Metformin Therapy in Girls with Polycystic Ovary Syndrome: A Self-Controlled Clinical Trial

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Background: Polycystic ovary syndrome is not uncommon in women of reproductive age. We conducted this study to determine the clinical, hormonal, and biochemical effects of metformin therapy on girls with polycystic ovary syndrome.

Methods: In a self-controlled clinical trial conducted at the Gynecology Center of Yahyanejad Hospital, affiliated to Babol University of Medical Sciences, Babol, North of Iran, 36 girls with polycystic ovary syndrome were studied. The patients were treated with 500 mg of metformin three times a day for six months. Clinical symptoms, menstrual pattern, and hirsutism, as well as serum concentration of sex steroid (follicular stimulating hormone, luteinizing hormone, dihydroepiandrosterone, testosterone, 17-OH progesterone, estradiol), and lipids (triglyceride, cholesterol, high-density lipoprotein, low-density lipoprotein) were assessed pre- and posttreatment.

Results: Sixteen girls (53% of those with menstrual disturbances) experienced more regular cycles during the treatment. A significant decrease in weight ($P = 0.004$) and body mass index ($P = 0.006$) was noticed after six months of treatment. The number of patients with hirsutism was also decreased. The mean levels of triglyceride ($P = 0.03$) and low-density lipoprotein ($P = 0.0.01$) were decreased while high density lipoprotein ($P = 0.003$) was increased significantly. We also found a significant decrease in luteinizing hormone ($P = 0.006$), estradiol ($P = 0.005$), and dihydroepiandrosterone ($P = 0.026$) after treatment. Changes in the follicular stimulating hormone and 17-OH progesterone levels were not significant.

Conclusion: Metformin therapy has many useful effects in these patients.

Keywords: Hirsutism • metformin • polycystic ovary syndrome • obesity

Introduction

Polycystic ovary syndrome (PCOS), with an incidence of 5 – 10% in women of reproductive age,¹ is characterized by anovulation, infertility, hyperandrogenism, and clinical manifestations of irregular menstrual cycles, hirsutism, obesity, and acne, thus PCOS resembles different metabolic syndromes such as type 2 diabetes mellitus, lipid profile disorders, or atherosclerosis.²

Metabolic disturbances such as elevated serum concentration of luteinizing hormone (LH), testosterone, insulin, and prolactin are common. By the age of 40, up to 40% of patients would have type 2 diabetes mellitus or impaired glucose tolerance.³ PCOS is therefore an important healthcare problem affecting young women nowadays.⁴ In these patients, the chronic hyperinsulinemia leads to over-production of ovarian androgens, which cause chronic anovulation, menstrual disturbances, and hirsutism.⁵ The associated insulin resistance increases the risk of developing glucose intolerance, type 2 diabetes mellitus, and gestational diabetes mellitus.⁶ – ⁸

As a consequence, drugs that reduce insulin levels by improving sensitivity to insulin may provide a new therapeutic option for patients with PCOS. Metformin, an oral biguanide-insulin sensitizing agent, acts by suppressing hepatic

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gluconeogenesis accompanied by a reducing circulating insulin levels and improving hyperandrogenemia.9–11

The most common side-effect of metformin is gastrointestinal disturbance. This can be reduced by taking metformin with meals and increasing the dosage up to the effective dose of 1.5 – 2 g/day slowly. Lactic acidosis is another side-effect, which is extremely rare.12

Vrbikova et al reported that after six months of treatment with metformin (1 g/day), 58% of patients showed a significant improvement in their menstrual cycle pattern. Also, a significant reduction in gonadotropin-releasing hormone analogue and stimulated levels of testosterone ($P<0.05$), LH ($P<0.05$), and estradiol ($P<0.01$) were found.13

Moghetti et al evaluated the effects of long-term administration of metformin (500 mg three times a day) on obese (with a mean ± SD body mass index [BMI] of 30.0 ± 1 kg/m²) patients with PCOS who maintained their usual dietary habits. In about 50% of subjects improvement of menstrual abnormalities was noticed. Women receiving metformin showed a reduction in plasma insulin levels and an increase in sensitivity to insulin. Concurrently, ovarian hyperandrogenism was attenuated as indicated by significant reduction in the serum free testosterone level after stimulation test. In subjects with regular menses, 80% of cycles were ovulatory after the treatment but only minor changes were found in BMI.14

Patients with PCOS may or may not be insulin-resistant. Insulin resistance may explain the effectiveness of metformin in certain populations such as Venezuelan or Finnish women, but not in American or Turkish ones.15

These kinds of studies have been mostly performed on infertile patients (induction of ovulation) and not on unmarried girls; so, we decided to evaluate the effect of metformin on single girls suffering from PCOS.

**Patients and Methods**

This self-controlled clinical trial was conducted on 36 girls with PCOS attending to the Gynecology Clinic of Yahyanejad Hospital, affiliated to Babol University of Medical Sciences, Babol, North of Iran, from April 2001 through April 2002. The study protocol was approved by the Ethics Committee of Babol University of Medical Sciences.

The girls with at least three of the following criteria were included in this study:
- Menstrual disturbances (oligomenorrhea, amenorrhea, and polymenorrhea).
- Obesity, hirsutism, and acne.
- A LH to follicular stimulating hormone (FSH) ratio of >3.

Polycystic ovary was confirmed by abdominal ultrasonography in all patients. All ultrasonographies were performed by one gynecologist with an Aloka ultrasonography unit (Aloka 500, Japan) with a 5 MHz probe. After obtaining a written consent from each patient, they were treated with metformin for six months.

Hirsutism was evaluated using Ferryman-Galloway criteria. Nine body areas were assessed and classified as: no (0), minimal (1), moderate (2), severe (3), marked, and very severe hirsutism.4

The BMI was calculated by dividing the weight in kilograms by squared height in meters. A BMI of <25 was considered normal; BMI of 25 – 29 was considered “overweight”; and a BMI of >30 was considered “obese.”

A menstrual cycle was considered as normal if it lasted from 21 to 35 days with less than seven days of bleeding. An infrequent, irregularly timed episode of bleeding and very light menstrual flow was considered as “oligomenorrhea.” A frequent but regularly-timed episode of bleeding with normal amount of bleeding was considered as “polymenorrhea.” Amenorrhea was defined as the absence of menstruation for three normal cycles or six months in those who had previously normal menstrual cycles.

Biochemical laboratory tests included fasting blood sugar (FBS), 2-hour glucose tolerance test, fasting insulin, triglyceride (TG), total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol.

Hormonal assays were performed before the treatment and at the beginning of the follicular phase. They included FSH, LH, dihydroepiandrosterone (DHEA), testosterone, 17-OH progesterone, and estradiol. These tests were done using radioimmunoassay method. All laboratory tests were repeated six months after the beginning of the treatment with metformin to determine the effect of this drug on hormonal and biochemical parameters and on clinical presentations. All tests were done in the same laboratory using the same kits.
We explained the side-effects of the drug and duration of the treatment for all patients. The treatment was initiated after confirmation of a normal renal and hepatic function.

The patients were treated with Apometformin® (Aptotex, Canada) 500 mg three times a day. To prevent the side-effects of the drug, we prescribed one tablet daily in the first week, two tablets in the second, and three tablets in the third week.

The patients who had taken other medications (e.g., oral contraceptive pills) or had changed their lifestyle or nutritional habits (e.g., weight loss) were excluded from the study.

Data were encoded and analyzed by SPSS. Paired sample Student’s t- and McNemar tests were used to compare before and after treatments. A P value of < 0.005 was considered statistically significant.

Results

Of 36 patients found eligible to enter the study, six were excluded from the study; two for nausea and vomiting and drug intolerance, two for consumption of oral contraceptive pills, and two for lack of compliance. Thirty patients completed the study.

The patients had a age of 22.5 ± 4.0 (mean ± SD) (range: 15 – 29) years. The height of them was 63.4 ± 3.8 cm. The weight, waist circumference, and BMI before and after treatment with metformin are shown in Table 1.

Metformin treatment induced normal menstrual cycles in 67% of the patients (Table 2). The number of patients with hirsutism and the severity of the disease was significant reduced after metformin therapy (P = 0.026). Before the treatment, 7% of the patients had no hirsutism; 13% had mild, 50% moderate, and 30% severe hirsutism. After the metformin therapy, 20% of the participants had no hirsutism; 60% had mild, and 20% had moderate hirsutism — no one had severe hirsutism.

Metformin treatment also ameliorated acne (20 patients before the treatment vs. 8 after metformin therapy; P = 0.003) and ultrasonographic features of PCOS (30 vs. 14 patients).

The fasting insulin dropped from 24.7 ± 12.4 to 19.5 ± 8.0 mIU/mL (P = 0.004), with a reduction of 5.3 ± 6.9 mIU/mL. The FBS also dropped from 89.7 ± 17.4 to 83.8 ± 11.0 mg/dL (P = 0.037), with a reduction of 5.9 ± 4.3 mg/dL. The mean 2-hour glucose level decreased from 114.0 ± 30.0 to 112.3 ± 29.3 mg/dL (P = 0.52).

The mean levels of TG, total and LDL cholesterol had significant reduction; the mean level of HDL cholesterol was increased significantly (Table 3).

When FBS to fasting insulin ratio is <4.5, resistance to insulin is present. Before the treatment, we had insulin resistance in 19 patients; insulin resistance remained in 16 patients after metformin therapy (P = 0.25).

A significant reduction in the serum level of LH, DHEA, and testosterone was observed after the treatment (P < 0.05). No significant changes in FSH and 17-OH progesterone levels were observed (Table 4).

Discussion

PCOS is a common endocrine disorder that affects many women in reproductive ages. Recognition of insulin resistance as an important factor in the pathogenesis of PCOS causes vast use of insulin-lowering agents called insulin-sensitizing agents. Metformin is the most common insulin-lowering agent used in the treatment of PCOS.

In our study, 30 unmarried girls with PCOS were treated with metformin 500 mg three times a day, the same dose administered as in most studies. Acbay and Gundogdu, Ehrmann et al., and Diamanti-Kandarakis et al., however, prescribed a higher dose of 850 mg, two or three times a day.

<p>| Table 1. Weight, waist circumference, and BMI before and after metformin therapy. |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th></th>
<th></th>
<th>Difference</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>73.56 ± 11.82</td>
<td>71.13 ± 11.22</td>
<td>2.43 ± 16.3</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>85.6 ± 13.3</td>
<td>84 ± 12.5</td>
<td>1.1 ± 18.2</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.5 ± 4.4</td>
<td>26.6 ± 4.1</td>
<td>0.9 ± 1</td>
<td>0.006</td>
<td></td>
</tr>
</tbody>
</table>

| Table 2. Menstrual abnormalities before and after treatment with metformin. |
|------------------|------------------|------------------|
| Menstrual cycle | Number of patients (%) | p value |
| Regular          | 4 (13)            | 20 (67)          | 0.0004 |
| Oligomenorrhea   | 9 (30)            | 4 (13)           | 0.063  |
| Amenorrhea       | 14 (47)           | 5 (17)           | 0.004  |
| Polymenorrhea    | 3 (10)            | 1 (3)            | 0.5    |
times a day.

In our study, the mean weight loss was 2.47 kg and the mean change in BMI was 0.89 kg/m². Crave et al. and Kelly and Gordon also reported improved weight loss with metformin. Some researchers mentioned a little reduction in BMI, albeit statistically significant, but others did not report significant changes in BMI.

Pouliot et al. showed that a waist circumference of >90 cm in women is predictive of abnormal endocrinology and metabolic function and is associated with increasing risk of cardiovascular diseases. In our study, the mean change in waist circumference was 1.1 cm. Velazquez et al. reported a reduction in waist circumference after metformin therapy, but Morin-Papunen et al. and Acbay and Gundogdu did not show any changes in waist circumference after treatment with metformin. According to the significant reduction of weight loss, BMI, and specially waist circumference with metformin, this drug can play a role as a preventive agent in cardiovascular disease and metabolic disturbances.

In our study, the mean fasting insulin and FBS reduced significantly. However, there was no significant difference in oral glucose tolerance test before and after the treatment. Most studies agree with the decrease in insulin level after metformin therapy. But Acbay and Gundogdu, and Ehrmann et al. reported no change in the insulin level after treatment with metformin. According to the significant reduction of weight loss, BMI, and specially waist circumference with metformin, this drug can play a role as a preventive agent in cardiovascular disease and metabolic disturbances.

In one study, metformin administration had no effect on insulin resistance in very obese women with PCOS. The women with anovulation and hyperinsulinemia, metformin therapy decreased hyperandrogenism, but made no changes in body weight; although, the reduction of waist to hip ratio was associated with reduction of hyperinsulinemia. Studies have shown that obese and nonobese hyperinsulinemic patients respond to metformin treatment.

Hyperinsulinemia increases the risk of cardiovascular disease indirectly by its atherogenic activity and directly by its adverse effects on lipid profile. Women with anovulation, hyperandrogenism, and hyperinsulinemia are at a great risk of developing noninsulin-dependent diabetes mellitus and the onset of the disease is approximately 30 years earlier than the general population. Therefore, control of blood sugar and lipid profile in these patients in premenopausal ages is very important.

Morin-Papunen et al. and Acbay and Gundogdu demonstrated no changes in lipid profiles with metformin. Chou et al. prescribed metformin to 30 obese, nondiabetic women with PCOS. After 90 days of treatment, significant reduction in total cholesterol level was observed, which is in agreement with our results.

The lipid profile in androgenized women with PCOS is the same as men, i.e., higher levels of TG, total and LDL cholesterol, and lower levels of HDL, which is independent of body weight.

In our study, the LH level was significantly reduced after the treatment ($P = 0.006$); no

### Table 3. Changes in the blood lipid levels before and after treatment with metformin.

<table>
<thead>
<tr>
<th>Parameter (mg/dL)</th>
<th>Mean ± SD Before treatment</th>
<th>Mean ± SD After treatment</th>
<th>Mean ± SD difference</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>203.5 ± 47.3</td>
<td>189.5 ± 40.7</td>
<td>14 ± 17.9</td>
<td>0.008</td>
</tr>
<tr>
<td>TG</td>
<td>151.4 ± 83.9</td>
<td>140.9 ± 67.52</td>
<td>10.5 ± 26.6</td>
<td>0.039</td>
</tr>
<tr>
<td>LDL</td>
<td>124.4 ± 34.7</td>
<td>117.3 ± 32.9</td>
<td>7.1 ± 14.1</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL</td>
<td>37 ± 10.1</td>
<td>48.7 ± 13</td>
<td>11.6 ± 11.6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### Table 4. Changes in the hormone levels before and after treatment with metformin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD Before treatment</th>
<th>Mean ± SD After treatment</th>
<th>Mean ± SD difference</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH (mIU/mL)</td>
<td>11.2 ± 5</td>
<td>9.6 ± 4.3</td>
<td>1.6 ± 2.21</td>
<td>0.006</td>
</tr>
<tr>
<td>FSH (mIU/mL)</td>
<td>5.8 ± 3.9</td>
<td>5.2 ± 2.9</td>
<td>0.6 ± 3.2</td>
<td>0.149</td>
</tr>
<tr>
<td>DHEA (µg/mL)</td>
<td>3.5 ± 1.5</td>
<td>2.9 ± 1.29</td>
<td>0.6 ± 0.8</td>
<td>0.001</td>
</tr>
<tr>
<td>Testosterone (ng/mL)</td>
<td>2.1 ± 1.8</td>
<td>1.5 ± 1.2</td>
<td>0.6 ± 0.9</td>
<td>0.001</td>
</tr>
<tr>
<td>17-OH progesterone (ng/mL)</td>
<td>1.8 ± 1.3</td>
<td>1.6 ± 1.1</td>
<td>0.2 ± 3.4</td>
<td>0.36</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>90.4 ± 37.6</td>
<td>80.2 ± 36.6</td>
<td>0.6 ± 1.1</td>
<td>0.005</td>
</tr>
</tbody>
</table>
significant change was observed in the FSH level ($P = 0.149$). Kazerooni and Dehghan-Kooshkyhazizi demonstrated that metformin treatment has no effect on FSH and LH levels, whereas Nestler and Jakubowicz, and Velazquez et al showed a significant reduction in LH level $P = 0.36$ (Table 3).

We found a significant reduction in the testosterone ($P = 0.005$), DHEA ($P = 0.0001$), and estradiol ($P = 0.001$) levels after metformin therapy, but we did not find any significant differences in the 17-OH progesterone level before and after the treatment ($P = 0.36$) (Table 3).

Kazerooni and Dehghan-Kooshkyhazizi reported no change in DHEA level, but Velazquez et al reported a significant reduction in androgen levels, and denoted a significant reduction in circulatory estradiol level in patients taking metformin.$$^{15, 16, 17}$$

The patients with acne improved remarkably after the treatment ($P = 0.003$). Moreover, 20 of the patients developed regular menses ($P = 0.008$). Casmiri et al, Morin-Papunen et al, and Kazerooni and Dehghan-Kooshkyhazizi demonstrated improvements in acne status and menstrual cycles after metformin therapy.$$^{11, 14, 18, 19, 25}$$

In our study, metformin therapy was very effective on hirsutism. Four patients were completely cured, and after the treatment, no one had very severe hirsutism ($P = 0.026$). In addition to abnormal uterine bleeding, amenorrhea, hirsutism, acne, and unopposed estrogen effect put the patient in a remarkable risk of endometrial and probably breast cancers. The risk of endometrial cancer increases up to three folds in these patients; therefore, it is very important to reduce circulatory androgen levels with a drug.

General goals of treatment in unmarried girls with PCOS include reducing the production and circulatory levels of androgens, protection of endometrium against unopposed estrogen, reducing the risk factors of cardiovascular disease, and avoiding hyperinsulimnic effects on the development of cardiovascular diseases and diabetes mellitus. It seems that metformin can provide all these goals.

With regards to the above-mentioned studies, variable effects of metformin on PCOS were reported. As these studies differ in their inclusion criteria, ethnic background, method of measuring insulin sensitivity, as well as the BMI of the patients and dosage and length of treatment of metformin, it seems difficult to compare them. The results of our study in the northern part of Iran proved that metformin has many useful effects on these patients. However, for long-term treatment with metformin, more investigations are required. Since the type of patients with PCOS may differ, it is important, in future investigations, to look over different points including lean vs. obese, the degree of hyperandrogenemia, and the way insulin resistance is measured.

References


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