

ROLE OF METFORMIN IN CORRECTING HYPERINSULINEMIA, MENSTRUAL IRREGULARITY AND ANOVULATION IN POLYCYSTIC OVARY SYNDROME

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Background: Previous studies suggest that metformin by reducing hyperinsulinemia is clinically useful in the treatment of polycystic ovary syndrome (PCOS). Our Objective was to observe the role of metformin in correcting oligomenorrhea/amenorrhea and anovulation within six month in hyperinsulinemic women with PCOS. Another aim was to assess the decrease in hyperinsulinemia and body weight by metformin in our population. **Methods:** This study was carried out at the Department of Obstetrics and Gynaecology, Islamic International Medical Complex (IIMC) Islamabad, from October 2001 to March 2003. Fifty women fulfilling the clinical and biochemical criteria for PCOS and hyperinsulinemia were enrolled. Metformin was started at an oral dose of 500mg/day and maintained at 1500mg for 6 months. Besides ultrasonography and body weight, serum FSH, LH, fasting insulin, fasting blood sugar and creatinine levels were performed. After six months menstrual cyclicality, fasting insulin levels, day 21 serum progesterone and body weights were assessed. **Results:** After six months of Metformin therapy, menstrual regularity was achieved in 19 out of 22 women (86%). Out of these 11 women (50%) were ovulating at six months. On Metformin, the median fasting serum insulin decreased from 23.6 micro U/ml to 20.2 micro U/ml ($P < 0.05$). There was no significant weight reduction ($p = 0.096$) with Metformin in six months. Data was analyzed using SPSS by paired t-test.

Key words; Metformin, PCOS, menstrual irregularity

INTRODUCTION

Polycystic ovarian syndrome originally described in 1905 by Stein and Leventhal, is the commonest endocrine disorder in women of reproductive age leading to menstrual irregularity; which is one of the cardinal clinical features of PCOS.¹ Insulin resistance accompanied by compensatory hyperinsulinemia produces the hyperandrogenism interfering with the pituitary ovarian axis, leading to increased LH levels, anovulation, amenorrhea, and infertility. Hence the improvement of insulin sensitivity by insulin sensitizers may be of therapeutic value in the management of clinical manifestations of hyperinsulinemia and hyperandrogenemia.² Various treatments have so far been tried to treat the clinical manifestations of PCOS. Antiandrogens as a sole treatment or combined with oral contraceptives are considered the treatment of choice for the manifestations of PCOS, but there is no agreement about their efficacy on the metabolic sequelae e.g., hyperinsulinemia. The improvement of insulin sensitivity by insulin sensitizers e.g., metformin is now thought to be of therapeutic value directly and/or indirectly in the management of PCOS.³ Metformin increases the effectiveness of insulin at the peripheral cell level and results in a decline of insulin, leading to significant improvement of clinical manifestations of hyperandrogenism.⁴ Our purpose was to study the effect of Metformin therapy on menstrual cyclicality and ovulation for six months period in our

population. The effect of this therapy on serum insulin levels and body weight were also assessed.

MATERIAL AND METHODS

This prospective study was carried out at the outpatients department of Gynaecology, Islamic International Medical Complex from October 2001 to March 2003. The plan was to do a randomized controlled study however women refused to the possibility of inclusion in a control group. Fifty consecutive women reporting in the outpatients with oligomenorrhea or amenorrhea consented for the study and were investigated for polycystic ovary syndrome and hyperinsulinemia. PCOS was diagnosed by characteristic appearance of multiple 6-9mm peripheral cysts in the ovaries on ultrasonography and by FSH: LH ratio of $\geq 1:3$. Hyperinsulinemia was defined as fasting insulin levels ≥ 20 microU/mL. Weights in kilograms and fasting blood sugars were recorded. Women with reduced renal function (creatinine >1.5) were excluded from the study because of a risk of lactic acidosis with metformin. Metformin was advised with meals to avoid the gastric side effects, in a dosage of 500 mg daily orally for the first week, followed by twice daily in the second week and finally thrice daily (1500 mg) for 6 months. At six months, menstrual cyclicality, fasting insulin and blood sugar levels, midluteal progesterone to assess ovulation (in women achieving regular cycles) and

weights in kg were measured. The data was analyzed on SPSS using paired t-test.

RESULTS

22 women completed the study. Four women discontinued the medication because of nausea, abdominal cramps and diarrhea. Unsatisfactory compliance in 3 and concomitant use of other drugs in 6 women were other excluding factors. One woman had abnormal creatinine levels and was excluded. Fifteen women were lost to follow up or failed to complete the investigations. The age range was 13-39 yrs. After six months of Metformin, regular menstrual cycles were established in 19 women (Fig-1), out of whom 11 had midluteal serum progesterone within the ovulatory range (>30 nmol/l) (Fig-2). On Metformin, the median fasting serum insulin decreased from 23.6 micro U/ ml to 20.2 micro U/ml (P=0.00) (table-1).The mean weight decreased from 74.4 kg to 73 kg (p=0.096) which was statistically insignificant (table2).

DISCUSSION

Our study demonstrates the usefulness of metformin therapy in achieving menstrual cyclicity in the majority of women in our population within six months. The same has been reported in some western studies previously.⁵ Oral contraceptives and anti androgens have been the mainstay of treatment of PCOS, but as these women with oligo/amenorrhea are anovulating and want to conceive, metformin is a better option as it helps women to become pregnant and is safe even during pregnancy.^{6,7} Secondly metformin corrects the metabolic abnormalities eg. hyperinsulinemia as well⁸ in both PCOS and controls.⁹ We wanted to observe whether our population also responds in the same manner .This was proved by the decrease in fasting serum insulin levels in our study group after metformin treatment . Some studies have shown a reduction in post-glucose load insulin levels as well,¹⁰ which was not performed by us due to financial constraints. Half of the women achieved ovulation at the end of six

months; other studies have also resulted in higher frequency of ovulation during treatment than before treatment.¹¹⁻¹²

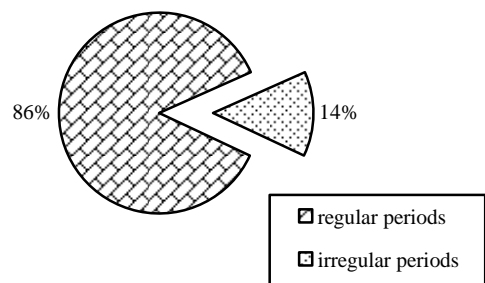


Fig.1 Menstrual regularity after six months of metformin therapy n=22

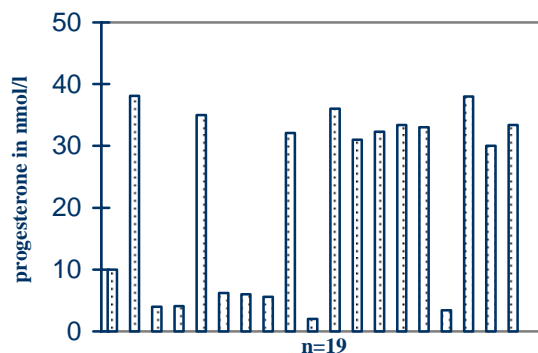


Fig-2: Midluteal serum progesterone after six months of Metformin

Table 1.Statistical analysis of decrease in serum insulin levels with metformin

	Mean	95% CI for mean	Standard Deviation	Median	Average Absolute Deviation from Median	Result of paired t- test
Insulin before treatment	23.6	23.21-24.02	0.911	23.8	0.636	T = -14.7 Degrees of freedom = 21 p= 0.000
Insulin after treatment	20.2	19.91-20.55	0.727	20.2	0.495	
Difference	-3.39	-3.86 thru-2.9	1.08	-3.75	0.759	

Table – 2: Statistical analysis of change in body weight with metformin therapy

	Mean	95% CI for mean	Standard Deviation	Median	Average Absolute Deviation from Median	Result of paired t-test
Body weight before treatment	74.4	69.04-79.78	12.1	73.5	-9.86	t = 1.74 Degrees of freedom = 21 p= 0.096
Body weight after treatment	73.7	68.54-78.91	11.7	73	9.55	
Difference	0.68	-0.13-1.49	1.84	0.05	1.44	

Weight loss alone is expected to have several beneficial effects upon clinical, endocrinological and metabolic features of women presenting with PCOS moreover insulin sensitizing therapy with metformin is shown to decrease the leptin concentrations in obese PCOS women.¹³ Though waist to hip ratio decreased with metformin in various studies,¹⁴⁻¹⁵ no significant changes were recorded in body weight in our population suggesting an independent correction of clinical and metabolic abnormalities. We do realize that body mass index (BMI) which is more scientific, should have been performed by us, however a few other studies have also not shown any change in body weight with metformin.¹⁶ The weight response may be varied in different populations and BMI on a larger sample size should be performed to reach a conclusion.

Metformin therapy was well tolerated by the majority of our patients which is consistent with other studies.¹⁷

CONCLUSION

In women with PCOS metformin treatment reduced hyperinsulinemia, corrects menstrual irregularity in majority, results in higher ovulation rates, independently of changes in body weight.

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