Original Article

Polycystic ovarian syndrome: Response to metformin therapy

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ABSTRACT

Objective: To determine the response of polycystic ovarian syndrome (PCOS) to metformin therapy.

Methodology: This study was conducted from January 2006 to December 2007 at Peoples Medical College Hospital Nawabshah. All the patients presenting with infertility, menstrual irregularity and increase body mass index (BMI) were included. Diagnosis was confirmed by clinical presentation and ultrasound finding. Patients diagnosed with PCOS were given metformin for six months, the clomiphene was added for three months if the patients did not conceive. Later metformin alone was continued and patients were re-evaluated after one year.

Result: Total 63 patients, mean age of PCO was 24.49 ± 4.87 years and married were 52 (82.53%) cases, 44 (69.83%) cases were present with menstrual irregularity, 31–74% were overweight, 6.34% obese. 52 cases with infertility in which 39 (74.98%) cases had conceived.

Conclusion: Metformin significantly increase ovulation and conception rate.

KEY WORDS: Polycystic Ovarian Syndrome, Metformin, Mesntrual Irregularity, Infertility.

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INTRODUCTION

Polycystic ovarian syndrome (PCOS) is a common endocrine disorder of women in their reproductive years with prevalence of upto 10%.[1] The PCOS is the commonest endocrine disturbance leading to anovulatory infertility and oligomenorrhoea.[2]

Polycystic ovarian syndrome was first recognized in 1935 by two gynaecologists Dr. Irving Stein and Dr. Michael Leventhal. PCOS is heterogenous disorder, associated with amenorrhoea, infertility, variable level of hirsutism and obesity in the presence of bilateral enlarged ovaries.[3] PCOS is characterized by the presence of enlarged ovaries with multiple small cysts (2–8 mm in diameter) and a hypervascularized androgen secreting stroma.[4]

The disease is manifested clinically by signs of androgen excess including hirsutism, alopecia, obesity and menstrual cycle disturbance either oligomenorrhoea or amenorrhoea.[5] Normal ovulatory mechanism which includes selection of an ovarian follicle which grows in response to appropriate secretion of FSH became dominant and ovulates, gets disturbed in women with PCOS due to androgen excess and hyperestrogenism.[6]

Ovarian overproduction of androgens is due to hyperinsulism and raised insulin levels are recognized as an important feature of PCOS.[7] Insulin lowering therapies such as metformin can bring improvement in insulin resistance and ovarian hyperandrogenism.[8] It has also been shown that the ovulatory response to clomiphene for

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induction can be increased in PCOS by decreasing insulin secretion with metformin.[9] The association of insulin resistance contributing to anovulation has led to normal and promising therapy administering insulin sensitizing agent to women with PCOS in order to restore ovulation and enhance fertility.[10]

The objective was to evaluate the effect of metformin therapy in patients with polycystic ovarian syndrome.

METHODOLOGY

This cross-sectional study was conducted in the Department of Obstetrics & Gynaecology at Nawabshah Medical College & Hospital, Nawabshah during the period from January 2006 to December 2007. Total 63 patients included in the study were evaluated, menstrual cycle, past obstetrical history, History of drug use and abnormal menstrual cycle was categorize further in three groups, Oligomenoorhoea with Hypomenorrhoea, Oligomenorrhoea alone and Amenorrhoea.

Family history of PCOS, endometrial cancer or diabetes was also taken. Detailed examination was carried out in every patient with calculation of body mass index (BMI) which was classified in four groups. Group-I was having BMI < 25, Group-II having BMI 25–30, Group-III having BMI 31–35 and group-IV having > 35. Ultrasound of pelvis was done to assess follicular status. Presence of eight or more follicles in one or both ovaries with absence of mature follicle was taken as diagnostic of PCOS. Metformin was started with a dose of 250 mg once daily initially for the first week then gradually adjusted to 500 mg three times a day. Weight loss encourage by diet and exercise which was part of treatment. Patients were evaluated after six months for achievement of the menstrual regularity, fertility and change in the body mass index (BMI). Patient who failed to conceive after six months of treatment with metformin was given clomiphene citrate as per protocol starting with 50 mg daily, the first cycle upto maximum of 150 mg in third month. In women who failed to conceive after three doses of clomiphene citrate, then metformin alone was continued and fertility was re-evaluated at the end of one year.

Table-II: Body Mass Index (BMI).

BMI	*No. of Cases*	*Percentage*
< 25	17	26.98%
25 – 30	22	34.92%
31 – 35	20	31.74%
> 35	04	06.34%

Table-I: Age Distribution.

Age Group	*No. of Cases*	*Percentage*
18-23 years	27	42.85%
24-29Years	25	39.68%
30 Years and above	11	17.46%

RESULTS

Total 63 patients were included in this study, mean age of patients was 24.49 ± 4.87 years, majority of the patients aged between 18–23 years were 27 (42.83%); Fifty two patients were married while 11(17.46%) were unmarried. Seventy three percent of the patients had weight gain problem. 87% cases had infertility of which 19 (36.53%) cases conceived within six months, another twelve (23.07%) conceived within one year, another eight patients (15.38%%) conceived after one year while 13 remained infertile, 70% patients had menstrual irregularity and 30% cases had regular cycle. Twenty (31.74%) cases had oligomenorrhoea, 10 (15.87%) cases had hypomenorrhoea and 14 (22.22%) cases had Amenorrhoea.

DISCUSSION

In this study, the effect of metformin therapy in achieving menstrual regularity, pregnancy, reducing weight and hyperinsulinemia in patients with polycystic ovarian syndrome was observed. It was seen that women in increased body mass index category, moved to lower body mass index after 6 months of treatment. Weight reduction by diet, exercise and metformin is important. The frequency of spontaneous ovulation induced by clomiphene citrate can be increased in obese women with the PCOS by decreasing serum insulin concentration with metformin.

Weight loss might also have been prompted by simultaneous exercise and diet control. The most common clinical features of PCOS included menstrual irregularities, hirsutism and obesity.[3,11]

In a study carried out by Balen et al[12], oligomenorrhoea found in 47% of the cases. This figure correlate well with our finding as it was present in 47.61% of our cases. Amenorrhoea was present in 14.2% patients of Balen et al as compared to 22.22% in our patients. In a study carried out by

Table-III: Fertility. (52 married patients)

Fertility	*No. of Cases*	*Percentage*
Conceived < 6 Months	19	36.53%
Conceived at First Year	12	23.07%
Conceived after One Year	08	15.38%
Not Conceived	13	25%

Fouzia et al[13] in Pakistani patients, Oligomenorrhoea was found in 75% of their cases and in another study 64% cases were Oligomenorrhoic.[14] Although amenorrhoea and oligomenorrhoea are the most common findings, normal menses may be present in PCOS.[12,15] Balen et al[12] found normal menses in 29.7% of their cases which is in agreement with our figure of 30.15% patients who had normal menses. In another study from Pakistan 30% patients presented with normal menstrual cycle.[14]

PCOS demonstrates the levels of sex steroids in relatively steady state in contrast to the fluctuating level of normal menstrual cycle. An exaggerated response of serum LH to gonadotrophins releasing hormone as compared with that occurring in various phases of normal menstrual cycle which has been well documented in PCOS since long.[16,17] As serum FSH may be low and LH may not always be elevated, it has been suggested that use of the LH:FSH ratio would be most discriminatory for a hormonal diagnosis and a ratio of greater that two in the presence of clinical feature and ultrasound finding is taken as diagnostic.

The criteria fulfilling sufficient specificity and sensitivity to define the PCO should have at least one of the following either 12 or more follicle measuring 2–9 millimeters in diameter or increased ovarian volume > 10cm.[3] PCOS is a disorder in which an association exist between insulin resistance and altered ovarian function. PCOS most of the time, co-exist with insulin resistance, which is the key function for aggravation of ovulation dysfunction and metabolism disarrangement.

The basic problem is the ovary conversion of normal oestrogen micro-environment to abnormal androgen environment. This is due to failure of granulose cell to convert testosterone produced by ovary to estrogen.[18] The androgen excess in PCOS is milder than that observed in ovarian tumour and hyperthecosis and circulating level does not generally exceed 150 ng/dl.[19] Insulin resistance giving rise to hyperandrogenesis with resultant anovulation is a recently realized important pathogenetic mechanism in PCOS.[5,6,20] Insulin resistance occurs not only in obese women with PCO where it might be expected because obesity is often associated with insulin resistance but also in 50% of normal weight women with PCOS.[21] Almost 70% of subjects experienced an amelioration of menstrual irregularities. Mean androstenedione, testosterone, and 17-hydroxyprogesterone levels and hirsutism score were significantly improved by metformin.[22]

Clomiphene citrate and gonadotrophin are most commonly used drugs for ovulation induction in PCO, but realization of this pathogenetic mechanism has given a new direction to the treatment of PCOS with insulin sensitizing drugs, giving promising results and significantly higher success rates of ovulation and pregnancy[23,24] as compared with clomiphene citrate.[24,25] In another study, metformin plus clomiphene citrate increase the cumulative ovulation rate from 49.0 to 60.40%.[26] The pregnancy rate was 8% with clomiphene citrate and 24% with metformin and clomiphene citrate in another study.[27] In yet another study, conception was found 46% with metformin and clomiphene citrate combination therapy.[28] Among these drugs, metformin is most widely used being safe without any teratogenic effects.[7,8]

After this new development many studies have been carried out worldwide to establish the role of metformin in patient of PCOS.[8,25,29] In one study by Vandemolen et al[25], 25% of patients taking metformin and clomiphene citrate, whereas only 27% of the patients taking clomiphene citrate only ovulated and conception rate in those with metformin group was 75%. In another study, carried out by Malikwai and Qublan[29], ovulation rate 68.8%, Imtiaz et al[30], studied the role of metformin in ovulation induction and subsequent conception in Pakistan patients of PCOS having hyperinsulinaemia 72% of patients ovulated within three to nine months of treatment of metformin and 32.5% of those who ovulated conceived. The ovulation rate was 62.5% with metformin in one study.[31] In other study, addition of metformin along with clomiphene citrate significantly increased the ovulation rate during 6 months treatment 68% of patients.[15]

In this study, the clinical symptomatology of infertility was most common in 82% of which 36.53% conceived spontaneously within 6 months. Further 38% conceived after taking clomiphene citrate therapy. So, overall fertility achieved at the end of one year was 74%. Our findings on the role of metformin increasing the ovulation rate and conception rate is comparable with result of above quoted studies.

CONCLUSION

Iinsulin resistance positively correlates with severity of polycystic ovarian morphology in patients with polycystic ovarian syndrome and Metformin therapy significantly increases the ovulation and conception rate.

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