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ORIGINAL RESEARCH

A Clinical Prospective Study to Determine the Effect of Metformin on Clinical Features, Metabolic, Endocrine Profile and Insulin Sensitivity in Polycystic Ovarian Syndrome (PCOS) Patients at Newly Established Tertiary Care Center

[1]Dr. Shubha Choudhary, [2]Dr. Balgopal Singh Bhati, [3]Dr. Neha Garg, [4]Dr. Shivani Gupta

[1,3,4]Assistant Professor, Department of Obstetrics & Gynaecology, Government Medical College, Pali, Marwar, Rajasthan, India
[2]Associate Professor & Unit Head, Department of Obstetrics & Gynaecology, Government Medical College, Pali, Marwar, Rajasthan, India

Corresponding author
Dr. Shubha Choudhary
Assistant Professor, Department of Obstetrics & Gynaecology, Government Medical College, Pali, Marwar, Rajasthan, India
Email: manuauss@gmail.com

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a heterogenous disorder and current proposed diagnostic criteria include a number of disorders with similar phenotypes but radically different etiologies. Menstrual irregularities are the most common finding among women with PCOS. The aim of this study to determine the effect of metformin on clinical features, metabolic, endocrine profile and insulin sensitivity in polycystic ovarian syndrome (PCOS) patients at newly established tertiary care center.

Materials& Methods: A hospital based prospective study done on 30 obese women with PCOS attending in the department of Obstetrics and Gynaecology at Government Medical College, Pali, Marwar, Rajasthan, India. Thirty females aged 18-35 years having polycystic ovarian syndrome were enrolled and studied for a period of 6 months. The observations were recorded on day 0 and day 180 for various parameters and they were statistically evaluated by using student (paired) t-test for comparison from day0 to day180.

Results: Metformin treated patients showed significant improvement in all parameters i.e. Physiological parameters (Bodyweight, BMI, Systolic blood pressure except diastolic blood pressure), Metabolic parameters (Fasting blood glucose, Fasting serum insulin), Endocrinal parameters (Serum testosterone) indicating that Metformin is of benefit in reducing insulin resistance.

Conclusion: We concluded that Metformin treated patients showed significant improvement in all parameters (except diastolic blood pressure) indicating that Metformin is of benefit in reducing insulin resistance. It seems that Metformin has a direct effect on human ovarian steroidogenesis in addition to reduction of weight and body mass index.

Keywords: Polycystic Ovarian Syndrome (PCOS), FBS, Fasting Serum Insulin, Metformin.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common disorder occurring in 6-10% of women of reproductive age[1], It is characterized by chronic anovulation with either oligomenorrhoea or amenorrhoea and hyperandrogenism and is the most common cause of anovulatory infertility and hirsutism.[2] PCOS is a heterogenous disorder and current proposed diagnostic criteria include a number of disorders with similar phenotypes but radically different etiologies. However, there is no single sign or symptom that is currently accepted as the sine qua non of the syndrome. Therefore, there is no "gold standard" test of this sign or symptom from which to determine the sensitivity and specificity of screening tests.

Menstrual irregularities are the most common finding among women with PCOS. The symptoms include oligomenorrhoea and amenorrhoea (irregular or absent menses respectively). A major reproductive concern for those women with PCOS that are able to become pregnant is miscarriage. Approximately one-third of all pregnancies in PCOS patients end in spontaneous abortion. The reasons for this are unclear. The increased rate of abortion possibly has something to do with elevated levels of luteinizing hormone (LH), deficient progesterone secretion and abnormal endometrium.

PCOS affects approximately 13 million women which is about 6% to 10% of the female population.[3] Because awareness of the syndrome has spread from obstetricians and gynaecologists to family practitioners, the number of women diagnosed with PCOS is growing. Unfortunately, it is often not until a couple decides to have children that a woman finds out she may be infertile due to polycystic ovaries. It is unclear whether the disease is more prevalent among certain ethnic groups.

The most widely accepted clinical definition of the polycystic ovary syndrome is the association of hyperandrogenism with chronic anovulation in women without specific underlying diseases of the adrenal or pituitary glands.[4] Hyperandrogenism is characterized clinically by hirsutism, acne and androgen-dependent alopecia and biochemically by elevated serum concentration of androgens, particularly testosterone and androstenedione. Obesity is common but not universal.[5,6] Typically these features are associated with hypersecretion of luteinizing hormone and androgens but with normal or low serum concentrations of follicle stimulating hormone.[7-9]

Insulin also acts on the liver to inhibit the production of sex hormone binding globulin and insulin like growth factor 1 binding protein. A reduction in sex hormone binding globulin leads to an increase in the biologically available free testosterone. Thus insulin resistance not only increases secretion of ovarian androgens but also promotes an increase in the proportion of free (active) hormone. The aim of this study to determine the effect of metformin on clinical features, metabolic, endocrine profile and insulin sensitivity in polycystic ovarian syndrome (PCOS) patients at newly established tertiary care center.

MATERIALS& METHODS

A hospital based prospective study done on 30 obese women with PCOS attending In the department of Obstetrics and Gynaecology at Government Medical College, Pali, Marwar, Rajasthan, India.

INCLUSION CRITERIA

1. Women aged 18-35 yrs
2. Body Mass Index: >26kg/m^2
3. Euthyroid Patient
4. Not on any medications

THE CLINICAL DIAGNOSIS OF PCOS WILL BE MADE USING THE ROTTERDAM CRITERIA WHEN WOMEN HAD AT LEAST TWO OF THREE CRITERIA

1. Ovulatory dysfunction (oligoovulation or anovulation)
2. Excess androgen activity (hirsutism, acne, or elevated serum androgens)
3. Polycystic ovaries by ultrasound.

Oligomenorrhoea defined as fewer than eight menses per year or cycles longer than 35 days in length. Hirsutism defined as a Ferriman Gallwey score. Polycystic ovarian morphology diagnosis by using trans vaginal ultrasound when at least one ovary had 8-12 antral follicles with a mean diameter <9 mm and/or a total ovarian volume >10 cm.

EXCLUSION CRITERIA

1. Hypothyroidism women
2. Hyperprolactinemia
3. Cushing syndrome
4. Non classical congenital adrenal hyperplasia
5. Androgen-secreting tumors of the ovaries or adrenal glands
6. Women with PCOS were also excluded from the study if they had taken any medication within 3 months before the study that could affect glucose or sex hormone metabolism, such as Metformin or hormonal contraceptives.

METHOD OF COLLECTION OF DATA

After the enrollment, demographic data such as age, religion, education, socio economic status, were obtained through an interview. Detailed history including complaints, married life, obstetric, sexual, menstrual, medical and pharmacological history was documented and clinical examination was performed. Routine investigations like Hb%, TLC, DC and special investigations like Thyroid profile, Serum Prolactin, Fasting blood glucose levels, Serum Androgens, Serum insulin levels and Ultrasound were carried out. The patients were then prescribed Metformin for a period of 6 months.

Metformin effects on menstrual abnormalities of women with PCOS were evaluated by assessing post-treatment changes in frequency of cycles. Furthermore, changes in several endocrine and metabolic features of the syndrome were along with insulin sensitivity were also assessed.

Table 1: Base Line Characteristics of Patients

Signs and Symptoms	No. of patients (N=30)	Percentage
Oligomenorrhoea	21	70%
Irregular cycles	09	30%
Acanthosis nigricans	02	6.66%
Male type baldness	03	10%
Acne	08	26.66%
Hirsutism (Face, arms & Legs)	20	66.66%
Ultrasound pelvis (multiple small ovarian cysts)	22	73.33%

Table 2: Changes in Patient Variables From "Day-0" To "Day-180"

Characteristics	Day 0 Mean ± S.D.	Day 180 Mean± S.D.	P-value
Weight (kg)	70.75± 9.30	66.24 $\pm$8.36	<0.001*
BMI (kg/m^2)	29.53 ± 2.56	27.29 $\pm$1.85	<0.001*

Blood pressure (mmHg): Systolic	130 ±15.7	120 ±11.3	0.001*
Diastolic	84 ± 8.0	82 ±7.8	>0.05
Fasting Serum glucose (mg/dl)	93.52 ±12.6	85 ±8.6	<0.001*
Fasting Serum Insulin (µU/ml)	20.3 ± 10.8	9.62 ±5.35	<0.001*
Serum Testosterone (ng/ml)	3.06 ± 0.78	2.63 ±0.62	0.001*

Table 3: Changes in Patient Variables After Treatment

Characteristics	**At Day-180**		
	Increase	**Decrease**	**No Change**
Weight (kg)	8 (24%)	23 (76.66%)	0
Body mass index (BMI) kg/m2	8 (24%)	23 (76.66%)	0
Blood Pressure: Systolic	3 (9%)	16 (48%)	14 (42%)
Diastolic	8 (24%)	10 (30%)	15 (45%)
Fasting serum glucose (mg/dl)	11 (36.66%)	19 (63.33%)	-
Fasting serum Insulin (µU/ml)	0	30 (100%)	-
S. Testosterone	5 (16.66%)	25 (83.33%)	-

RESULTS

Our study showed that 21 (70%) patients had oligomenorrhoea while 9 (30%) had irregular cycles making a total of 30 patients. Acanthosis nigricans (a darkening of the skin at the nape of the neck and underarms) was found in 2 (6.66%) patients. Male type bladness was seen in 3 (10%) patients. Acne on face was found in 8 (26.66%) patients. Hirsutism (excessive hairs on face, arms and legs) were detected in 20 (66.66%) patients. Out of a total of 30 patients, 22 (73.33%) were found to have multiple small ovarian cysts on ultrasound pelvis (Table1).

In our study, we found a significant reduction (P<0.001*) in body weight from 70.75+ 9.30 to 66.24 ±8.36Kg and in BMI from 29.53 ± 2.56 to 27.29 ±1.85 Kg/m^2 (table 2).

Mean systolic blood pressure showed a significant reduction (P<0.001*) from 130 ±15.7 to 120 ±11.3mm of Hg after 6 months of Metformin therapy. We also observed a decrease in diastolic blood pressure from 84 ± 8.0 to 82 ±7.8 mm of Hg but it came out to be non-significant (P>0.05) on statistical evaluation (table 2).

Fasting glucose level reduced significantly from 93.52 ±12.6 to 85 ±8.6 mg/dl in our study. As regard to the fasting serum insulin level, we observed a significant reduction in the mean fasting serum insulin level from 20.3 ± 10.8 to 9.62 ±5.35 µU/ml. We observed a significant decrease in the serum testosterone levels from 3.06 ± 0.78 to 2.63 ±0.62 (table 2).

DISCUSSION

Polycystic ovary syndrome (PCOS) which is characterized by chronic an ovulation and hyperandrogenism affects approximately 5% to 10% of women of reproductive age. Polycystic ovary syndrome is probably the most prevalent endocrinopathy in women and by far the most common cause of an ovulatory in fertility.[10] Hyperinsulinemia may have a direct effect on the hypothalamus and/ or pituitary to increase serum luteinizing hormone concentrations and therefore in directly increase LH-dependent ovarian androgen biosynthesis possibly resulting in abnormal LH and follicle stimulating hormone release and subsequent oligomenorrhoea.

Women with PCOS who are anovulatory and wishing to become pregnant have traditionally been treated with the antiestrogen clomiphene citrate as the first line medical therapy to induce ovulation. Given the importance of hyperinsulinemia in the development of hyperandrogenism and disrupted folliculogenesis it seems likely that medications that act as insulin sensitizing agents may be more useful in restoration of normal endocrinologic and clinical parameters of this condition. The most extensively studied insulin sensitizing drug in

the treatment of PCOS is Metformin.[11] Metformin has been administered to women with PCOS to reduce insulin resistance and the sequelae of hyper insulinemia including hyperandrogenism.[12]

Velazquez et al. (1997)[13] reported the results of 22 women with PCOS completing 6 months of Metformin therapy 500 mg three times per day. All patients in his study had chronic oligomenorrhoea or amenorrhoea, hirsutism and polycystic ovaries as assessed by ultrasound. Kolodziejczyk et al. (2000)[14] and Vandermolen et al. (2001)[15] also have demonstrated that Metformin administrated at a dose of 500mg three times daily increased menstrual cyclicity, improved spontaneous ovulation and promoted fertility. Acbay (1996)[16] and Ehrmann (1997)[17] have failed to demonstrate salutary effect of metformin in PCOS. In the later study the mean body mass index of the women approached 40 Kg/m^2 and Metformin is said to be not effective in cases of morbid obesity.

Conway et al. (2000)[18] reported the incidence of male pattern baldness in approximately 8% and acanthosis nigricans in 5% of women with PCOS. Conway et al[18] also found that all 20 patients included in his study were hirsute and none of them had acanthosis nigricans.

Pasquali (2001)[19] and Glueck (1999)[20] also have found significant reduction in the body weight of the patients. The latter has shown significant reduction of weight in 28 (65.1%) patients out of a total of 43 while we have observed significant decrease in 23(76.66%) patients out of a total of 30 patients.

Velazquez (1997)[13] in 22 patients found significant reduction in BMI from 26.79±4.13 to 26.22±3.99 Kg/m^2 and Glueck (1999)[20] in 43 patients observed significant reduction in BMI from 36.4$\pm$7.0 to 35.1±6.7Kg/m^2. These are in favour of our study as we have observed in 30 patients significant reduction in BMI from 29.53 ± 2.56 to 27.29 $\pm$1.85 Kg/m^2 whereas Hung (2001)[21] has observed an on significant increase in BMI from 23.8 to 24.1Kg/m^2 in 10 PCOS patients.

Nestler et al (1996)[22] on analysis of their studies have shown a significant reduction in both the systolic and diastolic blood pressures. In the study conducted by Nestler systolic blood pressure decreased from 128±2 to127±2 mm of Hg and diastolic blood pressure reduced from 87±1 to 83±1 mm of Hg respectively. Fasting glucose level reduced significantly from 93.52 ±12.6 to 85 $\pm$8.6 mg/dl in our study which is coinciding with the study of Morin-Papunen et al. (2000)[23]. He observed significant reduction in fasting glucose level of 8PCOS patients from5.2±0.1 (92.85 mg/dl) to 4.9±0.1 (87.5 ng/dl) mmol/L (-mmol/L by 0.056 conversion factor to gel mg/dl) after 3 months of Metformin therapy. Whereas Marea et al. (2002)[24] in 15 PCOS women after 35-40 days of Metformin therapy and Kolodziejczyk (2000)[14] in 35 women after 12 weeks of Metformin therapy found non-significant reduction in the fasting glucose level.

Kazeroonietal[25] found a decrease in the serum testosterone levels following 8 weeks of Metformin therapy. Another study done by K. H. Chouetal[26] also found a decrease in serum testosterone levels following 90 days of Metformin therapy.

Metformin therapy increases insulin sensitivity and decreases insulin levels in patients with the polycystic ovary syndrome. Improvement of hyperinsulinemia is associated with decreased levels of total and free testosterone and increased estradiol levels. Clinically administration of Metformin improves hirsutism, normalizes menstrual cycles and induces ovulation in a substantial number of patients with the polycystic ovary syndrome.[27]

CONCLUSION

We concluded that Met form in treated patients showed significant improvement in all parameters (except diastolic blood pressure) indicating that Metformin is of benefit in reducing insulin resistance. It seems that Metformin has a direct effect on the human ovarian steroidogenesis in addition to reduction of weight and body mass index.

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