Evaluation of The Effect of Metformin and Progesterone on The Endometrium in Cases of Peri Menopausal Bleeding

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Abstract: Background: Numerous epidemiologic and experimental studies have suggested that unopposed estrogen may be a major factor in the development of benign, premalignant, and malignant endometrial lesions. Objective: To assess the unique effects of progesterone and metformin on simple endometrial hyperplasia and disorganized proliferative endometrium, and to ascertain if metformin is clinically helpful in this situation. Patients and Methods: The study was conducted between April 2023 and September 2023 at the obstetrics and gynecology department of Damanhur Medical National Institute. The study was a double blinded randomized study. 100 patients were involved in this study who were divided into 2 groups: The 1st one (50 cases) was treated with metformin (Glucophage) 500 mg in the first week then raise the dose to reach 1000 mg in the 4th week, for three months long. The 2nd group (50 cases) was administered medroxy progesterone acetate (Provera) 4mg once per day for 3 months long. Next 3 months all cases in both groups were gone for 2nd time endometrial biopsy for assessment of response of treatment and will have ultrasound examination every three months also. Result: Uterine hemorrhage after treatment and endometrial thickness after treatment did not statistically differ between the two study groups. Additionally, there was no statistically significant difference in patient satisfaction or hysterectomy between the two study groups. There was no discernible difference in the two groups' treatment lengths. While there was a high statistical rise in the incidence of nausea, vomiting, and diarrhea in group 2 compared to group 1, there was a strong statistical increase in the incidence of sore breasts, weakness, and metallic taste in group 1 compared to group 2. Conclusion: Progesterone and metformin may both be useful in treating benign endometrial proliferative lesions. To prevent its problems, endometrial proliferative lesions should be identified and treated properly**.**

Keywords: Metformin, Progesterone, Endometrium and Perimenopausal Bleeding.

1. Introduction

It has been theorized that unopposed estrogen has a focal job being developed of endometrial benevolent, premalignant, and threatening sores [1]. Endometrial disease is the most well-known threat of the female genital tract, and the fourth most basic malignancy in ladies in created nations. EC is the seventh most normal disease in ladies worldwide [2].

Endometrial adenocarcinoma is gone by a progression of histopathological change considered endometrial hyperplasia that is amiable to treatment. Endometrial hyperplasia is treated with progesterone and its engineered structure, medroxyprogesterone acetic acid derivation (MPA). MPA can likewise be utilized in cutting edge or recurrent EC, in those cases who wish to save their ripeness [3].

The job of progesterone on the endometrium is essentially to incite cellularly separation and to estrange estrogen intervened cell expansion. The progesterone demonstrates its antitumor impact by authoritative to the atomic receptors, and enacting the interpretation of a few qualities, which are associated with cross converse with other flagging pathways, for example, development factors and their receptors [4].

As of late, an expanding assortment of proof proposes that weight, diabetes, and insulin obstruction are solid hazard factors for EC, and insulin-like development factors (IGFs) assume a noteworthy job in carcinogenesis and malignant growth movement [5]. Besides, it has been demonstrated that insulin receptor quality articulation is managed all through the menstrual cycle of solid ladies, empowering insulin to influence stromal cell decidualization[6].

Considering the connection between endometrial hyperplasia, insulin, and its middle people, insulin sensitizers have turned into the most well-known subject of examination for their antiproliferative impacts [7]. Metformin is an

oral biguanide utilized in diabetes, insulin obstruction, and polycystic ovarian disorder. Ongoing reports demonstrate that metformin may diminish the neoplastic multiplication of cells by means of balancing the glucose metabolism, insulin affectability and intracellular sign pathways [8].

As of late, metformin has been accounted for to hinder the attack of human endometrial carcinoma cells, in vitro [9]. Anovulatory cycles are normal at menarche and menopause and as a rule incite generous endometrial multiplication including disarranged proliferative endometrium and straightforward endometrial hyperplasia without atomic atypia [10].

Drawn out anovulatory cycles due to PCO or other hyper estrogenic states, for example, estrogen discharging tumors frequently lead to expanded endometrial multiplication and cause complex hyperplasia with or without atypia, endometrial polyps, or type I endometrial carcinoma [11]. Although there is no uncertainty respect to job of estrogenic specialists in creating of strange endometrial multiplication, ongoing comprehension of hereditary and sub-atomic premise of endometrial carcinoma led to another phrasing for favorable and genuine premalignant endometrial injury proposed by global gathering of pathologist in 2000.

The present study compared the impact of metformin on confused proliferative endometrium and straightforward endometrial hyperplasia in correlation with progesterone to survey metformin clinical value in these circumstances.

2. PATIENT AND METHODS

The study was conducted between April 2023 and September 2023 at the obstetrics and gynecology department of Damanhur Medical National Institute.

The study was a double blinded randomized study. The study toke 6 months, starting from 1st of April 2023 till 30th of September 2023, 100 patients were involved in this study. This study included all patients who will be referred for unusual uterine bleeding (perimenopausal) and had an endometrial biopsy or D&C, with a tissue diagnosis of disordered proliferation endometrium (DPE) or simple hyperplasia (SH).

The patients were divided into 2 groups: The 1st one (50 cases) was treated with metformin (Glucophage) 500 mg in the first week then raise the dose to reach 1000 mg in the 4th week, for three months long. The 2nd group (50 cases) was administered medroxy progesterone acetate (Provera) 4mg once per day for 3 months long.

Next 3 months all cases in both groups were gone for 2nd time endometrial biopsy for assessment of response of treatment and will have ultrasound examination every three months also. Every patient signed an informed written consent for acceptance of the operation.

Inclusion criteria: Age: 40y-55y, patients who complain of abnormal uterine bleeding (peri menopausal), diagnosed with disordered proliferation of endometrium or simple hyperplasia.

Exclusion Criteria: sensitivity to Metformin, chronic kidney disease, general weakness, anemia, skin allergy, diabetes mellitus, any sort of gynecological cancers, patients take any estrogenic content or progesterone will be excluded, and patients who had received any medications affecting glucose metabolism for at least 3 months before the study.

All subjects were fulfilled to the following: Full history taking: Personal history. Complaint: abnormal uterine bleeding before age of menopause (age of menopause between 45 and 55 years of age). History of present illness: had been analyzed the abnormal uterine bleeding. Menstrual history: included age of menarche, regularity of cycles, frequency, duration, amount of bleeding and time of last menstrual period. Obstetric history: included parity, method and place of previous delivery, time of last delivery or abortion if happened and any complication happened after deliveries or abortions. Contraceptive history: last method used as contraceptive, types, duration, causes of removal

and were cycles regular at that period or not. History: special interest was directed towards history of systemic diseases, surgical, and drugs as hormonal therapy, and family history.

Clinical examination: Clinical examination was done including general examination, abdominal examination, pelvic examination, laboratory, and imaging. Laboratory testing: All patients were tested for pregnancy test (urine or serum B-HCG), complete blood count, other hormonal tests as (prolactin, androgens, estrogen). The platelet count, prothrombin time, partial thromboplastin time, and endometrial sampling. Imaging: Transvaginal and Abdominal ultrasonography were done.

2.2 Ethical aspects: The study protocol was approved by the Ethics Committee of the GOTHI research center. Written informed consent was obtained from the patients or their legal representatives according to the patient's condition before enrollment.

2.3. Analysis of the Results

Statistical analyses were performed using SPSS Statistics v 27.0 (IBM Corp., Armonk, NY, USA). The statistical significance of the difference in categorical data were determined using the Chi-square test or Fisher's exact test. Continuous variables were compared between groups (after one CS versus after two or more CS; CS scar niche group versus non-niche group) using the Mann–Whitney U-test. $p < 0.05$ will be considered statistically significant. To determine systematic bias, the mean of differences and its standard error (SEM) are calculated. The limits of agreement between the two investigators will be calculated for each measurement as the mean ± (1.96 × SD). For inter-and interobservers agreement, the intraclass correlation coefficient (ICC) will be calculated. High absolute agreement corresponds to a high ICC (close to 1), with values > 0.75 indicative of a test with good agreement.

3. RESULTS

Table (1) showed that the mean age in the Metformin group was 46±2.1 years that ranged from (42–50) years, while the mean age in the Progesterone group was 48 ± 2.15 that ranged from (44–52) years with no significant difference between both groups.

Table 1: Age distribution of the patients in metformin and progesterone groups

	Groups	Mean± SD	p-value
Age (years)	**Metformin (No.=50)**	**46±2.1**	**0.24**
	Progesterone (No.=50)	**48±2.15**	

Table (2) showed that according to gravidity; there was no significant difference between Metformin and Progesterone groups. Consistent with parity, there was no significant difference between Metformin and Progesterone groups. According to BMI, there's also no significant difference between Metformin and Progesterone groups.

Table 2: Comparison between gravidity, parity, and BMI of the patients for metformin and progesterone groups

	Groups	Mean± SD	P-value
Gravidity	Metformin (No.=50)	3.98±1.15	0.331
	Progesterone (No.=50)	3.98± 0.7	
Parity	Metformin (No.=50)	3.75±0.8	0.387
	Progesterone (No.=50)	3.3±1.2	
BMI (kg/m^2)	Metformin (No.=50)	33.3±4	0.243
	Progesterone (No.=50)	33.85±2.98	

Table (3) showed that 80% of metformin group and 92% in progesterone group had blood sugar levels of less than 126 mg/dl before treatment with no significant difference between both studied groups. 86% of metformin group and

88% in progesterone group had blood sugar levels of less than 126 mg/dl after treatment with no significant difference between both studied groups.

Table 3: Blood sugar level before and after treatment with metformin and progesterone studied groups

Group	Blood sugar level before treatment			P-value
	< 126 mg/dl No (%)	126 – 200 mg/dl No (%)	> 200 mg/dl No (%)	
Metformin (No.=50)	40 (80.0)	4 (8.0)	4 (8.0)	0.74
Progesterone (No.=50)	46 (92.0)	3 (6.0)	3 (6.0)	
Total	86 (86.0)	7 (7.0)	7 (7.0)	
	Blood sugar level after treatment			
Metformin (No.=50)	43 (86.0)	4 (6.0)	3 (6.0)	
Progesterone (No.=50)	44 (88.0)	3 (8.0)	3 (6.0)	
Total	87 (87.0)	7 (7.0)	6 (6.0)	0.91

Table (4) showed that about 30% of patients in the metformin group had simple hyperplasia and the remaining (70%) had disordered proliferative endometrium. 32% of patients in the progesterone group had simple hyperplasia and the remaining 68% had disordered proliferative endometrium.

Table 4: Pathology of the metformin and progesterone groups

Pathology	Metformin group No (%)	Progesterone group No (%)
Simple hyperplasia (S.H)	15 (30.0)	16 (32.0)
Disordered proliferative endometrium (D.P.E)	35 (70.0)	34 (68.0)
Total	50 (100.0)	50 (100.0)

As indicated in Table 5, there was no significant difference in uterine bleeding after therapy (p=0.47) or endometrial thickness after treatment (p=0.706) between the two investigated groups. In addition, there was no significant difference between the two groups investigated in terms of patient satisfaction or hysterectomy. The treatment time did not differ significantly between the two groups.

Table 5: Outcome among studied groups

		Metformin group n=50	Progesterone group n=50	p- value
AUB before treatment	**Heavy**	50 (100.0%)	50 (100.0%)	
AUB after treatment	**Heavy**	20 (40.0%)	21 (42.0%)	p=0.69
	Controlled	30 (60.0%)	29 (58.0%)	
ET before treatment	**Mean ± SD**	17.04 ± 3.21	16.06 ± 2.95	p=0.46
ET after treatment	**Mean ± SD**	11.5 ± 3.21	11.20 ± 4.25	p=0.71
Treatment (duration/weeks)	**Mean ± SD**	11.02 ± 0.89	10.6 ± 1.1	p=0.96
Patient satisfaction	**Satisfied**	43 (86.0%)	45 (90.0%)	p=0.5
	Not satisfied	7 (14.0%)	5 (10.0%)	
Hysterectomy	**No**	43 (86.0%)	45 (90.0%)	p=0.5
	Yes	7 (14.0%)	5 (10.0%)	

There was a significant statistical rise in the incidence of sore breast, weakness, and metallic taste in group 1 compared to group 2, while nausea, vomiting, and diarrhea increased in group 2 compared to group 1. (Table 6).

Table 6: Treatment complications distribution among studied groups.

Treatment complications	Group 1 Metformin group n=50		Group 2 Progesterone group n=50		p-value
	N	%	N	%	
Epigastric pain	5	8.0%	0	0.0%	P=0.118
Headache	13	24.0%	7	12.0%	p=0.118
Painful breast	10	18.0%	2	2.0%	p=0.008*
Nausea, vomiting and diarrhea	5	8.0%	23	44.0%	p<0.001*
Weakness	49	98.0%	9	16.0%	p<0.001*
Metallic taste	50	100.0%	9	16.0%	P<0.001*

4. DISCUSSION

According to many epidemiologic and experimental studies, unopposed estrogen is assumed to have a crucial role in the development of endometrial benign, premalignant, and malignant lesions [12]. Prolonged ovulatory cycles induced by PCO or other high estrogenic diseases such as estrogens secreting tumors can result in complex hyperplasia with or without atypia, endometrial polyps, or type I endometrial cancer [13].

While there is no doubt about the role of estro genic agents in the progression of abnormal endometrial propagation, an international group of pathologists demonstrated a new terminology for benign and true premalignant endometrial lesions in 2000 based on recent research into the genetic and molecular basis of endometrial carcinoma (13). Endometrial hyperplasia (simple or complex) without nuclear atypia and endometrial polyps are classified as benign, whereas those with genetically altered crowded glands with clonal expansion (endometrial intraepithelial neoplasia-EIN) are classified as true premalignant [14].

Exogenous hormone therapy has been used as an effective therapeutic technique in a variety of circumstances caused by steroid hormones on the endometrium. High-dose progesterone therapy can help patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer who need to keep their fecundity or aren't suitable candidates for hysterectomy [15] [16]. Progesterone at high doses should induce dormant or atrophic glands in a decidualized stroma, as well as reverse the aberrant cell shape and nuclear atypia [17].

Many studies in recent years have suggested that metformin, in combination with effectively antiproliferative activity in hyperplasia of endometrium low-grade endometrial carcinoma, and even in an endometrial serous carcinoma cell line, may play a role in lowering the outcome of endometrial neoplastic changes in PCOS patients. Progesterone works against tumors by attaching receptors to nuclei and triggering the transcription of many genes involved in crosstalk [18]. The purpose of this study was to compare the effects of metformin and progesterone on disorganized proliferative endometrium and simple endometrial hyperplasia to discover whether metformin is therapeutically effective in this situation.

There was no statistically significant difference between the two study groups in terms of patient characteristics. The mean and standard deviation for group 1 was 46±2.1for age, 33.3±4 for BMI (kg/m2), 3.98±1.15 for gravidity and 3.75±0.8 for parity. In group 2, the mean and SD for age was 48±2.15, 33.85±2.98 for BMI (kg/m2), 3.98±0.7 for gravidity and 3.3±1.2 for parity. Our study was agreed to **Hussein et al; 2022** study [27] who showed that according to gravidity, a little difference was found between Metformin and Progesterone groups. Consistent with parity, no statistically significant variance was found between Metformin and Progesterone groups. According to BMI, there's also no significant alteration in result between both groups.

According to the results of the study, there was no statistically significant difference between the two groups in terms of post-treatment endometrial thickness (P=0.69) or uterine hemorrhage (p=0.46). Additionally, there was no statistically significant difference in patient satisfaction or hysterectomy between the two study groups. Both groups received treatment for a three-month period, with no differences in length.

In Group 1, Abnormal Uterine Bleeding was Heavy in every instance prior to therapy, but Heavy in only 20 (40.0%) of the cases following treatment and controlled in 30 (60.0%). According to ET, the mean 17.04±3.21 before treatment. After therapy, however, Mean & SD were 11.5±3.21. Patients who were satisfied made up 43 (86.0%), while 7 (14.0%) were dissatisfied. Seven (14.0%) cases involved hysterectomy. Treatment time per week was 11.02 ± 0.89.

In group 2 Abnormal Uterine Bleeding before treatment was Heavy in all cases but after treatment it was heavy in only 21 (42.0%) and controlled in 29 (58.0%). According to ET before treatment of mean 16.06±2.95. However, after treatment Mean & SD was 11.20±4.25. Satisfied patients were 45 (90.0%) and 5 (10.0%) were not satisfied. Hysterectomy done in 5 (10.0%) of cases. treatment duration per week reached 10.6 ± 1.1. Our study was agreed to **Hussein et al; 2022** study **[27]** who showed that there was no difference between the two studied groups concerning uterine bleeding after treatment (p=0.47), endometrial thickness after treatment (p=0.706). Also, there was no big difference between the two studied groups as regards patient satisfaction and hysterectomy. The duration of treatment didn't differ significantly between the two groups.

According to gravidity, **Elgarhy et al**. **[19]** observed no statistically significant difference between the progesterone group's mean of 3.46 and SD of 1.67 and the metformin group's mean of 3.64 and SD of 1.83. There was no statistically significant difference between the progesterone group with a mean of 3 and SD of 1.47 and the metformin group with a mean of 2.96 and SD of 1.74.

In the Metformin group, 30.0 % of patients exhibited simple hyperplasia, and the remaining 70% had disordered proliferative endometrium, according to our study. However, in the progesterone group, 32% of patients had simple hyperplasia, and the remaining 68% had endometrium that was disorderedly proliferative.

In the metformin and progesterone groups, 82% of patients and 86% of patients respectively had good drug responses, however there was no statistically significant difference between the two groups.

In our study, there were 7 (14.0%) and 5 (10.0%) patients who underwent hysterectomies, respectively. These patients did not comply with the procedure due to heavy bleeding, pelvic pain associated with endometriosis, fibroid and adenomyosis, and the duration of the study was too long for some patients to see results, so they eagerly anticipated the procedure.

Perfect responders should keep getting cycling progesterone medication or, if necessary, a combination of cyclic and continuous hormone replacement therapy. If a partial response is attained, a three-month study using MPA (10 mg orally four times daily) or megestrol acetate (80 mg orally five times daily) may be conducted. A trans-abdominal hysterectomy may be beneficial for non-responders and individuals with intractable hemorrhage **[20]**.

DPE and EH without atypia were classified as benign in the revised classification for endometrial proliferative diseases and pre-cancerous lesions, whereas aplasia (EIN) was classified as a real precancerous lesion with a substantial connection to coexistence or eventual uterine endometriod carcinoma **[21].**

According to **Wheeler et al. [21].,** endometrial intrepithelial neoplasia (EIN) was classified as a true precancerous sore with notable co-existence or subsequent uterine endometriod carcinoma. DPE and endometrial hyperplasia without atypia were combined into benevolent categorization with no negative effects.

After accounting for age, sex, A1c hemoglobin, hardship, smoking, and other drug use, Libby et al. reported that high glucose intolerance patients who had used metformin had a disease rate that was considerably lower than diabetic patients who were never on metformin. According to our research, group 1 experienced statistically higher rates of aching breasts, weakness, and metallic taste than group 2, whereas group 2 experienced statistically higher rates of nausea, vomiting, and diarrhea **[22]**. Our study was agreed to **Hussein et al; 2022** study **[27]** who showed that there was a high statistically increase in incidence of painful breast, weakness and metallic taste in group 1

compared to group 2 while there was increasing in incidence of nausea, vomiting and diarrhea in group 2 associated to group 1.

5, 13, 10, 49, and 50 members of group 1 in the study reported experiencing epigastric pain, headaches, sore breasts, weakness, and metallic tastes. Nausea, vomiting, and diarrhea were noted in five patients. Seven, two, nine, and nine members of group two in group 2 experienced headache, sore breast, weakness, and metallic taste. There were 23 patients who experienced nausea, vomiting, and diarrhea, but none of them experienced epigastric pain.

Di Carlo et al. (23) found that cyclic progesterone-associated bleeding was significantly higher in Groups C and D than in Group A (194 (77.9%) and 163 (69.4%) vs. 125 (55.8%); p 50.01 and p 50.01, respectively). But Group D fared worse than Group C (163 (69.4%) as opposed to 194 (77.9%); p 50.05. Regular bleeding caused by progesterone was also significantly more prevalent in Group C than in Group B (194 (77.9%) vs. 145 (61.2%); p 50.01).

Huang et al. [24] found that cancer incidence was significantly lower in metformin-using diabetes patients than in non-metformin-using diabetic patients after adjusting for age, sex, hemoglobin Alc, deprivation, smoking, and other drug usage.

A potential contributing factor to metformin's anti-proliferative impact, according to Huang et al. (24), is that it activates the AMPK pathway and enhances AMPK enactment by LBK1, which reduces cell vitality and cancer growth. According to continuing research center confirmations, 3 separate medications (AMPK-activator) delayed carcinogenesis in mice susceptible to tumors. This study raises the possibility that AMPK activators can help in the treatment of cancer.

Metformin may be helpful in addressing the insulin resistance impact of high androgen levels in PCO patients, according to Zhang et al.'s discovery that it acts as a testosterone antagonist on endometrial glandular cell lines**[20]**.

Yang et al. state that "Table S2 summarizes adverse events between the two groups." Weight increase was the most common treatment-related adverse event, which was reported by 41.9 percent of women taking MA alone and 34.2 percent of women taking metformin plus megestrol acetate MA **[25].**

In contrast to the MA-only group, which gained 5.0 kg (0 to 10.0), the metformin+MA group averaged 2.5 kg (1.0 to 6.0) after treatment (P=0.01). However, grade 1-2 diarrhea was more prevalent in the metformin + MA group than in the MA-only group (15.8% vs. 4.1 %; P = 0.03).

The metformin + MA group appeared to have a decreased risk of adverse effects than the MA-only group, except for diarrhea. Although none of the intragroup differences were statistically significant, the metformin plus MA group had fewer patients with uterine hemorrhage (7.9% vs. 17.6%), increased nocturnal urine (0 vs. 4.1%), or breast pain (4.0 vs. 10.8%) when compared to the MA-only group. It has philosophical importance.

According to **Shao et al. [26],** essential events in the pathogenesis of human endometrial atypical hyperplasia and E.C. include the activation of PI3K/AKT/mTOR signaling, the loss of PTEN expression, and the initiation of insulin/IGF-1 signaling through overexpression of INSR and/or IGF-1R. In addition to its anti-neoplastic effects on cellular metabolism and the AMPK and mTOR axis in the endometrium, metformin's ability in reversing early E.C to a normal one may be attributed to its systemic qualities. Although significant progress has been made in understanding the potential molecular mechanisms underlying metformin's therapeutic role in treating women with PCOS and early-stage EC, more work is still required to fully understand the regulatory mechanisms governing metformin and how they contribute to its anticancer activity.

CONCLUSION

Like progesterone, metformin may be helpful in treating benign endometrial proliferative lesions. Endometrial proliferative lesions should be appropriately detected and treated to avoid problems. Treatment with metformin results in endometrial atrophy, which limits abnormal cell growth and lowers perimenopausal hemorrhage in people with abnormal endometrial proliferation (DPE, simple hyperplasia, and complex hyperplasia).

Declarations

Ethics approval and consent to participate

Consent for publication

Not applicable.

Availability of data and materials

All data and materials are fully presented in the manuscript.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Authors wrote the protocol, and have collected the specimens, follow up on the cases, taken the history, and fulfill inclusion, exclusion criteria and analyzed the results together.

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