Endometrial Cancer: Risk Factors and Early Diagnosis in Low-Resource Countries

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Abstract

Many risk factors are recognized for the development of endometrial cancer (EMC). A strong risk factor for hereditary nonpolyposis colonic cancer is an indication for EMC screening. Any women at risk must be counseled and evaluated in detail about their risk for many cancers, especially colonic and EMC. This is usually done in higher levels of health service rather than in a low resource setting. Also, the data concerning risk have been derived in these higher resource settings and are not necessarily transferable to other populations. For EMC, the screening methods comprise an annual transvaginal ultrasound beginning at 30–35 years of age and periodic endometrial sampling. EMC screening is not recommended in any woman with low or moderate risk or those without familial predisposition. Nevertheless, patients should be educated for the signs or symptoms suggesting an endometrial lesion, such as postmenopausal bleeding. An endometrial biopsy with a small cannula is considered an initial diagnostic step. This procedure can be performed in an out-patient setting while uterine curettage is reserved for a woman with inadequate, inconclusive, or hyperplasic tissue from endometrial biopsy. Transvaginal ultrasonography may be useful as an adjunct in selected cases depending on the availability, physician training, or resource setting. Hysteroscopy, as a diagnostic and therapeutic maneuver, requires specialized operative skill and may not be available in limited health care environments.

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Introduction

Endometrial cancer (EMC) is the third most-common gynecologic cancer after breast and cervical cancers worldwide. EMC appears more important in terms of number of new cases than in terms of mortality [1, 2].

A trend of increasing incidence of EMC was seen in the global statistic report 2008 compared to 2002. This increase was in both developed and developing countries [1, 2]. A total number of 145,000 new cases in 2008 were reported in developing countries and 142,300 in developed countries [1]. The corresponding figures of mortality had also increased to a total of 41,000 and 32,000 deaths, respectively. These resulted in a higher "mortality to new case ratio" in developing than in developed countries: 0.28 compared to 0.23.

Early diagnosis is a key factor for success in cancer treatment. This is particularly true for EMC. Early detection of the cancer as well as timely treatment usually results in a good outcome. Aside from stage of disease and an appropriate intervention, intrinsic risks of cancer development and characteristic features of each cancer type are also important prognostic factors. EMC has been classified according to different pathophysiologic pathways. Type I involves exposure to high levels of estrogen while type II is independent of hormone exposure [3]. Type I is represented by endometrioid histology while type II is composed of high grade histologies with more aggressive behavior, i.e., serous or clear cell carcinomas. In later years, EMC associated with Lynch syndrome has been added as type III [4].

With the burden of cancer in low and middle income countries leading to increases in cancer-related morbidity, mortality, and economic cost, it is prudent to evolve cancer control strategies aimed at improving outcome while minimizing toxicity and cost. Towards that goal, guidelines should encompass the entire management spectrum from primary prevention, screening, and diagnosis at one end to palliative treatment of advanced EMC at the other end.

We have published an article involving management of EMC in Asia in 2009 [5]. The specific recommendations involving screening, diagnosis, and treatment were made according to the evidence-based consensus panel process to create resource-sensitive guidelines. The model was the breast cancer management framework formulated by the Breast Health Global Initiative (BHGI) [6]. This Initiative has developed and applied to a four-tier system as follows: basic level, limited level, enhanced level, and maximal level resources. This chapter will focus on the risk factors and screening together with early diagnosis of EMC in low resource settings or at the basic and limited levels.

Risk Factors

As mentioned earlier, EMC can arise through three different pathophysiologic pathways based on the relationship with the levels of estrogen and familial risk. Some characteristic features of three types of EMC are shown in Table 8.1. Any conditions that are associated with the high status of estrogen are risk factors, particularly for type I EMC. The risk relationship to each factor is variable. Some recognized risk factors are exemplified in the following sections.

High Estrogen Level

The source of estrogen may be endogenous or exogenous. Estrogen as a single entity increases relative risk between 3.1 and 15 [7, 8]. This depends on the amount and duration of exposure [8, 9]. The recommendation for hormonal replacement therapy in a perimenopausal woman with an intact uterus is a combined use of estrogen and progesterone [10]. Herbal or traditional medicines may contain estrogen constituents, either natural or manmade. Long-term users of these estrogen-containing substances may have a risk of EMC.

Another source of estrogen is endogenous, i.e., hormone-producing tumors [11], polycystic ovary syndrome, or chronic anovulation [12].

Table 8.1 Characteristic features in each type of endometrial cancer

	Type I (low grade)	Type II (high grade)	Type III (familial)
Age at diagnosis	Perimenopause	Late postmenopause	Approximately 10 years younger than common age incidence in type I
Risk factors	Estrogen related	Not estrogen related	Familial risk (Lynch syndrome)
Endometrial background	Hyperplastic	Atrophic	–
Diabetes mellitus, obesity	Often associated	No association	No association
Grading and pathology	Low grade, endometrioid, mucinous, villoglandular	High grade, non-endometrioid CA: clear cell or serous CA	More commonly non-endometrioid CA
Stage	Low stage	advanced stage	–
Myometrial invasion	Minimal	Deep	–
Clinical course and prognosis	Slow progressive, favorable prognosis	Aggressive behavior, unfavorable prognosis	–

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These conditions can cause high circulating estrogen levels without or inadequate counteracting progesterone. A prolonged high estrogen will subsequently result in endometrial hyperplasia and eventually carcinoma.

Endometrial Hyperplasia

The risk of progression of endometrial hyperplasia to EMC can be as high as 47 % [13]. Although histochemical stains, analysis of ploidy or molecular studies may help in distinguishing endometrial hyperplasia from EMC [14–16], these tests require special laboratory techniques and may not be available in basic or limited resource settings. Standard histologic evaluation remains the most important tool for a diagnosis [17]. One must also be aware that EMC may readily coexist with endometrial hyperplasia in up to 43 % cases [18].

Tamoxifen Use

Tamoxifen, an antiestrogen, is used in the adjuvant treatment for hormone receptor positive breast cancer. However, the compound exerts a weak estrogenic activity on the endometrium and can stimulate endometrial proliferation, hyperplasia, and cancer. The risk of developing EMC seems to depend on the duration and dose of tamoxifen [19]. The relative risk ranged from 1.9 to 7.5 [20–23], with an absolute annual risk of about 2 per 1,000 patients [24, 25]. Many factors contribute to this wide range of risk, including the failure of some studies to control for confounding risk factors such as concurrent use of hormone replacement therapy or obesity [20, 21]. Furthermore, the conclusions of many studies are limited by the retrospective nature of those studies.

Proven benefits in preventing or controlling recurrences of breast cancer and occurrence of cancer in the contra lateral breast must be weighed against its risk. Findings from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial suggested that an aromatase inhibitor, i.e., anastrozole, was superior to tamoxifen as adjuvant therapy for breast cancer. It is hoped that tamoxifen-induced EMC will become a diminishing problem [26]. However, the relatively higher cost of an aromatase inhibitor makes the continued usage of tamoxifen more likely in developing countries. This risk factor for EMC will probably persist for several years.

Obesity

The incidence of EMC is relatively higher in obese woman. Any woman with a 5 kg/m^2 increase of body mass index (BMI) will have 1.59-fold relative risk of EMC [27].

Diabetes Mellitus and Hypertension

A woman with diabetes mellitus and hypertension, with or without obesity, will have higher risk of EMC. This relationship is related to an insulin-resistance with associated higher levels of insulin-like growth factors and hyper-insulinemia [27–29].

Familial Genetic Factor

Although there has been no specific or highly predictive genes directly related to familial EMC, there is an increased chance that EMC will occur in a first-degree relative of a patient with the diagnosis. The better recognized familial cancer related to EMC is hereditary nonpolyposis colorectal cancer or Lynch syndrome. Any woman affected with this syndrome will have a lifetime risk of 27–71 % for EMC, much higher than the 3 % risk in the general population. The age at diagnosis in these women is approximately 46–54 years old or generally younger than that of a sporadic case of EMC [30, 31].

Women with Lynch syndrome who are diagnosed with colorectal cancer will have a sixfold increased risk of developing EMC compared to the general population. Indeed, approximately one fourth of them will have EMC within the following 10 years [32].

Breast Cancer

Women with a history of breast cancer certainly have a higher risk of developing EMC due to common risk factors such as obesity and nulliparity. A woman with breast cancer who carries the BRCA1 gene mutation has a relative risk of approximately 2.6, especially when she is also a tamoxifen user [33].

Nulliparity

The risk of EMC is inversely related to the number of pregnancies. This is somewhat related to the anovulatory condition which is frequently found in woman with fertility problems [34].

Nutrition

There have been no definitive data regarding the modification of caloric or food intake to reduce the risk of EMC [35]. Long-term consumption of phytoestrogen from soy bean products [36] or alcohol intake [37] may be a risk factor for endometrial hyperplasia and cancer. On the other hand, coffee or green tea beverages have been reported as protective factors [38, 39].

Screening

There is no proven role for screening in asymptomatic women who are at average or medium-risks for the development of EMC. These risk groups include women with nulliparity, late menopause, or even receiving tamoxifen therapy [19]. Screening should only be considered for high-risk women who may be genetic mutation carriers of Lynch syndrome or those with suspected autosomal predisposition to colon cancer [40]. An annual transvaginal ultrasonography and endometrial aspiration biopsy for endometrial assessment should be started at 30–35 years of age [41]. Some researchers have proposed beginning at a younger age of 25 years [42]. One systematic review made the recommendation that individuals with an inherited predisposition to Lynch syndrome begin genetic counseling and basic medical surveillance at age 21 [43]. Colonoscopy should start at ages 20–25 years (or 10 years less than the youngest age of diagnosis

Table 8.2 Summary for screening and diagnosis

	Consensus based on level of resource			
Areas of discussion	Basic	Limited	Enhanced	Maximal
Screening				
Normal women[a]	No	No	No	No
High-risk women[b]	No	No	Yes	Yes
Diagnosis[c]	Yes	Yes	Yes	Yes

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[a]Screening for endometrial cancer in average or medium risks women is not recommended except for history taking and physical examination including pelvic examination which could be done in all levels

[b]Screening in high-risk women requires detailed familial history and genetic evaluation, endometrial biopsy, and ultrasound of the pelvis in addition to complete physical and pelvic examination. These are generally not available in basic and limited settings

[c]Diagnostic tools include endometrial sampling biopsy or uterine curettage with or without transvaginal ultrasound evaluation depending on the availability of the instrument and the operative setting

in the family) for every 1–2 years, and endometrial sampling and transvaginal ultrasound of the uterus (and ovaries) should begin at ages 30–35 years [43]. These recommendations should be individualized after appropriate discussion with the patient and probably be best conducted by an expert with genetic counseling support. In basic or limited resource medical levels, this may be difficult. The management of such families in populations where the genetics are either ill undefined or unavailable remains a major clinical challenge.

Some authors have proposed genetic testing for first-degree relatives of woman aged <50 years with double primary cancers of colorectum and endometrium. In addition, the patients should have measurements of the serum cancer antigen (CA) 125 and endometrial biopsy with optional hysteroscopy [44]. DNA replication errors, which represent microsatellite-marker analyses of tumor DNA [45], and associated germ line mutations in MLH1, MSH2, and MSH6 [44] are reported in women with Lynch syndrome. These tests require special laboratory techniques which may not be available or are too expensive in the basic or limited resource settings.

The summary of EMC screening based on the four tiers of resource settings is shown in Table 8.2 [5].

Early Diagnosis

Although women with average- or medium-risks for EMC are not recommended for a routine screening, all women should be educated for abnormal symptoms or signs associated with endometrial lesions.

Indications

Cervical cytology is not an acceptable method used to screen for or used to make a diagnosis of endometrial pathology because of its low sensitivity. Nevertheless, the presence of endometrial cells on a pap smear in a postmenopausal woman or atypical glandular cell in a woman aged ≥35 years old are indications for endometrial tissue assessment [46].

Abnormal uterine bleeding is the most common sign and symptom of EMC found in 90 % of the patients [47]. Five to twenty percent of postmenopausal women with uterine bleeding have EMC. The presence of such bleeding is certainly an indication for an evaluation of endometrial tissue pathology. Other indications are pyometria in a postmenopausal woman, abnormal bleeding in a woman ≥40 years old, or a younger age woman with risk factors for endometrial lesions [47].

Ultrasonography

A detailed discussion on endometrial sonography appears next. Transvaginal ultrasonography, which is a noninvasive procedure, can suggest a possible cause of endometrial lesion. This is especially true when caused by an atrophic endometrium. The latter is the most common cause of postmenopausal uterine bleeding. A postmenopausal woman with an endometrial thickness of less than 4–5 mm has minimal risk for significant endometrial pathology [48, 49]. The risk of EMC in women with postmenopausal bleeding but whose endometrial thickness on transvaginal ultrasound is less than 5 mm is only 1 in 917 [48]. Nevertheless, this negative predictive value of the endometrial thickness has been validated only in postmenopausal women. Aside from this caveat, additional limitations of ultrasound exist, i.e., the presence of fibroids, previous surgery, marked obesity, and an axial uterus [49]. Figures 8.1, 8.2, 8.3, 8.4, 8.5, 8.6, and 8.7 show various physiologic and pathologic changes of endometrium seen on transvaginal ultrasonography.

Obtaining Endometrial Tissue for Histopathology

The operative procedure to obtain endometrial tissue for pathology can be achieved by endometrial sampling which is considered a gold standard. An endometrial aspiration biopsy can be performed through a plastic cannula (e.g., Pipelle®, Cooper Surgical, Trumbull, CT) instrument which is widely available at present. The procedure can be done in an out-patient setting. The cost is nominal compared to conventional uterine curettage under anesthesia. The pathology obtained by endometrial biopsy correlates well with that obtained by uterine curettage, with 85–98 % accuracy compared to the standard dilatation and curettage [50, 51]. One systemic review and meta-analysis compared the results from endometrial sampling to those from hysteroscopic biopsy or hysterectomy in over 7,000 women [50]. Less than 5 % had inadequate tissue for diagnosis. The sensitivity of endometrial biopsy to determine EMC and endometrial hyperplasia was 99.6 % in postmenopausal women and 91 % in premenopause. The specificity ranged from 98 to 100 %.

Nevertheless, histologic tumor grading from a small piece of tissue obtained by endometrial biopsy may not be highly accurate. Tumor grade from a hysterectomy specimen is upgraded from the earlier biopsy sample in approximately 30 % [52, 53]. This issue should be particularly concerning when hysterectomy for EMC is intended in the basic or limited settings wherein complete surgical staging including lymph node surgicopathological evaluation may not possible.

Another limitation of endometrial biopsy, aside from the accurate grading, is when the endometrial pathology is focal or involving an area less than 50 % of the uterus. Such conditions may result in inadequate diagnostic tissue as often as 15 % of cases (Fig. 8.8a) [54]. A formal uterine curettage is then required to rule out the presence of malignancy. Also, hyperplasic endometrial tissue in the endometrial biopsy is an indication for uterine curettage because of the possibility of coexisting EMC. This has even greater importance if complete surgical staging for EMC is not possible or a standard practice in that particular setting. Figure 8.8a–f shows the histopathology of inadequate tissue for diagnosis (Fig. 8.8a), simple and complex hyperplasia (Fig. 8.8b, c), and various types of endometrial carcinoma (Fig. 8.8d–f).

Uterine curettage is necessary when the index of suspicion for EMC is high, when the biopsy is inconclusive or inadequate, or when unexplained recurrent uterine bleeding without a clear etiology [54]. In these events, hysteroscopy to directly evaluate gross endometrial lesion and to assist in selecting area for tissue biopsy is another useful procedure. Although this hysteroscopy may cause dissemination of EMC cells into the peritoneum, the impact on survival has not been evidenced [55]. Nevertheless, hysteroscopy requires special expertise and additional expense. Hysteroscopy use in basic and limited resources may not be practical.

Figure 8.9 shows an algorithm of procedures used for EMC diagnosis.

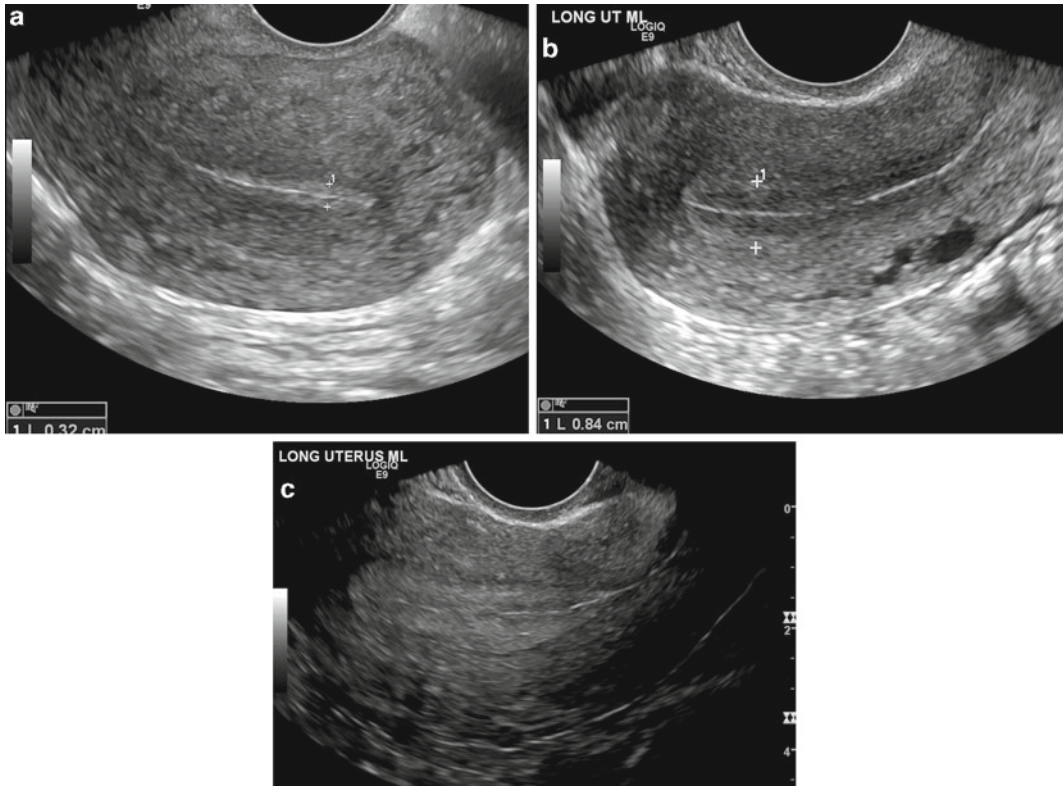

Fig. 8.1 Transvaginal sonographic images of the premenopausal endometrium. (**a**) Menstrual phase. (**b**) Proliferative phase. (**c**) Secretory phase

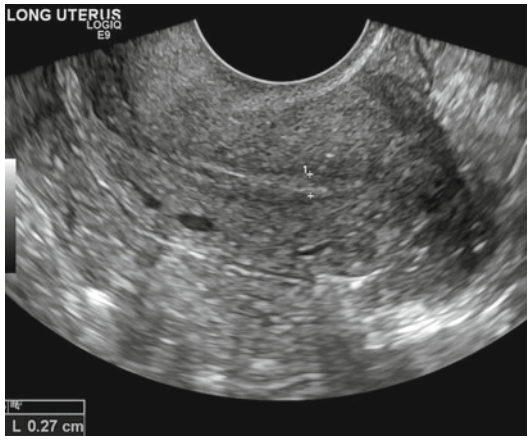

Fig. 8.2 Sixty-five-year-old postmenopausal woman with abnormal bleeding. Sagittal endovaginal sonogram demonstrated a thin 3 mm endometrium suggestive of endometrial atrophy

Endometrial Sonography

The endometrial lining of the uterus is optimally evaluated by sonography. The endometrial stripe is well visualized on transabdominal ultrasound with a full bladder; however, the most detailed analysis of the endometrium is best performed by endovaginal sonography (EVS). Higher resolution of the transducer combined with a shorter distance to the area of interest results in superior visualization of the endometrium and allows optimal measurement of the endometrial thickness and assessment of endometrial abnormalities. EVS in the symptomatic postmenopausal woman with endometrial sampling in those with an abnormal endometrium is of proven benefit in the early detection of EMC.

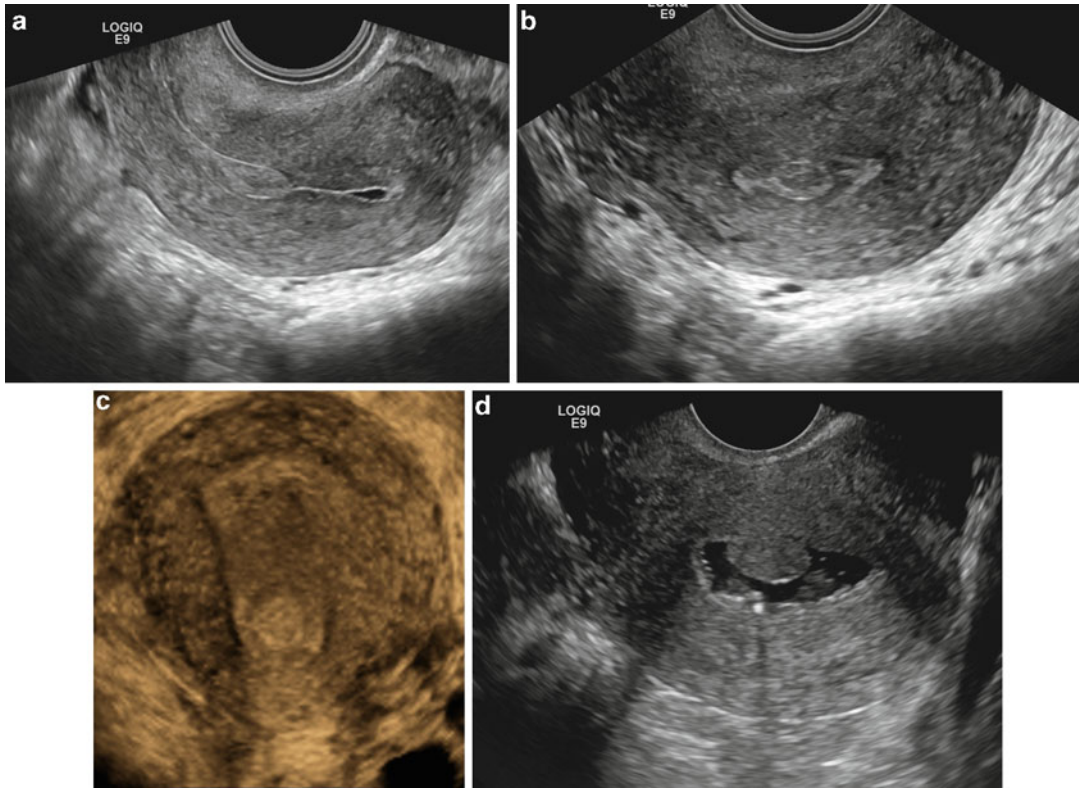

Fig. 8.3 Sonographic images demonstrating an endometrial polyp in the uterus. (**a**) An image in the sagittal plane demonstrating an intracavitary hyperechoic mass suggestive of a polyp. (**b**) An image in the transverse plane showing the polyp in the endometrial cavity. (**c**) 3D Image of the uterus shows an intracavitary mass. (**d**) Sonohysterogram demonstrates a broad based polyp outlined by saline distended endometrial cavity

Normal Appearance of the Endometrium

Ultrasound is the primary imaging modality for assessment of the endometrium. The spectrum of normal appearance of the endometrium varies depending on the menstrual status of the patient and the phase of the menstrual cycle.

Premenopausal Endometrium

In a premenopausal woman, the appearance of endometrium varies depending on the phase of the menstrual cycle. During the menstrual phase, the endometrium is the thinnest and appears as an echogenic line measuring 4 mm or less (Fig. 8.1a). The thickness is measured during an endovaginal scan in the sagittal plane of the uterus with cursors placed at the echogenic border with the myometrium. During the proliferative phase of the menstrual cycle (days 6–14), the endometrium becomes thicker and progressively echogenic relative to the myometrium [56]. In the preovulatory phase, the endometrium assumes a multilayered appearance with a hyperechoic basal layer, a hypoechoic inner layer, and a thin central echogenic layer; the endometrial thickness can measure up to 11 mm (Fig. 8.1b). Such a multilayered appearance disappears after ovulation. There is progressive thickening and increased echogenicity of the endometrium in the secretory phase during which a thickness of 16 mm may be reached (Fig. 8.1c). During the secretory phase, there may also be increased echogenicity and posterior acoustic enhancement of the endometrium; such an appearance has been attributed to the presence of stromal edema and distended glands [56]. An understanding of the physiologic cyclic changes in the appearance of the endometrium is important in order to distinguish normal from endometrial hyperplasia.

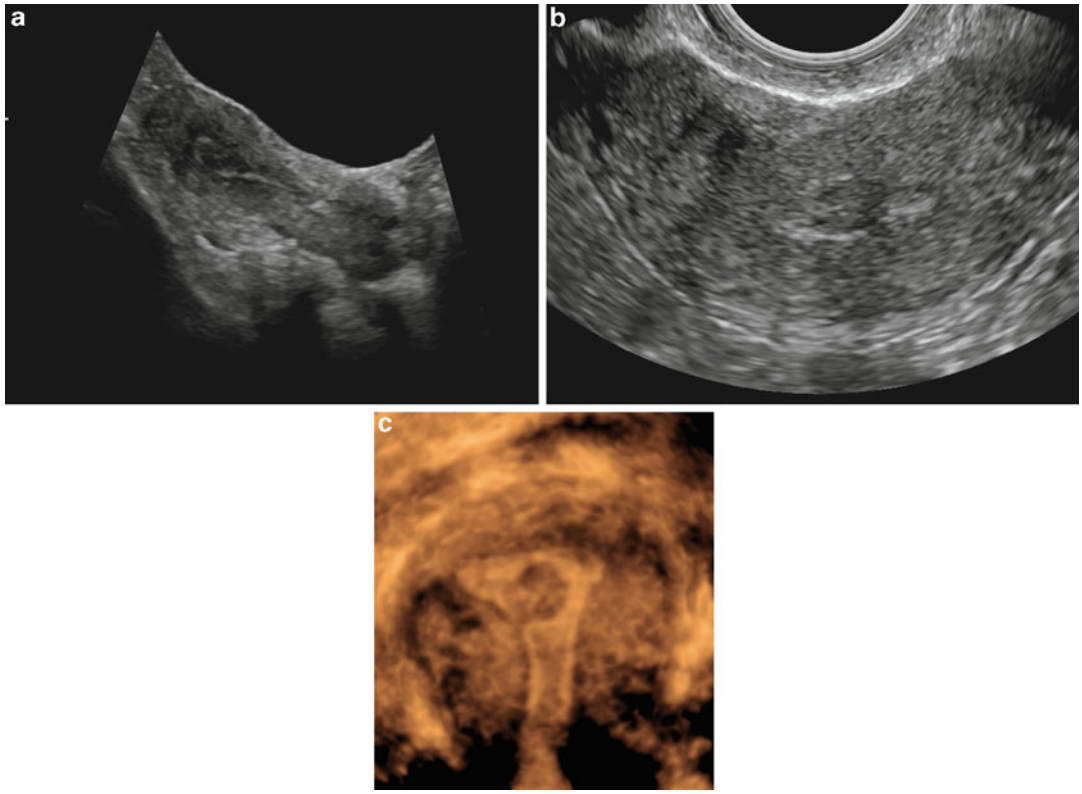

Fig. 8.4 Sonographic images demonstrating an intracavitary fibroid. (**a**) Sagittal image of the uterus on a transabdominal scan demonstrates a hypoechoic intracavitary mass proven to be an intracavitary fibroid. (**b**) An image in the transverse plane on endovaginal scan showing the intracavitary mass. (**c**) A 3D Image demonstrating the intracavitary fibroid

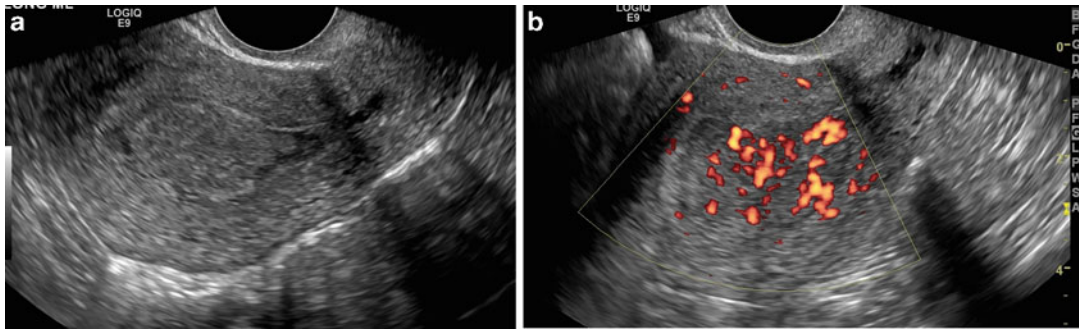

Fig. 8.5 A 31-year-old woman with abnormal uterine bleeding and history of polycystic ovarian disease. Endovaginal sonographic images show abnormally thickened endometrium with increased blood flow seen on color Doppler imaging. Histology showed complex endometrial hyperplasia. (**a**) Sagittal image of the uterus. (**b**) Color Doppler image of the endometrium demonstrating increased vascularity within the thickened endometrium

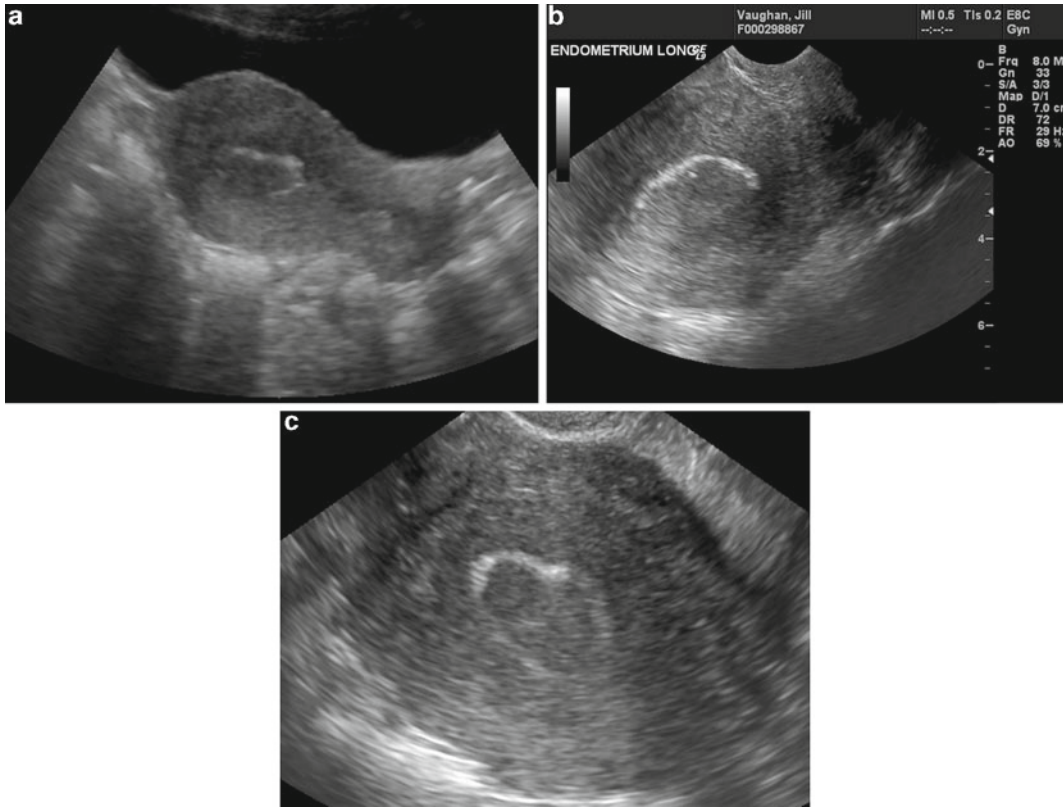

Fig. 8.6 Fifty-six-year-old postmenopausal woman with abnormal uterine bleeding. Sonographic images demonstrate a hypoechoic endometrial mass. Histology showed endometrial cancer. (**a**) Sagittal image of the uterus on a transabdominal scan. (**b**) Sagittal image of the uterus on an endovaginal scan. (**c**) Transverse image of the uterus on an endovaginal scan

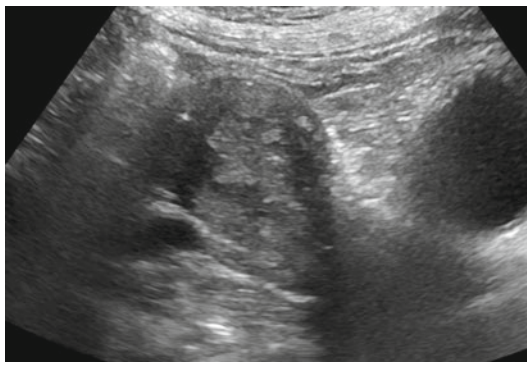

Fig. 8.7 Sixty-year-old postmenopausal woman with abnormal uterine bleeding. Transabdominal sonogram of the uterus in a sagittal plane demonstrates an irregularly thickened endometrium. Histology showed endometrial cancer

Postmenopausal Endometrium

The normal endometrium in a postmenopausal woman is thin, homogenous, and echogenic and does not significantly change during menopause [57]. A thickness of less than 5 mm without focal thickening is considered a normal appearance for the endometrium in a postmenopausal woman (Fig. 8.2). In those on hormone replacement, a thickness of up to 8 mm is considered normal [56].

Endometrial Abnormalities

Benign endometrial abnormalities account for nearly 90 % of postmenopausal bleeding. The most common cause accounting for 75 % of the cases is endometrial atrophy. Other causes include

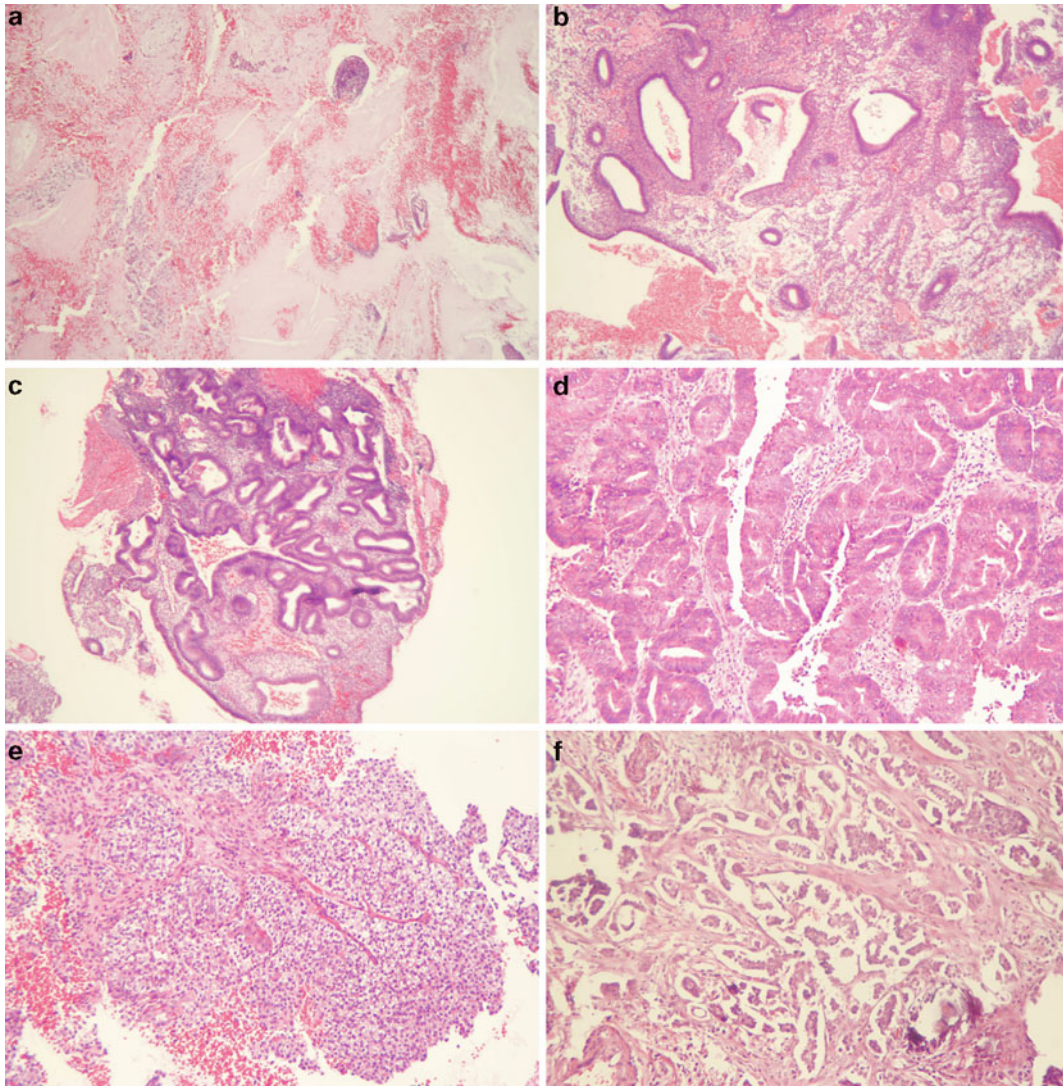

Fig. 8.8 (**a**–**f**) Spectrum of histopathological abnormalities of the endometrium. (**a**) shows inadequate specimen with only few tiny pieces of endometrial tissue floating in mucinous material. (**b**) shows fragments of endometrial tissues with slightly glandular proliferation and some cystic dilated glands. (**c**) demonstrates features of complex hyperplasia with endometrial glandular proliferation in tubular pattern in excess of stromal tissue. (**d**) shows endometrioid carcinoma evidenced from aspiration biopsy. (**e**) shows a small piece of tissue from endometrial biopsy that exhibits characteristic feature of clear cell carcinoma with papillary structure lined by epithelial cells with clear cytoplasm. (**f**) shows serous carcinoma characterized by papillary structures of malignant glands and foci of psammoma bodies

endometrial polyps, submucosal fibroids, endometrial hyperplasia, and estrogen withdrawal. About 10 % of cases of postmenopausal bleeding are caused by endometrial carcinoma [58]. Imaging assessment of the endometrium is best performed after the bleeding has stopped, if feasible. Some of the common benign endometrial abnormalities are described next.

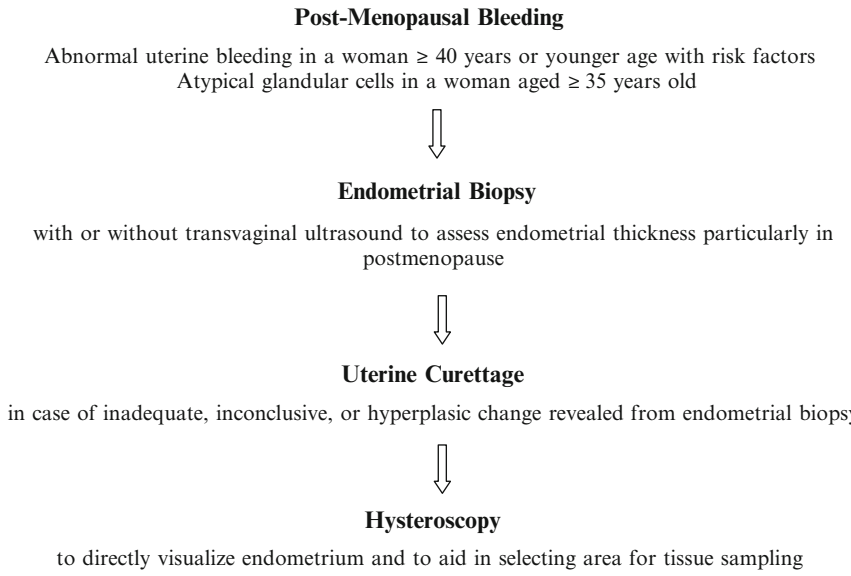

Fig. 8.9 Algorithm of procedures used for endometrial cancer diagnosis

Endometrial Polyp

An endometrial polyp is an underlying cause of bleeding in a significant number of postmenopausal women. Polyps are also seen more frequently in women who are on tamoxifen treatment. Sonographically, polyps appear as circumscribed hyperechoic or hypoechoic masses best delineated when surrounded by fluid either during sonohysterography or when surrounded by fluid in the endometrial cavity. Cystic spaces when seen within a polyp represent dilated glands. Polyps may be pedunculated or broad-based and sessile; often, a vascular stalk is demonstrated on color Doppler imaging (Fig. 8.3a–d).

Fibroids

Uterine leiomyomas may cause abnormal bleeding when they are submucosal or intracavitary. They appear as hypoechoic masses protruding into the endometrial cavity or lying predominantly in the endometrial cavity when intracavitary (Fig. 8.4a–c). Fibroids have a heterogeneous appearance and often demonstrate posterior acoustic shadowing. Sonographic assessment of the extent of a submucosal fibroid is important in the management, as those that are predominantly in the cavity (>50 %) may be amenable to hysteroscopic resection.

Endometrial Hyperplasia

Endometrial hyperplasia refers to abnormal proliferation of the endometrial stroma and glands and may be a precursor to EMC. Sonography reveals diffuse and less often focal thickening of the endometrium; endometrial thickness often exceeds 10 mm (Fig. 8.5a, b). The sonographic appearance of endometrial hyperplasia can overlap with that of EMC and distinction then can only be made by endometrial biopsy [56].

Endometrial Adenocarcinoma (EMC)

In endometrial carcinoma, the endometrium is thickened and has a heterogeneous and irregular appearance. There may be an overlap in the appearance with benign endometrial abnormalities such a polyps and endometrial hyperplasia. A specific sign of EMC is focal thickening and irregularity

as well as irregularity of the endometrium-myometrium border, a finding that is also indicative of an invasive disease [56] (Figs. 8.6a–c and 8.7). Sonography can be used to assess the depth of myometrial invasion, a finding that has a bearing on the likelihood of lymph node involvement and, consequently, on the staging and surgical management of a patient with EMC. Myometrial invasion greater than 33 % has a negative impact on prognosis. In one study, ultrasound was shown to accurately identify deep myometrial invasion in all cases where there was one [59]. Ultrasound may, however, be limited in identifying myometrial invasion in women with adenomyosis and/or fibroids, where it can overdiagnose myometrial invasion [59]. Ultrasound accuracy in predicting myometrial invasion has been compared to intraoperative frozen section sampling. In a series of 155 patients with endometrial malignancy, sensitivity, specificity, positive, and negative predictive values and accuracy of ultrasound was 75, 89, 86, 79, and 81 %. Intraoperative frozen section performed better than sonography at 92, 92, 89, 94, and 92 %. The authors of this study concluded that, although ultrasound did well in identifying myometrial invasion, for optimal surgical management in patients with EMC, intraoperative frozen section to determine myometrial extent is still recommended [60]. In another series comparing 64 women with EMC, TVS and TVS with CDI performed as well as intraoperative frozen section and the more expensive MRI in determining the depth of deep myometrial invasion [61].

Triaging of Women with Postmenopausal Bleeding

Abnormal vaginal bleeding is a frequent symptom encountered in a gynecological practice. In most instances, 98 % of women in one series, particularly in young premenopausal patients, the underlying cause are benign endometrial abnormalities such as a polyp, fibroid, or hyperplasia [62]. In postmenopausal women, one should add endometrial atrophy to the list of benign causes for bleeding. These benign causes account for 90 % of cases; in the remaining 10 % of women, EMC is the underlying abnormality. Sonography, therefore, is of value since benign endometrial diseases are readily diagnosed and is also a cost-effective alternative to blind endometrial biopsy [63]. Advantages of endovaginal ultrasound over endometrial biopsy include a less invasive procedure, no complication or pain, and equal or better sensitivity particularly in benign endometrial diseases [64]. A study reported a 0.6 % prevalence of EMC in women with PMB with sonographic measured endometrial thickness of 4 mm or less and 19 % when 5 mm or thicker. It has been suggested that, based on these findings, endometrial biopsy may not be required when thickness is less than 4 mm [64]. The false negative rates with EVS are better than the reported false negative rate of 5–15 % for office-based endometrial sampling. Ultrasound is also able to visualize the entire extent of the endometrium compared to the blind office-based biopsy [65–68]. Office-based endometrial sampling has several recognized limitations. Some of these include insufficient sampling, especially when abnormalities are small and focal, difficulty in gaining access to endometrial cavity due to cervical stenosis, and difficulty in diagnosing some of the benign causes of PMB. Ultrasound has the advantage of being able to see the entire endometrial lining and to accurately identify benign causes of endometrial bleeding such as polyps, fibroids, and atrophy. In one study of women with known EMC, 17 % the samples were found to be negative for malignancy [63].

Performing EVS to triage patients for sampling is therefore the most sensible approach. It has been shown that use of sonography to triage patients has a cost savings of 16 % in women with normal or average risk [68]. A study group of 339 postmenopausal women with bleeding reported that 13 % (44/339) had EMC or AEH (1.5 %). There were no cancers in women with an endometrial thickness of <4 mm. The reliability of endometrial thickness (cutoff value 4 mm) as a diagnostic test for EMC was: sensitivity, 100 %; specificity, 60 %; positive predictive value, 25 %; and negative predictive value, 100 %. Transvaginal sonographic scanning is an excellent tool for the determination of whether further investigation

with curettage or some form of endometrial biopsy is necessary [69]. The consensus group of the Society of Radiologists in Ultrasound recommends that a cutoff of 5 mm be used. The group concluded that either the US or office-based endometrial biopsy can be used in the initial evaluation of a postmenopausal woman with vaginal bleeding [70].

The triage of patients with postmenopausal bleeding proposed by Goldstein is most appropriate: (1) no anatomic pathology best treated expectantly; (2) a global endometrial process, in which case random blind endometrial sampling is appropriate; or (3) a focal endometrial abnormality in which case endometrial sampling should be done with the visualization offered by hysteroscopy [71]. The issue of postmenopausal women having a thickened endometrium that is found incidentally with no associated bleeding needs to be addressed, as this may occur not infrequently; reported in 10–17 %, such a finding in the absence of bleeding is not an indication for endometrial biopsy [71]. It is also important to understand that, in a symptomatic woman, when the entire endometrium is not seen or is obscured by a fibroid, sonographic evaluation must be considered incomplete. Such a scenario should prompt endometrial sampling to exclude EMC. In a study of 4,454 women with PMB, in whom 5.9 % were diagnosed with EMC, in 174 of 4,454 women (4 %), the endometrium was not visualized on sonography. In this subgroup where the endometrium was not well seen, there were 26 EMCs, proving the need to perform additional testing such as hysteroscopy and/or endometrial sampling [72].

Screening for Endometrial Cancer with Ultrasound

Screening for EMC in the asymptomatic patient is not justified and has not been shown to be of proven benefit. A study of 1,926 women from the general population found just one case of cancer and four cases of atypical endometrial hyperplasia [73]. However, there may be benefit in EMC screening postmenopausal women who are at an elevated risk for EMC [74] as has been discussed earlier in this chapter. A nested case–control study of postmenopausal women who underwent TVS in the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) was performed to evaluate the role of sonography in screening for EMC. UKCTOCS is a prospective trial of ovarian cancer screening; endometrial thickness was measured as part of this study, providing an opportunity to determine the value of this measurement as a possible screening tool for EMC. The cohort of 37,038 women included 136 women who developed EC or AEH. One hundred and thirty-three had endometrial thickness measured, and three had endometrial abnormalities. One hundred and twelve women were asymptomatic during the last EVS, and 24 were symptomatic. The control group had 36,888 women, and in this group there were 23 cases of EMCs. The endometrium had a thickness of >5 mm in 81 % of women diagnosed with EC; 33 of these were symptomatic and 74 asymptomatic. The positive predictive value and the negative predictive value for a cutoff of endometrial thickness of 5 mm in the symptomatic group was 30.8 and 93.1 % compared to only 1.4 and 99.9 % in the asymptomatic group [74]. These investigators concluded that TVS has a high sensitivity for diagnosing EMC and may be of benefit to screen women at risk for developing EMC, but they did not advocate its use to screen asymptomatic women.

Diagnosis of Endometrial Cancer with Ultrasound

The value of endometrial sonographic assessment in the diagnosis of EMCs in the symptomatic population has been extensively studied. A meta-analysis of 35 studies including a cohort of 5,892 women reported that 96 % of women with EMC had an abnormal finding on EVS; 92 % of women with endometrial disease malignant and nonmalignant such as polyp and atypical hyperplasia had abnormal findings using a cutoff value of 5 mm. Ultrasound did equally well in identifying endometrial disease irrespective of whether

women were on HRT [75]. However, hormone replacement did affect the findings in women without endometrial disease; in those who were not on HRT, ultrasound performed better, being abnormal only in 8 % with a normal histology compared to 23 % in women who were on HRT. For a postmenopausal woman with vaginal bleeding, the probability of EMC dropped from a pretest value of 10 % to a postnormal test value of only 1 %. Overall, ultrasound has a very high sensitivity for EMC in the range of 96 %, but specificity is low especially in those on HRT as discussed above [75].

Postmenopausal Bleeding in Women Under 50 Years of Age

The significance of postmenopausal bleeding in women under the age of 50 has also been reported. In a study group of 4,454 women with postmenopausal bleeding, 260 women (5.8 %) were younger than 50 years, 130 women had an endometrium of thickness less than 5 mm and hence did not undergo biopsy but were followed for 1–5 years, and in the remaining group biopsy was performed. There were no cancers in women under the age of 50 years. These findings may suggest that the need to investigate women under the age of 50 years is probably less urgent [76].

Role of 3D Power Doppler Ultrasound in Diagnosis of Endometrial Cancer

3D power Doppler angiography has been evaluated as adjunctive tool to 2D real-time ultrasound in the diagnosis and staging of EMC [77, 78]. In a series of 99 women with PMB and an endometrium of thickness >5 mm, 3D-PDA was used prior to endometrial biopsy. There were 44 EMCs in this group of patients. Endometrial volume, vascularity index, and vascularity flow index were all shown to be significantly higher in malignant versus benign conditions; of these, the vascularity index was reported to be the best predictor of malignancy [77]. In another series, 99 women with known EMC were interrogated with endovaginal 3D ultrasound and power Doppler angiography. Endometrial volume and 3D-PDA indices such as vascularization index, flow index, and vascularization flow index were calculated using a virtual organ computer-assisted method. Only endometrial volume and vascularity index were associated with myometrial invasion, of which only endometrial volume correlated with depth of myometrial invasion, and vascularity index was associated with the tumor grade. This is easy to understand since tumor size determines the depth of myometrial invasion, and there is greater degree of angiogenesis and consequently flow in high grade tumors [78].

Contrast Enhanced Ultrasound Evaluation of the Endometrium [79–81]

The value of using contrast enhancement during sonographic assessment of the endometrium has been studied in small group of patients. The examination involves administration of intravenous SonoVue® (Bracco, Milan, Italy). A slow bolus injection of 2.5 mL SonoVue is followed by a flush with 5 mL saline that is administered through an intravenous catheter placed in an arm vein. This technique may hold promise as an adjunct to transvaginal sonography such as in identifying malignancy in women with a thin otherwise normal appearing endometrium, in determining the presence of deep myometrial invasion, and in distinguishing benign from malignant abnormalities [79–81]. One study of 35 patients with EMCs reported an accuracy of 85.3 % for determining myometrial infiltration depth when using arcuate vascular plexus involvement as a marker for deep myometrial invasion. The added value of increased tumor-to-tissue contrast made it useful in women with an otherwise normal appearing thin endometrium. The utility of distinguishing benign from malignant abnormalities was studied in a small series of 17 women with EC and 17 with benign abnormalities. Doppler indices were measured before and after contrast enhancement: the pulsatility index and the resistive index were measured before and following administration of intravenous ultrasound contrast.

These indices were considerably lower in vessels of malignant tumors than in benign endometrial polyps after enhancement by intravenous contrast. There was no difference between benign and malignant lesions in PI, RI velocity index, flow index, or velocity flow index before contrast enhancement or in VI, FI, or VFI after contrast enhancement [79–81].

In summary, sonographic assessment of the symptomatic postmenopausal patient proceeds by triaging patients into three groups—one without an abnormality who can be treated expectantly, one with a global endometrial abnormality who can undergo blind endometrial biopsy, and one with a focal abnormality who needs to undergo biopsy under hysteroscopic visualization. A significant number of postmenopausal women without symptoms may have a thickened endometrium (10–17 %) [71], and invasive endometrial sampling may not be appropriate in these women unless there are coexisting risk factors such as obesity, diabetes, and history of polycystic ovarian disease. Similarly, polyps in asymptomatic women with endometrial polyps may not need endometrial sampling since less than 0.1 % may have EMC in the polyp [82]. Endometrial assessment by sonography is indicated to exclude cancer in any woman older than 35 years having anovulatory uterine bleeding [71]. Finally, a note from the American College of Obstetricians and Gynecologists: the gynecological committee is of the opinion that when a thin distinct endometrial echo of 4 mm or less is seen on transvaginal sonography, risk of malignancy is less than 1 in 917 and therefore endometrial biopsy is not required [71].

Conclusion

Risk factors of EMC should be recognized. Although there have been no clear data regarding the different risks in developing or developed countries, each factor should be related to the characteristics of the women in each population area. Screening is recommended only in high-risk women with genetic predisposition. This requires genetic counseling services and specialized laboratory evaluations. Also, the familial risk data and reported genetic abnormalities may not be applicable to all population subsets. The appropriate methods of genetic management remain a significant clinical challenge in developing countries. Therefore, there are no recommendations for screening with basic and limited resource availability. Instead, early diagnosis and timely treatment are the fundamental principles of endometrial management in low resource countries. This can be achieved by proper patient education and prompt investigation for any abnormal signs or symptoms suggesting endometrial lesions. Histopathology is mandatory for a diagnosis and can be obtained with a biopsy in the outpatient setting, which is cost-efficient and well tolerated by patients. Ultrasonography is a cost-effective modality to triage patients so as to offer endometrial aspiration biopsy only to those who have an endometrial abnormality. In those few instances where abnormality is determined to be focal by sonography and aspiration biopsy is inconclusive, a dilation and curettage procedure can be performed.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010;127:2893–917.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
3. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol. 2000;13:295–308.
4. Sorosky JI. Endometrial cancer. Obstet Gynecol. 2008;111:436–47.
5. Tangjitgamol S, Anderson BO, See HT, Lertbutsayanukul C, Sirisabya N, Manchana T, et al. Asian Oncology Summit. Management of endometrial cancer in Asia: consensus statement from the Asian Oncology Summit 2009. Lancet Oncol. 2009;10:1119–27.
6. Anderson BO, Yip CH, Smith RA, Shyyan R, Sener SF, Eniu A, et al. Guideline implementation for breast healthcare in low-income and middle-income countries: overview of the Breast Health Global Initiative Global Summit 2007. Cancer. 2008;113:2221–43.
7. Henderson BE. The cancer question: an overview of recent epidemiologic and retrospective data. Am J Obstet Gynecol. 1989;161:1859–64.

8. Persson I, Adami HO, Bergkvist L, Lindgren A, Pettersson B, Hoover R, et al. Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. BMJ. 1989;298:147–51.
9. Persson I, Weiderpass E, Bergkvist L, Bergstrom R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement. Cancer Causes Control. 1999;10:253–60.
10. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002;288:321–33.
11. Aiman J, Forney JP, Parker Jr CR. Secretion of androgens and estrogens by normal and neoplastic ovaries in postmenopausal women. Obstet Gynecol. 1986;68: 1–5.
12. Coulam CB, Annegers JF, Kranz JS. Chronic anovulation syndrome and associated neoplasia. Obstet Gynecol. 1983;61:403–7.
13. Silverberg SG. Hyperplasia and carcinoma of the endometrium. Semin Diagn Pathol. 1988;5:135–53.
14. Fenoglio CM, Crum CP, Ferenczy A. Endometrial hyperplasia and carcinoma. Are ultrastructural, biochemical and immunocytochemical studies useful in distinguishing between them? Pathol Res Pract. 1982;174:257–84.
15. Sherman ME, Silverberg SG. Advances in endometrial pathology. Clin Lab Med. 1995;15:517–43.
16. Silverberg SG. Problems in the differential diagnosis of endometrial hyperplasia and carcinoma. Mod Pathol. 2000;13:309–27.
17. Kendall BS, Ronnnett BM, Isacson C, et al. Reproducibility of the diagnosis of endometrial hyperplasia, atypical hyperplasia, and well differentiated carcinoma. Am J Surg Pathol. 1998;22:1012–9.
18. Trimble C, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ, et al. Concurrent endometrial carcinoma in women with biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106:812–9.
19. Committee on Gynecologic Practice, The American College of Obstetricians and Gynecologists. ACOG committee opinion. Tamoxifen and endometrial cancer. Int J Gynecol Obstet. 2006;107:1475–8.
20. Formander T, Rutqvist LE, Cedermark B, Glas U, Mattsson A, Silfverswärd C, et al. Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. Lancet. 1989;2:117–20.
21. Andersson M, Storm HH, Mouridse HT. Carcinogenic effects of adjuvant tamoxifen treatment and radiotherapy for early breast cancer. Acta Oncol. 1992;31: 259–63.
22. Fisher B, Costantino JP, Redmond CK, et al. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. J Natl Cancer Inst. 1994;86:527–37.
23. Curtis RE, Boice Jr JD, Shriner DA, et al. Second cancer after adjuvant tamoxifen therapy for breast cancer. J Natl Cancer Inst. 1996;88:8332–4.
24. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol. 2004;94:256–66.
25. Magriples U, Naftolin F, Schwartz PE, Carcangiu ML. High grade endometrial carcinoma in tamoxifen-treated breast cancer patients. J Clin Oncol. 1993;11:485–90.
26. Cuzick J, Sestak I, Baum M, Buzdar A, Howell A, Dowsett M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. Lancet Oncol. 2010;11:1135–41.
27. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet. 2008;371:569–78.
28. Soliman PT, Wu D, Tortolero-Luna G, Schmeler KM, Slomovitz BM, Bray MS, et al. Association between adiponectin, insulin resistance, and endometrial cancer. Cancer. 2006;106:2376–81.
29. Zhang Y, Liu Z, Yu X, Zhang X, Lü S, Chen X, et al. The association between metabolic abnormality and endometrial cancer: a large case-control study in China. Gynecol Oncol. 2010;117:41–6.
30. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control. 2009;16:14–22.
31. Ollikainen M, Abdel-Rahman WM, Moisio AL, Lindroos A, Kariola R, Järvelä I, et al. Molecular analysis of familial endometrial carcinoma: a manifestation of hereditary nonpolyposis colorectal cancer or a separate syndrome? J Clin Oncol. 2005;23: 4609–16.
32. Obermair A, Youlden DR, Young JP, Lindor NM, Baron JA, Newcomb P, et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer. 2010;127:2678–84.
33. Beiner ME, Finch A, Rosen B, Lubinski J, Moller P, Ghadirian P, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol. 2007;104:7–10.
34. Parazzini F, Negri E, La Vecchia C, Benzi G, Chiaffarino F, Polatti A, et al. Role of reproductive factors on the risk of endometrial cancer. Int J Cancer. 1998;76:784–6.
35. Prentice RL, Thomson CA, Caan B, Hubbell FA, Anderson GL, Beresford SA, et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. J Natl Cancer Inst. 2007;99:1534–43.
36. Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril. 2004;82: 145–8. quiz 265.
37. Setiawan VW, Monroe KR, Goodman MT, Kolonel LN, Pike MC, Henderson BE. Alcohol consumption

and endometrial cancer risk: the multiethnic cohort. Int J Cancer. 2008;122:634–8.
38. Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, et al. Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. Am J Obstet Gynecol. 2009;200:130–5.
39. Tang NP, Li H, Qiu YL, Zhou GM, Ma J. Tea consumption and risk of endometrial cancer: a metaanalysis. Am J Obstet Gynecol. 2009;201:605.e1–8.
40. Smith RA, Cokkinides V, Brawley OW. Cancer screening in the United States, 2009: a review of current American Cancer Society guidelines and issues in cancer screening. CA Cancer J Clin. 2009;59:27–41.
41. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med. 2003;348:919–32.
42. Brown GJ, St John DJ, Macrae FA, Aittomäki K. Cancer risk in young women at risk of hereditary nonpolyposis colorectal cancer: implications for gynecologic surveillance. Gynecol Oncol. 2001;80:346–9.
43. Lindor NM, Petersen GM, Hadley DW, Kinney AY, Miesfeldt S, Lu KH, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA. 2006;296:1507–17.
44. Aaltonen LA, Salovaara R, Kristo P, Canzian F, Hemminki A, Peltomaki P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med. 1998;338:1481–7.
45. Lu KH, Schorge JO, Rodabaugh KJ, Daniels MS, Sun CC, Soliman PT, et al. Prospective determination of prevalence of lynch syndrome in young women with endometrial cancer. J Clin Oncol. 2007;25:5158–64.
46. Wright TC, Massad S, Dunton C, Spitzer M, Wilkinson EJ, Solomon D, for the 2006 American Society for Colposcopy and Cervical Pathology—sponsored Consensus Conference ASCCP. 2006 consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol. 2007;197:346–55.
47. Sorosky JI. Endometrial Cancer. Obstet Gynecol. 2012;120:383–97.
48. Karlsson B, Granberg S, Wikland M, Ylöstalo P, Torvid K, Marsal K, et al. Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding—a Nordic multicenter study. Am J Obstet Gynecol. 1995;172:1488–94.
49. Goldstein S. The role of transvaginal ultrasound or endometrial biopsy in the evaluation of the menopausal endometrium. Am J Obs Gyn. 2009;201:5–11.
50. Dijkhuizen FP, Mol BW, Brolmann HA, Heintz AP. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: a meta-analysis. Cancer. 2000;89:1765–72.
51. Lipscomb GH, Lopatine SM, Stovall TG, Ling FW. A randomized comparison of the Pipelle, Accurette, and Explora endometrial sampling devices. Am J Obstet Gynecol. 1994;170:591–4.
52. Larson DM, Johnson KK, Broste SK, Krawisz BR, Kresl JJ. Comparison of D&C and office endometrial biopsy in predicting final histopathologic grade in endometrial cancer. Obstet Gynecol. 1995;86:38–42.
53. Frumovitz M, Singh DK, Meyer L, Smith DH, Wertheim I, Resnik E, et al. Predictors of final histology in patients with endometrial cancer. Gynecol Oncol. 2004;95:463–8.
54. Clark TJ, Mann CH, Shah N, Khan KS, Song F, Gupta JK. Accuracy of outpatient endometrial biopsy in the diagnosis of endometrial hyperplasia. Acta Obstet Gynecol Scand. 2001;80:784–93.
55. Obermair A, Geramou M, Gucer F, Denison U, Graf AH, Kapshammer E, et al. Impact of hysteroscopy on disease-free survival in clinically stage I endometrial cancer patients. Int J Gynecol Cancer. 2000;10:275–9.
56. Nalaboff KM, Pellerito JS, Ben-Levi E. Imaging the endometrium: disease and normal variants. Radiographics. 2001;21:1409–24.
57. Zalud I, Conway C, Schulman H, et al. Endometrial and myometrial thickness and uterine blood low in postmenopausal women: the influence of hormonal replacement therapy and age. J Ultrasound Med. 1993;12:737–41.
58. Fleischer AC. Sonographic assessment of endometrial disorders. Semin Ultrasound CT MR. 1999;20:259–66.
59. Sahakain V, Syrop C, Turner D. Endometrial carcinoma: transvaginal ultrasonography prediction of depth of myometrial invasion. Gynecol Oncol. 1991;43:217–9.
60. Savelli L, Testa AC, Mabrouk M, Zannoni L, Ludovisi M, Seracchioli R, et al. A prospective blinded comparison of the accuracy of transvaginal sonography and frozen section in the assessment of myometrial invasion in endometrial cancer. Gynecol Oncol. 2012;124(3):549–52.
61. Ozdemir S, Celik C, Emlik D, Kiresi D, Esen H. Assessment of myometrial invasion in endometrial cancer by transvaginal sonography, Doppler ultrasonography, magnetic resonance imaging and frozen section. Int J Gynecol Cancer. 2009;19(6):1085–90.
62. Dubinsky TJ. Value of sonography in the diagnosis of abnormal vaginal bleeding. J Clin Ultrasound. 2004;32:348–53.
63. Gull B, Carlsson SA, Karlsson B, et al. Transvaginal ultrasound in the endometrium in women with postmenopausal bleeding: is it always necessary to perform an endometrial biopsy? Am J Obstet Gynecol. 2000;182:509.
64. Einerth Y. Vacuum curettage by the Vabrar method: a simple procedure for endometrial diagnosis. Acta Obstet Gynecol Scand. 1982;61:373–6.
65. Lidor A, Ismajovich B, Confino E, David MP. Histopathological findings in 226 women with postmenopausal uterine bleeding. Acta Obstet Gynecol Scand. 1986;65:41–3.
66. Ferenczy A, Shore M, Guralnick M, Gelfand MM. The Kevorkian curette: an appraisal of its effectiveness in endometrial evaluation. Obstet Gynecol. 1979;54:262–7.

67. Stovall TG, Photopulos GJ, Poston WM, Ling FW, Sandles LG. Pipelle endometrial sampling in patients with known endometrial carcinoma. Obstet Gynecol. 1991;77:954–6.
68. Medverd JR, Dubinsky TJ. Cost analysis model: US versus endometrial biopsy in evaluation of peri- and postmenopausal abnormal vaginal bleeding. Radiology. 2002;222:619–27.
69. Gull B, Karlsson B, Milsom I, Granberg S. Can ultrasound replace dilation and curettage? A longitudinal evaluation of postmenopausal bleeding and transvaginal sonographic measurement of the endometrium as predictors of endometrial cancer. Am J Obstet Gynecol. 2003;188:401–8.
70. Goldstein RB, Bree RL, Benson CB, Benacerraf BR, Bloss JD, Carlos R, et al. Evaluation of the woman with postmenopausal bleeding: Society of Radiologists in Ultrasound—sponsored consensus conference statement. J Ultrasound Med. 2001;20:1025–36.
71. Goldstein SR. Modern evaluation of the endometrium. Obstet Gynecol. 2010;116(1):168–76.
72. Burbos N, Musonda P, Crocker SG, Morris EP, Nieto JJ, Duncan TJ. Management of postmenopausal women with vaginal bleeding when the endometrium cannot be visualized. Acta Obstet Gynecol Scand. 2012;91(6):686–91.
73. Fleischer AC, Wheeler JE, Lindsay I, et al. An assessment of the value of ultrasonographic screening for endometrial disease in postmenopausal women without symptoms. Am J Obstet Gynecol. 2001;184:70–5.
74. Jacobs I, Gentry-Maharaj A, Burnell M, et al. Sensitivity of transvaginal ultrasound screening for endometrial cancer in postmenopausal women: a case-control study within the UKCTOCS cohort. Lancet Oncol. 2011;12:38–48.
75. Smith-Bindman R, Kerlikowske K, Feldstein VA. Endovaginal ultrasound to exclude endometrial cancer and other endometrial abnormalities. JAMA. 1998;280(17):1510–7.
76. Burbos N, Musonda P, Crocker SG, Morris EP, Nieto JJ, Duncan TJ. Outcome of investigations for postmenopausal vaginal bleeding in women under the age of 50 years. Gynecol Oncol. 2012;125(1):120–3.
77. Alcazar JL, Galvan R. Three-dimensional power Doppler ultrasound scanning for the prediction of endometrial cancer in women with postmenopausal bleeding and thickened endometrium. Am J Obstet Gynecol. 2009;200:44.e1–6.
78. Galvan R, Merce L, Jurado M, et al. Three-dimensional power Doppler angiography in endometrial cancer: correlation with tumor characteristics. Ultrasound Obstet Gynecol. 2010;35:723–9.
79. Liu ZZ, Jiang YX, Dai Q, Yang M, Zhu QL, Zhao DC, et al. Imaging of endometrial carcinoma using contrast-enhanced sonography. J Ultrasound Med. 2011;30(11):1519–27.
80. Lieng M, Qvigstad E, Dahl GF, Istre O. Flow differences between endometrial polyps and cancer: a prospective study using intravenous contrast-enhanced transvaginal color flow Doppler and three-dimensional power Doppler ultrasound. Ultrasound Obstet Gynecol. 2008;32(7):935–40.
81. Song Y, Yang J, Liu Z, Shen K. Preoperative evaluation of endometrial carcinoma by contrast-enhanced ultrasonography. BJOG. 2009;116(2):294–8; discussion 298–9.
82. Ferrazzi E, Zupi E, Leone FP, Savelli L, Omodei U, Moscarini M, et al. How often are endometrial polyps malignant in asymptomatic postmenopausal women? A multicenter study. Am J Obstet Gynecol. 2009;200:235.e1–6.