

Evaluation of the Effect of Additive Metformin to Progesterone on Patients With Endometrial Hyperplasia

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Abstract

Background and Objectives: Endometrial hyperplasia (EH) is an abnormal overgrowth of endometrium that may lead to endometrial cancer, especially when accompanied by atypia. The treatment of EH is challenging, and previous studies report conflicting results. Metformin (dimethyl biguanide) is an anti-diabetic and insulin sensitizer agent, which is supposed to have antiproliferative and anticancer effects and the potential to decrease cell growth in endometrium. While some studies have evaluated the anticancer effect of metformin, studies on its potential effect on EH are rare. To address this gap, in this comparative trial study, we evaluate the effect of additive metformin to progesterone in patients with EH.

Methods: In this clinical trial, 64 women with EH were randomized in two groups. The progesterone-alone group received progesterone 20 mg daily (14 days/month, from the 14th menstrual day) based on the type of hyperplasia, and the progesterone-metformin group received metformin 1000 mg/d for 3 months in addition to progesterone. Duration of bleeding, hyperplasia, body mass index (BMI), and blood sugar (BS) of the patients were then compared between the two groups.

Findings: Mean age of 44.5 years, mean BMI of 29 kg/m² and mean duration of bleeding of 8 days were calculated for the study sample. There was no significant difference in age, BMI, gravidity, bleeding duration, and duration of disease at baseline between the two groups. While all patients in the progesterone-metformin group showed bleeding and hyperplasia improvement, only 69% of the progesterone-alone patients showed such an improvement, with the difference between the two groups being significant ($P=.001$). Although the difference between two groups in the posttreatment endometrial thickness was not significant ($P=.55$), posttreatment BMI in the progesterone-metformin group was significantly lower than in the progesterone-alone group ($P=.01$). In addition, the BS reduction in the progesterone-metformin group was significantly larger than that in the progesterone-alone group ($P=.001$).

Conclusions: Our results indicated that administration of progesterone 20 mg/d plus metformin 1000 mg/d can significantly decrease bleeding duration, hyperplasia, BMI, and BS in women with EH.

Keywords: Endometrial hyperplasia, Metformin, Progesterone

Background and Objectives

Endometrial hyperplasia (EH) is an abnormal overgrowth of endometrium that may lead to endometrial cancer, especially when accompanied by atypia.¹ Although the effect appears only in 5% of asymptomatic patients, its prevalence in patients with polycystic ovarian syndrome (PCOS) and oligomenorrhea is about 20%.² Body mass index (BMI) and nulliparity

are two main risk factors for EH. Other risk factors include chronic anovulation, early menarche, late onset of menopause and diabetes,³ which are related to increased circulating estrogen.⁴ The treatment of EH is challenging and previous studies report conflicting results.⁵ Age, fertility, and severity of EH in histology are the most important factors determining the treatment option.⁵ Most studies have addressed hysterectomy in patients with atypical EH,⁵ particularly those with PCOS, and have led to conflicting results.⁵⁻¹¹ Metformin (dimethyl biguanide) is an anti-diabetic and insulin sensitizer agent that is used in type-2 diabetes to decrease the activity of gluconeogenesis pathway.

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It has been practiced in patients with PCOS due to the associated insulin resistance. Metformin is proposed to have anti-proliferative and anticancer effects and to decrease cell growth in endometrium.¹²⁻¹⁴ While several studies have evaluated the anticancer effect of metformin, investigations of the effect of metformin on EH are rare.¹⁴⁻¹⁶ To address this gap, this comparative trial attempts to evaluate the effect of additive metformin to progesterone in patients with EH.

Methods

In this clinical trial (registration number in the Iranian Registry of Clinical Trial: IRCT2014082018866N1), 64 women with EH proved by hysteroscopy referring to Arash Women's hospital from 2013 to 2014 were recruited. The criteria for enrollment were: age higher than 18 and less than 75 years, EH in biopsy, lack of contraindication for metformin intake, creatinine clearance > 90, and Hb > 10. Exclusion criteria were metformin intake in the last 6 months, hepatorenal diseases, blood sugar (BS) higher than 200 and lower than 65, alcohol consumption, vitamin B12 malabsorption, pregnancy, history of insulin injection and BMI < 25. The blood samples were taken, and the level of complete blood count (CBC), platelets (PLT), creatinine (Cr), blood urea nitrogen (BUN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) was measured. Fasting blood sugar (FBS) was also assessed after 12 hours fasting. The enrolled patients were randomized in two groups. The first group was set to receive 20 mg/d progesterone for 14 days of a month for 3 months (progesterone-alone group, n = 32) and the second group was set to receive metformin in addition to progesterone for three months (1000 mg during the first month and 2000 mg for the remaining two months) (progesterone-metformin group, n = 32). At the end of the study, the bleeding duration, BMI, CBC, PLT and hepatorenal indices were measured again and hysteroscopy was performed for all patients.

Statistical Analyses

Data were analyzed using SPSS version 20 software package. Categorical data are presented as numbers (%), and continuous data as mean (SD). We used the chi-square test to compare the categorical variables, and the Student's *t* test, and the paired *t* test were used to compare the continuous variables. *P* < .05 was considered as statistically significant.

Ethical Issues

The study was approved by the Ethical Committee of

Tehran University of Medical Sciences (TUMS). The participants were briefed on the study purpose and procedure, and their informed written consent was obtained.

Results

Table 1 compares the average age and physiological characteristics among the two study groups. No significant difference in these characteristics was identified between the two groups (Table 1). Response to treatment was defined as bleeding and hyperplasia decrease. All patients in the progesterone-metformin group showed improved bleeding and hyperplasia. In the progesterone-alone group, improving in bleeding and hyperplasia occurred in 22 of 32 and in 23 of 32 patients, respectively; the difference between the two groups was significant (*P* = .001) (Table 2). The difference between two groups regarding endometrium thickness posttreatment was not significant (*P* = .55). However, posttreatment BMI in the progesterone-metformin group was significantly lower than that in the progesterone-alone group (*P* = .01). Additionally, the reduction of BS in the progesterone-metformin group was significantly higher than that in the progesterone-alone group (*P* = .001) (Table 2).

Discussion

The treatment of EH is a major aspect of gynecologic care. In most cases, using progesterone, EH can be effectively treated without the need for surgery.¹⁻⁸ Previous trials have indicated that metformin increases the expression of progesterone receptors in patients with EH.¹⁶ Our study indicated that metformin decreases the duration of bleeding, hyperplasia, BMI, and BS in patients with EH. In line with our findings, Tas et al showed that metformin reduces estrogen-induced EH.¹⁸ Consistently, Wang et al in an experimental study on rats found that metformin increases progesterone receptors' expression and reduces hyperplasia in endometrium.¹⁹ These results agree with those observed by Tan et al in 2011 who demonstrated that 6-month treatment with metformin in patients with EH and PCOS significantly reduces the level of hyperplasia in comparison with the control groups.²⁰ However, the findings of previous reports about the efficacy of metformin in patients with endometrial cancer are conflicting and, generally, inconsistent with our results.²⁰⁻²³

Previous studies have established that obesity and diabetes increase the risk of endometrial cancer.²⁴⁻²⁸ In the present study, we showed that treatment with metformin significantly decreases BMI and BS level. These findings suggest that the possible anticancer

Table 1. Baseline Demographic and Physiological Characteristics the Study Groups

Variable	Progesterone-Metformin Group		Progesterone-Alone Group		P Value
	Mean	SD	Mean	SD	
Age	45.31	5.47	44.32	25.25	0.92
Gravidity	2.25	1.34	2.35	1.22	0.55
Bleeding (day)	18.16	6.27	18.66	5.18	0.73
Duration (month)	2.76	0.97	3.03	0.93	0.27
BMI	28.76	1.68	29.21	1.56	0.31
AST	87.81	5.77	60.91	5.56	0.84
ALT	17.71	5.95	69.71	5.78	0.86
BUN	12.18	2.29	12.34	2.26	0.78
Cr	0.72	0.12	0.73	0.12	0.84
WBC	6447.18	2309.39	67.39.75	2058.33	0.52
Hb	11.20	1.21	11.311	1.23	0.72
PLT	237750.0	7599.49	237906.30	7586.29	0.99

Abbreviations: BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; WBC, white blood cell; Hb, *hemoglobin*; PLT, platelets.

Table 2. Comparison of Bleeding, Hyperplasia, Endometrium Thickening, MI and BS After Treatment Between the Two Study Groups

Variable	Progesterone-Metformin Group		Progesterone-Alone Group		P Value
	Mean	SD	Mean	SD	
Bleeding improvement	32		22	68.5	0.001
Hyperplasia decreasing	32		23	70.5	0.001
Endometrium thickening (after)	6.25	2.48	7.01	2.36	0.55
BMI	28.26	1.83	29.29	1.47	0.01
BS	115.03	16.11	124.12	19.92	0.04

Abbreviations: BMI, body mass index; BS, blood sugar.

effect of metformin may be modulated by reduction of weight and improving menstrual cycles, both of which being the major risk factors of endometrial cancer.

Study Limitations

This uncontrolled comparative study compared the impact of progesterone-alone and progesterone-metformin in a small sample of EH women without a control group. Therefore, our study could not conform the notion that metformin is true disease modifier due to lack of control group. On the other hand, conduction of such controlled trials in patients with bleeding and

hyperplasia is restricted by moral and ethical issues. In addition, short duration of follow-up (3 months) in the present study limits our ability to evaluate the possible long-term effect of metformin in EH patients. Further investigations are recommended with longer follow-ups and larger series to validate the findings reported here. Finally, there is a necessity for more trials considering the role of metformin in reduction of EH risk in patients with PCOS.

Conclusions

Our results indicated that administration of progester-

one 20 mg/d plus metformin 1000 mg/d can significantly decrease bleeding duration, hyperplasia, BMI and BS in women with EH.

Competing Interests

The authors declare that they have no competing interest.

Authors' Contributions

AT made the major contribution to designing the study and drafting the manuscript. NZ took part in analyzing the data and revising the manuscript. AS was involved in interpretation of the pathologic data. SP and FA contributed to collection of data and drafting manuscript. All authors read and revised the final manuscript.

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