



THE EFFECT OF METFORMIN ON ENDOMETRIAL HYPERPLASIA IN PATIENTS WITH PCOS IN PAKISTANI WOMEN. AN OBSERVATIONAL STUDY.

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Conflicts of Interest: Nil

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Abstract:

Objective: To compare the effects of metformin therapy in patients with polycystic ovarian syndrome having irregular heavy menstrual cycle and thickened endometrium (hyperplasia) on transvaginal ultrasound

Design: observational study.

Setting: Tertiary care hospitals of Gujranwala, Pakistan.

Patient(s): The study comprised a total of 100 women with PCOS taking the metformin therapy.

Intervention(s): metformin was started initially in low dose (500-100 mg/day) and was adjusted to 1500 mg/day over next 4-6 weeks..

Main Outcome Measure(s): endometrial thickness, menstrual cycle regulation

Result(s): The mean age of the studied group was 32.1 ± 5.7 years, mean BMI was 26.3 ± 0.27 kg/m² and parity ranged from 0 to 2. A significant decrease of BMI of the investigated cases after metformin therapy was observed. A significant decrease of LH level from 9.17 ± 2.84 Miu/ml to 6.18 ± 3.6 Miu/ml and also a significant decrease in fasting insulin level after metformin therapy were also observed. There was a significant decrease of LH/FSH ratio in the studied cases after metformin administration as compared to before therapy. Pretreatment mean endometrial thickness was 23.25mm(SD=3.85) while after treatment with metformin mean endometrial thickness was 18.38mm(SD=3.72). Paired sample t-test was applied for the comparison of pre and post endometrial thickness. A p-value < 0.05 was considered as significant.

Conclusion: Metformin therapy in patients with PCOS restores normal menstrual cycle, induces ovulation and showing decrease in LH level and reduce the endometrial thickness.

Key words: Endometrial hyperplasia, Metformin, Polycystic ovarian syndrome

Introduction:

Polycystic ovary syndrome (PCOS) is a condition characterized by several hormonal and biochemical alterations ^[1]. The symptoms of PCOS may include menstrual irregularities, hirsutism, acne and oily skin. Hyper insulinemia is one of the hormonal characteristics, while infertility is not uncommon. The prevalence of PCOS is estimated to be around 15–20% based on the Rotterdam criteria, but it varies depending on which criteria are used for diagnosis ^[2, 3]. A total of 4 distinct PCOS phenotypes have been described, that is, classic, ovulatory, norm androgenic and non-PCO ^[4, 5]. Insulin resistance (IR) and subsequent hyper insulinemia is a significant factor in the pathogenesis of this syndrome. There are differences in the literature with some authors claiming that 50–70% of women with PCOS have IR ^[6], while others believing that IR is a universal

characteristic of the syndrome ^[7]. Metformin, a biguanide agent (dimethyldigouanide), is an oral medication for the treatment of type 2 diabetes mellitus ^[8]. Administration of metformin results in a decrease of glucose levels in hyperglycemic states but does not induce hypoglycemia in normoglycemic patients (euglycemic agent) ^[9]. Metformin is also used for the treatment of PCOS. The administration of this drug as monotherapy, in order to induce ovulation in anovulatory naive women with PCOS, has only a little clinical effect and is not recommended as first-line approach, unless there is impaired glucose tolerance ^[10–12]. Nevertheless, IR is not always taken into account when metformin is prescribed. On the other hand, evidence has been provided that metformin in combination with clomiphene citrate increases the ovulation and pregnancy rates in women with PCOS, who demonstrated resistance to clomiphene ^[13–15]. However, based on systematic

reviews regarding the use of metformin for infertility treatment in PCOS, no conclusive evidence exists that this drug improves the clinical outcome [16–18]. Information on whether metformin can have an impact on the endometrium is limited to only one study in which a group of healthy volunteer women with normal menstrual cycles and no PCOS received this drug for experimental purposes [19]. The results of that study showed that metformin reduced the expression of corticotropin-releasing hormone (CRH) and of urocortin (UCN) in the endometrium as compared to no treatment [19]. It has been shown that progesterone (PRG) and CRH contribute to a decidualizing local pathway within the human endometrium, while estradiol (E2) and medroxyprogesterone acetate induce UCN in human endometrial stroma cells in-vitro [20, 21]. On the other hand, the expression of UCN in the endometrium is higher in the late secretory phase inducing decidualization of cultured human endometrial stromal cells [20]. It is evident that these 2 substances are important regulators of decasualization and therefore may influence receptivity and implantation [22]. Concerning CRH, this molecule participates in local inflammatory changes associated with blastocyst implantation and regulates the pro-apoptotic potential of human trophoblastic cells [23]. The action of this peptide is exerted via specific receptors in the endometrium [24]. Regarding women with PCOS, there are only few clinical data, according to which treatment with metformin improved the thickness and the morphological pattern of the endometrium [25], but there are no data on the effect of metformin on endometrial maturation and receptivity in such patients. There are only data in women with or without PCOS, being affected by endometrial hyperplasia and cancer, who received metformin as an adjunct treatment. It has been shown that in such patients, metformin, by affecting various molecular pathways, demonstrated antineoplastic effects, while in women with cancer, it increased the overall survival rate [26– 29]. Possible mechanisms of metformin action in the endometrium of PCOS women involve organic cation transporters and multidrug and toxin extrusion proteins [30]. The aim of the present study was to investigate the effect of metformin on the endometrial hyperplasia in PCOS patients.

PATIENTS AND METHODS

This observational study was conducted on outpatient clinic of Obstetrics Gynecology and Pathology Department of tertiary care hospitals of Gujranwala, Pakistan during the period from May 2018 to June 2019. An informed consent was taken from each woman participating in this study. This study included 100 patients fulfilling the inclusion criteria:

Inclusion criteria:

1. Patients at childbearing period (20-40 years).
2. Patients diagnosed as PCOS by Rotterdam criteria, if 2 of the 3 features were present (oligo-ovulation or anovulation, hyper androgenism & PCO by U/S that showing 12 or more 2-9 mm ovarian follicles in one or two ovaries).
3. Use of metformin alone for 3 consecutive months (850 mg/day) and past history of infertility.

Exclusion criteria:

1. Age 40 years.
2. Other causes of hyper androgenemia.
3. Use of oral contraceptive pills or clomiphene citrate.

Procedure

All the patients in the current study were subjected to menstrual history, drug history and any symptoms that are suggestive of PCOS including infertility, hirsutism and obesity. General examination including hair distribution all over the body was done according to the modified Ferriman Gallwey score. This scoring system evaluates nine different body parts (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, and thigh). A score greater than 8 indicates hirsutism. Estimation of the body weight and height were assessed while the patient was standing and wear light clothes with no shoes. BMI was calculated as weight in kg/height in m² (25; overweight, >30; obese, > 35; moderate obesity, >40: morbid obesity). Transvaginal ultrasonography and laboratory investigations (including LH, FSH, fasting insulin level and free testosterone level) were done. These investigations were done before and after 3 months of metformin administration.

Statistical analysis:

The collected data were organized, tabulated and statistically analyzed using statistical package for social sciences (SPSS) V22. For quantitative data, mean standard deviation (SD), minimum and maximum were calculated. For comparison between

two measurements, the independent samples (t) test was used. Pearson correlation co-efficient (r-test) was used for correlating different variables. For all tests p value 0.05 were considered insignificant.

Results

The mean age of the studied group was 32.1 ± 5.7 years, mean BMI was 26.3 ± 0.27 kg/m² and parity ranged from 0 to 2 (Table 1). A significant decrease of BMI of the investigated cases after metformin therapy was observed (Table 2). A significant decrease of LH level from 9.17 ± 2.84 Miu/ml to 6.18 ± 3.6 Miu/ml and also a significant decrease in fasting insulin level from 14.3 ± 4.3 to 8.2 ± 5.9 after metformin therapy were also observed (Table 3). There was a significant decrease of LH/FSH ratio in the studied cases after metformin administration as compared to before therapy. Pretreatment mean endometrial thickness was 23.25mm(SD=3.85)while after treatment with metformin mean endometrial thickness was 18.38mm(SD=3.72). Paired sample t-test was applied for the comparison of pre and post endometrial thickness.A p-value < 0.05 was considered as significant.

Table 1: Demographic data of studied case

Variable	Mean±SD
Age (years)	32.1±5.7
BMI (kg/m ²)	26.3±0.27
Parity	Range (0-2)

Table 2: Comparison between the studied cases before and after metformin administration as regard BMI

Groups Parameter	Before Treatment	After Treatment	P value
BMI (kg/m ²) Mean±SD	25.3±0.27	16.3±0.28	<0.003

Table 3: Comparison between the studied cases before and after metformin administration as regard endocrine parameters

Groups Parameter	Before Treatment	After Treatment	P value
FSH (mIU/ml)	3.87±1.8	4.85±2.67	>0.05
LH (mIU/ml)	9.17±2.84	6.18±3.6	<0.05*
Testosterone (pg/ml)	1.58±0.83	1.38±0.44	>0.05
Fasting insulin (µIU/L)	14.3±4.3	8.2±5.9	<0.05*

P value < 0.05 significance

Discussion

We report as observed that endometrial proliferation as a result of unopposed estrogen production in subjects with PCOS is significantly reduced in response to metformin therapy when studied over one year time period. Researchers have found that excess insulin levels stimulated endometrial growth leading to proliferation³¹.Jakubowicz³² observed that metformin may have an impact on the endometrium hypothetically both improving the potential for a successful pregnancy implantation and reducing the long term risks of unopposed endometrial proliferation. Palomba³³studied uterine vascularization, endometrial thickness and endometrial pattern in 37 patients with an ovulatory PCOS treated with metformin for 6 months, and in 30 age matched control subjects. In the patients with PCOS, metformin was observed to improve a majority of parameters of endometrial receptivity including endometrial thickness. Another study conducted by Tracy suggested pharmacological therapies along with life style modifications as the mainstay of treatment in subjects having clinical manifestations of PCOS especially if they are obese as well and among the recommended therapies is hormonal treatment , anti-androgen therapy, metformin and thiazolidinediones³⁴.Metformin has been shown to have an anti-proliferative effect on endometrial glands as seen by Session etal, Shen etal,Takenura etal. On the other hand metformin has been shown to inhibit FSH, insulin-stimulated progesterone and estradiol production in granulosa cells²¹. Thus metformin may inhibit endometrial hyperplasia and endometriosis through suppression of both ovarian and local production of estrogen. Recently it has been reported that metformin not only effects endometrial hyperplasia but effects endometrial cancer cells. Metformin potentially may serve as adjuvant treatment in the management of patients with endometrial cancer. Metformin appears to improve ultrasound detected markers of endometrial receptivity and endometrial histology through (1) improved ovulatory function (2) reducing circulating levels of insulin and (3) other endometrial factors. Consequently, metformin administration has the potential to reduce the risk of unopposed endometrial proliferation, hyperplasia or carcinoma by improving the

regularity of ovulatory function and by reducing the effect of hyperinsulinemia on the endometrium. However definitive randomized studies are required in future.

Conclusion

Metformin therapy in patients with PCOS restores normal menstrual cyclicity, induces ovulation and showing decrease in LH level and reduce the endometrial thickness.

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