Endometrial Hyperplasia

Kristina Williams and Emily Ko

Abstract

Endometrial hyperplasia (EH), a known precursor to endometrial adenocarcinoma, is a common gynecologic diagnosis among women, typically resulting from an increase in endogenous or exogenous unopposed estrogen. EH is a histologic diagnosis that is characterized by one of the two classification schemas: either the widely used WHO94 criteria or the more standardized endometrial intraepithelial neoplasia (EIN) criteria. The risk of progression to cancer varies and depends on the severity of the lesion. Lesions with atypia have the highest risk of progression to cancer and the diagnosis of concurrent endometrial cancer. EH mainly effects perimenopausal or postmenopausal women. Significant risk factors for EH include obesity, chronic anovulation as seen in disorders such as PCOS, estrogen only hormone replacement, tamoxifen use, and Lynch syndrome. Clinical manifestations include abnormal uterine bleeding, postmenopausal bleeding, or atypical endometrial glands on pap smear, which require a diagnostic workup in peri-/postmenopausal women. Transvaginal ultrasound (TVUS) is typically the first diagnostic study to be performed in a woman with abnormal uterine bleeding (AUB). Either office endometrial biopsy (EMB) or dilation and curettage (D&C) with or without hysteroscopy can be performed to diagnose EH. When EH is diagnosed, management includes surveillance, hormone therapy, or hysterectomy and choice of therapy depends on the type of EH, potential risk for endometrial cancer, and patient characteristics (i.e., desire to maintain fertility and surgical candidacy). There are no current recommendations for screening for endometrial hyperplasia in the general population.

Keywords

Endometrial hyperplasia • Endometrial intraepithelial neoplasia • Abnormal uterine bleeding • Postmenopausal bleeding • Unopposed estrogen • Endometrial cancer

Contents

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1 Introduction

Endometrial hyperplasia is a common condition defined histologically as an abnormal overgrowth of endometrial glands contained within the uterus. Clinically, it is important to recognize this condition as a precursor and marker for endometrial adenocarcinoma, the most common gynecologic cancer among American women (ACOG 2015; Armstrong et al. 2012; Trimble et al. 2012).

Normal endometrium changes throughout the menstrual cycle in response to estrogen and progesterone. Estrogen causes the endometrial lining to thicken by proliferation. After ovulation, the corpus luteum produces progesterone. If pregnancy is to occur, progesterone stabilizes the endometrium by inhibiting proliferation and stimulating differentiation. If pregnancy does not occur, progesterone production decreases and allows for shedding of the endometrial lining (Trimble et al. 2012).

Typically, in endometrial hyperplasia, unopposed estrogen (i.e., a lack of progesterone) causes the endometrial glands to proliferate such that there is an increase in gland to stroma ratio. Thus, endometrial hyperplasia affects those women that have intermittent or absence of ovulation (i.e., PCOS) or those women that have higher levels of circulating estrogens postmenopausally (i.e., HRT, obesity). The most common clinical manifestation of hyperplasia is abnormal uterine bleeding, which always requires diagnostic evaluation in a perimenopausal or postmenopausal woman. The mainstay of management of hyperplasia is the detection or prevention of endometrial cancer. This chapter will discuss the classification, epidemiology and risk factors, diagnosis, and management of endometrial hyperplasia.

2 Histology and Classification

The classification of endometrial hyperplasia is based on histology. There are currently two diagnostic classification systems used to categorize endometrial hyperplasia; the World Health Organization 1994 classification schema and the Endometrial Intraepithelial Neoplasia (EIN) diagnostic schema (Table 1).

2.1 WHO Classification

The WHO classification system divides endometrial hyperplasia into four subcategories based on glandular complexity and nuclear atypia (Fig. 1). The four subcategories include: (1) simple hyperplasia, (2) complex hyperplasia, (3) simple hyperplasia with atypia, and (4) complex hyperplasia with atypia. Simple hyperplasia is defined histologically as an overall increase in the number of endometrial glands with mild crowding. Frequently the glands exhibit dilation. Complex hyperplasia consists of a greater than 50% gland to stromal ratio ("crowding"), which is a much higher ratio than that seen for simple hyperplasia. Additionally, the glands typically appear disorganized with mitoses present. In either simple or complex hyperplasia, the glandular cells may also show features of nuclear atypia. Nuclear atypia refers to the presence of nuclear enlargement, prominent nucleoli, or rounded nuclei (normally elongated) with either evenly or irregularly dispersed chromatin.

The widespread use of this classification schema is based on retrospective data showing correlation of risk of endometrial cancer with the presence or absence of nuclear atypia. The risk of

Table 1 Classification systems used for defining precancerous endometrial lesions

World Health Organization 1994 (WHO 94) classification system			
Class	Risk of progression (%)	Treatment	
Simple	1	Hormone therapy	
Complex	3	Hormone therapy or surgical treatment	
Simple with atypia	8	Surgical treatment or hormone therapy[a]	
Complex with atypia	29	Surgical treatment or hormone therapy[a]	
Endometrial intraepithelial neoplasia (EIN) classification system			
Class	Diagnostic criteria	Risk of malignancy	Treatment
Benign hyperplasia	Exclusion of EIN or cancer	0.60%	Hormone therapy or surveillance
Endometrial intraepithelial neoplasia	Topographically diffuse	19%	Hormone therapy or surgery
	Gland area > stromal area		
	Cells of lesion are cytologically different from background		
	Max linear dimension > 1 mm		
	Exclusion of carcinoma and "benign mimics"		
Endometrial cancer	N/A	N/A	Surgery

[a]Hormone therapy in these cases is reserved for women who desire to preserve fertility or for women who are poor surgical candidates or decline surgical treatment after being appropriately counseled References: (Armstrong et al. 2012; Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015; Trimble et al. 2012)

progression to endometrial cancer in a woman with simple hyperplasia is exceedingly low (1%), while the risk of progression in a woman with complex atypical hyperplasia is as high as 29%, requiring invasive treatments (Table 1; Kurman et al. 1985; Lacey et al. 2010). In this sense, the WHO classification system correlates well with risk of progression and is currently the most commonly used schema by pathologists.

Although this classification system has been in use for many years, it has never been subjected to rigorous verification, putting into question the validity of this schema. Furthermore, two of the subcategories of classification are relatively rare in the population, simple EH with atypia and complex EH without atypia. Simple EH is thought to be a benign lesion resulting from estrogen effect, whereas atypical EH is thought to be a precancerous lesion resulting from the combination of estrogen effect and genetic effects; thus some experts question the biologic significance of simple hyperplasia as it is overall benign and may frequently spontaneously resolve. Additionally, some experts have questioned the WHO classification given that each of the subclasses fails to be tied to a specific or different treatment option. Rather, largely the same treatments have been offered across EH subtypes.

The largest limitation of the WHO classification system is that there are no specific criteria for histologic diagnosis and thus interpretation is subjective and leads to high interobserver variability, especially when diagnosing cellular atypia. In a large prospective multicenter cohort study of complex EH with atypia, unanimous agreement of a diagnosis among three pathologists was observed in less than half of all diagnoses, and pathologists agreed with the initial diagnosis in only 38% of cases (Zaino et al. 2006). For this reason, many have recommended the use of the EIN classification system rather than the WHO system, although this has not been universally adopted.

2.2 EIN System

The EIN classification system, developed and introduced by the International Endometrial Collaborative Group, uses three subcategories to

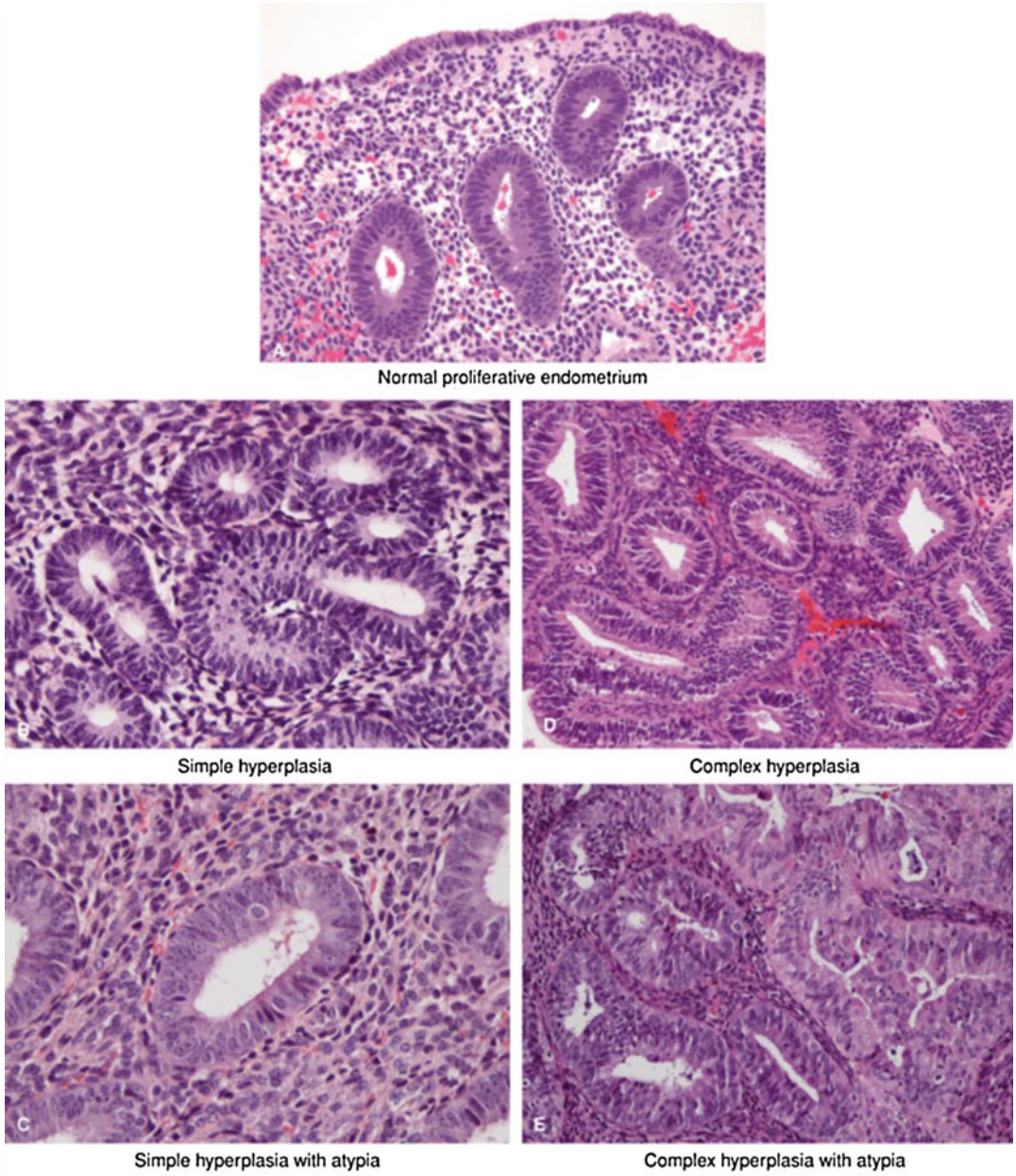

Fig. 1 Histology of endometrial hyperplasia (Originally published in Hoffman BL, Schorge JO, Schaffer JI, Halvorson LM, Bradshaw KD, Cunningham FG*: Williams Gynecology* , 2nd Edition' with kind permission of The McGraw-Hill Companies, Inc. All rights reserved. Photomicrographs display normal proliferative endometrium contrasted with different types of hyperplastic endometrium. (**a**). This high-power view of normal proliferative endometrium shows regularly spaced glands composed of stratified columnar epithelium with bland, slightly elongate nuclei and mitotic activity. (**b**). In simple hyperplasia, glands are modestly crowded and typically display normal tubular shape or mild gland-shape abnormalities. Nuclei are bland. (**c**). In this case, glands are only mildly crowded, but occasional glands, such as the one pictured in this high-power view, have nuclear atypia characterized by nuclear rounding and visible nucleoli. Cytologic atypia accompanies complex hyperplasia more often than it does simple hyperplasia. (**d**). In complex hyperplasia, glands are more markedly crowded and sometimes show architectural abnormalities such as papillary infoldings. In this case, gland profiles are fairly regular but the glands are markedly crowded. (**e**). Glands are markedly crowded and some show papillary infoldings. Nuclei show variable nuclear atypia. Some of the atypical glands have an eosinophilic cytoplasmic change (Photographs contributed by Dr. Kelley Carrick))

define abnormal endometrial tissue based on quantitative pathologic criteria (Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015). The three subcategories include: (1) benign endometrial hyperplasia, (2) endometrial intraepithelial neoplasia, and (3) carcinoma. The pathologic diagnostic criteria of endometrial intraepithelial neoplasia include lesions that have a minimum dimension of 1 mm, increased gland to stroma ratio, a difference in cytology of the lesion as compared to the background tissue, and the exclusion of benign mimics (i.e., polyps, secretory endometrium, effects of exogenous estrogen), and cancerous lesions (Table 1). These criteria can be applied clinically by pathologists or by using formal computerized analysis to assign a D score, which correlates specifically to benign tissue versus EIN. The development of this specific criteria using histomorphologic, genetic, clinical, and biological data attempts to truly differentiate precancerous lesions from benign lesions while maintaining a high degree of sensitivity for detecting precancerous lesions. In a prospective multicenter study using the D score to assign a diagnosis of EIN, the classification system was shown to have a 100% sensitivity in detecting progression to cancer and a 38% positive predictive value, compared to the 91% sensitivity and 16% positive predictive value of the WHO classification system (Baak et al. 2001). In addition, the EIN system has shown that interobserver reproducibility of the EIN system is greater than the WHO94 (Hecht et al. 2005).

Although the EIN criteria represent a more quantitative classification system than the WHO94 criteria, the latter represent a more widely used classification system. Thus, most studies use the WHO94 classification system when performing analyses, and most of the current knowledge, including epidemiologic risk factors and management strategies, pertain specifically to the four-tier classification of EH. Epidemiology studies of EIN remain limited. The EIN nomenclature and system, however, falls in line with the nomenclature of other precancerous lesions of the gynecologic tract, for example, vulva intraepithelial neoplasia (VIN) or cervical intraepithelial neoplasia (CIN). Currently, the EIN classification system lumps all premalignant lesions into a single category. Current research is attempting to further divide the EIN category into grades or classes, to further delineate which lesions are more severe and to determine which lesions would be responsive to hormonal treatment versus require surgical management (Mutter 2000). Still, the EIN classification system is currently the preferred schema of the American Congress of Obstetricians and Gynecologists and the Society of Gynecologic Oncologists for classifying abnormal endometrial epithelium given the quantitative and reproducible nature of this classification system.

3 Epidemiology

Endometrial hyperplasia mainly effects postmenopausal women and women in their later reproductive years with irregular ovulation. This disorder has historically and most commonly been classified by the WHO criteria, and thus much of the epidemiologic data focus on the subcategories of this classification system. Endometrial hyperplasia affects approximately one out of 1000 women annually (Lacey et al. 2012). This condition is highest in women aged 50–54 and rare in women less than 30 years of age. The incidence of endometrial hyperplasia decreases after the age of 70. In asymptomatic postmenopausal women, the prevalence of endometrial hyperplasia with and without atypia is 0.54% and 4.86%, respectively (Gol et al. 2001).

4 Risk Factors

Risk factors for endometrial hyperplasia are generally similar to that of endometrial cancer. There is a strong association with disorders that involve exposure of the endometrium to an increase in either endogenous or exogenous unopposed estrogens. Thus, some of the most notable risk factors include Tamoxifen use, obesity, and polycystic ovarian syndrome (chronic anovulation). Other risk factors include Lynch syndrome, nulliparity and infertility, and diabetes.

4.1 Obesity

Obesity is associated with a higher level of circulating endogenous estrogens, which is secondary to the conversion of androstenedione from adipose tissue to estrone, increased rates of anovulation, and a decrease in circulating sex hormone globulins. There is a proportional relationship between BMI and risk of endometrial hyperplasia. Obese women have approximately six times the risk of endometrial hyperplasia compared to nonobese women (Balbi et al. 2012). In morbidly obese postmenopausal women (BMI $>$ 40), the risk of endometrial hyperplasia with atypia is as high as eightfold. In morbidly obese premenopausal women, this risk is estimated to be as high as 13-fold, possibly suggesting an earlier age of diagnosis in women with obesity (Epplein et al. 2008).

4.2 Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS), an endocrinologic disorder that is associated with chronic anovulation, affects approximately 8–12% of women of reproductive age (March et al. 2010). Women with PCOS have a threefold increased risk of endometrial cancer (Haoula et al. 2012). Among women with PCOS, the prevalence of endometrial hyperplasia is estimated to be approximately 35–49%, with a prevalence of approximately 13% for atypia (Cheung 2001; Tingthanatikul et al. 2006). The association of PCOS with endometrial hyperplasia is thought to be due to chronic anovulation. PCOS is also associated with obesity and diabetes, which are both independent risk factors for endometrial hyperplasia.

4.3 Hormone Replacement Therapy (HRT)

HRT, with either unopposed estrogen or estrogen and progesterone combinations, has been used for decades to combat the unacceptable effects of declining endogenous estrogens in women at the time of menopause. Long-term use of unopposed estrogen for the relief of vasomotor symptoms related to menopause is associated with a 10–20-fold increase risk of endometrial cancer (ACOG 2015). Use of unopposed estrogen as HRT is associated with a 5-fold to as high as 16-fold increase in the likelihood of developing endometrial hyperplasia with high doses or prolonged use (Lethaby et al. 2000). The estimated prevalence of women who use a moderate dose of estrogen alone for up to 3 years is 28% for simple endometrial hyperplasia, 23% for complex endometrial hyperplasia, and 11.8% for endometrial hyperplasia with atypia (Judd et al. 1996). The risk of progression is likely similar to that of any woman in the general population that carries the diagnosis of EH. Addition of progesterone to the HRT regimen greatly reduces the risk of endometrial hyperplasia. Thus, the recommended use of estrogen replacement therapy includes using the lowest dose for the shortest duration possible. In addition, the use of combined progesterone in continuous or cyclic fashion to counteract the proliferative effects of estrogen alone is recommended (ACOG 2015).

4.4 Tamoxifen Use

Tamoxifen is a selective estrogen receptor modulator (SERM), which acts as an estrogen antagonist in breast tissue and thus is used to prevent and treat breast cancer. Unlike other SERMs, such as raloxifene, tamoxifen acts as an estrogen receptor agonist in endometrial tissue, thus its use is associated with an increase in risk of EH and endometrial cancer (approx. 2.5-fold increase in risk) (ACOG 2015). This effect is evident in postmenopausal women rather than premenopausal women (Fisher et al. 2005). The incidence of EH among women with long-term use of tamoxifen is estimated to be 4.4 per 1000 women annually (Runowicz et al. 2011). In women with breast cancer who are treated with tamoxifen and also have a preexisting endometrial hyperplasia, the risk of progression to a higher grade of EH or endometrial cancer is approximately 20% (Garuti et al. 2006).

4.5 Lynch Syndrome

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer (HNPCC), is a highly penetrant autosomal-dominant condition associated with an increased risk of the early onset of a variety of cancers, including endometrial cancer and colon cancer. The syndrome is characterized by an inherited defect in mismatch repair genes. The lifetime risk of endometrial cancer in women with lynch syndrome is estimated to be as high as 60% and may exceed the risk of colorectal cancer (Committee on Practice Bulletins- Gynecology and Society of Gynecologic Oncology 2014). Up to 18% of women with lynch syndrome will develop endometrial cancer prior to the age of 40. Although the risk of endometrial hyperplasia in women with Lynch syndrome is unknown, studies have shown a prevalence of 2.8–4.5% of EH among women with Lynch syndrome undergoing surveillance screening with endometrial biopsy (Nebgen et al. 2014).

4.6 Reproductive Factors

Nulliparity and infertility have both been shown to be independent risk factors for EH in premenopausal women with abnormal uterine bleeding (Farquhar et al. 1999). Increasing parity is inversely proportional to the risk of EH among premenopausal women (Epplein et al. 2008).

5 Clinical Presentation

The most common clinical manifestation of endometrial hyperplasia is abnormal uterine bleeding (AUB). In women with postmenopausal bleeding, the prevalence of hyperplasia is as high as 15%, compared to a prevalence of <6% in asymptomatic women (Espindola et al. 2007). In perimenopausal women with AUB – characterized as prolonged, heavy, or irregular menstrual cycles – the prevalence of endometrial hyperplasia is estimated to be 10–36% (Ash et al. 1996; Jetley et al. 2013). Depending on the histologic findings, the risk of endometrial hyperplasia progressing to cancer is as high as 29% and the risk of concomitant endometrial cancer is 42%. Thus, it is important to perform a diagnostic evaluation in any woman over the age of 45 with postmenopausal bleeding or AUB. In women under the age of 45 with AUB, whether or not to perform a diagnostic evaluation depends on risk factors and clinical suspicion (i.e., risk factors, persistence of symptoms). Occasionally, abnormal endometrial cells can be seen on cervical cytology in asymptomatic women. A finding of adenocarcinoma on cytology requires diagnostic evaluation in all women. Atypical glandular cells on cytology in women greater than 35 years of age or in women less than the age of 35 who are symptomatic (AUB) is a worrisome finding that requires evaluation of the endometrium. Postmenopausal women with endometrial cells on cervical cytology also require diagnostic evaluation of the endometrial cavity. Asymptomatic premenopausal women with findings of benign endometrial cells on cervical cytology do not require further workup (ACOG 2013).

6 Diagnostic Evaluation

The algorithm for diagnostic evaluation for women greater than the age of 45 with a clinical presentation concerning for endometrial hyperplasia is outlined in Fig. 2. Transvaginal ultrasound (TVUS) has a high negative predictive value for endometrial cancer and can be reliably used as the initial test in the diagnostic workup when evaluating a postmenopausal woman with bleeding. In a postmenopausal woman with a endometrial stripe less than or equal to 4 mm, the risk of cancer is less than 1%. In perimenopausal woman, ultrasound is less useful in ruling out endometrial carcinoma based on EMS; however, it can be used to detect any focal lesion or grossly thickened endometrial stripe (ACOG 2015). Any postmenopausal woman with an EMS of >4 mm or a focal lesion on TVUS requires endometrial sampling with either an endometrial biopsy (EMB) or dilation and curettage (D&C).

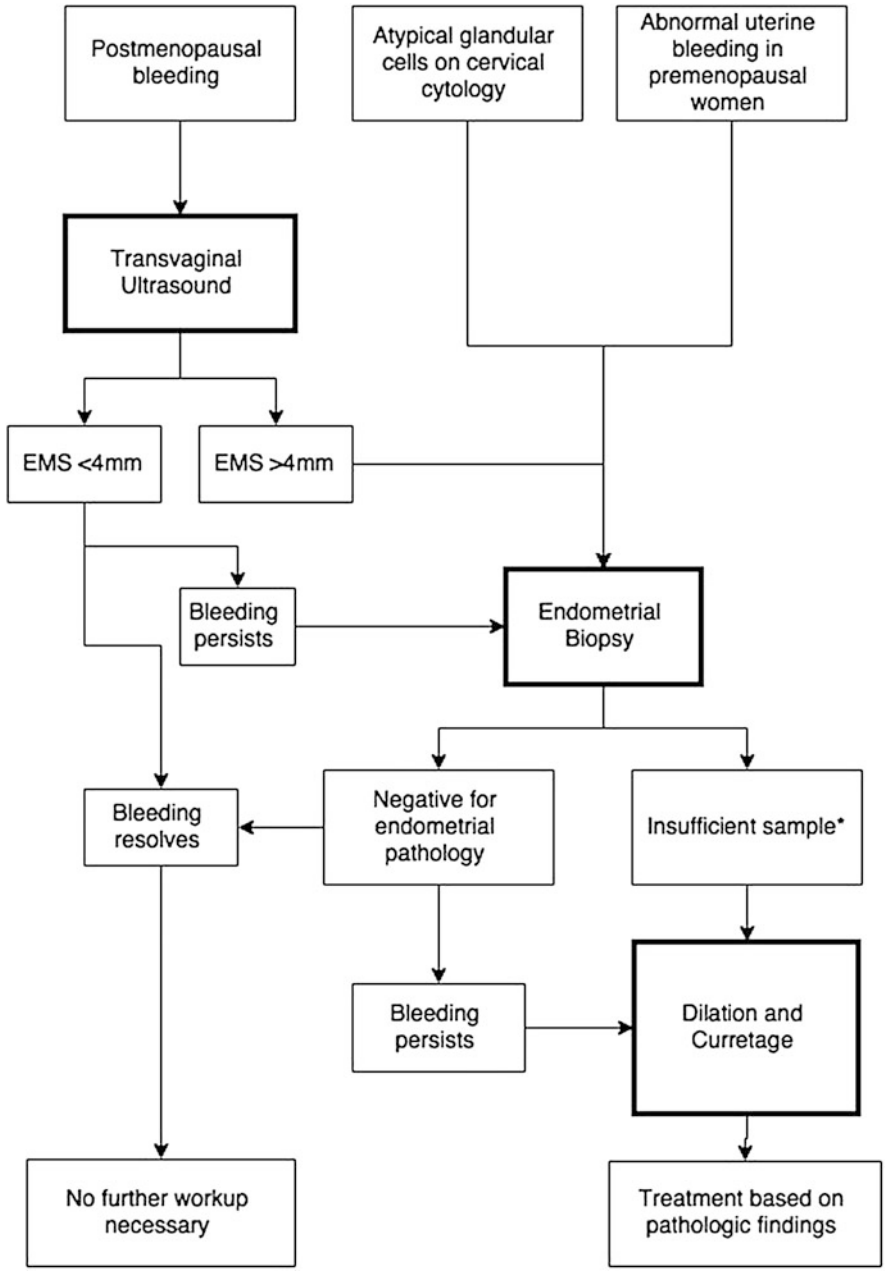

Fig. 2 Algorithm for the diagnostic evaluation for suspected endometrial hyperplasia (*It is reasonable to repeat EMB with one insufficient result. After two insufficient results, dilation and curettage is indicated)

EMB can be performed in the office setting and is the gold standard diagnostic test in the setting of abnormal uterine bleeding and/or abnormal ultrasound findings. Because EMB can be done in an outpatient setting rather than in the OR, several advantages exist for an EMB over a D&C including less procedural time, minimal anesthesia (if any), less cost, need for minimal cervical dilation (if any), and decreased risk of uterine perforation. However, the ability for EMB to detect endometrial disease depends on whether the endometrial disease is focal or global. On

average, EMB samples approximately 4% of the endometrial surface. Based on a metaanalysis, the endometrial pipelle technique of EMB has a sensitivity of 81% and a specificity of 98%, and the detection rates for endometrial cancer in postmenopausal and premenopausal women are 99.6% and 91%, respectively (Dijkhuizen et al. 2000). The negative predictive value for detecting endometrial cancer in women with complex atypical hyperplasia is higher for D&C than EMB (69% vs. 55%) (Suh-Burgmann et al. 2009). Thus it is not unreasonable to perform a D&C prior to hysterectomy, particularly if it would change surgical management regarding hysterectomy and possible staging strategies if concomitant endometrial cancer were known to exist.

In approximately 4–15% of women, an EMB will return with insufficient tissue for cytological evaluation. Postmenopausal women or women with a thin EMS have a higher likelihood of insufficient sampling (Elsandabesee and Greenwood 2005; Polena et al. 2007). If an insufficient result is obtained, it is reasonable to either repeat the EMB or proceed with D&C. After two insufficient results, endometrial sampling with D&C is indicated. In a postmenopausal woman, if the EMB is negative but the bleeding abnormality persists, D&C is indicated. The American Congress of Obstetricians and Gynecologists recommends a hysteroscopy with D&C for detection of any focal lesions that may be present (Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015).

7 Management

In a patient who has been newly diagnosed with endometrial hyperplasia or endometrial intraepithelial neoplasia, after concurrent adenocarcinoma has been ruled out, the goal of treatment is prevention of progression to endometrial cancer. Generally, management options include surveillance, medical management, and surgical management. When choosing between these management options, the potential of concurrent malignancy or progression to endometrial cancer, desire to preserve fertility, and surgical candidacy must all be considered. While surgical management is an effective and definitive means of treating higher-risk endometrial hyperplasia in women who have completed childbearing, nonsurgical treatment options are not as well defined for EH.

7.1 Surveillance

Surveillance by serial EMB is a management option for patients with either hyperplasia without atypia (WHO classification) or benign hyperplasia (based on EIN classification). The risk of progression to endometrial cancer for these entities is 1–3% for hyperplasia without atypia (based on WHO) or 0–2% for benign hyperplasia (based on EIN classification), respectively (Baak et al. 2005; Kurman et al. 1985). Furthermore, spontaneous regression has been estimated to be approximately 70% in women with hyperplasia without atypia (Reed et al. 2009). Although not the recommended management option, given the low risk of progression and high rate of regression, it is reasonable to monitor patients who either have a contraindication to progestin therapy or who decline medical/surgical management. These patients should be evaluated by EMB every 3–6 months until normal endometrium is found. There is not a defined time point for declaring failure to regress; however, most studies have shown median time to regression on hormonal management to be approximately 6 months, and therefore 6 months is likely a reasonable window for conservative management as well. Once regression is achieved, it is also worth considering repeat EMB to ensure stability of regression, and it is important to resample the endometrium in the future if abnormal uterine bleeding recurs.

7.2 Medical Management

Medical management involves the use of hormone therapy to reverse EH. It is the first-line treatment in women with hyperplasia without

Table 2 Progestin therapies commonly used for treatment of Endometrial Hyperplasia or EIN

Hormone	Route	Dosage	Comment	Common side effects
Medroxyprogesterone Acetate (MPA)[a]	Oral	10–20 mg daily or cyclic 12–14 days/month	First-line therapy for non-atypical hyperplasia. Cyclic therapy may be superior to continuous	Irregular bleeding, acne, abdominal pain/nausea
Megestrol Acetate (MA)[a]	Oral	40–320 mg daily	More potent than MPA thus usually reserved for women with atypical hyperplasia	Weight gain, abdominal pain/nausea/diarrhea, Insomnia/mood swings, hypertension, alopecia
Micronized progesterone	Vaginal	100–200 mg daily or cyclic 12–14 days/month	For use in women without atypia	
Depot medroxyprogesterone	Intramuscular	150 mg every 3 months	Regressions rates are likely similar to that of oral MPA	Amenorrhea, acne, Weight gain, headache
Levonorgestrel	Intrauterine	20 mcg/day releasing device	Estimated to be more effective than oral therapy.	Amenorrhea, abdominal pain, acne, irregular bleeding (first 90 days after insertion)

[a]Regression rates overall for oral progestin therapy based on systematic review is 66–69%. These regimens have been shown to have poor compliance compared to the IUD (Armstrong et al. 2012; Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015; Gallos et al. 2010; Guven et al. 2001; Trimble et al. 2012)

atypia or benign hyperplasia as, again, the risk of progression to cancer is low. In women with atypical hyperplasia or EIN, medical management is acceptable in patients who wish to preserve fertility or who are poor surgical candidates. In women desiring to spare fertility, the goals of management are complete clearance of the disease, return of normal endometrial function, and prevention of invasive endometrial cancer. In patients who are poor surgical candidates (i.e., elderly patient with multiple comorbidities), the goals of management include disease stabilization and risk reduction of developing endometrial cancer.

Progestin is the most commonly used hormone to treat EH. In normal endometrium, progesterone counterbalances the endometrial proliferation caused by estrogen and stimulates secretory differentiation (Kim and Chapman-Davis 2010). In precancerous lesions, the mechanism by which progesterone is therapeutic involves apoptosis in neoplastic endometrial glands associated with tissue sloughing during withdrawal shedding, as well as activation of progestin receptors, which leads to stromal decidualization and thinning of the endometrium (Kim and Chapman-Davis 2010). When used to treat EH, progestins have an impact on the endometrial lining as early as 10 weeks after initiation.

Progestin has been shown to be clinically effective in treating endometrial hyperplasia in a variety of routes, doses, and formulations (Table 2) A pooled analysis has estimated regression rates with use of oral therapy to be 66–69% (Gallos et al. 2010). Medroxyprogesterone acetate (MPA) and megestrol acetate (MA) are the most common progestin therapies. MA is known to be more potent than MPA, thus MA is typically used as first line in women with EH with atypia. In one prospective study, regression rates with the use of MA were as high as 90%. MPA may be administered via oral or intramuscular routes. Studies comparing various routes and formulations of oral progestin therapy have been inconclusive, thus an optimal regimen has not been determined. However, multiple single arm and retrospective studies of progestin-based therapies have been conducted and have been deemed acceptable for use (of any of the aforementioned regimens). Limited data exists for the use of vaginal

progesterone in endometrial hyperplasia; however, the estimated regression rate is 90% in women with simple and complex hyperplasia without atypia (Affinito et al. 1994). For reproductive aged women without a contraindication to estrogen, combined oral contraceptives (COC) may be used, though these are typically used to manage women with EH without atypia. COCs are estimated to reduce the risk of endometrial cancer by approximately 50%.

In addition to systemic hormone therapy, the levonorgestrel-releasing intrauterine device (IUD) provides a feasible and possibly superior alternative to oral therapy. The local acting progesterone has a stronger effect on the endometrium while having lower systemic progesterone levels, reducing the incidence of side effects. The estimated regression rates for non-atypical and atypical hyperplasia with the use of the levonorgestrel IUD are 90% and 96%, respectively (Gallos et al. 2010). A recent metaanalysis comparing the levonorgestrel IUD with oral progesterone therapy suggest that the IUD is approximately three times as effective as oral progestin therapy with continual use for 6 months (Abu Hashim et al. 2015).

The median time to regression in most studies, defined by a biopsy revealing normal endometrium, is approximately 6 months, after which if abnormal endometrium still exists, treatment failure is probable (Mentrikoski et al. 2012). Progestin therapy should be continued for at least 12 months in women who do not desire pregnancy or until progression is identified. In women who desire pregnancy, oral progestins should be continued for 3–6 months or until EH is no longer found on endometrial biopsy.

Endometrial sampling can be performed via EMB and is usually performed at 3–6 month intervals. EMB can be performed with an IUD in place. D&C can also be performed for surveillance and is usually repeated every 3–6 months. EMBs generally can be done in the office whereas D&C's frequently require the operating room. For women who have a persistent or progressive lesion, surgical management should be considered on an individual basis.

7.3 Surgical Management

Total hysterectomy with or without bilateral salpingo-oophorectomy (BSO) is the most effective treatment for either atypical hyperplasia (AH) or EIN and provides definitive assessment of a possible occult carcinoma. Independent risk factors for concurrent endometrial cancer include age, obesity, and complex hyperplasia with atypia (Matsuo et al. 2015). Thus, this treatment option is the standard of care for EIN or AH in women who are done with childbearing, especially those with the aforementioned risk factors. Hysterectomy is also indicated in patients with EH with or without atypia if medical management has failed. Hysterectomy is curative for patients with a final postoperative diagnosis of endometrial hyperplasia.

Surgical approaches include abdominal, vaginal, and minimally invasive approaches with laparoscopic or robotic technique. All modalities are acceptable and depend on clinical and patient-specific factors, as well as the skill of the surgeon and the extent of the procedure. For example, clinical patient factors such as complex anatomy, uterine size, body mass index, and prior surgical history should all be considered when determining route of hysterectomy. Currently, vaginal hysterectomy is recommended as the preferred route for performing hysterectomy for nonmalignant conditions (Aarts et al. 2015). However, it is important to note that it may be technically difficult to perform a BSO from a vaginal approach, and surgical staging (i.e., retroperitoneal lymphadenectomy) cannot be performed. It is also preferred that the hysterectomy not require any form of morcellation or deconstruction of the uterus as it may disrupt proper evaluation of the endometrium, particularly when looking for occult cancer and may potentially cause iatrogenic metastases if cancer were present. Thus uterine size must be accounted for if considering a vaginal or minimally invasive approach (which typically requires delivering the uterus through the vagina).

If endometrial cancer is identified, one must also consider the strategy for surgical staging. In general, it may be challenging to diagnose occult endometrial cancer on intraoperative uterine

analysis or frozen section. In one study, the negative predictive value for identifying endometrial cancer in patients with complex hyperplasia with atypia was only 73% (Morotti et al. 2012). Thus it is possible that over one quarter of patients who have endometrial cancer may not be detected by use of frozen section. Therefore, it is generally most effective to identify endometrial cancer in formalin fixed paraffin embedded tissue rather than by frozen section assessment. Surgeons may worry that the patients would then require a second surgery if endometrial cancer were identified on the permanent analysis of the hysterectomy specimen. However, the majority of these occult endometrial cancers are low grade, early stage cancers, which do not necessarily require lymphadenectomy; simple hysterectomy would be considered complete and definitive treatment. The premise of this staging strategy is based on a schema developed at the Mayo clinic, by which endometrial cancer cases of low grade (1–2), less than 2 cm tumor diameter on intraoperative evaluation and less than 50% myometrial invasion by frozen section, do not require lymphadenectomy, as the chance of identifying metastases is about 1% or less (Bogani et al. 2014; Mariani et al. 2000, 2008).

Whether or not to perform a bilateral salpingo-oophorectomy (BSO) depends on the presence or absence of endometrial cancer, patient characteristics, and presence of a primary indication for BSO. There is ovarian involvement in approximately 5% of endometrial cancer cases and BSO is indicated in known endometrial cancer cases. However, there are no current standardized recommendations about whether or not to perform a BSO for EH. In general, it has not been required. However, in most cases, there is relatively low surgical risk to performing a BSO. That being said, if a vaginal hysterectomy is performed, a separate abdominal approach either open or minimally invasive may be required to access the adnexa located high on the pelvic brim and complete the BSO. In postmenopausal women, it is reasonable to perform a BSO. In premenopausal women, however, risks of BSO including possible loss of bone density, increased cardiovascular events, and early onset of menopausal symptoms including hot flashes, decreased libido, and disrupted sleep patterns must be considered. Thus, in premenopausal women, BSO at the time of hysterectomy is not required unless there are other indications for removal of the ovaries. This must be considered against the risk of needing a separate surgery in the future for BSO.

Supracervical hysterectomy is contraindicated in patients with endometrial hyperplasia or EIN. The American Congress of Obstetricians and Gynecologists recommends against this approach because of concerns for underlying malignancy, which can reside in the lower uterine segment (ACOG 2007; Committee on Gynecologic Practice and Society of Gynecologic Oncology 2015). Hyperplasia can also reside in the lower uterine segment and there is risk of retained endometrium with supracervical hysterectomy. Morcellation and endometrial ablation are absolutely contraindicated in the surgical management of endometrial hyperplasia as morcellation has been associated with spread of occult cancers and endometrial ablation has an unknown effectiveness in treatment for hyperplasia because it is difficult to assess the endometrial lining after this procedure is performed.

8 Screening and Prevention

There currently are no recommendations for routine screening for endometrial hyperplasia (or endometrial cancer) in the asymptomatic general population. Lifestyle modifications, prophylactic medical management, and/or prophylactic surgery are indicated for some patients based on risk factors. In obese women or women with diabetes, lifestyle modifications such as diet, exercise, and weight loss, are recommended. In women with diabetes, glucose lowering agents such as metformin may decrease the risk of EH or endometrial cancer, although the evidence remains very preliminary and controversial and is limited to retrospective studies. In women with chronic amenorrhea or PCOS, progestin therapy can be used to lower the risk of development of EH or endometrial cancer. When hormone replacement therapy is indicated, the addition of

progesterone to the estrogen regimen will reduce the risk of EH associated with HRT, and thus all women who retain a uterus should receive combination hormonal replacement therapy and not estrogen alone.

The prevalence of EH among women with ER positive breast cancer is estimated to be 7%. Therefore it is reasonable to screen women for preexisting endometrial pathology prior to the initiation of tamoxifen therapy (Garuti et al. 2006). Any woman that is to initiate tamoxifen therapy should be informed of the effects that tamoxifen may have on the uterus. They should be counseled appropriately and the importance of reporting any abnormal vaginal symptoms, specifically abnormal bleeding, should be evaluated (ACOG 2014). In women with lynch syndrome, endometrial biopsy every 1–2 years starting at age 30–35 years is recommended. In a multicenter, retrospective, case control study, the risk of endometrial cancer in women with lynch syndrome was significantly reduced from 33% to 0% with a prophylactic hysterectomy; therefore, risk-reducing surgery should be recommended to any woman with lynch syndrome that is done with childbearing (Committee on Practice Bulletins-Gynecology and Society of Gynecologic Oncology 2014; Schmeler et al. 2006).

9 Conclusion

It is critical for all gynecologic clinicians to understand diagnosis and management of EH. This precursor to endometrial cancer can be easily diagnosed based on clinical symptoms with minor gynecologic procedures. When detected, progression to invasive endometrial cancer can often be effectively reduced using progestin therapy with close follow-up and surveillance. Endometrial hyperplasia frequently resolves with hormonal treatment and is definitively cured with hysterectomy. In a small proportion of cases, concurrent endometrial cancer may be diagnosed on the final hysterectomy specimen. Fortunately, most cases of concurrent endometrial cancer are typically of early stage and low-grade histology, which bears a very favorable prognosis even with hysterectomy alone. Treatment for EH should account for individualized characteristics (i.e., desire to preserve fertility, surgical candidacy), risk factors, severity of the lesion, and persistence or progression of the lesion or clinical symptoms. Patients and providers should discuss all these aspects of EH in order to manage the condition effectively.

10 Cross-References

- Conservative Management of Endometrial Cancer
- Diagnosis and Management of Postmenopausal Bleeding
- Impact of Obesity on Gynecological Diseases
- Management of Abnormal Uterine Bleeding: Later Reproductive Years

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