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Research Article

DIAGNOSTIC, CLASSIFICATION AND MANAGEMENT OF ENDOMETRIAL PRECANCEROUS LESION

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ABSTRACT

Endometrial hyperplasia (EH) is a pathological condition characterised by hyperplastic changes in endometrial glandular and stromal structures lining the uterine cavity. Endometrial hyperplasia known as a precursor lesion to adenocarcinoma of the endometrium. Most of these risk factors involve exposure of the endometrium to continuous estrogen unopposed by progestin. Unopposed estrogenic stimulation of the endometrium causes proliferative glandular epithelial changes, including glandular remodelling relative to the stroma, resulting in variably shaped, irregularly distributed glands. The classification system currently most widely used is, which uses architectural features and cytological atypia (glandular complexity and nuclear atypia) to identify precursor lesions, termed atypical endometrial hyperplasia (AEH).For New WHO 2014 classification of endometrial hyperplasia consist of Non-atypical endometrial hyperplasia (benign hyperplasia) and Atypical endometrial hyperplasia or Endometrial Intraepithelial Neoplasia (EIN)/well differentiated carcinoma. Management is guided by the following clinical factors, such as type of EH (i.e., with or without atypia), menopausal status, desire for fertility in premenopausal patients, contraceptive needs in premenopausal patients.

Keywords: Endometrial hyperplasia, remodelling, classification, management.

INTRODUCTION

Endometrial hyperplasia (EH) is a pathological condition characterised by hyper plastic changes in endometrial glandular and stromal structures lining the uterine cavity. Endometrial hyperplasia known as a precursor lesion to adenocarcinoma of the endometrium. The precursor lesion of type I endometrioid adenocarcinoma is endometrial intraepithelial neoplasia. Most cases of EH result from high levels of oestrogens, combined with insufficient levels of progesterone. Unopposed oestrogenic stimulation of the endometrium causes proliferative glandular epithelial change.[1]Endometrial hyperplasia is one of the most frequent causes of abnormal uterine bleeding, which leads to EC if left untreated. In 10% of premenopausal women with abnormal uterine bleeding, histological findings show endometrial hyperplasia, and in 6% of postmenopausal women with uterine bleeding EC is found. The primary role of endometrial sampling in patients with AUB is to determine whether carcinomatous or premalignant lesions are present by evaluating histological samples.[3]

Most of these risk factors involve exposure of the endometrium to continuous estrogen unopposed by progestin. This effect may be due to an endogenous (e.g., obesity, ovulatory dysfunction) or exogenous (e.g., medications, including non-prescription and topical therapies) source of estrogen.[4] EH is most common in per menopausal or early postmenopausal patients. In a study including females ages 18 to 90, the overall incidence of EH was 133 per 100,000 woman-years. The incidence of EH without atypia was highest in patients ages 50 to 54 years (between 142 and 213 per 100,000 woman-years) whereas the rate of EH with atypia was highest in patients ages 60 to 64 (56 per 100,000 woman-years).[4]

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PATHOGENESIS

Unopposed estrogenic stimulation of the endometrium causes proliferative glandular epithelial changes, including glandular remodelling relative to the stroma, resulting in variably shaped, irregularly distributed glands. Glandular epithelium may undergo metaplastic changes, most commonly to a ciliated tubal type epithelium. The response to estrogenic stimulation in the normal epithelium reflects a field effect, which is relatively uniform. Prolonged hormonal exposures may act as positive (oestrogens) or negative (progestins) selection factors for sporadically mutated endometrial glands. In these cases, the background hormonal effects appear to be punctuated by localized proliferation of a positively selected clone having a more crowded density and altered cytology. These two biologically distinct types of lesions, those that represent hormonal field effects and those that are true precancerous lesions (EIN), thus represent different processes that may either present independently or coexist in the same patient. Making the distinction between hyperplasia and true neoplasia has significant clinical impact, as their differing cancer risks must be matched with an appropriate intervention to avoid under- or over-treatment.[4]

ENDOMETRIAL HYPERPLASIA CLASSIFICATION SYSTEMS

Compared the reproducibility of histological findings, respectively, to three hyperplasia current classifications: WHO, EIN, and EWG. That all classifications of endometrial hyperplasia are associated with marked interobserver variability, even among expert gynecological pathologists. Compliance of diagnosis among pathologists re-evaluating hyperplasia samples in accordance with current classifications is 28% for the WHO system, 39% for EIN, and 59% for EWG. With only two diagnostic categories, full agreement among all pathologists increased to 70% in the WHO classification, 69% in the EIN classification, and 72% in the EWG classification.[3]

The classification system currently most widely used is, which uses architectural features and cytological atypia (glandular complexity and nuclear atypia) to identify precursor lesions, termed atypical endometrial hyperplasia (AEH). Parallel use of the older classification system of WHO 1994 led to confusion among clinicians. World Health Organisation 1994 (WHO94) classification: Simple hyperplasia, Complex hyperplasia, Simple hyperplasia with atypia and Complex hyperplasia with atypia. The categories of WHO 94 division are descriptive and their interpretation does not suggest any specific management algorithms. Various studies indicate poor reproducibility of individual case classification.[1,3]

The EWG classification, established for use only on endometrial biopsy/curettage specimens, has two diagnostic categories: hyperplasia and endometrioid neoplasia. The authors combined atypical hyperplasia and well-differentiated adenocarcinoma in one category – endometrioid neoplasia (EN), and simple and complex hyperplasia without atypia into benign hyperplasia.[3] For EIN classification of endometrial hyperplasia in 2000, another group of pathologists (the International Endometrial Collaborative Group) proposed a new classification system based on a constellation of quantitative morphological measures associated with clonality assessment. It uses the term endometrial intraepithelial neoplasia (EIN). Endometrial intraepithelial neoplasia is a premalignant lesion, characterised by increased volume of glandular crowding (greater than the stromal volume), the presence of cytological alterations, size of lesion larger than 1 mm, and exclusion of mimics or carcinoma. EIN classification included three categories: benign (benign endometrial hyperplasia), premalignant (endometrial intraepithelial neoplasia), and malignant (well-differentiated endometrial adenocarcinoma). EIN diagnostic criteria have been developed based on histopathological correlation with clinical outcome, molecular changes, and objective computerised histomorphometry.[1,2,3]

For New WHO 2014 classification of endometrial hyperplasia consist of Non-atypical endometrial hyperplasia (benign hyperplasia) and Atypical endometrial hyperplasia or Endometrial Intraepithelial Neoplasia (EIN)/well differentiated carcinoma. Differential diagnosis between benign uterine lesions and atypical hyperplasia/EIN is based mainly on morphological criteria but may be supported by additional immuno his to chemical markers and molecular alterations in problematic cases. Atypical hyperplasia and EIN had similar sensitivity and negative predictive values for coexisting endometrial cancer. Others found the EIN classification to be better at predicting progression to cancer. ACOG and SGO Committee Opinion recommend use of the EIN schema for more clear terminology to distinguish premalignant lesions.[3]

DIAGNOSTIC

As hyperplasia is a histologic diagnosis, a Pipelle office endometrial biopsy (EMB) or outpatient dilatation and curettage (D & C) are suitable choices for endometrial sampling. The American College of Obstetricians and Gynecologists (2014a) recommends such sample for women older than 45 years with AUB. EMB is also considered for those younger than 45 with chronic excess estrogen exposure (exogenous or endogenous), failed medical management, and persistent AUB.[7] In those with AUB, transvaginal sonography to measure endometrial thickness is also a feasible method for predicting endometrial hyperplasia. Transvaginal ultrasonography has excellent negative predictive value for endometrial cancer in women with postmenopausal bleeding.[1] In postmenopausal women, endometrial stripe thickness measurements ≤4 mm are associated with bleeding that is attributed to endometrial atrophy (American College of Obstetricians and Gynaecologists, 2013). An endometrial thickness greater than 4 mm in patient with postmenopausal bleeding should trigger alternative evaluation (such as sonohysterography, office hysteroscopy, or endometrial biopsy), as should an inability to adequately visualize endometrial thickness. Postmenopausal women with a thicker endometrium warrant biopsy. Sonography may also identify abnormal echo structural changes in the endometrium. Cystic endometrial changes suggest polyps, homogeneously thickened endometrium may indicate hyperplasia, and a heterogeneous structural pattern is suspicious for malignancy. For premenopausal women, transvaginal sonography is often performed to exclude structural sources of abnormal bleeding. Similarly, researchers have attempted to create endometrial thickness guidelines. However, endometrial thicknesses can vary considerably among premenopausal women during normal menstrual cycling. From studies, suggested evidence based abnormal thresholds range from >4 mm to >16 mm. Of other tools, hysteroscopy is more sensitive for focal endometrial lesions. Hyperplastic endometrium is grossly indistinct.[7]

MANAGEMENT OF ENDOMETRIAL INTRAEPITHELIAL NEOPLASIA

The primary objectives in a patient in whom endometrial intraepithelial neoplasia has been newly diagnosed are the following: ruling out a concurrent adenocarcinoma, designing a treatment plan that can accommodate delayed discovery of an occult carcinoma, and preventing the progression to endometrial carcinoma.[1]When managing patients with EH, the goal is to identify coexisting, and prevent progression to, endometrial carcinoma.[6]At present, management of AEH/EIN can be divided into surgical and non-surgical options. Although total hysterectomy is an effective means of treating a biopsy diagnosis of AEH/EIN, parameters guiding non-surgical management are not as well defined.[5] Management is guided by the following clinical factors, such as type of EH (ie, with or without atypia), menopausal status, desire for fertility in premenopausal patients, contraceptive needs in premenopausal patients. Risk factors for disease recurrence or progression, including: age >50 years, body mass index (BMI) >25 kg/m^2, nulliparity, diabetes mellitus, EH with atypia, uterine size ≥9 cm, endometrial lesion size >2 cm, lack of adequate progestin therapy.[6]

Nonatypical Endometrial Hyperplasia

The risk of progression of EH without atypia to endometrial carcinoma has not been well studied but appears to be less than 10 percent, based on studies with up to 20 years of follow-up.[5]In management of Premenopausal Women with nonatypical lesions may spontaneous regress without therapy. However, progestins are generally used to address the underlying etiology, that is, chronic anovulation and excess estrogen. Premenopausal women with nonatypical endometrial hyperplasia typically require a 3to 6month course of low-dose progestin therapy. Cyclic medroxy progesterone acetate (MPA) (Provera) given orally for 12 to 14 days each month at a dose of 10 to 20 mg daily is commonly used. Continuous daily dosing with MPA 10 mg is suitable and may be more effective than cyclic administration in reversing hyperplastic changes. Another frequently used option is COC pills for those without contraindications. The levonorgestrel-releasing IUD is also effective. After regression, a key point is to continue endometrial protection. Thus, once hyperplastic changes resolve, patients are continued on progestins and observed until menopause. Additional endometrial sampling is required for new bleeding.[7] Postmenopausal women with nonatypical endometrial hyperplasia may also be treated with low-dose oral cyclic MPA or a continuous 10-mg daily regimen. D & C may be indicated in some

circumstances, especially if the tissue from Pipelle sampling is scant or if recurrent bleeding is noted. progestin therapy is used to treat endometrial hyperplasia without atypia. But, affected post-menopausal patients who have a contraindication to progestin therapy or who cannot tolerate the therapy can be expectantly managed. With either complex or simple hyperplasia without atypia, office endometrial biopsy is recommended every 3 to 6 months until lesion resolution is achieved.[5,7] In cases of endometrial hyperplasia without atypia, the risk of progression to endometrial cancer is low (1 to 3 percent). The overall clinical and pathologic regression rates to progestin therapy range from 70 to 80 percent for nonatypical endometrial hyperplasia. Patients with persistent disease on repeated biopsy may be switched to a higher-dose regimen such as MPA, 40 to 100 mg orally daily. Also, megestrol acetate (Megace), 160 mg daily or 80 mg twice daily, is suitable. It can be increased even up to 160 mg twice daily if no regression is initially achieved. Again, a clinician must confirm that hormonal ablation has occurred by resampling the endometrium after a suitable therapeutic interval, usually 3 to 6 months. Hysterectomy may also be considered for lesions that are refractory to medical management. Hysterectomy is curative for EH and is performed in postmenopausal patients in whom progestin therapy is declined or contraindicated, in those with bothersome bleeding, in those at highest risk of developing endometrial carcinoma, or in those who desire definitive therapy.[6]

Atypical Endometrial Hyperplasia

The risk of progression of EH with atypia (endometrial intraepithelial neoplasia [EIN]) to endometrial carcinoma is higher than that of EH without atypia and is between 15 and 40 percent.[6] Hysterectomy is the preferred treatment for women with atypical endometrial hyperplasia because the risk of progression to cancer over time approximates 29 percent. There is also a high rate of finding concurrent invasive malignancy coexistent with the atypical hyperplasia. In postmenopausal women, a hysterectomy with removal of both tubes and ovaries is recommended. [1,5,7]

In premenopausal women who have completed childbearing, hysterectomy is performed for atypical hyperplasia. Risk reducing salpingectomy is encouraged to potentially lower cancer risk that arises from the fallopian tubes (American College of Obstetricians and Gynecologists, 2015d). Premenopausal women who strongly wish to preserve fertility can be treated with progestins. High-dose progestin therapy, megestrol acetate 80 mg orally twice daily. The IUD that releases 20 µg of intrauterine levonorgestrel daily (Mirena) is also suitable. Resolution of the hyperplasia must be confirmed by serial endometrial biopsies every 3 months until response is documented. Otherwise, hysterectomy is recommended. Once fertility is complete, hysterectomy is again recommended.[1,7]Historically, with increasing data regarding efficacy of pharmacologic therapy, and after the introduction of the levonorgestrel (LNG)-releasing intrauterine device (IUD; LNG 52), progestins became an alternative treatment for some patients, though long-term surveillance and medical therapy are required and treatment may not be curative, as with hysterectomy. We consider progestin therapy a reasonable alternative to hysterectomy for the following : Premenopausal patients who desire future fertility, Patients of any reproductive status who decline hysterectomy, and patients at high risk of surgical complications.[6]

CONCLUSION

Endometrial hyperplasia (EH) is a pathological condition characterised by hyperplastic changes in endometrial glandular and stromal structures lining the uterine cavity. The newest classification consist of classification of endometrial hyperplasia consist of Non-atypical endometrial hyperplasia (benign hyperplasia) and Atypical endometrial hyperplasia or Endometrial Intraepithelial Neoplasia (EIN)/well differentiated carcinoma. As hyperplasia is a histologic diagnosis, a Pipelle office endometrial biopsy (EMB) or outpatient dilatation and curettage (D & C) are suitable choices for endometrial sampling. Management is guided by the following clinical factors, such as type of EH (i.e., with or without atypia), menopausal status, desire for fertility in premenopausal patients, contraceptive needs in premenopausal patients.

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