the most common referred symptoms are dysmenorrhea and abnormal uterine bleeding. The gold standard in diagnosing adenomyosis was, and in some cases still is, histological. The first description of the JZ came, as endomyometrial interface, from MRI [11]. It is also called archimyometrium or inner myometrium on high-resolution transvaginal sonography (TVS), the JZ is often visualized as a subendometrial hypochoic 'halo'.

Growing evidence suggests that the normal JZ architecture associated with hyperplasia may modify the coordinated peristaltic activity of the inner myometrium [1,12].

Retrograde menstruation appears to be potentially responsible for endometriosis and some symptoms, frequently observed in women with adenomyosis, such as dysmenorrhea and/or menorrhagia, could facilitate the process of peritoneal implantation of endometrial cells [13,14]. Another important clinical point is the association of modifications of the JZ and severe endometriosis [4,15]. Other studies underlined the correlation among disruption or modification of the JZ and some fertility or obstetrical complications [9,11]. TVS and MRI are the two consolidated imaging techniques accepted worldwide in the diagnostic process for endometriosis.

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MRI criteria for the diagnosis of adenomyosis include thickening ≥ 12 mm of the JZ, a ratio of $JZ_{max}/total\ myometrium > 40\%$, and a 5 mm difference between the JZ maximum and minimum thickness ($JZ_{max} - JZ_{min}$) [16]. The most accurate criteria seem to be the difference (JZ_{diff}) between JZ_{max} and JZ_{min} thickness, and abnormal JZ thickness is controversial. Other authors propose that JZ thickness ≥ 8 mm due to stromal gland hyperplasia should be considered suggestive of adenomyosis [16,17]. MRI can help in diagnosing adenomyosis with some particular features obtained on T2-weighted images. Modifications such as hyperplasia or hypertrophy of myocytes are detected as diffuse or focal thickening of JZ. Also the intensity of the signal in the JZ may be interpreted as a localization of heterotopic tissue.

The advent of 3D transvaginal sonography (3D TVS) offers an opportunity for increased visibility of the JZ, which previously was best visualized with MRI. 3D TVS evaluation of JZ is more accurate than conventional 2D TVS for detection of adenomyosis. The 3D TVS markers $JZ_{diff} \geq 4$ mm was the most accurate (85%) in diagnosing adenomyosis; JZ infiltration had the highest sensitivity (88%). Total accuracy for 3D TVS in the diagnosis of adenomyosis was 89%, similar to the accuracy reported in MRI studies [18,19].

The enhancement in diagnosing adenomyosis is strictly related to the views coming from the so-called coronal plane. It appears clearly at the 3D evaluation and it gives the chance to detect and diagnose all the physiological and pathological aspects of the JZ. To date, the 2D scan does not obtain the same level of accuracy in detecting some particular aspects, such as the fundal or lateral views of the JZ. These results have been demonstrated by comparing 3D features with the histological specimens taken from hysterectomies. Exacoustos *et al.*, demonstrated that $JZ_{max} \geq 8$ mm and $JZ_{diff} \geq 4$ mm were significantly associated with adenomyosis, more than other 2D aspects [18].

In the vast majority of cases, all the modifications of the JZ are related to the presence of adenomyosis. With ultrasound sonography we can detect adenomyosis as a multifaceted pathology. It can appear as a diffuse lesion or a focal lesion as well as it can determine the alterations of the JZ [18].

All these features and the protrusion of the endometrium inside the myometrium may be strictly related to the contemporary presence of an endometriosis at its early stage.

The JZ, if altered, is correlated to adenomyosis, and seems to be involved in the process that determines pelvic endometriosis [4,5,13].

Exacoustos *et al.* demonstrated in patients with endometriosis a significantly higher JZ thickening and higher percentage of alterations compared with those without endometriosis. In a previous article, they showed that these 3D ultrasound JZ alterations are associated with adenomyosis [18]. 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 [15]. Also, their 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 [20].

Conclusion

Minimal and mild stages of endometriosis are often associated with JZ alterations, this could be considered a useful indirect sign to make a minimally invasive diagnosis of the disease. Today we do not have enough data to demonstrate the strict correlation among the JZ modifications and the presence of endometriosis (stage 1 or 2 American Society of Reproductive Medicine [ASRM]) but the important role endometriosis plays in infertility and pain suggests we need to find, as soon as possible, a noninvasive, earlier diagnostic trial when there are no other sonographic signs of pelvic endome-

triosis, in order to anticipate the potential progression of the disease and to limit the related damage.

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