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Weight-Loss and Metformin-Use Improve the Reversal Rate in Patients with Endometrial Hyperplasia

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Objective: To evaluate the therapeutic outcomes of weight loss and metformin use in patients with endometrial hyperplasia (EH), and to identify the factors influencing treatment efficacy.

Methods: This study included data from patients diagnosed with either EH or endometrial atypical hyperplasia (EAH). Patients selected a progestin treatment regimen based on their diagnosis. Those with concurrent obesity or insulin resistance received additional weight management support and metformin therapy. Follow-up assessments were conducted every 3–6 months.

Results: A total of 202 patients were included. The metformin group exhibited significantly greater improvement in abnormal uterine bleeding (91.5% vs 57.1%, $p < 0.001$) and in ultrasound findings (91.5% vs 66.7%, $p < 0.001$) than the non-metformin group. Patients who achieved >3% weight loss and those using metformin showed a significantly higher rate of disease reversal than those with ≤3% weight loss (91.2% vs 77.6%, $p = 0.034$) and the non-metformin group (93.2% vs 52.4%, $p < 0.001$). At follow-up durations exceeding 12 months, metformin use was associated with a significantly higher disease reversal rate (82.1% vs 42.9%, $p = 0.048$) and a lower recurrence rate (12.8% vs 28.6%, $p = 0.048$). Weight loss of >3% (odds ratio: 0.041, 95% confidence interval: 0.004–0.437, $p = 0.008$) and metformin use (odds ratio: 0.059, 95% confidence interval: 0.011–0.311, $p = 0.001$) were both independently associated with improved reversal rates in patients with EH/EAH.

Conclusion: Combining progestin therapy with weight loss and metformin is more effective in reversing EH than progestin alone. Regular metformin use, alongside weight loss, serves as a protective factor in EH management, with the protective effect of metformin increasing with longer use.

Keywords: endometrial hyperplasia without atypia, comprehensive management, weight management, metformin

Background

Endometrial hyperplasia (EH) refers to an imbalance in the ratio of glands to stroma in the endometrium.[1] The overall incidence of EH is 133 per 100,000 women,[2] with a notable increase in older age groups. EH is rarely seen in women under 30 and peaks between the ages of 50 and 54 years.[3] Most women with EH present with abnormal uterine bleeding (AUB). A British study[4] of 3,006 premenopausal patients with AUB found that 1.2% of those with simple hyperplasia (SH) and 0.6% with dysplasia were younger than 40 years old. Meanwhile, 2.2% of patients with SH and 1.8% with dysplasia were aged between 45 and 50 years. Similarly, a Turkish study[5] involving 2,516 premenopausal women with AUB reported that the incidence of EH without atypia was approximately 9% in women younger than 40 years and increased to 15.4% in those aged 45–50 years. Another Japanese study[6] of 1,837 women with AUB aged 26 and older found that the incidence of EH and endometrial cancer was positively correlated with age, with a prevalence of 3.8% in patients aged 26–34 years, rising to 10% in women over 50 years old. Several

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risk factors contribute to the development of EH, including obesity, insulin resistance, oligomenorrhea, and polycystic ovary syndrome (PCOS).[7,8] In 2014, the World Health Organization (WHO) classified EH into two categories: EH without atypia and EAH.

Patients with EH may present with symptoms such as AUB, infertility, and abnormal findings on gynecological ultrasound. These abnormalities often include uneven endometrial thickening or intrauterine lesions. The primary goal of EH treatment is to manage AUB while reducing the risk of progression to endometrioid endometrial carcinoma (EEC). Current conservative treatment options for EH primarily involve oral progestins or the levonorgestrel intrauterine system (LNG-IUS). The complete remission (CR) rate for EH without atypia is 67–72% with oral progestins and 81–94% with LNG-IUS.[9–11] In cases of endometrial atypical hyperplasia (EAH), the CR rate ranges from 76.2% to 85.6%, while the recurrence rate is between 26% and 40.6%. Recurrence is observed in 30.3% of women treated with oral progestins and 13.7% of those using LNG-IUS.[12] These findings indicate that progestin treatment alone is not entirely satisfactory. Oral progestin therapy is associated with short-term side effects such as headaches, mood changes, acne, breast tenderness, or weight gain, as well as long-term risks like thromboembolic events or breast cancer. These side effects reduce patient adherence and negatively affect the efficacy of progestin treatment.

Obesity, PCOS, and type II diabetes mellitus are established risk factors for EH. The presence of chronic conditions such as type II diabetes, insulin resistance, and obesity significantly impacts the outcomes of EH treatment. Several meta-analyses have identified a body mass index (BMI) ≥25 kg/m^2 as a potential risk factor for EEC recurrence,[13–15] while weight loss has been shown to improve CR rates and reduce recurrence. Metformin, a first-line treatment for type II diabetes mellitus, is commonly used in patients with EH who also have obesity, insulin resistance, or type II diabetes. However, it remains unclear whether metformin can enhance treatment outcomes for patients with EH. Given that EH may be a progressive condition, it is reasonable to consider it a chronic disease requiring long-term management. In addition to progestin therapy, addressing individual risk factors is particularly crucial. The aim of this study is to analyze the therapeutic effects of weight loss and metformin in patients with EH, as well as the related influencing factors.

Methods

Inclusion and Exclusion Criteria

Patients were prospectively recruited from Tianjin Medical University General Hospital. The inclusion criteria were as follows: (1) pathology-confirmed diagnoses of EH without atypia or EAH, (2) no contraindications for progestogen therapy or pregnancy, and (3) premenopausal women. The exclusion criteria were as follows: (1) hepatic or renal insufficiency, (2) presence of other malignant tumors, (3) pregnancy or suspected pregnancy, (4) missing clinical or pathological data, and (5) history of venous thrombosis or family history of deep vein thrombosis. Based on these criteria, 202 patients were finally enrolled in the study from January 2018 to February 2022.

Progestin Treatment

All patients received an individualized progestin treatment regimen based on their endometrial pathology. Patients with EAH were treated with medroxyprogesterone acetate (MPA), megestrol acetate (MA), or LNG-IUS. Patients with EH without atypia were treated with dydrogesterone or LNG-IUS. All patients underwent a uterine curettage procedure prior to initiating medical treatment.

Weight Management

Weight management involves both lifestyle interventions and weight loss medications, with lifestyle changes being the primary approach. The weight-loss group was defined as those who achieved a weight loss of >3% of their body weight following weight management interventions.

Metformin

Insulin resistance was defined as a Homeostatic Model Assessment for Insulin Resistance score of >2.69. Patients with insulin resistance were treated with the insulin sensitizer metformin. The initial dose of metformin hydrochloride tablets (Sino-US Shanghai Squibb Pharmaceutical Co., Ltd.) was 0.5 g taken twice daily with meals. If no significant adverse

reactions (such as diarrhea, nausea, or vomiting) were observed, the dose was gradually increased by 0.5 g per week, up to a maximum of 0.5 g three times a day, which was then maintained. The metformin group was defined as patients who took metformin continuously for at least 3 months.

Follow-Up

Follow-ups were conducted every 3–6 months. During each routine visit, patients' weight, BMI, symptoms of AUB, endometrial ultrasound imaging, and endometrial pathology were recorded. In patients with EAH, hysteroscopy was performed every 3–6 months.

During the first month of treatment, patients were required to return to the outpatient clinic for a check-up. For those with AUB prior to treatment (including symptoms such as prolonged menstrual bleeding, intermenstrual bleeding, irregular uterine bleeding, or abnormal changes in the menstrual cycle, period, and volume), the degree of improvement was assessed. "Significant improvement in AUB symptoms" was defined as the absence of the aforementioned symptoms during treatment, except for bleeding following progesterone withdrawal. The timing of the next review was then determined, typically within the following 1–2 months, depending on the patient's condition at the initial follow-up.

Disease outcomes were defined based on the effectiveness of fertility preservation in patients with early-stage EEC or EAH.[16–18] The definitions were as follows:

1. Reversal: No abnormal hyperplastic changes in the secretory endometrium, proliferative endometrium, or other types of endometrium were observed on pathological examination after treatment.
2. Partial relief: Pathology results after treatment showed low-grade EH; for instance, patients with SH or complex hyperplasia (CH) exhibited irregular EH or patients with EAH showed SH/CH.
3. Stable: Pathological results after treatment were consistent with those before treatment.
4. Progression: During treatment, pathology results indicated progression to a higher degree of hyperplasia or even EEC.
5. Recurrence: EH recurs after hyperplasia is reversed. All pathological diagnoses were made by gynecological pathologists from the Pathology Department at Tianjin Medical University General Hospital.

All patients were followed up until May 31, 2022. This study adhered to the STROBE checklist for reporting (Supplementary material-STROBE checklist). The follow-up aimed to compare the rates of improvement in AUB symptoms, ultrasound endometrial imaging, and the reversal and recurrence rates of EH across the different treatment groups.

Statistical Analysis

Data conforming to a normal distribution were expressed as the mean ± standard deviation ($x \pm s$). For continuous variables, a one-way analysis of variance was used, with the Bonferroni method applied for multiple comparisons. For data with a skewed distribution, the median (interquartile range) was reported, and the Kruskal–Wallis test was used for group comparisons, with Dunnett's method employed for further comparisons between multiple groups. Categorical variables were analyzed using Pearson's chi-square (χ^2) test or Fisher's exact test. All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA) or GraphPad Prism version 8.0.1. Tests were two-tailed, and p-values of <0.05 were considered statistically significant.

Results

Patients' Characteristics

The mean age of the patients was 37.10 years, with a follow-up duration of 3–55 months and a median follow-up duration of 17.5 months. Among the patients, 82.7% (167/202) were diagnosed with EH without atypia, and 17.3% (35/202) had EAH. The prevalence of comorbid conditions was as follows: hypertension (10.4%), diabetes mellitus (6.9%), insulin resistance (38.1%), dyslipidemia (24.3%), and PCOS (19.3%) (Table 1).

Table 1 Demographic and Clinical Characteristics of the Study Patients

Characteristic	Cases	*x±s/%/median(IQR)*
Basic situation		
Age (years)	202	37.10 ± 7.11
Parity(time)		
0	76	37.6%
≥1	126	62.4%
Gravidity (time)		
0	103	51.0%
≥1	99	49.0%
Body Mass Index (kg/m^2)		
≥24	137	67.8%
<24	65	32.2%
Menstrual regularity		
Yes	118	58.4%
No	84	41.6%
Chief complaint		
Abnormal uterine bleeding	171	84.7%
Asymptomatic	31	15.3%
Pathology diagnoses		
EH without atypia	167	82.7%
EAH	35	17.3%
Comorbidities		
Hypertension		
Yes	21	10.4%
No	181	89.6%
Diabetes mellitus		
Yes	14	6.9%
No	188	93.1%
Insulin resistance		
Yes	77	38.1%
No	125	61.9%
Dyslipidemia		
Yes	49	24.3%
No	153	75.7%
Polycystic ovarian syndrome		
Yes	39	19.3%
No	163	80.7%
Intervention		
Weight loss >3%		
Yes	57	59.9%
No	85	40.1%
Metformin		
Yes	59	73.8%
No	21	26.3%
Follow-up time (months)	202	17.5 (9, 28)

Abbreviations: EAH, endometrial hyperplasia with atypia; EH, endometrial hyperplasia.

Effectiveness of Interventions in Patients with EH

Patients who achieved more than 3% weight loss showed a significantly higher reversal rate compared to those with ≤3% weight loss (91.2% vs 77.6%, p = 0.034) (Figure 1). The metformin group demonstrated significant improvements in AUB symptoms (91.5% vs 57.1%, p < 0.001) and ultrasound findings (91.5% vs 66.7%, p < 0.001) compared with the

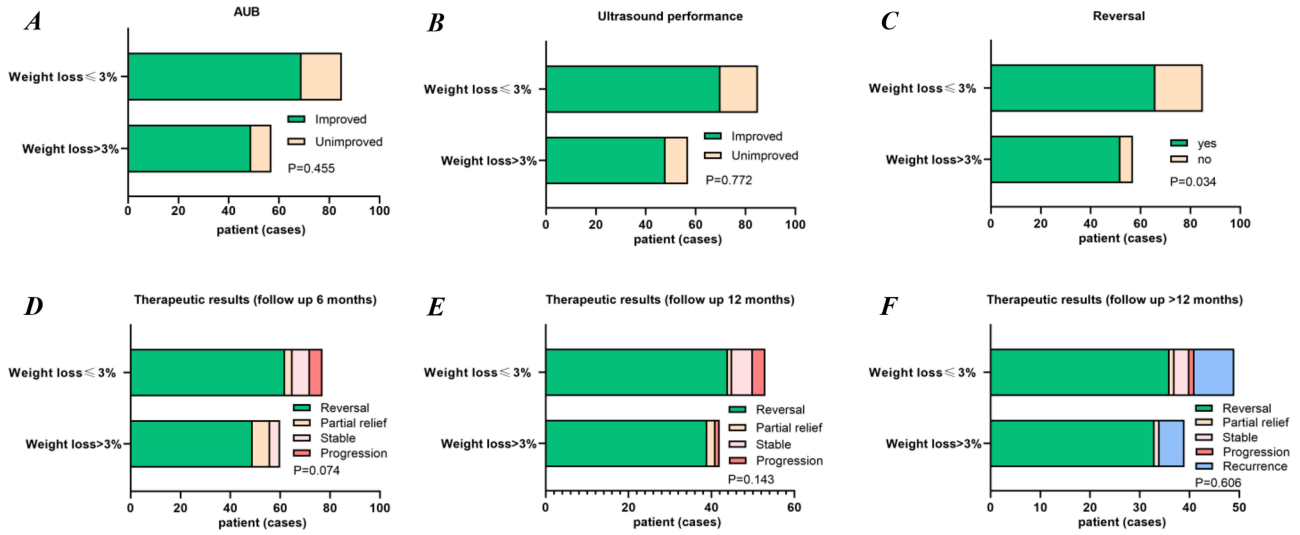

Figure 1 Therapeutic outcome of Weight loss in EH without atypia or EAH patients. (**A** and **B**) Effect of weight loss on AUB and Ultrasound performance in EH without atypia or EAH patients. **(C)** Reversal outcome of weight loss in EH without atypia or EAH patients. (**D–F**) Therapeutic outcome of weight loss at follow up 6, 12, and >12 months in EH without atypia or EAH patients.
Abbreviations: AUB: Abnormal Uterine bleeding, EH: endometrial hyperplasia, EAH: endometrial atypical hyperplasia.

non-metformin group. Furthermore, the reversal rate was significantly higher in the metformin group than in the non-metformin group (93.2% vs 52.4%, $p < 0.001$) (Figure 2).

After more than 12 months of follow-up, metformin use significantly enhanced the disease reversal rate (82.1% vs 42.9%, $p = 0.048$) and reduced the recurrence rate (12.8% vs 28.6%, $p = 0.048$) (Figure 2). Combining progestins with additional interventions, such as >3% weight loss and metformin, resulted in a significantly higher reversal rate compared with progestin-only treatment ($p < 0.001$) (Figure 3). Pairwise comparisons revealed no significant differences in reversal rates between progestin combined with weight loss of >3% and progestin combined with metformin.

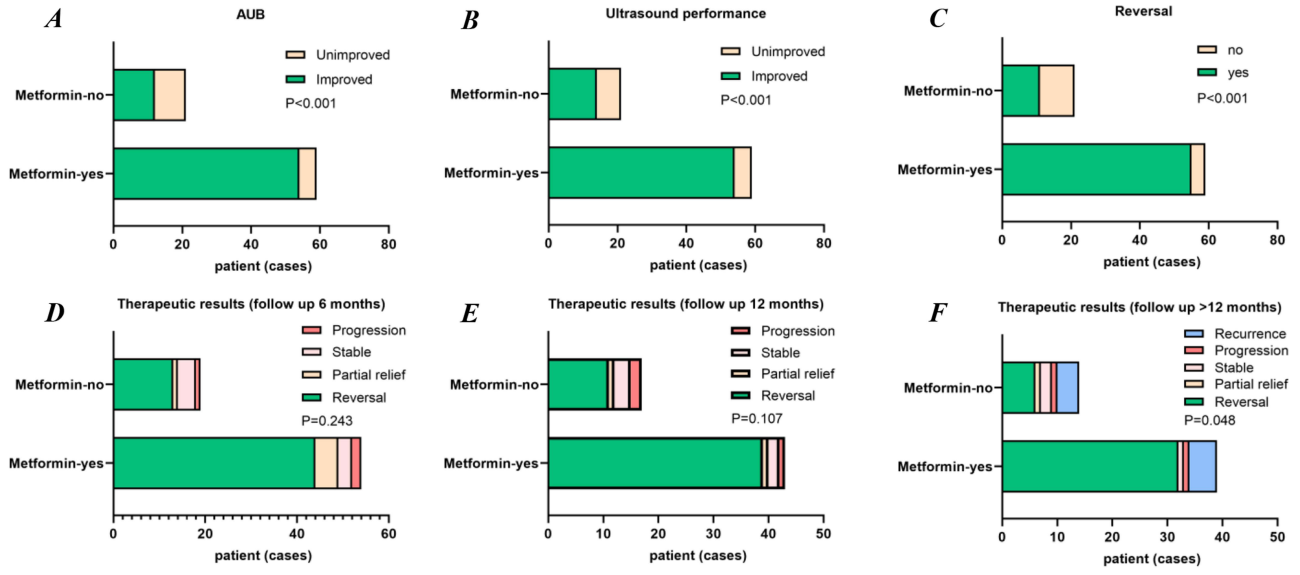

Figure 2 Therapeutic outcome of Metformin-use in in EH without atypia or EAH patients. **(A** and **B**) Effect of metformin use on AUB and Ultrasound performance in EH without atypia or EAH patients. (**C**) Reversal outcome of metformin use in EH without atypia or EAH patients. (**D–F)** Therapeutic outcome of metformin use at follow up 6, 12, and >12 months in EH without atypia or EAH patients.
Abbreviations: AUB: Abnormal Uterine bleeding, EH: endometrial hyperplasia, EAH: endometrial atypical hyperplasia.

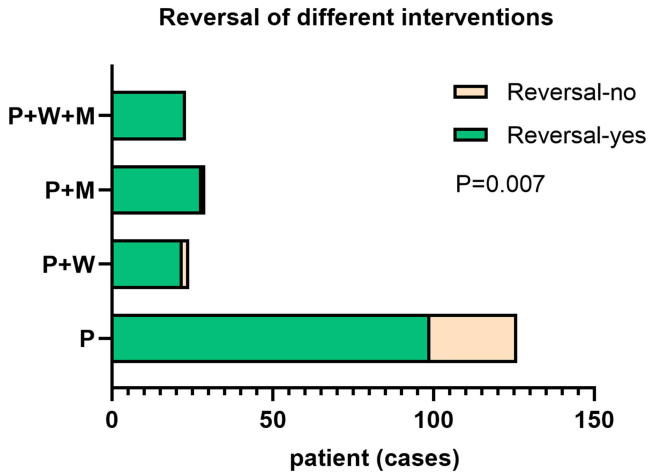

Figure 3 Reversal rate of different interventions in EH without atypia or EAH patients.
Abbreviations: EH: endometrial hyperplasia, EAH: endometrial atypical hyperplasia, P: Progesterone; W: Weight loss >3%; M: Metformin-use.

Influencing Factors of Reversal Rate Among Patients with EH

In patients with EAH, the reversal rate was significantly higher than in those with EH without atypia (97.1% vs 82.6%, p = 0.034). Among patients who experienced >3% weight loss and those using metformin, the reversal rate was significantly higher than those who did not experience >3% weight loss (91.2% vs 77.6%, p = 0.034) and the non-metformin group (93.2% vs 52.4%, p < 0.001). However, no significant differences were observed in reversal rates based on age, parity, gravidity, BMI levels, menstrual regularity, chief complaint, or the presence of combined conditions such as hypertension, diabetes mellitus, insulin resistance, dyslipidemia, and PCOS (all p > 0.05) (Table 2). Multivariate logistic regression analysis revealed that >3% weight loss (odds ratio: 0.041, 95% confidence interval: 0.004–0.437, p = 0.008) and metformin use (odds ratio: 0.059, 95% confidence interval: 0.011–0.311, p = 0.001) were significantly associated with a higher reversal rate in patients with EH (see Table 3).

Table 2 Influencing Factors of the Reversal Among EH Patients

	Reversal		F/χ^2	P value
	Yes	No		
Basic situation				
Age (years)	36.90±7.17	38.27±6.71	0.943	0.333
Parity (time)			1.228	0.309
0	110(87.3%)	16(12.7%)		
≥1	62(81.6%)	14(18.4%)		
Gravidity (time)			0.077	0.845
0	85(85.9%)	14(14.1%)		
≥1	87(84.5%)	16(15.5%)		
Body Mass Index (kg/m^2)			2.394	0.142
≥24	113(82.5%)	24(17.5%)		
<24	59(90.8%)	6(9.2%)		
Menstrual regularity			0.351	0.689
Yes	99(83.9%)	19(16.1%)		
No	73(86.9%)	11(13.1%)		
Chief complaint			0.775	0.432
Abnormal uterine bleeding	144(84.2%)	27(15.8%)		
Asymptomatic	28(90.3%)	3(9.7%)		

(*Continued*)

Table 2 (Continued).

	Reversal		F/χ^2	P value
	Yes	No		
Pathology diagnoses			4.816	0.034
EAH	34(97.1%)	1(2.9%)		
EH without atypia	138(82.6%)	29(17.4%)		
Comorbidities				
Hypertension			–	>0.99
Yes	18(85.7%)	3(14.3%)		
No	154(85.1%)	27(14.9%)		
Diabetes mellitus			2.239	0.232
Yes	10(71.4%)	4(28.6%)		
No	162(86.2%)	26(13.8%)		
Insulin resistance			0.406	0.546
Yes	64(83.1%)	13(16.9%)		
No	108(86.4%)	17(13.9%)		
Dyslipidemia			0.632	0.489
Yes	40(81.6%)	9(18.4%)		
No	132(86.3%)	21(13.7%)		
PCOS			1.959	0.213
Yes	36(92.3%)	3(7.7%)		
No	136(83.4%)	27(16.6%)		
Intervention				
Weight loss >3%			4.481	0.041
Yes	52 (91.2%)	5 (8.8%)		
No	66 (77.6%)	19 (22.4%)		
Metformin			17.892	<0.001
Yes	55 (93.2%)	4 (6.8%)		
No	11 (52.4%)	10 (47.6%)		

Abbreviations: EAH, endometrial hyperplasia with atypia; EH, endometrial hyperplasia; PCOS, polycystic ovarian syndrome.

Table 3 Multiple Logistic Regression Analysis of the Reversal Rate Factor Among EH Patients

	OR	95% CI	P value
Pathology diagnoses			
EH without atypia (Ref)	1		
EAH	0.373	0.030–4.651	0.444
Weight loss >3%			
No (Ref)	1		
Yes	0.041	0.004–0.437	0.008
Metformin			
No (Ref)	1		
Yes	0.059	0.011–0.311	0.001

Abbreviations: EH: endometrial hyperplasia; EAH: endometrial hyperplasia with atypia;

Influencing Factors of Recurrence Among Patients with EH

No significant differences were noted in recurrence rates based on age, parity, gravidity, BMI levels, menstrual regularity, chief complaint, pathology diagnoses, or the presence of combined conditions such as hypertension, diabetes mellitus, insulin resistance, dyslipidemia, and PCOS, as well as >3% weight loss and metformin use (all $p > 0.05$) (Table 4).

Table 4 Influencing Factors of Recurrence in EH Patients

	Recurrence		F/χ^2	P value
	No	Yes		
Basic situation				
Age (years)	37.14±7.16	36.71±6.74	0.058	0.810
Parity (time)			3.555	0.070
0	119(94.4%)	7(5.6%)		
≥1	66(86.8%)	10(13.2%)		
Gravidity (time)			1.397	0.313
0	93(93.9%)	6(6.1%)		
≥1	92(89.3%)	11(10.7%)		
Body Mass Index (kg/m^2)			1.796	0.278
≥24	123(89.8%)	14(10.2%)		
<24	62(95.4%)	3(4.6%)		
Menstrual regularity			0.229	0.798
Yes	109(92.4%)	9(7.6%)		
No	76(90.5%)	8(9.5%)		
Chief complaint			0.076	>0.99
Abnormal uterine bleeding	157(91.8%)	14(8.2%)		
Asymptomatic	28(90.3%)	3(9.7%)		
Pathology diagnoses			0.401	0.742
EAH	33(94.3%)	2(5.7%)		
EH without atypia	152(91.0%)	15(9.0%)		
Comorbidities				
Hypertension			2.154	0.226
Yes	21(100.0%)	0(0.0%)		
No	164(90.6%)	17(9.4%)		
Diabetes mellitus			0.672	0.613
Yes	12(85.7%)	2(14.3%)		
No	173(92.0%)	15(8.0%)		
Insulin resistance			1.729	0.202
Yes	68(88.3%)	9(11.7%)		
No	117(93.6%)	8(6.4%)		
Dyslipidemia			1.231	0.373
Yes	43(87.8%)	6(12.2%)		
No	142(92.8%)	11(7.2%)		
PCOS			0.212	0.747
Yes	35(89.7%)	4(10.3%)		
No	150(92.0%)	13(8.0%)		
Intervention				
Weight loss >3%			0.127	0.782
Yes	52 (91.2%)	5 (8.8%)		
No	76 (89.4%)	9 (10.6%)		
Metformin			1.734	0.232
Yes	54 (91.5%)	5 (8.5%)		
No	17 (81.0%)	4 (19.0%)		

Abbreviations: EAH, endometrial hyperplasia with atypia; EH, endometrial hyperplasia; PCOS, polycystic ovarian syndrome.

Discussion

Progestins are commonly used as a treatment for EH due to their ability to counteract estrogen's effects on the endometrium, induce apoptosis, and reduce angiogenesis. In clinical practice, the duration and cycle of progestin therapy vary based on the type of progestin used, but typically, treatment for EH requires a minimum of 6 months to induce

reversion.[14] Oral progestin therapy often necessitates not only adherence to a specific dosing schedule but also prolonged treatment duration. However, some patients may experience side effects such as AUB and weight gain, which can lead to premature discontinuation of therapy if patients are not adequately informed about these potential adverse effects. This discontinuation can result in insufficient exposure to progestin, thereby diminishing its therapeutic effect on the endometrium and impacting overall treatment outcomes.

Obesity has a strong association with both the incidence and prognosis of EH.[19,20] Women with EEC who have a BMI of >40 kg/m^2 face a six-fold increased risk of mortality compared with women of normal weight.[21] Numerous studies have identified weight gain as a primary risk factor for EH.[20,22] In patients with obesity, the excessive adipose tissue contributes to the conversion of androstenedione into estrone, as well as the aromatization of androgens into estradiol. This leads to elevated estrogen levels in women with obesity, which, without the balancing effects of progesterone, stimulate endometrial cell proliferation, thereby increasing the risk of endometrial lesions. Additionally, obesity is closely associated with insulin resistance, which stimulates the ovaries and adrenal glands, leading to higher circulating estrogen levels. Adipokines, such as adiponectin and leptin, also play a role in the proliferation and malignant transformation of endometrial cells. Furthermore, obesity induces a chronic inflammatory state, with inflammatory markers such as interleukin-6, insulin-like growth factor-binding protein-1, tumor necrosis factor-α, and C-reactive protein all contributing to the development and progression of endometrial lesions. In a prospective cohort study, only 3% of patients with EH and a BMI of <35 kg/m^2 treated with LNG-IUS experienced recurrence after a mean follow-up of 67 months, whereas the recurrence rate was 33% in patients with a BMI of ≥35 kg/m.[219] Faina et al[23] reviewed modifiable risk factors for EH and EEC, identifying obesity and lack of exercise as the primary modifiable factors. Other factors included dietary habits and the use of hormonal therapy, all of which align with the weight management interventions employed in this study. The importance of addressing modifiable risk factors in promoting disease remission should not be underestimated.

Weight loss enhances both oncologic and reproductive outcomes in patients with EH. Balescu et al[24] found that bariatric surgery and consistent weight reduction can significantly lower the risk of progression of endometrial lesions in postmenopausal women with morbid obesity. In their study, they included five patients with SH and one with CH, all with a mean BMI of 43.5 kg/m^2. Following bariatric surgery, their BMI decreased to an average of 26.5 kg/m^2 after 1 year, and four out of the six patients showed complete reversal of their endometrial lesions. Similarly, Chen et al[25] examined the efficacy of fertility-preserving therapy in patients with early EEC or EAH with a BMI of ≥30 kg/m^2. They found that weight loss of >10% improved CR rates, increased pregnancy rates, and reduced recurrence rates. Aubrey et al[26] reported results consistent with Chen, reinforcing the positive impact of weight loss on these outcomes. In contrast, Park's study[27] indicated that weight changes had little effect on CR and recurrence rates during fertility-preserving therapy. However, obesity itself was identified as an important predictor of lower CR rates and higher recurrence rates, suggesting that while weight loss may not directly influence these rates, maintaining a healthy weight is still crucial for positive outcomes. Weight reduction may enhance CR rates and decrease recurrence by altering EH/EEC-related biomarkers, such as adipokines and inflammation-related factors, and improving the endocrine metabolic environment.[28] Haggertya et al[23] performed lifestyle interventions in patients with obesity and EH/EEC and found that serum interleukin-2 levels increased significantly after 6 months (27.15 pg/mL vs 5.18 pg/mL, p = 0.0495), further supporting the impact of weight management on endometrial health. In our study, the combination of progestins and a weight loss of >3% significantly improved CR rates compared with progestin-only treatment. The >3% weight-loss group exhibited a notably higher CR rate than the ≤3% weight-loss group, with weight loss of >3% acting as a protective factor in the management of EH. These findings are consistent with previous research, highlighting the importance of weight management in treating EH.

In patients with EH who also have obesity, weight management may serve as an effective intervention in addition to progestin therapy. However, research indicates that only 18–42% of women are aware of the link between EEC and obesity.[29] A study by Jernigan[30] found that after educating patients about the benefits of weight loss, over 90% of patients with EAH expressed a willingness to lose weight, with 59% attempting weight loss within three months. Similarly, another study showed that educating patients with obesity and EEC increased their willingness to undergo weight loss treatment from 3.7% (2/54) to 25.9% (14/53).[31] A meta-analysis[32] by Leslea demonstrated that weight management

programs extending beyond 6 months in prediabetic populations were associated with a lower incidence of diabetes mellitus.

When patients become aware of the benefits of a healthy diet and regular exercise for disease management, they may be more likely to adopt these practices, contributing to disease improvement. In our study, we used a comprehensive educational approach involving both physician-to-patient and patient-to-patient interactions. Education was delivered through various methods, including lectures, interactive sessions, and follow-up discussions. Face-to-face outpatient education served as the primary method, supplemented by other formats such as WeChat groups, public forums, follow-up visits, and outpatient lectures. The content covered areas such as disease awareness, medication guidance, diet, exercise, and psychological support. We hope this educational strategy will positively influence patient outcomes and improve reproductive health.

Insulin resistance is a recognized risk factor for EH. A cross-sectional study indicated that metabolic disorders play a role in early abnormal endometrial proliferation, with elevated insulin levels strongly associated with EH. Moreover, higher Homeostatic Model Assessment for Insulin Resistance values correspond to more severe endometrial lesions.[33] Hyperinsulinemia has a direct mitogenic effect on endometrial cells, promoting cell proliferation and potentially leading to carcinogenesis. Specific insulin receptors have been identified in both normal endometrial tissue and endometrial cancer cells. Insulin also activates insulin-like growth factor receptors, further contributing to cell growth.[34]

Metformin, an insulin-sensitizing biguanide, is an oral hypoglycemic agent that works by inhibiting hepatic gluconeogenesis and reducing sugar production, thus lowering circulating glucose and insulin levels. This drug not only decreases blood glucose and insulin levels but also inhibits endometrial cell proliferation.[35] Additionally, metformin acts on the mammalian target of rapamycin, mitogen-activated protein kinase, and Akt pathways, inhibiting cellular protein synthesis and ultimately suppressing endometrial cell proliferation.[36,37] Furthermore, metformin has been shown to increase progesterone receptor expression in patients with EH, enhancing the effectiveness of progestin therapy.[38]

Metformin has increasingly been incorporated into fertility-preserving therapies for patients with EAH and early EEC. A systematic review[39] demonstrated that metformin, when combined with progestin, is more effective in treating EAH, with most cases showing a return to normal endometrial tissue. In a study by Mitsuhashi et al[40] the improvement of abnormal metabolic conditions in patients was found to directly or indirectly enhance the endometrium's proliferative state. The addition of metformin significantly reduced the recurrence rate in EAH/EEC patients undergoing fertility-preserving therapy, from 86.5% to 26%. In another study by Mitsuhashi,[41] 36 patients with EH were included, of whom 27 had a BMI of ≥25 kg/m^2 (mean: 31 kg/m^2, range 19–51 kg/m^2) and 24 had an insulin resistance index of ≥2.5. The CR rate was 80.56% among those treated with MPA combined with metformin. A meta-analysis by Cinthia G. et al[39] also confirmed that adding metformin to progesterone therapy for EAH patients significantly contributes to the reversal of EAH to a normal endometrial state.

Matsuo et al[42] found that the use of LNG-IUS combined with metformin resulted in a higher CR rate in predominantly patients with obesity and EAH. Additionally, a prospective cohort study[43] showed a CR rate of 75% (6/8) in patients with EAH treated with metformin and oral MA, compared with a 25% (2/8) response rate with those treated with MA alone.

In an estrogen-induced EH model in rats, metformin's anti-proliferative effects were found to be comparable to those of MPA. Both MPA and metformin significantly reduced the rate of endometrial cell proliferation and hyperplasia.[44] A clinical trial[45] demonstrated that patients with EH/EEC treated with metformin alone had a reversal rate of 95.5% (21/22) compared with 61.9% (13/21) in patients treated with MPA alone. These findings suggest that metformin can serve as an effective alternative therapy for EH. In another randomized clinical trial, Sharifzadeh et al[46] examined 42 patients with SH. After 12 weeks, the cure rate was 81.8% (18/22) in the metformin + MPA group and 60% (12/20) in the MPA-only group, though the difference was not statistically significant ($p = 0.11$). Further supporting metformin's efficacy, a double-blind, placebo-controlled trial[47] involving 60 patients with EH compared the effects of megestrol alone versus megestrol combined with metformin. All patients were treated with megestrol acetate (40 mg once daily, 14 days a month) and divided into a treatment group (metformin 1000 mg daily) and a placebo group (two placebos daily). After 3 months, the CR rate in the metformin group was 93.1%, significantly higher than the 70.4% observed in the placebo group ($p = 0.028$). Additionally, the treatment group showed greater reductions in BMI and blood glucose levels ($p <$

0.001). In a randomized controlled trial by Ramya et al[48] 51 patients with EH were treated with either metformin combined with LNG-IUS or LNG-IUS alone for six months. The CR rate was 100% in the metformin + LNG-IUS group and 95.45% in the LNG-IUS-only group, with no significant difference between the two groups ($p = 0.478$). However, the metformin group exhibited a significantly greater reduction in BMI (mean decrease of 0.63 kg/m^2, $p = 0.023$), suggesting that metformin enhances treatment response in patients with obesity. Yates et al[49] found that metformin use was associated with preventing weight gain and inducing weight loss, making progestins combined with metformin a potentially beneficial strategy in the comprehensive management of EH.

In our study, the metformin group showed significantly greater improvement in AUB symptoms and ultrasound findings than the non-metformin group. The combination of progestins with metformin significantly increased the reversal rate of EH compared with progestin-only treatment. The reversal rate was notably higher in the metformin group than in the non-metformin group, suggesting that regular use of metformin acts as a protective factor in EH treatment. Furthermore, the protective effect of metformin was more pronounced with prolonged use. By the end of the study, there were 17 cases of recurrence (2 patients with EAH and 15 patients with EH). No risk factors were identified for EH recurrence, which could be due to the small number of recurrent cases.

There is growing evidence that insulin resistance plays a key role in the pathogenesis of PCOS and is closely associated with EH. Thus, insulin-sensitizing agents such as the combination of metformin and pioglitazone are more effective than metformin alone in reducing insulin resistance and managing blood glucose levels in patients with PCOS, as demonstrated in two randomized controlled trials.[50,51] Further research is required to explore the potential benefits of combining metformin with pioglitazone in the treatment of EH.

EH is often accompanied by metabolic abnormalities, including obesity and insulin resistance. The imbalance in estrogen and progesterone secretion not only affects systemic metabolic status but is also influenced by it. Therefore, a treatment approach combining weight loss and metformin, in addition to progestin therapy, is advantageous for improving the prognosis of EH and EAH. Moreover, ultrasonographic markers, including endometrial uniformity, Doppler flow patterns, and the presence of AUB, are effective predictors for EH and cancer. As such, regular ultrasound monitoring in patients with EH is essential.[52]

Ethics Approval and Consent to Participate

This study adheres to the principles outlined in the Declaration of Helsinki, ensuring the protection of patient privacy and confidentiality. The studies involving human participants were reviewed and approved by The Committee for Medical Research Ethics at Tianjin Medical University General Hospital (Ethical No. IRB2023-WZ-003). The patients provided their written informed consent to participate in this study. Written informed consent was obtained from the individuals for the publication of any potentially identifiable images or data included in this article.

Data Sharing Statement

Data are available from the corresponding author upon reasonable request.

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Author Contributions

All authors made a significant contribution to the reported work from its conception, designing, execution, data acquisition, analysis, and interpretation; all authors participated in drafting, revising, or critically reviewing the article; gave their final approval of the version to be published; have agreed on the journal to which the article has been submitted; agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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