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Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial

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Objective To assess the efficacy of metformin in megestrol acetate (MA)-based fertility-sparing treatment for patients with atypical endometrial hyperplasia (AEH) and endometrioid endometrial cancer (EEC).

Design A randomised, single-centre, open-label, controlled trial conducted between October 2013 and December 2017.

Setting Shanghai OBGYN Hospital of Fudan University, China.

Population A total of 150 patients (18–45 years old) with primary AEH or well-differentiated EEC were randomised into an MA group (n = 74) and an MA plus metformin group (n = 76).

Methods Patients with AEH or EEC were firstly stratified, then randomised to receive MA (160 mg orally, daily) or MA (160 mg orally, daily) plus metformin (500 mg orally, three times a day).

Main outcomes and measures The primary efficacy parameter was the cumulate complete response (CR) rate within 16 weeks of treatment (16w-CR rate); the secondary efficacy parameters were 30w-CR rate and adverse events.

Results The 16w-CR rate was higher in the metformin plus MA group than in the MA-only group (34.3 versus 20.7%, odds ratio [OR] 2.0, 95% confidence interval [CI] 0.89–4.51, P = 0.09) but the difference was more significant in 102 AEH patients (39.6 versus 20.4%, OR 2.56, 95% CI 1.06–6.21, P = 0.04). This effect of metformin was also significant in non-obese (51.4 versus 24.3%, OR 3.28, 95% CI 1.22–8.84, P = 0.02) and insulin-sensitive (54.8 versus 28.6%, OR 3.04, 95% CI 1.03–8.97, P = 0.04) subgroups of AEH women. No significant result was found in secondary endpoints.

Conclusion As a fertility-sparing treatment, metformin plus MA was associated with a higher early CR rate compared with MA alone in AEH patients.

Keywords Atypical endometrial hyperplasia, endometrioid endometrial cancer, fertility-sparing, megestrol acetate, metformin.

Tweetable abstract For AEH patients, metformin plus MA might be a better fertility-sparing treatment to achieve a higher early CR rate compared with MA alone.

Linked article This article is commented on by W Atiomo, p. 858 in this issue. To view this mini commentary visit https://doi.org/10.1111/1471-0528.16183.

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Introduction

Progestin therapy is widely accepted as the main fertility-sparing treatment for young women with atypical endometrial hyperplasia (AEH) and well-differentiated endometrioid endometrial cancer (EEC). However, 20–30% of these patients who still fail to achieve a complete response (CR) rate and lost fertility after hysterectomy.[1] Progestin efficacy might be improved by higher doses and prolonged treatment period;[2] this, however, could also cause more side effects and weaken patient compliance. Thus, new regimen to achieve a better CR rate within a short treatment time is urgently needed.

Basic and clinical research supports the use of metformin in the fertility-sparing treatment for AEH and EEC patients.[3–10] Metformin has been demonstrated to suppress the growth of breast, ovarian, prostate and endometrial cancer cells via altering glucose metabolism and inhibiting the PI3K-AKT-mTOR signalling pathway.[3–8] Furthermore, metformin has been shown to increase expression of the progesterone receptor and sensitise progestin-resistant endometrial cancer cells to medroxyprogesterone (MPA)-induced apoptosis.[9,10] The latest meta-analysis showed an anti-cancer role of metformin after reviewing all the eligible articles (n = 19) on metformin use in AEH and endometrial cancer (EC).[7] In spite of the high heterogeneity of the analysed studies, metformin was suggested to synergise with progestin by reversing AEH to normal endometrial histology, reducing cancer-progression biomarkers and improving overall survival for EC patients.[7] Notably, a phase II non-controlled trial reported that metformin plus MPA led to a CR rate of 81% and a recurrence rate of 10% in obese women with AEH and early EC.[8] Thus, it is logical to hypothesise that metformin would improve the early CR rate of progestin-based fertility-preserving therapy for AEH and EEC patients.

Despite early positive findings, there is no direct evidence suggesting metformin plus progestin provide a better therapeutic effect than progestin alone. Most studies are retrospective or non-controlled, and the population size was relatively small. We have conducted a prospective randomised controlled trial to investigate the efficacy of metformin plus megestrol acetate (MA) compared with MA alone as fertility-sparing therapy for patients with AEH and EEC.

Method

Trial design and participants

This single-centre, open-label, phase II randomised controlled trial (NCT01968317) was designed to assess the efficacy of metformin plus MA compared with MA alone as fertility-sparing therapy for patients with AEH and EEC. The study was conducted from October 2013 to October 2017 in the Obstetrics and Gynaecology Hospital of Fudan University, Shanghai, China.

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Women who were eligible patients met the following criteria: 18–45 years old, pathologically diagnosed with AEH or EEC (endometrioid, grade I, without myometrial invasion) for the first time; desire to preserve their fertility; no signs of suspicious myometrial invasion or extrauterine metastasis by enhanced magnetic resonance imaging (MRI), enhanced computed tomography (CT) or transvaginal ultrasonography (TVUS); no contraindication for metformin, MA or pregnancy; no hormone or metformin treatment within 6 months before entering the trial; 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.

The exclusion criteria were patients who had one or more of the following conditions: allergy history or contraindications for MA or metformin; pregnant when initiating the study; alcoholism, severe infection, severe chronical diseases (dysfunction of heart, liver, lung or kidney); high risk of thrombosis; recurrent AEH or EC; other malignancy history.

All patients were pathologically diagnosed by endometrial biopsy through dilation and curettage (D&C) with or without hysteroscopy (HSC). Pathological diagnosis was confirmed by two experienced gynaecological pathologists according to the World Health Organization (WHO) pathological classification (2014). If their opinions differed, a seminar was held in the pathology department to determine the final diagnosis. None of the pathologists who assessed the specimens was aware of the treatment allocations.

The trial was conducted in accordance with applicable regulatory requirements and the principles of the Declaration of Helsinki. This study was also approved by the

Ethics Committees of Obstetrics and Gynaecology (OB&GYN), Hospital of Fudan University. All patients were given full information regarding this clinical trial, and risks of both surgical and conservative treatments. Patients provided written informed consent before their enrolment.

Randomisation and masking

Patients were first stratified according to pathological type (AEH or EEC), and then randomly assigned (1:1) to receive either metformin plus MA or MA-only treatments. A computer-based procedure of simple randomisation (SPSS for Mac, version 20.0; IBM, Armonk, NY, USA) was used for participant enrolment and randomisation. Before a woman was successfully enrolled, her treatment assignment remained concealed. This trial was open label: patients and study physicians were aware of treatment assignment.

Treatment and assessment

Patients in the MA-only group received continuous MA (160 mg orally, daily), whereas women in the metformin plus MA group received continuous MA (160 mg orally, daily) plus metformin (500 mg orally, three times a day).

After initiating the treatment, hysteroscopic evaluation was performed every 3 months during the therapy, following the standard procedure as described previously.[11] One senior specialist (Dr H. W. Zhang) performed all the hysteroscopies and was unaware of this trial. Briefly, each suspected lesion or cluster in the endometrium was recorded in detail including the location, number and size, and removed completely under the principle of minimising the 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. In addition, enhanced pelvic MRI was conducted every 6 months during the entire course of treatment for EEC patients.

The response to conservative treatment was assessed histologically using specimens obtained during each hysteroscopic evaluation. CR was defined as the reversion of AEH/EEC to proliferative or secretory endometrium. Partial response (PR) was defined as pathological improvement. No response (NR) was defined as the persistence of disease as initially diagnosed. Progressive disease (PD) was defined as any appearance of endometrial malignancy in AEH patients or any appearance of grade II–III EC, myometrial invasion, and extrauterine lesions in EEC patients were recognised. Relapse was defined as the presence of complex hyperplasia, AEH or EC after CR.

Patient continued metformin plus MA or MA-only treatment for at least 6 months if CR was not achieved. Patients ceased fertility-sparing treatment if unacceptable side effects were found at any time. Definitive hysterectomy was suggested if patients had PD at any time or remained NR for more than 6 months, or had PR for more than 9 months. For patients who refused hysterectomy, a multiple disciplinary discussion was held for each individual case, and alternative treatments were considered. Once the patient achieved CR, the same regimen was administered for another 2–3 months for treatment consolidation. After achieving CR, patients were followed up every 3–6 months, and TVUS and endometrial biopsy by Pipelle were used to assess the endometrium. Enhanced pelvic MR, serum CA-125 and serum HE4 were followed up for EEC patients annually.

For CR patients without a current need to conceive, low-dose cyclic progestin, oral contraceptive pills or a levonorgestrel intrauterine system (LNG-IUS) was administered to prevent disease recurrence. For CR patients who desired to conceive soon, assisted reproduction technology (ART) was recommended, which was under a close surveillance of our multiple disciplinary team. Patients who successfully delivered a live birth were suggested to undergo definitive surgery.

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 were performed at 08:00 h after fasting overnight. Body mass index (BMI), waist/hip ratio (WHR) and the homeostasis model assessment-insulin resistance (HOMA-IR) index were subsequently calculated. The HOMA-IR index (FBG [mmol/l] ×FINS [microU/ml]/22.5) was used to evaluate insulin resistance (IR) status. Patients with HOMA-IR ≥2.95 were considered to be insulin-resistant.[12,13] BMI ≥25 kg/m^2 was defined as overweight.[12] Obesity was defined as BMI ≥ 28 kg/m^2 followed criteria for Chinese adults.[14,15] Statuses of metabolic syndrome (MS), hypertension and diabetes were also evaluated according to established criteria.[16–18] Adverse effects were recorded according to National Cancer Institute Common Toxicity Criteria version 4.

Outcomes

The primary objective was to determine whether metformin plus MA would be associated with a higher CR rate at 3 months of treatment compared with MA alone. Secondary objectives were between-group comparisons of the cumulative CR rate at 6 months treatment and adverse events. However, for patients who eventually underwent the first and second hysteroscopies for endometrium evaluation within 16 and 32 weeks of the treatment, the cumulative CR rates within 16 and 32 weeks (16w-CR and 32w-CR rates) were analysed as first and secondary end points instead of the CR rate at 3 and 6 months.

Statistical analysis

For the primary endpoint, we set a baseline CR rate of 25% in the MA group, and an expected CR rate of 50% in

the metformin plus MA group, according to results in our previous pilot study,[19] with a power of 0.9 at a two-sided significance level of 0.05, requiring an accrual of 150 eligible patients (lost to follow-up rate <5%). Intention-to-treat analyses were performed for patients who eventually underwent endometrial evaluation at the primary and secondary time points (within 16 and 32 weeks of treatment). All 150 patients were included in the safety analysis. Continuous variables were summarised by means and standard deviations, or median and interquartile range (IQR). Categorical variables were presented as frequency with percentage. The intragroup differences of continuous variables were investigated by Student's *t*-test or the Mann–Whitney *U*-test where appropriate. The Chi-square test or Fisher's exact test was used to analyse the difference between categorical variables. Adjusted odds ratios (OR) and 95% confidence interval (95% CI) were estimated with a logistic regression model. Estimates of time to CR were calculated using the Kaplan–Meier method. A 2-tailed *P*-value of <0.05 was considered statistically significant. SPSS 22.0 (SPSS, Inc., Chicago, IL, USA) was used for all the statistical analyses.

Results

Patients and treatment

The flow of patients in the trial is reported in Figure 1. Enrolment concluded with 307 patients; 157 were deemed ineligible, most commonly because of progestin-use history or AEH/EC history before the enrollment. Between October 2013 and October 2017, 150 patients who met all the inclusion and exclusion criteria were randomly allocated to receive metformin plus MA (n = 76, 61 AEH and 15 EEC)

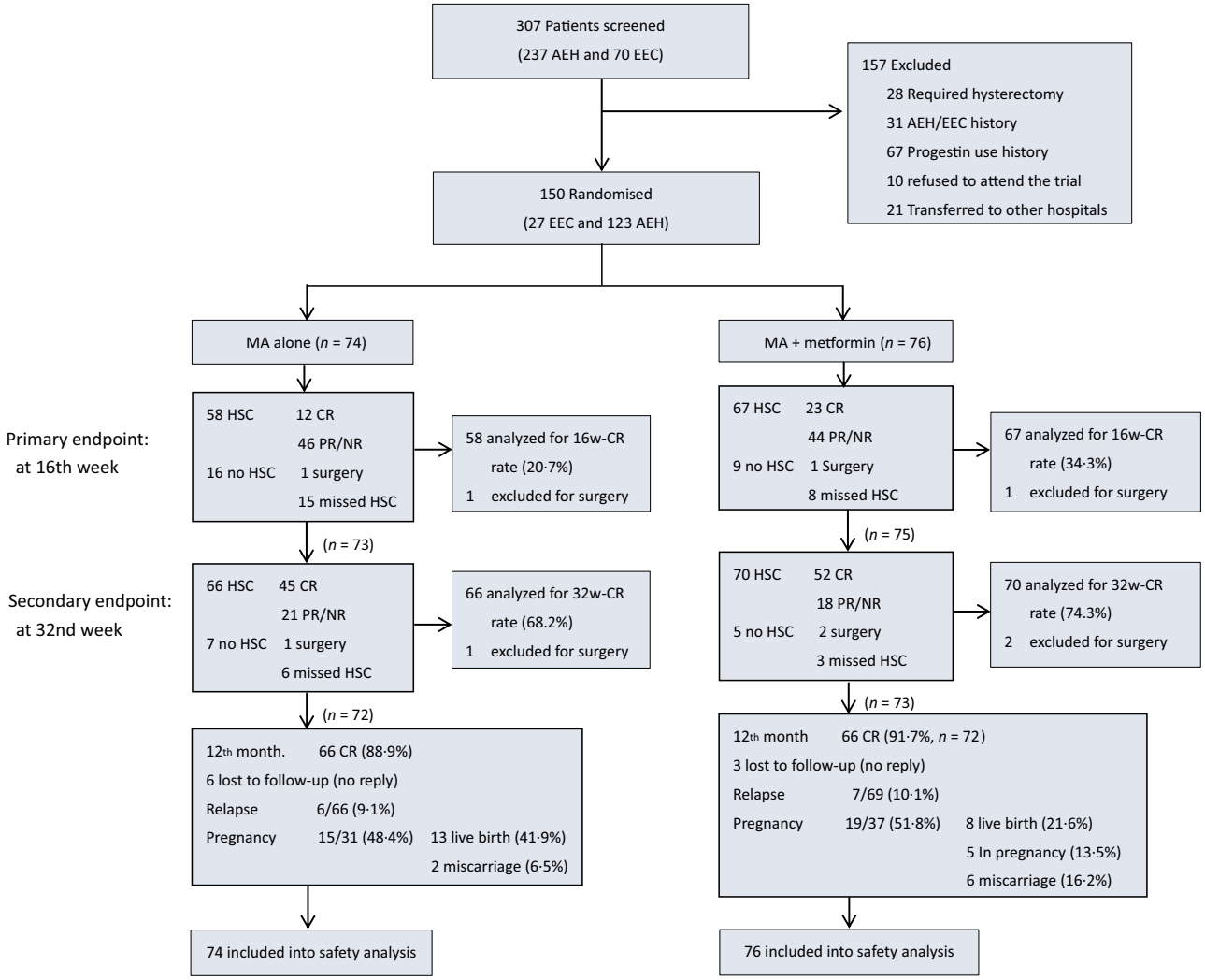

Figure 1. Trial profile. 16(32)w-CR rate: cumulative CR rate at 16 (32) weeks after initiating the treatment; AEH, atypical endometrial hyperplasia; CR, complete response; EEC, endometrioid endometrial cancer; HSC, hysteroscopy; MA, megestrol acetate; NR, no response; PR, partial response.

Table 1. The 16-week CR rates of subgroups according to histological subtypes and metabolic status

16-week CR rate	All patients (n = 125)		AEH patients (n = 102)	
	MA	MA + metformin	MA	MA + metformin
AEH	20.4% (10/49)	39.6% (21/53)	–	–
EEC	22.2% (2/9)	14.3% (2/14)	–	–
Obese	7.1% (1/14)	10.0% (2/20)	8.3% (1/12)	12.5% (2/16)
Non-obese	25.0% (11/44)	44.7% (21/47)	24.3% (9/37)	51.4% (19/37)
IR	8.3% (2/24)	15.4% (4/26)	9.5% (2/21)	14.3% (3/21)
Non-IR	29.4% (10/34)	45.0% (18/40)	28.6% (8/28)	54.8% (17/31)
MS	13.6% (3/22)	26.5% (9/34)	15.0% (3/20)	32.1% (9/28)
Non-MS	25.0% (9/36)	42.4% (14/33)	24.1% (7/29)	48.0% (12/25)
Hypertension	33.3% (1/3)	0% (0/4)	33.3% (1/3)	0% (0/2)
Nonhypertension	20.0% (11/55)	36.5% (23/63)	19.6% (9/46)	41.2% (21/51)
Diabetes	20.0% (1/5)	0% (0/3)	20.0% (1/5)	0% (0/2)
Nondiabetes	20.8% (11/53)	35.9% (23/64)	20.5% (9/44)	41.2% (21/51)

AEH, atypical endometrial hyperplasia; CR, complete response; EEC, endometrioid endometrial cancer; IR, insulin resistance; MA, megestrol acetate; MS, metabolic syndrome.

or MA alone (n = 74, 62 AEH and 12 EEC). Five patients required surgery before the first or second hysteroscopical evaluation. In total, 125 and 136 women eventually underwent the first and second hysteroscopy within 16 and 32 weeks of treatment, respectively. Thus, intention-to-treat analyses were performed for these 125 and 136 patients. All patients were followed up till February 2019 (Figure 1).

Baseline characteristics for the eligible 150 patients are summarised in Table S1. All the participants were Chinese Asian and were enrolled in Shanghai OB&GYN Hospital of Fudan University. Stratification factor (AEH or EEC) was balanced between the treatment groups. There was no difference in age, histology subtypes, pretreatment BMI or IR status between two treatment groups. On average, 40.0% of patients were overweight, 26.7% were obese and 40.0% were insulin-resistant. Most patients had no history of hypertension or diabetes.

The 16w-CR rate (primary endpoint)

The cumulative 16w-CR rate was higher in the metformin plus MA group than in the MA-only group (34.3 versus 20.7%), although this result regarding primary end point did not reach significance (OR 2.00, 95% CI 0.89–4.51, P = 0.09). However, as AEH and EEC patients were stratified before randomization, analyses were also performed separately in AEH and EEC subgroups. Results showed AEH patients (n = 102) might have benefited more from metformin: the 16w-CR rate in the metformin plus MA group was almost two-fold higher than in the MA-only group (39.6 versus 20.4%, OR 2.56, 95% CI 1.06–6.21, P = 0.032), adjusted by BMI and HOMA-IR index (Table 1, Figure 2). In EEC patients (n = 23), the difference in 16w-CR rate of the metformin plus MA and MA-only groups did not reach the significance (14.3 versus 22.2%, OR 0.58, 95% CI 0.07–5.11, P = 0.63; Table 1, Figure 2).

We retrospectively investigated whether the efficacy of metformin correlated with metabolic status. In all eligible patients, metformin was found to have no significant impact on 16w-CR rate in subgroups according to metabolic status (Figure 3). In AEH women, the 16w-CR rates of two treatments were similar in subgroups of obese (BMI ≥28 kg/m^2, n = 28, 12.5 versus 8.3%, OR 1.57, 95% CI 0.13–19.67) and insulin-resistant patients (HOMA-IR ≥ 2.95, n = 42, 14.3 versus 9.5%, OR 1.55, 95% CI 0.24–10.61; Table 1, Figure 3). Surprisingly, in non-obese (BMI <28 kg/m^2), insulin-sensitive (HOMA-IR <2.95), nonhypertension or nondiabetic subgroups of AEH women, we found metformin was significantly associated with a higher 16w-CR rate. In 74 non-obese AEH patients, the 16w-CR rate was 51.4% in metformin plus MA group and 24.3% in MA-only group (OR 3.28, 95% CI 1.22–8.84, P = 0.02; Table 1, Figure 3). This difference remained significant in insulin-sensitive (n = 59, 54.8 versus 28.6%, OR 3.04, 95% CI 1.03–8.97; P = 0.04), nonhypertension (n = 97, 41.2 versus 19.6%, OR 2.88 95% CI 1.15–8.97; P = 0.20) and nondiabetic AEH women (n = 95, 41.2 versus 20.5%, OR 2.72, 95% CI 1.08–6.84, P = 0.03, Table 1, Figure 3), respectively.

The 32w-CR rate (secondary endpoint)

At 32 weeks of treatment, the cumulative CR rate in the metformin plus MA group was slightly higher than in the MA-only group (74.3 versus 68.2%, OR 1.35, 95% CI 0.64–2.84, P = 0.43; Figure 2). Similar results were also found in subgroups of AEH and EEC patients (Figure 2). However, neither difference was statistically significant.

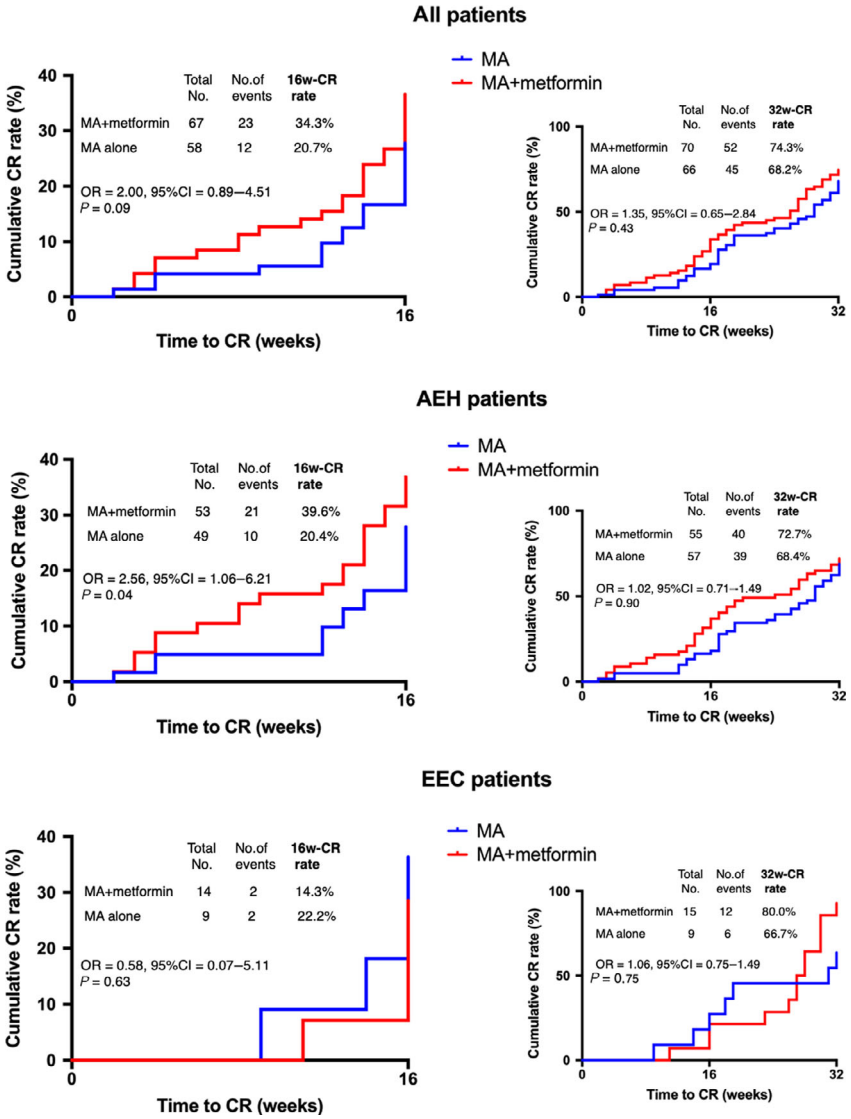

Figure 2. Differences in 16w-CR rate and 32w-CR rate between two treatments in all patients and subgroups of AEH and EEC patients. AEH, atypical endometrial hyperplasia; CR, complete response; EEC, endometrioid endometrial cancer; MA, megestrol acetate.

Long-term onco-fertility results

Definitive surgery was suggested for all patients who failed to achieve CR after at least 9 months of treatment. One EEC patient accepted hysterectomy and one AEH patient progressed to grade I EEC and then moved to another hospital for alternative therapy. The rest of patients insisted on continuing the fertility-sparing therapy until CR. All patients were followed up till February 2019. Nine patients were lost to follow up (three in the metformin plus MA group and six in the MA-only group; Figure 1). During a median follow-up period of 33.4 (26.0–44.0) months after CR, recurrence occurred in seven of 69 patients in the metformin plus MA group and in six of 66 in the MA-only group (Figure 1). After achieving CR, 68 women planned for parenthood immediately, and 63 of them received assisted reproductive treatment including ovulation induction and/or *in vitro* fertilisation and embryo transfer. The pregnancy rates were 51.8% in the metformin plus MA ($n = 37$) group and 48.4% in the MA-only group ($n = 31$, $P = 0.8$; Figure 1).

Adverse events (secondary endpoint)

All the eligible 150 patients were included in the safety analysis. Adverse events between two groups are summarised in Table S2. Weight gain was the most common treatment-emergent side effect, occurring in 34.2% of women in the metformin plus MA group and 41.9% in the MA-only group. During the treatment, median weight gain in the metformin plus MA group was 2.5 kg (−1.0 to 6.0),

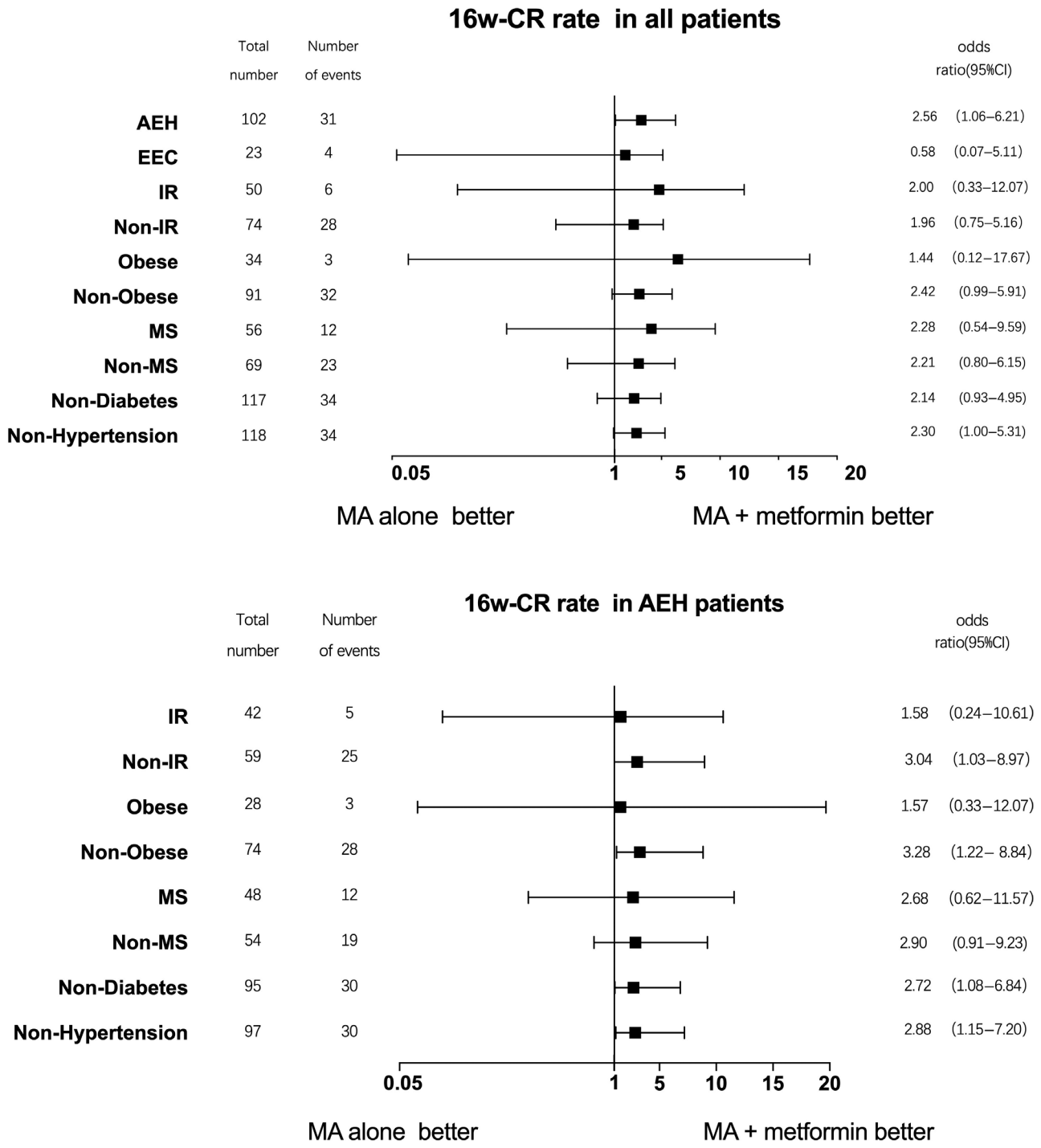

Figure 3. Subgroup analyses according to histology subtypes and metabolic statuses. AEH, atypical endometrial hyperplasia. IR, insulin resistance; MA, megestrol acetate; MS, metabolic syndrome; Results of hypertension or diabetic subgroups were not shown in the figure because of their limited size for statistical analysis ($n < 10$).

compared with 5.0 kg (0 to 10.0) in the MA-only group ($P = 0.01$). Nevertheless, grade 1–2 diarrhoea occurred more often in the metformin plus MA group than in the MA-only group (15.8 versus 4.1%; $P = 0.03$). Except for diarrhoea, other adverse events appeared less likely to occur in the metformin plus MA group than in the MA-only group. Fewer patients in the metformin plus MA group presented uterine haemorrhage (7.9 versus 17.6%),

increased nocturnal urine (0 versus 4.1%) or breast pain (4.0 versus 10.8%) compared with the MA-only group, although none of the intragroup differences was statistically significant.

Discussion

Main findings

The present trial demonstrated that no significant difference was found between MA-only and MA plus metformin regarding therapeutic outcomes. However, in AEH patients, metformin plus MA was associated with an improved 16w-CR rate compared with MA alone. This improvement also remained significant in non-obese, insulin-sensitive, nonhypertension or nondiabetic subgroups of AEH women. No patients reported fatal adverse events in our study, supporting the safety of metformin, which was generally well tolerated.

Strengths and limitations

To our knowledge, this is the first prospective randomised controlled trial with the largest sample size (n = 150), assessing the effect of metformin on AEH and EEC patients in fertility-sparing therapy. Our results also for the first time showed the efficacy of metformin in AEH women without obesity, insulin resistance, hypertension or diabetes in a Chinese population. However, the study has some limitations. First, it was a single-centre phase II trial, with a relatively small sample size of EEC participants. The lack of double-blinding design and placebo was also a weakness of this trial. Moreover, although hysteroscopic evaluation was scheduled for all patients every 3 months (12 weeks, 24 weeks, etc.), some patients eventually delayed (for 2–4 weeks) or cancelled the hysteroscopy for various reasons, such as vaginitis and the conflict with their working hours. Another reason was the travel delay caused by long journeys, as this was a single-centred study in Shanghai, and many patients lived in other cities far away. Thus, most (125 and 136) women underwent hysteroscopies within 16 and 32 weeks of treatment and were included in intention-to-treat analyses. Nevertheless, the lack of sufficient cases for statistical analyses could generate bias and might be the reason why the difference between two treatments failed to achieve statistical significance. In addition, the repeated hysteroscopy use might conceal the role of metformin, although increasing evidence supports hysteroscopy combined with progestin as a first-line fertility-sparing treatment.

Interpretation

Our findings confirmed previous retrospective, non-controlled or small-population studies showing that metformin plus MA was associated with an improved early CR rate compared with MA alone in AEH patients.[7,19] These findings are clinically important because metformin may help patients achieve CR in a shorter treatment time, reducing the risk of side effects caused by long-term progestin use, and endometrium injury by repeated endometrium sampling. Thus, metformin might be an appropriate adjunctive therapy in fertility-sparing regimens for AEH patients. It is also safe, of low cost and available worldwide.

Major participants were diabetic or obese in previous studies on metformin, considering it is an insulin sensitiser. Mitsuhashi et al. reported an anti-cancer effect of metformin in AEH and EEC patients of a Japanese population, but also mentioned that mean BMI was 31 kg/m^2 and 67% of recipients were insulin-resistant.[8] A few studies reported the benefit of metformin in nondiabetic patients with other diseases[20–24] such as breast cancer and colorectal adenomatous polyps. As many young Chinese women with AEH or EEC are non-obese or insulin-sensitive, as with most of the patients in our trial, it is necessary to assess metformin use for such population. Our findings suggest that in addition to increasing insulin sensitivity, other effects of metformin may play an important role. No improved early CR rate was found in obese or insulin-resistant AEH women in our trial, which might be partially because of the limited sample size in such subgroups.

The improved CR rate with metformin might be attributed to enhanced efficacy of progestin and a direct/indirect anti-cancer function of metformin.[7,9,10] Previous investigators demonstrated that metformin promoted expression of progesterone receptor via inhibition of mTOR in ECs, and sensitised progestin-resistant EC cells to progestin-induced apoptosis by downregulating glycosylase I (Glo I) expression.[10] Conversely, metformin altered expression of estrogen receptor to inhibit the estradiol-induced proliferation in EC cells by raising the ER-β while reducing the ER-α isoforms.[25] Furthermore, metformin inhibits oxidative phosphorylation (OXPHOS) at mitochondrial level, activating adenosine monophosphate kinase (AMPK) to induce a myriad of tumor suppressor genes.[3] Lord et al.[5] also reported a clinical dose of metformin suppressed proliferation of breast cancer cells by increasing FDG (a marker of glucose uptake) flux into tumors and reducing levels of mitochondrial metabolites. Such findings should be further verified in AEH/EEC to stratify metformin responders for more precise fertility-sparing therapy.

The effect of metformin was not significant in EEC patients in our study, in contrast to the patients in the AEH group. This was probably because of the small sample size for EEC participants. As AEH and EEC patients were stratified and both randomly allocated into MA/metformin and control groups, the efficacy of metformin on AEH patients was still convincing. Larger trials on EEC patients should be conducted to verify the suitability of metformin use in such a population for fertility preservation.

In addition, we found the intragroup difference in 32w-CR rate was narrowed compared with the 16w-CR rate. This might be due to the repeated hysteroscopic evaluations. Recently, hysteroscopy has been applying to achieve higher CR rates alongside with progestin therapy, because of its advantage in complete removal of endometrial lesions.[11,26] Our early large-scale ($n = 152$) study also reported an improved 12-month CR rate of 88.9% in AEH and 91.4% in EEC patients by hysteroscopy combined with MA.[11] Collectively, the long-term merits of metformin might be concealed by repeated hysteroscopy in our trial. Nevertheless, patients in the metformin plus MA group might also experience fewer hysteroscopic evaluations because of their better early CR rate.

Conclusion

In conclusion, no significant difference was found between two treatments regarding therapeutic outcomes. However, the early CR rate for AEH patients might be improved by adding metformin into MA therapy, including for AEH women without obesity, insulin resistance, hypertension or diabetes in a Chinese population. This is the first randomised controlled study with the largest sample size to demonstrate the efficacy of metformin in fertility-sparing therapy. Nevertheless, the results are not yet strong enough to support metformin plus progestin treatment as a clinical routine. Phase III trials including a sufficient number of EEC patients are needed to validate further the effect of metformin.

Disclosure of interests

The authors have no conflict of interests. Completed disclosure of interests forms are available to view online as supporting information.

Contribution to authorship

Xiao-jun Chen and Jun Guan contributed to the study design and data interpretation. Bing-yi Yang, Gulinazi Yierfulati, Cheng-cheng Ning, Ya-li Cheng, Wei-wei Shan, Xue-zhen Luo, Hong-wei Zhang, Qin Zhu, Feng-hua Ma, Jia Liu, Li Sun and Min Yu contributed to the data collection. Bing-yi Yang, Gulinazi Yierfulati and Jun Guan contributed to literature search, figures, tables and data analyses. Yan Du also contributed to data analyses. This article was written by 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 xiao-junchen2013@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 31 March 2014, with the approval number OB&GYNG Ethics approval [2014]-11.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Baseline characteristics of all eligible patients (n = 150).

Table S2. Safety analysis between two treatments (all eligible patients). ■

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