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Original Article

Comparison of Metformin and Ethinyl Estradiol-Cyproterone Acetate in the Management of Polycystic Ovary Syndrome

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Abstract

Background: To compare ethinyl estradiol-cyproterone acetate and metformin for polycystic ovarian syndrome in terms of mean hirsutism score and waist hip ratio (WHR).

Methods: A total of 120 patients (60 patients in each group) were included in the study. Group-A received metformin 500mg and group-B was given ethinyl estradiol 35 mg as treatment of polycystic ovary disease (PCOD), mean hirsuitism and waist to hip ratio was measured at 6months. Hirsuitism was measured according to Ferriman Gallway score. Circumferences were measured with an anthropometric tape over light clothing. Waist girth was measured at the minimum circumference between the iliac crest and the rib cage and hip girth at the maximum width and their ratio was calculated as baseline and after 6 months of treatment.

Results: Mean age was 25.87±6.46 and 25.60±6.74, respectively. Mean waist hip ratio at presentation and after 6 months was proportionate in the two groups. Mean hirsutism score at baseline was tantamount in both groups but at 6 months significant reduction (p<0.001) was seen in Group-B (Ethinyl estradiol Cyproterone acetate) when compared with Group-A (Metformin). Mean BMI was 29.77±3.77 and 29.82±3.02 in group-A and B, respectively. Stratification with regard to age and BMI in terms of waist to hip ratio and mean hirsutism score was also carried out.

Conclusion: Ethinyl estradiol cyproterone acetate (EE-CA) proved beneficial for reduction of mean hirsutism score in patients with PCOS, but it has no role in reducing WHR when compared with metformin.

Key Words: Polycystic ovary syndrome, Metformin,Ethinyl estradiol-cyproterone acetate

Introduction

Polycystic ovary syndrome (PCOS) is an important cause of hyperandrogenemia in women with familial predisposition. The rudimentary quandary is in the hypothalamic pituitary axis leading to incremented LH/FSH ratio[1]. The cumulation of anovulation and hyperandrogenism denotes the classic form of PCOS which exhibits the adverse metabolic phenotype of the syndrome. Clinical and biochemical features of these patients may vary well-according to race, ethnicity and the diagnostic criteria used. [2] Hyper-androgenism may result in acne and hirsutism. Hirsutism afflicts 5-15% of females and is a paramount denouement of background hyper-androgenemia. The manifestations of polycystic ovary syndrome depends largely on obesity, which exacerbates the reproductive and metabolic aberrations in women tormented by PCOs. Further studies conclude that obesity might promote the phenotypic expression of PCOS in a population at risk of this disease.[1,2]

Well known risk determinants for cardiovascular disease are abnormal glucose tolerance and diabetes myelitis. A proportion (18-20%) of overweight women suffering from polycystic ovary syndrome demonstrate to have an impaired glucose tolerance[3]. Most of the women suffering from type 2 diabetes under the age of 45 years have polycystic ovaries. Insulin resistance coalesced with abdominal obesity is considered to be associated with higher pervasiveness of T2DM in PCOS. There is a concomitant incremented risk of gestational diabetes[4]

As metabolic syndrome and T2DM is more common in our part of the world it would be interesting to see how individuals fare in such a comparative trial in our part of the world.

Patients and Methods

This randomized controlled trial was conducted in Department of Gynaecology/Obstetric , MH/CMH Rawalpindi. It was carried out over a period of six months from January 2014 to June 2014 (follow up completed on 31-10-2014). A total of 120 patients were taken. All Women diagnosed to be having PCOS between 15-40 years were included excluding pregnant women, hypertensive or diabetics. The

patients were included on the basis of non-probability consecutive sampling. Baseline waist to hip ratio and hirsutism score (according to Ferrimen Gallway score) of women having polycystic ovaries is noted. Waist and hip circumferences were quantified with an anthropometric tape by AFNS officer. BMI measured and waist girth was quantified at the minimum circumference between the iliac crest and the rib cage and hip girth at the maximum width. Patients were randomized by lottery method to the metformin or oral contraceptive pill group [ethinylestradiol (35 mcg), CA (2 mg) 21 days/month followed by a 7-day gap]. The metformin was given in dose of 500mg thrice a day. After 6 months of treatment waist to hip ratio and hirsutism score (according to Ferrimen Gallway score) was noted. Independent sample t-test was applied for comparison of WHR and Hirsutism score in two groups. A p-value < 0.05 was considered statistically significant. Stratification was done to control effect modifiers like age and BMI.

Results

A total of 120 patients (60 patients in each group) were taken in present study during the study period of six months.Group-A received metformin 500mg while Group-B was administered ethinyl estradiol 35 mg.

In group-A, 42 patients (70.0%) and in group-B, 44 patients (73.3%) were between 15-30 years of age. Eighteen patients (30.0%) from group-A and 16 patients (26.7%) from group-B were 31-40 years old. Mean age was 25.87±6.46 and 25.60±6.74, respectively.Mean waist hip ratio at baseline and after 6 months was comparable in both groups (Table-1)..

Table 1:Comparison of mean waist hip ratio

Group	At booking	At 6 months
Group-A(Metformin)	0.821±0.049	0.812±0.043
Group-B(Ethinyl estradiol Cyproterone acetate)	0.836±0.056	0.800±0.055
p value	p=0.131	p=0.205

Table 2:Comparison of mean hirsutism score

Group	At booking	At 6 months
Group-A(Metformin)	20.38±3.15	18.78±3.29
Group-B(Ethinyl estradiol Cyproterone acetate)	19.62±2.95	15.08±3.06
p- value	P=0.172	P<0.001

Mean hirsutism score at baseline was comparable in both groups but at 6 months significant reduction (p<0.001) was seen in Group-B (Ethinyl estradiol Cyproterone acetate) when compared with Group-A (Metformin) (Table-2). Mean BMI was 29.77±3.77 and 29.82±3.02 in group-A and B, respectively(Table-3).Stratification with regard to age and BMI in terms of waist to hip ratio and mean hirsutism score

Table 3:Comparison of BMI

BMI	Group-A (Metformin)	Group-B Ethinyl estradiol Cyproterone acetate
< 25	07 (11.7%)	4 (6.7%)
> 25	53 (88.3%)	56 (93.3%)
Total	60 (100.0%)	60 (100.0%)
Mean±SD	29.77±3.77	29.82±3.02

Discussion

Polycystic ovary syndrome (PCOS) accounts for a high prevalent endocrine abnormality inflicting reproductive age females, being annotated by anovulation, hyperandrogenemia, obesity and resistance to insulin.[1,2] The general presentation of PCOS are menstrual irregularities encompassing oligo/amenorrhea or dysfunctional uterine bleeding; hyperandrogenism features including hirsutism, acne, oily skin and androgenic alopecia; along with infertility and obesity. Impaired glucose tolerance (IGT), type-2 diabetes mellitus, metabolic syndrome[5], non-alcoholic steatohepatitis, sleep apnea syndrome, endometrial, ovarian or breast malignancy and increased cardiovascular risk are other clinical conditions related with PCOs.[3-5]

A lengthy evolution process and environmental adaptations lead to variation in human body composition.[5] Conspicuously, the morphological body parameters, physiological and biochemical indices are intricate and hence they complicate the interdependent system.[6] According to recent literature, overweight or obese women account for more than 50%. [7]The reproductive and metabolic functions of a female is affected adversely even more if PCOS induced waist circumference and waist-to-hip ratio increases.[8] The subcutaneous and visceral fat topography has been proved to be the strongest sexual dimorphism sign which shows that the women suffering from PCOS have higher fatty deposits in abdomen, waist and upper arms compared to other women[6,9].

Decrease in weight and decrement in waist–hip ratio has been proclaimed while utilizing metformin.[10] Weight loss and metformin cause virtually similar effects in women suffering from PCOS thus some authors consider metformin-induced weight loss to be

the actual indirect sequel of amelioration compared to the direct effect of metformin.[11] Alleviation of body mass index (BMI) and waist–hip ratio can indubitably accord to amelioration.[12]

Hirsutism is excess hair growth in characteristic male distribution areas, like chin, upper lip, breasts, back, and abdomen.[2,3] Hirsutism is classically, thought of as a marker of incremented levels of androgens in women either from adrenals or ovarian disease[13]. Ovarian types of hyperandrogenism being the polycystic ovarian syndrome (PCOS) and ovarian tumors ,Hyperandrogenic insulin-resistant acanthosis nigricans syndrome (HAIR-AN)[15] being less common cause. [14,15]

Hirsutism has led to psychological constraints causing women to have anxiety and depression.[16] One study concluded that the average time spent per week in dealing with facial hair by women suffering from hirsuitism due to PCOS was 104 minutes with majority checking facial hair frequently and upto 75% showed clinically significant concern and anxiety.[17]Hirsutism is a universal medical complaint of females in reproductive age[18],with a prevalence of 3 to 15% in Blacks and Whites[19] and 1-3% in Asians.[18-20] Recent epidemiological surveys however have restricted hirsuitism to adolescence and youth with a prevalence ranging from 8 to 13%.[20,21] Polycystic ovary syndrome (PCOS) represents the commonest cause of hirsuitism.[22] A recent report by the Androgen Excess-PCOS Society reviewed 18 studies published from 1983 to 2007, including 6281 females suffering from PCOS, and concluded that 74.7% of females had hirsutism on initial diagnosis with a severer form and abdominal phenotype obesity.[23,24] Interestingly, albeit hirsutism does not plenarily soothsay ovulatory dysfunction, few authors concluded that it might prognosticate the metabolic aftermath or conception failure despite infertility treatment in patients of PCOS.[21,23]

Combined oral contraceptives contain a progestin and a synthetic estrogen i.e ethinyl estradiol.[11,12] Other progestins including Drospirenone and cyproterone acetate (CPA), show antiandrogenic activity but are not structurally testosterones. CPA inhibits androgen receptors and hence 5-α-reductase activity, thus alleviating androgen levels in serum.[21] Drospirenone however lowers the blood pressure due to its additional anti-mineralocorticoid property.[22] Conclusively, drospirenone in CPA and COCs suppresses the ovarian androgen production by blocking LH secretion, decreases serum free testosterone levels by augmenting SHBG synthesis in the liver and blocks androgen receptors.[24] COCs are being used in the management of PCOS for approximately 30 years, with multiple studies elucidating the role of COCs on carbohydrate metabolism, lipid profile and cardiovascular risk parameters.[24,25]

Metformin decrements production of ovarian androgen by mitigating the serum insulin levels and insulin resistance, leading to decreased serum testosterone level, eventually the hirsutism score and menstrual dysfunction improves and hence reversal of infertility. [13,21]

In present study, reduction in waist hip ratio was comparable at 6 months (p=0.205) when Metformin and Ethinyl estradiol Cyproterone acetate group compared. Comparison of hirsutism score between Metformin and Ethinyl estradiol group reveals significant reduction in Ethinyl estradiol Cyproterone acetate group (18.78±3.29 vs 15.08±3.06) p<0.001. Results of present study are comparable with the findings of El Maghraby et al.[25]

Conclusion

1.Ethinyl estradiol cyproterone acetate (EE-CA) appears to be an adequate therapeutic option for reduction of mean hirsutism score in patients with PCOS, but it has no role in reducing WHR when compared with metformin.

2.Metformin alleviates hyperandrogenism, hyperinsulinemia, and menstrual cyclicity, due to its affirmative effect on insulin clearance and abdominal obesity.

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