Endometrial surveillance in tamoxifen users: role, timing and accuracy of hysteroscopic investigation: observational longitudinal cohort study

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Abstract

To determine the role, timing and indications for endometrial hysteroscopic investigation in relation to the clinical, ultrasound and histological features of the endometrium during tamoxifen (TAM) use. We performed an observational longitudinal cohort study (years 2007–2012) that investigated the endometria of 151 TAM users with hysteroscopy and histology. For all patients, gynaecological history, years of adjuvant treatment, ultrasound endometrial thickness measurement and indications for hysteroscopy were recorded. Hysteroscopic findings showed that 100% of patients referred for simple follow-up had no evidence of endometrial disease. We found a strong correlation between previous history of abnormal uterine bleeding (with or without endometrial thickening) and hysteroscopic suspicion of endometrial atypia that was confirmed by histology. Hysteroscopy had 83.3% sensitivity, 99% specificity, 83.3% positive predictive value (PPV) and 99% negative predictive value (NPV) in detecting endometrial atypia. No significant correlation was found between endometrial thickening to < 5 mm without bleeding and histological atypia. Similarly, the duration of treatment was not related to endometrial thickening and histological atypia. Endometrial stromal hyperplasia was detected by histology in 70.5% of patients with endometrial thickness measurements ranging from 5 to 10 mm. In contrast, no atypia was detected when endometrial thickness was < 5 mm. Ultrasound performed using a 5-mm cut-off threshold for endometrial thickness resulted in 100% sensitivity, 15% specificity, 4% PPV and 100% NPV in detecting endometrial atypia, while a 10-mm cut-off threshold resulted in 84% sensitivity, 69% specificity, 10% PPV and 99% NPV. Low-risk TAM users do not require different endometrial surveillance than the general population. Hysteroscopy could play a fundamental role in determining the endometrial status of patients before the initiation of TAM treatment and in assessing the endometrial status of patients when bleeding occurs.

Key Words
- endometrial surveillance
- tamoxifen
- breast cancer
- adjuvant therapy
- follow-up
- hysteroscopy

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Introduction

Breast cancer is the most common cancer worldwide and the second most common cause of cancer death in the female population (Siegel et al. 2011). The breast cancer mortality rate has decreased in recent decades in developed countries as a result of increased screening and advances in adjuvant treatment (Berry et al. 2005).

Randomised clinical trials demonstrated survival benefits associated with the use of adjuvant therapies, with estimated reductions in the annual odds of death ranging from 8 to 28%, depending on the type and duration of therapy, the age of the patient and the characteristics of the tumour (Aebi et al. 2011).

Tumours with detectable (≥ 1%) expression of oestrogen receptors (ER) and/or progesterone receptors (PgR) are considered hormone receptor positive and are usually well differentiated with a low mitotic index and consequently, a good prognosis (Hammond et al. 2010). In 75–80% of patients with early breast cancer who have ER-positive tumours, treatment with 5 years of tamoxifen (TAM) immediately and substantially reduces local, contralateral and distant recurrence rates and decreases the 15-year breast cancer mortality rate. Therefore, tumours with high or uncertain hormone responsiveness (ER>1%) should be treated with endocrine therapy (Dowsett et al. 2010).

The Cochrane review performed by Clarke (2008) affirmed that years of adjuvant TAM treatment substantially improve the 10-year survival rate of women with ER-positive tumours or tumours of unknown ER status by reducing breast cancer recurrence and mortality.

However, it is universally accepted that standard TAM dosages may be responsible for endometrial proliferation, hyperplasia, polyp formation, invasive carcinoma and uterine sarcoma (ACOG 2006).

Recent data from Iqbal et al. (2012) showed that the risk ratio (RR) for endometrial cancer is low (RR: 1.19) in women receiving TAM therapy who are < 50 years old but is significantly increased in those older than 50 years old (RR: 3.32).

Therefore, for many years patients treated with TAM strictly underwent yearly/half-yearly transvaginal ultrasound (TVS) examinations, often with subsequent hysteroscopic and histopathologic investigation.

Although there are not clearly defined and universally accepted guidelines for follow-up examination of TAM-treated patients, the most common test used is endometrial surveillance. This approach can result in clinical overtreatment in women with no known risk of endometrial cancer who require only routine gynaecological care. It can also result in undertreatment in high-risk women.

Althuis et al. reported 13 years ago that half of breast carcinoma survivors were tested for uterine abnormalities and that 38% of TAM users never had a test despite their increased risk for abnormalities. The authors concluded that clear guidelines needs to be established for early detection of uterine abnormalities among TAM-treated breast carcinoma patients to identify the most appropriate method and frequency of investigation (Althuis et al. 2000).

Although ultrasound is the primary diagnostic tool for endometrial follow-up of post-menopausal patients, the absence of a defined endometrial thickness cut-off for the TAM-treated subgroup reduces ultrasound accuracy and increases the number of patients referred for unnecessary hysteroscopy (Dijkhuizen et al. 1996, Bertelli et al. 1998).

Despite the high accuracy of hysteroscopic investigation, significant TAM-related endometrial changes occur throughout the years of treatment, including atrophic-cystic, hypervascularization, endometrial polyps and lesions suspicious for malignancy. Poor understanding of the severity of these potential side effects of TAM treatment could be responsible for the use of invasive and costly diagnostic procedures (e.g. endometrial biopsy) that often give negative results, particularly in the absence of reports of abnormal uterine bleeding (AUB; Pérez-Medina et al. 2011).

The aim of this study is to determine the role, timing and indications for endometrial hysteroscopic investigation in TAM-treated patients in relation to the clinical, sonographic and histological features of the endometrium.

Materials and methods

We performed an observational longitudinal cohort study on patients referred to the hysteroscopic service of the endoscopy unit of the gynaecologic and obstetric clinic at Padua University from June 2007 to June 2012.

All enrolled patients were properly informed about the aim of the study, and they consented in a written consent form describing the use of their privacy data (Italian law 675/96).

All patients were consecutively enrolled by the researcher who conducted the hysteroscopic examination.

Eligible patients were recruited from a large cohort of patients with previous surgically treated breast cancer.
All patients were positive for ER and were taking TAM as adjuvant treatment after adequate chemotherapy or radiotherapy according to international guidelines (ABSG 2009, Aebi et al. 2011, NCCN 2011). Patients received annual gynaecological exams in combination with TVS and pelvic sonography.

All patients received an office hysteroscopy with a continuous-flow hysteroscope (Karl Storz, Tuttlingen, Germany) using saline solution as a distension medium and 30° angle view optics (2.9 mm diameter).

The indications for a hysteroscopy referral were asymptomatic endometrial thickening of more than 5 mm (Group A_ind), AUB without sonographic evidence of endometrial thickening (Group B_ind), AUB with sonographic evidence of endometrial thickening (Group C_ind) or endometrial monitoring in cases with no previous signs of AUB or endometrial thickening (Group D_ind).

We collected the following data about each patient: age, parity, hormonal status (pre-menopausal, perimenopausal and physiologic or iatrogenic post-menopausal), previous Oestrogen Progesterone Therapy, duration of TAM treatment (Group A_tam: 1 year; Group B_tam: 2 years; and Group C_tam: 3 or more years), and endometrial thickness measured within 30 days before hysteroscopic investigation (Group A_eco: <5 mm; Group B_eco: between 5 and 10 mm; Group C_eco: >10 mm).

We also reported the following hysteroscopic findings: endometrial atrophy (Group A_hys); endometrial atrophy with areas of focal hyperplasia (Group B_hys); endometrial polyps without atypia (Group C_hys); endometrial hyperplasia with suspicion of atypia or unusual polyps (Group D_hys); and suspected endometrial cancer (Group E_hys).

For all patients, an office endometrial biopsy or resectoscopy (i.e. polyp removal or focal endometrial resection) was performed, which enabled histological diagnosis and appropriate therapy.

Histological findings were grouped into the following categories: negative for neoplasia (Group A_istol); glandular hyperplasia without atypia (Group B_istol); stromal hyperplasia with or without oedema or fibrosis (Group C_istol); glandular hyperplasia with atypia (Group D_istol); and endometrial cancer (Group E_istol).

We excluded patients from the study with inadequate samples for histological diagnosis, absent previous TVS, discontinuous TAM treatment, concomitant or previous adjuvant aromatase inhibitor therapy, previous LH-RH analogues and absent or ambiguous histology.

Our primary goal was to compare histological diagnosis with indications for hysteroscopic investigation.

Our secondary goal was to compare the duration of treatment, endometrial thickness and histology and the correlation between endometrial thickness and detection of stromal hyperplasia.

We also compared the detection rate of endometrial atypia and endometrial thickness. Finally we report the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of TVS (cut-off of 5 or 10 mm) and hysteroscopy for detection of atypical or malignant endometrial lesions.

Table 1 General, gynaecological, hysteroscopic, sonographic and histological features of study patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± s.d. (range)</td>
<td>58.31 ± 10.86</td>
<td>(35–85)</td>
</tr>
<tr>
<td>Duration of TAM treatment (years)</td>
<td></td>
<td></td>
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<tr>
<td>Group A_tam</td>
<td>43 (28.5)</td>
<td></td>
</tr>
<tr>
<td>Group B_tam</td>
<td>41 (27.2)</td>
<td></td>
</tr>
<tr>
<td>Group C_tam</td>
<td>67 (44.3)</td>
<td></td>
</tr>
<tr>
<td>Mean ± s.d. (range)</td>
<td>2.56 ± 1.58 (1–12)</td>
<td></td>
</tr>
<tr>
<td>Endometrial thickness (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A_eco</td>
<td>22 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Group B_eco</td>
<td>80 (53)</td>
<td></td>
</tr>
<tr>
<td>Group C_eco</td>
<td>49 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Mean ± s.d. (range)</td>
<td>9.26 ± 5.05 (2–36)</td>
<td></td>
</tr>
<tr>
<td>Parous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>23 (15.2)</td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>128 (84.8)</td>
<td></td>
</tr>
<tr>
<td>Hormonal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-menopause</td>
<td>31 (20.05)</td>
<td></td>
</tr>
<tr>
<td>Post-menopause</td>
<td>120 (79.5)</td>
<td></td>
</tr>
<tr>
<td>Indications to hysteroscopic exam</td>
<td></td>
<td></td>
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<tr>
<td>Group A_ind</td>
<td>12 (74.2)</td>
<td></td>
</tr>
<tr>
<td>Group B_ind</td>
<td>7 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Group C_ind</td>
<td>10 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Group D_ind</td>
<td>22 (14.6)</td>
<td></td>
</tr>
<tr>
<td>Hysteroscopic results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A_hys</td>
<td>79 (52.3)</td>
<td></td>
</tr>
<tr>
<td>Group B_hys</td>
<td>28 (18.5)</td>
<td></td>
</tr>
<tr>
<td>Group C_hys</td>
<td>38 (25.2)</td>
<td></td>
</tr>
<tr>
<td>Group D_hys</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>Group E_hys</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Histological results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group A_istol</td>
<td>86 (57)</td>
<td></td>
</tr>
<tr>
<td>Group B_istol</td>
<td>15 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Group C_istol</td>
<td>44 (29.1)</td>
<td></td>
</tr>
<tr>
<td>Group D_istol</td>
<td>6 (4)</td>
<td></td>
</tr>
<tr>
<td>Group E_istol</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Group A_tam, 1 year of treatment with tamoxifen; Group B_tam, 2 years of treatment with tamoxifen; Group C_tam, more than 2 years of treatment with tamoxifen. Group A_eco, <5 mm endometrial thickness; Group B_eco, endometrial thickness between 5 and 10 mm; Group C_eco, endometrial thickness >10 mm. Group A_ind, asymptomatic endometrial thickening to more than 5 mm; Group B_ind, uterine bleeding without sonographic evidence of endometrial thickening; Group C_ind, abnormal uterine bleeding in association with sonographic endometrial thickening; Group D_ind, endometrial monitoring in cases with no previous signs of abnormal uterine bleeding or endometrial thickening. Group A_hys, endometrial atrophy; Group B_hys, endometrial atrophy with areas of focal hyperplasia; Group C_hys, endometrial polyps without atypia; Group D_hys, endometrial hyperplasia with suspicion of atypia or unusual polyps; Group E_hys, suspected of endometrial cancer. Group A_istol, negative for neoplasia; Group B_istol, glandular hyperplasia without atypia; Group C_istol, stromal hyperplasia with or without oedema or fibrosis; Group D_istol, glandular hyperplasia with atypia; Group E_istol, endometrial cancer.
Statistical analysis was performed using SPSS statistical software version 19 for Windows. The results were expressed in absolute numbers and percentages for discrete variables and in average ± S.D. for continuous variables.

We performed appropriate parametric and non-parametric statistical tests when possible using the Kolmogorov–Smirnov test as a normal distribution of the sample. Continuous variables were analysed by t-test, and categorical variables were analysed by the χ² test or Fisher’s exact test. P values of <0.05 were considered statistically significant.

Results
For this study, we recruited 455 patients with a history of breast cancer and subsequent TAM therapy. Among them, only 151 patients, ranging in age from 35 to 85 years old (mean age 58.31 ± 10.86 years), were eligible for the study (Table 1).

Data describing parity, hormonal status, menopause duration, years of TAM treatment, endometrial thickness, hysteroscopic indications and findings and histological diagnosis are reported in Table 1.

Analysis of the relationship between the indications for office hysteroscopy and hysteroscopic findings showed that 100% of patients referred for simple follow-up had no hysteroscopic evidence of disease (P < 0.01).

We also found a strong correlation between previous history of AUB (with or without endometrial thickening) and hysteroscopic evidence of atypia, which was independent of the indications for hysteroscopy (P < 0.01).

In no case of endometrial thickening without signs of AUB did the hysteroscopic features suggest a suspicion of atypia.

In our sample, a comparison of hysteroscopic reports and histological diagnosis showed that hysteroscopy had 83.3% sensitivity, 99% specificity, 83.3% PPV and 99% NPV in detecting atypia (Table 2).

All cases of endometrial biopsy in patients receiving hysteroscopic investigation with the intent of follow-up and in the absence of clinical symptoms were negative for atypia (P < 0.001).

However, 83.3% of the histological endometrial atypia cases were detected in patients with a previous history of AUB, and only in one case (16.7%) was the patient asymptomatic and referred to hysteroscopy on the basis of endometrial thickening (P < 0.05).

With the exception of this single case, no significant correlation was found between endometrial thickening (> 5 mm) without AUB and histological atypia.

We did not find any statistically significant correlation between the duration of treatment and endometrial thickening. However, over 50% of the TAM-treated patients had endometrial thickness between 5 and 10 mm. In particular, the thickening was detected in 53.5% of patients during the first year of treatment, in 51.2% during the second year and in 53.7% after the second year.

There was no significant correlation between TAM treatment duration and the histological diagnosis of atypia. However, it is important to note the following trend linking atypia to the duration of treatment: one case of endometrial atypia in the first year of therapy, one case of endometrial atypia in the second year of therapy and four cases of endometrial atypia after the second year of therapy. The overall rate of atypia detection was 2.3% in the first year, 2.4% in the second year and 6% after the second year of treatment.

Stromal hyperplasia with or without oedema and fibrosis was detected histologically in 70.5% of patients with endometrial thickness between 5 and 10 mm. In contrast, no stromal hyperplasia was detected in patients with endometrial thickness <5 mm (P < 0.01).

Table 2 Comparison of TVS investigation with 5 or 10 mm cut-off and hysteroscopy relative to atypia detection that is histologically confirmed.

<table>
<thead>
<tr>
<th></th>
<th>TVS 5 mm cut-off</th>
<th></th>
<th>TVS 10 mm cut-off</th>
<th></th>
<th>Hysteroscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Value</td>
<td>95% CI</td>
<td>Value</td>
<td>95% CI</td>
<td>Value</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>1</td>
<td>0.60–1</td>
<td>0.84</td>
<td>0.44–0.97</td>
<td>0.83</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.15</td>
<td>0.10–0.21</td>
<td>0.69</td>
<td>0.62–0.76</td>
<td>0.99</td>
</tr>
<tr>
<td>PPV</td>
<td>0.04</td>
<td>0.02–0.10</td>
<td>0.1</td>
<td>0.05–0.22</td>
<td>0.93</td>
</tr>
<tr>
<td>NPV</td>
<td>1</td>
<td>0.86–1</td>
<td>0.99</td>
<td>0.66–1</td>
<td>0.99</td>
</tr>
</tbody>
</table>

95% CI was estimated by Wilson method and by binomial exact test, when necessary.
Interestingly, we observed that of the patients with endometrial thickness <10 mm (102 patients), only one had endometrial atypia (0.98%), which occurred along with AUB. All remaining cases of endometrial atypia were detected in patients with endometrial thickness >10 mm (P<0.01).

Finally, TVS detected endometrial atypia with 100% sensitivity, 15% specificity, 4% PPV and 100% NPV when an endometrial thickness cut-off value of 5 mm was used. TVS detected endometrial atypia with 84% sensitivity, 69% specificity, 10% PPV and 99% NPV when a cut-off value of 10 mm was used (Table 2).

Discussion

TAM, like all selective oestrogen-receptor modulators, acts as an oestrogen agonist or antagonist in different tissues. This feature is related to the specific actions of TAM on at least two distinct ERs whose proportions differ depending on the tissue type (Aebi et al. 2011).

TAM has been approved by the United States Food and Drug Administration with the following indications: adjuvant therapy of breast cancer, metastatic breast cancer and reduction of the incidence of breast cancer in high-risk women (Siegel et al. 2011).

Endometrial polyps are the most commonly diagnosed pathologies in TAM-treated patients, especially in post-menopausal women (Osborne 1998, Deligdisch et al. 2000, Polin & Ascher 2008).

Similarly, 25.2% of hysteroscopic examinations in our sample revealed the presence of one or more endometrial polyps (58.2% of non-negative reports). Moreover, only in one case was endometrial glandular atypia reported (2.6%), which is similar to the findings of Ramondetta et al. (1999) and Cohen (2004).

Most of the uncertainty regarding TAM use is related to the increased risk of endometrial atypia and subsequent cancer development, while only in rare cases has TAM been reported as a risk factor for mixed Müllerian tumours (Wickerham et al. 2002, Curtis et al. 2004). A meta-analysis conducted by Braithwaite et al. (2003) based on 32 clinical trials and including 52 929 patients has shown that the risk of endometrial cancer is significantly increased in women taking TAM to an estimated relative risk of 2.7.

Even if the use of TAM increases the risk of pre-neoplastic and neoplastic endometrial disease, several large-scale randomised clinical trials have shown that the therapeutic benefit of TAM for adjuvant treatment of breast cancer exceeds the risks related to stimulation of the endometrium (Cuzick et al. 2002, Fisher et al. 2005, Bevers et al. 2010, EBCTCG 2011).

Despite the widespread use of TAM, there are currently no universally accepted international guidelines for its use, with the exception of the 2006 ACOG committee opinion. This may be because the studies on TAM treatment have reported data from heterogeneous populations with recurrent bias related to unknown endometrial status prior to treatment (ACOG 2006).

Nevertheless, ACOG recognised the importance of hormonal status in estimating the risk linked to TAM treatment, because pre-menopausal women have no known increased risk for endometrial cancer and require no further investigation beyond routine gynaecological checks.

In fact, our data indicate that of 31 pre-menopausal patients, only two (6%) developed endometrial atypia and none developed endometrial cancer. This is comparable with the incidence of endometrial hyperplasia with atypia in the general population reported by Cohen (2004) and Polin & Ascher (2008).

For post-menopausal women, ACOG recommended an annual gynaecological check-up in the absence of symptoms related to the development of endometrial hyperplasia (e.g. AUB, spotting and vaginal discharge). However, they did not define the most appropriate algorithm for following women at increased risk for endometrial disease.

According to ACOG suggestions, AUB is the clinical sign most commonly linked to endometrial disease that requires investigation to exclude the possible onset of endometrial atypia (Love et al. 1999, Seoud et al. 1999). In fact, our data showed that the 83.3% of histological endometrial atypia was preceded by AUB.

Currently, there is abundant scientific evidence (Garuti et al. 1999, Bronz 2000, Litta et al. 2005, Gruwadayarhalli et al. 2007, Tinelli et al. 2008) that hysteroscopic examination is the gold standard for the management of AUB, with curettage of the uterine cavity required only for the treatment of haemostatic urgencies and when active bleeding is present.

A study of 310 TAM-treated patients by Giorda et al. (2002) found that hysteroscopy has 96% PPV and 65% NPV for atypical endometrial hyperplasia or endometrial cancer. Similar to our results, Ceci et al. (2003) reported 97% sensitivity, 100% specificity, 100% PPV and 96% NPV of hysteroscopy relative to histological diagnosis.

On this basis, office hysteroscopy could be considered a safe, well-tolerated diagnostic test that enables targeted endometrial biopsies because it accurately distinguishes

Although TVS is an effective test with a high NPV in post-menopausal women when endometrial thickness is <5 mm, its accuracy is reduced in TAM-treated patients. Currently, the debate over using TVS in TAM-treated patients is on-going, though numerous points have been clarified.

In a study of 80 TAM-treated patients, Seoud et al. (1999) showed that all patients who developed abnormalities had AUB but found no correlation between endometrial thickness and endometrial pathology. In this study, the only patient who developed endometrial cancer had endometrial thickness of 3 mm.

Recently, several authors (Dijkhuizen et al. 1996, Cheng et al. 1997, Bertelli et al. 1998, Polin & Ascher 2008, Goldstein 2010) attempted to improve the PPV of TVS in detecting endometrial atypia during TAM therapy. In a study of 164 asymptomatic women with previous breast cancer and TAM treatment, Bertelli et al. (1998) reported no correlation between endometrial thickness ≥5 mm (54% of patients) and endometrial atypia. The authors concluded that in the absence of symptoms, it is not recommended to base routine follow-up on ultrasound and biopsy.

Fung et al. (2003) reported that 32% of 304 TAM-treated patients had endometrial thickening. Of these, only six patients had endometrial atypia that was always associated with AUB. In an attempt to improve the PPV of ultrasound examination, these authors proposed a 9-mm cut-off that achieved 63.3% sensitivity with 43.3% PPV. They concluded that ultrasound is not recommended for the screening of endometrial abnormalities in asymptomatic TAM-treated women.

Other large-scale studies have proposed cut-off values >5 mm, resulting in ~50% false positives (Dijkhuizen et al. 1996, Love et al. 1999). This percentage is not improved with the help of the Doppler flowmetry, which results in 84.1% sensitivity and 58.2% specificity for cut-off values up to 10 mm (Fong et al. 2003).

Our results agree with most recent evidence, showing that a cut-off of 5 mm for ultrasound has 100% sensitivity, 15% specificity, 4% PPV and 100% NPV; these values are more acceptable than previous results but not satisfactory. However, by moving the cut-off to 10 mm we obtained 84% sensitivity, 69% specificity, 10% PPV and 99% NPV.

Achiron et al. (1995) explained the low accuracy of TVS in atypia detection by demonstrating that TAM-induced stromal hypertrophy is responsible for the apparent endometrial thickening observed by sonography. This concept was subsequently investigated by other authors (Achiron et al. 1995, Neis et al. 2000, Gao et al. 2011) who reported that TAM may have a pro-oestrogen effect in the cells of the endometrial stroma in post-menopausal women, inducing specific changes in the endometrium. These findings explain the discrepancy between the sonographic, hysteroscopic and histological reports (Gao et al. 2011). Neis et al. (2000) performed hysteroscopic endometrial biopsies in 89 patients with sonographic endometrial thickening and found stromal hyperplasia associated with glandular atrophy and no atypia in 37% of cases.

The evidence that TAM has a pro-proliferative role in the stroma was confirmed by Decensi et al. (1996) such that all patients with sonographic endometrial thickening had stromal proliferation directly proportional to the duration of treatment. We had similar results, with no evidence of benign stromal lesions in patients with endometrial thickness <5 mm in ultrasounds, while 70.5% of patients with a diagnosis of benign stromal lesions had endometrial thickness between 5 and 10 mm.

In post-menopausal TAM-treated women, the increased atypia risk, the low sensitivity of TVS for endometrial atypia detection and the high specificity of hysteroscopy lead many oncologists to suggest follow-up hysteroscopy even in the absence of AUB with or without TVS thickening (Althuis et al. 2000, Taponce et al. 2002).

Although hysteroscopy has a high predictive value and specificity for the diagnosis of endometrial atypia, it cannot be used in place of histological examination, which remains the gold standard.

Our results showed no evidence of atypia when hysteroscopy was performed as simple follow-up in the absence of AUB, with or without endometrial thickening. This suggests that in asymptomatic women, there is no rationale for TVS follow-up and hysteroscopy.

Despite reports that the duration of TAM treatment is directly proportional to atypia onset (ACOG 2006, EBCTCG 2011), we observed a positive trend but no significant correlation between the duration of treatment and the occurrence of endometrial atypia. This result could be affected by the small size of our sample (151 patients); therefore, it would be worthwhile to validate our results with prospective large-scale studies.

Although our data were obtained from a non-screened single series of 151 research participants, the results suggest that in clinical practice when the estimated risks are low and bleeding is absent, TAM users do not
require different endometrial surveillance than the general population. Hysteroscopy could play a fundamental role both in determining endometrial status before the initiation of treatment and in assessing endometrial status when bleeding occurs.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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