OPEN AIMJ ORIGINAL ARTICLE

A Comparison Between The Effect Of Metformin And Progesterone On The Endometrium In Cases Of Peri Menopausal Bleeding

Obstetrics & Gynecology

Ibrahem Reyad Hussein [1,*] M.B.B.Ch, Fahd Abdel-Aal Elomda [1] MD, Adel Aly Elboghdady [1] MD

Corresponding Author:

Ibrahem Reyad Hussein

Ibrahemreyad053@gmail.com

Received *for publication December 06, 2021;* ***Accepted*** *April 14, 2022;* ***Published online*** *April 14, 2022.*

doi: *10.21608/aimj.2022.108415.1691*

[1]*Obstetrics and Gynecology Department, Faculty of Medicine, Al-Azhar University Cairo, Egypt.*

ABSTRACT

Background: Unopposed oestrogen is have an effective role in the progress of endometrial benign, premalignant, and malignant lesions, according to various epidemiologic and experimental investigations.

Aim of the work: To compare the special effects of metformin and progesterone on disorganised proliferative endometrium and simple endometrial hyperplasia and determine whether metformin is clinically effective in this circumstance.

Patients and methods: This was a two blinded randomized controlled trial, was carried out on 100 patients at The Department of Obstetrics & gynecology at Al-Hussein University Hospital and El-Mahalla General Hospital, divided into 2 groups: (group1); 50 cases treated with metformin (Glucophage) five hndred milligram in the 1st week to one thousand milligram in the 4th week, (group2); 50 cases was managed medroxyprogesterone acetate (provera) 4mg once aday for three months.

Results: The two group had similar result at dfenitive point such as uterine bleeding after treatment (p= 0.47), endometrial thickness after medication (P= 0.706). Also, there was no such big difference between the two studied groups as regards patient's satisfaction and hysterectomy. The duration of treatment didn't differ between the two groups. There was high statistically increase in incidence of painful breast, weakness and metallic taste in group 1 compared to group 2 while there was high statistically increase in incidence of nausea, vomiting and diarrhea in the 2nd group.

Conclusion: Metformin could have the exact effect as progesterone in resolving of simple endometrial hyper plasia . Endometrial proliferative lesions should be detected with good management to avoid its complications.

Keywords: *Metformin; Progesterone; Endometrium; Perimenopausal bleeding.*

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. The Article Processing Charge was paid for by the authors.*

Authorship: *All authors have a substantial contribution to the article.*

INTRODUCTION

Unopposed oestrogen is thought to play a key part in development of endometrial benign, pre malignant, and malignant lesions, according to various epidemiologic and experimental investigations.[1]

Com plex hyper plasia with or without atypia, endometrial polyps, or type I endometrial cancer can occur as a result of prolonged ovulatory cycles caused by PCO or other high estrogenic conditions such as oestrogen secreting tumours. [2]

While there is no distrust about the role of estro genic agents in the change of abnormal endo metrial propagation, a new terminology for benign and true premalignant endo metrial lesions was demonstrated by an international group of pathologists in 2000 based on recent thoughtful of the genetic and molecular basis of endometrial carcinoma. [2]

Proliferations that are caused by hormonal field effects, such as disordered proloferative endo metrium, endo metrial hyper plasia (simple or complex) without nuclear atypia, and endo metrial polyp, are classified as benign, whereas those that have genetically altered crowded glands with clonal expansion (endometrial intraepithelial neoplasia-EIN) are classified as true premalignant. [3]

Exo genous hormone treatment has been employed as an effective therapeutic strategy in numerous scenarios that generated by steroid hormones on the endometrium. Cases with atypical hyperplasia of endometrium and well-differentiated endo metrial cancer who need to keep their fecundity or aren't good candidates for hysterectomy can benefit from high-dose progesterone therapy. 4,5 High-dose progesterone should generates dormant or atrophic glands in a decidualized stroma, as well as reverse the abnormal cell form and nuclear atypia. [6]

Through recent years, a lot of studies have suggested that metformin, in combination with effectively anti proliferative activity in hyperplasia of endometrium low- grade endometrial carcinoma, and even in an endometrial serous carcinoma cell line, may be have role in falling the outcome of endometrial neoplastic changes in PCOS patients. Progesterone exerts its anti-tumor effect by attached to receptors on nuclei and activating the transcription of several genes involved in cross-talk. [7]

The goal of this study was to assimilate the outcome of metformin and progesterone on disorganised proliferative endometrium and simple hyperplasia of endometrium in order to determine whether metformin is clinically operative in this condition or not .

PATIENTS AND METHODS

This was a double blinded randomized study carried out at The Department of Obstetrics & Gynecology at El-Hussein University Hospital and El-Mahalla General Hospital. This study had taken 6 months, starting from 1st of January 2021 till 30th of June 2021, 100 patients had involved in that study . This study included all patients who were referred for unusual uterine hemorrhaging (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) 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 administrated medroxy progesterone acetate (provera) 4mg once per day for 3 months long.

Next 3 months all cases in both groups goes for 2nd time endo metrial biopsy for assessment of response of treatment and had been ultrasound examination every three months also.

An approval of the study was approved from Al-Azhar University academic and ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Inclusion criteria: Age: 40y-55y, patients who referred for abnormal uterine bleeding (peri menopausal), diagnosis were disordered proliferation of endometrium or simple hyperplasia.

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

All subject were fulified to the following:

Full history taking: Personal history. Complain: abnormal uterine bleeding before age of menopause (age of menopause between 45 and 55 years of age). History of present illness: had been analysed the abnormal uterine bleeding. Menstural history: included age of menarche, regularity of cycles, frequency, duration, amount of bleeding and time of last menstural 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. Past history: special interest was directed towards past history of systemic diseases, surgical, and drugs as hormonal therapy, and family history.

Clinical examination: Clinical examination had been done including general examination, abdominal examination, pelvic examination, laboratory and imaging.

Laboratory testing: All patients had been tested for pregnancy test (urine or serum Bhcg) , 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 had been done .

Statistical analysis:

Data were uploaded to the computer and considered using IBM SPSS software package version 22.0. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) & inter quartile range for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogrov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. Chi-Square test for comparison of 2 or more groups. Monte Carlo test as correction for Chi-Square test when more than 25% of cells have count less than 5 in tables (>2*2). Fischer Exact test was used as correction for Chi-Square test when more than 25% of cells have count less than 5 in 2*2 tables. Student t-test was used to compare 2 independent groups.

RESULTS

	Group	Min	max	mean	SD	p-value
age (years)	Metformin (No.=50)	44	52	47.28	2.28	0.250
	Progesterone (No.=50)	46	54	46.04	2.39	

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

Table (1) showed that the mean age in the Metformin group was 47.28± 2.28 years that ranged from (44 – 52) years, while the mean age in the Progesterone group was 46.04 ± 2.39 that ranged from (46 – 54) years with no big difference between both groups.

	Group	Mean	SD	P-value
Gravida	Metformin (No.=50)	4.08	1.12	0.331
	Progesterone (No.=50)	3.91	0.98	
Parity	Metformin (No.=50)	3.7	0.94	0.387
	Progesterone (No.=50)	3.5	1.05	
BMI (kg/m^2)	Metformin (No.=50)	34.03	4.29	0.243
	Progesterone (No.=50)	32.85	3.48	

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

Table (2) showed that according to gravidity, alittle difference was found between Metformin and Progesterone groups. Consistent with parity, no statistical significant variance was found between Metformin and Progesterone groups. According to BMI, theres also no significant alteration in result between the both groups.

Group	BS before treatment			P-value
	< 126 mg/dl No (%)	126 – 200 mg/dl No (%)	> 200 mg/dl No (%)	
Metformin (No.=50)	41 (82.0)	5 (10.0)	4 (8.0)	0.760
Progesterone (No.=50)	43 (86.0)	3 (6.0)	4 (8.0)	
Total	84 (84.0)	8 (8.0)	8 (8.0)	
	BS after treatment			
Metformin (No.=50)	44 (88.0)	3 (6.0)	3 (6.0)	
Progesterone (No.=50)	43 (86.0)	4 (8.0)	3 (6.0)	0.926
Total	87 (87.0)	7 (7.0)	6 (6.0)	

Table 3: Blood sugar before and after in metformin and progesterone groups application.

Table (3) showed that the majority of tested ones (82%) in metformin group and (86%) in progesterone group had blood sugar levels of less than 126 mg/dl before treatment with alittle difference between both groups. The majority of patients (88%) in metformin group and (86%) in progesterone group had blood sugar levels of less than 126 mg/dl after treatment with no statistical significant difference between both.

Pathology	Metformin group No (%)	Progesterone group No (%)
Simple hyperplasia (S.H)	16 (32.0)	14 (28.0)
Disordered proliferative endometrium (D.P.E)	34 (68.0)	36 (72.0)
total	50 (100.0)	50 (100.0)

Table 4: Pathology of the metformin and progesterone groups.

Table (4) showed that about one third (32%) of patients in the metformin group had simple hyperplasia and the remaining (68%) had disordered proliferative endometrium. 28% of patients in the progesterone group had simple hyperplasia and the remaining 72% had disordered proliferative endometrium.

		Group 1 n=50	Group 2 n=50	p- value
AUB before treatment	Heavy	50 (100.0%)	50 (100.0%)	
AUB after treatment	Heavy	21 (42.0%)	19 (38.0%)	p=0.683
	Controlled	29 (58.0%)	31 (62.0%)	
ET before treatment	Mean ± SD	16.04 ± 6.21	15.06 ± 5.95	p=0.47
ET after treatment	Mean ± SD	11.01 ± 5.21	10.26 ± 4.25	p=0.706
Patient satisfaction	Satisfied	44 (88.0%)	46 (92.0%)	p=0.505
	Not satisfied	6 (12.0%)	4 (8.0%)	
Hysterectomy	No	44 (88.0%)	46 (92.0%)	p=0.505
	Yes	6 (12.0%)	4 (8.0%)	
Treatment duration/weeks	Mean ± SD	12.02 ± 0.98	11.84 ± 1.42	p=0.97

Table 5: Outcome among studied groups .

There was no abig 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's satisfaction and hysterectomy. The duration of treatment didn't differ significantly between the two groups (Table 5).

Treatment complications	Group 1 n=50		Group 2 n=50		p- value
	N	%	N	%	
Epigastric pain	4	8.0%	0	0.0%	P=0.118
Headache	12	24.0%	6	12.0%	p=0.118
Painful breast	9	18.0%	1	2.0%	p=0.008*
Nausea, vomiting and diarrhea	4	8.0%	22	44.0%	p<0.001*
Weakness	49	98.0%	8	16.0%	p<0.001*
Metallic taste	50	100.0%	8	16.0%	P<0.001*

Table 6: Treatment complications distribution among studied groups.

There was 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 (Table 6).

DISCUSSION

According to patient characteristics between studied groups, there was no statistically substantial difference between the two studied groups. In group 1 Mean &SD for age was 47.28±2.28, for BMI (kg/m2) was34.03±4.29, for Gravidity was 4.08±1.12, for Parity was 3.7±0.94 & for Abortion was 1.11±0.60.

In group 2 mean and SD for age was 46.04±2.39, for BMI (kg/m2) was 3.91±0.98, for Gravidity was 3.91±0.98, for Parity was 3.5±1.05& for Abortion was 1.14±0.38.

According to the outcome among studied groups there was no statistically significant difference between the two studied groups regarding uterine bleeding after treatment (p= 0.47), endometrial thickness after treatment (P= 0.706). Also, there was no statistically big difference between the two studied groups as regards patient's satisfaction and hysterectomy. The duration of treatment didn't differ between the two groups all have three months duration.

In group 1 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 16.04. However after treatment Mean & SD was 11.01 ± 5.21. Satisfied patients were 44 (88.0%) and 6 (12.0%) were not satisfied. Hysterectomy done in 6 (12.0%) of cases. treatment duration per weeks reached 12.02 with SD of 0.98.

In group 2 Abnormal Uterine Bleeding before treatment was Heavy in all cases but after treatment it was heavy in only 19 (38.0%) and controlled in 31 (62.0%). According to ET before treatment of mean 15.06. However after treatment Mean & SD was 10.26 ± 4.25. Satisfied patients were 46 (92.0%) and 4 (8.0%) were not satisfied. Hysterectomy done in 4 (8.0%) of cases. treatment duration per weeks reached 11.84 with SD of 1.42.

In Elgarhy et al.[8] according to gravidity, no statistical significant difference was found between Metformin with Mean of 3.64 & SD of 1.83 and Progesterone groups with mean of 3.46 and SD of 1.67. No statistical significant difference was found between Metformin with Mean of 2.96 & SD of 1.74 and Progesterone groups with mean of 3 and SD of 1.47.

According to our study, In Metformin group about one third (32%) of patients had simple hyperplasia and the remaining (68%) had disordered proliferative endometrium. However, in progesterone group 28% of patients in the progesterone group had simple hyperplasia and the remaining 72% had disordered proliferative endometrium.

According to response to medication in metformin and progesterone groups, 82% of patients and 86% of patients in the progesterone group showed positive response to medication with no statistical significant reference.

After treatment in the metformin group, 11 out of 16 patients (68.8%) with simple hyperplasia transformed into atrophic endometrium whereas, 25 out of 34 patients (73.5%) with disordered proliferative endometrium transformed into atrophic endometrium. After treatment in the progesterone group, 10 out of 14 patients (71.4%) with simple hyperplasia transformed into atrophic endometrium whereas, 26 out of 36 patients (72.2%) with disordered proliferative endometrium transformed into atrophic endometrium.

In our study, the patient that had ahysterectomy in first group 6 (12.0%) and in second group is 4 (8.0%) and that because of heavy bleeding that they don't compliance with it ,pelvic pain associated with enodometriosis ,fibroid and adenomyosis that don't correlate with the treatment, and to some patient the duration of study is too long to show its effect so looked forward to Hystrectomy operation .

Perfect responders should continue to receive cycling progesterone therapy, or a mix of cyclic and continual hormone replacement therapy if necessary.

A three month study with MPA (0.1 mg orally 4 times per day) or megestrol acetate (80 mg orally five times per day) may be done if a partial response is achieved. Nonresponders and patients with intractabile bleeding may benefit from a trans-abdominal hysterectomy. [9]

In the revised classification for endometrial proliferative diseases and pre-cancerous lesions, DPE and EH without atypia were classified as benign, whereas aplasia (EIN) was classified as a real precancerous lesion with a substantial connection of coexistence or eventual uterine endometriod carcinoma. [10].

DPE and endo metrial hyperplasia without atypia were merged into benevolent categorization with no harmful effect, while endometrial intrepithelial neoplasia (EIN) was deemed a true precancerous sore with notable co-existance or subsequent uterine endometriod carcinoma, according to Wheeler et al.[10].

After accounting for age, sex, A1c haemoglobin, hardship, smoking, and other drug use, Libby et al.[11] discovered that high glucose intolerance patients who had taken metformin had a disease rate that was much lower than diabetic patients who were never on metformin.

Our research found that group 1 had a higher statistically increased incidence of aching breasts, weakness, and metallic taste than group 2, while group 2 had a higher statistically increased incidence of nausea, vomiting, and diarrhoea than group 1.

Epigastric pain, headache, painful breast, weakness, and metallic taste were reported by 4, 12, 9, 49, and 50 individuals in group 1. In four patients, nausea, vomiting, and diarrhoea were reported. Headache, painful breast, weakness, and metallic taste were reported by 6, 1, 8, and 8 individuals in group 2. In 22 patients, nausea, vomiting, and diarrhoea were reported, but no epigastric pain was reported.

Cyclic progesterone-associated bleeding was substantially higher in Groups C and D than in Group A, according to Di Carlo et al.12 (194 (77.9%) and 163 (69.4%) vs. 125 (55.8%); p 50.01 and p 50.01, respectively). However, Group D scored significantly lower than Group C (163 (69.4%) vs. 194 (77.9%); p 50.05. Regular progesterone-related bleeding was also substantially more common in Group C than in Group B (194 (77.9%) vs. 145 (61.2%); p 50.01).

After controlling for age, sex, Alc haemoglobin, deprivation, smoking, and other drug use, Huang et al.13 discovered that cancer incidence in metformin-using diabetes patients was considerably lower than in non-metformin-using diabetic patients.

According to Huang et al.[13], a possible component of metformine's anti-proliferative effect is that it initiates the AMPK pathway and improves AMPK enactment by LBK1, which leads to a reduction in cell vitality and tumour growth. 3 different drugs (AMPK-activator) post poned carcinogenesis in tumor-prone animals, according to ongoing research centre confirmations. This finding suggests that AM P K activators may have a beneficial effect on cancer treatment .

Zhang et al.[9] revealed that metformin acts as a testosterone anta-gonist on endometrial glandular cell lines, implying that met formin could be use ful in resolving the insulin resistance impact of elevated androgen levels in PCO patients.

According to Yang et al.[14], "Table S2 summarises adverse occurrences between the two groups. The most prevalent treatment-emergent side event was weight gain, which was reported by 34.2 percent of women in the metformin + MA group and 41.9 percent of women in the MA-only group.

The metformin + MA group gained 2.5 kg (1.0 to 6.0) on average during therapy, compared to 5.0 kg (0 to 10.0) in the MA-only group (P = 0.01). Nonetheless, grade 1–2 diarrhoea was more common in the metformin + MA group (15.8% versus 4.1 percent; P = 0.03) than in the MA-only group.

Other than diarrhoea, the metformin + MA group appeared to have a lower risk of side events than the MA-only group. When compared to the MA-only group, the metformin plus MA group had fewer patients with uterine haemorrhage (7.9% vs. 17.6%), increased nocturnal urine (0 vs. 4.1%), or breast pain (4.0 vs. 10.8%), though none of the intragroup differences were statistically significant ""It is philosophically significant".

The beginning of insulin/I G F-1 signalling through over expression of INSR and/or IGF-1R, the activation of PI3K/AKT/m.TOR signalling, and the loss of PTEN expression are all key processes in the patho genesis of human endo metrial atypical hyperplasia and E.C, according to Shao et al.15. In adding to it,s systemic properties, metformin's success in restoring early E.C to normal one may be related to its anti-neoplastic effects on cellular metabolism and the AMPK and mTOR axis in the endometrium. Though important progress has been made in perceotion the possible molecular mechanisms behind metformin's therapeutic role in women with PCOS and EC, more research is needed into the regulatory mechanisms of metformin and their contribution to its anticancer activity before it can become a widely use for treating women with PCOS and early-stage EC.

CONCLUSION

Metformin, like progesterone, may be useful in the treatment of benign endometrial proliferative lesions. To avoid difficulties, endometrial proliferative lesions should be diagnosed early and treated properly.

Metformin treatment of individuals with aberrant endometrial proliferation (DPE, simple hyperplasia, and complicated hyperplasia) causes endometrial atrophy, which inhibits abnormal cell growth and, as a result, decreases perimenopausal haemorrhage.

REFERENCES

1. LaCroix A, Simunic V, Vukicevic S. Uno]pposed estrogen and endometrial cancer: association or

causation?. *Croatian Medical Journal*. 2019; 60(4): 389-43.

2. Lax SF. Pathology of endometrial carcinoma. In Molecular Genetics of Endometrial Carcinoma. Springer, *Cham*. 2017; Pp. 75-96.
3. Dey P. Pathology of Endometrium: Benign Lesions, Preneoplastic Lesions and Carcinomas. In Color Atlas of Female Genital Tract Pathology. Springer, *Singapore*. 2019; Pp. 187-236.
4. Chandra V, Kim JJ, Benbrook DM, Dwivedi A, Rai R. Therapeutic options for management of endometrial hyperplasia. *Journal of Gynecologic Oncology*. 2016; 27(1): 1-5.
5. Gompel A. Progesterone and endometrial cancer. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2020; 69: 95-107.
6. Auclair MH, Yong PJ, Salvador S, Thurston J, Colgan TT, et al. Guideline No. 390-Classification and Management of Endometrial Hyperplasia. *Journal of Obstetrics and Gynaecology Canada*. 2019; 41(12): 1789-800.
7. Njoku K, Abiola J, Russell J, Crosbie EJ. Endometrial cancer prevention in high-risk women. *Best Practice & Research Clinical Obstetrics & Gynaecology*. 2020; 65: 66-78.
8. Elgarhy IM, Sabry N, Elfeky AM. Antiproliferative Effect of Metformin on the Endometrium in cases of perimenopausal bleeding. *The Egyptian Journal of Hospital Medicine.* 2019; 76(4): 4007-12.
9. Zhang ZJ, Zheng ZJ, Kan H, Song Y, Cui W. Reduced risk of colorectal cancer with metformin therapy in patients with type 2 diabetes: a meta-analysis. *Diabetes Care*. 2011; 34(10): 2323-8.
10. Wheeler DT, Bristow RE, Kurman RJ. Histologic alterations in endometrial hyperplasia and well-differentiated carcinoma treated with progestins. *The American Journal of Surgical Pathology.* 2017; 31(7): 988-98.
11. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, et al. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. *Diabetes Care*. 2009; 32(9): 1620-5.
12. Di Carlo C, Tommaselli GA, Gargano V, Savoia F, Bifulco G, et al. Transdermal estradiol and oral or vaginal natural progesterone: bleeding patterns. *Climacteric*. 2010; 13(5): 442-6.
13. Huang X, Wullschleger S, Shpiro N, Fleming S, Alessi D, et al. Important role of the LKB1–AMPK pathway in suppressing tumorigenesis in PTEN-deficient mice. *Biochemical Journal*. 2008; 412(2):211-21.
14. Yang BY, Gulinazi Y, Du Y, Ning CC, Cheng YL, et al. Metformin plus megestrol acetate compared with megestrol acetate alone as fertility-sparing treatment in patients with atypical endometrial hyperplasia and well-differentiated endometrial cancer: a randomised controlled trial. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2020; 127(7): 848-57.
15. Shao R, Li X, Feng Y, Lin JF, Billig H. Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma. *Journal of Experimental & Clinical Cancer Research*. 2014; 33(1): 1-11.