Endometrial pathology in the postmenopausal woman – an evidence based approach to management

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Key content
• This article outlines how to identify the symptoms and signs associated with endometrial pathology and how these correlate with the final diagnosis.
• The evidence for and against intervention in asymptomatic women with a coincidental finding of endometrial pathology is discussed.
• This article looks at how best to investigate symptomatic women on hormone replacement therapy (HRT) and selective estrogen receptor modulators (SERMs).
• Screening for endometrial pathology is discussed.

Learning objectives
• To be able to identify risk factors associated with postmenopausal endometrial pathology, as well as symptoms and signs.
• To learn about the models of care for different endometrial pathology.
• To understand the contentious issues and the risk-benefit profile of different strategies for the management of asymptomatic women.

Ethical issues
• Does an incidental finding of a thick endometrium in asymptomatic postmenopausal women warrant further investigation?
• Should asymptomatic women receiving HRT or SERMs be routinely screened and investigated?

Keywords: endometrial cancer / hormone replacement therapy / menopause / postmenopausal bleeding

Introduction

Postmenopausal bleeding (PMB) is the most common reason for referral to gynaecological rapid access clinics. Strategies for the investigation and treatment of women presenting with PMB have evolved since the early 1990s with the advent of transvaginal ultrasound (TVUS) and outpatient hysteroscopy. With the shift in demographics in the UK towards an ageing, increasingly obese population, we are likely to see a rise in estrogen dependent endometrial pathology, including endometrial cancer, so clinicians need to be familiar with the evidence base and recommendations for investigation and diagnosis. There are also more complex issues to consider, such as unscheduled bleeding on hormone replacement therapy (HRT) and how to manage suspected endometrial pathology found incidentally on pelvic imaging for other indications.

During the past few decades, the number of postmenopausal women has increased in association with an increasingly aged population. In the UK the average age for a woman to reach the menopause is 52 years. The RCOG Expert Advisory Group Report, High Quality Women’s Health Care: A Proposal for Change, has highlighted the need for an adaptable and evolving approach to the provision of women’s health care, focusing on lifestyle changes, alongside an increasing demand for medical expertise in the management of postmenopausal health problems. This is further highlighted by the fact that the prevalence of obesity, a known independent risk factor for endometrial cancer, has more than doubled in the past 25 years within the UK. We can anticipate some 40% of Britons being obese by 2025 and that this will grow to 50% of adult women being obese by 2050. In tandem with these changes in demand, we are likely to see a rise in estrogen-dependent endometrial pathology, including endometrial cancer and its precursors.1,2

Postmenopausal women present with a range of the common gynaecological symptoms and complaints including postmenopausal bleeding and abnormal bleeding
on HRT. Women may also be referred to rapid access clinics with a co-incidental finding (e.g. on imaging for other reasons) of a thickened endometrium, fibroids or polyps that are completely asymptomatic. It is essential therefore that gynaecologists have knowledge of the normal physiological changes that occur around the menopause, and also the normal ultrasound appearance of the endometrium during the menstrual cycle and menopause.

This article provides an overview of the normal changes in the endometrium during the menopause, and reviews the evidence for the investigation and management of symptomatic and asymptomatic women with endometrial pathology. Endometrial cancer is highlighted in relation to other pathologies but not detailed as it is out of the scope of this article.

**Normal postmenopausal endometrium**

The histological appearance of the endometrium is dependent on the last hormonal pattern before the menopause. When the last cycle ends in deficient proliferation or secretion, simple atrophy will appear as sparse, narrow glands lined by atrophic epithelium within a dense, fibrous stroma. Cystic atrophy becomes apparent if irregular proliferation or cystic glandular hyperplasia occurs prior to the decline in estrogen levels. In cases of protracted hormonal decline, incomplete to complete atrophy will result (Figure 1).

After the menopause, endometrial thickening may be indicative of proliferation, cystic atrophy, simple hyperplasia, complex hyperplasia, atypical hyperplasia, or endometrial cancer. However, the ultrasound appearance of an apparently thickened endometrium may actually represent abnormalities within the endometrium or underlying myometrium such as endometrial polyps, submucous fibroids, adenomyosis or intrauterine adhesions.

**Endometrial polyps**

Endometrial polyps are common, with their prevalence appearing to increase with age. A screening study of the general population found more endometrial polyps in postmenopausal (11.8%) than premenopausal women (5.8%).

The exact aetiology of endometrial polyps is unknown. Estrogen and progesterone regulate the balance of proliferation and apoptosis in normal endometrium. In postmenopausal women, estrogen receptors are more prevalent in polyps than in adjacent normal endometrium. Genetic factors may explain polyp development, with reports identifying clusters of anomalies in chromosomes 6 and 12, which may alter the proliferative process, resulting in polyp formation in some women. Women using tamoxifen are at specific risk for the development of endometrial polyps with evidence from non-randomised studies suggesting a 30–60% prevalence in this group. Other risk factors include obesity and hypertension. In obese women it is the increased circulating levels of estrone that is likely to be the cause of polyp development and growth. The link with taking anti hypertensive medication and endometrial polyps is less clear but is independent of the antihypertensive used or BMI.

**Histopathology**

The microscopic appearance of endometrial polyps is typically a mixture of dense fibrous tissue (stroma), large and thick-walled vascular channels, and glandular spaces of varying shapes and sizes, covered by a surface epithelium. Typically the endometrial glands are arranged with the long axis of the glands parallel to the surface epithelium.

**Presentation**

Although vaginal bleeding is common on presentation, endometrial polyps may be asymptomatic, and an incidental finding on imaging for other indications. They account for 2–12% of all causes of PMB, (Table 1). Symptoms do not appear to correlate with the polyp number, size or location.

Co-existing cervical and endometrial polyps will be present in 24–27% of women at presentation.

**Malignant potential**

Most endometrial polyps are benign. A recent meta-analysis reviewed malignant risk in detail and suggested that the risk is highest in postmenopausal women with vaginal bleeding (2.3%).

A retrospective multicentre study looking at how often endometrial polyps were malignant in asymptomatic postmenopausal women found only one case of stage 1.
grade 1 endometrial carcinoma in the 1152 asymptomatic women who had endometrial polyps removed. The prevalence was 10 times lower than that in symptomatic women (\( P < 0.001 \)). The risk of polypoid cancer in asymptomatic women was 0.3%, which is 10 times less than symptomatic patients. The prevalence of atypical hyperplastic polyps was 1.2% in asymptomatic women compared with 2.2% in symptomatic women; \( P < 0.005 \).

At multivariate analysis, the polyps’ diameter was the only variable which was significantly associated with an abnormal histology, suggesting that when the mean diameter of an asymptomatic polyp was greater than 18 mm, the odds for an abnormal finding should be multiplied by 6.9.15

**Diagnosis**

TVUS in postmenopausal women has a reported sensitivity of 97%, specificity of 74%, positive predictive value (PPV) of 3.7 and negative predictive value (NPV) of 0.04 for the detection of endometrial abnormalities, compared with hysteroscopic biopsy.16

On TVUS polyps typically appear as hyperechoic lesions with regular contours within the uterine cavity, surrounded by a thin hyperechoic halo (Figure 2).17 Cystic spaces may also be present and correspond to dilated glands filled with proteinaceous fluid.18 The finding of a single feeding vessel to a suspected polyp has been demonstrated to confirm the presence of a polyp with a specificity and NPV of 95% and 94% respectively (Figure 3).19

In addition, colour Doppler can be used to differentiate between endometrial polyps and submucosal fibroids20 and it may also be helpful to distinguish between benign and malignant pathology. One prospective study suggests a sensitivity and specificity for endometrial cancer of 78.8% and 100% and of hyperplasia, 57.1% and 88.3% respectively.21

Saline contrast hysterosonography is accurate in evaluating the uterine cavity of pre- and postmenopausal women suffering with abnormal uterine bleeding (Figure 4). However, it fails more often in postmenopausal women compared with premenopausal women (13.5% versus 5.2%, \( P < 0.01 \)).22 This can be further attributed to an increased likelihood of cervical stenosis with advancing age, backflow or distention problems. There also seems to be a learning curve to perform the procedure, which once acquired, should reduce the failure rates to around 10%.

Saline infusion sonography (SIS) may be useful if there is any uncertainty about the presence or location of a polyp and may help in predicting endometrial malignancy of a focal lesion (Figure 4).23 Distension difficulties should also raise a suspicion of malignancy.24

Gel instillation sonography (GIS) is an alternative to SIS. A prospective study comparing the feasibility and accuracy of the two showed that GIS is a feasible, accurate alternative for the evaluation of women with abnormal bleeding with fewer technical failures.25

Hysteroscopy with guided biopsy is considered to be the gold standard with a sensitivity of 100% and a specificity of 97%, with an accuracy of 91% in diagnosing endometrial polyps.26 It also has the advantage of enabling removal if...
required, but inevitably carries operative morbidity and should not be used as the primary diagnostic tool.

Management
Endometrial polyps diagnosed in women with abnormal bleeding should be removed. The significance and management of asymptomatic polyps is less clear. The risk of malignancy of an asymptomatic polyp is low particularly if it is <18 mm in diameter. The risk of perforation during hysteroscopy is higher in asymptomatic women. Therefore the decision to remove such polyps must be weighed against the operative risks of hysteroscopic resection.

Endometrial hyperplasia
Endometrial hyperplasia is defined as a proliferation of glands of irregular size and shape with an increase in the gland:stroma ratio. A total of 15% of women presenting with PMB will be diagnosed with endometrial hyperplasia. The peak incidence of simple hyperplasia of 142 per 100,000 woman-years, and of complex hyperplasia of 213 per 100,000 woman-years, are both in the early 50s; while that of atypical hyperplasia (56 per 100,000 woman-years) is in the early 60s. Age-adjusted incidence decreases over time, especially for atypical hyperplasia.

Histopathology
Endometrial hyperplasia is classified into simple and complex hyperplasia based on the complexity and crowding of the glandular framework. Simple hyperplasia is a proliferative lesion with minimal glandular complexity and crowding with abundant stroma between glands. Complex hyperplasia represents a proliferative lesion with severe glandular complexity and crowding. The glands are variable in size and minimal stroma is seen between them. Usually, the glands are closely packed and represent a back-to-back position, although intervening stroma is consistently present. There should be at least twice as many glands as stroma in any field for a gland:stroma ratio of more than 2:1.

Complex/simple hyperplasia can be further classified by the presence of cytologic atypia where there are enlarged epithelial cells that are hyperchromatic with prominent nucleoli and an increased nuclear:cytoplasmic ratio. The diagnosis of atypia is based mainly on specific nuclear features and is usually accompanied by true stratification. The incidence of coexisting endometrial carcinoma ranges 6.4–43% in women undergoing hysterectomy for atypical hyperplasia.

The presence of endometrial hyperplasia is associated with exposure of the endometrium to unopposed estrogen. This can be from endogenous or exogenous sources.

Endogenous sources include increased levels of estrogen secondary to peripheral conversion of androstenedione in adipose tissue in women who are obese; estrogen secreting ovarian tumors such as, granulosa cell tumors and ovarian thecomas, and rarely androgen-secreting tumors. Exogenous sources include unopposed estrogen in hormone replacement therapy (HRT) preparations and selective estrogen receptor modulators (SERMs).

Presentation
Postmenopausal patients with endometrial hyperplasia will almost invariably present with vaginal bleeding.

Malignant potential of endometrial hyperplasia
The natural history of endometrial hyperplasia suggests that the risk of progression to endometrial carcinoma is dependent on the cytological appearance. A retrospective review of women with hyperplasia who remained untreated found that women who had been originally diagnosed with hyperplasia without atypia had a 2% risk of progression to carcinoma and these cases progressed to atypical hyperplasia before carcinoma. Of those with an initial diagnosis of atypical hyperplasia (simple or complex) 23% progressed to endometrial carcinoma. This figure rose to 29% in women with an initial diagnosis of complex atypical hyperplasia.

Endometrial carcinoma can be divided into two categories based on clinical features and pathogenesis. Type 1 tumors are associated with hyper-estrogenism and are characterised by low tumor grade, young age at diagnosis (age-specific incidence rates rise sharply from around the age of 40 years and peak in the 70–74 years age group then subsequently decline gradually), endometrioid histology, and a good prognosis. Type 2 tumours are not associated with a hyper-estrogenic state and generally occur in older women, are high-grade, include papillary serous and clear-cell histologies, and carry a relatively poor prognosis. There are also genetic differences between the two types outlined in Table 2.

Diagnosis
Ultrasonography
Endometrial hyperplasia can be seen on TVS as a thickened hyperechoic, often cystic endometrium (Figure 5). The absence of a focal lesion, negative sliding sign and no obvious feeding vessel would be more suggestive of hyperplasia, prompting endometrial biopsy. If there is any uncertainty, SIS may be useful for further delineation.

An endometrial thickness of ≤4 mm in a symptomatic postmenopausal woman is unlikely to be associated with the development of endometrial carcinoma. However, a recent systematic review and meta-analysis looked at the capacity...
for the endometrial thickness measurement to diagnose endometrial carcinoma in asymptomatic postmenopausal women. This concluded that using endometrial thickness as a screening test for endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic postmenopausal women not using HRT could not be justified. 

**Table 2. Different characteristics of type 1 and type 2 endometrial cancer**

<table>
<thead>
<tr>
<th>Characteristic feature</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed estrogen</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Menopausal status</td>
<td>Peri-postmenopausal</td>
<td>Postmenopausal</td>
</tr>
<tr>
<td>Precursor lesion</td>
<td>Atypical hyperplasia</td>
<td>Endometrial intraepithelial carcinoma</td>
</tr>
<tr>
<td>Tumour grade</td>
<td>Low</td>
<td>Often minimal</td>
</tr>
<tr>
<td>Myometrial invasion</td>
<td>Often minimal</td>
<td>Often deep</td>
</tr>
<tr>
<td>Histologic subtype</td>
<td>Endometroid</td>
<td>Serous and clear cell</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Indolent</td>
<td>Aggressive</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>PTEN mutation</td>
<td>P53 mutation</td>
</tr>
<tr>
<td></td>
<td>Microsatellite instability</td>
<td>K-RAS mutation</td>
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</table>

**Pipelle endometrial biopsy**
Endometrial sampling with a pipelle is an effective and relatively inexpensive method of collecting tissue for histologic diagnosis. One study found a 99% sensitivity for the detection of endometrial cancer; this has been found to be lower for endometrial hyperplasia. The insufficient biopsy rate with a pipelle is slightly higher compared with curettage, although there is no difference between the two when compared with pathology at hysterectomy.

Routine screening with endometrial biopsy (EMB) in asymptomatic women on tamoxifen is of limited value. All abnormal bleeding or spotting should be investigated but pipelle EMB rarely provides useful diagnostic information in women treated with tamoxifen; therefore symptomatic women with a thickened endometrium should be investigated with a hysteroscopy and targeted biopsy. This is primarily because of tamoxifen-induced subepithelial stromal hypertrophy. Pipelle endometrial biopsy can yield a small amount of tissue suitable for diagnosis. It could result in no tissue identified, tissue inadequate for diagnosis, no endometrium identified, and endometrium inadequate for diagnosis. Minimal tissue yield for diagnosis is evident in patients with thin, regular endometrium with an endometrial thickness not exceeding 7 mm, as examined hysteroscopically or ultrasonically. Interpretation of focal changes of glandular tortuosity and crowding in disrupted endometrial fragments that are subject to considerable biopsy artefact represent another difficulty.
Hysteroscopy and/or dilatation and curettage

Hysteroscopy is generally accepted as the gold standard for evaluating the endometrial cavity. Historic dilation and curettage alone however is no longer acceptable. Outpatient hysteroscopy with targeted biopsies has become common place. It has been evaluated and in conjunction with targeted biopsies, outpatient hysteroscopy has a sensitivity, specificity, PPV, and NPV of 98%, 95%, 96%, and 98%, respectively, when compared with the histologic findings at hysterectomy.

Management of endometrial hyperplasia

Several studies have demonstrated the efficacy of conservative management of endometrial hyperplasia with progestins and gonadotropin-releasing hormone-agonists (GnRH-agonists).

The consideration of conservative management in women with endometrial hyperplasia depends on several factors, including the patient’s age, reproductive status, surgical risk and the presence of cytologic atypia in the biopsy specimen.

A cohort study of women with an average age of 55.9 years assessed the likelihood of histologic persistence/progression of complex hyperplasia and atypical hyperplasia in those treated with progestogens versus untreated. It found that treatment of atypical hyperplasia with at least a medium dose of progestogen, for a duration of at least 3 months was associated with a substantial increase in the likelihood of regression of the lesion. However, one quarter of the women with atypical hyperplasia and who were treated had persistence or progression.

Another retrospective cohort study compared the outcomes of women with either complex or atypical endometrial hyperplasia who received either progestogen or no treatment. The follow up was for a median of 5.3 years and the study reported that the endometrial carcinoma risk was reduced three- to five-fold in women with complex or atypical hyperplasia who had taken progestin. The hysterectomy risk was also decreased.

A systematic review and meta-analysis comparing the regression rate of endometrial hyperplasia between oral progestogens and levonorgestrel-releasing intrauterine system (LNG-IUS), found that oral progestogens achieved a lower rate compared with LNG-IUS for complex and atypical hyperplasia. There was no statistical difference in simple hyperplasia.

A recent multicentre randomised trial compared the treatment of endometrial hyperplasia with LNG-IUS; oral medroxyprogesterone acetate (MPA) 10 mg administered for 10 days per cycle, or continuous oral MPA 10 mg daily, for 6 months. The LNG-IUS-treated group achieved 100% histologically normal endometrium after 6 months of therapy however it has shown 96% and 69% for women in the continuous oral group and cyclical progestogens, respectively.

There have been some small studies showing that a GnRH-agonist with either LNG-IUS or tibolone show favourable results in the treatment of premenopausal woman with atypical hyperplasia, however, close monitoring of the endometrium was recommended after the cessation of treatment due to the probability of relapse.

Hormone replacement therapy

Postmenopausal women taking estrogens without a progestogen are at increased risk of endometrial hyperplasia and carcinoma. Of 1176 healthy postmenopausal women randomised to receive unopposed estradiol or continuous combined estradiol and progestogen (of varying doses), 14.6% of women in the unopposed group developed endometrial hyperplasia (two of which were atypical). Less than 1% of patients in the continuous combined groups developed endometrial hyperplasia. A 10-year study of endometrial appearance in women on sequential or combined HRT compared with no treatment concluded that women on HRT had a thicker endometrium and a higher incidence of bleeding. No difference in the incidence of endometrial cancer was identified between the two groups, however it concluded that women with unscheduled bleeding on HRT require further investigation by hysteroscopy and biopsy if the endometrial thickness was greater than 8 mm.

Comparing combined HRT to sequential HRT, the likelihood of identifying an endometrial pathology was significantly higher in patients with endometrial thickness >4 mm than the incidence observed in patients with unscheduled bleeding.

Selective estrogen receptor modulators

Tamoxifen-induced stromal hypertrophy can be confused with endometrial thickening on ultrasound (Figure 5). The
endometrial thickness increases with increasing duration of tamoxifen use at a rate of 0.75 mm a year, with the mean endometrial thickness being 12 mm after 5 years of use (range 6–21 mm). After discontinuation of treatment, the endometrium decreases by 1.27 mm a year.52 A randomised, double-blind trial conducted in 1994 assessed the effect of 20 mg of tamoxifen per day on the uterus and ovaries in postmenopausal women at high risk for developing breast cancer.53 During the follow-up period (3–75 months), 16% of women receiving tamoxifen developed atypical hyperplasia. There were no cases of hyperplasia in the placebo group. Thirty-nine percent of women receiving tamoxifen developed other types of abnormal histology including endometrial proliferation, polyps or mitotic cells. Endometrial thickness of >5 mm was found in more than 80% of women after 1 year of tamoxifen use.59

A recent randomised controlled trial observed the effect of LNG-IUS used prophylactically on women with breast cancer treated with tamoxifen. It observed women over a 5-year follow-up period and found that LNG-IUS prevented de novo endometrial polyps developing. However, the role in preventing endometrial hyperplasia and adenocarcinoma, as well as its effect on risk of breast cancer recurrence remained uncertain.54

Raloxifene is a SERM used in postmenopausal women for the prevention of osteoporosis. It has an estrogen agonist activity on bone and serum lipid metabolism, and antagonistic activity in the uterus and breast. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial assessed the efficacy and safety of raloxifene in postmenopausal women with osteoporosis. This found that women were significantly more likely to have a documented endometrial thickness greater than 5 mm on at least one follow-up ultrasound without an increased risk of endometrial hyperplasia or endometrial carcinoma.55

Atrophic endometritis

After the menopause, chronic endometritis can easily develop in low resistance atrophic endometrium and may be associated with necrotic polyps or carcinoma. Due to atrophy of the endometrium and diminution of its blood supply, ascending infection may occur with organisms of low virulence. Tuberculosis is a rare cause, although in some countries tuberculosis is not an uncommon aetiologic agent. Radiotherapy or chemotherapy can also cause senile endometritis.

Histopathology

Although the causative organisms of acute endometritis are numerous, the inflammatory reactions to them are generally the same. Stroma and glands are diffusely or focally infiltrated with polymorphonuclear leukocytes intermixed with lymphocytes and occasional plasma cells which are suggestive of chronic endometritis.3

Presentation

Generally postmenopausal women with endometritis are asymptomatic but may present with generalised vulval and vaginal itching, vaginal discharge or PMB. Pyometra can occur in association with cervical stenosis and pus may accumulate in conjunction with chronic endometritis. This generally presents with purulent or bloody discharge but can present with lower abdominal pain, rigors and fever.

Diagnosis

While the sonographic appearance of the uterus and endometrium may be normal in early endometritis, findings may include thickened, heterogeneous endometrium with intracavitary fluid with or without signs of intrauterine gas.56 EMB may be sufficient to make the diagnosis along with genital swabs, however, exclusion of coexisting malignancy may require hysteroscopy and EMB with antibiotic prophylaxis.57

Management

Management of atrophic endometritis will depend mainly on the clinical presentation and identification of an infective cause. The atrophy associated with the postmenopausal withdrawal of estrogen can be treated with topical estrogen cream, without the need for progestogen therapy.58 Long-term treatment may be required as symptoms frequently recur after cessation of treatment.

Figure 6. Tamoxifen-associated endometrial lesion. Transvaginal US scan of an asymptomatic patient receiving tamoxifen reveals a markedly thickened, heterogeneous endometrial stripe with multiple cystic areas.
Screening for endometrial pathology

Uterine corpus cancer was the fourth most common cancer in women in the UK in 2011 (approximately 92% endometrial cancer, the remainder being uterine carcinosarcomas and sarcomas). The age specific incidence of uterine cancer has increased by 23% since the last census in 2000–2002.

TVUS is useful for 'triaging' women presenting with PMB to determine which ones require further diagnostic tests and which women can be reassured. Generally, 5 mm is used as the threshold to define abnormal endometrial thickening.35

If the endometrial thickness is not adequately seen in a symptomatic woman, a hysteroscopy should be recommended. A cross-sectional study observing the risk of endometrial cancer in these women found that the odds of endometrial cancer in women whose endometrial thickness was not visualised were significantly higher than women with an endometrial thickness of 5–9.9 mm.60 It is possible that this relates to the blurring of the endometrial/subendometrial interface on ultrasound in the presence of invasive endometrial cancer.

Endometrial thickness and endometrial sampling have also been proposed as possible screening modalities for endometrial cancer in asymptomatic women. There is a baseline incidence of a thickened endometrium (>4.5 mm) in postmenopausal women of up to 17%, while there is a low incidence of cancer <1% in an unselected population.61–63 However, an incidental finding of an endometrial thickness of >5 mm in an asymptomatic woman often triggers a referral to the gynaecologist.

A systematic review and meta-analysis evaluated the sensitivity and specificity of TVS to diagnose endometrial carcinoma in asymptomatic postmenopausal women. This found the sensitivity and specificity changed from 0.83 and 0.72 when using a 5-mm cut-off to 0.33 and 0.94 for a 6-mm cut-off. The authors conclude that using endometrial thickness as a screening test for endometrial carcinoma and atypical endometrial hyperplasia in asymptomatic postmenopausal women not using HRT could not be justified.35

A retrospective review of postmenopausal women subjected to a hysteroscopy with particular attention to those with endometrial thickening as the indication, found that using TVS as a screening tool in asymptomatic postmenopausal women generated 93.2% false positive results. This again suggests that this is not a beneficial screening tool.64

Screening asymptomatic women seems to have no prognostic advantage compared to the screening of symptomatic women and only increases the number of unnecessary procedures. The length that women have their symptoms however strongly correlates with the tumour stage.63

Likewise, the routine screening of asymptomatic women on HRT is not recommended. The Postmenopausal Estrogen/Progesteron Interventions (PEPI) trial64 found no cases of cancer or atypical hyperplasia in women with an endometrial thickness of <5 mm. TVS had a PPV, NPV, sensitivity, and specificity for endometrial hyperplasia or carcinoma of 9%, 99%, 90%, and 48% respectively. Using a 5 mm cut-off in asymptomatic women on HRT would have required more than 50% of the subjects to undergo an EMB, when only 4% had serious disease.

Mossa et al. found that although women on HRT had a thicker endometrium than women without HRT, there was no difference in the incidence of endometrial cancer. They recommended that only symptomatic women with an endometrial thickness of >8 mm should undergo a hysteroscopy and biopsy.50

Routine ultrasound surveillance for asymptomatic women using tamoxifen is not suggested due to the low specificity and low positive predictive value.39 Pipelle EMB also rarely provides useful diagnostic information.38 Therefore, evaluation of the endometrium in these women should be limited to those experiencing vaginal bleeding.39

Conclusion

Postmenopausal women presenting with bleeding should be further investigated and managed accordingly. Ultrasound measurement of endometrial thickness is a useful noninvasive technique for preliminary evaluation of such women. EMB is indicated in symptomatic women with a thickened endometrium or persistent bleeding.

An incidental finding of endometrial pathology in asymptomatic postmenopausal women often poses a clinical management dilemma. Polyps found in asymptomatic women do not routinely need to be removed, however, consideration should be taken regarding the size and clinical background and the benefits of removal should be weighed against the risks of the procedure.

Asymptomatic women with an incidental finding of an increased endometrial thickness need to be managed on an individual basis, taking into consideration any risk factors for endometrial cancer, the actual thickness of the endometrium and any other positive findings on TVS.

The routine investigation of women with asymptomatic postmenopausal pathology cannot be justified on the basis that it would reduce morbidity or mortality due to endometrial carcinoma.

The literature does not support routine screening of asymptomatic postmenopausal women for endometrial cancer as it has not proven efficacious or cost effective.

Contribution of authorship

MO initiated the idea of reviewing the subject. MO/JF performed the literature search on the subject and compiled the review with JR/HS/JJ as supervisors. All authors approved
the final version of this article. Ultrasound images provided by MO/JR/JJ.

Disclosure of interests
The authors of this article have no conflict of interest to disclose.

References
23 Epstein E, Valentin L. Gray-scale ultrasound morphology in the presence or absence of intrauterine fluid and vascularity as assessed by color Doppler for discrimination between benign and malignant endometrium in women with postmenopausal bleeding. Ultrasound Obstet Gynecol 2006;28:89–95.

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Management of endometrial menopausal pathology


