Clinical Trial Note

Comparison of diagnostic accuracy between endometrial curettage and pipelle aspiration biopsy in patients treated with progestin for endometrial hyperplasia: a Korean Gynecologic Oncology Group Study (KGOG 2019)

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Abstract

A prospective multicenter trial has been started in Korea to evaluate the diagnostic accuracy of endometrial aspiration biopsy compared with dilatation and curettage in patients treated with progesterin for endometrial hyperplasia. For conservative treatment of endometrial hyperplasia, orally administered progestins are most commonly used method with various treatment regimens and more recently, the levonorgestrel-releasing intrauterine system also has been used successfully to treat endometrial hyperplasia. However, there is no report about the accuracy of endometrial sampling during hormonal treatment for follow-up evaluation of endometrial hyperplasia. Patients with histologically confirmed endometrial hyperplasia are offered hormonal treatment with any one of the following three options: oral medroxyprogesterone acetate 10 mg/day for 14 days per cycle, continuous oral medroxyprogesterone acetate 10 mg/day or insertion of levonorgestrel-releasing intrauterine system. Histological surveillance is performed at 3 months or 6 months following initial treatment. Endometrial tissues are obtained via endometrial aspiration biopsy using a pipelle and dilatation and curettage. In the case of levonorgestrel-releasing intrauterine system, endometrial aspiration biopsy will be done with levonorgestrel-releasing intrauterine system in uterus and then, after the removal of levonorgestrel-releasing intrauterine system, dilatation and curettage will be done. The biopsy findings will be compared. The primary endpoint is to compare the pathological outcome of endometrial aspiration with dilatation and curettage. The secondary endpoint is the response rate with three types of progestin treatment at 6 months.

Key words: endometrial hyperplasia, progesterone, LNG-IUS, dilatation and curettage, endometrial aspiration biopsy
**Introduction**

Endometrial hyperplasia (EH) is a premalignant lesion of endometrial cancer (EC), which is the most common gynecological malignancy in developed countries (1). The recent increasing rate, in terms of annual percent change, was high (6.9% for all women) and especially for young women (11.2% for women <30 years) in Korea (2). Therefore, fertility preserving treatment for EH or EC will be strongly needed. In the same context, accurate diagnosis and proper management of EH are clinically significant to prevent the development of EC.

The treatment modality of EH mostly depends on the histological diagnosis and the woman’s desire to retain fertility. The risk of cancer progression is low for women with non-atypical EH (<5%) but increases up to 30% for women with atypical EH (3,4). In this respect, hysterectomy is recommended for the treatment of atypical EH. Meanwhile, for patients with non-atypical EH or for young patients with atypical EH who strongly desire to preserve their fertility, various conservative therapies using progestin have been used. Traditionally, orally administered progestins such as megestrol acetate (MA) and medroxyprogesterone acetate (MPA) are most commonly used method with various treatment regimens (5,6). More recently, the levonorgestrel-releasing intrauterine system (LNG-IUS), which achieves higher local concentrations of progestogens in the endometrium with lower systemic side effects, also has been used successfully to treat EH (7–14).

However, there has been limited data for the accuracy of endometrial sampling during hormonal treatment for EH or the best technique for follow-up evaluation of EH. A recent study comparing the histological results of pipelle biopsy and dilatation and curettage (D&C) reported almost equal EH-diagnostic success rates (15). Meanwhile, these results were obtained for cases where the LNG-IUS was not in the uterus and there were no progestin effects on the endometrium.

Therefore, we conducted a large multicenter prospective study to compare the diagnostic accuracy of endometrial aspiration biopsy with D&C in follow-up evaluation of patients treated with progestin for EH.

**Protocol of the study**

**Purpose**

This prospective study aims to evaluate the diagnostic accuracy of endometrial aspiration biopsy compared with D&C in patients treated with progestin for EH and to analyze the treatment efficacy of hormonal treatment in patient with EH.

**Endpoints**

The primary endpoint of the study is to compare the pathological outcome of endometrial aspiration with D&C. The secondary endpoint is the response rate.

**Study setting and protocol review**

This study is a prospective observational, multi-institutional study. The protocol has been approved by the institutional review board (IRB) of each institution participating in the clinical trial.

**Planned clinical trial period**

Patient selection and enrollment: 24 months after IRB approval of the clinical trial is obtained.

**Treatment methods**

Patients with histologically confirmed EH are offered hormonal treatment, one of the following three options: oral MPA 10 mg/day for 14 days per cycle, continuous oral MPA 10 mg/day or insertion of LNG-IUS. The initial histological diagnosis of EH is based on endometrial curettage specimens, obtained by D&C (Fig. 1).

Follow-up and treatment response assessment will be implemented at 3 months or 6 months after initial treatment. Endometrial tissues are obtained via endometrial aspiration biopsy using a pipelle and followed by D&C. In the case of using LNG-IUS, endometrial aspiration biopsy will be done with LNG-IUS in uterus and then, followed by D&C after removal of LNG-IUS. The biopsy findings of aspiration biopsy and D&C will be compared to evaluate the diagnostic accuracy.

To assess histological treatment response, follow-up histologic results obtained by D&C at 6 months following treatment will be compared with initial histologic diagnosis. Complete response is defined as endometrial atrophy, edematous fibrotic stroma or pseudodecidualization with no evidence of hyperplasia.

The histologic diagnosis of all specimens will be made by central pathologic review. (All the samples will be reviewed by two independent gynecological pathologists.)

**Investigational product**

(i) General name/brand name: LNG-IUS/Mirena—Schering.

Active ingredient: levonorgestrel 52 mg

Description: mirena is a hormone-releasing T-shaped intrauterine system. A removal thread is attached to a loop at the end of the vertical stem of the T-body.

(ii) General name/brand name: Provera Tablet 10 mg—Pfizer

Active ingredient: MPA

**Eligibility criteria**

All subjects will meet the following inclusion criteria before their participation in the trial:

1. Patients who are histological confirmed as endometrial hyperplasia.
2. Patients who desire to preserve fertility potential.
3. Patients signed the written informed consent voluntarily.

The exclusion criteria are as follows:

1. Pregnancy or suspected pregnancy.
2. Patients who have severe underlying disease or complication.

**Figure 1. Study design. MPA, medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; D&C, dilation and curettage; EM biopsy, endometrial biopsy.**
3. Treatment for metastatic cancer from other organs or cancer therapy within the preceding 5 years.
4. Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity.
5. Acute liver disease or kidney disease.
6. Thrombosis or phlebothrombosis requiring treatment.
7. Genital (vaginal, uterine or ovarian) infection.
8. Acute severe disease of the arteries such as stroke or heart infarction, or a history of artery disease.
9. Hypersensitivity to any component of this product.

Planned number of subjects
Seventy-five patients with biopsy proven EH.

Statistical consideration
The primary objective of this study is to compare the pathological outcome of endometrial aspiration with D&C after hormonal treatment of EH. Kappa statistics was used. The expected kappa value is 70% with a margin of error of 11%. The sample size required for this estimate is 75 patients, after allowing for a 10% loss to follow-up.

The secondary objective is to estimate the treatment efficacy of hormonal treatment; cyclic oral MPA, continuous oral MPA, LNG-IUS in patients with EH in terms of their response rates. A response rate with a 95% confidence interval will be generated and the Z-test will be used to compare the response rates.

Participating institutions
Samsung Seoul Medical Center, Seoul National University Hospital, Seoul Asan Medical Center, Gangnam CHA Medical Center, CHA University, Gyeongsang National University Hospital, Konkuk University Hospital, National Cancer Center.

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Conflict of interest statement
None declared.