Review Endometrial hyperplasia

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Key content:

- The most common presenting symptom of endometrial hyperplasia is abnormal uterine bleeding.
- In the UK, hysteroscopy remains the gold standard of investigations for abnormal uterine bleeding.
- The clinical importance of endometrial hyperplasia largely relates to the risk of progression to endometrial carcinoma.
- Progestin therapy is appropriate for most women with endometrial hyperplasia without atypia.
- The risk of endometrial carcinoma in the presence of cytological atypia deems hysterectomy an appropriate management.

Learning objectives:

- To learn about the aetiology and pathology of endometrial hyperplasia.
- To be able to select appropriate investigations and treatment.

Ethical issues:

- When is it appropriate to perform hysterectomy for the treatment of endometrial hyperplasias?

Keywords abnormal uterine bleeding / endometrial carcinoma / endometrial intraepithelial neoplasia (EIN) / estrogen / progestogen

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Introduction

In broad terms, endometrial hyperplasia relates to excessive cellular proliferation leading to an increased volume of endometrial tissue, where an increase of endometrial glands to stroma is seen at a ratio of greater than 1:1. Endometrial hyperplasia is further classified on the basis of the complexity of endometrial glands and any cytological atypia, resulting in a classification system of simple or complex hyperplasia, with or without atypia.[1]

Irrespective of classification, the most common presenting symptom of endometrial hyperplasia is abnormal uterine bleeding.[2] This includes menorrhagia, intermenstrual bleeding, postmenopausal bleeding and irregular bleeding on hormone replacement therapy or tamoxifen. Endometrial hyperplasia affects both premenopausal and postmenopausal women, accounting for approximately 15% of cases of women presenting with postmenopausal bleeding.[3] Conversely, endometrial hyperplasia can also be asymptomatic and may, in some cases, regress spontaneously without ever being detected.

The symptomatology of abnormal uterine bleeding is problematic but the clinical importance of endometrial hyperplasia largely relates to the risk of progression to endometrial carcinoma when hyperplasia is associated with cytological atypia. It is believed that the majority of endometrial cancers follow a continuum of histologically distinguishable hyperplastic lesions, ranging from endometrial hyperplasia without atypia, to endometrial hyperplasia with atypia, to well-differentiated endometrial carcinoma.

Aetiology

Estrogen stimulates endometrial proliferation. A relative excess of estrogen, be it exogenous or endogenous, compared with progesterone, is thought to be one of the primary aetiological factors in both endometrial hyperplasias and endometrial carcinomas.[4,5] Notably, however, serous, clear cell and some endometrioid-type adenocarcinomas (type 2 carcinomas, prototype serous carcinomas) do not arise on the basis of endometrial hyperplasia.

It is clear that postmenopausal women treated with supplemental estrogens are at increased risk of endometrial hyperplasia and carcinoma if a progestin is not used to oppose the proliferative actions of estrogen on the endometrium. The degree of risk increases with dose and duration of therapy, with an approximately 10-fold increased risk associated with each decade of use.[6] Postmenopausal women who are obese, particularly if nulliparous, are at greater risk of developing endometrial hyperplasia; diabetes and hypertension have also been identified as associated risk factors.[2,7]

Polycystic ovary syndrome results in unopposed estrogenic stimulation secondary to anovulation. Women younger than 40 years diagnosed with simple, complex and atypical endometrial hyperplasia have been shown to have a history of polycystic ovary syndrome in 26%, 47% and 28% of cases, respectively.[2]

Women with hereditary nonpolyposis colonic cancer (Lynch syndrome), who are known to be at increased risk of both endometrial and colonic carcinomas, also tend to develop complex atypical endometrial hyperplasia at an earlier age.[8] The peripheral conversion of androgens to estrogens in androgen-secreting tumours of the adrenal cortex is a rare cause of endometrial hyperplasia.[5]

Tamoxifen has a partial agonist effect and can induce a proliferative effect on the endometrium, the increased risk persisting after cessation of treatment. A randomised, double-blind trial of 111 women found that 16% of women treated with tamoxifen 20 mg/day developed atypical hyperplasia and a total of 39% developed abnormal endometrial histology.[5,9]

Pathology

The histopathological assessment of endometrial hyperplasia should include observation of nuclear, architectural and cytological abnormalities. As previously discussed, endometrial hyperplasia is defined as a proliferation of glands of irregular shape and size with an increase in the gland to stroma ratio. It is further categorised into simple and complex, based on the complexity and crowding of the glandular architecture.[5] The World Health Organization (WHO)[1] classification system for endometrial hyperplasia, revised in 2003, forms the basis of both the Gynecologic Oncology Group (GOG) and International Society of Gynecological Pathologists (ISGP) classifications (**Figure 1**). The challenge to the pathologist is to identify the demarcation between hormone-dependent, reversible changes and preneoplastic and neoplastic changes. Data[2] suggest that most hyperplasias without atypia probably represent early, highly-reversible lesions in the pathogenesis of endometrial carcinoma and that atypical endometrial hyperplasia is a precursor of endometrioid endometrial cancer.

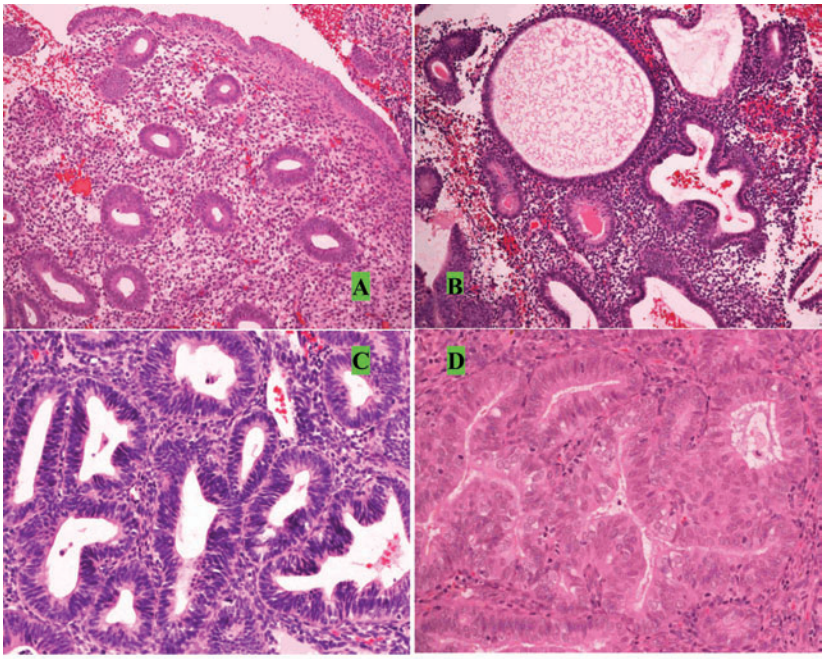
Estrogens are potent inducers of endometrial proliferation, which means that endometrial hyperplasia commonly precedes or coexists with endometrial cancer.[8] The link between the different histological types of endometrial hyperplasia and cancer is a complex issue. It is believed that

endometrial carcinomas in which estrogen stimulation is an aetiological factor are usually low grade and slow growing, with limited potential for metastasis.[10] The theorised 'dualistic model' for endometrial carcinogenesis proposes two pathways. The 'classic' pathway (type 1) proposes a mechanism by which indolent tumours develop from hyperplastic precursors in an estrogen-rich milieu, with the majority corresponding to endometrioid-type endometrial cancers. The 'alternative' pathway (type 2) is thought to account for the development of more aggressive tumours that are neither associated with hyperplasia nor estrogen excess, including most serous carcinomas and other aggressive types,[11] i.e. without excess estrogen, carcinoma develops in a background of normal or atrophic endometrium, as opposed to a hyperplastic endometrium, and is poorly differentiated and more aggressive.

In 2000, the Endometrial Collaborative Group[12] designated atypical endometrial hyperplasia as a premalignant lesion of the endometrium and redefined the terminology of such lesions as endometrial intraepithelial neoplasia (EIN). This terminology is in keeping with that used for cervical, vaginal and vulval neoplastic lesions, with the understanding that EIN lesions confer an increased risk of developing carcinoma and require treatment.[12] Endometrial intraepithelial neoplasia is diagnosed by: the presence of cytological demarcation; crowded glandular architecture, with a minimum size of 1 mm; and careful exclusion of mimics.[13] The similar appearance of atypical endometrial hyperplasia and well-differentiated endometrioid-type endometrial carcinomas underscores the pathogenetic relationship between these two lesions.[6] On the basis that benign endometrial lesions, with overlapping morphologies, are excluded, it has been suggested that endometrioid endometrial cancer precursors should, therefore, be designated as EIN. The WHO 2003 classification[1] defines EIN as a ' histological presentation of premalignant endometrial disease as identified by integrated molecular genetic, histomorphometric and clinical outcome data', with only 79% of atypical hyperplasias translating to EIN. Comparison of the WHO and EIN classification systems for endometrial hyperplasia has, however, shown EIN to be superior in discriminating lesions with the highest risk of conversion to malignant disease.[14] **Figure 2** illustrates the defined histopathological variations.

Risk of progression

Simple hyperplasia represents the lowest risk of cancer progression. It is reported that the majority spontaneously regress,[2,15] approximately 18% persist,[2] 3% progress to complex atypical hyperplasia[15] and 1% progress to endometrial adenocarcinoma.[2]



Panel A Proliferative endometrium: the endometrial glands are tubular and regularly spaced in abundant stroma. The glands are lined with pseudostratified nuclei. Mitotic figures are easily found both in glands and stroma.

Panel B Simple hyperplasia: irregular glands showing variation in shape and size are set in abundant stroma. Cystic glands are present. The glandular cells show nuclear pseudostratification but there is no nuclear atypia.

Panel C Complex hyperplasia: the glands are closely packed and in contrast to simple hyperplasia the stroma is relatively sparse. Nuclei are uniform, oval and pseudostratified, similar to that of normal proliferative endometrium. Nucleoli are indistinct.

Panel D Complex atypical hyperplasia: the glands are irregular and tightly packed, with very little intervening stroma. Nuclei are large and vesicular, with chromatin clumped along the nuclear membrane, and often contain prominent nucleoli.

Figure 1
Endometrial hyperplasia: histological classification

Complex hyperplasia is, again, reported to regress in the majority of cases,[2,15] with 22% persisting and 4% progressing to endometrial carcinoma, with a mean duration to progression of approximately 10 years.[2] Both simple and complex hyperplasias are, therefore, not considered preneoplastic forms.

The presence of cytological atypia is the most important prognostic factor for progression to carcinoma.[5] Complex atypical hyperplasia has been reported to progress in 29% of cases, with a mean duration to progression of 4.1 years.[2] Endometrial hyperplasia with cytological atypia may carry a higher risk of coexistent invasive carcinoma than previously believed,[16] with recent studies showing up to 50% of women with atypia having an endometrial carcinoma in subsequent hysterectomy specimens.[16–21] Endometrial carcinomas with concomitant hyperplasias are thought to be associated with less aggressive disease, tending to be of lower grade and stage with significantly lower recurrence risk and higher 5-year survival rates.[21] Conversely, Widra *et al.*[16]

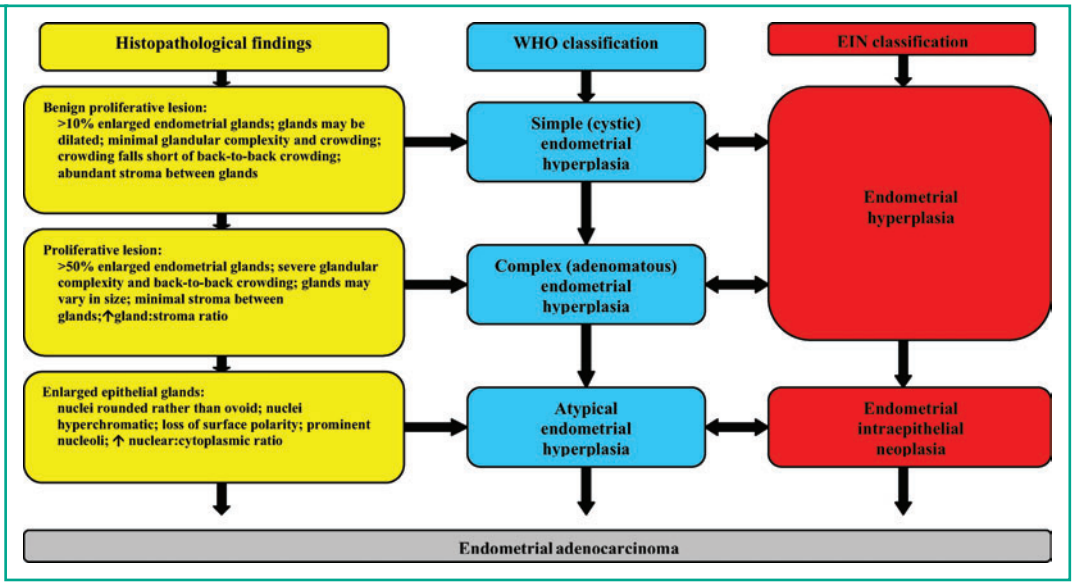


Figure 2
Schematic representation of the relationships of endometrial hyperplasia and endometrial intraepithelial neoplasia (EIN)

found 37.5% of women with concomitant atypical hyperplasia and endometrial carcinoma to be FIGO stage IB or higher.

Investigation

In the UK, hysteroscopy remains the gold standard investigation for abnormal uterine bleeding. Other investigative techniques include: blind endometrial biopsy, directed biopsy, dilatation and curettage, transvaginal ultrasound and sonohysterography.

Blind endometrial biopsy techniques are commonly performed using the Pipelle® (Punimar, Wilton, Connecticut, USA), Vabra® aspirator (Berkeley Medevices, Richmond, California, USA) and endometrial lavage. Meta-analysis[22] of 7914 women has shown Pipelle biopsy to have the highest sensitivity (81%) for overall detection of atypical endometrial hyperplasia. The sensitivity of the Vabra (66.7%) and endometrial lavage (53%) was reported as lower, although specificity of all three remained high (>98%). Meta-analysis[23] to determine the diagnostic accuracy of outpatient endometrial biopsy in determining hyperplasia revealed a failure rate of 3% and an inadequate specimen rate of 1.5%. A prospective randomised control trial[24] of Pipelle versus curette in women with abnormal uterine bleeding revealed a 96% agreement between biopsy pathology and final diagnosis for both procedures.

Both Pipelle and dilatation and curettage are blind endometrial biopsy techniques and they do not sample the entire endometrial cavity. Hysteroscopy allows the whole surface of the endometrium to be visualised but hysteroscopy performed alone has a reported high false-positive rate for detecting endometrial hyperplasia.[25] Hysteroscopy with targeted biopsy or dilatation and curettage, however, has excellent sensitivity and specificity for detecting endometrial pathology.[5,26] The combination of hysteroscopy with dilatation and curettage or endometrial biopsy, therefore, appears to be a superior diagnostic tool compared with hysteroscopy, dilatation and curettage or endometrial biopsy performed alone.

Transvaginal ultrasound assessment of endometrial thickness is of proven value in the investigation of abnormal uterine bleeding. When considering an endometrial thickness of >5 mm, meta-analysis[27] of 35 studies revealed high sensitivity and specificity for detecting endometrial disease. Studies on sonohysterography and Pipelle biopsy have shown sensitivities (94%) comparable to that for hysteroscopy and dilatation and curettage in detecting endometrial pathology.[28] Both transvaginal ultrasound and sonohysterography should, however, be performed in conjunction with endometrial biopsy.

In general, women with risk factors for endometrial carcinoma and a thickened endometrial stripe of >5 mm should undergo tissue sampling by endometrial biopsy, yet routine screening for women at high risk of endometrial hyperplasia has not proven efficacious or cost-effective. An unassessable (inadequate) endometrial biopsy sample is an indication for further investigation and, if a satisfactory outpatient biopsy has been performed, additional assessment with hysteroscopy and/or transvaginal ultrasound should be undertaken, especially if symptoms persist.[23]

Treatment

As most types of endometrial hyperplasia do not progress to endometrial carcinoma, treatment regimens should be individualised and hysterectomy considered a somewhat aggressive form of management in the majority of cases. The presence of cytological atypia, however, with its risk of either concomitant carcinoma or progression to

carcinoma, presents a more challenging clinical scenario, especially in the presence of fertility issues or medical comorbidity necessitating preferential avoidance of surgical management.

Simple or complex endometrial hyperplasia in the absence of cytological atypia can be treated conservatively, as these lesions pose an extremely low risk of progression to carcinoma.[2] Available data suggest that persistent or progressive disease will be found in approximately one-third of conservatively managed cases.[29] Progestin therapy is appropriate for most women with endometrial hyperplasia without atypia and may result in its complete disappearance. Progestogens have both indirect anti-estrogenic and direct antiproliferative effects on the endometrium.[30] Progestogens can be delivered systemically, either alone or in combination with estrogen (in the form of the combined oral contraceptive pill or hormone replacement therapy), or locally in the form of the levonorgestrel intrauterine device (Mirena®, Schering Health, Burgess Hill, West Sussex, UK). Both systemic and local administration of progestogens has shown a 75–90%[7] and 90–100%[31,32] conversion rate of nonatypical endometrial hyperplasia to normal endometrium, respectively.

A study[33] considering progestogen treatment for atypical endometrial hyperplasia in women younger than 40 years reported a 94% success rate with 3–18 months of therapy; five women became pregnant, delivering at full term. In postmenopausal women, a 25% risk of progression to carcinoma has been reported in those treated with medroxyprogesterone acetate.[34] Progestogen concentration should be adjusted based on endometrial histology.[5] If treating with high-dose progestogen therapy, however, resampling of the endometrium should be performed after suitable therapeutic intervals (3–6 months) to ensure that hormonal ablation has occurred.[5,10] In the presence of persistent symptoms or nonregressive disease, recommendation of hysterectomy, even for complex hyperplasia, seems appropriate.[29] Where fertility or significant surgical risk is not an issue, complex hyperplasia with atypia is regarded as a mandate for hysterectomy in view of the risk of coexisting malignancy or progression to cancer.[2,5,8,12] Because of the risk of concomitant endometrial carcinoma in women with atypical endometrial hyperplasia and the possibility of a coexistent carcinoma being of higher stage in some cases than previously believed, women should also, perhaps, be carefully evaluated for the possibility of more advanced disease prior to surgery.[16,18]

Conclusion

Endometrial hyperplasia is a relatively common gynaecological condition. It affects women of all age groups, the majority presenting with abnormal uterine bleeding. Transvaginal ultrasound and hysteroscopy are commonly used to diagnose endometrial hyperplasia but should be performed in conjunction with endometrial biopsy. The presence of persisting symptomatology or an unassessable biopsy specimen warrants further investigation because of the risk of progression in the presence of cytological atypia.

Although nonatypical forms may regress spontaneously, the majority of persistent lesions can be successfully treated with progestogen therapy. The presence of cytological atypia represents the greatest risk of progression and coexistence of endometrial cancer. This risk deems hysterectomy an appropriate management unless precluded by other factors; these women should, perhaps, be carefully evaluated prior to surgery for the possibility of more advanced disease.

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