

THE EFFECT OF METFORMIN ON ENDOMETRIAL HYPERPLASIA IN PATIENTS WITH POLYCYSTIC OVARIAN SYNDROME (PCOS)

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ABSTRACT

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

Study Design: Quasi – experimental study.

Place and Duration of Study: The study was conducted in Military Hospital Rawalpindi, department of gynae / obs unit- I from January 2009 – June 2010.

Patients and Methods: A total of 100 patients in the age group of 40-47 years who reported to gynae OPD with irregular heavy menstrual cycles with or without clinical features of hyperandrogenism were selected and informed consent was taken. Transvaginal ultrasound (TVS) was performed on them by the same operator and those who had polycystic ovaries (enlarged ovaries with > 8-9 follicles peripherally enlarged) and endometrial thickness > 12 mm in the follicular phase of the cycle were selected. Total 100 patients were included in the study, but 10 patients were dropped out. Metformin was started after explaining the purpose of the study initially in low dose (500-1000 mg/day) and was adjusted to 1500 mg/day over next 4-6 weeks. Patients with abnormal liver or renal functions and those already taking hormonal therapy or on tamoxifen were excluded from the study. The endometrial thickness was assessed on monthly follow up visits and final findings were recorded and presented at the end of one year.

Results: Of 90 patients, mean age of patients was 43.25 years (SD = 1.91), mean pretreatment endometrial thickness was 20.25 mm (SD= 4.85) mean and post treatment endometrial thickness was 16.38mm (SD = 4.72). There was a significant reduction in endometrial thickness after treatment with metformin.

Conclusion: Metformin therapy (1500 mg/day) significantly reduces endometrial thickness (hyperplasia) in patients with PCOS.

Keywords: Endometrial hyperplasia, Metformin, Polycystic ovarian syndrome.

INTRODUCTION

It was in 1935 when Stein and Levanthal¹ published their report describing what is now called the polycystic ovary syndrome (PCOS), It is in the last two decades that we have seen a flurry of interest in this disorder. PCOS affects 7-10% of women of reproductive age and is the most common cause of oligoovulatory infertility, and accounts for a significant fraction of health care costs²⁻⁴.

Hyperinsulinemia is a cornerstone of both the metabolic syndrome and PCOS. Insulin resistance (IR) and secondary hyperinsulinemia affect approximately 65-70% of women with

PCOS^{5,6}. Many of these women are also obese, which further exacerbates their IR. Insulin stimulates ovarian theca cell androgen production and secretion, and suppresses the hepatic production of sex hormone-binding globulin. The increased intraovarian androgens then disrupt folliculogenesis⁷. Hyperinsulinemia may also directly cause premature follicular atresia and antral follicular arrest⁸. The resulting anovulation also leads to unopposed estrogen production and endometrial proliferation in women with PCOS, leading to an increased risk of endometrial hyperplasia.

The unopposed endometrial proliferation in women with PCOS stimulated by estrogen in particular, 17 β – estradiol (E2) within a progesterone deficient milieu leads to endometrial hyperplasia⁹. Upto 35% of PCOS women have endometrial hyperplasia; which predisposes to endometrial cancer¹⁰.

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Endometrial cancer is the most common malignancy of female genital tract and the fourth most common cancer in women in the United Kingdom and the United States of America following breast, colon and lung cancers^{10,11} world wide and the seventh most common malignancy in women¹¹.

Insulin sensitizing agents particularly, the biguanide metformin is widely used in the management of women with PCOS¹². Metformin not only ameliorates insulin resistance and hyperinsulinemia in PCOS women, but its long term use improves ovulation and menstrual cycle regularity¹². It has well established function of suppressing glucose production in the liver and is recently known to have beneficial effects on adipose tissue, skeletal muscle and vascular endothelium¹². More recently, metformin has been reported to inhibit breast cancer cell growth¹³.

We have studied the effects of metformin on women with PCOS who had endometrial hyperplasia.

PATIENTS AND METHODS

This quasi experimental study was conducted in Military Hospital Rawalpindi – gynaecology and obstetrics unit from January 2009 to Jun 2010. The patients were selected from gynaecology outdoor clinics. Patients between the ages of 40-47 yrs, with or without clinical features of hyperandrogenism e.g. hirsutism, obesity, acne etc, who presented with irregular heavy vaginal bleeding, polycystic ovaries diagnosed on TVS and (enlarged ovaries and > 8 follicles in stroma) those with endometrial thickness of more than 12 mm in the follicular phase of the cycle were included in the study. Patients with renal function abnormalities or abnormal liver function tests and those who were already taking hormone replacement therapy or tamoxifen were excluded from the study.

A total of hundred (n=100) patients were recruited for the study by using random sampling technique. At the end of one year data of 90 patients was presented. Six patients were

non compliant to the side effects of metformin so they were dropped out. Two patients were found to have increasing endometrial thickness on regular follow up visits, endometrial biopsy was carried out which revealed atypical hyperplasia so they were dropped out in favour of definitive surgical treatment. Two patients were lost to follow up.

Detailed history was taken and examination was carried out. Written and informed consent was taken. The patients’ information was collected on data collection sheets. The purpose of therapy was explained to the patients and

Table-1: Distribution of patients according to age group.

S.no	Age Group	No of Patients	Percentage
1	40 – 43 years	30	33%
2	43 – 45 years	52	57%
3	45 – 47 years	08	8.8%

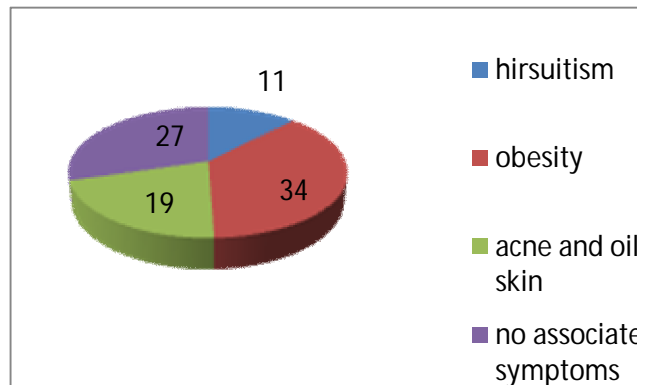


Figure:- Description of associated symptoms of patients (n=90).

metformin was started initially in low dose (500-100 mg/day) and was adjusted to 1500 mg/day over next 4-6 weeks. The patients were called for regular monthly follow up visits. The endometrial thickness was the outcome measure, it was assessed on 6 months and then 1 year time period and results were recorded. The data was analysed using SPSS version 17. Descriptive statistics were used to describe the results. Paired sample t-test was applied for the comparison of pre and post endometrial thickness. A p value of <0.05 was considered significant.

RESULTS

Total 90 patients were included in the study, mean age of patients was 43.25 years (SD = 1.91) (table). Irregular heavy menstrual bleeding was a common presenting complaint in all of them however 11 (12%) had associated hirsutism, 34 (38%) had associated obesity, 19 (21%) had acne and oily skin while 27 (30%) had no associated presentation as shown in figure. The patients were given metformin (1500 mg/day) and the outcome noted in the form of reduction in endometrial thickness on TVS. Pretreatment mean endometrial thickness was 20.25 mm (SD= 4.85) while after treatment with metformin mean endometrial thickness was 16.38 mm (SD= 4.72). Data was analysed using SPSS version 17. Descriptive statistics were used to describe the results. Paired sample t-test was applied for the comparison of pre and post endometrial thickness. A p -value < 0.05 was considered as significant.

A total of 10 (11%) patients experienced nausea, dry mouth and gastric indigestion when started with metformin therapy but they had improvement in their symptoms with simple measures and dose adjustment.

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 proliferation¹⁴. Jakubowicz¹⁵ 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. Palomba¹⁶ studied uterine vascularization, endometrial thickness and endometrial pattern in 37 patients with anovulatory 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 thiazolidinediones¹⁷.

Metformin has been shown to have an anti-proliferative effect on endometrial glands as seen by Session et al¹⁸, Shen et al¹⁹, Takenura et al²⁰. 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 cancer²².

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 significantly reduces endometrial thickness in patients with PCOS, so is useful in women with polycystic ovary syndrome. The decision to prescribe this drug should be made on

an individual basis. This drug is found to have far reaching effects on endometrial glands and cells and may be used as an adjuvant treatment of endometrial hyperplasia and endometrial cancer.

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