Role of Metformin in Improving the Symptoms of Polycystic Ovarian Disease

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ABSTRACT

Objectives: To study the effect of metformin in regularity of menstrual cycle, resumption of ovulation and hirsuitism and weight reduction of women with polysyctic ovarian disease.
Study design: Quasi experimental study was conducted.Study was carried out in Gynae Unit II, Jinnah Hospital, Lahore, which is territory care hospital.
Duration of study: Study was completed in six months from 29 September 2008 to 29 March 2009
Subjects and Methods: Hundred patients with polycystic ovarian disease constituted the study sample. Fifty women were non-randomly allocated to the Experimental group and given metformin (Group A) and fifty women were in the control group who did not receive any therapy (Group B) were the control group.A Non-probability convenience sampling technique was used to obtain the required sample. The Experimental group (Group A), was given Metformin 850 mg twice a day for three month and was also counseled for weight reduction. While the Control group (Group B) was managed as usual with no medication and only counseling for weight reduction. Data collection tools included patient's history & clinical examination. Data was recorder on a pre-designed checklist and was analyzed by using SPSS computer software. The p value, 0.05 was be used as a cut off point for statistical significance.
Results: After six months of commencement of intervention, there was significant reduction in menstrual irregularities and improvement in resumption of fertility. However, there was no significant reduction in hirsuitism or change in body mass index (BMI).
Conclusion: Metformin improves menstrual irregularities, and resumption of fertility in Polycystic ovarian disease [PCOD]. However, further work up is needed in which larger number of patient and longer duration of study is needed.
Keywords: Metformin, polycystic ovarian disease, fertility, menstrual cycle

INTRODUCTION

The exact pathogenesis and etiology of PCOD is not clearly understood. In recent years there has been lot of speculation regarding the causative factors but it is still not clear whether it is ovarian dysfunction or hypothalamo-hypophyseal and ovarian disarrangement which leads to an ovulation and abnormal production of hormones[1,2]. Poly ovarian disease is heterogenous disorder, which presents with symptoms of obesity, hyperandrogenism, oligomennorrhoea / amennorrhoea & infertility which may occur either singly or in combination. The patient may be asymptomatic in certain case[3]. Although its etiology is unknown but the most suggestive cause is inappropriate feedback signals to hypothalamic pituitary unit. It is commonest endocrine disorder of women & is familial condition possibly autosomal

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dominant. It appears during adolescence & is thought to be associated with weight gain during puberty[4]. However the polycystic ovary gene has not yet been identified and the effect of environmental influences such as weight changes and circulating hormone concentration and the age at which these occur is unknown[5]. In polycystic ovarian disease, there was be increased serum level of testosterone, androstenedione, LH, fasting insulin, prolactin, oestradiol and oestrone level but decrease serum sex hormone binding globulin[6]. It has been recognized increasingly that polycystic ovarian disease and insulin resistance are intimately related with respect to pathogenesis, endocrine disturbances and molecular biology[7]. Women with polycystic ovarian disease have greater frequency of both hyperinsulinaemia and insulin resistance, increased insulin level stimulate ovarian secration of androgens[8]. Metformin is the most widely used drug. This therapeutic intervention has been shown to exert beneficial effects on the endocrine and metabolic disturbance that characterize the syndrome and, more recently, to improve the reproductive outcome

in women with polycystic ovary syndrome. With rapid progress in this area, metformin use has also been extended to the management of lean polycystic ovary syndrome patients[9].

PATIENTS AND METHODS

A novel therapeutic approach using insulin-sensitizing agents has been extensively investigated in polycystic ovarian disease in women of reproductive age group. In most studies conducted, to date, metformin have resulted in improved insulin sensitivity, resumption of regular menses and decreased serum androgen levels. Metformin belongs to Biguanide group of oral hypoglycaemic drugs which act by decreasing glucose absorption from gut and increase insulin sensitization to glucose with a dosage of 850 mg twice a day for one month.

The present study was be conducted to appraise the therapeutic effect of metformin in improving symptoms of polycystic ovarian disease and to make further recommendations for its use. Metformin markedly improves the symptoms of polycystic ovarian disease, namely irregularities of menstrual cycle, infertility, hirutism and obesity, if present. The objective of the study was to observe the effect of metformin in married women in reproductive age group, presenting with polycystic ovarian disease with respect to:

- Regulation of menstrual cycle
- Resumption of fertility
- Reduction in hirsutism
- Change in Body Mass Index (BMI)

The study was conducted in Gynae unit II, at Jinnah Hospital, affiliated with Allama Iqbal Medical College, Lahore. The study population consisted of all women in the reproductive age group (between ages of 15 to 49 years) presenting with polycystic ovarian disease, confirm on ultrasonography and hormonal profile, in the outpatient Department of Gynae unit. The study sample consisted of a total of 100 patients, who agreed to participate in the study. Out of which, 50 women with polycystic ovarian disease allocated the experimental group, receiving metformin therapy (Group A) and another 50 women with polycystic ovarian disease acted as the control group who never receive any therapy (Group B).
A Nonpropability convenience sampling technique was used to obtain the required sample.
The inclusion criteria were:
a) Married Women in Reproductive Age (MWRA)
b) Women having symptoms of polycystic ovarian disease
c) Polycystic ovarian disease diagnosed on ultrasound
The exclusion criteria were:

a) Infertility due to any other cause
b) Androgen producing tumors
c) Other causes of amenorrhoea / oligomenorrhoea
d) Patients on certain drugs interfering in the disease process under study

From the sample of 100 participants of the study, 50 were selected in a non-random way to be the experimental group (Group A) and the rest of 50 patents were the control group (Group B). Group A was given Metformin 850 mg twice a day for three months, and was also counseled for weight reduction. Group B was managed with no medication and only counseling for weight reduction.

A predesigned, semi-structured, and pre-tested, proforma was self-administered by the researcher to collect the required information from both the experimental and control groups. The proforma generated information on the presenting complaints,sexual, obstetric and menstrual history, past and family history of the patient.General physical examination [GPE], conducted at the start and the end of data collection period, including weight in kilograms and height in meters to calculate the BMI at the beginning and the end of the study.Abdominal and pelvic examinations, conducted at the beginning of the study.Laboratory Investigations, carried at the beginning of the study to check the levels of FSH, LH, Serum Prolatin, Serum Testosterone. Trans-abdominal scan conducted at the beginning of the study for diagnosis.

Data was collected in 6 months time from September 2008 to March 2009. Data was analyzed using Statistical Package for Social Scientist (SPSS). Data was double entered on SPSS package 10 computer programs. Data cleaning was done through checks and validity modules of SPSS and Rec. files were made for the final analysis. Analysis was planned according to the following variables both in the Experimental and Control Groups, based on the history and clinical examination:

- Regulation of menstrual cycle
- Resumption of fertility
- Reduction in hirsutism
- Change in Body Index (BM)

Data analysis was done for frequency listing of simple tables. The Chi-Square (x2) test was applied to study the relationship between different categorical variables in the Experimental and the Control groups. The p-value of 0.05 was used as a cut off point for statistical significance.The women who were included in the study were explained the purpose of the study, and the complete procedures involved. The control group was provided the usual management for polycystic ovarian disease which only entails counseling for weight reduction as well as explained that they was receive a new therapy which is not

used in routine for the management of their problem. Verbal consent was acquired from the patients included in the study for publication of the study results.

RESULTS

The frequency distribution of 100 respondents by age was calculated. In the Experimental Group A, 3 women (6%) and In the Control Group B, 4 women (8%) were less than 20 years of age. In the Experimental Group A, 12 women (24%) and in the Control Group B, 11 women (22%) were in the age group between 20-24 years. Among the Experimental Group A, 18 respondents were women (36%) and in the Control Group B, 21 women (42%) were between the ages of 25-29 years. In the Experimental Group A, 15 women (30%) while in Control Group B, 13 women (26%) had ages between 30-34 years. Only 2 respondents (4%) in the Experimental Group A and 1 respondent (2%) in Control Group B were between the ages of 35-39 years. Regarding frequency distribution of 100 respondents by infertility before intervention it was observed that in Experimental Group A, 34 women (68%) and in Control Group B, 32 women (64%) had primary infertility. In Experimental Group A, 16 respondents (32%) and in Control Group B, 18 respondents (36%) had secondary infertility in 100 respondents before intervention. Duration of infertility in respondents before intervention was measured. In the Experimental Group A, 28 women (56%) and in the Control Group B, 25 women (50%) had infertility of about 1-2 years. Infertility of around 3-4 years was reported by 13 women (26%) in the Experimental Group A and 14 women (28%) in Control Group B. In Experimental Group A, 9 respondents (18%) and in Control Group B, 11 respondents (22%) gave a history of infertility for more than 5 years. The sonographic findings respondents before intervention revealed, polycystic ovaries in 21 women (52%) in Experimental Group A and in 23 women (56%) in Control Group B. Increased Ovarian size was observed among 12 women (24%) in the Experimental Group A and in 13 women (26%) in Control Group B. Normal ovaries were observed among 17 respondents (34%) from the Experimental Group A & 14 respondents (28%) in Control Group B.

Before intervention, menstrual history was taken from all 100 women, they were also examined for the presence of Hirsuitsm and their BMI, they was calculated. It was observed that majority of patients presented with history of menstrual irregularities, including, oligomennorrhoea or amennorrhoea.

Among these, 37 women (74%) were in Experimental Group A, and 34 women (68%) were in Control Group B. Hirsutism was reported by 12 respondents (24%) in Experimental Group A and 10 respondents (20%) in Control Group B. Regarding mass index (BMI) of respondents before intervention, BMI of less than 18 was observed in 2 respondents (4%) in the Experimental Group A and in 3 respondents (6%) in Control Group B. Women with BMI between 18-25 were 16 in number (32%) in Experimental Group A and 19 number (38%) in Control Group B. However, there was no significant difference in menstrual irregularities, hirsuitism or BMI between experimental and control groups (p>0.05). After six months of commencement of intervention, the patients were again examined for menstrual cycle irregularities, resumption of fertility, reduction in hirsuitism and change in body mass index (BMI). ***Table 1*** shows that compared with only 2 respondents in the Control Group B (4%) 12 women in the Experimental Group A (24%) had regular menstrual cycle, while 28 women in the Experimental Group A (56%) and 32 women in the Control Group B (64%) had irregular menstrual period. However, there was no information available on the menstrual cycle of 7 respondents in the Experimental Group A (14%) as well as 8 respondents in the Control Group B (16%). The difference between the Experimental Group A and the Control Group B for menstrual cycle regularity was highly statistically significant (p=0.004).

Table 2 depicts the resumption of fertility in the two groups under study. Compared with 3 women in the Control Group B (6%), 12 women in the Experimental Group A (24%) showed sings of ovulation. Spontaneous pregnancy was observed only in 5 women, all in the Experimental Group A (10%). After six months of intervention, 26 women in the Experimental Group A (25%) and 39 women in the Control Group B (78%) still did not conceive. This difference in resumption of fertility in the two study groups was highly statistically significant (p=0.001). Table 3 and 4 highlights that even after six months of intervention, there was no significant reduction in hirsuitism or change in the BMI in the Experimental Group A compared with Control Group B.

Table 1: Pattern of menstrual cycle among 100 patients of PCOD after intervention

Menstrual cycle	Experimental Group A		Experimental Group B	
	=n	%age	=n	%age
Regular	30	60.0	12	24.0
Irregular	20	40.0	38	76.0
Total	50	100.0	50	100.0

$X^2 = 8.04$, df = 1, P = 0.004

Table 2: Resumption of fertility among 100 patients (PCOD) after intervention

Pattern of fertility	Experimental Group A		Experimental Group B	
	=n	%age	=n	%age
Ovulation	22	44.0	03	06.0
Spontaneous pregnancy	07	14.0	03	06.0
No conception	20	40.0	36	72.0
No follow-up	01	02.0	08	16.0
Total	50	100.0	50	100.0

X^2 = 19.26, df = 1, P = 0.001

Table 3: Hirsuitism among 100 patients of PCOD after intervention

Hirsuitism	Experimental Group A		Experimental Group B	
	=n	%age	=n	%age
Reduction	04	08.0	00	00.0
No reduction	39	78.0	42	84.0
No follow up	07	14.0	08	16.0
Total	50	100.0	50	100.0

Table 4: Change in Body Mass Index (CBMI) among 100 patients of (pcod) after intervention

Change in BMI	Experimental Group A		Experimental Group B	
	=n	%age	=n	%age
< 18/	08	16.0	06	12.0
18 – 25	16	32.0	16	32.0
25 – 30	21	42.0	12	24.0
> 30	03	06.0	09	18.0
No follow-up	02	04.0	08	16.0
Total	50	100.0	50	100

X^2 =3.13, df =3, P = 0.37

DISCUSSION

In early decades of last century there were lot of misconception about etiology and pathogeneses i.e. anterior pituitary hormonal disorder, infection and cystic degeneration. The treatment offered to these patients was classical ovarian wedge resection and laproscopic ovarian drilling. These surgical interventions lead to surgical complications[11,12].

With the advancement of medical sciences and the availability of ultrasonography and hormonal profile, it was discovered that PCOD is a metabolic disease, in which there is insulin resistance. Insulin-sensitizing agents have been recently proposed as the therapy of choice for polycystic hyperinsulinemia and are recognized as important pathogenetic factors of the syndrome. Moreover, since almost all obese PCODS women and more than half of those of normal weight are insulin resistant, and therefore present some degree of hyperrinsulinemia, the use of insulin sensitizers should be suggested in most patients with PCODS. Insulin sensitizing agents like troglotazone were found to be hepatotoxic and were banned in the UK[13].

In the present study, conducted on 100 patients of PCOD, it was observed that there were significant changes in the Experimental Group A, in which 60% of patients showed regular menstrual cycle within six months of treatment whereas in control group no significant result seen in patients of PCOD developed normal pattern of menstrual cycle. Similar results were obtained in the study conducted by Essah[14], whose results showed that metformin is highly effective in normalizing menstrual cycle in women with polycystic ovary syndrome and the overall response rate in his study was that 88% of patients achieved normal cycle, with a treatment duration of 6 months or longer. In the present study there were significant improvement in ovulation and spontaneous pregnancies i.e. there was 44% improvement in ovulation and 14% of patient conceived with the six months therapy. In a study conducted by, Zafar[15], after six months of Metformin therapy, menstrual regularity was achieved in 19 out of 22 women (86%). Out of these 11 women (50%) were ovulating at six months.

Another study Eisenhardt[16], menstrual disturbance was successfully improved in the metformin-treated group, depending on IR (12 of 15 vs. 3 of 17), whereas women without IR (four of seven vs. four of six) had no significant amelioration of their menstrual regulations (P<0.05). Sixty seven percent of metformin-treated women had at least one ovulation, compared with only 45% in the placebo group.

In a local study conducted by Hasan and Memon[17], significant effect of metformin therapy was observed at 3 months follow-up visit, as 5(16.7%) women achieved pregnancy while 20(66.6%) women had a regular menstrual cycle (p=0.001).

CONCLUSON

Diagnosis of PCOD was made if polycystic ovaries on ultrasound were found in combination with one or more of clinical and biochemical features of androgen excess and chronic anovulation.

In an attempt to resolve the debate, PCOD consensus workshop group agreed that two of the following three criteria were required in order to diagnose the condition after exclusion of other causes of androgen excess, these three criteria were: Oligomennorrhoea and / or anovulation, clinical and / or biochemical sings of hyperandrogenism; and polycystic ovary morphology on ultrasound scan.

The treatment is now aimed towards measures to improve insulin resistance as these have been shown to improve the regularity menstrual cycles.

Ovulation, androgen levels and surrogate makers for longer term risk of diabetes and heart diseases. Life style modification and metformin which both improves insulin resistance have, therefore, been the focus of recent research. There is clear evidence that metformin improves menstrual irregularities and ovulation in PCODS and can be offered to all women (obese and non-obese) with an ovulatory infertility. Also the risk of hypoglycaemia with metformin treatment in PCODS is low. It does not required surgical intervention, thus does not need hospitalization. Metformin can be given on outpatients' basis. It has been observed a good results of metformin in terms of initiation and persistence of regular ovulatory cycles and pregnancy rate.

Drug is useful in lowering of insulin levels so promote reduction in weight, spontaneous return of ovulation and normal menstrual rhythm with six months of the therapy. It is, however, recommended that metformin is used as stand-alone first-line therapy, for at least six months.

If pregnancy has not occurred, after a year of metformin alone or metformin plus clomiphene combination therapy, alternative treatments within (laparoscopic ovarian drilling, gonadotrophins or In Vitro Fertilisation (IVF) are used. There are currently no clear guide lines on the role of follicle tracking in women on metformin monotherapy as in theory the risk of multiple pregnancy and ovarian hyperstimulation are absent. Metformin is usually discontinued once pregnancy is confirmed although there is no evidence of animal or human fetal teratogenicity. Still in an absence of clear and consistent data about the effects of metformin on pregnancy rates, live-birth, or in reducing the potential longer term health risk of PCODS.

REFERENCES

1. Palmer R, deBrux J. Resultants histologiques, biochemiques et therapeutiques obtenus chez les femmes don't les ovaries avaient etc diagnostiques stein-Leventhal a la coelioscopic. Bull Fed Soc Gynaecol Obstet Lang Fr 1967;19:405-12.
2. Gjoannaess H, Polycystic ovarian syndrome treated by ovarian electrocautry through the laparoscope. Fertil 1984;41;20-25.
3. Awartani KA, Cheung AP. Metformin and polycystic vary syndrome a literature review. J Obstet Gynaecol Can 2002;24:393-401.
4. Hundal RS, Inzucchi SE. Metformin: new understandings, new uses. Drugs 2003;63:1879-94.
5. Massin N, Galey J, Basille C, Theron-Gerard L, Bry-Gauilladr H, Cedrin-Durnein I, et al. Should infertile women with polycystic ovarian syndrome be treated with metformin? Gynecol Obstet Fertil 2003;31:265-74.
6. Mitkov M, Pekhkivanov B, Simeonov S, Velchev G. [Our experience in the treatment of polycystic ovary syndrome with Metformin] Akush Ginekol (Sofiia). 2001;40:25-7.
7. Nardo LG, Rai R. Metformin therapy in the management of polycystic ovary syndrome: endocrine, metabolic and reproductive effects, Gynecol Endocrinol 2001;15:373-80.
8. Nazir F, Saeed S, Malik M, Aziz H, Aliya S, Rana S. Polycystic ovary syndrome (PCODS) – diagnosis and management in fertility deprivation. Park J Obstet Gynaecol 1999;12:59-71.
9. Seli E, Duleba Aj. Should patients with polycystic ovarian syndrome be treated with metformin? Hum Reprod 2002;17:2230-6.
10. Siddiq S, Zaman F, Khan RL. Four years review of incidence and management of ovarian hyperstimulation syndrome in a Specialized Canter for Reproductive Medicine in Pakistan. Ann Coll 2002; 8:63-5.
11. Hasan AJ, Memon UG. Impact of metformin therapy in patients with Polycystic ovarian syndrome J Coll Physicians Surg Pak 2005;11:712- 5.
12. Zafar S, Role of Metformin in correcting hyperinsulinemia, menstrual irregularity and anovulation in Polycystic Ovary Syndrome J Ayub Med Coll Abottabad 2005;4:54-6.
13. Adil F, Ansar H, Munir AA, Polycystic ovarian syndrome and HyperinsulinemiaJ Liaquat Uni Med Health Sci 2005;3:89-93.
14. Eisenhardt S, Schwarzmann N, Henschel V, Germeyer A, von Wolff M, Hamann A, Strowitzki T, Early effects of metformin in women with Polycystic ovary syndrome: a prospective randomize, double-blind, Placebo- controlled trial. J Clin Endocrinol Metab. 2006;91:946-52.
15. Hasan JA, Memon GU, Impact of metformin therapy in patients with Polycystic ovarian syndrome. J Coll Physicians Surg Pak. 2005;11:712-5.
16. Allen HF, Mazzoni C, Heptulla RA, Murray MA, Miller N, Koenigs L, et al. Randomized controlled trial evaluating response to metformin versus Standard therapy in the treatment of adolescents with polycystic ovary syndrome. J Pediatr Endocrinol Metab. 2005;8:761-8.
17. Raja A, Hashmi SN, Sultana N, Rashid H, J Ayub Med Coll Abbottabad. Presentation of polycystic ovary syndrome and its management with clomiphene alone and in combination with metformin. J Ayub Med Coll Abbottabad. 2005;2:50-3