Diabetes & Metabolic Syndrome: Clinical Research & Reviews 10S (2016) S95–S98

Contents lists available at ScienceDirect

Diabetes & Metabolic Syndrome: Clinical Research & Reviews

journal homepage: www.elsevier.com/locate/dsx

Original Article

A comparative study to illustrate the benefits of using ethinyl estradiol-cyproterone acetate over metformin in patients with polycystic ovarian syndrome

Noorhan S. Mhao [a], Ahmed S.A. Al-Hilli [a], Najah R. Hadi [b], Dina A. Jamil [c], Hayder A. Al-Aubaidy [c,*]

[a] Department of Medicine, College of Medicine, Kufa University, Najaf, Iraq
[b] Department of Pharmacology, College of Medicine, Kufa University, Najaf, Iraq
[c] School of Medicine, University of Tasmania, TAS, 7001, Australia

ARTICLE INFO

Keywords:
Ethinyl estradiol-cyproterone acetate
Metformin
Metabolic regulation
Polycystic ovarian syndrome

ABSTRACT

Aim: This study was done to illustrate the clinical and biochemical effects of ethinyl estradiol-cyproterone acetate (EE-AC) and metformin in this disease.
Methods: This was a randomized control trial study, done on twenty-six female patients already diagnosed as cases of PCOS. Participants were divided into two study groups: group one (Group 1), received metformin of 500 mg twice daily and the second group (Group 2), was given ethinyl estradiol–cyproterone acetate for 21 consecutive days followed by 7 days drug-free. The course of the treatment for both groups was continued for three consecutive months.
Results: Group 1 showed a statistical significant increase in serum high density lipoprotein cholesterol (HDL-C) levels ($P = 0.006$) and a decrease in the level of triglyceride (TG) ($P = 0.006$). In addition, Group 1 had a significant reduction in the levels of very density lipoprotein cholesterol (VLDL-C) ($P = 0.006$). Group 2 had a significant increase in serum TG levels ($P = 0.01$), associated with a significant decrease in serum LDL-C ($P = 0.04$). Serum testosterone was significantly reduced in group 1 ($P = 0.038$). This was associated with an improvement in glucose tolerance test (GTT) and BMI in the same group (group 1). Group 2, had an improvement in the menstrual cycle control; hirsutism and acne.
Conclusion: This study showed that metformin treatment is beneficial in improving serum lipids; glucose homeostasis and BMI, however, the ethinyl estradiol-cyproterone acetate is superior in improving the clinical manifestation of patients with PCOS, including menstrual cycle regulation, hyperandrogenic state.

1. Introduction

Polycystic ovary syndrome (PCOS) is an endocrine-metabolic disorder characterized by wide hormonal disturbances, which can cause hyperandrogenic manifestations like infertility (non-ovulatory). PCOS accounting for approximately 6–15% of these cases [1]. Indeed, its optimal diagnosis is often hindered due to its apparent similarities with several other pathologies remarkably, obesity as well as Cushing's syndrome, ovarian and adrenal neoplasms, and congenital adrenal hyperplasia [1].

The etiology of PCOS is uncertain. Some evidences suggesting a genetic predisposition [2]. Pathophysiology of PCOS includes excessive androgen secretion by stromal theca cells which causes the cardinal clinical manifestation of the PCOS, and also, inhibiting the follicular growth resulting in increased production of the immature follicles [2]. As insulin hormone can act as a potent stimulus to androgen secretion by the ovary, it (insulin) can amplifies the effects of luteinizing hormone (LH) and magnifies the degree of hyperandrogenism by suppressing liver production of the main sex hormone binding globulin (SHBG) and thus elevating the free androgen index [3]. The diagnostic criteria of PCOS include menstrual cycle disturbance; infertility; clinical and/or biochemical signs of hyperandrogenism; and the presence of polycystic ovaries in ultrasound. The presence of two of those key features must be present to allow the diagnosis of PCOS [2]. Hirsutism is characterized by terminal hair growth as a male pattern. Modified

* Corresponding author at: School of Medicine, University of Tasmania, Hobart, TAS, 7000, Australia. Tel.: +61 0 362266975.
E-mail address: h.alaubaidy@utas.edu.au (H.A. Al-Aubaidy).

http://dx.doi.org/10.1016/j.dsx.2015.10.001
1871-4021/

Ferriman and Galloway score can be used to evaluate the degree of hirsutism before and during treatment [4,5]. Obesity, in addition acanthosisnigricans occur in about 5% of the PCOS patients. Glucose tolerance test is impaired in approximately one third of the patients [5]. Fasting lipid profile showing elevated triglyceride, low density lipoprotein cholesterol and decreased high density lipoprotein. The increased androgens can be coming from either the ovaries (testosterone, androstenadione) or adrenals (dihydroepiandrosterone). This is associated with a decrease in SHBG [6].

Oral contraceptive pills (OCPs) like ethinylestradiol-cyproterone acetate (traditional name Dianette), contain ethinylestradiol (35 mg) in combination with cyproterone acetate (2 mg). This type of OCPs, strong oral contraception, are effective in treating menstrual disturbance and hyperandrogenism. The estrogen component of the OCPs can suppresses gonadotrophine secretion; suppresses ovarian androgens and adrenal steroid biosynthesis. Cyproterone acetate is a pregnane-derived progestrogen without androgenic activity. It can be used in the treatment of acne and hirsutism [7,8]. Metformin (glucophage), a biguanideantihyperglycemic drug, is used for the treatment of type 2 diabetes mellitus. It has been shown to have a beneficial effect on serum lipids by decreasing the concentration of plasma triglyceride, total cholesterol and LDL [9]. Moreover, it improves insulin sensitivity by increase the process of gluconeogenesis thus inhibiting hepatic glucose production. It can also increases the target tissue sensitivity to insulin; slowing of glucose absorption from gastrointestinal tract and reduces free testosterone level leading to a marked drop in hirsutism score [9]. Metformin can help over 40% of the PCOS women to achieve an ovulatory cycle and reduces the manifestation of hirsutism [10].

2. Patients and methods

This study was approved by the human ethics committee in College of Medicine, University of Kufa. The study included twenty-six female participants, aging (14–40 years), and were diagnosed with PCOS at the time of the study. These participants were attending the infertility clinic, the teaching hospital, seeking treatment for their infertility and/or cycle abnormalities. All participants were informed about the nature of the study and they signed the consent form before they included in the study. Full history were taken including the type of infertility (primary or secondary); the duration of infertility; the age of participants when diagnosed; parity and gravidity; and associating menstrual cycle disturbances. Participants were examined to look for evidence of hirsutism which scored (>7) according to Ferriman and Gallwey [9]; acne and body mass index (BMI) (weight (kg)/height (m^2); (overweight BMI25.1–30; obese BMI >30 kg/m^2) [11]. Waist and hip circumference (W/H ratio) were also measured using a soft tape at narrowest part of the torso and at the widest part of the gluteal region.

Fasting venous blood samples were drawn at early follicular phase of menstrual cycle (1–7 days) after spontaneous or progestin induced (dydrogesterone, 10 mg/day for 10 days in amenorrheic women) before treatment, for the measurement of serum testosterone, serum lipids. After obtaining the basal blood samples, a 2-h oral glucose tolerance test (OGTT) was immediately performed with an oral glucose load of 75 g dissolved in 300 ml of water, and blood samples were obtained after 30, 60, 90 and 120 min to measure blood glucose levels [12]. OGTT considered to be impaired when fasting blood glucose is >5.6 mml/l and/or 2-h blood glucose is >7.8 mml/l [12].

Participants were divided into two study groups: group one (Group 1), received metformin of 500 mg twice daily (Bristle laboratories Ltd, unit 3, canalside, Northbridge road Berkhamsted, hertfordshire, HP4 1EG, UK) and the second group (Group 2), was given ethinyl estradiol (EE) 35 μg – cyproterone acetate (CA) 2 mg (Diane 35 SCHERINGA/Berlin Germany) for 21 consecutive days followed by 7 days drug-free. The course of the treatment for both groups was continued for three consecutive months.

All basalmeasurement (clinical examination and investigation) were repeated and followed up at the end of the study. The data were analyzed using SPSS (v15) and Microsoft Excel (Office2007, Microsoft). All values were expressed as mean ± std. Statistical analyses were performed using a one-way ANOVA followed by paired *t*-test. *P*-value was set to be statistically significant at or below 0.05.

Table 1
The clinical parameters of Group 1 participants (16 in total) before and after treatment with metformin (values expressed as mean ± std).

Clinical parameters	At base line	Post-treatment	*P*-value
BMI kg/m^2	27.226 ± 5.443	26.122 ± 5.534	0.000*
Waist/hip ratio	0.7728 ± 0.055	0.7758 ± 0.058	0.594
Infertility	16	5 pregnant	
Abnormality of menstrual cycle	14	9 improved	
Hirsutism F-G score	Score (8.5–12.3) Mean 10.1	Score (7.9–11.8) Mean 9.2	
Acne	4	2 improved	

* *P*-value is significant at or below 0.05.

3. Results

Group 1 included sixteen participants, while group 2 included ten participants. Tables 1 and 2, showed the clinical parameters for the participants of this study before and after treatment (see Tables 1 and 2). Both groups had significant improvement in their BMI levels, but no significant results were noticed with regards to W/H ratio (Tables 1 and 2). Infertility outcomes have been improved in the metformin group; five patients became pregnant within this group. Menstrual irregularity also improved in both groups, from 14 patients, 9 of them got regular menses during metformin treatment, while 6 from 8 patients with menstrual irregularities got regular menses on EE-CA however, hirsutism and acne improved in EE-CA treated group much more than in the metformin group.

Group 1 (metformin group) had a significant increase in serum high density lipoprotein cholesterol (HDL-C) level (39.78 ± 7.43 mg/dl) after the treatment compared to the baseline measurement (35.36 ± 7.63 mg/dl) (*P*-value = 0.006). This was associated with a significant decrease in triglyceride level from (110.36 ± 16.19 mg/dl) to (95.72 ± 16.62 mg/dl) at (*P*-value = 0.006) (Table 3). Moreover, both serum low density lipoprotein cholesterol (LDL-C) and serum total cholesterol levels were also reduces but not reaching a significant levels (Table 3).

Group 2 showed a significant increase in serum triglyceride level from (90.86 ± 18.54 mg/dl) to (92.86 ± 13.27 mg/dl) (*P* = value

Table 2
The clinical parameters of Group 2 participants (10 in total) before and after treatment with EE-CA (values expressed as mean ± std).

Clinical parameters	At base line	After treatment	*P*-value
BMI	30.498 ± 5.307	29.580 ± 5.021	0.048*
Waist/hip ratio	0.836 ± 0.073	0.839 ± 0.084	0.808
Infertility	4	1 pregnant	
Abnormality of menstrual cycle	8	6 improved	
Hirsutism F-G score	Score (7.8–11.2) Mean 9.3	Score (6.2–9.2) Mean 7.9	
Acne	5	4 improved	

* *P*-value is significant at or below 0.05.