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 pro-forma. 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.

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 obes-
sity, hypertension, abnormal triglycerides, glu-
cose 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 sensi-
tizer that reduces insulin resistance and insulin
secretion followed by a reduction of ovarian an-
drogen production. Direct action of metformin
on ovarian theca cells also reduces androgen
production6.

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

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 Lia-
quat 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 hypothyroid-
  ism, Cushing syndrome.

Intervention:

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

Main outcome measures

Clinical symptoms including hirsutism, men-
strual cycle, BMI, fasting insulin levels and fast-
ing 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 per-
centage were used for categorical variables like
presenting complaints, family history of diabe-
tes 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 Met-
formin. All of the patients belonged to reproduc-
tive 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 hirsutism (73.3%).
According to Ferriman and Gallwey, hirsutism
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-
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 to 30.67±2.51

**Discussion:**

PCOS can manifest in a number of ways. There is persistent 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 cardiovascular 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 cardiovascular disease and diabetes mellitus.8

So the objective of the study was to see the effect of metformin on the clinical and hormonal indices 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, hirsutism 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-
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Hirsutism is a common problem for women with PCOS and has potentially serious psychosocial sequelae. 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. Literature also supports this. In a study, Christopher JG Kelly, Gorden 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.

**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 cardiovascular 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.

**References:**
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Metformin is an effective insulin sensitizer treating type 2 diabetes mellitus. However, the functional consequences of metformin administration throughout pregnancy on gestational diabetes mellitus (GDM) with polycystic ovary syndrome (PCOS) have not been assessed. We therefore performed a meta-analysis and system review to determine the effect of metformin on GDM in PCOS. A meta-analysis was performed on the published studies before December, 2013. Meta-analysis examined whether metformin could reduce GDM occurrence in PCOS with a fixed effect model. The odds ratio (OR) with 95% confidence interval. The polycystic ovary syndrome (PCOS) is characterized by both oligo/amenorrhea and androgen excess in women. When fully expressed, the manifestations include ir. Metformin reduces risk of ovarian hyperstimulation syndrome in patients with polycystic ovary syndrome during gonadotropin-stimulated in vitro fertilization cycles: a randomized, controlled trial. Fertil Steril 2011; 96:1384. Al-Inany HG, Youssef MA, Ayeleke RO, et al.