

# Treatment with Medroxyprogesterone Acetate Plus Levonorgestrel-releasing Intrauterine System for Early-stage Endometrial Cancer in Young Women: Single-arm, Prospective Multicenter Study: Korean Gynecologic Oncology Group Study (KGOG2009)

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A prospective multicenter trial has been started in Korea to investigate the treatment efficacy of a levonorgestrel-releasing intrauterine system plus medroxyprogesterone acetate in young women with early-stage endometrial cancer. A number of studies have reported the effectiveness of hormonal therapy using systemic progestin in women clinically diagnosed with early endometrial adenocarcinoma at Stage IA, Grade 1, who want to maintain reproductive potential. In addition, several recent studies reported the use of a levonorgestrel-releasing intrauterine system to treat patients at a high risk of perioperative complications who cannot tolerate systemic progesterone because of its adverse effects. However, there has been no prospective multicenter trial that investigated the effectiveness of treatment with systemic progesterone in combination with intrauterine progesterone in young women with endometrial cancer. Young patients with histologically confirmed Grade 1 endometrioid adenocarcinoma that is presumably confined to the endometrium, who desired to preserve their fertility potential, undergo levonorgestrel-releasing intrauterine system insertion and are administered medroxyprogesterone acetate at a dosage of 500 mg/day concurrently. The follow-up and treatment response assessment were implemented at a 3-month interval with office endometrial aspiration biopsy with the levonorgestrel-releasing intrauterine system in place, and dilatation and curettage after removal of the levonorgestrel-releasing intrauterine system. The primary endpoint is the complete response rate. The secondary endpoint is to estimate the consistency of the results of the office endometrial aspiration biopsy with the levonorgestrel-releasing intrauterine system in the uterus and a dilatation and curettage after removal of the levonorgestrel-releasing intrauterine system.

*Key words: endometrial cancer – progesterone – LNG-IUS – medroxyprogesterone acetate*

## INTRODUCTION

Endometrial cancer is the world's second most common gynecologic malignancy and the incidence is rising steadily. Because most patients present their clinical symptoms, such as vaginal bleeding, early, almost 70% of cases are Stage I cancer at diagnosis (1,2). Endometrial cancer is relatively rare in women younger than 40 years, and only 2–14% of the cases occur in this age group. However, in recent years, the incidence of endometrial cancer in younger patients is increasing. In most cases, the endometrial cancer in young age group is a well-differentiated endometrioid adenocarcinoma with infrequent myometrial invasion or lymph node metastasis and has a clinically low grade. Therefore, it tends to show a good prognosis (3,4).

The standard treatment for endometrial cancer is total hysterectomy and bilateral salpingo-oophorectomy, peritoneal cytology and lymph node dissection (5). However, young patients who desire to preserve their potential for fertility may find this standard treatment difficult to accept. Therefore, the conservative treatment for these patients has remained a challenge. A number of studies have reported the effectiveness of hormonal therapy using systemic progestin in women clinically diagnosed with early endometrial adenocarcinoma at Stage IA, Grade 1, who want to maintain reproductive potential (6–12). In addition, several recent studies reported the use of a progesterone-containing intrauterine system (LNG-IUS) to treat patients at a high risk of perioperative complications who cannot tolerate systemic progesterone because of its adverse effects (13,14). However, they failed to show satisfactory results. Kim et al. (15) performed a pilot study of medroxyprogesterone acetate (MPA) plus LNG-IUS for early-stage endometrial cancer in young women and the study found that the treatment was effective and safe. Nevertheless, there has been no prospective multicenter trial that investigated the effectiveness of treatment with systemic progesterone in combination with intrauterine progesterone in young women with endometrial cancer.

Based on this result, we designed a larger multicenter prospective study to evaluate the effectiveness of the treatment of the presumably early-stage Grade 1 endometrial cancer in young women who desire to preserve fertility by using oral MPA in combination with LNG-IUS.

## PROTOCOL OF THE STUDY

### PURPOSE

This prospective study aims to analyze the treatment efficacy of LNG-IUS plus MPA in young women with early-stage endometrial cancer and to analyze the diagnostic accuracy of office endometrial aspiration biopsy with LNG-IUS in place compared with dilatation and curettage after removal of LNG-IUS.

### ENDPOINTS

The primary endpoint of the study is the complete response rate. The secondary endpoint is to estimate the consistency of the results of the office endometrial aspiration biopsy during the LNG-IUS being placed in the uterus and a dilatation and curettage (D&C) after removal of LNG-IUS.

### STUDY SETTING AND PROTOCOL REVIEW

This study is a single-arm, prospective 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: 36 months after IRB approval of the clinical trial is obtained.

### TREATMENT METHODS

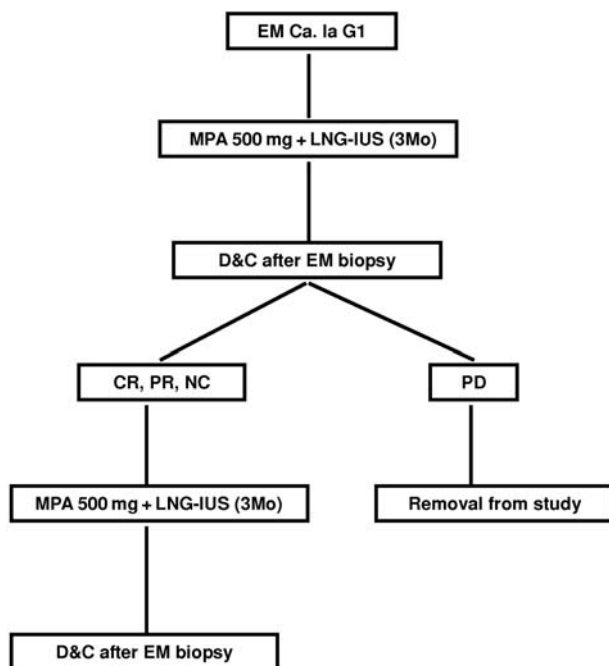
Patients with histologically confirmed Grade 1 endometrioid adenocarcinoma that is presumably confined to the endometrium go through LNG-IUS insertion and are administered MPA at a dosage of 500 mg/day concurrently. The follow-up and treatment response assessment will be implemented at a 3-month interval with transvaginal ultrasonography, endometrial aspiration biopsy with LNG-IUS in place and D&C after removal of LNG-IUS. If there is no worsening finding, the treatment is continued for 3 more months (Fig. 1). Complete response is defined as the absence of any hyperplastic or cancerous lesion. Partial response is defined as residual lesion with degeneration and atrophy of endometrial glands. No change is defined as residual lesion without degeneration or atrophy of endometrial glands. Progressive disease was defined as the appearance of Grade 2 or 3 endometrial carcinoma.

The histologic diagnosis of all specimens will be made by central pathologic review. (All the samples were reviewed two independent gynecological pathologists.) The biopsy findings of endometrial aspiration biopsy with LNG-IUS in place and D&C after removal of LNG-IUS will be compared.

In this trial, we will investigate complete response rate at 3 and 6 months after initiation of treatment. Therefore, in patients who do not obtain a complete response after 6 months, whether to continue this treatment or not is depend on the discretion of each doctor. After obtaining a complete response, whether to keep mirena or not is also depend on doctor's opinion.

### INVESTIGATIONAL PRODUCT

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



**Figure 1.** Study design. EM ca, endometrial carcinoma; G1, grade 1; MPA, medroxyprogesterone acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; D&C, dilation and curettage; EM biopsy, endometrial biopsy; CR, complete response defined as the absence of any hyperplastic or cancerous lesion; PR, partial response defined as residual lesion with degeneration and atrophy of endometrial glands; NC, no change defined as residual lesion without degeneration or atrophy of endometrial glands; PD, progressive disease was defined as the appearance of Grade 2 or 3 endometrial carcinoma; Mo, month.

- (ii) Active ingredient: levonorgestrel 52 mg
- (iii) 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.
- (iv) General name/brand name: Farlutal tab. 500 mg-Pfizer
- (v) Active ingredient: MPA.

#### ELIGIBILITY CRITERIA

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

- (i) Patients younger than 40 years.
- (ii) Patients who are histological confirmed as endometrial adenocarcinoma Grade I that is presumably confined to the endometrium based on the MRI evaluation.
- (iii) Patients who desire to preserve fertility potential.
- (iv) Patients signed the written informed consent voluntarily.

The exclusion criteria are as follows:

- (i) Patients who have severe underlying disease or complication.
- (ii) Treatment for metastatic cancer from other organs or cancer therapy within the preceding 5 years.
- (iii) Acute liver disease or kidney disease.

- (iv) Thrombosis or phlebothrombosis requiring treatment.
- (v) Patients with past history of thrombosis.
- (vi) Congenital or acquired uterine anomaly, including fibroids if they distort the uterine cavity.
- (vii) Genital (vaginal, uterine or ovarian) infection.
- (viii) Acute severe disease of the arteries, such as stroke or heart infarction, or a history of artery disease.
- (ix) Hypersensitivity to any component of this product.

#### PLANNED NUMBER OF SUBJECTS

Thirty-nine patients with biopsy proven Grade 1 endometrioid adenocarcinoma that is presumably confined to the endometrium.

#### STATISTICAL CONSIDERATION

The primary objective of this study is to estimate the treatment efficacy of the oral MPA in combination with LNG-IUS in young women with early-stage endometrial cancer in terms of their complete response rates. This study is a single-arm design with historical comparison. The expected complete response rates at the new treatment would be 75 vs. 55% in standard treatment. With 80% power and a 5% one-sided Type I error, 35 patients will be needed. After considering 10% of loss to follow-up, a total of 39 patients will be enrolled.

A complete response rates with a 95% confidence interval will be generated and the Z-test will be used. The secondary objective is to estimate the consistency of the office endometrial aspiration biopsy during the LNG-IUS being placed in the uterus and D&C after removal of LNG-IUS results. Kappa statistics will be used.

#### PARTICIPATING INSTITUTIONS

Catholic University of Korea St. Vincent's Hospital  
 Catholic University of Korea Seoul St. Mary's Hospital  
 National Cancer Center  
 Samsung Medical Center  
 Seoul National University Hospital  
 Seoul Asan medical Center  
 Yonsei University Gangnam Severance Hospital  
 Yonsei University Sinchon Severance Hospital  
 Ewha Women's University Mokdong Hospital  
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#### Conflict of interest statement

None declared.

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