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ORIGINAL ARTICLE

Comparative study about the use of Metformin Versus Progesterone as a treatment in cases of Simple Endometrial Hyperplasia without atypia

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Abstract

Background: ***In endometrial hyperplasia (EH), the tissue of the endometrium is stimulated estrogenically without progesterone's counterbalancing behaviors, leading to an abnormal growth of endometrial glands. Metformin, a biguanide, is used widely as a first-line pharmacological treatment in cases with type 2 diabetes.***

Aim and Objectives: ***To compare the metformin effects & progesterone on simple endometrial hyperplasia without atypia in order to determine if Metformin is clinically efficient in these conditions.***

Patients and methods: ***This is a cohort prospective research that included a total of (60) women who have perimenopausal bleeding with histopathologically confirmed simple endometrial hyperplasia without atypia by D&C at the Department of Gynecology & obstetrics at Al-Zahra University Hospital Al Azhar university hospital from January 2022 to July 2023. All cases were split into two equal groups (thirty cases each): progesterone group (A) received progesterone 10mg twice per day for three months. Metformin group (B) received metformin 500mg twice per day for three months.***

Results: ***There is no statistical significance between both groups in relation to age, parity, BMI, medical diseases, abortion, previous CS, and endometrial thickness before treatment. There is a statistical significance among group A (progesterone) & group B (Metformin), rendering to bleeding time, clinical improvement after treatment, pathological changes after treatment, and success rate after treatment.***

Conclusion: ***Metformin and progesterone were effective & safe in the cure of endometrial hyperplasia without atypia.***

Keywords: Metformin; Progesterone; Simple endometrial hyperplasia; Endometrial atypia

1. Introduction

EH is an abnormal growth of endometrial glands caused by an imbalance between progesterone & estrogen, which leads to unopposed estrogenic stimulation of the endometrial tissue. It's a possible precursor to endometrial malignancy & a major cause of really abnormal bleeds from the vagina. [1]

When estrogen levels are high & progesterone levels are low, endometrial hyperplasia develops. Obesity, estrogen-secreting ovarian tumors, perimenopause, PCOS, & anovulatory cycles are the most common reasons for an excess of estrogen produced internally. Tamoxifen, which is utilized to treat breast cancer, hormone replacement therapy (HRT), & unopposed estrogen therapy are examples of external causes. [2]

Older age or postmenopausal status, infertility, early menarche or delayed menopause, menopausal transition, anovulation, tamoxifen use, polycystic ovarian syndrome, obesity, diabetes, hypertension, or Lynch syndrome are all factors that increase the risk of endometrial hyperplasia. [3]

The most popular method for treating EH without atypia is progesterone medication, which inhibits estrogen-mediated cell proliferation & encourages cellular separation. Controlling symptoms & preventing the development of EH are the main goals of therapeutic therapies in these situations. The anticancer effects of progesterone are brought about by its binding to atomic receptors & the activation of the interpretation of a few features correlated with cross-convergence with other signaling pathways, such as those involving development factors & their receptors. [4]

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Metformin, a biguanide used widely as a 1st-line pharmacological cure in cases with type 2 DM, polycystic ovarian disease, & insulin resistance. It has an anti-invasive, anti-proliferative, anti-metastatic & anti-estrogenic effect on the endometrium, acting by the activation of AMP-activated protein kinase in muscle, adipose tissue, and liver. [5]

However, it's not well known if its effects on endometrial tissues, or these effects may include PI3K/AKT signaling-mediated activities that might be useful in the cure of endometrial hyperplasia. In vitro, Metformin induces progesterone receptors in endometrium which may inhibit the attack of human endometrial cancer cells. [6]

In this research, we aimed to examine the effects of progesterone & Metformin on simple endometrial hyperplasia without atypia. We wanted to know whether Metformin is clinically useful for these kinds of conditions.

2. Patients and methods

This was a cohort prospective research that included a total of (60) women who have perimenopausal bleeding with simple endometrial hyperplasia without atypia by D&C at the Department of Gynecology & obstetrics at Al-Zahraa University Hospital, Al Azhar University Hospital from January 2022 to July 2023.

Inclusion criteria: Women with perimenopausal bleeding from the age of 40 to 55 years old and have simple endometrial hyperplasia without atypia by endometrial sampling with high BMI >28.

Exclusion criteria: Hypersensitivity to metformin or progesterone, Intolerance to progesterone or Metformin, Known hepatic or renal disorders, Diabetic patient type1 or 2, Patient with hypoglycemia <60 mg/dl, Patients with atypical endometrial hyperplasia and other gynecologic neoplastic disorders.

All subjects were randomly split into two groups: Progesterone group (A): thirty women who received progesterone 10mg twice per day for three months. &Metformin Group (B): thirty females who received Metformin 500mg twice per day for 3 months.

At the end of the duration of the treatment, endometrial sampling was conducted to evaluate the endometrium pathological changes for both groups.

Sample size estimation.

The statistical calculator MedCalc® version 12.3.0.0 "Ostend, Belgium" was utilized to estimate the sample size, ninety-five percent confidence interval, & power of the study (eighty percent with a five percent α error). A prior investigation conducted byTehranian et al.[7] demonstrated that all individuals assigned to the progesterone-metformin group received a reduction in hyperplasia & hemorrhage, whereas 68.5 percent of those assigned to the progesterone-alone group did the same. This distinction among both groups was statistically significant (P=.001). Therefore, it can be inferred that the sample size for the present investigation was computed using these values; a minimum of forty cases (twenty cases in each group) was sufficient to detect the variation in question.

Methods

Following the ethics committee's approval, written informed consent was obtained from every case, & a selected group of cases were following that exposed to Full history taking (Personal history, History of present illness, Menstrual history, Obstetric history, Past medical and family history & surgical history), Full general examination, Abdominal and vaginal examination, Ultrasound examination by Versana essential ultrasound (endometrial thickness). Routine lab investigation, pre-operative preparation, anesthesia approval, and D&C to demonstrate the type of hyperplasia of the endometrium.

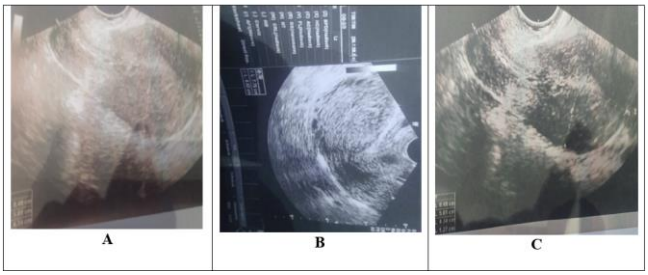

Figure 1. Showed ultrasound images of hyperplasia lesions when the endometrium measures A) 13mm B) 12 mm, and C) 12.7 mm.

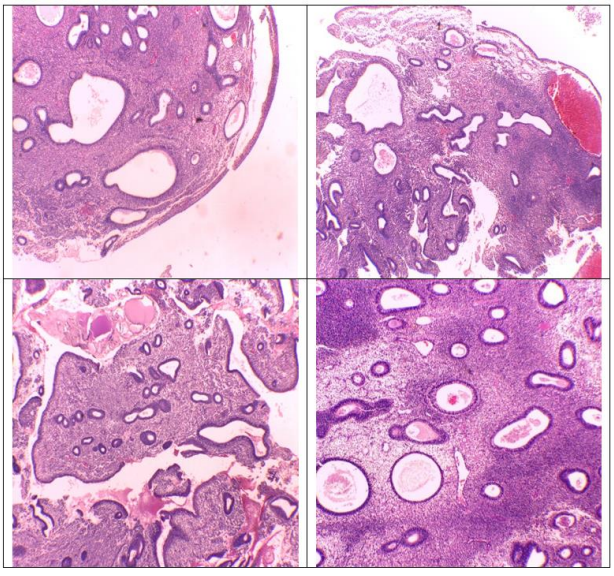

Figure 2. Showed Simple endometrial hyperplasia without atypia.

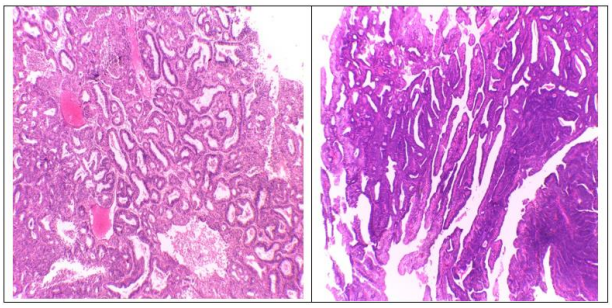

Figure 3. Showed Complex hyperplasia without atypia.

Statistics analysis: The Statistical Package for Social Science (IBM SPSS) version 24 was used when the data were gathered, reviewed, & coded before being loaded into the program. In cases where the distribution of the quantitative data was found to be parametric, the data were provided as mean, standard deviation, & ranges. In cases where the distribution was found to be nonparametric, the data were presented as median with inter-quartile range (IQR). Quantitative & percentage-based representations of qualitative data were also included.

3. Results

Table 1. Demographic data in both groups.

VARIABLE	GROUP A (N= 30)	GROUP B (N= 30)	P. VALUE
	Mean ± SD	Mean±SD	
AGE (37–53 YEARS)	46.17±4.43	45.12±4.19	4.286(NS)
PARITY	3.57±1.13	3.80±1.09	0.457(NS)
BMI (KG/M²)	31.83±1.84	32.70±1.89	0.626(NS)
MEDICAL DISEASES			
FREE	27(71.1%)	27(71.1 %)	0.891(NS)
HTN ON TREATMENT	3 (7.9 %)	2 (5.3 %)	0.732(NS)
DM ON ORAL TREATMENT	0 (0 %)	1 (2.6%)	-
ABORTION	1.60±0.89	2.01±1.22	0.531(NS)
PREVIOUS CS	2.50±0.54	2.33±1.27	0.731(NS)

NS = non-significant (p value> 0.05), S = significant (p value< 0.05),

HS = highly significant (p value< 0.01).

This table showed the comparison among group A (progesterone) & group B (metformin) according to the demographic data which revealed statically no significance between both groups in relation to age, parity, BMI, medical diseases, abortion, and previous CS.

Table 2. Comparison among group A (progesterone) and group B (metformin) as regard to bleeding time.

	GROUP A (N= 30)	GROUP B (N= 30)	P. VALUE
	Mean ±SD	Mean±SD	
BLEEDING TIME	12.23 ± 11.213	14.56 ± 13.721	0.047(S)

This comparison among group A (progesterone) & group B (metformin) according to bleeding time revealed statically significance between both groups and the bleeding time.

Table 3. Comparison among group A (progesterone) and group B (metformin) as regard to the endometrial thickness before treatment.

	GROUP A (N= 30)	GROUP B (N= 30)	P. VALUE
	Mean± SD	Mean± SD	
ENDOMETRIAL THICKNESS (MM)	11.71± 6.143	11.63± 5.113	0.896 (NS)

This table revealed no statically significance among group A (progesterone) & group B (metformin) in regard to endometrial thickness before treatment.

Table 4. comparison among group A (progesterone) and group B (metformin) as regard to complain of the patient after treatment.

	GROUP A (N= 30)		GROUP B (N= 30)		P. VALUE
	N	%	N	%	
IMPROVED	22	73.3%	17	56.7%	0.0421 (S)
NON IMPROVED	8	26.7%	13	43.3%	0.0324 (S)
TOTAL	30	100%	30	100%	

This table revealed that both groups showed a statically significant clinical improvement after treatment but, group A (progesterone) had a clinical improvement after treatment more than group B (metformin).

Table 5. comparison among group A (progesterone) and group B (metformin) as regard to pathological changes after treatment.

	PROGESTERONE GROUP (N= 30)		METFORMIN GROUP (N= 30)		P. VALUE
	N	%	N	%	
SIMPLE EH WITHOUT ATYPIA	11	36.7%	13	43.3%	0.042(S)
DISORDERED PROLIFERATIVE ENDOMETRIUM	19	63.3%	3	10%	0.000(HS)
NORMAL ENDOMETRIUM WITH INFLAMMATORY CHANGES	0	0	14	46.6%	

This table showed the pathological changes after treatment in group A (progesterone) and group B (metformin) which revealed a high statically significant improvement in group A(progesterone) and astatically significant in group B (metformin).

Table 6. Success rate after treatment of the patient by group A (progesterone) and group B (metformin).

	GROUP A (N= 30)		GROUP B (N= 30)		P. VALUE
	N	%	N	%	
SUCCEEDED	19	63.3%	17	56.7%	0.0421 (S)
FAILED	11	36.7%	13	43.3%	0.0342 (S)
TOTAL	30	100%	30	100%	

This table showed that success rate was higher in group A(progesterone) more than group B (metformin) with statically significant less failed cases.

4. Discussion

There have been a lot of studies in the past few years that suggest that Metformin may help lower the risk of endometrial cancer in PCOS patients. It does this by effectively stopping the growth of high-grade endometrial carcinoma cells & even an endometrial serous carcinoma cell line. Progesterone fights cancer by attaching to receptors on nuclei and starting the production of several genes that are involved in crosstalk. [8]

According to demographic data, we find that there wasn't statistical significance among both groups in relation to age, parity, body mass index, medical diseases, abortion, and previous cesarean sections.

Our findings consist of Sharifzadeh et al. Tehranian et al. looked at what megestrol & Metformin did for uterine hyperplasia and compared them. Results showed no statistically significant variations among both groups of women when comparing factors such as age, body mass index, parity, gravidity, & abortion history. [7,9]

According to laboratory investigations there was a statically significant between group (A) progesterone and group (B) metformin and hemoglobin and random blood sugar; on the other hand, there wasn't statically significance between both groups in relation to Platelets, creatine and liver function tests.

Consistent with the present investigation, Hussein et al. have not statically significant in both groups and random blood sugar before and after treatment. [10]

Elgarhy et al. also show no statistically significant variance among both groups and random blood sugar before treatment. [11]

The current study showed that no statistical significance was found between the progesterone group and the metformin group in terms of endometrial thickness before treatment.

This finding is in line with that of Taha et al. who compared the efficacy of Metformin with that of levonorgestrel intrauterine system (LNG-IUS) in reducing endometrial hyperplasia. Fifty cases were split evenly among both groups in their research. cases treated with Metformin were grouped with those treated with levonorgestrel-releasing intrauterine systems. In terms of endometrial thickness prior to treatment, they discovered no statistically significant distinction among the two groups. [12]

According to post-treatment, the current study revealed that both groups had a statically significant clinical improvement after therapy; group (A) progesterone showed a higher statistically significant improvement of complaints compared to group (B) metformin by 73.3% vs. 56.7%, respectively, with ($p<0.05$).

In a study comparing the unique effects of Metformin & progesterone on simple endometrial hyperplasia & disordered proliferative endometrium, Hussein et al. found that Metformin was clinically helpful in this case. The researchers split a hundred cases into two groups & administered Metformin (Glucophage) to Fifty of them in one group & medroxyprogesterone acetate (Provera) to Fifty in the other. In terms of endometrial thickness prior to treatment, they found no statistically significant variations among the groups. [10]

According to post-treatment, our study revealed that both groups showed a statically significant clinical improvement after treatment; the use of progesterone resulted in significantly higher

improvement compared to metformin treatment (73.3% vs. 56.7%, respectively, with p<0.05).

Our study agreed with Taha et al. as it showed that the progesterone intrauterine system succeeded more than Metformin in the treatment of endometrial hyperplasia. There was a significant lower in the endometrial thickness after treatment in both groups (17.65 ± 4.62 & 5.3 ± 2.01 in the progesterone group with a p-value < 0.001) (19.57 ± 6.84 & 11.22 ± 7.51 in the metformin group with a p-value lower than 0.001). [12]

As regard to the pathological changes after receiving treatment demonstrated that there was a higher statically significant improvement in group A (progesterone) more than in group B (Metformin), as in group A (progesterone), 19 cases out of 30 cases were pathologically changed, and 11 cases out of 30 cases failed to change from endometrial hyperplasia without atypia by pathological examination. On the other hand, group B (metformin) showed a change in 17 cases out of 30 cases, and 13 cases out of 30 cases failed to change from endometrial hyperplasia without atypia by pathological examination.

Similar to the study of Ko et al., who demonstrated that 56% (9/16) of patients showed pathologic response after Metformin treatment. [13] The study of Taha et al. reported that significant regression of hyperplasia was noted in the Metformin group among (sixty-four percent) which was higher than our results. [12] Also, the research of Elgarhy et al. showed that among the metformin group, 82% of patients showed positive responses. [11]

Sharifzadeh et al. also showed that 18 women (81.8%) in the metformin group had normal endometrial histology after twelve weeks of treatment.[9] Also, the study of Tabrizi et al. demonstrated that Metformin could induce endometrial atrophy in twenty-one out of twenty-two cases (95.5%). [14]

Regarding success rate, the current study showed that progesterone group have a statically significantly higher success rate compared to metformin group (63.3% vas 56.7% respectively with p=0.042). As well as progesterone group has less failed cases than metformin group (36.7% vas 43.3% respectively with p=0.034).

In line with our study, Taha et al. confirmed the superiority of progesterone in the intrauterine system over Metformin in the treatment of endometrial hyperplasia. Significant regression of hyperplasia was noted in the progesterone group (ninety-six percent) VS (sixty-four percent) in the Metformin group (p-value 0.009). [12]

On the other hand, Hussein et al. discovered that Metformin may work just as well as progesterone in treating simple endometrial hyperplasia; in fact, the two groups showed no significant differences at the endpoints measured by endometrial thickness (P=0.706) & uterine bleeding (p=0.47). When comparing the two groups, there was also little variation in patient satisfaction & hysterectomy incidence. [10]

The current study showed that progesterone resulted in improvement among 73.3% of patients with a 63.3% success rate.

Also, our study is consistent with Sayyah-Melli et al., who reported that among the progesterone group, 95.1% of patients had positive responses.[15]

The current study showed that Metformin resulted in improvement among 56.7% of patients with a 56.7% success rate. Similar to the study of Ko et al., who demonstrated that 56% (9/16) of patients showed pathologic response after Metformin treatment. [13]

the study of Tabrizi et al. demonstrates that Metformin could induce endometrial atrophy in twenty-one out of twenty-two cases (95.5%). [14]

The present study demonstrated that the success rate was greater in group A (progesterone) than in group B (Metformin), with statistically significantly fewer failed cases.

Our study contradicted the results of Shan et al., who looked at how treating uterine hyperplasia with metformin & megestrol acetate together compared to treating it with megestrol acetate alone. The metformin group had a seventy-five percent full reaction rate, while the megestrol group only had a twenty-five percent response rate.[16]

Also, in females detected with atypical endometrial hyperplasia/endometrial carcinoma, the present study contradicted the findings of Acosta-Torres et al., who observed no variation in complete response rates among progestogen-only & progestogen &Metformin groups (69 percent vs 68 percent, p-value 0.90). [17]

4. Conclusion

Metformin has a significant correlation with body mass index and random blood sugar which proves the strong relationship between endometrial hyperplasia and obesity &increase random blood sugar. On the other hand, progesterone has a significant correlation with bleeding time and hemoglobin. The therapy methods are tolerated well by the patients with no complications mentioned.

Both Metformin and progesterone were safe and effective in curing of endometrial hyperplasia with on atypia. The use of progesterone showed better outcome (higher clinical and pathological improvement) compared to Metformin.

We recommend the use of Metformin for patients who have perimenopausal bleeding with

endometrial hyperplasia without atypia, especially in obese patients and patients with high random blood sugar.

Disclosure

The authors have no financial interest to declare in relation to the content of this article.

Authorship

All authors have a substantial contribution to the article

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Conflicts of interest

There are no conflicts of interest.

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