ORIGINAL ARTICLE

Effect of metformin therapy in patients with Polycystic Ovary Syndrome

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Abstract :
Objective: To determine the effect of 12 week of metformin therapy on clinical and hormonal indices of patients with Polycystic Ovary Syndrome.
Study design: Prospective
Study setting: The study was carried out at the outpatient Department of Obstetrics & Gynaecology and Endocrinology from Sept. 2006 to April 2007. 30 women meeting the eligibility criteria were enrolled. They were interviewed using standardized proforma . Data was analyzed by using SPSS version 10. Paired t- test was used for comparison.
Intervention: Patients were treated with 500mg of tab.metformin three times daily for 12 weeks.
Main outcome measures: Hirsuitism, menstrual irregularities, BMI and fasting insulin levels were assessed before and after treatment .
Results: In 21 of 30 patients(70%) normal menstrual cycle resumed. There was significant reduction in the BMI ($p< 0.000$), and significant reduction in the fasting insulin Levels ($p<0.000$). 73.3% presented with hirsuitism and 33.3% showed improvement.
Conclusion: 12 week course of metformin is effective in the treatment of menstrual irregularities ,in reducing weight, fasting insulin levels and improving hirsuitism.

Key words: PCOS,insulin resistance, hyperinsulinemia, hyperandrogenism, metformin.

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Introduction:

Polycystic ovary is the most common endocrine disorder with incidence of 4% to 12% in the reproductive age.[1,2] Polycystic ovarian syndrome is considered a problem arising as a consequence of persistent anovulation with spectrum of etiologies and clinical manifestations that includes insulin resistance as well as hyperandrogenism.

Biochemical disturbances include elevated serum concentration of lutenizing hormones, testosterone, androstenedione and insulin. Hyperinsulinemia appears to be the key to the pathogenesis of the syndrome.[3]

Polycystic ovary syndrome can manifest in number of ways. At one end of the spectrum, the disease produces polycystic morphology and at the other end there are symptoms like obesity, hyperandrogenism, menstrual cycle disturbances and infertility. These symptoms may occur either singly or in combination. It has been shown that insulin resistance is associated with PCOS. In addition, hyperandrogenism and insulin resistance may also be linked to each other.[4]

Insulin resistance is defined as the decreased ability of insulin to stimulate glucose disposal in to target tissues, or a reduced glucose response to a given amount of insulin.[5] In this situation, the blood insulin levels are chronically higher which inhibits fat cells from giving up their en-

ergy stores, this in turn is associated with obesity, hypertension, abnormal triglycerides, glucose intolerance and type 2 diabetes mellitus. The discovery that insulin resistance has a key role in the pathophysiology of PCOS has led to promising form of therapy in the form of insulin sensitizing drugs. Metformin is an insulin sensitizer that reduces insulin resistance and insulin secretion followed by a reduction of ovarian androgen production. Direct action of metformin on ovarian theca cells also reduces androgen production[6].

Metformin is an oral biguanide well established for the treatment of hyperglycemia, that does not cause hypoglycemia in normoglycemic subjects.

The objective of the study was to determine the effect of twelve weeks of metformin therapy on clinical and hormonal indices of the women with PCOS. It will not only help treating the presenting complaints but will also prevent the long term health issues and will improve the quality of life.

Methodology

Study setting: This study was performed at Liaquat National Hospital Karachi with patients from Gynaecology and Endocrinology clinics for a period of 8 months. Thirty women who met the PCOS eligibility criteria were enrolled. The women were interviewed using proforma to keep the record. Data was analyzed by using SPSS version 10- statistical package. Paired t-test was used to compare the results.

Duration of study: 8 months

Sample technique: Non-probability purposive sampling

Study design: Prospective

Inclusion criteria: Women fulfilling any three out of the following criteria:

- Oligo and/or amenorrhea
- Obese women with BMI of ≥25 kg/m2
- Clinical hyperandrogenism
- Primary infertility
- Raised fasting insulin levels
- Reversed FSH:LH ratio in early follicular phase
- Poly cystic ovaries on ultrasound,

Exclusion criteria:

- Diabetic females
- Secondary infertility
- Other causes of obesity like hypothyroidism, Cushing syndrome.

Intervention:

Patients were treated with 500 mg of metformin three times daily for 12 weeks. The dose of metformin was fixed in all the patients.

Main outcome measures

Clinical symptoms including hirsutism, menstrual cycle, BMI,fasting insulin levels and fasting blood glucose were assessed before and after treatment with metformin.

Statistical analysis:

Data was collected on proforma; SPSS version 10 was used for analysis. Frequency and percentage were used for categorical variables like presenting complaints, family history of diabetes mellitus, menstrual irregularity. Mean and standard deviation were used for age, menstrual cycle, BMI and hirsutism. Paired t- test was used to compare the pre and post mean differences.

Results:

The study was done on 30 patients. All of the patients completed the 12 week course of Metformin. All of the patients belonged to reproductive age group. Ages of the patients were between 18 to 37 years. 15 patients were with positive family history of diabetes mellitus. Of the 30 patients who completed the 12 week course of metformin, 21 had normal menstrual cyclicity was restored (70%).

22 patients presented with hirsuitism (73.3%). According to Ferriman and Gallwey, hirsuitism score ranged from 7 to 18. Hirsutism was not completely treated in any of the patient although 10 patients (33.3%) showed some improvement. Treatment with metformin significantly reduced fasting serum insulin levels from 8.72±3.43 mi-

Figure 1: *Menstrual Cycle (before treatment)*

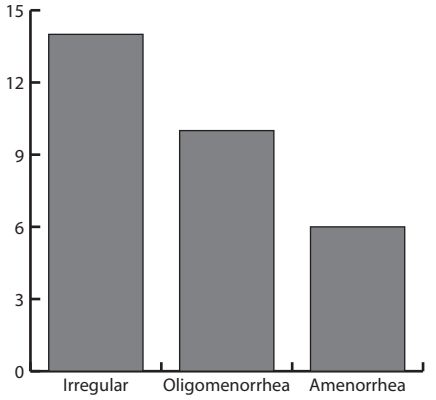

Figure 2: *Menstrual Cycle (after treatment)*

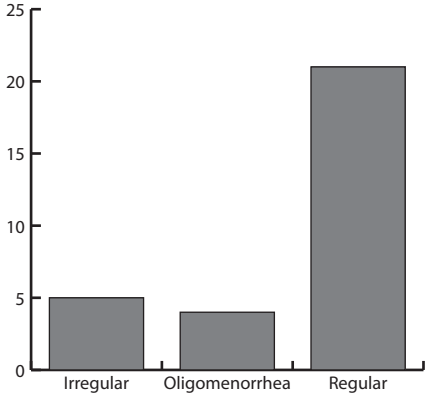

Table 1: *BMI before and after treatment with Metformin*

Comparison	Mean ± S.D.	t-value	Degree of freedom	p-value
BMI (before treatment)	32.2±2.5	7.594	29	0.000
BMI (after treatment)	30.67±2.51			

cro units/ml to 6.91± 1.93 micro units/ml with p value <0.00, which is significant. Metformin also reduced fasting blood sugar from 106.03±17.17 to 97.40±10.12 with p value <0.00 which is also significant.

Patient also showed significant decrease in their BMI (p<0.005) from 32.20±2.50 to30.67±2.51

Discussion:

PCOS can manifest in a number of ways. There is persistant state of anovulation which can manifest with both clinical and biochemical disturbances. These biochemical manifestations like raised levels of LH, testosterone, androstenedione and insulin levels can over a period of time have serious effects.

Hyperinsulinemia in non diabetic patient is independently associated with an increased risk of cardio vascular disease and metabolic abnormalities that include glucose intolerance and hyperlipidemia resulting in hypertension and type 2 diabetes mellitus.[7]

Also in PCOS menstrual irregularities are common and because of chronic anovulation, infertility is a common problem in married couples. Obesity by itself have long term consequences on the health of a person, these people are at higher risk of cardio vascular disease and diabetes mellitus.[8]

So the objective of the study was to see the effect of metformin on the clinical and hormonal indicies in a person suffering from PCOS. Metformin acts by reducing hepatic production of glucose, improves the tissue sensitivity to insulin, facilitating glucose utilization by skeletal muscles and adipocytes and reduced intestinal glucose absorption.[9,10]

We gave 30 females who fulfilled the criteria of PCOS, metformin tablets 500 mg, three times a day for 12 weeks and studied its effects on menstrual cyclicity, BMI, fasting insulin levels, hirsuitism and fasting blood glucose levels. It was seen that in 21(70%) out of 30 patients, normal menstrual cycle was restored after a 3 month course of metformin. Other investigators have reported similar results where metformin use resulted in decrease levels of androgens, increase in the levels of sex hormone binding proteins and resulting in restoration of normal menstrual cycles.[11,12,13,14,15] Another study done in Services Hospital Lahore showed that females treated with metformin resumed their normal menstrual cycle and started ovulating within 3 to 9 months of their treatment.[16]

Patient also showed significant decrease in their BMI (p<0.000) from 32.20±2.50 to 30.67±2.51 by improving tissue sensitivity to insulin and fa-

cilitating glucose utilization by skeletal muscles. This result was similar to the findings of a study done by Moghetti et al.[9] They also demonstrated improvement in menstrual cycle, fall in BMI due to improved tissue sensitivity to insulin.

The third effect which was assessed in the study was improvement in the fasting insulin levels and fasting blood glucose levels. It was seen that in all patients given metformin fasting insulin levels decreased significantly (p-value <0.005). This was similar to the result of Moghatti and co-workers [9] who conducted a double blind randomized study and it showed that Metformin group had significant reduction in fasting insulin levels.Similarly in another study, significant improvement was seen in the levels of fasting insulin levels and regular cycles in oligomenorrhic teenage girls with PCOS.[17]

Hirsutism is a common problem for women with PCOS and has potentially serious psychosocial sequelae[18]. In our study, 22 females had hirsutism and after receiving Metformin for 12 weeks ,we saw some improvement in Ferriman Galway score in 10(33.3%) patients. Litrature also supports this. In a study, Christopher JG Kelly, Gorden[19] demonstrated that when women treated with metformin for hirsutism, showed significant improvement in Ferriman Galway score. This was a double blind placebo controlled study. Kolodziejyle et al also showed similar effects on hirsutism.[20]

Conclusion:

From this study, we inferred that 500mg of metformin given thrice daily to the patients of PCOS will improve their menstrual cycle irregularity resulting in ovulation and pregnancy.It also has significant effect on the BMI and fasting insulin levels resulting in decreased risk of cardio vascular disease and diabetes mellitus type 2. Not a very significant improvement was seen in the hirsuits but maybe they require longer therapy. For this another study with large sample size and of longer duration is required. We can conclude that metformin has a definite roll in the treatment of Poly cystic ovary syndrome.

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