



# Management Strategy Change of Endometrial Hyperplasia

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## Abstract

Endometrial hyperplasia refers to irregular proliferation of endometrial glands, combined with an increased proportion of gland and mesenchyme. This kind of disease generally results from reproductive endocrine disorder, which is closely related to long-term estrogen stimulation without progesterone antagonism. In recent years, the views on the treatment and management of endometrial hyperplasia have been updated and changed with the deepening of research. This paper mainly focuses on the following aspects: classification change of endometrial hyperplasia, indication change of diagnostic curettage, management change of endometrial hyperplasia.

**Keywords:** Endometrial hyperplasia; Diagnostic curettage; Levonorgestrel-releasing intrauterine system; Management strategy

## Introduction

Endometrial hyperplasia refers to irregular proliferation of endometrial glands, combined with an increased proportion of gland and mesenchyme. Endometrial cancer is one of the most common gynecological malignant tumors, and its incidence ranks the second among female reproductive organ tumors, approximately 25.7/100,000[1]. The histological type of most endometrial cancers is endometrial adenocarcinoma with precancerous lesions. Endometrial hyperplasia (atypical hyperplasia) is a precancerous lesion of endometrial cancer, whose incidence is at least three times higher than that of endometrial cancer. If there is no intervention, endometrial cancer may occur [2]. The most common initial symptom of endometrial hyperplasia is abnormal uterine bleeding, which mainly includes increased menstrual blood volume, intermenstrual bleeding, irregular bleeding, irregular bleeding in estrogen replacement therapy and postmenopausal uterine bleeding [3]. In recent years, treatment and management strategies of endometrial hyperplasia have been updated and changed with the continuous development of studies, which will be briefly discussed in this paper.

## Classification evolution of endometrial hyperplasia

In 1975, the WHO divided endometrial hyperplasia into three types: cystic glandular hyperplasia, adenomatous hyperplasia, atypical hyperplasia. In 1987, the International Society of

Gynecological Pathologist (ISGP) divided it into simple hyperplasia, complex hyperplasia and atypical hyperplasia. In 1994, the WHO renewed the classification which included simple hyperplasia, complex hyperplasia, simple atypical hyperplasia and complex atypical hyperplasia. In 2003, the EIN classification divided it into benign hyperplasia, EIN (endometrial intraepithelial neoplasia), highly differentiated endometrial adenocarcinoma. In 2014, the WHO directly divided it into two types: non-atypical endometrial hyperplasia and atypical hyperplasia of endometrium [1,4].

## Indication change of diagnostic curettage

Previous indications ("2009 guidelines for clinical diagnosis and treatment of dysfunctional uterine bleeding (draft) in China") [5] are as follows:

The age should be equal to or greater than 40; Vaginal irregular bleeding lasts for more than half a year; Endometrium thickness exceeds 1.2cm.

The latest indications ("2014 guidelines for diagnosis and treatment of abnormal uterine bleeding in China") [6]: Age $\geq$ 45; High risk factors for endometrial cancer (such as hypertension, obesity, diabetes, etc.); Long-term irregular uterine bleeding; ultrasonic B suggests excessive thickening of endometrium and uneven echo; Medication effect is not significant.

The differences between the two diagnostic curettage indications: Age of subject increases by 5 years; duration of vaginal bleeding is not limited to more than half a year; ultrasonic B suggests excessive thickening of endometrium (not limited to more than 1.2cm) and it emphasizes uneven echo of endometrium. In addition, two indications were added to the latter one: High risk factors of endometrium; Medication effect is not significant (Consider taking medication first and then evaluating the efficacy). The new indications are more scientific and standardized, which do not emphasize specific values of bleeding time and endometrial thickness. Consider taking medication first and then evaluate the efficacy to avoid overuse of diagnostic curettage. In the meantime, diagnostic curettage is important when patients have a high-risk factor of endometrial cancer. (Do not overuse diagnostic curettage, but also avoid missed diagnosis and medication error in high-risk patient.)

### Views change of endometrial hyperplasia management

#### Previous views on endometrial hyperplasia treatment:

According to the previous views [7], endometrial hyperplasia was divided into simple hyperplasia, complex hyperplasia and atypical hyperplasia. For simple hyperplasia, consider periodic progesterone therapy. Methoxy progesterone acetate (MPA) is a commonly used drug (6-10mg qd×10-14d); For complex hyperplasia, a continuous regimen is recommended. The commonly used dose and course of MPA is 10mg tid and three months a course of treatment. Do not emphasize re-examination of endothelial biopsy after medication on patients with simple hyperplasia, while consider re-examination of endothelial biopsy after 3 months of medication on patients with complex hyperplasia to estimate the clinical efficacy. Atypical hyperplasia of endometrium is divided into three sub-types: mild, moderate and severe atypical hyperplasia. The medication regimen of mild atypical hyperplasia is similar with that of complex hyperplasia, i.e., high-dose (30mg) MPA continuous regimen. For moderate and severe atypical hyperplasia, adopt continuous medication regimen, however, there is no unified standard for MPA drug dose. Some reports suggested a small dose of MPA 10-30mg/d, some suggested a large dose of 200-400-800mg/d, but dose of 200-400-800mg/d is preferably adopted. The recommended dose is 40-160mg/d if megestrol acetate (MA) is used. As with the treatment of complex hyperplasia, pay more attention to re-examination of endothelium biopsy when adopting high-efficiency progesterone conservative treatment on patients with atypical hyperplasia, so as to evaluate curative effect and guide regimen adjustment following a recommended 3 months one course of treatment. Endometrial pathology should be reviewed at the end of the course of treatment and choose to terminate conservative treatment or adjust drug dose according to the results. If there is no improvement or aggravation during drug use phase, or relapse after drug withdrawal, seriously pay attention to endometrial cancer and consider surgical treatment.

### New views in management of endometrial hyperplasia

**Two-type classification is recommended:** According to "Guidelines on management of endometrial hyperplasia" [1] jointly issued by the Royal College of Obstetrics and Gynecology

(RCOG) and the British Society of Gynecology Endoscopy (BSGE) in February, 2016 and "2017 Consensus on diagnosis and treatment of endometrial hyperplasia in China" [8], It is recommended to use the classification method revised by WHO in 2014, that is, endometrial hyperplasia is divided into two types: non-atypical endometrial hyperplasia and atypical endometrial hyperplasia.

### Progesterone therapy is recommended

Treatment and follow-up strategies of the two kinds of endometrial hyperplasia are as follows:

For non-atypical endometrial hyperplasia, its risk of progression to endometrial cancer (EC) within 20 years is <5%, and most patients have an ability of self-remission, therefore observation and regular histological follow-up can be considered. However, the guidelines favor the progesterone treatment for higher remission rates. Progesterone therapy is recommended for patients who cannot spontaneously relieve or have AUB symptoms during follow-up [1,8].

#### Levonorgestrel-releasing intrauterine system or continuous oral progesterone regimen is recommended:

Give priority to recommend levonorgestrel-releasing intrauterine system for progesterone therapy, i.e., mirena intrauterine device (LIN-IUS for at least 6 months, preferably 5 years for patients with no birth plan), which can achieve a higher rate of remission. For oral progesterone, continuous regimen (MPA 10-20mg/d, or norethindrone 10-15mg/d) is recommended to use for at least 6 months, rather than periodic regimen [1,8].

#### Individualized follow-up should be emphasized:

Individualized histological follow-up should be emphasized, and the plan is as follows: one follow-up should be conducted every 6 months, and in the condition that two consecutive histological negative results are detected, consider terminating the follow-up. However, for patients with high risk factors of recurrence (for instance, BMI>35), histological follow-up should be conducted every 6 months, and when two consecutive histological negative results are detected, one-year follow-up plan could be adoptable [1].

For patients with atypical endometrial hyperplasia, hysterectomy is recommended. For patients with atypical hyperplasia of endometrial who need to preserve reproductive function, the first choice is levonorgestrel-releasing intrauterine system, followed by progesterone. More emphasis should be placed on individualized histological follow-up, and the follow-up plan is as follows: one follow-up every 3 months, and when two consecutive negative results are detected, conduct follow-up every 6-12 months until hysterectomy [1].

### Surgical indications in patients with endometrial hyperplasia

Non-atypical endometrial hyperplasia: most patients with non-atypical endometrial hyperplasia can return to normal after progesterone standard treatment. Therefore, drug therapy is the main treatment for such patients, and total hysterectomy is not the first choice. Surgical treatment can be considered in the following situations:

- a. Patients with disease progresses to atypical hyperplasia of endometrial during follow-up visit, and they are unwilling to continue the drug treatment.
- b. Endometrium reverse does not occur after 12 months' treatment.
- c. After completion of treatment with progesterone therapy, endometrial hyperplasia recurs.
- d. Symptom of abnormal uterine bleeding persists.
- e. The patient has poor compliance and refuses regular follow-up or drug treatment. Total hysterectomy is advisable, and endometrial resection is not recommended [8].

Atypical hyperplasia of endometrial: if the patient has no birth demand, surgery is preferred. Total hysterectomy is recommended rather than endometrial resection. Progesterone is the main treatment option for patients with birth demand or who cannot tolerate surgery. Conservative treatment of atypical hyperplasia of endometrial should meets the following conditions.

- a. The patient insists on reproductive function preservation.
- b. The patient's age is less than 45 years old.
- c. The patient has no drug use contraindications or pregnancy unsuitability.
- d. The patient has good compliance and can conduct follow-up regularly and receive pathological examination.

It needs to be emphasized that the median time of complete endometrium reversal is 6 to 9 months. If the lesion persists or the disease progresses during a 9 to 12 months 'treatment, surgery should be performed timely to remove the uterus. In addition, patients should be fully informed of the benefits and possible risks of conservative treatment and sign informed consent. Since conservative treatment has a high recurrence rate, if the patient has completed birth or gives up birth, hysterectomy is recommended [8].

### Summary and Prospect

In general, according to "the British guidelines for management of endometrial hyperplasia in 2016" and "the Chinese consensus

on diagnosis and treatment of endometrial hyperplasia in 2017", continuous progesterone regimen is more recommended for treatment of endometrial hyperplasia, whether it is non-atypical hyperplasia or atypical hyperplasia. Currently, for drug treatment of endometrial hyperplasia, levonorgestrel-releasing intrauterine system seems to have been placed in a very important position, which is slightly different from the previous view (levonorgestrel-releasing intrauterine system should be considered after conversion of atypical hyperplasia with high effective progesterone [5,7]). However, whether these new views can be widely and uniformly adopted, it remains to be tested by time and further researches.

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