# Long term tamoxifen treatment in breast cancer patients and imaging signs of adenomyosis

Silvia Gabbrielli<sup>1</sup>, Dilruba Tureli<sup>2,4</sup>, Icro Meattini<sup>3</sup>, Silvia Vannuccini<sup>4</sup>, Angela Gallone<sup>4</sup>, Kubra Ozpinar<sup>4,5</sup>, Milo Giani<sup>4</sup>, Massimiliano Fambrini<sup>4</sup>, Vittorio Miele<sup>1</sup> and Felice Petraglia<sup>4</sup>

<sup>1</sup> Department of Radiology, Careggi University Hospital, Florence Italy

<sup>3</sup> Department of Experimental and Clinical Biomedical Sciences M. Serio, Radiation Oncology Unit, University of Florence, Florence, Italy

<sup>4</sup> Department of Experimental and Clinical Biomedical Sciences, Obstetrics and Gynecology, University of Florence, Florence, Italy

<sup>5</sup> Department of Obstetrics and Gynecology, University of Health Sciences Turkey, Gulhane Training and Research Hospital, Ankara, Turkey

# ABSTRACT

**Background and aim:** Adenomyosis is a uterine disease defined by the presence and growth of endometrial or endometrial-like structures within the myometrium. Imaging, including transvaginal ultrasound (TVUS), or magnetic resonance (MRI), is used to non-invasively diagnose adenomyosis. The condition is normally identified in reproductive life, but it can also be detected in postmenopausal women. Due to the fact that tamoxifen treatment is usually prolonged in breast cancer (BC) patients as an adjuvant endocrine therapy, and considering the association between tamoxifen and the increased incidence of endometrial pathologies, the present study investigated the possible association between tamoxifen treatment and with imaging signs (TVUS and MRI) of adenomyosis.

**Methods:** The study group consisted of BC patients (*n*=25) without clinical or imaging signs of uterine disorders prior to the tamoxifen treatment. Patients were followed up for a period of 6 to 60 months during which TVUS was performed for the evaluation of endometrial thickness and, because of the identification of abnormal uterine imaging findings, an MRI examination was also performed.

**Results:** During follow up, TVUS evidenced diffuse (40%) or internal cystic (32%) adenomyosis, which was confirmed by MRI, with some difference in the phenotype, showing mainly internal cystic adenomyosis (80%).

**Conclusions:** The present data suggests that in some BC patients undergoing tamoxifen treatment, imaging follow-up with TVUS showing abnormal uterine findings further assessed by MRI may be useful in identifying adenomyosis.

#### **KEYWORDS**

Adenomyosis, imaging, tamoxifen, transvaginal ultrasound, magnetic resonance.

# Introduction

Adenomyosis is a pathologic condition defined by the presence and growth of endometrial or endometrial-like structures within the myometrium <sup>[1]</sup>. The advent of imaging modalities, such as magnetic resonance imaging (MRI) and transvaginal ultrasound (TVUS), has led clinicians and researchers to realize that adenomyosis is not exclusively a pathology of multiparous and elderly women <sup>[2]</sup>. The prevalence of adenomyosis may vary from 5% and 70% (mean 20%–30%), basically due to the complexity of the diagnostic process <sup>[3]</sup>. Additionally, adenomyosis has been reported to have a prevalence of 2-4% in postmenopausal women <sup>[4]</sup>.

Adenomyosis lesions originate from the basal layer of the endometrium that invaginates into the weakened junctional zone, as a result of tissue trauma or a predisposition of the myometrium, thus enabling endometrial tissue to migrate <sup>[1]</sup>. Upon diagnostic imaging, adenomyosis displays an enlarged uterine corpus with a globular configuration, with diffuse endometrial infiltrates which may predominate in one uterine wall or as focal nodules. Due to myometrial hyperplasia and hypertrophy in adenomyosis, the myometrium vascularity is generally increased <sup>[3]</sup>.

# Article history

Received 13 Nov 2024 - Accepted 16 Jan 2025

#### Contact

Felice Petraglia, MD; felice.petraglia@unifi.it Department of Experimental and Clinical Biomedical Sciences University of Florence, Obstetrics and Gynecology Careggi University Hospital Florence, Italy

#### DOI 10.53260/EG0.257015

Estrogen is essential for the establishment and growth of the ectopic endometrium outside the uterine cavity. Increased estrogen receptors (ERs) and/or a decrease of progesterone receptors (PRs), along with modulation of the immune system, likely contribute to the development and growth of adenomyosis lesions <sup>[5,6]</sup>. Tamoxifen, a selective estrogen receptor modulator (SERM), acting as an agonist to ERs in the uterus, induces adenomyosis in mice <sup>[7]</sup>. Furthermore, in a group of postmenopausal patients with BC who underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy after tamoxifen treatment a higher incidence of adenomyosis was observed compared to controls <sup>[8]</sup>.



<sup>&</sup>lt;sup>2</sup> Department of Obstetrics and Gynecology, Istanbul University Faculty of Medicine, Istanbul, Turkey

Tamoxifen is used as an adjuvant endocrine therapy for BC patients, being effective in reducing recurrence and increasing survival of ER-positive BC patients. Long term tamoxifen therapy (5-10 years) is associated with low recurrence and mortality rate <sup>[9]</sup>. Due to the hormonal stimulation of endometrial tissue, individuals undergoing tamoxifen treatment for BC may face an increased risk of developing endometrial pathologies, such as endometrial polyps or endometrial cancer; thus, clinical and imaging surveillance is commonly suggested <sup>[8,9]</sup>. Due to the possible contribution of adenomyosis to the development of endometrial polyps or endometrial is needed. Adenomyosis is detected in postmenopausal women by TVUS and MRI, showing similar molecular characteristics compared to reproductive age women <sup>[11]</sup>.

The present study investigated the effect of long term treatment with tamoxifen in BC patients on the appearance of newly developed adenomyosis diagnosed by imaging methods.

# Methods

## **Subjects**

The study group consisted of BC patients (n=25) aged between 40 and 76 years (mean 51.9 ± 8.11 years). The inclusion criteria were: treatment with tamoxifen for a period of at least 6 months and TVUS for the evaluation of endometrial thickness with abnormal uterine imaging findings, further assessed with MRI. Anamnestic data (body mass index [BMI] 27. ± 6.6 kg/m<sup>2</sup>), the presence of comorbidities and imaging findings were collected. All patients included in study had a TVUS before starting the tamoxifen treatment demonstrating no signs of adenomyosis.

Pelvic assessment was performed by 2D/3D TVUS (Toshiba Aplio 400), using the standardized Morphological Uterus Sonographic Assessment (MUSA) group terminology <sup>[3,13]</sup> to describe the sonographic features of adenomyosis. The diagnosis was based on the presence of direct signs: myometrial cysts, hyperechogenic islands, or subendometrial lines or buds. Additionally, indirect indicators were also assessed such as globular uterus, asymmetrical myometrial thickening, fan-shaped shadowing, translesional vascularity, irregular junctional zone (JZ), or interrupted JZ at 3D ultrasound <sup>[3,12]</sup>.

The MRI (Siemens Aera 1.5T) evaluation was performed in the group of 25 patients, according to the European Society of Urogenital Radiology ESUR guidelines [13] and included: turbo spin-echo (TSE) T2-weighted sequences on sagittal, coronal and axial planes, and T1 and T1 FS (fat-saturated)-weighted sequences. Contrast-enhanced T1 FS sequences (VIBE) were used in case of T2-weighted atypical features or in case of contemporary presence of other pelvic lesions, such as polyps or ovarian cysts. Diffusion-weighted imaging (DWI), allowing the mapping of the diffusion process of molecules, was used to differentiate adenomyosis from endometrial and myometrial cancer. Other direct and indirect signs typical of adenomyosis by MRI were also considered. These other considered features, which often overlap with those viewable with TVUS, were asymmetrical myometrial thickening, globular uterus, and diffuse or focal phenotype <sup>[13,14]</sup>.

# Results

During the course of follow up among the group of selected patients that used tamoxifen, the TVUS examination evidenced the appearance of signs of adenomyosisas follows: diffuse adenomyosis in 10 (40%); cystic adenomyosis in 17 (68%); adenomyoma in 7 (28%); thickened JZ in 5 (20%); subendometrial lines and buds in 16 (64%); fan-shaped shadowing in 2 (8%), and myometrial echogenic islands in 14 (56%) (Figure 1).

Adenomyosis was confirmed after MRI examination, with more details including: globular uterus in 1 (4%); asymmetric uterine walls thickness in 2 (8%); thickened JZ in 21 (84%). Adenomyosis was diagnosed in 24 (96%): diffuse adenomyosis in 10 (40%); cystic adenomyosis in 23 (92%); adenomyomas in 6 (25%) (Figure 2). Other associated pathologies were uterine fibroids, endometrial polyps and/or hyperplasia.

**Figure 1.** Transvaginal two-dimensional ultrasound images of a uterus affected by adenomyosis depicting lines and buds, myometrial cysts, JZ thickening.



## **Discussion**

The present study showed the appearance of signs of adenomyosis in BC patients treated with tamoxifen through imaging techniques (TVUS and MRI). Endometrial changes may occur during tamoxifen treatment among BC patients <sup>[9,15]</sup>. TVUS and MRI showed the same percentage of diffuse adenomyosis (40%), but more details were observed upon MRI: more cases of cystic adenomyosis and thickened JZ.

Indeed, TVUS has a good sensitivity and specificity when evaluating adenomyosis, corresponding to 64%-72% and 81%-84% respectively, when at least one or two sonographic criteria are present <sup>[16,17]</sup>. TVUS represents a minimally invasive, easily accessible, and inexpensive examination; however, the most important limitations are the operator-dependence in terms of the definition of adenomyosis type and JZ thickness, along with the contemporary presence of other uterine conditions that make more difficult to well define adenomyosis features.

The JZ is the same structure evaluated by TVUS, MRI and histology. The morphometric measurements of the low-signal-intensity band in MRI corresponds to the area composed of dense smooth-muscle fibers in the inner myometrium on histopathological slides <sup>[18,20]</sup>.

**Figure 2.** MRI features of adenomyosis. Sagittal (left) and Coronal (right) TSE T2w: Internal adenomyosis with diffuse pattern, endometrium rim thickened, tiny cysts with high intensity signal in TSE T2w images surrounded by a rim of low signal intensity in T2w corresponding to a layer of stroma and hypertrophic myometrium.



Modern imaging techniques allow the non-invasive diagnosis of adenomyosis and MRI has a central role thanks to its high diagnostic accuracy in the detection of both adenomyosis and uterine disorders. By MRI it is possible to identify the main direct (cystic component) and indirect (JZ features) signs of adenomyosis and discriminate the composition and location of various adenomyotic features<sup>[13]</sup>.

A standardized MRI protocol for the evaluation of adenomyosis, beyond endometriosis, has been developed. This protocol allows a proper interpretation of MRI images, minimizing possible pitfalls, such as focal JZ thickening due to transient uterine contraction, or such as the "pseudoenlargement of the endometrium" sign, represented by hyperintense linear striations radiating from the endometrium to the myometrium <sup>[13]</sup>.

MRI is considered the most reliable technique for endometriosis, with higher sensitivity (77%) and specificity (89%) and a lower operator dependence compared to TVUS. MRI shows elevated soft-tissue differentiation, also allowing the detection of uterine fibroids or endometriosis, the differentiation between various subtypes of adenomyosis, and the evaluation of surrounding pelvic structures, along with an improved identification of the JZ layer <sup>[6,14,20]</sup>. Our study confirmed the higher ability of MRI than TVUS in evaluating JZ thickness, thanks to its high contrast resolution.

In conclusion, the present study suggests that in some BC patients undergoing long term tamoxifen treatment, imaging follow-up with TVUS showing abnormal uterine findings further assessed by MRI may be useful in identifying adenomyosis.

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**Declaration of Interest** The authors report no conflict of interest.