Effect of Metformin in Patients of Polycystic Ovarian Disease (PCOD), a Comparative & Observational Study

[1)] Dr. Jayshree Awalekar. *M.D.* [2)]Dr. Chidanand Awalekar. *M.D.* [3)]Dr. Vidya M. Jadhav. *M.D,*
[4)] Dr. C. G. Chivate. *M.D.* [5)] Dr. M. H. Patwardhan, *M.D.D.M,*
Obstetrics & Gynaecology. (Endocrinology)
[1]Professor, Dept of Medicine, [2]Professor & Head Of Dept, [3]Medicine, Professor, Dept of Obstetrics & Gynaecology, [4]Associate Professor, Dept of Medicine, Bharati Vidyapeeth Deemed University Medical college & Hospital, Sangli.

Abstract

Polycystic ovarian disease (PCOD) is common endocrine disorder. Majority of young females are affected.Insulin resistance along with dysfunction of hypothalamopituitoryadrenal axis is a key etiological factor in development of all manifestations of PCOD[1]. They present with irregular menses, infertility, obesity, Hirsutism, Acanthosis Nigricans etc. Insulin resistance increases the chance of the metabolic syndrome, which increases chance of developing diabetes mellitus, heart disease, obesity, hypertension and increased levels of cholesterol[1,8,9].

Metformin is one of the widely accepted treatment modality allover the world [1,5]. we aimed to study efficacy of Metformin in PCOS. Here cases are diagnosed by using Rotterdam's criteria. We recruited 35 cases PCOD. BMI, Menstrual irregularity, infertility, Hirsutism, Acanthosis Nigricans, acne were common presenting features. Hormonal & biochemical profile was studied S.LH (Luteinizing Hormone), FSH (Follicle stimulating hormone), levels, Serum Insulin levels. Weight loss, menstrual regularity, LH/FSH Ratio,HOMA Index were studied initially & compared all parameters after 3 months of treatment with Metformin. Our study shows that, BMI was reduced from mean 29.64 to 27.13 after 3 months of Metformin treatment which is highly significant(p0.0000).LH/FSH ratio was mean 2.56,dropped to 1.70,(p0.000) after treatment, which is significant. HOMA index values before treatment were mean 25.85, & after treatment it was 15.21(p0.000) highly significant. Hyperprolactinemia corrected from Mean 24.11 to16.92 to 6.27 (p0.004) found to be statistically significant.

The present study gives us idea about efficacy of Metformin treatment in PCOD cases & will be useful in patient treatment schedules.

Key words- *PCOD (Polycystic ovarian Disease), Insulin Resistance(IR),Hyperinsulinemia, Metformin, BMI Body Mass Index),LH/FSH-Luteinizing hormone & Follicle stimulating hormone ratio,HOMA index-Homeostatic model assessment.*

I. INTRODUCTION

Nowadays PolyCystic Ovarian Disease (PCOD) is commonest endocrine disorder in young females.6-10% of women population is affected globally [2]. PCOS is also known as Stein Leventhal syndrome [1,2]. It is characterised by insulin resistance & is strongly implicated in its aetiology.Insulin resistance increases the chance of the metabolic syndrome, which increases chance of developing diabetes mellitus, heart disease, obesity, hypertension and increased levels of cholesterol[10].

"Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan"([5]) .In 2003 a consensus workshop sponsored by ESHRE/ASRM in Rotterdam indicated PCOS to be present if any 2 out of 3 criteria are met[(2,7,8)]it also includes many women without androgen excess too.

1. Oligoovulation and/or anovulation
2. Excess androgen activity
3. Polycystic ovaries (by ultrasound)- Ovaries are larger than normal and have multiple small ovarian cysts
   Other entities are excluded that would cause these.[(5,8)]

Insulin resistance(IR) & obesity is observed in majority of PCOD patients. Elevated insulin levels cause abnormal functioning of hypothalamic-pituitary-ovarian axis that lead to PCOS. Women with PCOS experience an increased frequency of hypothalamic GnRH pulses, which in turn results in an increase in the LH/FSH ratio[(6,8)].

IR is main causative factor for all these consequences & morbidity[13]. Failure of the target cells to respond to normal or ordinary levels of insulin is regarded as IR irrespective of the body mass index (BMI). Hyperinsulinaemia due to IR occurs in approximately 80% of PCOS women [1]. central obesity & 30%–40% of lean PCOS women [9,13]. Measurement of the fasting insulin concentration [(10)] is an easy marker to obtain, and values equal to 20 or higher indicate the presence of IR.

Hyperinsulinemia is the main causative factor in PCOD women both obese & lean[4,5] & cause hyperandrogenism [6]. Insulin directly promotes ovarian steroidogenesis, and inhibits liver release of the sex hormone binding globulin (SHBG) and production of insulin-like growth factor binding protein 1 (IGFBP-1). Increased concentrations of IGF-1 additionally promote ovarian release of androgens[26].

HOMA Index-It is a marker of IR, based on measurements of fasting glucose and insulin levels, is the homeostatic model assessment (HOMA-IR).Resistance to insulin is diagnosed at HOMA-IR levels ≥6.8[26].

Insulin resistance can manifest as follows:

1. Type II diabetes[1,4].
2. Weight gain/Obesity [1,3,14]
3. High blood pressure, in obese and/or during pregnancy.[1]
4. Cardiovascular disease-two fold increased risk of arterial disease in PCOS patients as compared to women without PCOS. [7,14]
5. Strokes [2,3]
6. Miscarriage [6,7]
7. Sleep apnoea, in obese[7,14]
8. Non-alcoholic fatty liver disease, in obese[14,10]
9. Acanthosis nigricans (patches of darkened skin under the arms, in the groin area, on the back of the neck[15].
10. Hirsutism-Adipose tissue enzyme, aromatase, converts androstenedione to estrone and testosterone to estradiol. The excess of adipose tissue in obese led excess androgen formation, which are responsible for hirsutism and virilization Excess estrogens inhibits FSH via negative feedback[15]. It is been treated with various treatment modalities successfully.

Metformin is found to be effective in PCOD ,It is a hepato-selective insulin sensitizer. It has beneficial properties of weight loss, lipid reduction and modulator of endothelial function. It is anatherostatic agent and also improves ovarian function in insulin-resistant women. It does not cause hyperinsulinaemia or hypoglycaemia[7].Beneficil effects of metformin on reducing androgen levels and restoring ovulation in women with polycystic ovary syndrome(PCOS) have been published[6,9].As insulin resistance as a predictor of diabetes, hypertension and coronary artery disease, metformin is increasingly prescribed to insulin-resistant women with PCOS[2].

Study Design, Size & Duration:

This is comparative observational was study done at Bharati Vidyapeeth Deemed University Medical College & Hospital, Sangli & Dr. Patwardhan's Endocrinology & Research Centre Miraj. In cases of PCOD effect of Metformin, was observed.

Sample size-calculated size 35.

Sampling Method-All diagnosed cases of PCOD by using to Rotterdam criteria.

Duration-It was carried out from June 2013 to June 2015.

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Inclusion Criteria- All diagnosed cases of PCOD by using to Rotterdam criteria

Criteria of Exclusion-.

1. Cushings syndrome
2. Thyroid disorders
3. Pituitory tumours
4. Diabetes Mellitus

Study Procedure-

A. Written consent is taken before starting examination.
   - History & Clinical examination is done.

Following points were considered for comparison.

1. Height in metre, weight in Kg & Body Mass Index(BMI) is calculated.
2. Menstrual irregularities are noted as amenorrhoea, oligomennorrhoea & irregular cycles.
3. Infertility.
4. Hirsutism, unwanted hair growth, acanthosis Nigricans - The features of excess androgen levels is noted.

B. Following investigations were done-

1. LH (Luteinizing Hormone).
2. FSH (Follicle stimulating hormone).
3. Serum.Prolactin levels-
4. Serum Insulin levels-

C.Following parameters were studied for comparison

1. BMI reduction-
2. LH/FSH Ratio-
3. HOMA Index-homeostatic model assessment (HOMA) -method used to quantify IR & beta-cell function.It also predicts cardiometabolic risk .Calcualated by using formula HOMA-IR = [Glucose] x [Insulin] / 405 (Glucose in mg/dl.

D. **Tab. Metformin 500mg TID** was advised half hour before meals was advised for 3 months. All parameters of comparison given above repeated after 3 months.

AFTER 3 MONTHS OF TREATMENT-
All these parameters were observed & compared.
Calculations- p value & percentage.

II. RESULTS

Table No. 1

Metformin (n = 35)		mean	sd	T	p value	Significance
BMI	Before	29.58	3.34	-8.512	0.000	Highly significant
	After	27.04	3.33			
Prolactin1.2-15	Before	24.11	13.76	-2.638	0.006	Highly significant
	After	17.12	6.26			
Homa Index	Before	25.57	16.34	-4.154	0.000	Highly significant
	After	15.22	13.69			

N=35	Mean	Std. Deviation	Std. Error Mean	T	p value
pre BMI	29.64	3.49	0.59	9.49	**0.000**
post BMI	27.13	3.48	0.58		
pre HOMA index	25.85	16.27	2.75	4.55	**0.000**
post HOMA index	15.21	13.69	2.31		
Pre LH/ FSH	2.56	0.24	0.04	12.60	**0.000**
Post LH/ FSH	1.70	0.28	0.04		

1. In our study In Metformin group n=35,before starting treatment BMI mean was 29.64,after 3 mths treatment with Metformin it reduced to 27.13(p 0.000)i.e highly significant statistically.
2. HOMA index pre treatment was mean 25.85, reduced to 15.21(p=0.000). i.e highly significant statistically.
3. LH/ FSH ratio which suggests insulin resistance was mean 2.56 before starting treatment. It slashed down to 1.7(p=0.000) i.e highly significant statistically.
4. Hyperprolactinemia corrected from Mean 24.11 to16.92 to 6.27 (p0.004) found to be statistically significant.

The present study gives us idea about efficacy of Metformin treatment in PCOD cases & will be useful in patient treatment schedules.

All these results suggests, Metformin is very good treatment option in PCOD.

III. DISCUSSION

PCOD patients present with menstrual irregularities like amenorroea, oligomenorrhoea about half of them have infertily because of anovulation caused by because of hormonal dysfunction & insulin resistance. Hirsutism, acne, obesity, miscarriages, hypertension, Ischaemic Heart Disease, diabetes, sleep apnoea etc.

Lord J.M [15] et al. have done meta-analysis showed Metformin has an effect in reducing fasting insulin concentrations & is effective in achieving ovulation in PCOD women, when compared Metformin with Placebo. Pregnancy rates were significant by treatment effect for metformin and clomifene. This study did not show any effect on body mass index or waist:hip ratio. Metformin was associated with a higher incidence of nausea, vomiting, and other gastrointestinal disturbance [(15)]. Its choice as a first line agent seems justified. It should be used as an adjuvant to general lifestyle improvements and not as a replacement for increased exercise and improved diet.

Morghetti P et al. In his study showed metformin showed reduced plasma insulin (at fasting: P = 0.057; during the clamp studies: P<0.01) and increased insulin sensitivity (P<0.05). ovarian hyperandrogenism was attenuated, as indicated by

significant reductions in serum free testosterone (P<0.05).Comparable minor changes in BMI were found both in the metformin group and in the placebo group. In the open, long-term trial 17 women (54.8%) showed striking improvements of their menstrual abnormalities and were considered as responders. They showed that plasma insulin, serum androstenedione, and menstrual history were independent predictors of the treatment's clinical efficacy. In 10 subjects whose menses proved regular after treatment, the great majority of cycles became ovulatory (32 out of 39 assessed, 79%). In conclusion, in women with PCOS metformin treatment reduced hyperinsulinemia and hyperandrogenemia, independently of changes in body weight. In a large number of subjects these changes were associated with striking, sustained improvements in menstrual abnormalities and resumption of ovulation. Higher plasma insulin, lower serum androstenedione, and less severe menstrual abnormalities are baseline predictors of clinical response to metformin.[10]

IV. CONCLUSIONS

Metformin significantly improves insulin sensitivity in IR patients. It was associated with improvement in insulin sensitivity in HOMA-IR defined insulin resistant patients.Metformin treatment reduced hyperinsulinemia and hyperandrogenemia[9,13.] Metformin did very well in all aspects we studied ,so it can be used as first line therapy in PCOD.

It reduces their long-term risks for diabetes, hypertension, dyslipidemia, and cardiovascular disease.Thus helps in reducing significant mortality & morbidity caused by PCOD. It is essential for all primary care providers to identify patients of PCOS. These patients should undergo the appropriate tests, councelling & treatement accordingly.

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