Megestrol Acetate plus Metformin to Megestrol Acetate in Patients with Endometrial Atypical Hyperplasia or Early Stage Endometrial Adenocarcinoma

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Synopsis of protocol

Enrolment criteria

Eligible patients will be women who 1) were 18-45 years old; 2) pathologically diagnosed with AEH or EEC (endometroid, grade I, without myometrial invasion) for the first time; 3) willing to preserve their fertility; 4) have no signs of suspicious endometrial invasion or extrauterine metastasis by enhanced magnetic resonance imaging (MRI), enhanced computed tomography (CT) or transvaginal ultrasonography (TVUS); 5) have no contraindication for metformin, MA or pregnancy; 6) have no hormone or metformin treatment within six months before the trial; 7) not pregnant when participating in the trial; 8) have good compliance for the treatment.

The exclusion criteria were patients who have either of followed conditions: 1) allergy history or contraindications for MA or metformin; 2) being pregnant when initiating the study 3) alcoholism, severe infection, severe chronical diseases (dysfunction of heart, liver, lung or kidney); 4) with high risk of thrombosis; 5) recurrent AEH or EC; 6) other malignancy history.

All patients will be pathologically diagnosed by endometrial biopsy through dilation and curettage (D&C) with or without hysteroscopy (HSC). Pathologic diagnosis will be confirmed by two experienced gynecological pathologists according to the World Health Organization (WHO) pathological classification (2014). If their opinions differ, a seminar will be held in the pathological department for the final diagnosis. This study is approved by the Ethics Committees of Obstetrics and Gynecology Hospital of Fudan University. Before initiation of study procedures, written informed consent will be obtained from each patient regarding risks of conservative treatments and agreement of using their clinical data for research purpose.

Randomization and masking

AEH and EEC patients will be firstly stratified, and then both randomly assigned (1:1) to receive MA treatment (control group) or metformin plus MA treatment (experimental group) until complete regression or disease progression or unacceptable side effects, whichever occurrs first. A computer-based procedure of simple randomization (SPSS for Mac, version 20·0; IBM) will be used for participant enrollment and randomization. Before an individual is successfully enrolled, her treatment assignment will remain concealed. This trial will be open label: patients and study physicians were aware of treatment assignment.

Outcomes

The primary end point is the accumulate CR rate within three months of

treatment. The accumulate CR rate within six, nine, twelve months of treatment, time to CR, adverse events, recurrence rate and pregnancy rate in two years are secondary end points.

Statistical analysis

For primary endpoint, a baseline CR rate of 25% in MA group and an expected CR rate of 50% in MA/metformin group were expected according to results in our previous pilot study, with a power of 0·9 at a two-sided significance level of 0·05, requiring an accrual 150 eligible patients (lost follow-up rate <5%). Relapse rate will be calculated among patients who achieved CR. Pregnancy rates will be evaluated among patients who planned to conceive once achieving CR. Continuous variables will be summarized by means and standard deviations, or median and interquartile range (IQR). Categorical variables will be presented as frequency with percentage. The intra-group differences of continuous variables will be investigated by Student's t-test or Mann-Whitney U test where appropriate. Chi-square test or Fisher's exact test will be used to analyze the difference between categorical variables. Adjusted Odds ratios (OR) and 95% CI will be estimated with Logistic regression model. Estimates of time to CR will be calculated using the Kaplan-Meier method. A 2-tailed p value of less than 0.05 will be considered as statistically significant. SPSS 20·0 (SPSS, Inc., Chicago, IL, USA) will be used for all the statistical analyses.