CLINICAL ARTICLE

Metabolic and endocrine effects of metformin and metformin plus cyclic medroxyprogesterone acetate in women with polycystic ovary syndrome

Bulent Haydardedeoglu ⁎, Erhan Simsek, Esra B. Kilicdag, Tayfun Bagis

Baskent University Faculty of Medicine, Department of Obstetrics and Gynecology, Adana, Turkey

ARTICLE INFO

Article history:
Received 9 September 2008
Received in revised form 28 October 2008
Accepted 6 November 2008

Keywords:
Medroxyprogesterone acetate
Metformin
Polycystic ovary syndrome

ABSTRACT

Objective: To evaluate the metabolic and endocrine effects of treatment with cyclic medroxyprogesterone acetate (MPA) plus metformin compared with metformin alone in women with PCOS. Methods: In this prospective randomized study of women with PCOS, 20 women received 850 mg of metformin twice a day, and 20 women received 850 mg of metformin plus 5 mg of MPA twice a day. Body mass index, hormonal and lipid blood profiles, homocysteine blood level, and insulin sensitivities assessed by homeostasis model assessment (HOMA) were recorded at baseline and at 3 months. Results: Total cholesterol levels decreased in the metformin plus MPA group (P=0.002) but did not change significantly in the metformin group (P=0.159). While homocysteine levels remained unchanged in the metformin plus MPA group, they increased significantly in the metformin group (P=0.002). Conclusion: There were no adverse effects of short-term cyclic MPA plus metformin treatment on metabolic parameters or insulin resistance in patients with PCOS over a 3-month treatment period.

© 2008 International Federation of Gynecology and Obstetrics. Published by Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting 5%–7% of women of reproductive age [1]. The hallmarks of PCOS are chronic anovulation and hyperandrogenism. Most women with PCOS are obese and insulin resistant or hyperinsulinemic. Hyperinsulinemia and insulin resistance (IR) play a major role in the pathogenesis of PCOS [2].

The optimal management of PCOS is still controversial, and each patient is treated according to their symptoms. It is important that treatment should be directed not only toward improving oligomenorrhea, hirsutism, or infertility but also toward the long-term risks associated with IR. It is known that women with PCOS are at risk of diabetes, cardiovascular disease, and endometrial cancer [3].

Patients with PCOS have irregular menses due to anovulation, which results from chronic progesterone deficiency. PCOS patients are assumed to be at increased risk of endometrial cancer because long-term exposure of the endometrium to estrogen without progesterone causes increased mitotic activity and expression of oncogenes in the endometrium [4]. Treatment with oral contraceptives or progestins may significantly reduce this risk in women with PCOS. However, treatment with these agents may present a major concern because of their detrimental effect on insulin sensitivity.

Evidence exists of an association between progesterone and decreased insulin sensitivity. Firstly, in the regular menstrual cycle insulin sensitivity is significantly lower during the luteal phase when progesterone levels are high than it is in the follicular phase [5]. In addition, in women without PCOS, long-term use of progestin-only contraceptives has been shown to increase insulin resistance [6]. This finding suggests that treatment with progestins may further reduce insulin sensitivity in women with PCOS.

Oral contraceptives are associated with a lower risk of endometrial and ovarian cancer [7]. They remain the mainstay of treatment in women with PCOS because they are effective in preventing pregnancy, controlling hirsutism, and regulating menstruation. However, current use of low dose oral contraceptive pills (OCPs) could be associated with increased risk of cardiac and vascular events [8]. Although the data about changes in insulin secretion after OCP use are limited, insulin sensitivity may deteriorate during OCP treatment in patients with PCOS [9].

Insulin resistance is strongly associated with the pathogenesis of cardiovascular disease and diabetes [10], and oral contraceptives should therefore be used with caution in women with PCOS, especially in obese women [11]. Because PCOS is often associated with obesity, dyslipidemia, and hyperinsulinemia, treatment with OCPs is therefore not always advisable [12].

Combination therapies of OCPs plus insulin sensitizers or progestins plus insulin sensitizers could be primary therapies for the long-term management of patients with PCOS. Although the combination of metformin with OCPs would seem to be a justifiable approach, the few studies that have been performed demonstrate that the effects of the addition of metformin to OCPs are small [13].
Our previous study demonstrated that administration of progestins (oral or vaginal micronized progesterone, or medroxyprogesterone acetate [MPA]) for 10 days had no harmful effects on the metabolic or endocrine parameters in women with PCOS [14].

The aim of the present study was to investigate the metabolic and endocrine parameters of intermittent cyclic MPA treatment concomitant with metformin therapy and to compare the results with those of metformin monotherapy in women with PCOS.

2. Materials and methods

Between April 2004 and February 2006, 40 women with PCOS took part in this prospective randomized study, which was conducted in the Department of Obstetrics and Gynecology, Baskent University School of Medicine, Adana, Turkey. The study was approved by the Ethical Committee of Baskent University. Informed consent was obtained from each patient before participation.

The diagnosis of PCOS was based on the Rotterdam Criteria [15]. All patients with oligomenorrhea (an irregular cycle duration greater than 45 days or less than 6 menstrual periods per year) and/or anovulation who also had at least one of the characteristics of hyperandrogenism (a hirsutism score of greater than 7 according to Ferriman and Gallway [16], and/or an elevated serum testosterone level) were diagnosed with PCOS after all the other causes of hyperandrogenism were excluded. Patients treated with hormonal medications within the previous 3 months were excluded from the study. Patients were randomized into two groups by an allocation sequence generated from a random numbers table and assigned through consecutively numbered opaque, sealed envelopes.

Group 1 (n = 20) received 850 mg of metformin twice a day (Glucophage; Merck Serono, Geneva, Switzerland), while Group 2 (n = 20) received 850 mg of metformin twice a day plus cyclic MPA 5 mg twice a day (Farlutal) between day 15 and day 25 of the menstrual cycle for 3 months (Fig. 1). The patients’ husbands were advised to use barrier methods of contraception during the study.

Hormonal parameters (follicle-stimulating hormone [FSH], luteinizing hormone [LH], estradiol [E2], total testosterone, free testosterone, dehydroepiandrosterone sulfate [DHEAS], and prolactin), lipid profiles (total cholesterol, high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], triglyceride [TG]), Hcy concentrations, and basal insulin levels were assessed. A 75-g oral glucose tolerance test was performed at baseline and after 3 months in all patients. Blood samples were obtained on the third day of menstruation or at any time after a spontaneous luteal phase was excluded by serum progesterone measurements (serum progesterone measurements <3 ng/mL) in patients with delayed menstruation or amenorrhea.

Blood samples were collected at 8:00 AM (12 hour fasting state) and at 120 minutes after 75 g glucose ingestion. Plasma glucose levels were measured using the glucose oxidase method; plasma insulin concentrations were measured by microparticle enzyme immunoassay (AxSYM insulin assay; Abbott Diagnostics, Abbott Park, IL, USA). Hcy levels were influenced by several variables, including smoking, renal function, vitamin B status, and enzyme dysfunction. Renal status was examined before the women took part in the study. All of the women were nonsmokers. None of the patients had been treated with metformin or MPA before the trial. Levels of plasma fasting glucose, total cholesterol, HDL-C, and TG were determined by calorimetry using a Cobas Mira Plus autoanalyzer (Roche Diagnostics, Mannheim, Germany). LDL-C levels were calculated using the Friedwald formula [17]. Insulin, LH, FSH, E2, prolactin, and Hcy concentrations were measured using an AxSYM hormone autoanalyzer (Abbott Diagnostics) using the microparticle enzyme immunoassay method. Total testosterone and DHEAS were measured in an Immulite One autoanalyzer (Bi Diagnostics Products Corp., Los Angeles, CA, USA) using the chemiluminescent method. Insulin sensitivity was calculated using the homeostasis model assessment (HOMA) formula: fasting glucose [mmol/L] multiplied by fasting insulin [µU/mL] divided by 22.5 [18]. The intra- and interassay coefficients of variation of glucose were 0.4% and 1.2% at 82.2 mg/dL, 0.6% and 1.3% at 81.4 mg/dL, and 0.7% and 1.1% at 80.5 mg/dL, respectively. The intra- and interassay coefficients of variation of insulin were 2.6% and 1.8% at 4.1% and 2.5% at 42.2 µU/mL, and 2.9% and 2% at 126.2 µU/mL, respectively.

Hcy, mixed disulphide, and protein-bound forms of Hcy in the sample were reduced to form free Hcy using dithiothreitol. Free Hcy was converted to S-adenosyl-L-homocysteine (SAH) using SAH hydrolase and excess adenosine. SAH and labeled fluorescein tracer compete for sites on the monoclonal antibody molecule. The intensity of polarized fluorescent light was measured using a fluorescence

![Fig. 1. Flow chart of participants through the study.](image-url)
polarization immunoassay (FPIA) optical unit. The coefficient of variation of FPIA was 4.6% at 7.99 μmol/L, 3.1% at 13.71 μmol/L, and 2.8% at 26.67 μmol/L.

Sample size calculations, assuming 80% power to detect 2 μmol/L changes in Hcy levels between the groups, indicated the need for 15 patients in each group. Data are expressed as means ± SD. The difference between the two groups was analyzed by independent t test. Homogeneity of variance was calculated by Levene test and Lilliefors significance correction test. Differences between the parameters, at baseline and at 3 months, were tested by paired sample test or Wilcoxon rank test when the Lilliefors significance correction was significant. Statistical analysis was performed using SPSS version 11.00 (SPSS, Chicago, IL, USA). P < 0.05 was considered significant.

3. Results

Age, weight, height, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) and metabolic parameters did not significantly differ between the groups. The mean age of the women in groups 1 and 2 was 24.37 ± 5.5 years and 25 ± 6.09 years, respectively (P > 0.05).

In group 1, after 3 months of treatment with metformin, Hcy levels increased significantly from 8.74 ± 1.9 μmol/L to 10.97 ± 3.31 μmol/L (P = 0.002), and FSH levels decreased from 6.17 ± 1.53 IU/L to 5.3 ± 1.02 IU/L (P = 0.029). Weight, BMI, fasting glucose, oral glucose tolerance test (OGTT), HOMA, lipid profile, and other hormonal parameters were not significantly different after metformin treatment (Table 1).

In group 2 patients treated for 3 months with metformin plus cyclic MPA, only the total cholesterol levels decreased significantly after treatment (174.35 ± 35.9 mg/dL vs 163.43 ± 30.7 mg/dL; P = 0.002) (Table 1).

4. Discussion

This study demonstrates that metformin plus cyclic MPA may be a reliable treatment option for patients with PCOS, with no detrimental effects on metabolic parameters. This treatment may also relieve the anxiety caused by irregular menstruation.

The long-term management of patients with PCOS is controversial. Although treatment with insulin-reducing agents is still an important option for these patients, anovulation and oligomenorrhea/amenorrhea rates after metformin treatment are still high. It has been demonstrated by meta-analysis that metformin is effective for achieving ovulation in women with PCOS (odds ratio 3.88; 95% CI, 2.25–6.69 for metformin vs placebo) [19]. However, in a recent multicenter study (PPCOS study) that examined ovulation induction in a population of PCOS patients who were infertile, the ovulation rates after metformin therapy were only 29% [20]. In addition, a more recent study by Palomba et al. [21] revealed that the effect of metformin on insulin sensitivity was no longer seen after 12 months of administration. Therefore, regarding the overall treatment modalities of women with PCOS, metformin monotherapy is not only unsatisfactory but also debatable in terms of long-term management.

Treatment with progestins has been shown to have a detrimental effect on insulin sensitivity, particularly in postmenopausal women receiving continuous combined hormone replacement therapy [22]. No studies have shown that treatment with estrogen alone decreases insulin sensitivity [23,24]. The reduction in insulin sensitivity seems to be reversible in postmenopausal women after continuous combined hormone treatment is stopped [22]. The depot form of progesterone used for contraception has also been shown to have detrimental effects on insulin sensitivity in women of reproductive age [6]. Hence, the inclusion of progestin in the treatment of women with PCOS may be expected to further reduce the already impaired insulin sensitivity. In the present study, short-term use of MPA with concomitant use of metformin did not reduce insulin sensitivity in women with PCOS.

Fiad et al. [25] showed that treatment with MPA for 5 days reduced integrated LH levels, LH response to gonadotropin-releasing hormone (GnRH), the LH/FSH ratio, and androstenedione levels in PCOS patients [25]. They postulated that progesterone deficiency might facilitate the development of hypothalamic–pituitary abnormalities in PCOS patients. In addition, serum levels of testosterone, androstenedione, and LH decreased after 1 week of MPA treatment [26]. Our results also revealed that treatment of PCOS patients with cyclic MPA plus metformin tended to reduce LH levels, but the effect was not statistically significant.

In our previous study, treatment for 10 days with micronized progesterone, orally or vaginally, had no harmful effect on metabolic or endocrine parameters in PCOS patients [14]. In that study, treatment with MPA for 10 days decreased androgen and LH levels, and, surprisingly, also reduced HOMA-IR levels; and was the reason for choosing MPA in the present study. This study also confirmed that the addition of progestins to metformin monotherapy in patients with

### Table 1
Characteristics of women with PCOS who received metformin only and metformin plus MPA

<table>
<thead>
<tr>
<th>Variable</th>
<th>Metformin group 1 (n = 20)</th>
<th>P value</th>
<th>Metformin plus MPA group 2 (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.84 ± 13.08</td>
<td>0.589</td>
<td>67.35 ± 14.4</td>
<td>0.066</td>
</tr>
<tr>
<td>BMI</td>
<td>25.78 ± 5.58</td>
<td>0.581</td>
<td>25.86 ± 5.66</td>
<td>0.062</td>
</tr>
<tr>
<td>Fasting glucose, mg/dL</td>
<td>86.46 ± 6.68</td>
<td>0.778</td>
<td>90.47 ± 6.38</td>
<td>0.378</td>
</tr>
<tr>
<td>OGTT</td>
<td>100.57 ± 27.3</td>
<td>0.416</td>
<td>100.52 ± 28.9</td>
<td>0.538</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>168.67 ± 29.5</td>
<td>0.159</td>
<td>174.35 ± 35.9</td>
<td>0.002</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>54.32 ± 14.27</td>
<td>0.404</td>
<td>47.61 ± 14.85</td>
<td>0.883</td>
</tr>
<tr>
<td>LDL-C, mg/dL</td>
<td>104.57 ± 30.08</td>
<td>0.071</td>
<td>107.87 ± 27.98</td>
<td>0.065</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>75.86 ± 37.4</td>
<td>0.990</td>
<td>89.76 ± 61.53</td>
<td>0.641</td>
</tr>
<tr>
<td>Insulin, mg/dL</td>
<td>12.3 ± 8.4</td>
<td>0.869</td>
<td>12.52 ± 6.63</td>
<td>0.31</td>
</tr>
<tr>
<td>Homocysteine, μmol/L</td>
<td>8.74 ± 1.9</td>
<td>0.002</td>
<td>12.82 ± 6.19</td>
<td>0.111</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.66 ± 0.88</td>
<td>0.84</td>
<td>2.81 ± 1.55</td>
<td>0.323</td>
</tr>
<tr>
<td>FSH, IU/L</td>
<td>6.17 ± 1.53</td>
<td>0.029</td>
<td>5.87 ± 2.09</td>
<td>0.316</td>
</tr>
<tr>
<td>LH, IU/L</td>
<td>13.68 ± 12.8</td>
<td>0.103</td>
<td>13.63 ± 9.2</td>
<td>0.052</td>
</tr>
<tr>
<td>Estradiol, pg/dL</td>
<td>93.80 ± 80.6</td>
<td>0.763</td>
<td>96.11 ± 52.7</td>
<td>0.282</td>
</tr>
<tr>
<td>DHEAS, ng/mL</td>
<td>2904 ± 1508.45</td>
<td>0.623</td>
<td>2405.94 ± 1644.76</td>
<td>0.329</td>
</tr>
<tr>
<td>Total testosterone, ng/mL</td>
<td>0.79 ± 0.36</td>
<td>0.123</td>
<td>1.01 ± 0.46</td>
<td>0.824</td>
</tr>
<tr>
<td>Free testosterone, pg/mL</td>
<td>2.14 ± 0.57</td>
<td>0.394</td>
<td>5.16 ± 1.86</td>
<td>0.339</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); DHEAS, dehydroepiandrosterone sulfate; FSH, follicle stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment insulin resistance; LH, luteinizing hormone; OGTT, oral glucose tolerance test; LDL-C, low-density lipoprotein cholesterol; PCOS, polycystic ovary syndrome.

* Values are expressed as mean ± SD.
PCOS seems to be effective but does not affect the already impaired insulin sensitivity.

In the present study, total cholesterol levels were decreased in the group receiving cyclic MPA plus metformin. In the metformin monotherapy group, there was also a tendency for decreasing total cholesterol and LDL levels but these reductions were not statistically significant. A possible explanation is that the slight stimulation of hepatic lipoprotein lipase action by MPA increases the catabolism of very-low-density lipoproteins [27].

After metformin treatment Hcy levels increase, and high levels of Hcy appear to be associated with increased cardiovascular disease [28]. We have previously demonstrated that metformin monotherapy increases Hcy levels [29], and β-group vitamins and folic acid counteract the increase in Hcy effect seen with metformin therapy [30]. The relationship between metformin and Hcy levels was also confirmed by the results of the present study. The Hcy levels increased significantly after metformin monotherapy, but treatment with MPA plus metformin did not result in any significant changes in Hcy levels in short-term therapy. MPA may counteract the effects of metformin on Hcy levels in some way.

Women with polycystic ovary syndrome are at risk of endometrial cancer due to obesity and abnormal body fat distribution together with the unopposed exposure of the endometrium to estrogen [3]. Administration of cyclic MPA might reduce the risk of endometrial cancer. In the present study, the addition of MPA to metformin monotherapy for PCOS for 3 months accomplished menstrual regularity and did not adversely affect metabolic or hormonal parameters or insulin sensitivity. Although the addition of MPA to metformin treatment for women with PCOS for three months appears promising, the long-term effects of MPA should be clarified by further long-term prospective studies.

References