Evaluation of the Clinical and Biochemical Effects of Medical Therapy in Women with Polycystic Ovary Syndrome

MARYAM MAHMOOD, M.D.*, EMAN A. EL-KATTAN, M.D.*; HODA ABD EL-AAL, M.D.*
AHMED EL LITHY, M.D.*; NEVEIN K. GHAMRY, M.D. and MARWA SHETA, M.D.**
The Departments of Obstetrics & Gynecology* and Chemical Pathology**, Kasr Al-Aini Teaching Hospital, Cairo University.

Abstract

Background: Oral contraceptive pills are commonly used in the treatment of PCOS; but, their influence on metabolic parameters is not well known. Metformin, a biguanide anti-hyperglycemic drug, has been shown to improve ovarian function and glucose metabolism in women with polycystic ovary syndrome (PCOS), but results concerning its effects are controversial.

Objective: The aim of the study is to evaluate the effects of ethinyl oestradiol-cyproterone acetate and those of metformin on clinical, endocrinial and metabolic parameters in patients with PCOS.

Setting: The study was conducted at gynaecology and obstetrics outpatient clinic in Kasr AlAini teaching hospital, Cairo University.

Patients and Methods: We conducted a randomized, clinical trial on forty two women with PCOS. Patients underwent clinical and biochemical evaluation at baseline. Clinical evaluation included recording of menstrual regularity, hirsutism scores, BMI and WHR. Laboratory investigations included androgen levels, lipid profile, and parameters of insulin resistance. Patients were randomized to either oral treatment with metformin (1000mg twice daily) or to the Diane 35 pill (35 µg of ethinyl-estradiol plus 2 mg of cyproterone acetate) for 16 wk.

The baseline evaluation was repeated after 16 wk of treatment in both groups.

Results: Forty two PCOS subjects participated in the study; twenty one in each group. All women had BMI >25. The patients in both groups were comparable at baseline. Subjects in the Diane arm had significant improvement of hirsutism and restoration of cycle regularity. Diane significantly decreased free testosterone and DHEAS levels. Total and HDL- cholesterol aas well as fasting triglycerides were significantly increased on Diane therapy. Subjects in the metformin arm had significant decrease in BMI and free testosterone levels paralleled with improvement in cycle regularity. Fasting blood glucose, fasting insulin and HOMA scores also significantly decreased on metformin therapy. Metformin significantly increased HDL- and reduced LDL-cholesterol.

Conclusion: Diane is superior to metformin in amelioration of hirsutism and restoration of cycle regularity. It has both beneficial and negative effects on lipid profile. Metformin improves parameters of insulin resistance as well as the lipid profile.

Key Words: Ethinylestradiol-cyproterone acetate – Metformin – Polycystic ovary syndrome.

Introduction

POLYCYSTIC ovary syndrome (PCOS), probably the most prevalent endocrinopathy in women, affects 4-8% of women of reproductive age. The disorder is characterized by chronic an-ovulation and hyperandrogenism and manifests as obesity, menstrual disturbances, infertility, recurrent abortions, hirsutism, acne vulgaris, male-pattern baldness, and psychosexual morbidity. Such a heterogeneous medical condition has thus brought gynecologists, endocrinologists, cardiologists, and dermatologists together [1].

Indeed, cardiovascular risk factors cluster in patients with PCOS. These patients present with increased frequencies of glucose intolerance (up to 30-35%) and type 2 diabetes (7 to 10%) [2], gestational diabetes [3], an unfavorable lipid profile characterized by decreased high-density lipoprotein (HDL)-cholesterol and increased triglycerides levels, and even increased low-density lipoprotein (LDL)-cholesterol [4]. Since 50% of women with PCOS are obese [5] and this obesity is characteristically central i.e the type included in classifications of the metabolic syndrome, in conceptual agreement, the prevalence of the metabolic syndrome is increased in PCOS patients [6].

The primary aetiology of PCOS is unknown. However, insulin resistance with compensatory hyperinsulinaemia is a prominent feature of the syndrome and appears to have a pathophysiological
role in the hyperandrogenism of the disorder for both lean and obese women with PCOS. Hyperinsulinaemia stimulates both ovarian and adrenal androgen secretion directly and suppresses sex hormone-binding globulin synthesis from the liver, resulting in an increase in free, biologically active androgens. This excess in local ovarian androgen production augmented by hyperinsulinaemia causes premature follicular atresia and anovulation along with the other clinical manifestations of hyperandrogenism such as hirsutism and acne [7].

Oral contraceptive (OCs) pills, which focus on restoring regular menses and ameliorating androgen excess, are considered the first-line medication for PCOS patients for decades when fertility is not desired. Diane-35 (35 µg ethinyl estradiol plus 2 mg cyproterone acetate) is the most commonly prescribed OC for PCOS. Some studies have demonstrated Diane-35 to increase insulin resistance and arterial stiffness [8] while others found it to be a safe drug which, considering classic metabolic cardiovascular risk factors, might even have favourable effects on the lipid profile of PCOS patients [9] and presented minor effects on glucose tolerance in PCOS patients [9,10,11].

On the other hand, the importance of hyperinsulinaemia in the development of hyperandrogenism and anovulation, has led to the advocacy of insulin-sensitizing drugs as an alternative long term treatment in the restoration of normal endocrinological and clinical parameters of PCOS [12].

It is the aim of the present study to evaluate the clinical and laboratory effects of ethinyl estradiol plus cyproterone acetate (EE/CA) and metformin in women with PCOS.

Patients and Methods

A randomized clinical trial including women with PCOS was performed between February 2009 and August 2009. The subjects were recruited from the gynaecology clinic of Kasr Al Aini teaching hospital in Cairo.

The diagnosis of PCOS was based on the criteria of the Androgen Excess and PCOS Society [13] i.e. the presence of [1] clinical and/or biochemical hyperandrogenism; [2] ovarian dysfunction, including oligo/anovulation and/or polycystic ovarian morphology and exclusion of secondary etiologies. Oligomenorrhea was defined as cycles lasting longer than 35 days, amenorrhea as less than two menstrual cycles in the past 6 months. Clinical hyperandrogenism was diagnosed in the presence of hirsutism with a modified Ferriman–Gallwey score (FG) of ≥7 [14]. Biochemical hyperandrogenism was defined as elevation of at least one circulating ovarian androgen. Secondary causes of amenorrhea and hyperandrogenism were excluded with clinical screening and hormonal profile. Pregnancy tests were negative before enrollment.

Exclusion criteria included hyperlactinaemia and galactorrhea, a personal history of diabetes mellitus, or hypertension or cardiovascular events, or contraindications to either metformin or Diane or history of treatment with oral contraceptives, antiandrogens, insulin sensitizers, or drugs that might interfere with regulation, lipid profile, or carbohydrate metabolism for the previous 6 months. Women were excluded from the study if an adnexal mass was noted on pelvic sonography.

At baseline all patients were evaluated by history taking, physical examination, ultrasonography, and laboratory investigations. All women underwent a personal interview with a physician, including an evaluation of demographic characteristics, presence of hirsutism, menstrual history and previous medication. The physical examination, apart from a general review of the systems, focused on the assessment of hirsutism, and anthropometry, (body mass index (BMI), and waist to hip ratio (WHR). Weight and height were obtained and BMI [weight (kg)/height (m)²] was calculated. Waist and hip circumferences were measured to the nearest centimeter with a soft tape at the narrowest part between the costal margin and the iliac crest and at the widest part of the gluteal region, respectively, and waist:hip ratio (WHR) was calculated. Hirsutism was evaluated using the modified FG score. This method to assess hirsutism requires the visual scoring of the extent of terminal hairs in nine body areas, named 1) upper lip, 2) chin, 3) chest, 4) upper abdomen, 5) lower abdomen, 6) upper back, 7) lower back, 8) thighs, and 9) upper arms. Each area was scored from 0 to 4. Hirsutism was diagnosed when a score ≥7 was evaluated. Patients who had depilated at the 1st visit were reassessed after 1 month. Patients were instructed not to depilate for at least 1 month before the last evaluation. PCO morphology on ultrasound was diagnosed if at least one ovary with at least 12 follicles of a diameter of 2-9 mm or a volume >10 ml was documented.

Serum and plasma samples were obtained during the early follicular phase of a spontaneous menstrual bleeding or withdrawal bleeding induced with progesterone at baseline or with the OC after the follow-up period. After fasting overnight for 10-12 h, blood samples were collected for the
following assays: follicle-stimulating hormone (FSH), luteinizing hormone (LH), free testosterone (T), 17-hydrox yprogesterone (17OHP), dehydroepiandrosterone sulfate (DHEAS), prolactin, TSH, triglycerides, total cholesterol, high and low density lipoproteins (HDL and LDL), fasting blood glucose and fasting insulin. Insulin resistance was measured using the HOMA (homeostasis model assessment) score. HOMA score was calculated as fasting serum insulin (I) x fasting plasma glucose (G) / 22.5 [15].

After baseline clinical and laboratory evaluation, the patients were randomized to receive OC or metformin. Randomization was produced from a computer-generated random list. The patients accordingly received Diane 35, Scherring, Germany (35 µg ethinyl estradiol plus 2 mg cyproterone acetate,) or Cidiphage, CID, Egypt (metformin 500mg). Diane 35 was administered in starting from day 5 of the cycle for 21 days/month, followed by a 7-d pill-free period. To minimize side effects, metformin therapy was initiated at a low dose taken with meals, and the dose was then doubled. Patients started with 500 mg of metformin twice daily for 1 week; then the dose was increased to 1000 mg twice daily. If the patient experienced side effects, the dose was decreased to the maximum tolerated dose. All patients were advised a low caloric diet and were also encouraged to exercise daily whenever possible, although these measures were not stressed thereafter. Patients were then followed up for 16 weeks and at the end of the follow-up period the baseline evaluation was repeated.

Regarding laboratory assays, hormones were measured by chemiluminescent immunoassay on Immulite (Abott), while serum lipids were measured using spectrophotometric technique on Hitachi (Rosche). Fasting blood sugar was measured by enzymatic method on (glucose oxidase) Hitachi (Rosche).

Data were statistically described in terms of mean ± standard deviation (± SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney U test for independent samples. Within group comparisons were done using Wilcoxon signed rank test for paired (matched) samples. For comparing categorical data, Chi square (χ²) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Forty eight women with PCOS who met the inclusion criteria were recruited and randomized to receiving either Diane or metformin. Four patients were lost to follow-up (three from the Diane arm and one from the metformin arm). Two more patients dropped from the metformin arm due to the occurrence of side effects (nausea and diarrhea). Forty two patients completed the study; 21 in each arm. In the metformin arm, two patients were on 500mg tid and the rest were on 1000mg bid. All the patients who completed the study had a BMI >25. The baseline clinical and metabolic characters of the two groups were comparable as shown in Table (1).

Table (1).  Forty eight women with PCOS who met the inclusion criteria were recruited and randomized to receiving either Diane or metformin. Four patients were lost to follow-up (three from the Diane arm and one from the metformin arm). Two more patients dropped from the metformin arm due to the occurrence of side effects (nausea and diarrhea). Forty two patients completed the study; 21 in each arm. In the metformin arm, two patients were on 500mg tid and the rest were on 1000mg bid. All the patients who completed the study had a BMI >25. The baseline clinical and metabolic characters of the two groups were comparable as shown in Table (1).

The effect of medical therapy on the clinical parameters is shown in Table (2). The mean BMI was significantly decreased in the metformin group (29.58±2.35 versus 28.16±2.08 p=0.001). Diane had non-significant effect on BMI while WHR remained stable in both groups.

Hirsutism significantly improved on Diane therapy (F/G score 9.71 ±1.85 vs 8.00±1.76, p=0.001). Menstual dysfunction significantly improved on both Diane and metformin but more in the Diane arm.

The hormonal profile of the studied cases is shown in Table (2). Serum LH was significantly decreased on Diane therapy (p=0.001). Free testosterone was significantly decreased in both Diane (p=0.005) and metformin (p=0.02) groups. DHEAS was significantly decreased in the Diane arm (273.19±32.83 vs 193.14±45.46, p=0.0003).

The metabolic parameters of the studied groups are shown in Table (3). Metformin therapy significantly reduced FBG, fasting insulin and IR (HOMA score) (p=0.03, 0.02, and 0.001 respectively). IR slightly increased on Diane therapy, but this increase was statistically non-significant (p=0.59).

Diane therapy led to significant increase in total (p=0.002) and HDL-cholesterol (p=0.001), as well as fasting triglycerides (p=0.001). Metformin, on the other hand, resulted in significant increase in HDL-cholesterol (p=0.002) and significant reduction of LDL-cholesterol (p=0.004).
Regarding the frequency of side effects in the subjects completing the study, 5 women in the Diane arm (24%) complained of mild breast tenderness, while 8 cases in the metformin arm (38%) complained of diarrhea and 3 (14%) complained of nausea.

### Table (1): Clinical and laboratory parameters of PCOS subjects before treatment.

<table>
<thead>
<tr>
<th></th>
<th>Diane group (n=21)</th>
<th>Metformin group (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.05±2.44</td>
<td>26.29±2.37</td>
<td>0.75</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>29.42±2.02</td>
<td>29.58±2.35</td>
<td>0.77</td>
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<tr>
<td>WHR</td>
<td>0.824±0.04</td>
<td>0.832±0.04</td>
<td>0.54</td>
</tr>
<tr>
<td>F/G score</td>
<td>9.71±1.85</td>
<td>9.38±1.91</td>
<td>0.54</td>
</tr>
<tr>
<td>Regular cycles</td>
<td>19%</td>
<td>23.8%</td>
<td>0.7</td>
</tr>
<tr>
<td>LH (mlU/ml)</td>
<td>6.68±1.58</td>
<td>7.14±1.71</td>
<td>0.31</td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>9.95±3.34</td>
<td>9.14±3.32</td>
<td>0.38</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>273.19±32.83</td>
<td>268.71±64.98</td>
<td>0.44</td>
</tr>
<tr>
<td>FBG (mg/dl)</td>
<td>91.9±9.34</td>
<td>90±11.01</td>
<td>0.57</td>
</tr>
<tr>
<td>Fasting insulin (µU/ml)</td>
<td>16.48±7.71</td>
<td>17.14±8.23</td>
<td>0.79</td>
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<tr>
<td>HOMA</td>
<td>3.91±2.13</td>
<td>4.02±2.29</td>
<td>0.89</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
<td>187.62±14.53</td>
<td>191.43±15.96</td>
<td>0.49</td>
</tr>
<tr>
<td>HDL-cholesterol (mg/dl)</td>
<td>40.76±7.09</td>
<td>39.71±5.24</td>
<td>1</td>
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<tr>
<td>LDL-cholesterol (mg/dl)</td>
<td>114.71±14.15</td>
<td>122.52±18.49</td>
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</tr>
<tr>
<td>Fasting triglycerides (mg/dl)</td>
<td>134.67±14.21</td>
<td>128.33±36.6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

### Table (2): Clinical and endocrinal parameters of PCOS subjects before and during treatment.

<table>
<thead>
<tr>
<th></th>
<th>Diane group (n=21)</th>
<th>Metformin group (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>29.42±2.02</td>
<td>29.51±2.33</td>
<td>0.22</td>
</tr>
<tr>
<td>WHR</td>
<td>0.824±0.04</td>
<td>0.825±0.04</td>
<td>0.76</td>
</tr>
<tr>
<td>F/G score</td>
<td>9.71±1.85</td>
<td>8.00±1.76</td>
<td>0.001</td>
</tr>
<tr>
<td>Regular cycles</td>
<td>19%</td>
<td>100%</td>
<td>0.001</td>
</tr>
<tr>
<td>LH (mlU/ml)</td>
<td>6.68±1.58</td>
<td>3.21±0.76</td>
<td>0.001</td>
</tr>
<tr>
<td>Free testosterone (pg/ml)</td>
<td>9.95±3.34</td>
<td>9.14±3.32</td>
<td>0.38</td>
</tr>
<tr>
<td>DHEAS (µg/dl)</td>
<td>273.19±32.83</td>
<td>193.14±45.46</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

### Table (3): Metabolic parameters of PCOS subjects before and during treatment.

<table>
<thead>
<tr>
<th></th>
<th>Diane group (n=21)</th>
<th>Metformin group (n=21)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG (mg/dl)</td>
<td>91.9±9.34</td>
<td>92±10.25</td>
<td>0.65</td>
</tr>
<tr>
<td>Fasting Insulin (µU/ml)</td>
<td>16.48±7.71</td>
<td>17.14±8.23</td>
<td>0.94</td>
</tr>
<tr>
<td>HOMA</td>
<td>3.91±2.13</td>
<td>4.02±2.29</td>
<td>0.59</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>187.62±14.53</td>
<td>191.43±15.96</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL-Cholesterol (mg/dl)</td>
<td>40.76±7.09</td>
<td>39.71±5.24</td>
<td>0.05</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dl)</td>
<td>114.71±14.15</td>
<td>122.52±18.49</td>
<td>0.07</td>
</tr>
<tr>
<td>Fasting Triglycerides (mg/dl)</td>
<td>134.67±14.21</td>
<td>128.33±36.6</td>
<td>0.001</td>
</tr>
</tbody>
</table>
Discussion

The ideal treatment for women with PCOS, would be one that prevents the consequences of chronic anovulation (dysfunctional bleeding and endometrial hyperplasia/cancer), that reduces the clinical manifestations of androgen action, and that modifies the metabolic problems related to PCOS: insulin resistance and dyslipidemia [16]. We, therefore, conducted a randomized clinical trial to evaluate the clinical and biochemical effects of Diane and metformin; two widely used therapeutic agents in women with PCOS. In this study, both Diane and metformin improved hyperandrogenemia. In contrast with metformin, the amelioration of biochemical hyperandrogenism brought about by Diane was mirrored by an amelioration of hirsutism scores and as expected 100% restoration of regular menstrual cycles. Indeed, OC therapy reduces hyperandrogenism via a number of mechanisms including suppression of LH secretion (and therefore ovarian androgen secretion) [17], stimulation of hepatic production of SHBG, thereby reducing serum free androgen concentrations, a reduction in adrenal androgen secretion, and a slight blockage in the binding of androgens to their receptor [18]. CA is a 17-hydroxyprogesterone acetate derivative with antiandrogen activity by virtue of its effects in inhibiting the androgen receptor and to a lesser degree in inhibiting 5α reductase activity [19]. CA competes with DHT for binding to the androgen receptor and reduces LH levels with subsequent decrease in androgen levels [20]. The efficiency of Diane in the amelioration of hyperandrogenism has been reported by several authors [8-10,16,21-24]. Indeed, the review by Costello et al. [25] has found that the OC was superior to metformin in reducing androgen levels and improving menstrual pattern.

Metformin has been suggested to directly inhibit androgen production in human theca cells [26]. This direct action of metformin on ovarian steroid secretion could secondarily induce an improvement of obesity, insulin action, and hyperinsulinemia [27]. In this study, metformin therapy was successful in restoration of menstrual cyclicity in 40% of oligomenorrheic subjects with PCOS. The restoration of regular menstrual cyclicity with metformin was reported by Tan et al. [28] in 40% of the patients, by Luque-Ramirez et al. [9] and Morin-Papunen et al. [10] in 50% of the patients, by Morin-Papunen et al. [21] and Costello et al. [25] in 60%, and by Roumaldi et al. [29] in >75% of the subjects with PCOS.

Although the ability of metformin to reduce circulating androgen levels has been reported by many authors [10,12,21,22,28,29], others [8,11], however, have failed to elicit such a change. Surprisingly, Harborne et al. [11] reported that not only metformin is an effective treatment for moderate to severe hirsutism in women with PCOS, but is more efficacious than Diane. They argued that addressing insulin insensitivity may be a more effective therapeutic approach to hirsutism than aggressive suppression of androgens in the form of antiandrogen therapy. The efficacy of metformin in improving hirsutism scores was also reported by Roumaldi et al. [29] and Meyer et al. [8]. However, we found no such improvement in hirsutism scores with metformin therapy. The reasons for such discrepancy are unclear but may be due to differences in the selection criteria for the PCOS participants, assessment method for hirsutism and the duration of treatment [25]. In fact, the widely used modified F/G score is not without limitations.

The subjective nature of the score assessment, the lack of consideration of androgen sensitive areas such as the side burns and buttocks, and the fact that it does not reflect the impact of hirsutism on the woman’s well being may raise questions about its reliability [18]. In addition to F/G scores, Harborne et al., appreciably measured hair diameter, and resorted to patient self-assessment of the hirsutism status and treatment effects both quantitatively (using a visual analog scale) and qualitatively [11]. In this study, hirsutism was measured by F/G scores solely and the investigators who determined the F/G scores were not blinded to the participant’s treatment arm. Besides, our study duration was short. However, the dose of metformin we prescribed was higher than that prescribed by Roumaldi et al. (500mg bid) [29], and Harborne et al. (500mg tid) [11]. Indeed, the current guidelines derived from meta-analysis of RCTs on medical treatments for hirsutism clearly stated that there is strong evidence that metformin is not a choice therapy for hirsutism and other strategies should be used [30]. A recent Task Force behalf the Endocrine Society in clinical practice guidelines suggested against the use of ISDs as therapy for hirsutism, whereas recommended OCs or antiandrogens [18]. Alternatively, the meta analysis by Costello et al. [25] found that there was no evidence of a difference in effect between metformin and the OC on hirsutism, and acne.

In this study, metformin therapy resulted in significant decrease in BMI while WHR was not affected. Initial data [12] of metformin treatment reported a loss in body weight in women with PCOS. Successively, the reduction of BMI with
metformin therapy has been reported in non obese subjects [31,32], in obese and morbidly obese women [32], in overweight and obese subjects [28], and in patients both with and without insulin resistance [33]. A significant reduction in abdominal obesity on metformin therapy has also been reported by some authors [10,21,32]. On the other hand, others [8,29] found no significant variations in BMI or WHR during metformin therapy. Similar data was reported in the metaanalyses by Lord et al. [34] and Costello et al. [25]. In this study, Diane resulted in a slight nonsignificant increase in BMI. This is consistent with current literature on the effects of Diane on BMI, both in non obese PCOS [22], and in overweight and obese PCOS [8,21,23,24,35].

Dyslipidemia is the most common metabolic abnormality in PCOS. These patients characteristically have decreased high-density lipoprotein (HDL)-cholesterol and increased triglycerides levels and even increased low-density lipoprotein (LDL)-cholesterol [4]. The present results demonstrate that metformin treatment improves the lipid profile in women with PCOS, whereas the EE–CA OC pill has both beneficial and negative effects on serum lipids. Metformin significantly increased HDL- and reduced LDL-cholesterol concentrations. The mechanisms by which metformin improves the lipid profile are not clear. Metformin has been suggested to reduce lipid uptake or synthesis in the intestine and in the hepatocytes [36]. The decreased release of free fatty acids (FFAs) from adipose tissue [10,21] could also partly explain the improvement of lipid profile during metformin treatment, at least in obese women [32]. The positive effect of metformin on HDL is in line with the data reported by several authors [8,32]. Lord et al. [34] detected that LDL-cholesterol was significantly reduced on metformin therapy. On the other hand, Velazquez et al. [12] has shown only a negligible effect on lipids in women with PCOS. These discrepancies may again be attributed to differences in study populations.

In this study, Diane had both beneficial and negative effects on serum lipids. Diane resulted in a significant increase in HDL-cholesterol and total cholesterol as well as fasting triglycerides. The effect of OC on lipids has been shown to depend on the dose of estrogen and the type and dose of progestin used [37]. The observed favourable effect on HDL cholesterol possibly involves the activity of plasma hepatic lipase, an enzyme that is remarkably sex steroid sensitive: estrogens decrease its activity, whereas androgens and androgenic progestins increase it [38]. Hence, the amelioration of hyperandrogenism in PCOS women, combined with the antiandrogenic properties of cyproterone acetate and the estrogen component of Diane 35, explains its beneficial effect in PCOS patients [16]. In PCOS patients, some investigators have documented a rise in HDL cholesterol along with a rise in total cholesterol, suggesting an estrogenic dominance of the treatment evident as early as the third month of therapy [24,32,35]. The positive effect of Diane on HDL has also been reported by Luque-Ramirez et al. [9], Harborne et al. [11], Villaseca et al. [16] and Lemay et al. [23]. However, in a meta-analysis by Costello et al. [25], the lipid patterns of PCOS patients treated with metformin and OCs were compared, and no significant difference in total cholesterol levels between treatments was observed. The tendency toward increasing levels of triglycerides, as presently observed, has been attributed to the cyproterone acetate component of the contraceptive pill [24]. Such an increase has been reported from the third month of EE/CA therapy by some [16,24,32] and from the sixth month of therapy by others [8,23,35]. Costello et al. [25] found that metformin resulted in a significantly lower triglyceride level than OCs. As women with PCOS already have increased prevalence of the metabolic syndrome [6], the detection of adverse effects on the lipid profile in a population like ours having the added burden of obesity highlights the need for the cautious use of EE/CA in such women.

In this study, metformin therapy significantly reduced fasting blood sugar, and fasting insulin, and significantly improved insulin resistance. Metformin has been shown to enhance insulin sensitivity in both the liver, where it inhibits hepatic glucose production, and the peripheral tissue, where it increases glucose uptake and utilization into muscle tissue. By increasing the sensitivity of peripheral tissues to insulin, metformin reduces insulin resistance, insulin secretion and hyperinsulinaemia [39]. Metformin also decreases the release of FFAs (i.e. lipolysis) from adipose tissue [21]. According to a hypothesis proposed by Randle et al. [40], the decreased competition between serum glucose and FFAs as energy substrates in peripheral tissues could result in an improvement of glucose oxidation and consequently insulin sensitivity and hyperinsulinemia [21,40]. Furthermore, the reduction in hyperandrogenaemia could secondarily induce an improvement of central obesity, insulin action, and hyperinsulinemia [27]. The effects of metformin therapy on insulin sensitivity in PCOS subjects have been controversial. A significant decrease in FBG has been observed both in obese [21] and non obese PCOS [22]. Significant decrease in fasting insulin concentrations was noted by several authors [10,11,21,25,28]. Some investigators have shown
significant improvement of insulin sensitivity during metformin treatment [8,12]. Furthermore, Tan et al. [28] reported that the improvement in the parameters of IR was irrespective of pretreatment IR or obesity. Others, however, have failed to confirm such an improvement [41].

In non-PCOS populations, the OC has been accused of increasing IR [42]. The increased IR has been reported to be both estrogen dose related [42] and progestin type and dose related [43]. Regarding carbohydrate metabolism, treatment with EE/CA did not modify the parameters measured and Diane did not worsen IR in this study. The lack of increase in IR by the EE/CA formulation used in this study could be related to the direct anti-androgenic action of CA. The results of studies involving CA in PCOS have been controversial. In agreement with the present observations, several investigators found no effect on insulin concentrations and sensitivity in PCOS in general [11,35], specifically obese PCOS [16,23,44], and non obese PCOS [10,22] as well. On the other hand, Morin-Papunen et al. [21] has shown significant worsening of glucose tolerance with EE/CA. Furthermore, Meyer et al. [8] reported that Diane increased IR by 25% as measured by AUC for insulin (while HOMA score did not change significantly). The authors, therefore, stressed that IR should be considered when selecting medical therapy in overweight women with PCOS [8]. The heterogenous data regarding drug effects on insulin sensitivity may be due to differences in the method used in evaluating insulin resistance. In fact, this is not a minor issue. To evaluate the effect of a drug on insulin resistance, the ideal methods are the hyperinsulinemic euglycemic clamp and the hyperglycemic clamp, expensive and complex techniques that quantify glucose uptake by the tissues in vivo, and therefore measure directly the tissue sensitivity to insulin. It would be necessary to study the impact of treatment with EE/CA on carbohydrate metabolism with the glucose clamp to have the answer regarding its effect on insulin resistance [16].

The present literature, therefore, shows that the available data on the effects of medical therapy in PCOS is conflicting. Differences between trial populations (including the heterogeneity of the syndrome itself), assessment methods, study duration, and drug side-effect profiles may have resulted in the heterogeneity [25]. Considering that PCOS is a chronic condition that requires long term therapy, the short duration of follow-up (3-12 months) is nonetheless a limitation to the reported observations including our own. The small study samples and the employed assessment methods to evaluate important outcome measures (like hirsutism and IR) are further limitations. Therefore, long-term outcome measures, including T2DM, CVD and endometrial cancer should be addressed in longer-term trials with large sample size.

We conclude that treatment of PCOS patients with EE/CA induces very important favourable changes regarding hyperandrogenism, both favourable and unfavourable changes on the lipid profile, and no significant change on carbohydrate metabolism. On the other hand, metformin induces positive effects on lipid profile and significantly improves parameters of IR. The choice for each drug necessitates meticulous consideration of the patient's clinical profile and preference. Not only should the cosmetic problems be considered but also assessment of each PCOS patient's personal cardiometabolic risk profile should be an essential component of the evaluation before prescribing OCs and also during follow-up. The use of combination therapy, as suggested by Elter et al. [22], may be essential to achieve complementary beneficial effects on endocrine–metabolic abnormalities and clinical symptoms.

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