

Original Article

Comparative analysis between ethinyl estradiol plus cyproterone acetate with or without metformin therapy in the treatment of polycystic ovarian syndrome induced hirsutism

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Abstract *Background* Hirsutism is growth of terminal hair in male pattern distribution in females. The great majority of these women have polycystic ovarian syndrome (PCOS). Current evidence suggests that patients with PCOS, whether slim or obese, have elevated levels of insulin which stimulates androgen production from ovaries, leading to hirsutism. Metformin has been shown to be effective in reducing serum insulin levels and in turn its effects.

Objective To compare the efficacy of ethinyl estradiol plus cyproterone acetate with or without metformin in polycystic ovarian syndrome-induced hirsutism.

Patients and method 160 patients of hirsutism were divided in two groups. Patients in group I were administered ethinyl estradiol 35µg with cyproterone acetate 2mg (Diane 35®) for 21 days and 100mg cyproterone acetate for first ten days of the menstrual cycle. While patients in group II were administered metformin 1000mg per day in addition to the above regimen. Patients were followed up at 1, 3, 6 and then 9 months interval. The variables assessed included; degree of hirsutism, menstrual cyclicity, body mass index, luteinising hormone levels, follicle stimulating hormone levels and LH/FSH ratio.

Results 137 patients were evaluable whereas 23 patients were lost to follow up. Out of 68 patients in group I, 22/31 (70.9%) patients improved from severe hirsutism to moderate grade. While 16/26 (61.5%) patients with moderate hirsutism improved to mild grade. Among the 69 patients of group II, 24 (72.7%) with severe hirsutism and 14 (63%) with moderate hirsutism improved to moderate and mild grades, respectively. However, there was little statistical difference between two regimens ($p>0.05$). Menstrual cyclicity improved in 41.1% of group I patients but in 79.7% of group II patients ($p<0.05$). Body mass index decreased in 23% of group I but in 44% of group II patients ($p<0.05$). Significant decrease in luteinising hormone levels and LH/FSH ratio with an increase in follicle stimulating hormone levels were seen.

Conclusion Metformin was found to be only marginally effective in treating hirsutism, but was highly effective in regulating menstrual cycle and decreasing obesity. It may also have an effect on improving fertility.

Key words

Hirsutism, polycystic ovarian syndrome (PCOS), metformin, cyproterone acetate.

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Introduction

Polycystic ovarian syndrome (PCOS) is a heterogeneous endocrinological disorder with variegated symptomatology of obesity, menstrual disturbances, anovulatory infertility, hyperandrogenism, hirsutism and acne.¹ Using ultrasound criteria, polycystic ovaries are found in 57% of women with anovulation and 50-80% of women with idiopathic hirsutism.² Traditionally, polycystic ovarian syndrome is an endocrinological condition secondary to aberration in the hypothalamo-pituitary ovarian axis manifesting as high luteinising hormone/follicle stimulating hormone ratio, increased production of androgen and high estrone levels.³ Peripheral conversion in adipose tissue of androgens are now highlighted with recent Rotterdam ESHRE/ASRM sponsored PCOS consensus, according to which oligo/and anovulation, clinical and/or biochemical signs of hyperandrogenism and polycystic ovary morphology on ultrasound are must for the diagnosis.⁴ This is supported by recent role of genetics,⁵ insulin resistance⁶ and the interrelationships between obesity and ghrelin⁷ (a gastric peptide with adipogenic activity). Despite resistance to insulin of whole body, ovaries have high responsiveness to insulin,^{7,8} which leads to ovarian hyperandrogenaemia and in turn hirsutism and acne.⁹ Both of these are very devastating cosmetic and psychosocial effects requiring dermatological treatment.

Ethinyl estradiol 35µg and cyproterone acetate 2mg, alone or in combination with 100mg cyproterone acetate for the first ten

days of the menstrual cycle, are the widely prescribed oral therapy worldwide.¹⁰ Metformin has been shown to be effective in lowering serum insulin levels and in turn inducing ovulation and regulating menstrual cycle.¹¹ It also improves objective measures of hirsutism. It is effective in both obese and lean individuals in some clinical trials.¹²⁻¹⁵ These trials have been done in patients with polycystic ovarian syndrome with the aim to assess its effect on menstrual cyclicity and fertility. We performed this clinical trial to see whether addition of metformin 1000mg gives better results than ethinyl estradiol plus cyproterone acetate 100mg alone or not.

Patients and methods

It was an open, prospective, clinical trial. The study was conducted by Department of Dermatology, Bahawal-Victoria Hospital, Quaid-e-Azam Medical College, Bahawalpur in collaboration with Department of Gynecology. It was conducted over a period of two years, 1st March 2003 to 28th February, 2005. Out of 200 patients of hirsutism, 160 fulfilled the clinical and ultrasound criteria of polycystic ovarian syndrome and were included in the study.

Each patient was fully examined and a detailed history was taken. Data regarding body mass index, waist hip ratio, Ferryman-Gallway hirsutism scoring, menstrual pattern, levels of fasting insulin, luteinising hormone and follicle stimulating hormone were recorded on a specified pro forma. These patients were divided into two groups. Group I received ethinyl estradiol 35µg with

cyproterone acetate 2mg for 21 days and 100mg of cyproterone acetate for the first 10 days of the cycle, while group II patients had addition of metformin 1000mg per day as well. Patients were called after 1, 3, 6 and 9 months for follow up. All the variables were assessed on every visit. Any side effect, that appeared was also noted. Overall assessment was done at 9 months of therapy. Chi-square test was applied for statistical analysis.

Results

At the end of the study, results were evaluated in 137 patients (68 in group I and 69 in group II). 23 patients were lost during the follow up. Average age of patients in group I was 25 ± 4 years while in group II it was 27 ± 4 years. Overall, the age range was from 16 to 38 years. In group I, hirsutism was severe in 31 (45%), moderate in 26 (38.2%) and mild in 11 (16%), while in group II these figures were; 33 (47.8%), 22 (31.8%) and 14 (20%), respectively (**Table 1**).

In group I, 10 (32%) of patients showed improvement from severe to moderate hirsutism after 6 months and 22 (70.9%) after 9 months. 8 (19%) improved from moderate to mild hirsutism after 6 months which increased to 16 (61.5%) after 9 months (**Table 2**). While in group II, 8 (24%) and 24 (72.7%) of the patients showed improvement from severe to moderate at six and nine months, respectively. Similarly improvement from moderate to mild in 3 (13%) patients and 14 (63%) patients at six and nine months was recorded, respectively (**Table 2**).

Statistically the difference in the results was not significant ($p > 0.5$).

Overall effect on menstrual irregularities was as follows; out of 68 patients of group I, 29 had amenorrhea and amongst them 16 (55.1%) showed improvement, while 39 with oligomenorrhea on treatment showed improvement in 12 (30.7%). In group II, out of 27 patients with amenorrhea, improvement occurred in 21 (77%) and oligomenorrhea improved in 34/42 (80.9%) [**Table 2**], ($p < 0.05$). Body mass index decreased and waist-hip ratio increased in 23% of group I patients and in 44% of group II patients, ($p < 0.05$).

Statistically significant decrease was seen in luteinising hormone and LH/FSH ratio with an increase in follicle stimulating hormone levels after nine months of treatment with metformin in group II patients.

With regards to adverse effects nausea, mild gastric upset were noted in 10% of group I patients while in group II, 36% of patients experienced severe nausea, vomiting and headaches and needed repeated counseling to continue.

Discussion

Polycystic ovary syndrome is a prevalent cause of menstrual disorders, acne and hirsutism presenting during reproductive life. It has late sequel of endometrial carcinoma, diabetes mellitus, dyslipidemia, hypertension and increased risk of cardiovascular disease. In the majority of cases, a familial trait is obvious but the offending genes have yet to be identified. However, much of the pathophysiology of

Table 1 Patients with various grades of hirsutism according to Ferryman-Gallway scoring system.

	<i>Mild</i>	<i>Moderate</i>	<i>Severe</i>
Group-I (n=68)	11 (16.3%)	26 (38.2 %)	31 (45.5 %)
Group-II (n=69)	14 (20.3%)	22 (31.9%)	33 (47.8%)
Total (n=137)	25 (18.3%)	48 (35.0%)	64 (46.7%)

Table 2: Results of treatment

	<i>Severe to moderate</i>		<i>Moderate to mild</i>	
	<i>Six months</i>	<i>Nine months</i>	<i>Six months</i>	<i>Nine months</i>
Group I (n=68)	10 (32%)	22 (70.9%)	08 (19%)	16 (61.5%)
Group II (n=69)	08 (29%)	24 (72.7%)	03 (13.6%)	14 (63%)

($p > 0.5$)

the syndrome causing the overproduction of ovarian androgens is now becoming clear i.e. hyperinsulinemia. It is important to diagnose and to treat the syndrome at an earlier stage to save an individual from the early and late stigma of the syndrome.

Antiandrogens are the most widely used medications in combination with estrogens, for the treatment of hirsutism and menstrual irregularities. However, endocrinologists are more likely to use insulin sensitizers, such as metformin for these indications, but dermatologists and gynecologists have doubt about their efficacy.

The present study showed that metformin had little effect in treating hirsutism but it was effective in regulating menstrual cycle. This effect was consistent with Cochrane systemic review and meta analysis of literature, which also reveals that metformin is effective in regulating menstrual cycle and in inducing ovulation, but has a marginal benefit in improving hirsutism. It is equally effective in both lean and obese individuals, a result also seen in many trials. The main side effects were gastrointestinal intolerance and vomiting. As the treatment of hirsutism

involves long term therapy, compliance was increasingly difficult and was the main reason for stopping treatment.

While treating these patients on three drugs as in group II, it is very important to consider the cost of the drugs in relation to its benefit. Results of the current study indicate that metformin no doubt improves the menstrual problems, obesity and hormonal profile of these patients, but has a marginal effect on treating hirsutism. Diane 35® along with 100mg of cyproterone acetate remains the best choice for treating hirsutism.

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