Comparison of the effect of levonorgestrel-intrauterine system with or without oral megestrol acetate on fertility-preserving treatment in patients with atypical endometrial hyperplasia: a prospective, open-label, randomized controlled phase II study

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Abstract

Objective To compare the effect of levonorgestrel-intrauterine system (LNG-IUS) with or without oral megestrol acetate (MA) versus MA alone on fertility preserving treatment in patients with atypical endometrial hyperplasia (AEH). Design Single-center phase II study with open-label, randomized and controlled trial conducted between July 2017 and June 2020. Setting Obstetrics & Gynecology Hospital of Fudan University, Shanghai, China Population A total of 180 patients (18-45 years) with primary AEH were randomly assigned (1:1:1) to MA group (N=60), LNG-IUS group (N=60), or MA+LNG-IUS group (N=60). Methods Patients received MA (160 mg orally daily), LNG-IUS, or MA+LNG-IUS (MA 160 mg orally daily plus LNG-IUS), respectively. Main outcomes and measures The primary endpoint was the complete response (CR) rate at 16 weeks of treatment. The secondary endpoints were the CR rate at 32 weeks of treatment, adverse events, recurrent rate, and pregnancy rate. Results LNG-IUS group yielded a higher 16-week CR rate than MA group (P=0.049; Odds ratio [OR], 2.44; 95% confidence interval [95%CI], 1.00-6.00). However, MA+LNG-IUS group did not yield better 16-week or 32-week CR rates than MA group (P=0.245; P=0.915) or LNG-IUS group (P=0.419; P=0.653). Meanwhile, less side-effects were found in LNG-IUS group compared with the other two groups. No significant difference was seen in recurrence rates and pregnancy rates among all three groups. Conclusions LNG-IUS might be considered as the first-line choice of fertility-sparing treatment in AEH patients with proper size of uterine cavity. LNG-IUS combined with MA might not provide better treatment effect than MA or LNG-IUS alone.

INTRODUCTION

As the precancerous stage of endometrioid endometrial cancer (EEC), the incidence of atypical endometrial hyperplasia (AEH) is increasing[1, 2], which makes fertility-preserving treatment in young AEH patients an important issue. Oral high-dose progestins, including megestrol acetate (MA) and medroxyprogesterone acetate (MPA), are traditional choices for fertility-preserving treatment in these women [3-5] with a complete response (CR) rate around 70%-80% . However, up to 30% of patients remain insensitive to progestin [6] and the median treatment duration to achieve complete response is 6 to 7 months[7-9]. Multiple adverse effects occurred accompanying long treatment duration, such as edema and weight gain, which usually hindered the patient's compliance to oral progestin [4, 8]. Therefore, more optimal fertility-preserving treatment for AEH patients is urgently needed.

Levonorgestrel-releasing intrauterine system (LNG-IUS), an intrauterine high-efficient progestin (levonorgestrel) releasing system, has been recommended as the first-line fertility-preserving treatment for AEH patients[10, 11]. Retrospective studies suggested that LNG-IUS might provide non-inferior efficacy with the

CR rates of 78.7%-90% compared with oral progestin[12-14] , and was associated with less systemic symptoms such as weight gain, decrease in bone mineral density, risk of venous thrombosis and breast cancer [15-19]. However, high quality evidence from randomized controlled study is still lacking to compare LNG-IUS alone with oral progestin as fertility-sparing treatment for AEH patients.

Another question that remains unclear is whether LNG-IUS combined with oral progestins may achieve higher treatment effects than LNG-IUS or oral progestins alone in AEH patients. A few retrospective or small sample-size prospective clinical studies suggested the efficacy in EEC patients might be improved when combining oral progestin with LNG-IUS[20-22]. A retrospective analysis [20]found that the CR rates were 77.8% (7/9), 50% (2/4) or 33.3% (1/3) in EEC patients receiving oral progestin plus LNG-IUS, oral progestin only or LNG-IUS only, respectively. However, the number of patients included in these studies were too small to draw a conclusion.

In order to address these questions, we conducted this prospective phase II study with randomized controlled design, to evaluate the effect of LNG-IUS with or without oral MA on fertility-preserving outcome in AEH patients. The primary endpoint was complete response (CR) rate at 16 weeks of treatment(16-week CR rate). The secondary endpoints were CR rate at 32 weeks of treatment (32-week CR rate), adverse events, recurrent rate, and pregnancy rate.

MATERIALS AND METHODS

Study design and patients

This single-center, open-label, randomized controlled phase II study (NCT03241888) was designed to investigate the efficacy of oral MA+LNG-IUS or LNG-IUS alone compared with oral MA alone as fertility-sparing treatment for AEH patients. This work was conducted from July 21th, 2017, to June 18th, 2020, in Obstetrics and Gynecology Hospital of Fudan University, Shanghai, China. 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), Shanghai sailing program (Grant No.19YF1404200) and Shen Kang clinical project (SHDC22021219).

Eligible AEH patients met the following inclusion criteria were 18-45 years old; pathologically diagnosed with AEH for the first time by endometrial biopsy through dilation and curettage with or without hysteroscopy; with no signs of suspicious endometrial invasion or extrauterine metastasis by transvaginal ultrasonography; with the longest uterine diameter (from the fundus to endocervix) <7 cm by ultrasound (as larger uterine cavity might lead to LNG-IUS expulsion or reduce the treatment effect); with strong desire to preserve fertility; no contraindication for progestin treatment or pregnancy; not pregnant when participating in the trial; willing to follow the trial arrangement after being fully informed of all the risks and inconveniences caused by the trial.

Exclusion criteria were diagnosis of recurrent AEH, allergy history or contraindications for MA or LNG-IUS; during pregnancy, severe infection, severe chronic diseases (dysfunction of heart, liver, lung, or kidney), high risk of thrombosis, receiving hormone treatment for more than three months within six months before entering the trial, other malignancy history, concurrent malignancy in genital or other systems.

Pathologic diagnosis was confirmed by two experienced gynecological pathologists (Dr. Zhu Q and Dr. Zhou XR), according to the World Health Organization (WHO) pathological classification (2014)[23]. If their opinions differed, a seminar was held in the pathological department for the final diagnosis.

The trial was approved by the Institutional Review Board of the Obstetrics and Gynecology Hospital, Fudan University (Approval No.: 2017-30), and all patients were fully informed of the benefits and risks of this clinical trial and provided written informed consent.

2. Randomization and masking

Patients were allocated (1:1:1) to one of three treatment arms: MA alone (control group), LNG-IUS alone, or MA+LNG-IUS group by the simple randomization. Randomization sequences were prepared according

to random-number tables. The treatment allocation was concealed before the participants were successfully enrolled. This study was open-labelled that all patients and study physicians were aware of the treatment assignment. None of the clinicians who performed the hysteroscopic evaluation on patients in this trial and none of the pathologists who assessed the specimens from this trial was aware of the treatment allocations.

3. Procedures

Patients in MA group received continuous oral megestrol acetate 160 mg once daily. LNG-IUS (containing LNG 52mg) insertion was administered in patients in LNG-IUS group. Patients in MA+LNG-IUS group received MA 160 mg once daily plus LNG-IUS insertion.

All patients received complete hysteroscopic evaluation and resection of lesions before the initiation of treatment in this trial. LNG-IUS was placed during the hysteroscopic evaluation when indicated. Hysteroscopic evaluations were performed every 3 months to evaluate treatment response after initiating the treatment by two specialists (Dr. Zhang HW and Dr. Zhu CY) following standard procedure as described previously[8]. Suspected lesions were recorded in detail and removed completely under the principle to minimize endometrial damage. 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.

During each hysteroscopic evaluation, the LNG-IUS was taken out, kept from contamination, and bacilli culture was performed. A new LNG-IUS was 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) complete response (CR), defined as no endometrial lesion. Another hysteroscope were held 3 months later for confirmation of CR; (2) partial response (PR), pathological improvement, such as endometrial hyperplasia; (3) stable disease (SD), persistence of disease as originally diagnosed; (4) progression disease (PD), any appearance of endometrial malignancy.

MA and/or LNG-IUS were administered until CR. Treatment were ceased when patients experienced unacceptable side effects. Definitive hysterectomy was suggested when patients remained SD after 7 months of treatment, or not achieving CR after 10 months of treatment, or had PD at any time of treatment [24]. For those who refused hysterectomy, alternative treatment was given based on multidisciplinary consensus. Duration of treatment time to achieve CR was calculated from initiation of treatment to the first time that the patient achieved pathological CR after hysteroscopic assessment.

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. Ultrasonography (every 3 months) and endometrial biopsy by Pipelle (every 6 months) were routinely used to assess the endometrium. For CR patients without recent plan to conceive, or those stopped breast breeding after delivery, cyclic oral dydrogesterone, oral contraceptive pills, or LNG-IUS was administered to prevent disease recurrence. Recurrence was defined as the presence of complex hyperplasia, AEH, or EC after achieving CR.

Data on age, height, weight, and metabolic status (fasting blood glucose (FBG), fasting insulin (FINS), and lipid panel) were collected before the initiation of treatment. Obesity was defined as body mass index (BMI)[?]28 kg/m^2 followed criteria for Chinese adults[25, 26]. Insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index, which was calculated as fasting blood glucose (FBG) (mmol/L) $\times$ fasting insulin (FINS) (mU/L)/22.5. HOMA-IR[?]2.95 was considered insulin resistant (IR) [27]. Metabolic syndrome (MS) was defined according to literature [28-30]. All patients were followed up from the date of treatment initiation to July 1st, 2021.

4. Outcomes

The primary endpoint was 16-week CR rate. Secondary endpoints were 32-week CR rate, treatment-related adverse events, recurrent rate and pregnancy rate. Safety assessment was assessed and graded following the

National Cancer Institute Common Toxicity Criteria version 4.0 at baseline (prior to treatment), during treatment, and at completion of treatment. Serious adverse events would be reported within 24 hours. The maximum extent of weight change during treatment was also measured.

5. Statistical analysis

According to literatures [7, 8, 12, 31-33], for the primary endpoint, we assumed that the 16-week CR rate was 25% in MA group, 50% in LNG-IUS group and 60% in MA+LNG-IUS group; with a power of 0.8 at a two-sided significance level of 0.05; requiring an accrual of 362 eligible patients (lost to follow-up rate <10%), which was too large to be carried out. Then we eventually decided to recruit 180 patients with 60 in each group as a phase II study. Modified intention-to-treat (ITT) analyses were performed for patients underwent endometrial evaluation at 16 or 32 weeks, and patients missed endometrial evaluation at 16 or 32 weeks but did not reach CR at subsequent endometrial evaluation. The latter was regarded as not reaching CR at 16 or 32 weeks. Patients missed endometrial evaluation at 16 or 32 weeks but reached CR at subsequent endometrial evaluation were excluded for 16 or 32-week CR rate analysis. ANOVA test or Kruskal-Wallis test was used for the comparison of continuous variables between the three groups, and Student's t-test or Mann-Whitney test was used for comparison between two groups. Chi-square 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. 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; Armonk, New York). COSORT guidelines were consulted to outline this study [34].

6. Role of the funding source

The funding bodies had no role in study design, data collection, data interpretation, data analysis, or drafting or editing of this manuscript.

RESULTS

1. Patients and treatment

The flow of the patients in the trial is reported in Figure 1. Totally 206 patients were screened, of them, 26 patients were deemed ineligible mostly because of progestin-use history or requirement of definitive surgery. Between July 21th, 2017 and June 18th, 2020, 180 patients who met all the inclusion and exclusion criteria were randomly 1:1:1 assigned to MA (n=60), LNG-IUS (n=60) or MA+LNG-IUS group (n=60) (Fig.1). One hundred and thirty-two patients and 146 patients were included in modified intention-to-treated analyses for 16-week or 32-week CR rates, respectively.

All the participants were Chinese Asian. Patient characteristics were well balanced among three treatment groups (Table S1). The median age was 33 (range 19-44) years old, and the median BMI was 25.0 (range, 16.4-47.5) kg/m^2. There was no difference in age, pretreatment BMI or IR status among the three groups. Fifty-five out of 180 patients (30.6%) were obese (BMI[?]28 kg/m^2) and 27.8% (50/180) of patients were insulin resistant (HOMA-IR[?]2.95).

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

In modified ITT analyses, the overall CR rate at 16 weeks was 36.4% (48/132). The 16-week CR rates were 25.6% (11/43) in MA group, 45.7% (21/46) in LNG-IUS group and 37.2% (16/43) in MA+LNG-IUS group, without statistical difference among the three groups (P=0.143) (Table 1; Fig.2A). However, LNG-IUS group yielded a higher 16-week CR rate compared with MA group (p=0.049, Odds ratio [OR], 2.44; 95% confidence interval [95%CI], 1.00-6.00). MA+LNG-IUS group did not achieve higher 16-week CR rate compared with MA group or LNG-IUS group (Table 1, Fig 2).

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

The overall CR rate at 32 weeks was 79.1% (117/148). The 32-week CR rates were 78.3% (36/46) in MA group, 82.7% (43/52) in LNG-IUS, and 79.2% (38/48) in MA+LNG-IUS group, without statistical difference among the three groups (P=0.842) (Table 1; Fig.2). MA+LNG-IUS group did not achieve higher 32-week CR rate compared with MA group or LNG-IUS group (Table 1).

4. 16- and 32-week CR rate in patients with different metabolic status

We performed post hoc analyses on 16-week and 32-week CR rates in patients with different metabolic status (Table 2). In participants with BMI[?]28 kg/m^2, LNG-IUS group achieved higher 16-week CR rate (41.7% [5/12]) compared with MA group (0% [0/12]); P=0.037). In patients without insulin resistance, LNG-IUS group also had higher 16-week CR rate (48.6% [18/37]) compared with MA group (25.0% [8/32]; P=0.037; Table 2). No difference was found in 32-week CR rate in patients with different metabolic status among the three groups (Table S2).

4. Safety analysis (secondary endpoint)

No treatment-related death or serious adverse events (grade 4) was observed during the study (Table 3). Among 114 patients using LNG-IUS with or without MA, no positive bacilli culturing result on LNG-IUS was found. LNG-IUS group achieved less weight gain (median, 0.0 kg; 95%CI, -1.0-1.3, P ¡0.001) compared with MA group (median, 5.0 kg; 95%CI, 2.3-8.1) or MA+LNG-IUS group (median, 5.0 kg; 95%CI, 3.2-7.8) (Fig.S1). Fewer patients in the LNG-IUS group experienced increased nocturnal urine, night sweats, insomnia, or edema face compared with the other two groups. MA group experienced similar adverse effects as MA+LNG-IUS group. Vaginal hemorrhage occurred more often in the MA+ LNG-IUS group than in the MA group (46.3% vs. 19.0%; P=0.002).

5. Long term onco-fertility results (secondary endpoint)

Median follow-up after initiation of treatment was 27.8 months (range, 3.2-47.5). At the time of last follow-up, 8 of the 180 patients were lost to follow-up, 1 withdrew the study, 2 received hysterectomy, 3 were still in treatment (1 remained PR and 2 remained SD), and the other 166 women achieved CR (Fig.1). None of the patients experienced PD during treatment. Thirty-four patients remained SD after 7 months of treatment or did not achieve CR after 10 months of treatment. Among these 34 patients, 24 used alternative treatment and the other 10 continued the original regimen.

The median treatment duration to achieve CR were 29.2 weeks (95% CI, 24.4-33.9) in MA group, 19.2 weeks (95%CI, 16.1-21.8) in LNG-IUS group and 25.7 weeks (95%CI, 17.0-34.4) in MA+LNG-IUS group, with no significant statistical difference among the three groups (log-rank P=0.316) (Table 2; Fig.2).

Among the 166 patients who achieved CR, 14 patients recurred during the follow up (Fig.1). The median follow-up after CR was 22.8 months (range, 0.0-44.3). The overall cumulative 1-year and 2-year recurrence rate after CR was 4.6% and 8.6%, without significant difference among the three groups (Fig.3A).

Among the 166 patients who achieved CR, 47 patients planned for parenthood. The pregnancy rate was 76.6% (36/47) in total, 66.7% (12/18) in MA group, 81.3% (13/16) in LNG-IUS group and 84.6% (11/13) in MA+LNG-IUS group without significant statistical difference among groups (Fig.1). Of the 36 women who had a successful pregnancy, 18 had a live birth, 12 had a miscarriage and 6 were still in pregnancy at the last follow up. The cumulative 1-year pregnancy rate after CR was 40.7% in MA group, 37.5% in LNG-IUS group and 38.5% in MA+LNG-IUS group (Fig.3B).

COMMENT

Main findings

Our data showed that LNG-IUS achieved higher 16-week CR rate than oral MA treatment. LNG-IUS had the fewest adverse events compared with MA or MA+LNG-IUS. We did not find better treatment effect

using MA+LNG-IUS compared with MA or LNG-IUS alone. No difference was found in recurrence rate or pregnancy rate among the three groups.

Strengths and Limitations

To our knowledge, this is the first prospective study with the largest sample size (n=180) and randomized controlled design, investigating the effect of systemic oral progestin with or without LNG-IUS on fertility-preserving outcome in AEH patients. However, it is undeniable that several limitations in this study warrant further discussion. First, it was a single-center phase II study. The lack of double-blind design and placebo was also a weakness of the clinical trial. Moreover, all three treatment groups were combined with hysteroscopic evaluation and resection of endometrial lesion, which might conceal the difference in efficacy of the regimens. In addition, the follow-up time after complete response was relatively short. The rates of recurrence, pregnancy and live birth will be further analyzed after all patients have been followed up for two years. Finally, the rate of lost to follow-up in our study is relatively high (26.6% and 17.1% at 16 weeks and 32 weeks of treatment), which may reduce the accuracy of the results. Some patients eventually delayed or cancelled the hysteroscopy for various reasons, such as the COVID-19 quarantine, vaginitis, the conflict with their working hours, resulting in a high rate of lost follow-up.

Interpretation

The main findings of our study that LNG-IUS achieved higher 16-week CR rate than MA in AEH patients were consistent with findings from previous retrospective studies [12, 13]. A meta-analysis evaluating 24 observational studies showed that oral progestin achieved lower pooled regression rate (69% vs. 90%, P=0.03) compared with LNG-IUS in AEH patients [13]. Although our study for the first time provides evidence from prospectively randomized and controlled trial, the sample size was not large enough to draw a conclusion. Further confirmation is needed in phase III study with sufficient sample size.

Our study also found that LNG-IUS was associated with fewer adverse events than MA or MA+LNG-IUS. This is important because fertility preserving treatment takes long time which is at least four to six months [7-9]. Long-term usage of MA might cause many adverse events such as weight gain, edema, vomiting that affect quality of daily life, and even cause thrombosis which is life-threatening[4]. In this context, LNG-IUS instead of oral progestin might provide patients with higher life-quality for less and milder side-effects, and thus, might increase the patient compliance of fertility-sparing treatment [35-37].

Data in our study suggested that the efficacy of LNG-IUS alone might be better than MA alone in AEH patients with BMI[?]28 kg/m^2. This is important because obesity has been shown to be the most important factor adversely affecting the fertility-preserving treatment in AEH and EEC patients[24, 38, 39]. Long term oral progestin usage might also lead to higher risk of thromboembolism in obese women. Our results support that LNG-IUS might be more suitable in AEH patients with BMI[?]28 kg/m^2.

Our data did not find better treatment effect using LNG-IUS plus MA compared with LNG-IUS or MA alone, which was an unexpected result. It might be because LNG is a highly effective progestin, and the drug concentration of LNG using LNG-IUS could reach nearly a thousand times in endometrium than oral MA [40]. Thus, LNG-IUS alone is effective enough on endometrial lesion, and adding systemic MA could not add more value on the treatment effect in endometrial lesion.

In our study, differences in the CR rate between groups became less significant from 16 weeks to 32 weeks of treatment. The reason might be that all patients received hysteroscopic evaluation and treatment which had been shown to effectively increase the CR rate in AEH and EEC patients [8]. With the prolongation of treatment time, the effect of lesion removal by hysteroscopy plays important role in improving treatment effect regardless of the different type of progestin treatment.

Conclusions

In conclusion, our data showed that LNG-IUS achieved higher 16-week CR rate than oral MA treatment. LNG-IUS had the fewest adverse events compared with MA or MA+LNG-IUS. MA+LNG-IUS did not

achieve higher treatment effect compared with MA or LNG-IUS alone. Our data support the usage of LNG-IUS as first line choice for fertility sparing treatment in AEH patients with proper uterine cavity size. Phase III clinical trials including a sufficient number of patients are needed to further validate the efficacy of LNG-IUS in AEH patients.

Disclosure of interests

The authors have no conflict of interest.

Contribution to authorship

Xiao-jun Chen and Jun Guan contributed to the study design and data interpretation. Zhi-ying Xu, Bing-yi Yang, Wei-wei Shan, Jiong-bo Liao, Wen-yu Shao, Peng-fei Wu, Shuang zhou, Cheng-cheng Ning, Xue-zhen Luo, Qin Zhu, Hong-wei Zhang and Feng-hua Ma contributed to the data collection. Zhi-ying Xu, Bing-yi Yang, and Jun Guan contributed to literature search, figures, tables and data analyses. This article was written by Zhi-ying Xu and Jun Guan. All authors critically reviewed the manuscript and approved the final version for submission.

Data sharing statement

The data collected for this study can be shared with researchers in de-identified form after the publication date, and in the presence of a data transfer agreement, and if it complies with China legislation. Requests for data and study proposal should be directed to xiaojunchen2013@sina.com, including a proposal that must be approved by the trial's steering committee.

Details of ethics approval

This study was approved by the Ethics Committees of Obstetrics and Gynaecology (OB&GYN) Hospital of Fudan University on 26 June 2017, with the approval number OB&GYNG Ethics approval [2017]-30.

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REFERENCES

1. McAlpine JN, Temkin SM, Mackay HJ. Endometrial cancer: Not your grandmother's cancer. *Cancer* . 2016 Sep 15;122(18):2787-98.

2. Corzo C, Barrientos Santillan N, Westin SN, Ramirez PT. Updates on Conservative Management of Endometrial Cancer. *J Minim Invasive Gynecol* . 2018 Feb;25(2):308-13.

3. Taylan E, Oktay K. Fertility preservation in gynecologic cancers.*Gynecologic oncology* . 2019 Dec;155(3):522-9.

4. Park JY, Kim DY, Kim JH, Kim YM, Kim KR, Kim YT, et al. Long-term oncologic outcomes after fertility-sparing management using oral progestin for young women with endometrial cancer (KGOG 2002). *Eur J Cancer* . 2013 Mar;49(4):868-74.

5. Falcone F, Laurelli G, Losito S, Di Napoli M, Granata V, Greggi S. Fertility preserving treatment with hysteroscopic resection followed by progestin therapy in young women with early endometrial cancer. *J Gynecol Oncol* . 2017 Jan;28(1):e2.

6. Wang Y, Yang JX. Fertility-preserving treatment in women with early endometrial cancer: the Chinese experience. *Cancer Manag Res* . 2018;10:6803-13.

7. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinoma: a systematic review. *Gynecol Oncol* . 2012 May;125(2):477-82.

8. Yang B, Xu Y, Zhu Q, Xie L, Shan W, Ning C, et al. Treatment efficiency of comprehensive hysteroscopic evaluation and lesion resection combined with progestin therapy in young women with endometrial atypical hyperplasia and endometrial cancer. *Gynecol Oncol* . 2019 Apr;153(1):55-62.

9. Mitsuhashi A, Habu Y, Kobayashi T, Kawarai Y, Ishikawa H, Usui H, et al. Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients. *J Gynecol Oncol* . 2019 Nov;30(6):e90.

10. Royal College of Obstetricians and Gynaecologists; British Society for Gynaecological Endoscopy. Management of endometrial hyperplasia: Green-top Guideline No. 67. *RCOG/BSGE Joint Guideline February 2016*. London: Royal College of Obstetricians and Gynaecologists; 2016.

11. Auclair MH, Yong PJ, Salvador S, Thurston J, Colgan TTJ, Sebastianelli A. Guideline No. 390-Classification and Management of Endometrial Hyperplasia. *J Obstet Gynaecol Can* . 2019 Dec;41(12):1789-800.

12. Mandelbaum RS, Ciccone MA, Nusbaum DJ, Khoshchehreh M, Purswani H, Morocco EB, et al. Progestin therapy for obese women with complex atypical hyperplasia: levonorgestrel-releasing intrauterine device vs systemic therapy. *Am J Obstet Gynecol* . 2020 Jul;223(1):103 e1- e13.

13. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and metaanalysis. *Am J Obstet Gynecol.* 2010 Dec;203(6):547 e1-10.

14. Pal N, Broaddus RR, Urbauer DL, Balakrishnan N, Milbourne A, Schmeler KM, et al. Treatment of Low-Risk Endometrial Cancer and Complex Atypical Hyperplasia With the Levonorgestrel-Releasing Intrauterine Device. *Obstet Gynecol* . 2018 Jan;131(1):109-16.

15. Cholakian D, Hacker K, Fader AN, Gehrig PA, Tanner EJ, 3rd. Effect of oral versus intrauterine progestins on weight in women undergoing fertility preserving therapy for complex atypical hyperplasia or endometrial cancer. *Gynecol Oncol* . 2016 Feb;140(2):234-8.

16. Lidegaard O, Nielsen LH, Skovlund CW, Lokkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. *BMJ* . 2012 May 10;344:e2990.

17. Bahamondes MV, Monteiro I, Castro S, Espejo-Arce X, Bahamondes L. Prospective study of the forearm bone mineral density of long-term users of the levonorgestrel-releasing intrauterine system. *Hum Reprod* . 2010 May;25(5):1158-64.

18. Jareid M, Thalabard JC, Aarflot M, Bovelstad HM, Lund E, Braaten T. Levonorgestrel-releasing intrauterine system use is associated with a decreased risk of ovarian and endometrial cancer, without increased risk of breast cancer. Results from the NOWAC Study. *Gynecol Oncol* . 2018 Apr;149(1):127-32.

19. Westin SN, Fellman B, Sun CC, Broaddus RR, Woodall ML, Pal N, et al. Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer. *Am J Obstet Gynecol.* 2021 Feb;224(2):191 e1- e15.

20. Cade TJ, Quinn MA, Rome RM, Neesham D. Progestogen treatment options for early endometrial cancer. *BJOG* . 2010 Jun;117(7):879-84.

21. Kim MK, Seong SJ, Kim YS, Song T, Kim ML, Yoon BS, et al. Combined medroxyprogesterone acetate/levonorgestrel-intrauterine system treatment in young women with early-stage endometrial cancer. *Am J Obstet Gynecol* . 2013 Oct;209(4):358 e1-4.

22. Hwang JY, Kim DH, Bae HS, Kim ML, Jung YW, Yun BS, et al. Combined Oral Medroxyprogesterone/Levonorgestrel-Intrauterine System Treatment for Women With Grade 2 Stage IA Endometrial Cancer. *Int J Gynecol Cancer* . 2017 May;27(4):738-42.

23. Zaino R, Carinelli SG, Ellenson LH, Eng C, Katabuchi H, Konishi I, et al. Tumours of the uterine corpus: Epithelial tumours and precursors. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds. *WHO classificationof tumours of female reproductive organs, 4th ed.* Lyon, France: IARC; 2014.

24. Zhou S, Xu Z, Yang B, Guan J, Shan W, Shi Y, et al. Characteristics of progestin-insensitive early stage endometrial cancer and atypical hyperplasia patients receiving second-line fertility-sparing treatment. *J Gynecol Oncol* . 2021 Jul;32(4):e57.

25. Zhou BF, Cooperative Meta-Analysis Group of the Working Group on Obesity in C. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults–study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci.* 2002 Mar;15(1):83-96.

26. Yang Z, Ding X, Liu J, Duan P, Si L, Wan B, et al. Associations between anthropometric parameters and lipid profiles in Chinese individuals with age >/=40 years and BMI <28kg/m2. *PLoS One* . 2017;12(6):e0178343.

27. Shan W, Ning C, Luo X, Zhou Q, Gu C, Zhang Z, et al. Hyperinsulinemia is associated with endometrial hyperplasia and disordered proliferative endometrium: a prospective cross-sectional study. *Gynecol Oncol* . 2014 Mar;132(3):606-10.

28. Yang B, Xie L, Zhang H, Zhu Q, Du Y, Luo X, et al. Insulin resistance and overweight prolonged fertility-sparing treatment duration in endometrial atypical hyperplasia patients. *J Gynecol Onco* l. 2018 May;29(3):e35.

29. Expert Panel on Detection E, Treatment of High Blood Cholesterol in A. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* . 2001 May 16;285(19):2486-97.

30. Eckel RH, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* . 2005 Apr 16-22;365(9468):1415-28.

31. Wildemeersch D, Janssens D, Pylyser K, De Wever N, Verbeeck G, Dhont M, et al. Management of patients with non-atypical and atypical endometrial hyperplasia with a levonorgestrel-releasing intrauterine system: long-term follow-up. *Maturitas* . 2007 Jun 20;57(2):210-3.

32. Pronin SM, Novikova OV, Andreeva JY, Novikova EG. Fertility-Sparing Treatment of Early Endometrial Cancer and Complex Atypical Hyperplasia in Young Women of Childbearing Potential. *Int J Gynecol Cancer* . 2015 Jul;25(6):1010-4.

33. Chen M, Jin Y, Li Y, Bi Y, Shan Y, Pan L. Oncologic and reproductive outcomes after fertility-sparing management with oral progestin for women with complex endometrial hyperplasia and endometrial cancer. *Int J Gynaecol Obstet* . 2016 Jan;132(1):34-8.

34. Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *Int J Surg* . 2012;10(1):28-55.

35. Shoupe D, Mishell DR Jr. The handbook of contraception: A guide for practical management. 2nd ed. 2016. In the series: *Current clinical practice.* Skolink NS, series editor. Totowa, NJ: Humana Press Inc.; 2016.

36. Apgar BS, Greenberg G. Using progestins in clinical practice.*Am Fam Physician.* 2000 Oct 15;62(8):1839-46, 49-50.

37. Mittermeier T, Farrant C, Wise MR. Levonorgestrel-releasing intrauterine system for endometrial hyperplasia. *Cochrane Database Syst Rev* . 2020 Sep 6;9:CD012658.

38. Onstad MA, Schmandt RE, Lu KH. Addressing the Role of Obesity in Endometrial Cancer Risk, Prevention, and Treatment. *J Clin Oncol.*2016 Dec 10;34(35):4225-30.

39. MacKintosh ML, Derbyshire AE, McVey RJ, Bolton J, Nickkho-Amiry M, Higgins CL, et al. The impact of obesity and bariatric surgery on circulating and tissue biomarkers of endometrial cancer risk. *Int J Cancer* . 2019 Feb 1;144(3):641-50.

40. Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T. Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. *Clin Endocrinol (Oxf)* . 1982 Dec;17(6):529-36.

Table 1. Fertility preserving treatment outcome.

Outcome	16-week CR rate	32-week CR rate	CR time (weeks, median and 95%CI)	1-year cumulative rec
MA group	25.6% (11/43)	78.3% (36/46)	29.2 (24.4-33.9)	8.0%
LNG-IUS group	45.7% (21/46)	82.7% (43/52)	19.2 (16.1-21.8)	3.7%
MA+LNG-IUS group	37.2% (16/43)	79.2% (38/48)	25.7 (17.0-34.4)	2.1%
P^a	0.143	0.842	0.316	/
P^b	**0.049**	0.580	0.118	/
P^c	0.245	0.915	0.496	/
P^d	0.419	0.653	0.471	/
OR/HR^b (95%CI)	2.44 (1.00-6.00)	1.33 (0.49-3.62)	1.34 (0.93-1.94)	/
OR/HRc (95%CI)	1.72 (0.69-4.34)	1.06 (0.39-2.84)	1.14 (0.78-1.66)	/
OR/HR^d (95%CI)	0.71 (0.30-1.65)	0.80 (0.29-2.16)	0.87 (0.60-1.27)	/

[a] Comparison between three groups;

[b] Comparison between MA group and LNG-IUS group.

[c] Comparison between MA group and MA+LNG-IUS group.

[d] Comparison between LNG-IUS group and MA+LNG-IUS group.

P-value<0.05 was the significant threshold in analysis.

Abbreviation: CR, complete response; MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; OR, odds ratio; HR, hazard ratio; 95%CI, 95% confidence interval.

Table 2. Subgroup analysis of complete response rates at 16 weeks.

16-week CR rate	MA group	LNG-IUS group	MA+LNG-IUS group	P^a	P^b	P^c
Age [?] 30 years	25.0% (7/28)	48.4% (15/31)	32.3% (10/31)	0.154	0.064	0.539
Age < 30 years	26.7% (4/15)	40.0% (6/15)	50.0% (6/12)	0.455	0.439	0.257
IR*	27.3% (3/11)	33.3% (3/9)	21.4% (3/14)	0.887	1.000	1.000
Non-IR*	25.0% (8/32)	48.6% (18/37)	44.8% (13/29)	0.109	**0.043**	0.104
BMI [?] 28 kg/m^2	0.0% (0/12)	41.7% (5/12)	14.3% (2/14)	**0.030**	**0.037**	0.483

16-week CR rate	MA group	LNG-IUS group	MA+LNG-IUS group	P^{a}	P^{b}	P^{c}
BMI < 28 kg/m^2	35.5% (11/31)	47.1% (16/34)	48.3% (14/29)	0.534	0.344	0.315
MS	23.5% (4/17)	42.1% (8/19)	29.4% (5/17)	0.472	0.238	1.000
Non-MS	26.9% (7/26)	48.1% (13/27)	42.3% (11/26)	0.265	0.111	0.244
Hypertension	25.0% (2/8)	100.0% (3/3)	10.0% (1/10)	**0.013**	0.061	0.559
Non-hypertension	25.7% (9/35)	41.9% (18/43)	45.5% (15/33)	0.192	0.136	0.089
Diabetes	25.0% (1/4)	66.7% (2/3)	0.0% (0/3)	0.400	0.486	1.000
Non-Diabetes	25.6% (10/39)	44.2% (19/43)	40.0% (16/40)	0.195	0.079	0.174

[a] Comparison between three groups;

[b] Comparison between MA group and LNG-IUS group.

[c] Comparison between MA group and MA+LNG-IUS group.

P-value<0.05 was the significant threshold in analysis.

* IR: HOMA-IR[?]2.95; Non-IR: HOMA-IR<2.95.

Abbreviation: CR, complete response; MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; IR, insulin resistance; BMI, body mass index; MS, metabolic syndrome.

Table 3. Safety analysis of the patients who received study drugs.

Toxicity	MA group (n=58)	LNG-IUS group (n=60)	MA+LNG-IUS group (n=54)	P^{a}	P^{b}	P^{c}	P^{d}
Weight gain: Grade 1-2	35 (60.3)	7 (11.7)	33 (61.1)	**<0.001**	**<0.001**	0.934	**<0.001**
Grade 3	25 (43.1)	5 (8.3)	24 (44.4)				
Increased nocturnal urine: Grade 1-2	10 (17.2)	2 (3.3)	9 (16.7)				
Night sweats: Grade 1-2	29 (50.0)	13 (21.7)	30 (55.6)	**<0.001**	**0.001**	0.556	**<0.001**
Insomnia: Grade 1-2	23 (39.7)	9 (15.0)	22 (40.7)	**0.003**	**0.003**	0.907	**0.002**
Libido decreased: Grade 1-2	21 (36.2)	8 (13.3)	18 (33.3)	**0.010**	**0.004**	0.750	**0.011**
Breast pain: Grade 1-2	21 (36.2)	15 (25.0)	23 (42.6)	0.132	0.186	0.489	**0.047**
Fatigue: Grade 1-2	19 (32.8)	12 (20.0)	13 (24.1)	0.270	0.115	0.309	0.600
Edema face: Grade 1-2	18 (31.0)	14 (23.3)	22 (40.7)	0.135	0.347	0.284	**0.046**
	14 (24.1)	3 (5.0)	14 (25.9)	**0.005**	**0.003**	0.827	**0.002**

Toxicity	MA group (n=58)	LNG-IUS group (n=60)	MA+LNG-IUS group (n=54)	P^{a}	P^{b}	P^{c}	P^{d}
Vaginal dryness: Grade 1-2 Grade 3	13 (22.4) 12 (20.7) 1 (1.7)	9 (15.0) 9 (15.0) 0 (0.0)	16 (29.6) 16 (29.6) 0 (0.0)	0.170	0.301	0.384	0.059
Abdominal distension: Grade 1-2	12 (20.7)	10 (16.7)	17 (31.5)	0.153	0.575	0.193	0.063
Back pain: Grade 1-2	12 (20.7)	10 (16.7)	17 (31.5)	0.153	0.575	0.193	0.063
Dizziness/Headache: Grade 1-2	11 (19.0)	12 (20.0)	14 (25.9)	0.629	0.887	0.377	0.451
Vaginal hemorrhage: Grade 1-2	11 (19.0)	16 (26.7)	25 (46.3)	**0.005**	0.319	**0.002**	**0.029**
Abdominal pain: Grade 1-2	10 (17.2)	3 (5.0)	8 (14.8)	0.099	**0.034**	0.727	0.076
Constipation: Grade 1-2	10 (17.2)	5 (8.3)	7 (13.0)	0.350	0.146	0.528	0.421
Hypertension: Grade 1-2 Grade 3	10 (17.2) 9 (15.5) 1 (1.7)	6 (10.0) 6 (10.0) 0 (0.0)	7 (13.0) 7 (13.0) 0 (0.0)	0.510	0.251	0.528	0.619
Alopecia: Grade 1-2	9 (15.5)	9 (15.0)	13 (24.1)	0.376	0.938	0.255	0.220
Increased alanine aminotransferase: Grade 1-2	7 (12.1)	1 (1.7)	4 (7.4)	0.085	**0.025**	0.407	0.188
Diarrhea: Grade 1-2	6 (10.3)	2 (3.3)	7 (13.0)	0.165	0.130	0.666	0.082
Rash: Grade 1-2	6 (10.3)	3 (5.0)	12 (22.2)	**0.017**	0.274	0.087	**0.007**
Dyspareunia: Grade 1-2	6 (10.3)	5 (8.3)	12 (22.2)	0.066	0.707	0.087	**0.038**
Nausea: Grade 1-2	5 (8.6)	3 (5.0)	8 (14.8)	0.193	0.487	0.306	0.076
Leukocytosis: Grade 1-2	5 (8.6)	3 (5.0)	5 (9.3)	0.644	0.487	1.000	0.474
Pruritus: Grade 1-2	5 (8.6)	1 (1.7)	9 (16.7)	**0.018**	0.111	0.198	**0.005**
Hypercoagulable status Grade 1-2	2 (3.4)	0 (0.0)	1 (1.9)	0.359	0.147	1.000	0.474
Vomiting: Grade 1-2	1 (1.7)	0 (0.0)	3 (5.6)	0.076	0.492	0.351	0.103

Toxicity	MA group (n=58)	LNG-IUS group (n=60)	MA+LNG-IUS group (n=54)	P^{a}	P^{b}	P^{c}	P^{d}
Thromboembolic event	0 (0.0)	0 (0.0)	0 (0.0)	/	/	/	/
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	/	/	/	/

P-value showed the difference in total adverse events between different groups. Chi-square test was used, or Fisher exact test was performed when expect counts were less than 5.

[a] Comparison between three groups;

[b] Comparison between MA group and LNG-IUS group.

[c] Comparison between MA group and MA+LNG-IUS group.

[d] Comparison between LNG-IUS group and MA+LNG-IUS group.

P-value<0.05 was the significant threshold in analysis. Safety analyses were assessed in patients who received study drugs for more than 3 months. Eventually, 172 out of 180 patients were included.

Abbreviation: MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system.

Figure legends

FIGURE 1. Flow diagram.

[a] Patients missed endometrial evaluation at 16 or 32 weeks but reached CR at subsequent endometrial evaluation were excluded for 16 or 32-week CR rate analysis.

[b] One patient in LNG-IUS group was included in the modified intention-to-treat analysis with no lesions detected at the initial hysteroscopic evaluation.

[c] Two patients in MA+LNG-IUS group were included in the modified intention-to-treat analysis with no lesions detected at the initial hysteroscopic evaluation. However, one of the them was not included in the safety analyses because MA was not used in the subsequent three months of treatment consolidation.

[d] In MA group, 2 patients had endometrial hyperplasia and 4 patients had AEH after CR.

[e] In LNG-IUS group, 2 patients had hyperplasia and 2 patients had AEH after CR.

[f] In MA+LNG-IUS group, 2 patients had hyperplasia, 1 patient had AEH, and 1 patient developed EC after CR.

Abbreviations: AEH, atypical endometrial hyperplasia; MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; HSC, hysteroscopy; CR, complete response; PR, partial response; SD, stable disease; EC, endometrial cancer.

FIGURE 2. Complete response rate and median CR time.

Kaplan-Meier survival curves for cumulative CR rate in patients received treatment.

Abbreviations: AEH, atypical endometrial hyperplasia; CR, complete response; HR, hazard ratio; MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; 95%CI, 95% confidence interval.

FIGURE 3. Recurrence rate and pregnancy rate of the patients achieved complete response.

(A) 1-year and 2-year cumulative recurrence rate after CR. (B) 1-year cumulative pregnancy rate after CR.

[a] Comparison between three groups;

[b] Comparison between MA group and LNG-IUS group.

[c] Comparison between MA group and MA+LNG-IUS group.

P-value < 0.05 was the significant threshold in analysis.

Abbreviations: AEH, atypical endometrial hyperplasia; CR, complete response; HR, hazard ratio; MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system; 95%CI, 95% confidence interval

FIGURE S1. Weight change during treatment in three groups.

*P-value < 0.05 was considered statistically significant.

Abbreviations: MA, megestrol acetate; LNG-IUS, levonorgestrel-releasing intrauterine system

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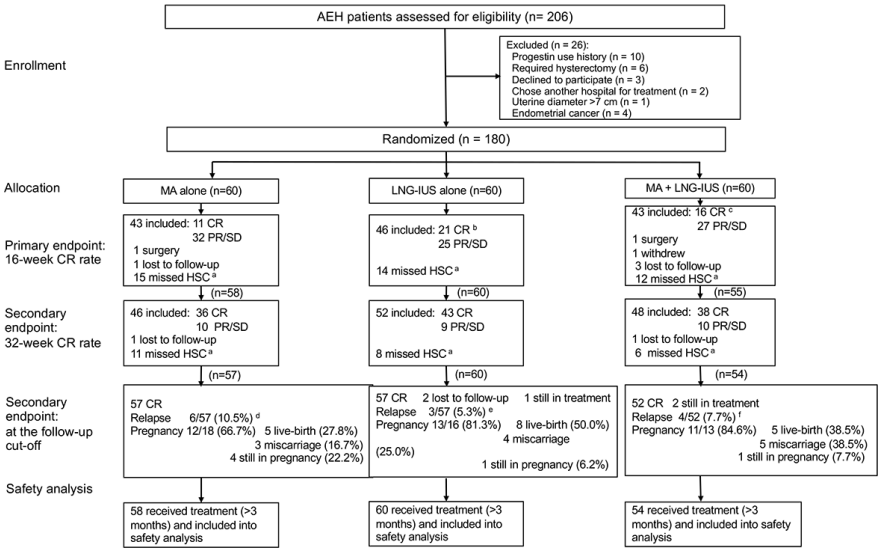

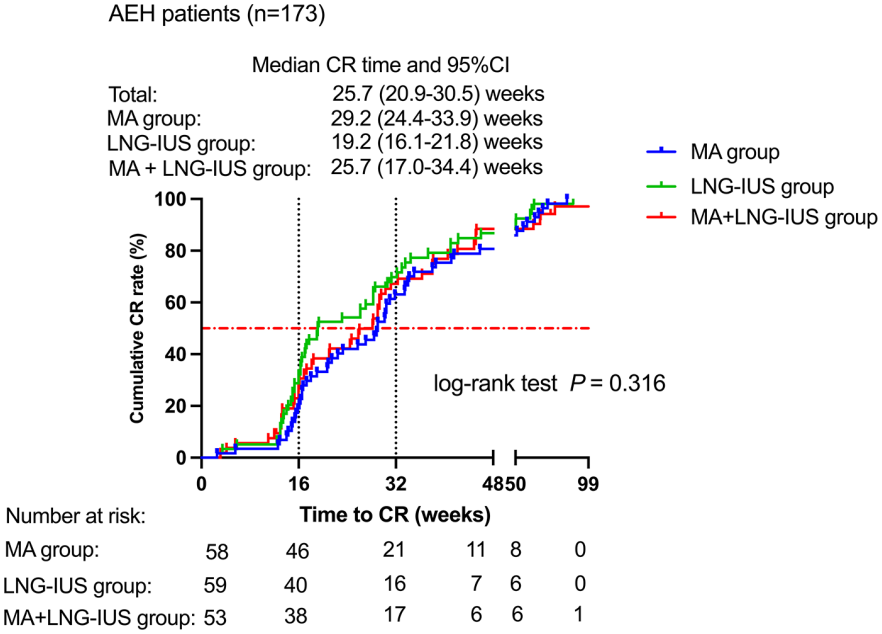

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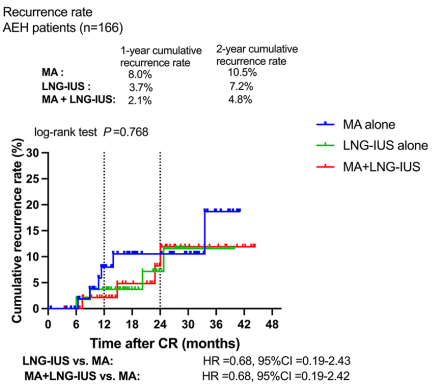

B.