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Progestin versus Metformin and Progestin in Treatment of Endometrial Hyperplasia without Atypia in premenopausal women

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ORIGINAL ARTICLE

Progestin Versus Metformin and Progestin in Treatment of Premenopausal Endometrial Hyperplasia Without Atypia

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Abstract

Background: **Endometrial hyperplasia (EH) is a probable precursor to endometrial cancer and a main cause of severe abnormal bleeding. Recently, metformin has been proposed as an adjunctive medicine for improved outcomes in treating EH. Metformin has been shown to have anticancer efficacy by reducing cell proliferation and slowing tumor growth, according to recent studies.**

Aim and objectives: **To compare between progestin versus metformin and progestin in the treatment of EH without atypia in premenopausal females.**

Patients and methods: **This comparative randomized controlled experiment was conducted at Al-Hussein University Hospital, obstetrics and gynecology department on 60 premenopausal women diagnosed by EH without atypia divided into two groups: (group 1); including 30 women took progestin for 6 months then endometrial biopsy was taken after treatment, (group 2); included 30 women took metformin and progestin for 6 months then endometrial biopsy was taken after treatment.**

Results: **Both the ET results after treatment and the Pathology results both before and after therapy, were significantly different among the two groups. There was no significant difference between both groups as regard age distribution, parity distribution, Sonographic Endometrial Thickness (mm) before treatment, and blood sugar before and after treatment.**

Conclusion: **According to our results, we found that Metformin in combination with a progestin has better effects in treating EH more than progestin alone with less adverse effects. Further studies are needed to confirm our results.**

Keywords: Atypia, Endometrial hyperplasia, Metformin, Premenopausal women, Progestin

1. Introduction

Unopposed estrogen actions on endometrial cells can lead to endometrial hyperplasia, which in turn can lead to severe abnormal uterine bleeding (AUB) and, eventually, endometrial cancer. Diabetes is always found in conjunction with endometrial hyperplasia (EH) and cancer,[1] women with diabetes are three to four times as likely to get endometrial cancer.[2] In addition, research has linked insulin resistance to endometrial cancer.[2,3]

EH describes a range of atypical morphological changes, the most prominent of which is an increased gland-to-stroma ratio in comparison to proliferating-phase endometrium.[4]

Polycystic ovarian syndrome, diabetes, obesity, and metabolic syndrome are just a few of the many conditions that might stimulate endometrial cell proliferation.[5]

The primary line of treatment for EH and malignancy is progestogens. Progestogens' primary method of action is to inhibit the proliferation of endometrial cells caused by estradiol. Adding progesterone to estrogen replacement therapy has been shown to lower, and in some cases completely eliminate, the risk of endometrial cancer (EC),

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which is why progestogens are also used for this purpose.[6]

Metformin, an oral anti-diabetic drug and biguanide that helps relieve many symptoms of PCOS in women, including AUB, is now recognized as safe and effective by the FDA.[7]

The aim of this work was to compare between progestin versus metformin and progestin in treatment of EH without atypia in premenopausal females.

2. Patient and methods

This comparative randomized controlled experiment was conducted at Al-Hussein University Hospital, obstetrics and gynecology department with consent from the hospital's ethics board. The time frame for this investigation was from June 1st, 2022, to December 31st, 2022, a total of 6 months.

Hysteroscopic guided biopsy revealed a tissue diagnosis of disordered proliferative endometrial (DPE) or simple hyperplasia (SH) in premenopausal women admitted for abnormal uterine hemorrhage at gynecological clinics and emergency rooms. Inclusion and exclusion criteria had been used to select patients.

2.1. Sample size

Totally 60 premenopausal women diagnosed by EH without atypia had been selected for this study.

This study base on a study carried out by Wang et al.[8] was used to calculate the sample size by considering the following assumptions: 95 % two-sided confidence level, with a power of 80 %. and α error of 5 %. The final maximum sample size taken from the output was 58. Thus, the sample size was increased to 60 patients to assume any dropout cases during follow-up.

$$\left(\frac{Z_{a/2}+Z_B}{P_1-P_2}\right)^2 (p_1q_1+p_2q_2)$$

(Takazawa and Morita[9]).

n = sample size

Z a/2 (The critical value that divides the central 95 % of the Z distribution)

ZB (The critical value that divides the central 20 % of the Z distribution)

p1 = Accuracy prevalence in TCD group

p2 = Accuracy prevalence in FL group

We classified patients in this study into two groups: first group: this group includes 30 women took progestin (Mirena IUD) for 6 months then endometrial biopsy was taken after treatment and second group: this group includes 30 women took metformin (Glucophage 500) twice daily orally and progestin (Mirena IUD) for 6 months then endometrial biopsy was taken after treatment. The idea of the study has been explained to the women who were included and their informed consent had been obtained before inclusion in this study.

2.2. Ethical committee

All patients provided informed consents after the study was approved by the ethics committee at the Faculty of Medicine at Al-Azhar University and after they were informed of the study's purpose, their treatment options, any potential adverse effects, and their right to withdraw from the study at any time.

2.3. Inclusion criteria for patients in this study

Pathological examination of endometrial tissues, which may have been obtained via hysteroscopic guided biopsy, demonstrates hyperplasia without atypia in women before menopause.

2.4. Exclusion criteria for patients in this study

Pregnant women, Medical disorder e.g. hypertension (HTN), heart diseases or renal disorders, Type II Diabetes Mellitus, those with a history of genital neoplasia, oral contraceptive use, a hypersensitivity to metformin, or intolerance to metformin or progesterone.

All patients will be subjected to the following to detect the inclusion and exclusion criteria: Full history taking, Physical examination (general examination, Abdominal examination and Pelvic examination), Ultrasonography study, Laboratory Investigations and Endometrial Biopsy.

2.5. Pathological findings

Both EH types that do not involve atypia-simple and complex-are common.

2.6. Statistical analysis and data interpretation

Data entered into the computer was analyzed using IBM's SPSS version 22.0. Qualitative data was expressed as numbers and percentages. The Kolmogorov-Smirnov test was used to determine whether or not the data were normally distributed, and then the median (minimum and maximum) and interquartile range were used to summarize nonparametric data, while the mean and standard deviation were used to summarize parametric data.

At the level of significance (0.05), the data obtained was accepted as reliable.

3. Results

Table 1.

This table shows that the mean age in Progestin group was 42.2 ± 2.4, in Metformin and Progestin group was 42.5 ± 2.7. There was insignificant difference between both groups as regard age (Table 2).

This table shows that the mean Parity in Progestin group was 3.3 ± 0.82, in Metformin and Progestin group was 3.1 ± 0.75. There was insignificant difference between both groups as regard Parity (Table 3).

This table shows that the mean Sonographic Endometrial Thickness (mm) in Progestin group was 15.98 ± 5.4, in Metformin and Progestin group was 15.69 ± 5.1. There was insignificant difference between both groups as regard Sonographic Endometrial Thickness (mm) (Table 4).

This table shows that in Progestin group, 26.66 % had Simple hyperplasia before treatment, 73.33 % had Complex EH (without atypia). After treatment Progestin group, 83.33 % develop regression, 10 % were persistent and 6.66 % become progressive. In Metformin and Progestin group, 33.33 % had Simple hyperplasia before treatment, 66.66 % had Complex EH (without atypia). After treatment in Metformin and Progestin group, 90 % develop regression, 6.66 % were persistent and 3.33 % become progressive. Despite of decreased the number of patients with C.H after treatment than before treatment in both groups but there was no significant difference between before and after treatment as regard the treatment regimen (Table 5).

This table shows that in Progestin group, 73.33 % had blood sugar before treatment less than 126 mg/dl, 20 % had 126–200 mg/dl, 6.66 % greater than 200 mg/dl. In Progestin group, 80 % had blood sugar after treatment less than 126 mg/dl, 13.33 % had 126–200 mg/dl, 6.66 % greater than 200 mg/dl. In Metformin and Progestin group, 80 % had blood sugar after treatment less than 126 mg/dl, 13.33 % had 126–200 mg/dl, 6.66 % greater than 200 mg/dl. In Metformin and Progestin group, 93.33 % had blood sugar after treatment less than 126 mg/dl, 6.66 % had 126–200 mg/dl. There was no significant difference among both groups according to blood sugar before and after treatment (Table 6).

Table 1. Age distribution among studied groups.

Age, years	Group	Min.	Max.	Mean ± SD	T test	*P* value
	Progestin (No. = 30)	40	50	42.2 ± 2.4	1.26	0.66
	Metformin and Progestin (No. = 30)	40	50	42.5 ± 2.7		

Table 2. Parity distribution among studied groups.

Parity	Group	Min.	Max.	Mean ± SD	T test	*P* value
	Progestin (No. = 30)	1	5	3.3 ± 0.82	1.19	0.74
	Metformin and Progestin (No. = 30)	1	5	3.1 ± 0.75		

Table 3. Sonographic endometrial thickness (mm) before treatment among studied groups.

Sonographic Endometrial Thickness (mm)	Group	Min.	Max.	Mean ± SD	T test	*P* value
	Progestin (No. = 30)	10	20	15.98 ± 5.4	1.93	0.22
	Metformin and Progestin (No. = 30)	10	20	15.69 ± 5.1		

Table 4. Pathology before and after treatment among studied groups.

	Progestin (No. = 30)	Metformin and Progestin (No. = 30)	Chi square test
Before treatment	**No (%)**	**No (%)**	***P*-value**
S.H	8 (26.66 %)	10 (33.33 %)	**0.573**
C.H	22 (73.33 %)	20 (66.66 %)	
After treatment	**No (%)**	**No (%)**	***P*-value**
Regression	25 (83.33 %)	27 (90 %)	**0.543**
Persistent	3 (10 %)	2 (6.66 %)	
Progression	2 (6.66 %)	1 (3.33 %)	

Complex endometrial hyperplasia (without atypia) (CH); Simple hyperplasia (S.H).

Table 5. Blood sugar before and after treatment among studied groups.

	Group	<126 mg/dl No (%)	126–200 mg/dl No (%)	>200 mg/dl No (%)	T test	*P* value
BS before treatment	Progestin (No. = 30)	22 (73.33 %)	6 (20 %)	2 (6.66 %)	0.2	0.88
	Metformin and Progestin (No. = 30)	24 (80 %)	4 (13.33 %)	2 (6.66 %)		
BS after treatment	Progestin (No. = 30)	24 (80 %)	4 (13.33 %)	2 (6.66 %)	1.4	0.47
	Metformin and Progestin (No. = 30)	28 (93.33 %)	2 (6.66 %)	0		
P bet. Before 2 groups after treatment	0.47					

Table 6. Outcomes of studied groups.

	Progestin (No. = 30)	Metformin and progestin (No. = 30)	T test	*P*
AUB before treatment				
Heavy	30 (100 %)	30 (100 %)	–	–
AUB after treatment				
Heavy	6 (20 %)	3 (10 %)	1.176	0.278
Controlled	24 (80 %)	27 (90 %)		
ET before treatment Mean ± SD	15.98 ± 5.4	15.69 ± 5.1	1.12	0.83
ET after treatment Mean ± SD	11.21 ± 4.01	10.01 ± 2.1	3.67	**0.02**
Hysterectomy	4 (13.33 %)	1 (3.33 %)	1.96	0.161

AUB, Uterine bleeding; ET, Endometrial thickness.

This table shows that in Progestin group, 100 % had heavy AUB before treatment, 20 % had heavy AUB after treatment, 80 % had controlled AUB after treatment. ET before was 15.98 ± 5.4, ET after was 11.21 ± 4.01, 13.33 % had Hysterectomy. In Metformin and Progestin group, 100 % had heavy AUB before treatment, 10 % had heavy AUB after treatment, 90.0 % had Controlled AUB after treatment. ET before was 15.69 ± 5.1, ET after was 10.01 ± 2.1, 3.33 % had Hysterectomy. There was significant difference among both groups as regard ET after treatment.

4. Discussion

When the endometrial glands multiply uncontrollably, this is called endometrial hyperplasia. It is caused by an inadequate amount of progesterone to counteract the effects of excess estrogen on the endometrial tissue. Several disorders, from those involving excess endogenous estrogen to those involving exogenous estrogen, exhibit this hormonal discord.[10]

The main results of this study were as follows:

As regard demographic data of the studied patients, the mean age in Progestin group was 42.2 ± 2.4, in Metformin and Progestin group was 42.5 ± 2.7. There were insignificant difference between both groups as regard age.

This study contradicted a previous one by Tehranian and colleagues which looked at 60 women with EH and no atypia. Their mean age was 44.85 ± 6.80 in metformin and megestrol group and 43.16 ± 6.08 in megesterol group.[11]

When comparing 42 cases of histopathologically verified simple EH without atypia, the current study contradicted Sharifzadeh and colleagues. The mean age was 46.32 ± 6.27 in metformin group and 43.05 ± 7.68 in megestrol group.[12]

In our study, the mean BMI in Progestin group was 31.15 ± 3.2, in Metformin and Progestin group was 31.14 ± 2.3. There was insignificant difference among both groups as regards BMI. In our study the mean BMI in metformin group was 27.106 ± 3.21 and in Megestrol group was 28.174 ± 4.14.

This was in line with Hussein and colleagues study, in which the mean BMI in metformin group was 34.03 and in Progesterone group was 32.85. There was insignificant difference between both groups in both studies.[13]

There was no statistically significant change in blood sugar levels before and after therapy in the current study.

This was in line with Tabrizi and colleagues study, in which there was no significance difference in blood sugar before and after treatment with metformin and megesterol.[5]

Hussein and colleagues study was supported by these findings; prior to therapy, the majority of those who were tested (82 % in the metformin

group and 86 % in the progesterone group) had blood sugar levels of less than 126 mg/dl. There was no statistically significant difference among the two therapy groups in terms of the percentage of patients whose blood sugar levels dropped to below 126 mg/dl after either metformin or progesterone.[13]

In our study, in progestin group, 26.66 % had Simple hyperplasia before treatment, 73.33 % had Complex EH (without atypia). In Progestin group, 66.66 % had Simple hyperplasia after treatment, 33.33 % had Complex EH (without atypia). In Metformin and Progestin group, 33.33 % had Simple hyperplasia before treatment, 66.66 % had Complex EH (without atypia). In Metformin and Progestin group, 80 % had Simple hyperplasia after treatment, 20 % had Complex EH (without atypia). There was high significant difference among before and after treatment as regard Pathology in each group. This indicate that use of metformin and progestin together is more effective than use than progestin alone in treatment of complex EH (without atypia) and Simple hyperplasia.

Session et al. found that metformin was effective in treating a case of atypical EH that had not responded to progesterone. Metformin was offered as an adjuvant medication for the treatment of endometrial hyperplasia, and a month after treatment began, the endometrial biopsy was transformed to proliferative endometrium.[1]

Regarding sonographic Endometrial Thickness, we found that the mean Sonographic Endometrial Thickness (mm) in Progestin group was 15.98 ± 5.4, in Metformin and Progestin group was 15.69 ± 5.1. There was insignificant difference between both groups as regard Sonographic Endometrial Thickness (mm).

This was consistent with the findings of the study by Hussein et al., which found no significant difference in post-treatment uterine bleeding ($P = 0.47$), or post-treatment endometrial thickness ($P = 0.706$), among the two groups. Regarding hysterectomy, there was again little to no difference in patient satisfaction among the two groups. There was no discernible difference in treatment duration among the two groups.[13]

According to outcomes of studied groups of our study, we found that in Progestin group, 100 % had heavy AUB before treatment, 20 % had heavy AUB after treatment, 80 % had Controlled AUB after treatment. ET before was 15.98 ± 5.4, ET after was 11.21 ± 4.01, 13.33 % had Hysterectomy. In Metformin and Progestin group, 100 % had heavy AUB before treatment, 10 % had heavy AUB after treatment, 90.0 % had Controlled AUB after treatment. ET before was 15.69 ± 5.1, ET after was 10.01 ± 2.1, 3.33 % had Hysterectomy.

Our results matched those of Shan and colleagues who also discovered a higher CR rate in the MET group (75 %) than in the MA group (25 %), and who also discovered that the CR rate was similar to the resolution rate (~70 %) with different doses of MPA (500–1000 mg/day or MA at 80–400 mg/day), but that the resolution time was shorter (3 months vs. 6–18 months).[14]

4.1. Conclusion

Our results showed that Metformin in combination with a progestin has better effects in treating EH more than progestin alone with less adverse effects. Further studies are needed to confirm our results.

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Authorship

All authors have a substantial contribution to the article.

Conflicts of interest

The authors declared that there were NO conflicts of Interest.

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