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A prospective multicenter trial has been commenced in Korea to investigate the treatment efficacy of the levonorgestrel-releasing intrauterine system in patients with endometrial hyperplasia. The levonorgestrel-releasing intrauterine system is an alternative to oral progesterone without the disadvantages of oral progestogens. Therefore, we hypothesize that if the therapeutic efficacy of the levonorgestrel-releasing intrauterine system is similar to or greater than that of oral progesterone, the levonorgestrel-releasing intrauterine system could become the standard treatment for endometrial hyperplasia patients who do not want a hysterectomy. The levonorgestrel-releasing intrauterine system is inserted into uteri of patients with histologically confirmed endometrial hyperplasia. An office endometrial aspiration biopsy and transvaginal ultrasound are conducted every 3 months at an outpatients clinic. The primary endpoint is the response rate. The secondary endpoint is to estimate the consistency of the results of the office endometrial aspiration biopsy during the levonorgestrel-releasing intrauterine system being placed in uterus and a dilatation and curettage procedure.

Key words: endometrial hyperplasia – progesterone – LNG-IUS – mirena

INTRODUCTION

Endometrial hyperplasia (EH) is a known precursor of endometrial cancer. In women presenting with atypical hyperplasia, the risk of developing endometrial carcinoma is estimated to be \(~30\%\) (1).

Consequently, hysterectomy has been the major treatment in the patients who do not want to become pregnant, especially in patients with atypical EH.

Oral progesterone products have been used as an alternative option in young women who wish to become pregnant. However, oral progesterone products are associated with poor compliance and systemic adverse effects such as headache, nausea, weight gain and thromboembolic events, which may limit the overall efficacy of the drugs. Moreover, the type of progestin product, the optimal dose and the duration of treatment are not clearly established (2).

The levonorgestrel-releasing intrauterine system (LNG-IUS) is an alternative to oral progesterone without its disadvantages. Local-acting progesterone has an effect on the endometrium several times stronger than that exerted by systemic products and with less systemic effect. Therefore, the dose of progesterone can be reduced and the adverse reactions minimized. If the therapeutic efficacy of the LNG-IUS is similar to or greater than that of oral

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progesterone, the LNG-IUS could become the standard treat-
ment for EH.

The effects of the LNG-IUS have been demonstrated in
several observational studies (3,4), and in a systematic
review (5) that included some limited studies (6–10), but no
large-scale prospective study has been undertaken.

Therefore, we designed a larger multicenter prospective
study to evaluate the effectiveness of the LNG-IUS in the
treatment of EH.

PROTOCOL OF THE STUDY

PURPOSE

This prospective study aims to analyze the treatment efficacy
of the LNG-IUS in patients with EH and to analyze the
accuracy of the office endometrial aspiration biopsy when
the LNG-IUS is placed in uterus.

ENDPOINTS

The primary endpoints of the study is the 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 uterus and a dilatation and
curettage (D&C) procedure.

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: 12 months after IRB
approval of the clinical trial is obtained.

TREATMENT METHODS

The LNG-IUS is inserted into the uteri of patients with his-
tologically confirmed EH. An office endometrial aspiration
biopsy and transvaginal ultrasound will be conducted, with
the LNG-IUS inside the uterus, every 3 months at an outpati-
ent clinic.

When the LNG-IUS has been inserted for a year, an endo-
metrial aspiration biopsy will be performed with the
LNG-IUS inside the uterus, and then D&C will be per-
formed under anesthesia after LNG-IUS removal. The histo-
logic diagnosis of all specimens will be made by central pathologic review. (All the samples were reviewed two inde-
pendent gynecological pathologists.) The biopsy findings
will be compared. If the office endometrial aspiration biopsy
shows exacerbation of the hyperplasia (from EH without
atypia to with atypia or from EH with atypia to carcinoma),
treatment with the LNG-IUS will be stopped and another
specific treatment initiated.

INVESTIGATIONAL PRODUCT

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

ELIGIBILITY CRITERIA

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

(i) Histologically confirmed EH.
(ii) A desire to avoid hysterectomy.
(iii) Written informed consent given voluntarily.

The exclusion criteria are as follows:

(i) Pregnancy or suspected pregnancy.
(ii) Treatment for metastatic cancer from other organs or
cancer therapy within the preceding 5 years.
(iii) Congenital or acquired uterine anomaly, including
fibroids if they distort the uterine cavity.
(iv) Genital (vaginal, uterine or ovarian) infection.
(v) Acute liver disease or liver tumor (benign or
malignant).
(vi) Thrombosis or phlebothrombosis requiring treatment.
(vii) Acute severe disease of the arteries, such as
stroke or heart infarction, or a history of artery
disease.
(viii) Hypersensitivity to any component of this product.

PLANNED NUMBER OF SUBJECTS

Eighty patients with biopsy-proven EH (54 patients without
atypical hyperplasia and 26 patients with atypical
hyperplasia).

STATISTICAL CONSIDERATIONS

The primary objective of this study is to estimate the treat-
ment efficacy of the LNG-IUS in patients with EH in terms
of their response rates. We expect different response rate
depending on the atypia status. The atypia status will be
determined with an office endometrial aspiration biopsy,
which will be performed before and 3 months after the
LNG-IUS is inserted. The expected response rate is 70% for
those with atypia and 85% for those without atypia.
Different estimation approaches will be used according to
the atypia status of the patients. For those patients without
atypia, the response rate will be estimated with a margin of
error of 10%. The sample size required for this estimate is
54 patients, after allowing for a 10% loss to follow-up. We
will compare patients with atypia in whom the expected response rate is 40%, with a historical control. The sample size required for this comparison is 26 patients to achieve 90% power and a 5% one-sided type I error, and 10% loss to follow-up. A response rate with a 95% confidence interval will be generated and the Z-test will be used to compare the response rates.

The secondary objective is to estimate the consistency of the office endometrial aspiration biopsy during the LNG-IUS being placed in uterus and D&C results. Kappa statistics will be used.

PARTICIPATING INSTITUTIONS
Gil Medical Center, Gachon Medical School, Kyungpook National University Hospital, Gyeongsang National University Hospital, Kyung-Hee University Medical Center, Kwandong University Cheil Hospital & Women’s Healthcare Center, Catholic University of Daegu School of Medicine, Seoul National University Hospital, Soonchunhyang University Bucheon Hospital, Soonchunhyang University Chunan Hospital, Ajou University School of Medicine, Ulsan University Hospital, Ewha Women’s University Mokdong Hospital, Inje University Sanggye Paik Hospital, Inje University Ilsan Paik Hospital, Inha University Hospital, Chonnam National University Hospital, Kangnam CHA Medical Center, Bundang CHA Medical Center.

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Conflict of interest statement
None declared.

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