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Original Article

Metformin combined with progesterone improves efficacy and reduces adverse reactions in early endometrial cancer

Junfei Li, Yanshan Hou, Dan Liao

Department of Gynecology, Xiangnan University Affiliated Hospital, Chenzhou 423000, Hunan, China

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Abstract: Objective: The purpose of this study was to explore the clinical value of metformin combined with progesterone in the treatment of early endometrial cancer (EC). Methods: A retrospective study was conducted involving 60 patients with early EC. According to the different treatment regimens, the patients were divided into the monotherapy group (n = 29, receiving progesterone monotherapy) and the combined treatment group (n = 31, receiving metformin combined with progesterone therapy). The clinical efficacy, serum tumor marker levels, body mass index, incidence of adverse reactions, and prognosis were compared between the two groups. Results: Compared to the monotherapy group, the combined treatment group had a higher total effective rate (96.77% vs. 72.41%), lower levels of connective tissue growth factor, angiogenin-2, carbohydrate antigen 125, vascular endothelial growth factor, carbohydrate antigen 19-9, and matrix metalloproteinase 9, and a lower BMI (between-group effect: $F = 24.710$, time effect: $F = 135.200$, interaction effect: $F = 20.490$, all $P < 0.001$). The total incidence of adverse reactions was lower in the combined treatment group (6.45% vs. 31.03%), and there was no significant difference in the recurrence rate between the two groups ($\chi^2 = 0.004$, $P = 0.953$). Conclusion: Metformin combined with progesterone exerts excellent clinical efficacy in the treatment of early EC. It can significantly reduce serum tumor marker levels and BMI, and decrease the occurrence of adverse reactions.

Keywords: Real-world, metformin, megestrol acetate, progesterone, early, endometrial cancer

Introduction

Endometrial cancer (EC) is a common malignant tumor of the female genital tract, classified into adenocarcinoma, adenosquamous carcinoma, clear cell carcinoma, serous papillary adenocarcinoma, and a few other uncommon types. It affects predominantly perimenopausal or postmenopausal women [1, 2]. EC is often associated with insulin resistance, obesity, and diabetes, which seriously threaten patients' health and life. In recent years, the incidence of EC has been increasing annually, and the age of onset has been shifting to a younger age Currently, the EC pathogenesis remains unclear [3]. Studies have shown that early diagnosis and effective treatment can prevent EC progression and reduce mortality [4]. Clinically, the primary treatment for early EC is surgery, followed by targeted therapy based on the clinical stage and combined recurrence risk factors. However, some patients are insensitive or intolerant to chemotherapeutic drugs in clinical practice, leading to poor treatment compliance and a further increased risk of death [5]. Therefore, it is urgent to explore new therapeutic strategies for early EC. Progesterone is a commonly used drug in clinical practice to preserve fertility in eligible patients but is prone to inducing adverse events such as drug resistance, thrombosis, and weight gain, thereby affecting therapeutic outcomes [6]. Metformin is a first-line drug for the clinical treatment of diabetes. Due to its antitumor properties, it can directly act on EC cells, delaying disease progression to a certain extent [7]. However, its efficacy is suboptimal when used alone in some patients [8]. Few studies have focused on the application of metformin combined with progesterone in EC treatment. Moreover, most existing studies mainly assess the efficacy and pregnancy rate in

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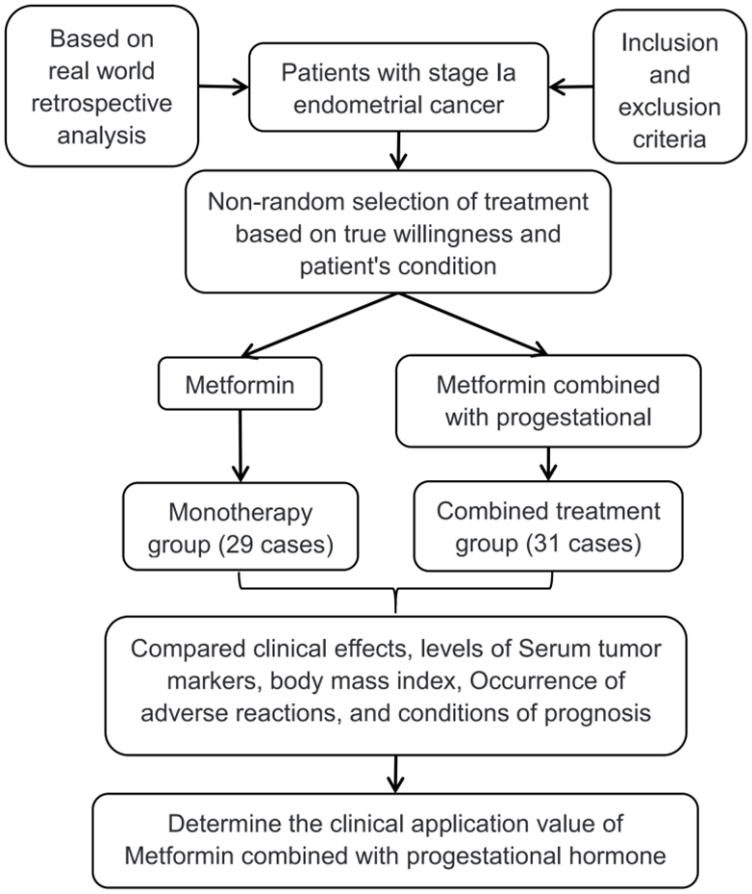

Figure 1. Research design framework.

patients with fertility requirements, without analyzing serum tumor marker levels, treatment safety, or long-term prognosis [8]. To explore further the therapeutic effect of metformin combined with progesterone on EC, this real-world study analyzed the effect of this combination therapy on EC efficacy, serum tumor marker levels, body mass index (BMI), adverse reactions, and prognostic recurrence, and was to provide new insight and data support for the clinical treatment of EC.

Materials and methods

Case selection

This study was approved by the Ethics Committee of Xiangnan University Affiliated Hospital. A retrospective real-world study was conducted on 60 patients with early EC admitted to Xiangnan University Affiliated Hospital from January 2021 to March 2024.

The subjects of this study were required to meet the following inclusion criteria: (1) Diagnosed with EC in accordance with the criteria specified in the International Federation of Gynecology and Obstetrics (FIGO)/International Gynecologic Cancer Society Guidelines for Gynecological Malignancies Staging and Clinical Practice (IV): Endometrial Cancer [9]; (2) Pathological stage classified as FIGO: stage IA; (3) No prior treatment received before diagnosis; (4) Normal coagulation function; (5) Treated with progesterone monotherapy or metformin combined with progesterone; (6) Good treatment compliance.

The subjects were excluded if they met the following exclusion criteria: (1) History of hormone drug use within the past six months; (2) Concurrent malignant tumors other than EC; (3) Known allergic to the study therapeutic drugs; (4) Severe liver or kidney dysfunction; (5) Complicated with primary immunodeficiency; (6) Incomplete clinical data.

According to the different treatment regimens, patients who received progesterone monotherapy were assigned to the monotherapy group (n = 29), and those who received metformin combined with progesterone therapy were assigned to the combined treatment group (n = 31). The study design is illustrated in **Figure 1**.

Interventions

All patients in both groups, who desired fertility preservation, underwent hysteroscopic surgery for pathologic confirmation.

The monotherapy group received oral megestrol acetate tablets (Shanghai Xinyi Tianping Pharmaceutical Co., Ltd., National Medical Products Administration (NMPA) Approval No.: H20053712; Specification: 160 mg) at a dose of 160 mg once daily for 3 months.

The combined treatment group was given oral metformin hydrochloride tablets (Squibb Pharmaceutical Co., Ltd., NMPA Approval No.: H20023370; Specification: 0.5 g) in addition to the same megestrol acetate regimen as the monotherapy group, at a dose of 0.5 g twice daily for 3 months.

Data collection

Primary indicators: 1. Clinical efficacy: Clinical efficacy was evaluated based on the Response Evaluation Criteria in Solid Tumor (RECIST) [10] during the 4-week follow-up after treatment completion. Complete response (CR): All target lesions disappeared, with no new lesions detected for at least 4 weeks. Partial response (PR): The sum of the maximum diameters of target lesions decreased by > 30%, maintained for at least 4 weeks. Progressive disease (PD): The sum of the maximum diameters of target lesions increased by ≥ 20% (or the appeared of new lesions). Stable disease (SD): The sum of the maximum diameters of target lesions did not meet the criteria for PR or PD. The total effective rate was calculated as the sum of the CR and PR rates. 2. Adverse reactions: Adverse reactions included gastrointestinal reactions, insomnia, headache, and weight gain. Weight gain was defined as an increase of more than 2.5 kg after treatment compared with pre-treatment body weight. 3. Prognosis: Patients were followed up for 12 months after treatment to assess tumor recurrence.

Secondary indicators: 1. Serum tumor markers: Serum levels of connective tissue growth factor (CTGF), angiogenin (Ang-2), carbohydrate antigen 125 (CA125), vascular endothelial growth factor (VEGF), CA19-9, and matrix metalloproteinase 9 (MMP9) were measured before and after treatment. 2. Ovarian function: Detect the levels of estradiol (E2), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) in ovarian function before and after treatment. 3. Body mass index (BMI): BMI data were collected from patients before treatment, 1 month, 2 months, and 3 months after treatment. 4. Sample collection and detection methods: Sample collection: Fasting venous blood (10 mL) was collected from each patient. The blood samples were routinely processed to separate serum, then centrifuged at 3000 r/min for 20 minutes (centrifugal radius: 5 cm) and stored at -80°C until detection. Detection of CTGF, Ang-2, and MMP9: The expression levels of CTGF, Ang-2, and MMP9 were detected by enzyme-linked immunosorbent assay (ELISA). Detection kits were purchased from Shanghai Ruifan Biotechnology Co., Ltd. (batch number: RF3154), and all operations were performed strictly in accordance with the manufacturer's instructions. Detection of CA125 and CA19-9: CA125 and CA19-9 levels were measured using an electrochemiluminescence immunoassay analyzer (Cobas e601, provided by Roche Diagnostics). Detection kits were supplied by Shanghai Enzyme Linked Technology Co., Ltd., and all operations followed the standard protocol.

Statistical methods

Data analysis was performed using SPSS 20.0 software. Quantitative data were expressed as "mean ± standard deviation (x±sd)". Independent samples t-test was used for comparisons between two independent groups, and paired samples t-test was applied for comparisons at two different time points within the same group. For comparisons of data at three or more different time points among groups, repeated-measures analysis of variance (ANOVA) followed by LSD test was adopted. Qualitative data were presented as n (%), and chi-square test or rank sum test was used. When the theoretical frequency was ≤ 1, the chi-square value needed to be corrected. The significance level of the test was set at $\alpha = 0.05$.

Results

Comparison of baseline data

Comparison of age, course of disease, and cancer type distribution between the monotherapy group and the combined treatment group showed no significant differences (all $P > 0.05$), as presented in **Table 1**.

Comparison of clinical efficacy

The clinical efficacy of the combined treatment group was significantly higher than that of the monotherapy group. The total effective rate of the combined treatment group was 96.77%, which was higher than 72.41% in the monotherapy group ($P < 0.05$), as shown in **Table 2**.

Table 1. Comparison of baseline data

Group	Age (x±s, years)	Course of disease (x±s, d)	Maximum length of lesion (cm)	Cancer types [n (%)]	
				Endometrial carcinoma	Mucous carcinoma
Monotherapy group (n = 29)	34.56±2.82	1.85±0.42	2.65±0.61	23 (79.31)	6 (20.69)
Combined treatment group (n = 31)	34.71±2.35	1.89±0.27	2.73±0.67	26 (83.87)	5 (16.13)
t/χ^2	0.224	0.392	0.482	0.208	
P	0.823	0.696	0.631	0.648	

Table 2. Comparison of curative effect [n (%)]

curative effect	Monotherapy group (n = 29)	Combined treatment group (n = 31)	Z/χ^2	*P*
PD	3 (10.34)	1 (3.23)	-2.661	0.008
SD	5 (17.24)	0 (0.00)		
PR	10 (34.48)	9 (29.03)		
CR	11 (37.93)	21 (67.74)		
Total effective	21 (72.41)	30 (96.77)	5.194	0.023

Not: PD: progressive disease; SD: stable disease; PR: partial response; CR: complete response.

Comparison of tumor marker levels

After treatment, the levels of CTGF, Ang-2, CA125, VEGF, CA19-9, and MMP9 in both the monotherapy group and the combined treatment group were lower than those before treatment (all P < 0.05). Furthermore, the above indicators in the combined treatment group were significantly lower than those in the monotherapy group (all *P* < 0.05), as shown in **Figure 2**.

Comparison of ovarian function levels

The levels of E2, LH, and FSH in the combined treatment group were higher than those in the monotherapy group (all *P* < 0.05), as shown in **Figure 3**.

Comparison of body mass index

Compared to the monotherapy group, the BMI of the combined treatment group was significantly lower (between-group effect: F = 24.710, P < 0.001). The BMI of both groups increased with time (time effect: F = 135.200, P < 0.001), and there was an interaction effect between group and time (interaction effect: F = 20.490, *P* < 0.001), as shown in **Table 3**.

Comparison of adverse reactions

The total incidence of adverse reactions in the combined treatment group was 6.45%, which was significantly lower than 31.03% in the monotherapy group (*P* < 0.05), as shown in **Table 4**. After targeted symptomatic treatment, the adverse reactions of the patients were gradually relieved until resolution.

Comparison of prognosis

Statistical analysis of follow-up results showed 2 cases of recurrence (6.90%) in the monotherapy group and 1 case (3.21%) in the combined treatment group. Comparison of the recurrence rates between the two groups showed χ^2 = 0.004, *P* = 0.953, indicating no significant difference.

Discussion

The development of EC is associated with genetics, obesity, diabetes, long-term estrogen exposure, and other factors [11]. Once EC occurs, it can cause irreversible harm to patients. Early diagnosis and effective treatment are crucial to ensure therapeutic efficacy and a favorable prognosis. Metformin and progesterone each have their own advantages and disadvantages when used alone in EC treatment. Therefore, it is necessary to explore the therapeutic effect of their combination in the management of EC.

The progesterone of choice in this study was megestrol acetate. We found that the total effective rate of patients treated with metformin combined with progesterone was 96.77%, which was significantly higher than that of patients treated with progesterone alone (72.41%). This outcome differed from previous studies [12]. This discrepancy may be related to the differences in the inclusion and exclusion criteria of the enrolled patients. Megestrol acetate, a derivative of natural progesterone, mainly acts on estrogen receptors in EC cells [13]. By bind-

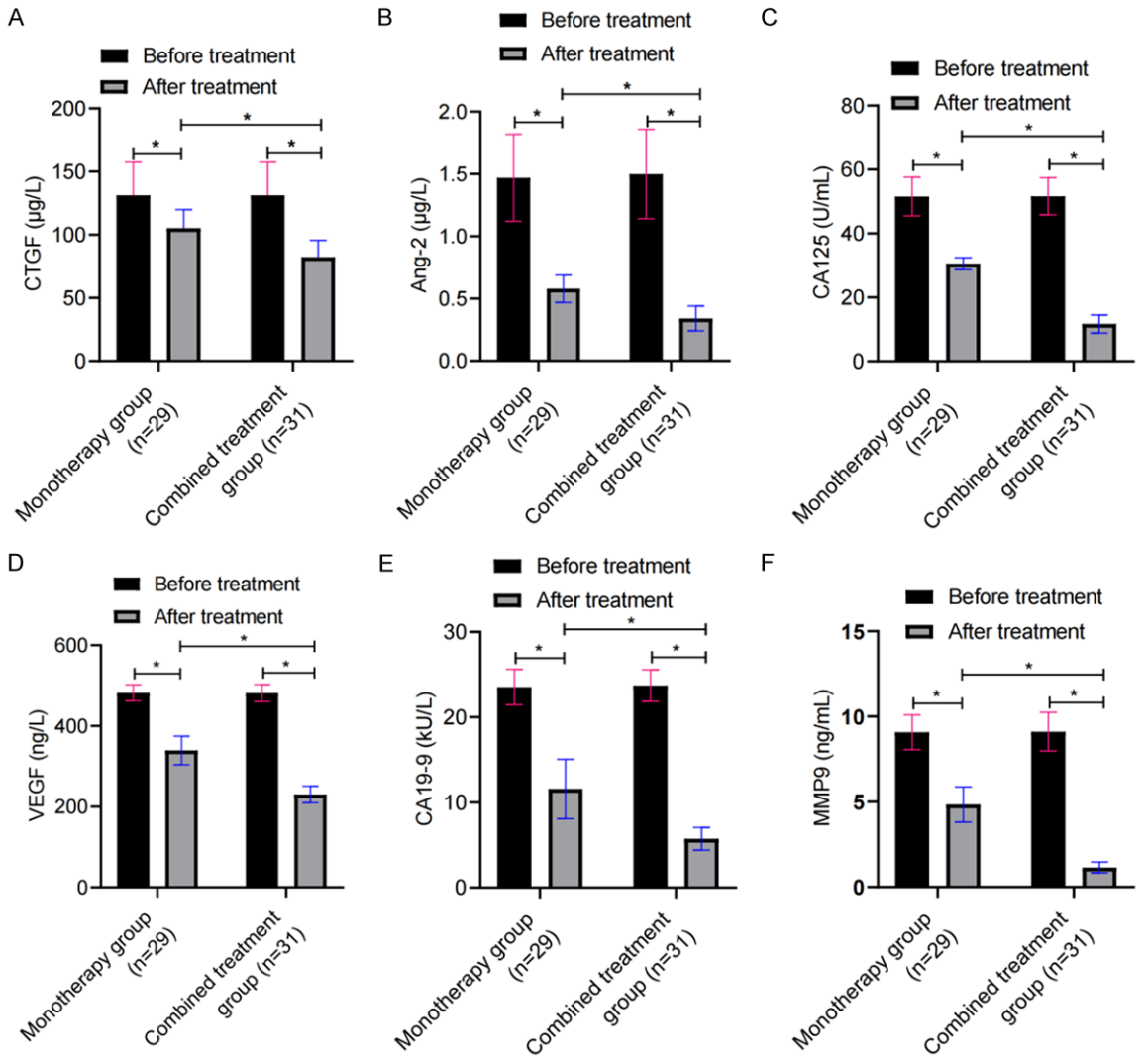

Figure 2. Comparison of Tumor marker levels. *Note*: * indicates comparison between two groups of data, $P<0.05$. *Note*: CTGF: connective tissue growth factor; Ang-2: angiogenin-2; CA125: carbohydrate antigen 125; VEGF: vascular endothelial growth factor; CA19-9: carbohydrate antigen 19-9; MMP9: matrix metalloproteinase 9. After treatment, the levels of CTGF, Ang-2, CA125, VEGF, CA19-9, and MMP9 in the monotherapy group and the combination therapy group were lower than those before treatment, and the above indexes in the combination therapy group were lower than those in the control group. A. The graph shows CTGF levels; B. The graph shows Ang-2 levels; C. The graph shows CA125 levels; D. The graph shows VEGF levels; E. The graph shows CA19-9 levels; F. The graph shows MMP9 levels.

ing to estrogen receptors and inhibiting estrogen secretion, megestrol acetate can effectively suppress the proliferation and metastasis of tumor cells, promote protein anabolism in patients, enhance their appetite, and reduce the risk of drug resistance [14]. Metformin is an insulin sensitizer that not only promotes anaerobic glycolysis but also exerts anti-tumor biological activity. It can activate adenosine monophosphate-activated protein kinase (AMPK), promote AMPK energy signal transduction, maintain cellular energy balance, and inhibit the mammalian target of rapamycin (mTOR) pathway. Through these mechanisms, metformin inhibits cancer cell proliferation and tumor growth, further alleviates EC-related symptoms, and improves therapeutic outcomes [15]. The synergistic effect of megestrol acetate and metformin can promote the regression of EC lesions, thereby enhancing the overall therapeutic efficacy.

Tumor markers are characteristic biological substances produced either directly by malig-

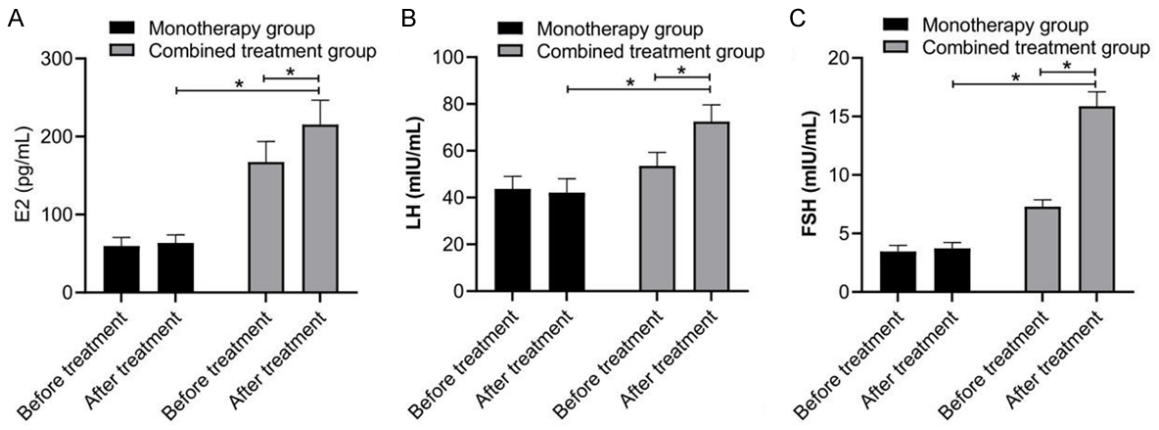

Figure 3. Comparison of Estrogen levels. *Note*: * indicates comparison between two groups of data, $P < 0.05$. *Not*: E2: estradiol; LH: luteinizing hormone; FSH: follicle-stimulating hormone. A. The graph shows E2 levels; B. The graphshows LH levels; C. The graph shows FSH levels.

Table 3. Comparison of body mass index ($\bar{x} \pm s$, kg/m^2)

Time	Monotherapy group (n = 29)	Combined treatment group (n = 31)	t	*P*
before treatment	33.31±3.07	33.24±3.36	0.084	0.933
1 month after treatment	33.22±3.25[a]	29.62±3.27[a]	4.274	< 0.001
2 months after treatment	33.01±3.34[a,b]	26.38±2.82[a,b]	8.327	< 0.001
3 months after treatment	32.92±3.28[a,b,c]	24.62±2.25[a,b,c]	11.490	< 0.001

[a]Compared with the pre-treatment values within the same group, [b]compared with the values 1 month after treatment within the same group, and [c]compared with the values 2 months after treatment within the same group-all comparisons were performed using Bonferroni post-hoc test following analysis of variance (ANOVA). In the Monotherapy group, all *P*-values were > 0.05; in the Combined treatment group, all *P*-values were < 0.05.

Table 4. Comparison of adverse reactions [n (%)]

Adverse reaction	Monotherapy group (n = 29)	Combined treatment group (n = 31)	Z/χ^2	*P*
Gastrointestinal reactions	2 (6.90)	1 (3.23)		
Insomnia	3 (10.34)	0 (0.00)		
Headache	2 (6.90)	1 (3.23)		
Weight gain	2 (6.90)	0 (0.00)		
Total incidence of adverse reactions	9 (31.03)	2 (6.45)	4.517	0.034

nant tumor cells or by the host in response to tumor stimulation. Changes in their levels can reflect the occurrence, development, and progression of tumors [16]. CTGF and Ang-2 are involved in the formation of tumor neovascularization. Among them, CTGF can also promote the proliferation and migration of tumor cells [17]. CA125 and CA19-9 are membrane antigens highly expressed in patients with EC, and their serum levels can reflect the disease severity and prognosis of patients [18]. VEGF, a platelet-derived growth factor, can stimulate the division and proliferation of vascular endothelial cells as well as the expression of cell genes, thereby increasing microvascular permeability and facilitating the growth, invasion, and metastasis of tumor cells [19]. MMP9, on the other hand, can reflect the malignant potential of tumors. It promotes the invasion and metastasis of tumor cells mainly by degrading the extracellular matrix and basement membrane, and its high expression in EC tissues is closely associated with the depth of myometrial invasion [20].

In this study, the levels of tumor markers (CTGF, Ang-2, CA125, VEGF, CA19-9, and MMP9) were significantly reduced in both groups after treatment, with a more pronounced reduction observed in the combined treatment group. These results suggest that metformin combined with progesterone can inhibit tumor growth, progression, and metastasis in EC, which is consistent with the research results of Zhang et al. [21]. This may be attributed to the dual effects of megestrol acetate (inhibiting tumor cell growth and metastasis) and the anti-tumor biological activity of metformin. Therefore, we speculate that metformin combined with progesterone can reduce the tumorigenic activity of EC, delay disease progression, and lower the risk of death, which holds practical clinical guiding significance [22]. This study also found that the combination of metformin and progesterone led to a significant reduction in BMI. This suggested that the combined application of the two drugs has certain advantages in reducing the BMI of EC patients, which is consistent with the findings of Yuan et al. [23]. Combined treatment based on metformin exerts a significant effect on reducing BMI, possibly because metformin inhibits the secretion of adipokines by adipocytes, key driving factors for the increased risk of obesity-induced endometrial cancer [24]. Studies have shown that a higher BMI is associated with an increased incidence of adverse surgical events after open or laparoscopic surgery for early EC [25]. The significant reduction in BMI among EC patients treated with metformin combined with progesterone may thus be more conducive to subsequent treatment. The total incidence of adverse reactions in the combined treatment group was lower than that in the monotherapy group (6.45% vs. 31.03%), and there was no significant difference in the recurrence rate between the two groups. This suggests that the combination of metformin and progesterone has good safety in EC treatment. Studies have shown that metformin combined with progesterone can help prevent EC recurrence [26], which is consistent with the results of this study. Notably, combination therapy reduces the incidence of adverse reactions without increasing the risk of EC recurrence, indicating that the treatment of EC with metformin combined with progesterone is clinically feasible.

Conclusion

Metformin combined with progesterone achieved a higher total effective rate, significantly reduced levels of tumor markers (CTGF, Ang-2, CA125, VEGF, CA19-9, and MMP9), a lower BMI, and a lower total incidence of adverse reactions, with no significant change in the recurrence rate. These findings indicate that combined treatment had significant advantages in the treatment of early EC making it worthy of further research and clinical application.

Shortcomings of this study: There are several limitations in this study. Since real-world studies were characterized by relying on large-scale, multi-center sample data to ensure statistical power, reduce random errors, and improve the generalizability of results, the small sample size in this clinical study was constrained by clinical practice conditions (e.g., limited recruitment scope, strict inclusion/exclusion criteria) and could not have been further expanded. This may have weakened the robustness of the statistical analysis, limited the feasibility of subgroup analyses for key influencing factors, or affected the external validity of the study conclusions, making it difficult to extrapolate the findings to a broader population of early EC patients. The hierarchical analysis of some influencing factors was limiting, and the results may have been biased. Finally. the time of this research was short, and there was no further follow-up study. Therefore, further clinical research needs to adopt a variety of data mining methods to generate more robust evidence-based data for TCM clinical practice.

To sum up, metformin combined with progesterone exerts excellent clinical efficacy in the treatment of early EC. It can significantly reduce serum tumor marker levels and BMI, as well as decrease the incidence of adverse reactions, with no significant increase in the recurrence rate.

Disclosure of conflict of interest

None.

Address correspondence to: Dan Liao, Department of Gynecology, Xiangnan University Affiliated Hospital, No. 25 Renmin West Road, Chenzhou 423000, Hunan, China. Tel: +86-0735-3725199; E-mail: liaodan3390@163.com

References

[1] Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, Romeo M, Bratos R, Brose MS, DiSimone C, Messing M, Stepan DE, Dutcus CE, Wu J, Schmidt EV, Orlowski R, Sachdev P, Shumaker R and Casado Herraez A. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer. J Clin Oncol 2020; 38: 2981-2992.

[2] Eskander RN, Ali S, Dellinger T, Lankes HA, Randall LM, Ramirez NC, Monk BJ, Walker JL, Eisenhauer E and Hoang BH. Expression patterns of the wnt pathway inhibitors dickkopf3 and secreted frizzled-related proteins 1 and 4 in endometrial endometrioid adenocarcinoma: an NRG oncology/gynecologic oncology group study. Int J Gynecol Cancer 2016; 26: 125-132.

[3] Matei D, Filiaci V, Randall ME, Mutch D, Steinhoff MM, DiSilvestro PA, Moxley KM, Kim YM, Powell MA, O'Malley DM, Spirtos NM, Small W Jr, Tewari KS, Richards WE, Nakayama J, Matulonis UA, Huang HQ and Miller DS. Adjuvant chemotherapy plus radiation for locally advanced endometrial cancer. N Engl J Med 2019; 380: 2317-2326.

[4] Westin SN, Fellman B, Sun CC, Broaddus RR, Woodall ML, Pal N, Urbauer DL, Ramondetta LM, Schmeler KM, Soliman PT, Fleming ND, Burzawa JK, Nick AM, Milbourne AM, Yuan Y, Lu KH, Bodurka DC, Coleman RL and Yates MS. Prospective phase II trial of levonorgestrel intrauterine device: nonsurgical approach for complex atypical hyperplasia and early-stage endometrial cancer. Am J Obstet Gynecol 2021; 224: 191.e1-191.e15.

[5] Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, DiSilvestro P, Pearl ML, Argenta PA, Powell MA, Zweizig SL, Warshal DP, Hanjani P, Carney ME, Huang H, Cella D, Zaino R and Fleming GF. Carboplatin and paclitaxel for advanced endometrial cancer: final overall survival and adverse event analysis of a phase III trial (NRG Oncology/GOG0209). J Clin Oncol 2020; 38: 3841-3850.

[6] Zaino RJ, Brady WE, Todd W, Leslie K, Fischer EG, Horowitz NS, Mannel RS, Walker JL, Ivanovic M and Duska LR. Histologic effects of medroxyprogesterone acetate on endometrioid endometrial adenocarcinoma: a gynecologic oncology group study. Int J Gynecol Pathol 2014; 33: 543-553.

[7] Xie H, Li M and Zheng Y. Associations of metformin therapy treatment with endometrial cancer risk and prognosis: a systematic review and meta-analysis. Gynecol Oncol 2024; 182: 15-23.

[8] Ronsini C, Romeo P, Andreoli G, Palmara V, Palumbo M, Caruso G, De Franciscis P, Vizzielli G, Restaino S, Chiantera V and Cianci S. Fertility-sparing treatments in endometrial cancer: a comprehensive review on efficacy, oncological outcomes, and reproductive potential. Medicina (Kaunas) 2025; 61: 471.

[9] Griesel M, Seraphin TP, Mezger NCS, Hämmerl L, Feuchtner J, Joko-Fru WY, Sengayi-Muchengeti M, Liu B, Vuma S, Korir A, Chesumbai GC, Nambooze S, Lorenzoni CF, Akele-Akpo MT, Ayemou A, Traoré CB, Wondemagegnehu T, Wienke A, Thomssen C, Parkin DM, Jemal A and Kantelhardt EJ. Cervical Cancer in Sub-Saharan Africa: a multinational population-based cohort study of care and guideline adherence. Oncologist 2021; 26: e807-e816.

[10] Schwartz LH, Litière S, de Vries E, Ford R, Gwyther S, Mandrekar S, Shankar L, Bogaerts J, Chen A, Dancey J, Hayes W, Hodi FS, Hoekstra OS, Huang EP, Lin N, Liu Y, Therasse P, Wolchok JD and Seymour L. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 2016; 62: 132-7.

[11] Haggerty AF, Huepenbecker S, Sarwer DB, Spitzer J, Raggio G, Chu CS, Ko E and Allison KC. The use of novel technology-based weight loss interventions for obese women with endometrial hyperplasia and cancer. Gynecol Oncol 2016; 140: 239-244.

[12] Ravi RD, Kalra J, Srinivasan R, Bagga R, Jain V, Suri V and Sachdeva N. A randomized clinical trial of levonorgestrel intrauterine system with or without metformin for treatment of endometrial hyperplasia without atypia in Indian women. Asian Pac J Cancer Prev 2021; 22: 983-989.

[13] Zaino RJ, Brady WE, Todd W, Leslie K, Fischer EG, Horowitz NS, Mannel RS, Walker JL, Ivanovic M and Duska LR. Histologic effects of medroxyprogesterone acetate on endometrioid endometrial adenocarcinoma: a gynecologic oncology group study. Int J Gynecol Pathol 2014; 33: 543-553.

[14] Myers AP, Filiaci VL, Zhang Y, Pearl M, Behbakht K, Makker V, Hanjani P, Zweizig S, Burke JJ 2nd, Downey G, Leslie KK, Van Hummelen P, Birrer MJ and Fleming GF. Tumor mutational analysis of GOG248, a phase II study of temsirolimus or temsirolimus and alternating megestrol acetate and tamoxifen for advanced endometrial cancer (EC): an NRG oncology/gynecologic oncology group study. Gynecol Oncol 2016; 141: 43-48.

[15] Mitsuhashi A, Kiyokawa T, Sato Y and Shozu M. Effects of metformin on endometrial cancer cell growth in vivo: a preoperative prospective trial. Cancer 2014; 120: 2986-2995.

[16] Li H, Liao H, Jing B and Wang Y. Effects of coagulation function indicators and tumor markers on diagnosis and clinicopathological characteristics of endometrial cancer. Int J Biol Markers 2023; 38: 214-222.
[17] Martin-Liberal J, Hollebecque A, Aftimos P, Jungels C, Martin-Romano P, Rodon J, Kremer JD, Zhang W and Bendell J. First-in-human, dose-escalation, phase 1 study of anti-angiopoietin-2 LY3127804 as monotherapy and in combination with ramucirumab in patients with advanced solid tumours. Br J Cancer 2020; 123: 1235-1243.
[18] Wang L, Chen YJ, Xu K, Xu H, Shen XZ and Tu RQ. Circulating microRNAs as a fingerprint for endometrial endometrioid adenocarcinoma. PLoS One 2014; 9: e110767.
[19] Bender D, Sill MW, Lankes HA, Reyes HD, Darus CJ, Delmore JE, Rotmensch J, Gray HJ, Mannel RS, Schilder JM, Hunter MI, McCourt CK, Samuelson MI and Leslie KK. A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: an NRG oncology/gynecologic oncology group study. Gynecol Oncol 2015; 138: 507-512.
[20] Li W, Cui Z, Kong Y, Liu X and Wang X. Serum levels of S100A11 and MMP-9 in patients with epithelial ovarian cancer and their clinical significance. Biomed Res Int 2021; 2021: 7341247.
[21] Zhang DD, Yao L and Jia XG. Effect of metformin combined with megestrol acetate in treating endometrial cancer patients and its influence on their tumor marker. Oncol Prog 2021; 19: 1378-1381.
[22] Oaknin A, Gilbert L, Tinker AV, Brown J, Mathews C, Press J, Sabatier R, O'Malley DM, Samouelian V, Boni V, Duska L, Ghamande S, Ghatage P, Kristeleit R, Leath C III, Guo W, Im E, Zildjian S, Han X, Duan T, Veneris J and Pothuri B. Safety and antitumor activity of dostarlimab in patients with advanced or recurrent DNA mismatch repair deficient/microsatellite instability-high (dMMR/MSI-H) or proficient/stable (MMRp/MSS) endometrial cancer: interim results from GARNET-a phase I, single-arm study. J Immunother Cancer 2022; 10: e003777.
[23] Yuan F, Hu Y, Han X and Li Q. Metformin in combination with progesterone improves the pregnancy rate for patients with early endometrial cancer. Contrast Media Mol Imaging 2022; 2022: 1961016.
[24] Mitsuhashi A, Habu Y, Kobayashi T, Kawarai Y, Ishikawa H, Usui H and Shozu M. Long-term outcomes of progestin plus metformin as a fertility-sparing treatment for atypical endometrial hyperplasia and endometrial cancer patients. J Gynecol Oncol 2019; 30: e90.
[25] Kondalsamy-Chennakesavan S, Janda M, Gebski V, Baker J, Brand A, Hogg R, Jobling TW, Land R, Manolitsas T, Nascimento M, Neesham D, Nicklin JL, Oehler MK, Otton G, Perrin L, Salfinger S, Hammond I, Leung Y, Sykes P, Ngan H, Garrett A, Laney M, Ng TY, Tam K, Chan K, Wrede DH, Pather S, Simcock B, Farrell R, Robertson G, Walker G, McCartney A and Obermair A. Risk factors to predict the incidence of surgical adverse events following open or laparoscopic surgery for apparent early stage endometrial cancer: results from a randomised controlled trial. Eur J Cancer 2012; 48: 2155-2162.
[26] Straubhar A, Soisson AP, Dodson M and Simons E. Successful treatment of low-grade endometrial cancer in premenopausal women with an aromatase inhibitor after failure with oral or intrauterine progesterone. Gynecol Oncol Rep 2017; 21: 10-12.