



REVIEW ARTICLE

A PROSPECTIVE STUDY ON THE EFFECTIVENESS OF METFORMIN AND ETHINYL ESTRADIOL-CYPROTERONE ACETATE IN THE MANAGEMENT OF HYPERANDROGENISM IN POLYCYSTIC OVARY SYNDROME PATIENTS

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ARTICLE INFO

Article History:

Received 22nd May, 2018

Received in revised form

27th June, 2018

Accepted 10th July, 2018

Published online 30th August, 2018

Keywords:

Hyperandrogenism,
Insulin resistance, Metformin,
Ethinyl Estradiol-Cyproterone Acetate.

ABSTRACT

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting 5-8% of women of reproductive age group characterized by associated problems such as infertility, diabetes mellitus, hypertension, dyslipidemia, endometrial cancer, depression and hyperandrogenism. The aim of the review is to evaluate the effectiveness of Metformin and Ethinyl Estradiol- Cyproterone Acetate (EE-CA) in the management of Hyperandrogenism in PCOS patients. As there are only few studies in Indian literature regarding the evaluation of effectiveness of the drugs in the management of hyperandrogenism associated with PCOS, the present review is undertaken. The review had shown that EE-CA is a more effective way of treating hyperandrogenism and menstrual dysfunction compared to Metformin which outperforms EE-CA in improving insulin resistance, reducing Body Mass Index and improving ovulation.

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INTRODUCTION

Polycystic Ovary Syndrome characterized by hyperandrogenism, hyperinsulinemia and menstrual dysfunction is the most common endocrine disorder among women. The exact cause of PCOS is not fully understood but excess insulin, excess androgen, genetics and low grade inflammation can be the factors. Insulin resistance appears to be the fundamental common pathway to disease amongst women with PCOS. Hence, women with PCOS produce higher levels of insulin. The impact of higher levels of insulin and Insulin like growth factor 1 on the ovary is the reason for the release of higher levels of testosterone. Insulin resistance is recognized as a major risk factor for the development of type 2 diabetes mellitus. Elevated androgens such as Dehydroepiandrosterone sulphate (DHEAS) and testosterone are associated with insulin resistance, obesity and altered lipid metabolism. Therefore, elevated androgens may raise the risk for cardiovascular disorders. Women of all ages with PCOS are at an increased risk of endometrial cancer and increased emotional stress such as depression as compared with non-PCOS women.

The main aim of the review is to evaluate the effectiveness of Metformin and Ethinyl Estradiol-Cyproterone Acetate in the management of hyperandrogenism in PCOS patients.

The objectives of the review include the comparison of Metformin and EE-CA in the management of hyperandrogenism in PCOS, to determine the impact of medication adherence in the management of the disease and to evaluate the ADR of Metformin and EE-CA. It was found that EE-CA showed greater effectiveness in the management of hyperandrogenism and its symptoms in PCOS when compared to Metformin. Medication adherence was evaluated by Morisky 8 item medication adherence scale and was found to be improved after follow up. Metformin was found to have lesser ADR's when compared to EE-CA. There is well documented evidence in the literature by Leopolo Falsetti *et al.* that suggest a significant decrease in the androgen level and hirsutism by treatment with the combination of Ethinyl Estradiol and Cyproterone Acetate. Also, improvement in frequency of menstruation, reduction in plasma insulin and increased insulin sensitivity upon treatment with Metformin was mentioned in previous literature by Paolo Moghetti *et al.* This review is done to compare the effectiveness of Metformin and EE-CA in the management of hyperandrogenism in PCOS patients.

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REVIEW OF LITERATURE

Gulam Saidunnisa Begum et al. (2017) conducted a study on the assessment of risk factors for development of Polycystic Ovarian Syndrome. A total 250 female subjects participated in the study including 69 PCOS subjects and 181 non PCOS subjects. Few variables such as family history of PCOS, fast food diet habits, involvement in physical exercise, body mass index and waist circumference of study participants were evaluated as risk factors for development of PCOS. Results showed that individuals with a positive family history of PCOS [RR 1.07 (CI 0.79-0.619)], fast food diet habits [RR 1.725 (CI 1.014-2.933)] and obesity [RR 1.741 (CI 1.054-2.877)] are at a higher risk of PCOS compared to participants without these predisposing factors. In conclusion it was stated that majority of the predisposing factors identified in the study participants were modifiable. Hence, careful monitoring and proper corrective steps may help in prevention and adequate management of PCOS.

John A Barry et al. (2014) conducted a systematic review and meta-analysis of observational study on the risk of endometrial, ovarian and breast cancer in women with PCOS. From 698 references, 11 studies (5 of endometrial cancer and 3 each of ovarian and breast cancer) met inclusion criteria for meta-analysis (919 women with PCOS and 72054 non-PCOS controls). Using the Mantel-Haenszel method, with fixed or random effects model as appropriate, women with PCOS were at a significantly increased risk of endometrial cancer (odds ratio 2.79; 95% CI, 1.31-5.95, $p < 0.008$) but the risk of ovarian and breast cancer was not significantly increased (OR, 1.41; 95% CI, 0.93-2.12, $p < 0.11$ and OR 0.95; 95% CI, 0.64-1.39, $p < 0.78$ respectively). In conclusion women of all ages with PCOS are at an increased risk of endometrial cancer but risk of ovarian and breast cancer was not significantly increased.

Lauren K Banting et al. (2014) conducted a study on the physical activity and mental health in women with polycystic ovary syndrome. Women aged 18-50 years with ($n=153$) and without PCOS ($n=64$) completed a questionnaire at one time point. The questionnaire included the Anxiety and Depression scale and a survey regarding levels of physical activity, physical activity barriers, motivators and supports. Women with PCOS displayed higher severity of depression ($F(1,210) = 8.32$, $p = 0.004$) and anxiety ($F(1,210) = 17.37$, $p < 0.001$) symptoms compared to controls. Women with PCOS were more likely to report a lack of confidence about maintaining physical activity, fear of injury and physical limitations as barriers to physical activity and were more likely to be motivated to be active to control a medical condition. Women with PCOS identified more sources of support compared to women without PCOS.

Johana Schmidt et al. (2011) conducted a study on the cardiovascular disease and risk factors in PCOS women of postmenopausal age. The prospective study included 35 PCOS women (61-79 yr) and 120 age matched controls. The study was performed 21 years after the initial study. 25 PCOS women and 68 controls participated in all examinations. Interventions included re examination, interviews and data collection. Blood pressure, glucose, insulin, triglycerides, total cholesterol, high and low density lipoprotein, apolipoprotein A1 and B, fibrinogen and plasminogen activator inhibitor antigen were studied. Incidences of MI, stroke, hypertension, diabetes, cancer, cause of death, and age at death were

recorded. Results indicated that PCOS women had a higher prevalence of hypertension ($p = 0.008$) and higher triglyceride levels ($p = 0.012$) than controls.

Magdalena Olszanecka-Glinianowicz et al. (2011) conducted a study on Serum adiponectin and resistin in relation to insulin resistance and markers of hyperandrogenism in lean and obese women with polycystic ovary syndrome. 41 women with PCOS (22 lean and 19 obese) and 16 healthy lean women were enrolled. Body mass and height were measured and body mass index were calculated. In addition to serum glucose, lipids, androgens and insulin, adiponectin and resistin concentration were assessed in the fasting state. The insulin resistance was calculated based on the HOMA-IR. Similar serum resistin concentrations were found in both PCOS subgroups and controls. Significant positive correlations between adiponectin to resistin ratio and plasma FSH ($r = 0.49$; $p = 0.003$) concentrations and a negative correlation with FAI ($r = -0.34$; $p = 0.03$) in PCOS group were found. In conclusion Obese but not normal weight women have lower adiponectin levels whereas resistin concentration did not differ in normal weight and obese PCOS compared to control subjects.

Leopoldo Falsetti et al. (2001) conducted a study to determine the efficacy of the combination ethinyl estradiol and cyproterone acetate on endocrine, clinical and ultrasonographic profile in polycystic ovarian syndrome. 140 studied women had polycystic ovaries and moderate or severe acne, 108 also presented hirsutism. The endocrine profile significantly modified after six cycles with a significant decrease in gonadotrophins, estrogens and androgens after 12 cycles, and a greater increase of sex hormone binding globulins and insulin-like growth factor-binding globulins. Between 12th and 6th cycle there was only a significant reduction of dehydroepiandrosterone sulphate. Ovarian volume, microcyst numbers and stroma percentage significantly decreased. The results suggest that acne and hirsutism are induced by different peripheral mechanisms.

Paolo Moghetti et al. (2000) conducted a study on Metformin effects on clinical features, endocrine and metabolic profiles and insulin sensitivity in polycystic ovary syndrome. 23 PCOS women were randomly assigned to double-blind treatment with metformin or placebo for 6 months, while maintaining their usual eating habits. Before and after treatment menstrual history, endocrine and metabolic profiles and insulin sensitivity were measured. After metformin treatment, mean frequency of menstruation improved. They showed reduced plasma fasting insulin and increased insulin sensitivity. No changes were found in the placebo group. In conclusion, in women with PCOS metformin treatment reduce 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.

Conclusion

PCOS is one of the most common endocrine disorders in women of reproductive age group. The parameters such as testosterone, LH, FSH, DHEAS were found to be lowered when treated with EE-CA than in case of Metformin. Also, Fasting Insulin, BMI, Waist Hip Ratio were reduced much more significantly in Metformin treatment when compared to EE-CA. It was observed that both EE-CA and Metformin are

safe and effective in treatment of PCOS patients, both drugs showing overall beneficial effects on most of the clinical complaints characteristic of this common disorder. However, the data suggest that EE-CA is a more effective way of treating hyperandrogenism and menstrual dysfunction, considering that the improvement in hirsutism, the amelioration of hyperandrogenemia, and restoration of regular menstrual cycles occur more frequently with EE-CA than with Metformin. On the other hand, Metformin clearly outperforms EE-CA in improving insulin resistance, reducing body mass index and also improving ovulation and proved to be with lesser ADRs when compared to EE-CA. With proper medication adherence and by modifying the lifestyle, the PCOS could be controlled to an extent. From this review it could be concluded that EE-CA proved to be much more effective in controlling Hyperandrogenism as compared to Metformin.

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