J Gynecol Oncol. 2023 Jan;34(1):e32
https://doi.org/10.3802/jgo.2023.34.e32
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article



# Comparison of the effect of oral megestrol acetate with or without levonorgestrel-intrauterine system on fertility-preserving treatment in patients with early-stage endometrial cancer: a prospective, open-label, randomized controlled phase II trial (ClinicalTrials.gov NCT03241914)



**Received:** Aug 31, 2022
**Revised:** Nov 6, 2022
**Accepted:** Dec 7, 2022
**Published online:** Dec 15, 2022

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## ABSTRACT

**Objective:** To evaluate the effect of levonorgestrel-releasing intrauterine system (LNG-IUS) plus oral megestrol acetate (MA) as fertility-preserving treatment in patients with early-stage endometrial cancer (EEC).
**Methods:** In this single-center, phase II study with open-label, randomized and controlled design, young patients (18–45 years) diagnosed with primary EEC were screened, who strongly required fertility-preserving treatment. Patients were randomly assigned (1:1) into MA group (160 mg oral daily) or MA (160 mg oral daily) plus LNG-IUS group. Pathologic evaluation on endometrium retrieved by hysteroscopy was performed every 3 months. The primary endpoint was complete response (CR) rate within 16 weeks of treatment. The secondary endpoints were CR rate within 32 weeks of treatment, adverse events, recurrent and pregnancy rate.
**Results:** Between July 2017 and June 2020, 63 patients were enrolled and randomly assigned. Totally 56 patients (26 in MA group; 28 in MA + LNG-IUS group) were included into primary-endpoint analyses. The median follow-up was 31.6 months (range, 3.1–94.0). No significant difference in 16-week CR rate were found between MA and MA + LNG-IUS groups (19.2% vs. 25.0%, p=0.610; odds ratio=1.40; 95% confidence interval=0.38–5.12), while the 32-week CR rates were also similar (57.1% and 61.5%, p=0.743), accordingly. More women in MA + LNG-IUS group experienced vaginal hemorrhage (46.4% vs. 16.1%; p=0.012) compared with MA group. No intergroup difference was found regarding recurrence or pregnancy rate.
**Conclusion:** Compared with MA alone, the addition of LNG-IUS may not improve the early CR rate for EEC, and may produce more adverse events instead.

**Trial Registration:** ClinicalTrials.gov Identifier: NCT03241914

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**Funding**
This study was supported by the National Key Research and Development Program of China (Grant No. 2019YFC1005200 and 2019YFC1005204), Shanghai Medical Centre of Key Programs for Female Reproductive Diseases (Grant No. 2017ZZ010616) and Shen Kang clinical project (SHDC22021219).

**Conflict of Interest**
No potential conflict of interest relevant to this article was reported.

**Author Contributions**
Conceptualization: G.J., C.X.; Data curation: X.Z., Y.B., S.W., L.J., S.W., C.X.; Formal analysis: X.Z., Y.B., G.J., C.X.; Investigation: X.Z., Y.B.; Methodology: X.Z., Y.B., G.J., C.X.; Project administration: X.Z., C.X.; Software: X.Z., G.J.; Supervision: G.J., C.X.; Validation: C.X.; Visualization: X.Z., Y.B.; Writing - original draft: X.Z., Y.B.; Writing - review & editing: G.J., S.W., L.J., S.W., C.X.

**Keywords:** Endometrial Hyperplasia; Endometrial Neoplasms; Conservative Treatment; Intrauterine Devices, Medicated

**Synopsis**
Megestrol acetate (MA) combined with levonorgestrel-releasing intrauterine system (LNG-IUS) may not achieve better efficacy but have more adverse effects than MA alone as fertility-preserving treatment for early-stage endometrial cancer patients. No intergroup difference was found regarding recurrence rate or pregnancy rate between two groups.

## INTRODUCTION

The incidence of endometrial cancer (EC) has been increasing in recent years, including reproductive-age women without completing childbearing [1,2]. The standard treatment for EC is complete surgical resection, which will consequently cause the permanent loss of fecundity in young patients [3]. For EC patients who desire to preserve their fertility, high-dose progestins have been applied as classic treatment regimen [4-6]. However, the complete response (CR) rates were difficult to exceed 70%–80% [7,8]. Although hysteroscopic lesion resection was reported to improve the CR rate of megestrol acetate (MA) with a cumulative 12 months CR rate of 91.4% and mean treatment duration of 6.4 months for early-stage endometrial cancer (EEC) patients [9], almost one-third of patients were still treated for more than 9 months before achieving CR [9]. In this circumstance, multiple adverse events will occur with the prolonged use of high-dose progestins, such as weight gain, impaired liver function, and thrombosis [8]. Therefore, it is urgently needed to explore more optimal algorithm of fertility-preserving treatment for EEC patients.

Several studies suggested that the local usage of levonorgestrel-releasing intrauterine system (LNG-IUS) combined with high-dose systemic progestin might be an effective regimen for EEC. Oral progestin leads to high plasma concentrations but low local concentrations in the endometrium, especially in obese patients, which may lower the treatment efficacy. Conversely, LNG-IUS releases highly effective progestin directly into the endometrium, resulting in the concentration of progestin in the endometrium 30 times higher than that in the plasma [10]. However, the efficacy of LNG-IUS combined with oral progestins as fertility-preserving treatment for EEC patients has not been well investigated.

Therefore, we conducted this prospective randomized phase II study, to evaluate the treatment outcome and safety of the LNG-IUS combined with MA compared with MA alone as fertility-sparing treatment for EEC patients.

## MATERIALS AND METHODS

### 1. Study design and patients

The single-center, open-label, randomized controlled phase II study (NCT03241914) aimed to address the treatment efficacy of MA combined with LNG-IUS (MA + LNG-IUS) compared with MA alone in EEC patients. This study was conducted between July 13th, 2017 and June 18th, 2020, in Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China.

The study was done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines following approval by the Institutional Review Board of the Obstetrics and Gynecology Hospital of Fudan University (Approval No. 2017-30). All patients were fully informed of the benefits and risks of this clinical and provided written informed consent.

Eligible patients were those met the inclusion criteria: pathologically diagnosed with primary grade 1 endometrioid endometrial carcinoma without myometrial invasion; 18–45 years old; had no signs of suspicious myometrial invasion or extrauterine metastasis by enhanced magnetic resonance imaging (MRI), enhanced computed tomography and transvaginal ultrasonography; with normal uterine size (the longest uterine diameter [from the fundus to endocervix] <7 cm by ultrasound, as larger uterine cavity might result in the dropping of LNG-IUS out of the body or reduced therapeutic effect of LNG-IUS); had strong desire to preserve fertility; had no contraindication for pregnancy.

Patients were excluded if they had the following situations: recurrent EC; allergy history or contraindications for MA or LNG-IUS; pregnancy; severe infection, severe chronic diseases (dysfunction of heart, liver, lung, or kidney); high risk of thrombosis; had hormone treatment for more than 3 months within 6 months before entering the trial; other malignancy history; concurrent malignancy in genital or other systems.

Pathologic diagnosis was confirmed by 2 experienced gynecological pathologists (Dr. Zhu Q and Dr. Zhou XR) according to the World Health Organization pathological classification (2014) [11]. A seminar was held in the pathological department for the final diagnosis if their opinions differed.

## 2. Randomization and masking

Patients were randomly assigned (1:1) to receive MA or MA + LNG-IUS by the simple randomization. Randomization sequences were prepared according to random-number tables. Treatment allocation was concealed before the participants were successfully enrolled. This study was open label that all study physicians and patients were aware of the treatment assignment. However, the pathologists were not aware of the treatment allocations.

## 3. Procedures

Patients in MA group received continuous MA (160 mg, orally, daily). The dosage of MA was decided according to International Federation of Gynecology and Obstetrics (FIGO) cancer report 2021 and European Society of Gynaecological Oncology 2020 guidelines [12,13]. Patients in MA + LNG-IUS group received MA (160 mg, orally, daily) combined with LNG-IUS (containing LNG 52 mg) insertion.

Complete hysteroscopic evaluation and resection of lesions were performed by 2 specialists (Dr. Zhang HW and Dr. Zhu CY) in all patients before the initiation of treatment in this trial. LNG-IUS was placed during hysteroscopy for those allocated to MA + LNG-IUS group. Hysteroscopy was scheduled to be performed every 3 months to evaluate treatment response after initiating the treatment following standard procedure as described previously. According to the result of MRI and ultrasound, all suspected lesions were removed completely until no lesions were visible to the naked eye. And the basal layer of endometrium should be protected as much as possible. A random endometrial biopsy was performed in the area where no obvious lesion was found. All the specimens were sent separately for the pathological diagnosis. Pathologic diagnosis was confirmed by 2 masked experienced

gynecological pathologists. If there was a disagreement between the 2 pathologists, a seminar was held in the pathological department for the final diagnosis [9].

The LNG-IUS was taken out during each hysteroscopic evaluation and kept from contamination. Bacilli culture was performed at the same time. A new LNG-IUS is suggested to be placed in uterine cavity after each hysteroscopic evaluation. If the patient insisted on using the old one, the LNG-IUS would be swabbed by iodophor for sterilization and reinserted in the uterine cavity. The LNG-IUS would be taken out immediately if bacilli culture reported positive result.

The treatment response was categorized as follows: (1) CR, defined as no endometrial lesion. Another hysteroscopy would be performed 3 months later for confirmation of CR; (2) partial response (PR), pathological improvement, such as endometrial hyperplasia or atypical endometrial hyperplasia (AEH); (3) stable disease (SD), persistence of disease as originally diagnosed; (4) progression disease (PD), any appearance of higher-grade EC, myometrial invasion, or extrauterine lesions in EEC patients were recognized. Treatment would be ceased if patients experienced unacceptable adverse effects. Definitive hysterectomy was suggested if the patient remained SD after 7 months of treatment, not achieving CR after 10 months of treatment, or PD at any time of treatment [14]. For those who refused hysterectomy, alternative treatment would be given based on multidisciplinary consensus. Duration of treatment time to achieve CR was calculated from the initiation of treatment to the first time that the patient was pathologically diagnosed as CR after hysteroscopy.

After achieving CR, the same regimen was administered for another 2–3 months for treatment consolidation and patients were encouraged to receive assisted reproductive treatment. Two to 3 months of treatment consolidation was based on our previous clinical experience. CR was defined as no lesion identified for 2 consecutive hysteroscopic evaluations. The same treatment was continued until a second CR was achieved. Ultrasonography (every 3 months) and endometrial biopsy by Pipelle (every 6 months) were routinely used to assess the endometrium. For CR patients without recent desire of conception, or those stopped breast breeding after delivery, cyclic oral dydrogesterone, oral contraceptive pills, or LNG-IUS was administered to prevent disease recurrence. Hysterectomy was suggested for patients who had completed childbearing. Recurrence was defined as the presence of simple hyperplasia, complex hyperplasia, AEH, or EC after CR.

Data on age, height, weight, size of waist/hip, and blood test results were collected before the initiation of treatment. Blood tests including fasting blood glucose (FBG), fasting insulin (FINS), and lipid panel. Obesity was defined as Body mass index (BMI) ≥28 kg/$m^2$ followed criteria for Chinese adults [15,16]. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index, which was calculated as FBG (mmol/L)×FINS (mU/L)/22.5. HOMA-IR ≥2.95 was considered insulin resistant [17]. Metabolic syndrome was defined according to literature [15,18,19]. ER, PR and DNA mismatch repair (MMR) proteins (MLH1, PMS2, MSH2 and MSH6) expression were assessed by immunohistochemistry (IHC) on formalin-fixed paraffin-embedded tumor samples before hormone treatment. IHC procedures were performed as we previously described [20-22]. All patients were followed up from the date of treatment initiation to January 30th, 2022.

## 4. Outcomes

The original primary endpoint was 3-month CR rate and the secondary endpoints were 6-month CR rate, treatment-related adverse events, recurrent rate, and pregnancy rate.


https://doi.org/10.3802/jgo.2023.34.e32

However, according to our previous study [23], most patients underwent the first and second hysteroscopic evaluation within 16 and 32 weeks. There were many patients delay hysteroscopy for various reasons, such as the coronavirus disease 2019 quarantine, vaginitis and temporary working arrangement. Thus, the CR rates within 16 weeks and 32 weeks of treatment (16-week CR rate and 32-week CR rate) were eventually included into the intention-to-treat (ITT) analysis for the primary and secondary endpoints instead of the 3-month and 6-month CR rates. Safety assessment was assessed in patients treated for more than 3 months and graded following the National Cancer Institute Common Toxicity Criteria version 4.0 at baseline (prior to treatment), at the time when assessing treatment response, and at completion of treatment. Serious adverse events were reported within 24 hours. The maximum extent of weight change during treatment was also assessed.

### 5. Statistical analysis

According to literatures [24-26] and the data of our previous study [23], for the primary endpoint, we assumed the 16-week CR rate was 20% in MA group and 30% in MA + LNG-IUS group; with a power of 0.8 at a 2-sided significance level of 0.05; requiring an accrual of 458 eligible patients (lost to follow-up rate <10%). Since the recruitment number was too large to be achieved, we eventually decided to conduct a phase II study with randomized controlled design, to recruit 60 patients with 30 in each group. Because the enrollment rate of EC patients meeting the inclusion criteria of this study in our center was about 30 patients per year and the enrollment period was 2 years. ITT analyses were performed for patients underwent endometrial evaluation within 16 or 32 weeks of treatment. Student's t-test or Mann-Whitney test was used for comparison between 2 groups. The $\chi^2$ test or Fisher's exact test were used for the differences in the categorical variable. Time-to-event endpoints were estimated with the Kaplan-Meier method. Log-rank test was used to compare the differences in survival curves. Logistic regression analysis was used to estimate odds ratio (OR) for 16-week or 32-week CR rates. Cox regression analysis was used to estimate hazard ratio for CR or recurrence. A 2-tailed p-value of <0.05 was considered statistical significant. All statistical analyses were performed using SPSS for windows (version 22.0; SPSS, Armonk, NY, USA). CONSORT guidelines were consulted to outline this study [27].

## RESULTS

### 1. Patients and treatment

All the participants were Chinese Asian. Flow chart in the trial is reported in **Fig. 1**. In total of 83 patients were screened, 20 of whom were deemed ineligible due to their progestin-use history or the requirement for definitive surgery. Eventually, 63 patients who met all the inclusion and exclusion criteria were randomly 1:1 assigned to MA (n=31) or MA + LNG-IUS group (n=32). Before approaching the primary endpoint, 2 patients required hysterectomy and 1 patient withdrew the trial in MA + LNG-IUS group. Five patients in MA group and one patient in MA + LNG-IUS group missed endometrial evaluation within 16 weeks of treatment. Hence, 26 patients in MA group and 28 in MA + LNG-IUS group were included in ITT analyses for 16-week CR rates (**Fig. 1**). Three patients in MA group and 3 patients MA + LNG-IUS group missed endometrial evaluation within 32 weeks of treatment. Among 29 patients using LNG-IUS plus MA, positive bacilli culturing result of cervical secretion was found in one patient at initial hysteroscopic endometrial evaluation, and the LNG-IUS was then taken out immediately to avoid further infection. Thus, this patient was excluded from the safety analyses. Eventually, 59 out of 63 patients treated for more than 3 months were included into the safety analysis (**Fig. 1**).


https://doi.org/10.3802/jgo.2023.34.e32

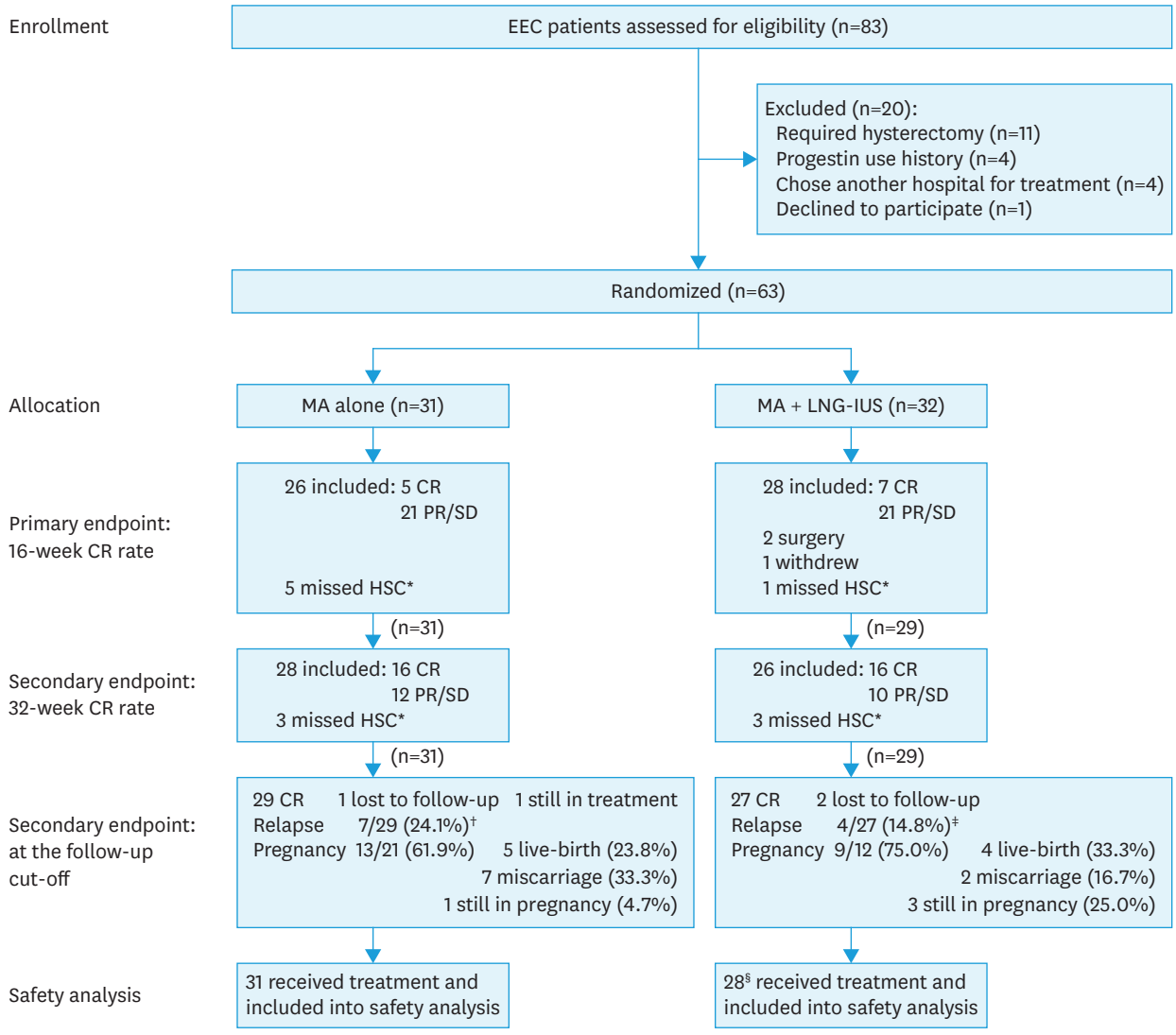


**Fig. 1.** Flow diagram.
CR, complete response; EEC, endometrioid endometrial cancer; HSC, hysteroscopy; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; PR, partial response; SD, stable disease.
*Patients missed endometrial evaluation at 16 or 32 weeks were excluded for 16- or 32-week CR rate analysis.
†In MA group, 5 patients had atypical endometrial hyperplasia and 2 patients had complex endometrial hyperplasia after CR.
‡In MA + LNG-IUS group, 1 patient recurred endometrial cancer, 1 patient had atypical endometrial hyperplasia, 1 patient had complex endometrial hyperplasia and 1 patient had simple endometrial hyperplasia after CR.
§In MA + LNG-IUS group, one patient was not included in the safety analyses because of less than 3 months of LNG-IUS use. The LNG-IUS was taken out after 4 days of initial hysteroscopic evaluation because positive bacterial culture of the cervical secretion.

Patient characteristics were well balanced between the 2 treatment groups (**Table 1**). The median age was 30 (range, 21–43) years old, and the median BMI was 25.0 (range, 18.0–51.6) kg/m$^2$. There was no difference in age at diagnosis, pretreatment BMI, IR status, lesion size, ER and PR expression between the 2 groups. Twenty-three out of 63 patients (36.5%) were obese (BMI ≥28 kg/m$^2$) and 38.1% (24/63) of patients were insulin resistant (HOMA-IR ≥2.95). MMR proteins IHC staining was evaluated in 49 patients, 3 of whom had MSH6 loss. And all these 3 patients were in MA group. Germline sequencing test was performed in 27 patients, including the 3 patients with MSH6 loss by IHC (the germline genes tested included FH, PTEN, POLE, BRCA2, BRCA1, TP53, STK11, POLD1, EPCAM, MSH2, MSH6, PMS1, MLH1,


https://doi.org/10.3802/jgo.2023.34.e32

**Table 1.** Demographic and clinical characteristics of eligible patients

| Characteristics | MA group (n=31) | MA + LNG-IUS group (n=32) | p |
|---|---|---|---|
| Age at diagnosis (yr) | 30 (21–43) | 30 (25–42) | 0.322 |
| BMI (kg/m$^2$) | 24.9 (18.0–37.1) | 25.6 (18.0–51.6) | |
| ≥28 | 10 (32.3) | 13 (40.6) | 0.929 |
| <28 | 21 (67.7) | 19 (59.4) | 0.490 |
| Fasting insulin (μU/mL) | 9.7 (5.2–35.6) | 11.1 (2.3–45.5) | 0.896 |
| Waist hip ratio | 0.87 (0.77–1.01) | 0.86 (0.76–1.17) | 0.923 |
| CA-125 (U/mL) | 19.3 (7.3–53.9) | 15.6 (4.2–58.7) | 0.234 |
| HOMA-IR | 2.23 (1.09–8.70) | 2.50 (0.92–10.51) | 0.891 |
| IR* | | | 0.921 |
| Present | 12 (38.7) | 12 (37.5) | |
| Absent | 19 (61.3) | 20 (62.5) | |
| Metabolic syndrome | | | 0.513 |
| Present | 12 (38.7) | 15 (46.9) | |
| Absent | 19 (61.3) | 17 (53.1) | |
| Hypertension | | | 0.474 |
| Present | 3 (9.7) | 6 (18.8) | |
| Absent | 28 (90.3) | 26 (81.3) | |
| Diabetes mellitus | | | 0.613 |
| Present | 2 (6.5) | 1 (3.1) | |
| Absent | 29 (93.5) | 31 (96.9) | |
| Nulliparous | | | 0.613 |
| No | 1 (3.2) | 3 (9.4) | |
| Yes | 30 (96.8) | 29 (90.6) | |
| Lesion size† (cm) | | | 0.561 |
| ≥4 | 5 (16.1) | 7 (21.9) | |
| <4 | 26 (83.9) | 25 (78.1) | |
| ER expression‡ (%) | 90 (60–100) | 90 (30–100) | 0.136 |
| PR expression‡ (%) | 90 (30–100) | 80 (50–100) | 0.249 |

BMI, body mass index; CA-125, cancer antigen 125; ER, estrogen receptor; HOMA-IR, homeostasis model assessment-insulin resistance; IR, insulin resistance; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; PR, partial response.
*HOMA-IR ≥2.95; †Lesion size was measured by magnetic resonance imaging before treatment; ‡The expression of ER and PR were the percentage of stained tumor cell nuclei in the immunohistochemical staining of the lesion before treatment among 47 patients.

MSH3, APC and PMS2). However, no germline pathogenic or likely pathogenic mutations were found in these patients.

Median follow-up after initiation of treatment was 31.6 months (range, 3.1–94.0). At the time of last follow-up, 1 patient withdrew the study, 2 received hysterectomy, 3 lost to follow-up (all 3 patients remained PR before lost to follow-up) and 1 was still in treatment (the patient currently remained PR), and the other 56 women achieved CR (**Fig. 1**). Of the 2 patients who underwent surgery, one withdrew after 2 months of treatment and the other withdrew after 1 month of treatment. The postoperative pathology of the former patient was early endometrial carcinoma limited to the endometrium (FIGO stage IA), while the postoperative pathology of the latter patient was AEH. None of the patients experienced PD during treatment. Twenty-six patients remained SD after 7 months of treatment or did not achieve CR after 10 months of treatment. Among these 26 patients, 12 used alternative treatment, 3 lost to follow-up and the other 11 continued the original regimen. The median treatment duration to achieve CR were 36.3 weeks (95% confidence interval [CI]=27.2–45.3) in MA group and 32.0 weeks (95% CI=28.0–36.0) in MA + LNG-IUS group, with no significant statistical difference between the 2 groups (p=0.491, hazard ratio [HR]=1.20; 95% CI=0.71–2.04; **Fig. 2**). The cumulative 1-year CR rate was 64.5% in MA group and 78.8% in MA + LNG-IUS group. The median follow-up after CR was 24.1 months (range, 8.16–49.7).


https://doi.org/10.3802/jgo.2023.34.e32

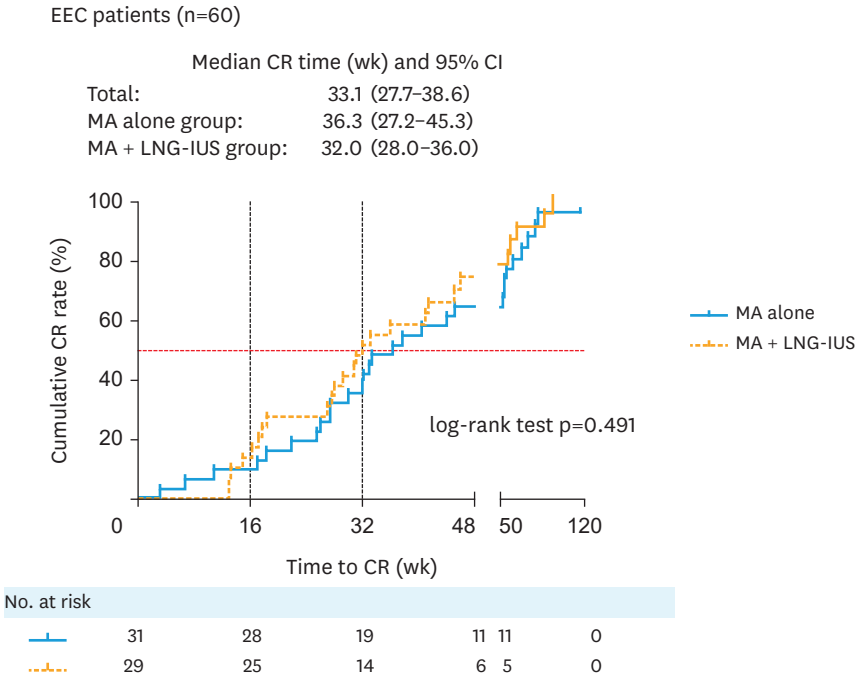


**Fig. 2.** CR rate and median CR time. Kaplan-Meier survival curves for cumulative CR rate in patients received treatment.
CI, confidence interval; CR, complete response; EEC, early-staged endometrial cancer; HR, hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate.

## 2. The 16-week CR rate (primary endpoint)

The overall 16-week CR rate was 22.2% (12/54). The 16-week CR rate was 19.2% (5/26) in MA group and 25.0% (7/28) in MA + LNG-IUS group. However, no statistical significance was observed (p=0.610; MA + LNG-IUS vs. MA: OR=1.40; 95% CI=0.38–5.12; **Table 2**, **Fig. 2**).

We retrospectively compared the 16-week CR rate in subgroups according to different metabolic status, such as BMI or IR status (**Table S1**). However, no significant difference was found between the 2 treatment groups.

## 3. The 32-week CR rate (secondary endpoint)

The overall 32-week CR rate was 59.3% (32/54). The 32-week CR rate was 57.1% (16/28) in MA group and 61.5% (16/26) in MA + LNG-IUS group, with no statistical significance between 2 groups (p=0.743; MA + LNG-IUS vs. MA: OR=1.20; 95% CI=0.40–3.56; **Table 2**). Similarly, no significant intergroup difference was found in 32-week CR rate according to different metabolic status (**Table S2**).

**Table 2.** Clinical outcome in MA group and MA + LNG-IUS group

| Outcome | MA group | MA + LNG-IUS group | p | OR (95% CI) | HR (95% CI) |
|---|---|---|---|---|---|
| 16-week CR rate (%) | 19.2 (5/26) | 25.0 (7/28) | 0.610 | 1.40 (0.38–5.12) | - |
| 32-week CR rate (%) | 57.1 (16/28) | 61.5 (16/26) | 0.743 | 1.20 (0.40–3.56) | - |
| CR time (wk; median and 95% CI) | 36.3 (27.2–45.3) | 32.0 (28.0–36.0) | 0.491 | - | 1.20 (0.71–2.04) |
| 1-year cumulative recurrence rate (%) | 14.3 | 7.6 | - | - | - |
| 2-yr cumulative recurrence rate (%) | 25.7 | 11.8 | - | - | - |
| 1-yr cumulative pregnancy rate (%) | 33.3 | 33.3 | - | - | - |

The p-value <0.05 was the significant threshold.
CI, confidence interval; CR, complete response; HR, hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate; OR, odds ratio.


https://doi.org/10.3802/jgo.2023.34.e32

## 4. Safety analysis

There was no treatment-related death or serious adverse events (grade 4) during the study. The most common side effects were increased nocturnal urine, libido decreased, weight gain, fatigue, night sweats and abdominal distension (**Table 3**). Compared with the MA group, more patients in the MA + LNG-IUS group experienced vaginal hemorrhage (16.1% vs. 46.4%; p=0.012) (**Table 3**). Conversely, no significance was found in weight change between MA group (median, 2.5 kg; 95% CI=−3.8–19.0) and MA + LNG-IUS group (median, 3.0 kg; 95% CI=−15–18.4; p=0.495; **Fig. S1**).

## 5. Long term onco-fertility results

Among the 56 patients who achieved CR, 11 patients recurred during the follow-up (**Fig. 1**; **Table S3**). All the recurrent patients chose conservative treatment except for one patient in MA group recurred AEH opted for hysterectomy. And the final pathology of the patient was endometrioid endometrial carcinoma invading less than half the myometrium (FIGO stage IA). The overall cumulative 1-year and 2-year recurrence rate after CR was 11.1% and 19.2%. No significant difference was observed in cumulative 1-year and 2-year recurrence rates between the 2 groups (**Table 1**; **Fig. 3A**).

Among the 56 patients who achieved CR, 33 patients had recent plan for parenthood. The overall pregnancy rate was 66.7% (22/33), 61.9% (13/21) in MA group and 75.0% (9/12) in

**Table 3.** Safety analyses

| Toxicity | MA group (n=31) | MA + LNG-IUS group (n=28) | p |
|---|---|---|---|
| Increased nocturnal urine (Grade 1–2) | 17 (54.8) | 21 (75.0) | 0.106 |
| Libido decreased (Grade 1–2) | 15 (48.4) | 18 (64.3) | 0.219 |
| Weight gain | 14 (45.2) | 14 (50.0) | 0.710 |
| Grade 1–2 | 12 (38.7) | 12 (42.9) | |
| Grade 3 | 2 (6.5) | 2 (7.1) | |
| Fatigue (Grade 1–2) | 14 (45.2) | 12 (42.9) | 0.859 |
| Night sweats (Grade 1–2) | 13 (41.9) | 17 (60.7) | 0.150 |
| Abdominal distension (Grade 1–2) | 12 (38.7) | 10 (35.7) | 0.812 |
| Dyspareunia (Grade 1–2) | 9 (29.0) | 7 (25.0) | 0.728 |
| Vaginal dryness (Grade 1–2) | 9 (29.0) | 9 (32.1) | 0.796 |
| Edema face (Grade 1–2) | 8 (25.8) | 8 (28.6) | 0.811 |
| Breast pain (Grade 1–2) | 8 (25.8) | 7 (25.0) | 0.943 |
| Abdominal pain (Grade 1–2) | 7 (22.6) | 2 (7.1) | 0.150 |
| Dizziness/Headache (Grade 1–2) | 7 (22.6) | 9 (32.1) | 0.409 |
| Alopecia (Grade 1–2) | 6 (19.4) | 5 (17.9) | 0.883 |
| Nausea (Grade 1–2) | 5 (16.1) | 6 (21.4) | 0.602 |
| Diarrhea (Grade 1–2) | 5 (16.1) | 4 (14.3) | 1.000 |
| Constipation (Grade 1–2) | 5 (16.1) | 4 (14.3) | 1.000 |
| Back pain (Grade 1–2) | 5 (16.1) | 6 (21.4) | 0.602 |
| Pruritus (Grade 1–2) | 5 (16.1) | 3 (10.7) | 0.709 |
| Vaginal hemorrhage (Grade 1–2) | 5 (16.1) | 13 (46.4) | **0.012** |
| Leukocytosis (Grade 1–2) | 5 (16.1) | 1 (3.6) | 0.198 |
| Insomnia (Grade 1–2) | 4 (12.9) | 6 (21.4) | 0.494 |
| Rash (Grade 1–2) | 4 (12.9) | 8 (28.6) | 0.135 |
| Increased alanine aminotransferase (Grade 1–2) | 4 (12.9) | 5 (17.9) | 0.723 |
| Hypertension (Grade 1–2) | 3 (9.7) | 2 (7.1) | 1.000 |
| Vomiting (Grade 1–2) | 2 (6.5) | 2 (7.1) | 1.000 |
| Hypercoagulable status (Grade 1–2) | 0 (0.0) | 1 (3.6) | 0.475 |
| Thromboembolic event (Grade 1) | 0 (0.0) | 1 (3.6) | 0.475 |
| Breast cancer | 0 (0.0) | 0 (0.0) | - |

Values are presented as number (%). The p-value showed the difference in total adverse events between different groups. The $\chi^2$ test was used, or Fisher's exact test was performed when expect counts were less than 5. p<0.05 are shown in bold.
MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system.


https://doi.org/10.3802/jgo.2023.34.e32

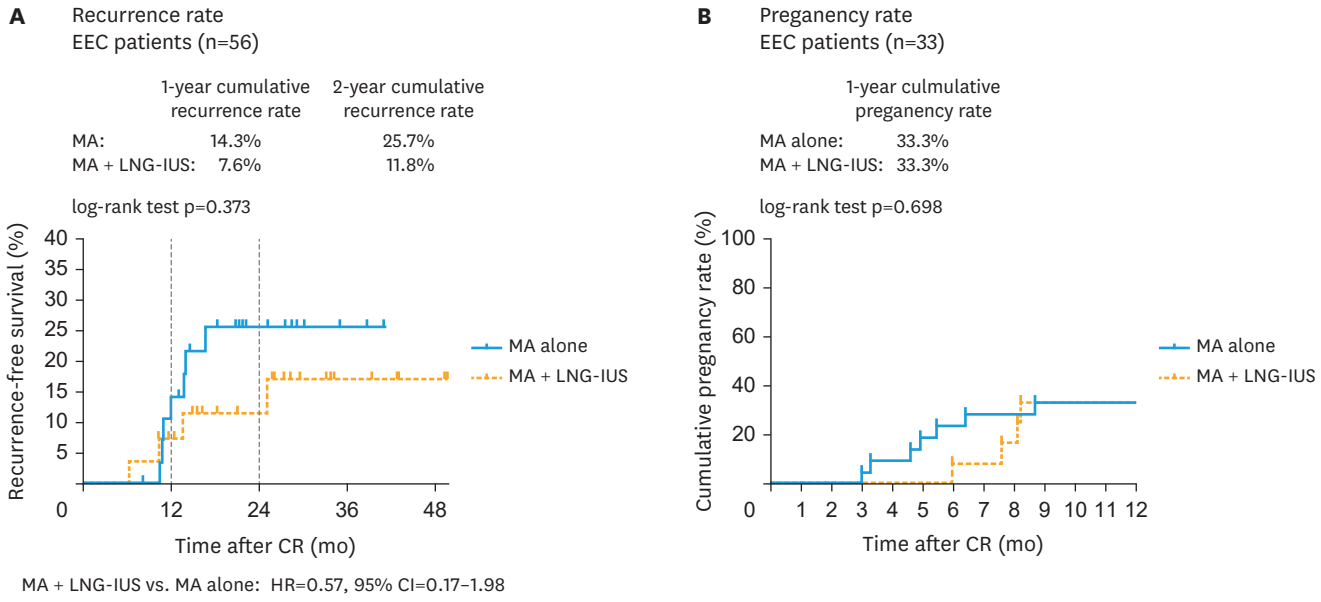


**Fig. 3.** Recurrence rate and pregnancy rate of the patients achieved CR. (A) The 1-year and 2-year cumulative recurrence rate in patients achieved CR. (B) The 1-year cumulative pregnant rate of patients achieved CR.
CI, confidence interval; CR, complete response; EEC, early-stage endometrial cancer; HR, hazard ratio; LNG-IUS, levonorgestrel-releasing intrauterine system; MA, megestrol acetate.

MA + LNG-IUS group (**Fig. 1**). Of the 22 women who had a successful pregnancy, 9 had a live birth, 9 had a miscarriage and 4 were still in pregnancy at the last follow-up. The live birth rate was 27.3% (9/33) in total, 23.8% (5/21) in MA group and 33.3% (4/12) in MA + LNG-IUS group (**Fig. 1**). The cumulative 1-year pregnancy rate after CR was 33.3% in MA group and 33.3% in MA + LNG-IUS group (**Fig. 3B**).

## DISCUSSION

Our data showed that MA + LNG-IUS might not improve fertility preserving treatment outcome compared with MA alone. Moreover, vaginal hemorrhage occurred more often in the MA + LNG-IUS group compared with the patients received MA alone. No difference was found in recurrence and pregnancy rate between MA group and MA + LNG-IUS group.

Our data support that MA remains the first-line fertility-preserving treatment for EEC patients. We found that the combination of MA and LNG-IUS did not achieve higher 16-week or 32-week CR rates and caused more vaginal bleeding instead. There is still a lack of evidence to establish the optimal way of progestin treatment. Several exploratory studies have shown that systemic progestin combined with LNG-IUS may be an effective regimen for EEC. Kim et al. [24] used medroxyprogesterone acetate (MPA) combined with LNG-IUS to treat EEC limited to endometrial layer, with curettage every 3 months, and the CR rate after 3 months of treatment was 25% (4/16), the overall CR rate was 87.5% (14/16), with the average CR time 9.8±8.9 months. Subsequently, Kim et al. [28] continued a multicenter prospective study, in which the CR rate after 6 months of treatment was 37.1% (13/35), and the PR rate was 25.7% (9/35). No progressive cases or treatment-related complications were found in that study. Cade et al. [26] found that combined use of systemic progestin and LNG-IUS led to a response rate of 77.8% (7/9) in EEC, and only 50% (2/4) in patients using systemic


https://doi.org/10.3802/jgo.2023.34.e32

progestin alone. In addition, a meta-analysis showed that the pooled CR rate of 87% (95% CI=75%–93%) for EEC and AEH patients who used oral progestin plus LNG-IUS, while the pooled CR rate for women using oral progestin alone was 71% (95% CI=63%–77%) [29]. There are might be several possible reasons causing the difference between our study and previous findings. Firstly, these studies were exploratory or retrospective with relatively small sample-sizes. Moreover, potential differences in the efficacy between MA and MPA might be one of the reasons for the inconsistency between our study and these retrospective studies. More researches are needed to explore the difference between MA and MPA. Additionally, the reason of adding LNG-IUS to oral progestins did not improve outcomes might be that the concentration of progestin from MA alone is effective enough on endometrial lesion, and adding LNG-IUS could not add more value on the treatment effect. Although the sample size was still modest, our study is the first randomized and controlled trial showing that MA plus LNG-IUS might not achieve higher 16- and 32-week CR rate than MA alone. More research is needed to further investigate the benefit regarding the combination of MA and LNG-IUS.

The reason why MA combined with LNG-IUS did not achieve better treatment efficacy than MA alone still remains unknown. Systemic MA might achieve adequate progestin concentration to treat EEC without additional progestin concentration from LNG-IUS. Korean Gynecologic Oncology Group 2002 study reported that a higher dose of MPA did not result in superior conservative therapeutic effects in EEC [8]. A Gynecologic Oncology Group study also reported that low-dose MPA (200 mg/day) was more effective than high-dose treatment (1,000 mg/day) even for advanced or recurrent endometrial carcinomas [30]. More research is needed to further investigate the benefit regarding the combination of these 2 therapies.

Additionally, our study found that MA + LNG-IUS was associated with more vaginal hemorrhage (46.4%) than MA alone (16.1%). Abnormal vaginal bleeding was common in patients treated by LNG-IUS [31]. It might be due to the high drug concentration of LNG-IUS in endometrium which inhibited the proliferation and repair of endometrium [10]. More vaginal hemorrhage can lead to discomfort and poor treatment compliance, which also does not support the additional use of LNG-IUS to treat EEC during the MA therapy.

The strengths of this study are the prospective nature and randomized controlled design. This is the first prospective randomized controlled phase II study with relatively large sample-size (n=63), investigating the effect of oral progestin with or without LNG-IUS on fertility-preserving outcome in EEC patients. The limitations include the lack of double-blind design and placebo, the single-center study, and insufficient sample size that impact the power of our study to compare the effect of these 2 treatment regimens. Moreover, both our 2 treatment groups used hysteroscopic evaluation and resection of lesion, which might conceal the difference of efficacy between 2 groups. In addition, the follow-up time after CR was short. The recurrence rate and pregnancy rate will be further calculated after all patients have been followed up for 2 years after CR.

In conclusion, MA combined with LNG-IUS might not improve early CR rate and had more adverse events compared with MA alone in EEC patients who desired to preserve fertility. Our data support the usage of MA alone as fertility preserving treatment for young EEC patients. Phase III clinical trial with larger sample size is needed to further validate our findings.


https://doi.org/10.3802/jgo.2023.34.e32

## ACKNOWLEDGEMENTS

We are grateful for the data work of Pengfei Wu, Shuang Zhou, Chengcheng Ning, Xuezhen Luo, Qin Zhu, Hongwei Zhang and Fenghua Ma. We thank all the patients who participated in the trial and Dr. Yan Du and Dr. Wei Zhang for their contributions to data analyses.

## SUPPLEMENTARY MATERIALS

### Table S1
Subgroup analysis of CR rates at 16 weeks

Click here to view

### Table S2
Subgroup analysis of CR rates at 32 weeks

Click here to view

### Table S3
Information of the 11 patients recurred after CR

Click here to view

### Fig. S1
Weight change during treatment in 2 groups. The p-value <0.05 was considered statistically significant.

Click here to view

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