Current management of endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN)

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Summary

Endometrial hyperplasia is a commonly seen disorder in daily gynecology practice. The clinical importance of this pathological entity is the underlying risk of carrying a concomittant genital cancer or risk of progression to endometrial carcinoma during the follow- up. Despite recent advances in non-invasive techniques to define underlying endometrial cancer during the initial diagnosis of endometrial hyperplasia, none of these studies are conclusive yet. Today, in spite of intense discussions and related studies which aimed to define certain prognostic factors (WHO94 vs EIN) to predict cases that would progress to cancer, we still do not have a practical and accurate system available to use during daily practice. Treatment of endometrial hyperplasias depends on the patient's age, fertility desire and the type of hyperplasia. Progestagens are still the most commonly used medical treatment modality in these patients. Response rates are higher for cases without atypia. In selected cases, hysterectomy may be performed as a definitive treatment modality. In this review article, the current management of endometrial hyperplasias is summarized in light of the associated literature. We also give a brief overview of the EIN classification and its clinical importance.

Key words: Endometrial intraepithelial neoplasia (EIN); Endometrial hyperplasia.

Introduction

Endometrial hyperplasia (EH) is a common disorder seen in gynecology clinics. Actual incidence is still unknown but it is estimated to be seen in about 1.5% of patients with abnormal uterine bleeding [1, 2]. The clinical significance of EH is the underlying genital malignancy which is around 5-10% [3-10], but the number of studies is still limited in the published literature. Therefore, there is an on-going debate about the diagnosis, classification and treatment options of endometrial hyperplasias. This review article analyzes the available published literature and summarizes the current management of endometrial hyperplasias.

Risk factors

Unopposed estrogen is the most well known risk factor for endometrial hyperplasia. Estrogen has both mutagenic and carcinogenic effects on endometrial glands and stromal cells. Excess estrogen results in hyperplastic lesions with the PTEN mutation, and depending on the total dose and time of estrogen exposure, hyperplasias convert into neoplastic lesions [1, 11]. Therefore, all hyperestrogenic conditions are risk factors for EH (chronic anovulation, obesity, tamoxifen usage, unopposed esrogen, etc.). Physicians should be alert for EH in the following risk groups:

1) Abnormal uterine bleeding in women > 40 years old
2) Abnormal uterine bleeding with the above-mentioned risk factors and < 40 years old
3) All abnormal bleeding refractory to medical treatment
4) Patients who received unopposed estrogen replacement therapy
5) Atypical glandular cells on cervical smears
6) Presence of endometrial cells in cervical smears of > 40-year-old patients
7) Patients with hereditary nonpolyposis colorectal cancer

Diagnosis

The most important step in the management of these patients is to collect sufficient tissue to make a definitive diagnosis of hyperplasia and differential diagnosis of hyperplasia and cancerous lesion. The gold standard for the diagnosis of EH is endometrial biopsy. However, new non-invasive technologies such as office hysterocopy, etc. are also under review for the diagnosis of EH and its differentiation from endometrial cancers.

Non-invasive methods

Cervical cytology is rarely useful. Recently endometrial cytologic screenings (using endocyte samplers) were also analyzed but there is still not sufficient data in this respect [12].

Some clinical studies have focused on the role of transvaginal ultrasonography (TVS). Gray scale sonographies were not found to be helpful in EH diagnosis. Sensitivity and specifity values are particularly low in premenopousal patients. The median endometrial thickness was 16.2 mm (1.4-73) for EH while it was 18.7 mm (5-90) for endometrial cancer patients [13]. However, some other studies found a negative sonographic finding (endometrial thickness < 4-5 mm) to be more predictive than a negative office hysteroscopy [14-16]. Recent studies analyzing color Doppler and 3D-power angio-

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sonography have had more promising results, however there are only a limited number of studies [13, 17, 18]. Intratumoral blood flow can differentiate endometrial cancers (median tumoral blood flow is 71.7%) from EH (median blood flow 5.6%) with a 97.4% success. However, neither the resistance nor the pulsatile indices and the peak systolic velocities were found to be significant [13, 17]. Another study also revealed endometrial and subendometrial flow indices found with 3D power Doppler angio to be potentially helpful in the differential diagnosis of cancer and EH [18]. However, we need more studies for a definitive conclusion.

Invasive methods

The gold standard for diagnosis of EH is endometrial biopsy. The optimal time for biopsy is just after the withdrawal bleeding since exogeneous progestagens may affect the pathological evaluation. What about the optimal sampling technique? Cost-effectiveness analysis reveals office biopsies to be better then classic dilatation and curettage biopsies [19]. Previous studies and meta-analyses revealed the Pipelle method to hasten the highest specifity and sensitivity in all age groups for the diagnosis of both EH and endometrial cancers [20-22]. Studies using the Pipelle and Vabra techniques found a 97-99% predictive value for endometrial cancer and 66.7-82.3% predictive value for EH [20-22]. In cases with insufficient material or in cases where the clinical suspicion continues, classic dilatation and curettage is indicated.

Starting with the new millenium, office hysteroscopy has been used more and more, similarly to sonography, for evaluation in out-patient clinics and has started to be used as a routine part of the gynecologic examination. EH may have a variety of gross appearances on hysteroscopic evaluation such as irregular regeneration areas, increased vascularity, bleeding, necrotic areas, assymetric thickening and polypoid structures [23-27]. Clark *et al.* reported a meta-analysis of 65 studies which evaluated the predictivity of these gross hysteroscopic findings to diagnose endometrial cancer [28]. They found a 71.8% cancer risk in patients with these gross abnormalities and the risk dropped to 0.6% in patients with a negative hysteroscopic finding. However, with respect to EH diagnoses there are a limited number of hysteroscopic studies. Office hysteroscopy was suggested to have a 48-71.4% positive predictivity and a 92-95.4% negative predictivity for EH.

As a conclusion, despite the good results of office hysteroscopy, there are still not adequate studies for a definite conclusion. Even hysteroscopic-guided endometrial biopsies may miss underlying endometrial cancer. Office hysteroscopy seems to be more effective in the diagnosis of polypoid lesions. Office hysteroscopy is insufficient for the differential diagnosis of cancer and EH. Moreover, despite the well known controversy on the prognostic role, there is a risk of peritoneal dissemination during office hysteroscopy in patients with endometrial cancer. Therefore, for patients suspicious for EH or cancer, the initial diagnostic attempt should be office biopsy and if hysteroscopy is needed, it should be performed using lower flow pressures.

Classifications

WHO94 System

EH was heterogeneously classified up to 1994 (mild, moderate and severe hyperplasias or cystic vs adenomatous hyperplasias). Later on, EH was classified with the classic WHO94 system depending on histopathological evaluation (Table 1) [29]. This system uses cellular atypias and structural patterns and EH subclasses correlated with the risk of cancer progression (Table 1) [6]. The most important criteria of WHO94 is the presence or absence of cellular atypia, and not the grade. With respect to structural pattern, EH is classified as simple in the presence of tubular glands without branching and as complex in the presence of branching tortuous and curvy glands. However the WHO94 system is now under debate for the following reasons [30-32]:

1) There is no consequtive progression between the EH classes. For example, a patient with simple EH without atypia may not have a progression to complex EH or complex EH with atypia but instead can directly progress into endometrial cancer.

2) WHO94 is excessively subjective. There is a high intra- and interobserver variation and the reproducibility is also low.

3) WHO94 can not clearly direct the management of EH patients.

4) Concomittant cancer lesions may be missed in this system. In some retrospective studies where the specimens were reevaluated, 45% of the patients with endometrial cancers were found to carry atypical EH and 17-62% of the patients with atypical EH were found to carry concomittant endometrial cancers. Of these concomittant cancers, 7.9-51% of the patients also had myometrial invasion [3-10].

5) Studies on endometrial carcinogenesis (clonality, PTEN, etc.) have also questioned the WHO94 system.

Table 1. — *Classification systems of endometrial hyperplasias.*

a) WHO94 System

Simple (adenomatous) hyperplasia	*Cancer progression risk (%)*
Without atypia	1
With atypia	3
Complex hyperplasia	
Without atypia	9
With atypia	29

b) EIN System

EIN terminology	Topography	Functional category	Treatment
Endometrial (benign) hyperplasia	Focal	Estrogen effect	Hormonal
EIN	Focal, Diffuse	Precancer	Hormonal or surgical
Cancer	Focal, Diffuse	Cancer	Surgical

Based on these findings and questions, in 2002 the Endometrial Colloborative Study Group developed a new classification system called endometrial intraepithelial neoplasia (EIN) [33-38].

EIN System

The EIN system was developed to have a better detection of the real cancer precursor lesions and also for a better direction of EH patients for further treatments (Table 1) [33-38]. This system classifies endometrial lesions into three classes:

1) Benign hyperplasias (benign structural changes due to unopposed estrogen)

2) EIN (a monoclonal and neoplastic lesion, initially local and then diffuse)

3) Carcinoma

EIN lesions may be diagnosed in two different ways (subjective vs objective criteria):

Subjective EIN Criteria

Volume percentage stroma (VPS) is the most important subjective criteria where the ratio of glandular areas versus stromal areas is checked. Lesions in which the stromal volume is less then < 55% are classified as EIN. However, some believe that VPS evaluation may be even more subjective than the WHO94 system. Another subjective criteria is the diameter of the lesions which would be at least 1 mm for a correct VPS calculation, to perform reliable morphometry and clonal analysis and finally for making the differential diagnosis.

Objective endometrial intraepithelial neoplasia (EIN) criteria

The D-score (morphometric score) is the most important objective criteria. The D-score is evaluated by using three main pathological criteria;

– VPS (volume percentage stroma should be < 55%);

– OSD (outer surface area measuring the branching of glands);

– SDSNA (standard deviation of shorter nuclear axis – a scale for nuclear variation).

The D-score is a measure for clonality and precancerogenity. D-scores vary between -4 and +4. If the D-score is < 1 there is a high propensity for progression. On the other hand, in patients with a D-score > 1, no progression was seen in 22 years of follow-up.

WHO94 vs the EIN System

The limited data available clearly point out the predictivity of D-scores for progression to cancer [39-41]. Overall the sensitivity and negative predictive value of the EIN system is around 100% while these figures are 89% and 94%, respectively, for the WHO 94 system [39-41].

EIN enables physicians to make more standardized diagnoses and therefore more algorithmic treatments. However we do not know the feasibility and cost-effectiveness of the EIN system for routine daily practice. Therefore there is still a debate on the routine use of the EIN system in daily practice.

In a study evaluating the concordance between WHO94 and EIN systems, in patients with EIN diagnoses, 63% had atypical hyperplasia, 27% harbored complex hyperplasia and 10% harbored simple hyperplasia. For WHO94, 79% of patients with atypical hyperplasia, 44% of patients with complex hyperplasia and 5% of patients with simple hyperplasia were found to have EIN lesions. As can be seen, there is actually not enough concordance between the two systems [42, 43].

Table 2. — *EIN diagnostic criteria* *.

a) Subjective criteria

Criteria	Definition
Structure	Gland > stroma area (VPS < 55%)
Cytology	Cytologic discrepancy between the normal endometrium
Diameter	Maximal linear diameter > 1 mm
Exclude the mimics	Secretory, polyps, repair
Exclude cancer	Solid areas, cribriform pattern

b) Objective criteria

Criteria	Definition
D-Score	EIN if D-Score < 1, benign hyperplasia if D-score > 1
Diameter	Maximal linear diameter > 1 mm
Exclude the mimics	Secretory, polyps, repair
Exclude cancer	Solid areas, cribriform pattern

*VPS = volume percentage stroma; D-Score = +0.6229+0.0439xVPS-3.9934xln(SDSNA)-0.1592xOSD; SDSNA = standard deviation of short nuclear axis; OSD = outer surface area.

Treatment

Treatment depends on the type and related malignant potential of EH, patient age and fertility desire, medical condition of the patient and also presence of other gynecologic disorders like ovarian tumors. Treatments are mainly divided into two groups; 1) Medical and 2) Surgical (Table 3) [43-65].

Table 3. — *Treatment of endometrial hyperplasia.*

A) Medical treatments

1) Progestins
   a) Low dose (12-14 days/month)
   – Medroxyprogesterone acetate (Provera®, Farlutal®): 10-20 mg/day
   – Norethindrone acetate: 5 mg/day
   – Micronized progesterone (Oral Progestan®, Vaginal Cyclogest®): 200 mg
   – Megestrol acetate (Megace®): 20-40 mg/day
   b) High dose (21 days/month)
   – Medroxyprogesterone acetate 40-100 mg/day
   – Micronized progesterone 300-400 mg/day
   – Megestrol acetate 80-160 mg/day
2) Oral contraceptives
3) Ovulation induction
4) Levanorgestrel containing intrauetine devices (Mirena®)
5) Danazol (400 mg/day, 3 months)
6) GnRH analogues (Triptorelin® 3.75 mg/days, 3-6 months)
7) Aromatase inhibitors
8) Danazol containing intrauterine devices
9) Mifepristone (RU486)

B) Surgical treatments

1) Dilatation and curettage
2) Endometrial ablation and resection
3) Hysterectomy

There are many studies which revealed successful outcomes with the use of progestins and GnRH analogues. Progestagens have been used for EH for more then 40 years. The side-effects of megestrol acetate are lower and also it is safer even in higher doses. A daily 160-320 mg dosage may cause a mild increase in total body weight, however it does not cause a significant change in serum glucose or lipid profile levels. Randall *et al.* followed 17 patients < 40 years old who had atypical hyperplasia or well differentiated carcinoma. They used 2 x 20 mg megestrol acetate or 10 mg medroxyprogestrone acetate and followed the patients with aspiration biopsies within three to six months. The doses were titrated depending on the biopsy results. Sixteen of the patients had a complete response. Median time for treatment was nine months (range 3-18) [49].

Cyclic medroxyprogesterone treatment was also successfully used in postmenopausal hyperplasia without atypia. Sixty-five patients were treated with cyclic 10 mg medroxy-progesterone acetate for 14 days/month. At the end of the first year of treatment, benign normal endometrium was observed in 92% of the patients. None of the patients had progressed to endometrial carcinoma [48].

Atypical EH can also be successfully treated by progestagens. However in postmenopausal patients hysterectomy should be preferred. Premenopausal patients under medical treatment, should be controlled by endometrial biopsies every three to six months and the doses should be titrated according to response.

GnRH analogues are also used for EH treatment. Forty-two patients (30 simple, 12 atypical EH) were treated with leuprolide or triptoreline acetate for six months. Except for the seven simple EH patients, all patients responded to the treatment [66]. Progestegens are also used successfully in atypical EH patients. In a report of 19 patients, 500 mg norethindrone acetate and six months of monthly 3.75 mg depot triptorelin were used. At five years of follow-up, complete regression was seen in 16 patients (53).

Some recent reports have focused on the use of topical progestagens. An 87% response rate was noted by the use of levonorgestrol containing intrauterine devices, irrespective of the type of EH. Also, 100 mg/day micronized progesterone cream usage in the 16-25 days of the cycle for three to six months was successful in 90% of patients with simple EH (52).

There are also some alternative medical treatments recently studied (danazole, mifepristone, aromatase inhıbitors, and intrauterine devices with danazole). However the number of available studies and sample sizes are not adequate for a final conclusion.

The heterogenity of EH treatment is still ongoing (surgery vs medical vs combined medical, progestagens vs others, megestrol acetate vs others, dose and duration of medical treatments and follow-up, etc.). However there is still not any randomized prospective study which can resolve these problems. At least we can summarize the basic principles of treatment as follows:

• There is no data showing whether cyclic or contineous treatment is better.

• Low-dose progestagens are preferred as the first-line treatment in EH cases without atypia (Table 1).

• In cases with atypical EH, high-dose progestagens or surgical treatments are preferred if there is no fertility desire (Table 1).

• Medical treatments are also preferred in young patients with fertility desire or in patients whose medical conditions are not appropriate for surgery. In young patients with ovulation problems or infertility, we can also advise the use of combined oral contraceptives or controlled ovarian stimulation or pregnancy.

• In medical treatment options, endometrial biopsies are required every three to six months.

• Dilatation and curettage or endometrial resection/ablation is preferred in women < 40 years old with EH without atypia.

• Indications for hysterectomy are: 1) EH cases with recurrent atypia ≤ 40 years; 2) EH cases with or without atypia > 40 years.

• EH cases should be treated by a gynecologist oncologist due to the risk of concomittant endometrial or ovarian cancers. Moreover, for further management plans an experienced pathologist is also a crucial part of the treatment.

• Progestagen treatments are still the most effective and the most cost-effective treatment options.

• Response rates to low-dose progestagen treatments in EH cases without atypia are around 80%, persistant rates are 6%, recurrence rates 14% and cancer progression rates are 0%. Response rates are better in patients without atypia [48].

• Response rates of atypical EH cases to high-dose progestagens are variable. However there is no significant difference with respect to type of progestagens used. Overall response rates are reported to be 87-100% [50, 51].

Conclusion

There is no sufficiently reliable objective criteria showing the progression of EH to cancer. The EIN system is prognostic compared to WHO94, however the usefulness in daily practice in still controversial. EH without atypia responds better to medical treatments. Conservative medical treatments are also the first choice for young patients with atypia. Hysterectomy is the final endpoint of the disease but is indicated only in certain subgroups. These patients should be cautiously evaluated with the help of a gynecologic oncologist and an experienced gynecopathologist due the risk of concomitant endometrial and hormone-secreting ovarian tumors.

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