

Metformin in Polycystic Ovary Syndrome Patients

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ABSTRACT

Objective: To determine the effect of metformin on the clinical presentation and metabolic disturbances of polycystic ovary syndrome.

Study Design: Observational study.

Place and Duration of Study: This study was conducted at the Department of Obstetrics and Gynecology Unit-I, Sandeman Provincial Hospital, Bolan Medical College, Quetta from 09-09-2018 to 06-06-2019

Materials and Methods: Fifty patients with clinical signs and symptoms of polycystic ovaries syndrome attending the OPD of department of obstetrics and gynecology Unit-I, Sandeman provincial hospital, Bolan medical college Quetta.

Results: A total of fifty women with Polycystic Ovary Syndrome were included in the study. The average age of the patients was found 26.46 ± 1.40 (95% CI: 23.64 to 29.28) years.

The signs and symptoms, of Acne was present in 33 patients (66 %), Hirsutism was present in 43 patients (86 %), Menstrual Irregularity was present in all patients (100 %), Obesity was present in 28 patients (56 %) and Infertility was present in 37 patients (74 %), were present in the patients before treatment.

Improvement in the signs and symptoms, of Acne was seen in 2 patients (6.06 %), Hirsutism was seen in 2 patients (4.65 %), Menstrual Irregularity was seen in 13 patients (26 %), Obesity was seen in 4 patients (5.40 %) and Infertility was seen in 2 patients (5.40 %), after 3 months' treatment.

Improvement in the signs and symptoms, of Acne was seen in 5 patients (15.15 %), Hirsutism was seen in 6 patients (13.95 %), Menstrual Irregularity was seen in 34 patients (68 %), Obesity was seen in 12 patients (42.85 %) and Infertility was seen in 5 patients (13.51 %), after 6 months' treatment.

Conclusion: Metformin administration to women who have signs and symptoms of polycystic ovarian syndrome is associated with marked improvement in menstrual irregularity resulting in regular menstrual cycles and achievement of pregnancy. Improvement in other signs and symptoms of PCOS was also seen with administration of Metformin for six months.

Key Words: Polycystic Ovary Syndrome, An ovulation, Menstrual Irregularities, Hirsutism and Infertility, Metformin.

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INTRODUCTION

Polycystic Ovary Syndrome (PCOS) can be found in 5–10% women in reproductive age. Women with PCOS are characterized by hyperandrogenaemia, hyperinsulinemia, hypothalamic-pituitary-ovarian axis dysfunction, and deranged adipok insecretion from the adipose tissue. These specific alterations interact in different tissues, such as fat, liver, muscle and ovaries, resulting in a variety of phenotypes of the syndrome.

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MATERIALS AND METHODS

A recent survey showed that metabolic disorders, obesity, and type 2 diabetes (T2D) were recognized as the most important long-term concerns related to PCOS¹. Moreover, longitudinal studies showed that worsening of insulin resistance (IR) over time in obese PCOS women is a risk factor for the early development of T2D².

Prenatal androgen overexposure has a direct and permanent effect on the developing female offspring, with a consequent increase in b-cell number. This provokes altered pancreatic islet function with consequent primary hyperinsulinemia response to glucose, which implies future metabolic derangements³. It was shown recently that impaired cortisol activity in granulosa cells and follicular fluid in ovaries of women with PCOS and IR could cause further aggravation of tissue specific IR⁴.

A better understanding of the pathogenesis of insulin resistance that is associated with the complications of

polycystic ovary syndrome had led to novel therapies- chiefly insulin lowering medication⁵.

Based on current guidelines, metformin is indicated in PCOS in some scenarios to improve fertility for management of menstrual irregularity if women are unable to take OCPs, and in co-existent prediabetes or DM2, where lifestyle modification fails. However key knowledge gaps remain on the efficacy of metformin and its specific role in PCOS, including in weight management⁶.

Women of reproductive age group (15-45) attending the outpatient department of Gynea/Obs BMCH/SPH Quetta with presence of hirsutism, acne, episodes of irregular menstrual bleeding, infertility will be advised ultra sound pelvis, serum androgen level (free testosterone), serum insulin level, LH/FSH ratio. Patients meeting the inclusion criteria were included in the study. Other causes of androgen excess e.g. adrenal gland tumor, late onset congenital adrenal hyperplasia, Cushing syndrome and increased level of insulin as in diabetes mellitus were ruled out. Use of any medication for acne and menstrual irregularity were stopped in the beginning of the study so as to control the confounding factors.

History of present condition and its duration were obtained and examination was done. After explaining the treatment modalities for polycystic ovary syndrome and their advantages and disadvantages, informed consent will be taken for study participation. Laboratory investigation (LH/FSH levels, serum free testosterone & insulin level) were performed the pelvic ultra sound for all patient's same ultra machine to control bias in the study.

These patients were prescribed, Tab. Metformin 500mg, 1 tablet for the first week. Patients were asked to return after 1 week. If there are no gastrointestinal symptoms, then 2 tablets of 500mg were given daily in the 2nd week and the patients were followed up for another 1 week. If still no symptoms this was maintained for 3 months and she was followed up after 3 months. Metformin will be continued for 3 months more. The effect of metformin will be observed by improvement in sign and symptoms such as hirsutism, menstrual cyclicity, acne, & levels of LH, serum androgen & insulin. Record was maintained on an especially designed Performa. Data was analyzed on computer by using the software SPSS V.10 Frequency and percentage was computed for categorical variables like presenting complaints, sign and symptoms (acne, hirsutism, and menstrual, cycle). Mean and standard deviation was estimated for quantitative variables like age, weight, blood pressure. Paired 't' test was used to compare effect of metformin in women with polycystic ovary syndrome before and after treatment for six months/ $P \leq 0.05$ was considered as significant.

RESULTS

A total of fifty women with Polycystic Ovary Syndrome were included in the study. The average age of the patients was found 26.46 ± 1.40 (95% CI: 23.64 to 29.28) years.

The signs and symptoms, of Acne was present in 33 patients (66 %), Hirsutism was present in 43 patients (86 %), Menstrual Irregularity was present in all patients (100 %), Obesity was present in 28 patients (56 %) and Infertility was present in 37 patients (74 %), were present in the patients before treatment.

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DISCUSSION

Polycystic ovarian syndrome (PCOS) is a heterogeneous collection of sign and symptoms that gathered together from a spectrum of disorders with a mild presentation in some, while in others severe disturbance of reproductive, endocrine and metabolic function. The pathophysiology of the PCOS appears to be multifactorial and polygenic.

The definition of the syndrome has been much debated. More recently, in an attempt to resolve this conflict, a joint consensus meeting of American society for the Reproductive Medicine & and European society of Human Reproduction and Embryology (ASRM / ESHRE) refined the definition of PCOS⁷.

A large retrospective study that compared 2566 women with PCOS with 2566 age matched controls in Australia and used several linked health datasets showed that having PCOS was associated with an increased risk of obesity (16 versus 3.7%), adult-onset diabetes (12.5 versus 3.8%), hypertensive disorder (3.8 versus 0.7%), ischemic heart disease (0.8 versus 0.2%), asthma (10.6 versus 4.5%), endometrial cancer (0.4 versus 0.02%), stress/anxiety (14 versus 5.9%), depression (9.8 versus 4.3%) and mortality (0.7 versus 0.4%). Women with PCOS had twice as many hospital admissions as women without the condition over the 15-year follow-up (Hart and Doherty, 2015)⁸.

Insulin resistance is further exacerbated by overweight and obesity, common finding in PCOS [risk ratio (95% confidence interval (CI)): 1.95(1.52, 2.50) and 2.77 (1.88, 4.10), respectively, for women with PCOS compared with controls from a systematic review⁹.

Consistently, weight loss through lifestyle modification comprising dietary modification, physical activity and/or behavioral change), medications (metformin, orlistat, incretin mimetics) or bariatric surgery improves insulin resistance, reduces hyperandrogenism and alleviates PCOS clinical severity¹⁰.

A Cochrane review²⁴ including 816 women across nine studies compared metformin with placebo or no treatment, before or during assisted reproductive technology cycles. Clinical pregnancy rates were improved in the metformin group (OR 1.52, 95% CI 1.07–2.15; five studies; n = 551). However, the number of events dropped from 775 for the pregnancy rates to 551 for the live birth rates (live birth rates are not reported in some studies), which may have weakened the power of the meta-analysis with regards to live birth rates. There was no effect on the miscarriage rate. Women given metformin were, however, at significantly reduced risk of ovarian hyperstimulation syndrome (OHSS) when a long gonadotrophin-releasing hormone (GnRH) agonist protocol was used. Metformin decreased the risk of OHSS in these patients, probably by modulating the ovarian response to the stimulation. However, currently, the short GnRH antagonist protocol is recommended for women at risk of OHSS, for which the role of metformin is unclear¹¹.

More recently, a subgroup analysis in a systematic review also indicated that metformin therapy combined with lifestyle modification achieved limited impact in obese women with PCOS¹².

Furthermore, metformin alone does not improve weight loss compared to placebo or no treatment¹³.

Hyperinsulinemia generally suggests a lack of receptor sensitivity to insulin effects for unknown reasons.¹⁴ Treatment with insulin-sensitizing agents is a relatively recent therapeutic strategy in women with polycystic ovary syndrome (PCOS) and insulin resistance¹⁵.

Several insulin-sensitizing agents have been tested in the management of PCOS. Metformin is the only drug currently in widespread clinical use for PCOS¹⁶.

Recent studies report that insulin-sensitizing agents, such as metformin, reduce hyperinsulinemia, reverse the endocrinopathy of PCOS and normalize endocrine, metabolic and reproductive functions, leading to the resumption of menstrual cyclicity and ovulation¹⁷.

Importantly, the action of metformin is not associated with an increase in insulin secretion, and hence, with hypoglycemia. It is possible that the weight loss which often accompanies protracted metformin therapy may account for some of the beneficial effects observed in many studies¹⁸.

Kolodziechczyk et al. treated 39 women with PCOS and fasting hyperinsulinemia with metformin (500mg X3 per day) for 12 weeks, and found a significant decrease in fasting insulin and total testosterone and an increase in SHBG, leading to a decrease in the free testosterone index. In addition, there was a significant decline in

mean BMI, waist-to-hip ratio, hirsutism, and acne, as well as an improvement in the menstrual cyclicity. No changes in LH level or in LH-to-FSH ratio were observed. The greatest decline in testosterone and its free index occurred in the patients with the most pronounced hyperandrogenemia. Women with high levels of DHEAS exhibited less improvement in menstrual cycle regularity, no change in hirsutism, and an increase in the levels of IGF-I¹⁹.

CONCLUSION

Metformin administration to women who have signs and symptoms of polycystic ovarian syndrome is associated with marked improvement in menstrual irregularity resulting in regular menstrual cycles and achievement of pregnancy. Improvement in other signs and symptoms of PCOS was also seen with administration of Metformin for six months.

Author's Contribution:

Concept & Design of Study:	Zubia Bugti.
Drafting:	Zubia Bugti.
Data Analysis:	Zubia Bugti.
Revisiting Critically:	Zubia Bugti.
Final Approval of version:	Zubia Bugti.

Conflict of Interest: The study has no conflict of interest to declare by any author.

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