The ATAC (‘Arimidex’, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: baseline endometrial sub-protocol data on the effectiveness of transvaginal ultrasonography and diagnostic hysteroscopy

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BACKGROUND: The ‘Arimidex’, Tamoxifen, Alone or in Combination (ATAC) trial is a randomized, double-blind trial comparing anastrozole (‘Arimidex’), alone or in combination with tamoxifen, relative to tamoxifen alone as 5 year adjuvant treatment for post-menopausal women with early breast cancer. Since tamoxifen is associated with endometrial pathology, the ATAC endometrial sub-protocol was initiated to establish the background prevalence of intrauterine pathology, and to assess prospectively the incidence and nature of intrauterine changes following endocrine therapy. Another aim was to provide data from which advice could be generated on the best endometrium screening method for patients receiving tamoxifen. METHODS: Patients underwent endometrial assessments at entry to the sub-protocol. The baseline investigations comprised transvaginal ultrasound scanning (TVUS), a hysteroscopy and an endometrial biopsy. RESULTS: A total of 285 gynaecologically asymptomatic women from 31 centres in 10 countries entered the endometrial sub-protocol. The mean uterine volume was 47.7 cm³. The median endometrial thickness overall was 3 mm. Twenty-four histologically confirmed, pathological changes were observed. Twenty-three pathologies were confirmed by TVUS, and 21 were confirmed by histopathology. CONCLUSIONS: The presence of pathology was associated with increased endometrial thickness. The relative sensitivity and specificity of hysteroscopy and endometrial thickness for the diagnosis of endometrial pathology was comparable to other studies. If screening of the endometrium prior to treatment is appropriate, this study supports the use of an endometrial thickness of 3 mm, as assessed by TVUS, as a threshold for needing further investigation. This study demonstrates that if the endometrial thickness is >3 mm, hysteroscopy and biopsy is the optimal method of detecting intrauterine pathology in women with breast cancer who are about to commence endocrine treatment.

Key words: ATAC trial/arimidex/early breast cancer/endometrial pathology/post-menopausal/tamoxifen

Introduction

The ‘Arimidex’, Tamoxifen, Alone or in Combination (ATAC) trial is a randomized, double-blind trial comparing anastrozole (‘Arimidex’), alone or in combination with tamoxifen, relative to tamoxifen alone as 5 year adjuvant treatment for post-menopausal women with early breast cancer. Since tamoxifen has been classed as an endometrial carcinogen by the International Agency for Research on Cancer (IARC, 1996), the ATAC endometrial sub-protocol was initiated to establish the background prevalence of intrauterine pathology, and to assess prospectively the incidence and nature of intrauterine changes following endocrine therapy. Another aim of the sub-protocol was to provide data from which advice could be generated on the best method of screening the endometrium of patients undergoing tamoxifen therapy. At the time of the ATAC study the majority of
studies investigating ‘screening’ for endometrial pathology were based on asymptomatic patients. Very few data exist on screening asymptomatic but ‘at-risk’ (e.g. tamoxifen-treated) patients.

There is considerable debate as to the relative merits of transvaginal ultrasound scanning (TVUS) versus hysteroscopy (direct visualization of the uterine cavity) for the detection of endometrial abnormalities in symptomatic postmenopausal women. It has been suggested by various authors that an endometrial thickness of ≤5 mm (as assessed by TVUS) excludes endometrial abnormality with reasonable certainty (Karlsson et al., 1995). However, in many of the published studies on TVUS, the diagnosis of endometrial abnormality has only been made following blind biopsy. It has been estimated that 50% of the endometrial cavity is sampled by curettage (Stock and Kanbour, 1975) while 4% is sampled by pipelle (Rodriguez et al., 1993). Word et al. (1958) found that 10% of endometrial lesions were missed by curettage. By contrast, Krampl et al., 1997) showed that pipelle sampling detects malignancy reliably but not endometrial abnormalities. Thus, blind biopsy also may not reliably detect endometrial abnormalities.

In a study by Granberg et al., 1997, 205 women with post-menopausal bleeding (PMB) were assessed using TVUS followed by blind curettage. All 48 women with intrauterine pathology had an endometrial thickness of >5 mm, while seven women had a thickened endometrium with no pathology. The sensitivity of a 5 mm threshold could not reliably be determined, since (as discussed above) blind curettage may miss pathology. Goldstein et al., 1990 assessed 30 women with PMB using TVUS and endometrial sampling. All 11 patients with an endometrial thickness of ≤5 mm had insufficient tissue for diagnosis. The study concluded that this was ‘safe’, despite not visualizing the cavity and the study numbers being so small. In a large study involving 1168 women with PMB, assessed using TVUS and curettage (Karlsson et al., 1995), no malignancy of the endometrium was detected in women with endometrial thickness <5 mm and the risk of finding pathological endometrium at curettage when the endometrium was ≤4 mm was 5.5%. Yet again, the uterine cavity was not visualized. In a trial investigating the effects of HRT, Langer et al. (1997) performed TVUS and endometrial biopsy on 448 women. At a threshold value of 5 mm for endometrial thickness, a biopsy was indicated in more than half of the women, only 4% of whom had serious disease. These studies indicate that without visualization of the endometrial cavity, the true prevalence of pathology is not known. In each of the studies using blind biopsy, few conclusions can be drawn about the usefulness of a threshold value of 5 mm for endometrial thickness.

In other studies, hysteroscopy has been performed only when the endometrium is shown to be thickened when screened by TVUS. Exacoustos et al. (1996) assessed 910 asymptomatic post-menopausal women with TVUS. Endometrial thickness of ≤5 mm was regarded as normal and not investigated further. Women with thickened endometrium were advised to undergo hysteroscopy and it was concluded that an endometrial thickness of 8 or 10 mm was an effective threshold to select candidates for more invasive procedures. As a large proportion of the women did not have an endometrial biopsy or visualization of the endometrial cavity, conclusions cannot be drawn from the limited data available. More recently, Loizzi et al., 2000 performed outpatient hysteroscopy on 155 symptomatic or asymptomatic post-menopausal women with endometrial thickness of ≥4 mm. In this study, hysteroscopy was found to have high positive and negative predictive values for pathology in both groups. However, the uterine cavity of women with endometrial thickness of <4 mm was not visualized.

In the context of women being treated with tamoxifen, there is an added confounding factor. It has been shown that the endometrium thickens during treatment with tamoxifen giving a high false-positive rate for abnormality, even when a threshold value of 10 mm for endometrial thickness is used (Gerber et al., 2000). In women on tamoxifen, the endometrial depth measurement obtained by ultrasound may be up to 3 mm greater than the histological measurement (Ballard et al., 2000). Basing a screening programme for endometrial abnormalities in asymptomatic patients on currently available evidence is, therefore, potentially unsound. It was with this in mind that the endometrial subprotocol was designed.

In women with PMB, the clinical concern is the presence of endometrial cancer. Approximately 10% of post-menopausal women aged <60 years presenting and referred with PMB have endometrial cancer. Among women aged >60 years presenting with PMB, 13% are assumed to have endometrial cancer based upon incidence rates from the Scottish Cancer Surveillance Group data (Harris et al., 1998). However, intrauterine pathology is not just confined to symptomatic post-menopausal women; asymptomatic post-menopausal women have also been shown to have intrauterine pathology (Duffy et al., 2003). The presence of this intrauterine pathology, which is asymptomatic and therefore clinically ‘hidden’, may logically be more susceptible to the negative effects of endocrine therapy for breast cancer than normal atrophic endometrium. Therefore, it is essential when seeking to determine cause and effect from endocrine therapy on uterine pathology that this intrauterine ‘hidden’ pathology is recognized before initiating any treatment.

A clinical dilemma exists in the management of post-menopausal patients starting endocrine therapy for breast cancer—if uterine screening before treatment is important, what is the most effective method? The use of TVUS as an initial screening test may not reduce the proportion of women requiring a hysteroscopy. All women with thickened endometrium and all women with an inconclusive TVUS are subjected to hysteroscopy with a potentially smaller proportion classed as negative by TVUS. Hysteroscopy may therefore be more appropriate. Post-menopausal women find outpatient hysteroscopy to be acceptable and tolerable (Kremer et al., 2000; Duffy et al., 2003). As hysteroscopy directly visualizes the uterine cavity, it is therefore more likely to detect pathology. In post-menopausal breast cancer patients, it has been found to be accurate in the detection of pathology (Duffy et al., 2003). However, used in the most
appropriate way, TVUS may have an important role. This paper sets out important information about the differences between hysteroscopy and TVUS in the assessment of the asymptomatic uterine cavity.

Materials and methods

The requirements for the randomization of patients into the main ATAC trial have been described elsewhere (ATAC Trials’ Group, 2002). A total of 380 centres recruited patients into this three-arm trial. They were randomized 1:1:1 to receive: (i) active anastrozole (1 mg) per day plus tamoxifen placebo, (ii) active tamoxifen (20 mg) per day plus anastrozole placebo, or (iii) active anastrozole (1 mg) per day plus active tamoxifen (20 mg) per day. Thirty-one of the 380 centres were identified as having the facilities and expertise to perform the investigations for the endometrial sub-protocol.

Patients were excluded from the endometrial sub-protocol if they had received neoadjuvant tamoxifen or had undergone either a hysterectomy or endometrial ablation. After obtaining informed written consent, the patients underwent endometrial assessments at entry and again at years 1, 2, 5 and 6. At the first assessment, the patient’s medical history was recorded including number of children (parity), age at menopause, and previous use of oral contraception or HRT. Patients were excluded from the endometrial sub-protocol at baseline if the endometrium was not accessible for hysteroscopic investigation or they had any endometrial lesion other than benign polyps and fibroids. The baseline investigations consisted of TVUS, a hysteroscopy and an endometrial biopsy. Details of the hysteroscopic investigations and biopsies are published elsewhere (Duffy et al., 2003). TVUS was used to measure endometrial thickness in millimetres in the longitudinal (sagittal) section of the midline plane at the widest point (‘double-sandwich’ technique). The texture of the endometrium (whether it was homogeneous or heterogeneous/cystic) was recorded. Using TVUS, findings of thickened heterogeneous endometrium are often classed as positive for abnormality. The uterine dimensions were measured and recorded in millimetres. The longitudinal diameter was measured from the outer aspect of the uterine fundus, in the longitudinal section, up to and including the cervix. The depth was measured in the longitudinal section at the widest diameter (outer edge to edge) and the width was measured in the transverse section at the widest diameter (outer edge to edge). If polyps or fibroids were detected, the number and maximum dimension in millimetres were recorded. Uterine volume was calculated with the use of the formula for a prolate ellipsoid: volume = 0.52 × length × anteroposterior diameter × transverse diameter (Pirhonen et al., 1993; Weeks et al., 1999). Ovarian ultrasound scanning was carried out to detect any abnormalities of either ovary, such as cysts or abnormal stromal density. Abnormal or screen-positive endometrium at TVUS was described as heterogeneous, thickened (>5 mm), or both.

The hysteroscopy was performed on an outpatient basis in most cases using either rigid or flexible instruments depending on the preference of the gynaecologist. General anaesthesia could be employed if preferred or if the outpatient procedure was not tolerated. A pipelle sample was taken at the time of hysteroscopy. Endometrial polyps and suspicious areas of endometrium were subsequently resected under direct vision, usually under general anaesthesia, before initiation of trial therapy. The presence of submucosal fibroids and their type was noted. Fibroids were not removed as part of the protocol. All histological samples were analysed centrally by a single specialist gynaecological pathologist to ensure consistency of interpretation within this trial.

Multicentre research ethics committee approval was obtained for both the main ATAC trial and this endometrial sub-protocol and the approval of the local research ethics committees in each hospital was gained.

Sample size calculations estimated that ≥500 patients should be recruited into this sub-protocol to provide sufficient power for statistical analyses of differences between treatments. Abnormalities at baseline were expressed as absolute values and percentages. The TVUS findings in relation to histopathology and the relative sensitivity, relative specificity, positive predictive value (PPV) and negative predictive value (NPV) for TVUS and hysteroscopy in relation to histopathology were determined. In order to calculate the relative sensitivity and specificity of TVUS and hysteroscopy for the diagnosis of endometrial pathology, 2 × 2 tables were constructed.

Results

In ∼30 months, the main trial recruited 9366 patients from 380 centres in 21 countries. In total, 285 gynaecologically asymptomatic women from 31 centres in 10 countries entered the endometrial sub-protocol. This study was unable to reach its target recruitment of 500 women as the main ATAC trial achieved its target event rate (and therefore stopped recruiting) before recruitment to the sub-protocol was completed. Patient characteristics are described in Table 1.

At randomization, seven women were withdrawn without having a TVUS or hysteroscopy (Figure 1). Six women had a TVUS without a hysteroscopy and three women had a

![Figure 1. Outcome of the 285 women randomized into the endometrial sub-protocol (hysteroscopy and transvaginal ultrasound scanning).](image-url)
hysteroscopy without a TVUS (Figure 1). In total, 275 women had a TVUS and 272 women had an attempted hysteroscopy.

A total of 269 women had both a TVUS and attempted hysteroscopy of which seven hysteroscopies failed, three of whom had a biopsy. In all, 262 women had a TVUS and hysteroscopy, 264 women had a TVUS and biopsy and 264 women had a hysteroscopy and biopsy (Figure 1).

**Uterine volume**

Uterine volume could be calculated in 260 of the 275 women who had a TVUS (Figure 2; Table II). Uterine volume was not calculated in the 15 remaining patients because of technical difficulties (the scanner was unable to measure all three planes). None of these 15 patients had uterine pathology.

The mean uterine volume was 47.7 cm$^3$ (range 5.6–276.6). Mean volumes are presented in Table II. The uterine volume tended to be greater in the presence of fibroids and pathology. Prior use of HRT, thicker (>5 mm) endometrium or heterogeneous endometrium was not associated with increased uterine volume.

**Endometrial thickness**

Median endometrial thickness overall was 3.0 mm [mean 4.0 mm; range 1–23; interquartile range (IQR) 2–5]. Those women who had taken HRT in the past had a median endometrial thickness of 3.0 mm (mean 3.9 mm; range 1–23; IQR 2–5). Women who had never taken HRT had a median endometrial thickness of 3.0 mm (mean 4.1 mm; range 1–18; IQR 2.2–5).

**Intrauterine pathology**

Twenty-four histologically confirmed, pathological changes were observed. Two of these were not identified by hysteroscopy and were only detected by histopathology. One patient had a polyp with atypia diagnosed by hysteroscopy and confirmed by histopathology but did not undergo TVUS. Hence, the total number of confirmed pathologies in the patients assessed by TVUS was 23. Twenty-one pathologies were identified by hysteroscopy and confirmed by histopathology. The women with intrauterine pathology had a median endometrial thickness of 5.0 mm (mean 5.5 mm; range 1.5–16; IQR 3.9–6). Women without pathology had a median endometrial thickness of 3.0 mm (mean 3.9 mm; range 1–23; IQR 2–5). This is shown in Figure 3.

Of the 23 women (8.8%) successfully assessed by TVUS who had confirmed endometrial pathology, 20 had benign polyps, one had a polyp with simple hyperplasia and two had polyps with cytological atypia. Eleven of these women (47.8%) had taken HRT. Of the 238 women with no pathology, 93 had taken HRT (39.1%).

Thirty-five (13.0%) of the 265 women who had successful hysteroscopies (seven failed) were found to have an abnormal hysteroscopy (34 polyps and one suspicious endometrium). Of the 22 of these 35 women with confirmed pathology, 19 had polyps with no atypia, one had a polyp with simple hyperplasia and two had polyps with cytological atypia. Of the remaining 13 women, eight had no pathology and five samples were lost or not sent to the laboratory. Hysteroscopy identified 91.3% of those with an intrauterine abnormality (Duffy et al., 2003).

![Figure 2. Uterine volume measurements calculated after transvaginal ultrasound scanning (n = 260).](https://academic.oup.com/humrep/article-abstract/20/1/294/671576/128x.png)

**Table II. Uterine volume measurements**

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>Mean volume (cm$^3$)</th>
<th>SD (cm$^3$)</th>
<th>Lower 95% CL of mean</th>
<th>Upper 95% CL of mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>260</td>
<td>47.6</td>
<td>38.0</td>
<td>43.0</td>
<td>52.2</td>
</tr>
<tr>
<td>With fibroids</td>
<td>80</td>
<td>69.3</td>
<td>55.1</td>
<td>57.2</td>
<td>62.2</td>
</tr>
<tr>
<td>Without fibroids</td>
<td>180</td>
<td>37.9</td>
<td>21.0</td>
<td>34.9</td>
<td>41.0</td>
</tr>
<tr>
<td>HRT</td>
<td>103</td>
<td>53.7</td>
<td>44.3</td>
<td>45.1</td>
<td>62.2</td>
</tr>
<tr>
<td>No HRT</td>
<td>157</td>
<td>44.6</td>
<td>33.9</td>
<td>39.3</td>
<td>49.9</td>
</tr>
<tr>
<td>Endometrial thickness &gt;5 mm</td>
<td>54</td>
<td>53.8</td>
<td>33.9</td>
<td>44.8</td>
<td>62.9</td>
</tr>
<tr>
<td>Endometrial thickness ≤5 mm</td>
<td>206</td>
<td>45.9</td>
<td>38.9</td>
<td>40.6</td>
<td>51.2</td>
</tr>
<tr>
<td>Heterogeneous endometrium</td>
<td>30</td>
<td>58.8</td>
<td>55.3</td>
<td>39.0</td>
<td>78.6</td>
</tr>
<tr>
<td>Homogeneous endometrium</td>
<td>230</td>
<td>46.1</td>
<td>35.0</td>
<td>41.6</td>
<td>50.6</td>
</tr>
</tbody>
</table>

CL = confidence limit.
Traditionally, findings of thickened or heterogeneous endometrium on TVUS are regarded as abnormal. In the present study, 76 women (76/275, 28%) with an abnormal TVUS presented as either heterogeneous or thickened (>5 mm) endometrium or both. Of these women, only 11 (14%) were confirmed to have pathology (eight polyps with no atypia, one polyp with simple hyperplasia, one polyp with atypia and one atypical hyperplasia) (Figure 4). In two of the remaining 65 women, no sample was sent and 63 had no pathology. Therefore, endometrial thickness >5 mm and/or heterogeneous endometrium on TVUS identified 48% (11/23) of those with an intrauterine abnormality. Endometrial thickness >4, >3, >2 mm and/or heterogeneity identified 57% (13/23), 78% (18/23) and 91% (21/23) of those with an intrauterine abnormality respectively. Ten women were thought to have endometrial polyps on TVUS. Of these, nine were confirmed at hysteroscopy. However, only three were polyps on histology, with four normal samples, one fibroid (classed as normal) and two samples missing.

The relationship between given pathologies and endometrial thickness or heterogeneity or hysteroscopy is presented in Table III (relative sensitivity and specificity of TVUS and hysteroscopy).

The findings presented in Table III provide detailed information on the accuracy of endometrial thickness and heterogeneity for the diagnosis of intrauterine pathology. Using this table, a threshold endometrial thickness of 2 mm would detect 87% of endometrial pathology (with relative specificity 30.9%). With endometrial thickness >3 mm, 78.3% of pathology would be detected with an improvement in specificity from 30.9% (threshold at 2 mm) to 56.0%. Endometrial thickness >4 mm had relative sensitivity and specificity of 52.2 and 71.7% respectively, while thickness >5 mm had relative sensitivity and specificity of 39.1 and 79.6% respectively.

The use of heterogeneity as an indicator of abnormality improves the detection of pathology when combined with an endometrial thickness of >5 mm (relative sensitivity and specificity of 47.8 and 73.1% respectively). However, at lower threshold values of endometrial thickness, heterogeneity does not improve sensitivity but actually reduces specificity, indicating an increase in the proportion classed as screen positive without benefit for the patient.
As part of the TVUS, an attempt was made to visualize both ovaries. As expected in this group of 275 asymptomatic post-menopausal women, one or both ovaries could not be visualized in 76 women (28%). Twenty-one women (8%) had ovarian cysts, two of which were considered suspicious but were benign on histology.

**Discussion**

The demographic features of this patient population were representative of the ATAC trial as a whole. Age at menopause and use of HRT in the past was comparable with the normal female population (ATAC Trialists’ Group, 2002). Reference ranges for uterine volume in asymptomatic post-menopausal women are presented in this paper. Although uterine volume has been found to be significantly greater in women using HRT compared with those not using HRT (Pirhonen et al., 1993), this was not the case in this study population. No patients were taking HRT at the time of their TVUS. It is likely that uterine enlargement in association with the use of HRT is reversible, which would explain the similarity in uterine volume of those who had or had not taken HRT in the past.

The presence of pathology was associated with increased endometrial thickness, as women with intrauterine pathology had greater endometrial thickness than those with no pathology. The prevalence of pathology in these patients was comparable with other asymptomatic post-menopausal women and less than that reported in women with post-menopausal bleeding (ATAC Trialists’ Group, 2002, Duffy et al., 2003).

Hysteroscopy had a relative sensitivity of 91.3% for the detection of intrauterine pathology (relative specificity 96.6%) (Table IV), missing one polyp and one case of atypical hyperplasia. Therefore, even in experienced hands,
the use of hysteroscopy without endometrial sampling is not recommended in this group of women.

The relative sensitivity and specificity of hysteroscopy (Table IV) and endometrial thickness (Table V) for the diagnosis of significant endometrial pathology in the asymptomatic women in the endometrial sub-protocol was comparable with that seen historically in women with PMB in other similar published series on TVUS and outpatient hysteroscopy (Cacciatore et al., 1994; Haller et al., 1996; Salmaggi et al., 1997; Garuti et al., 1999; Loverro et al., 1999). Hysteroscopy had a higher relative sensitivity for the detection of endometrial pathology than endometrial thickness of >3 mm (91.3 versus 78.3% respectively). Furthermore, the relative specificity of hysteroscopy for the detection of pathology was 96.6% whereas endometrial thickness of 3 mm had a lower relative specificity at 56.0%.

When devising screening guidelines for women about to commence endocrine therapy for breast cancer, the investigation method with the least discomfort and inconvenience to patients without compromising the safety of a screen-negative result has obvious benefits. Of the 255 women with recorded endometrial thickness and pathology, 120 (47%) had endometrial thickness >3 mm. If they had been regarded as screen positive by TVUS and had gone on to have a hysteroscopy and biopsy, 18 of them (15%) would have been found to have pathology. The 135 (53%) patients with endometrial thickness of ≤3 mm would have avoided hysterectomy and biopsy but four benign polyps and one simple hyperplasia would have been missed. Employing a threshold of 3 mm endometrial thickness would have detected 78% (18/23) and missed 22% (5/23) of the pathology present in the study population. A threshold endometrial thickness of 2 mm would have detected 87% (20/23) of the pathology but only 74 (29%) of patients would have avoided hysterectomy and biopsy. However, endometrial volume has been shown to be superior to endometrial thickness in the diagnosis of endometrial abnormalities (Gruboeeck et al., 1996). As endometrial volume is more easily and reproducibly measured using three-dimensional TVUS (Maymon et al., 2000; Yaman et al., 2002) this newer technique may provide a useful alternative option for the screening of women commencing endocrine therapy for breast cancer. The increased sensitivity and specificity of this method compared with conventional two-dimensional TVUS (La Torre et al., 1999) may also limit the need for more invasive and inconvenient assessments to be made.

This study demonstrates that hysteroscopy and biopsy is the best method of detecting intrauterine pathology in women with breast cancer who are about to begin endocrine treatment. If screening of the endometrium prior to treatment is considered appropriate, this study also provides the basis upon which TVUS could be used in this population. Such a programme balances efficiency and patient acceptability by reducing the need for hysteroscopy (although acceptable) by using endometrial thickness of 3 mm by TVUS as a threshold. If the endometrial thickness is ≤3 mm, patients should be regarded as negative and need no further investigations. If the endometrial thickness is >3 mm the optimal screening is by hysteroscopy, preferably in the outpatient setting, with endometrial biopsy.

References


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