DEBATE—continued

Should patients with polycystic ovarian syndrome be treated with metformin?

Proven and potential benefits

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The recognition of insulin resistance as a principal factor in the pathogenesis of polycystic ovarian syndrome (PCOS) has led to the use of insulin-lowering agents, also called ‘insulin-sensitizing drugs’, for its treatment. The most extensively studied insulin-lowering agent in the treatment of PCOS is metformin: an oral antihyperglycaemic agent used initially in the treatment of type 2 diabetes mellitus. Metformin is effective in the treatment of PCOS-related anovulation and infertility. Moreover, preliminary evidence indicates that metformin may also be effective in decreasing the risk of early spontaneous miscarriage in women with PCOS. Metformin also appears to induce cardioprotective effects on serum lipids as well as plasminogen activator inhibitor (PAI)-1 and may decrease the risk of development of type 2 diabetes. The highly promising therapeutic profile of metformin is related to the role of this agent in controlling an important aetiologic factor in the pathogenesis of PCOS: hyperinsulinaemia.

Key words: hyperinsulinaemia/metformin/polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies affecting 4–7% of women of reproductive age (Franks, 1995; Knochenhauer et al., 1998; Asuncion et al., 2000). Stein and Leventhal initially observed the association between amenorrhoea, hirsutism, infertility and polycystic ovaries in the first half of the 20th century (Stein and Leventhal, 1935). Since then, a broad range of other clinical and laboratory findings has been associated with PCOS. These findings include elevated serum LH, elevated LH/FSH ratio, elevated serum testosterone and/or dehydroepiandrosterone sulphate (DHEAS) and, more recently recognized findings, hyperinsulinaemia and hyperlipidaemia.

The classic symptoms of amenorrhoea, infertility and hirsutism do not all need to be present to diagnose PCOS. Many investigators stress the importance of morphological/ultrasonographic evidence of polycystic ovaries, while others de-emphasise this feature. Although considerable controversy remains with regard to the definition of PCOS, the most commonly used definition was proposed at a 1990 National Institutes of Health/National Institute of Child Heath and Development consensus conference. To fit this definition, a patient must have ovulatory dysfunction as well as evidence of hyperandrogenism and/or hyperandrogenaemia in the absence of other causes of hyperandrogenaemia. Whether defined by ultrasound or clinical/biochemical criteria, PCOS is one of the most common endocrine disorders, accounting for ~75% of anovulatory infertility (Adams et al., 1986; Hull, 1987).

While the mechanisms leading to the development of PCOS are still not completely understood, it has become apparent that insulin resistance and compensatory hyperinsulinaemia may play an important role in the pathophysiology of PCOS (Dunaif et al., 1987; Legro et al., 1999). Growing evidence indicates that high blood levels of insulin may mediate the development of hyperandrogenaemia, resulting in anovulation and infertility. Insulin resistance is also central to the development of syndrome X, which is characterized by insulin resistance, hypertension and an adverse lipid profile (Reaven, 1988). Individuals with this common syndrome are at increased risk for cardiovascular disease. Indeed, women with PCOS often have features of syndrome X and appear to be at increased risk for cardiovascular disease. Moreover, they are also more prone to developing type 2 diabetes (Dahlgren et al., 1992). Figure 1 presents a putative paradigm of the pathophysiology of PCOS and its sequelae. This paradigm also presents the rationale for our high expectations from therapy directed at improving insulin insensitivity in women with PCOS.

Rationale for the use of metformin

The recognition of insulin resistance as a principal factor in the pathogenesis of PCOS has led to the use of insulin-lowering agents, also called ‘insulin-sensitizing drugs’, for its treatment. The most extensively studied insulin-lowering agent in the treatment of PCOS is metformin. Metformin is an oral antihyperglycaemic agent used initially in the treatment of
type 2 diabetes mellitus. Metformin therapy improves insulin sensitivity, as shown by a reduction in fasting plasma glucose and insulin concentrations. Its beneficial effects on glycaemic control in diabetic patients are primarily the result of decreased hepatic glycogenolysis leading to a decreased hepatic glucose output and, to a lesser extent, increased peripheral glucose uptake (DeFronzo et al., 1991). Several other actions may contribute, such as increased intestinal use of glucose and decreased fatty acid oxidation (Bailey and Turner, 1996). Unlike sulphonylureas and insulin, metformin use does not result in increased serum insulin levels. There are also preliminary in-vitro data indicating that metformin may directly decrease ovarian androgen production (Attia et al., 2001).

**Menstrual cycle regulation and ovulation induction**

In 1994, Velazquez and co-workers published the first report on the use of metformin as a treatment for PCOS (Velazquez et al., 1994). In this study, 26 obese women with PCOS were treated with 1500 mg of metformin daily for 8 weeks. Metformin improved insulin sensitivity, lowered serum LH, total and free testosterone concentrations (by ~50%) and caused an elevation in serum FSH and sex hormone-binding globulin (SHBG) levels. Moreover, three spontaneous pregnancies occurred, and menstrual cycles were normalized in another seven women who continued the treatment. Subsequently, Nestler and Jakubowicz reported comparable findings in a placebo-controlled trial using metformin 1500 mg daily for 4–8 weeks in 24 obese women with PCOS (Nestler and Jakubowicz, 1996). Metformin use resulted in a decrease in circulating insulin levels as well as a 44% reduction in serum free testosterone levels. The latter was associated with increased SHBG. These effects occurred without a change in body weight among the metformin-treated women.

These initial observations were followed by several studies investigating the effect of metformin on women with PCOS (Table I). While most of these studies suffered from low power and lacked control groups, they showed improvements in ovulation and/or a reduction in androgens with metformin treatment in obese women with PCOS (Velazquez et al., 1997a; Diamanti-Kandarakis et al., 1998; Morin-Papunen et al., 1998; Glueck et al., 1999; Pirwany et al., 1999; Unluhizarci et al., 1999; Kolodziejczyk et al., 2000). More recently, two randomized, prospective, placebo-controlled trials evaluated the effects of relatively long-term metformin treatment in obese PCOS women. First, Moghetti et al. treated obese PCOS women with metformin or placebo for 6 months (Moghetti et al., 2000). Similar to previous reports, this study demonstrated that metformin treatment reduced hyperinsulinaemia and hyperandrogenaemia independently of changes in body weight. In the majority of patients these changes were associated with striking and sustained improvements in menstrual abnormalities and resumption of ovulation. The authors also identified higher plasma insulin, lower serum androstenedione, and less severe menstrual abnormalities as baseline predictors of clinical response to metformin (Moghetti et al., 2000). Most recently, Fleming et al. reported the results of the largest randomized, prospective, placebo-controlled trial in 94 obese women with PCOS treated with metformin or placebo for 16 weeks (Fleming et al., 2002). In this study, metformin improved ovulation frequency in the absence of significant changes in serum androgens or insulin sensitivity. Patients with higher plasma androgen levels and/or body mass index (BMI) >37 kg/m² were less likely to respond.

While a proportion of women with PCOS are obese, 20–50% of patients are lean (Robinson et al., 1993; Franks, 1995). Lean women with PCOS are more insulin-resistant than their healthy, eumenorrheic, weight-matched counterparts (Dunaif et al., 1989). Furthermore, hyperinsulinaemia in PCOS correlates with increased cardiovascular risks irrespective of obesity (Mather et al., 1999). These observations provided a rationale for metformin use in the treatment of lean women with PCOS. Nestler and Jakubowicz treated lean and normal-weight PCOS patients with metformin for 6–8 weeks (Nestler and Jakubowicz, 1997). Similar to their findings in obese women with PCOS, metformin decreased fasting and glucose-stimulated insulin levels, decreased basal and GnRH-stimulated LH release, decreased free and total testosterone concentrations, and increased SHBG. More recently Ibanez et al. evaluated the effects of metformin in 10 non-obese adolescent girls with hirsutism, ovarian hyperandrogenism, oligomenorrhea, dyslipidaemia and a history of precocious pubarche associated with hyperinsulinism (Ibanez et al., 2000). Metformin treatment for 6 months resulted in a marked decline in hirsutism score, insulin response to oral glucose tolerance test, free androgen index, and serum testosterone, androstenedione, DHEA and DHEAS levels. Serum triglyceride, total cholesterol and low-density lipoprotein (LDL) cholesterol levels decreased and high-density lipoprotein (HDL) cholesterol rose, while BMI was not affected. All girls reported regular menses within 4 months. Withdrawal of metformin treatment was followed within 3 months by a consistent reversal toward pretreatment state (Ibanez et al., 2000).

In contrast to the reports summarized above, four studies failed to demonstrate a beneficial effect of metformin treatment in PCOS (Crave et al., 1995; Acbay and Gundogdu, 1996; Ehrmann et al., 1997; Ng et al., 2001). Two of these studies had questionable inclusion criteria. Crave et al. reported that in obese women with PCOS, metformin did not offer additional benefit beyond the effects of weight loss alone (Crave et al., 2001).
### Table I. Summary of studies evaluating the effects on metformin on PCOS

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Criteria used to diagnose PCOS</th>
<th>n</th>
<th>Mean BMI</th>
<th>Time</th>
<th>Effect on serum insulin</th>
<th>Effect on serum free T</th>
<th>Effect on cardiovascular risk factors</th>
<th>Effect on ovulation</th>
<th>Effect on pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Velazquez et al., 1994</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>26</td>
<td>29.1</td>
<td>8 wk</td>
<td>↓</td>
<td>↓</td>
<td>↓ BMI, ↓ SBP, ↑ HDL, ↓ TC, ↓ TG, ↑ DBP</td>
<td>NA</td>
<td>3/26 pregnant</td>
</tr>
<tr>
<td>Crave et al., 1995</td>
<td>Prospective, randomized, placebo-controlled</td>
<td>Hirsutism, obesity</td>
<td>24</td>
<td>35.2</td>
<td>16 wk</td>
<td>↑</td>
<td>↓</td>
<td>↓ BMI, ↑ HDL, ↑ TC, ↓ TG</td>
<td>3/12 of metformin of placebo group resumed regular cycles</td>
<td>NA</td>
</tr>
<tr>
<td>Nestler and Jakubowicz, 1996</td>
<td>Placebo-controlled</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>24</td>
<td>34.6</td>
<td>4–8 wk</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI, ↓ HDL</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Achuy and Gandogdu, 1996</td>
<td>Placebo-controlled cross-over</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>16</td>
<td>30.2</td>
<td>10 wk</td>
<td>↑</td>
<td>↑</td>
<td>↑ BMI, ↑ HDL</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ehrmann et al., 1997</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>14</td>
<td>39.0</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI, ↑ HDL</td>
<td>NA</td>
<td>1/20 pregnant</td>
</tr>
<tr>
<td>Velazquez et al., 1997</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>22</td>
<td>27.7</td>
<td>6 m</td>
<td>↓</td>
<td>↓</td>
<td>↓ BMI</td>
<td>21/22 resumed regular cycles</td>
<td>NA</td>
</tr>
<tr>
<td>Nestler and Jakubowicz, 1997</td>
<td>Prospective, non-randomized, placebo-controlled</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>31</td>
<td>21.6</td>
<td>4–6 wk</td>
<td>↓</td>
<td>↑</td>
<td>↑ BMI</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diamanti-Kandarakis et al., 1998</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>16</td>
<td>33.6</td>
<td>6 m</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI</td>
<td>7/16 resumed regular cycles</td>
<td>2/16 pregnant</td>
</tr>
<tr>
<td>Morin-Papunen et al., 1998</td>
<td>Case series</td>
<td>US criteria and oligo/amenorrhea or hirsutism or acne</td>
<td>20</td>
<td>31.5</td>
<td>4–6 m</td>
<td>↓</td>
<td>↑</td>
<td>↑ BMI, ↑ HDL, ↑ LDL, ↑ TG</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Unluhizarci et al., 1999</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, hyperandrogenemia, US criteria</td>
<td>17</td>
<td>29.7</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>NA</td>
<td>4/16 resumed regular cycles</td>
<td>1/17 pregnant</td>
</tr>
<tr>
<td>Pirwany et al., 1999</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>15</td>
<td>37</td>
<td>8 wk</td>
<td>↑</td>
<td>↓</td>
<td>↑ BMI</td>
<td>2/20 resumed regular cycles</td>
<td>NA</td>
</tr>
<tr>
<td>Glueck et al., 1999</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>43</td>
<td>36.3</td>
<td>1.5 to 2.36 m</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI, ↑ HDL, ↑ LDL, ↑ TG</td>
<td>10/10 resumed regular cycles</td>
<td>NA</td>
</tr>
<tr>
<td>Ibanez et al., 2000</td>
<td>Case series</td>
<td>Non-obese, adolescent (mean age 16.8 years), precocious pubarche, oligo/amenorrhea, hirsutism, hyperandrogenemia</td>
<td>10</td>
<td>21.9</td>
<td>6 m</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI, ↑ HDL, ↑ LDL, ↑ TG</td>
<td>13/13 resumed regular cycles</td>
<td>NA</td>
</tr>
<tr>
<td>Moghetti et al., 2000</td>
<td>Prospective, randomized placebo-controlled</td>
<td>Chronic anovulation, hirsutism, hyperandrogenemia</td>
<td>32</td>
<td>30</td>
<td>6 m</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI, ↑ HDL, ↑ LDL, ↑ TG</td>
<td>15/13 resumed regular cycles</td>
<td>NA</td>
</tr>
<tr>
<td>Kolodziejczyk et al., 2000</td>
<td>Case series</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>39</td>
<td>32.5</td>
<td>12 wk</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI</td>
<td>Menstrual cycles shortened</td>
<td>NA</td>
</tr>
<tr>
<td>Ng et al., 2001</td>
<td>Prospective, randomized placebo-controlled</td>
<td>Oligo/amenorrhea, hirsutism, US criteria</td>
<td>20</td>
<td>24.0</td>
<td>3 m</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI, ↑ HDL, ↑ LDL, ↑ TG</td>
<td>10/10 resumed regular cycles</td>
<td>unchanged</td>
</tr>
<tr>
<td>Fleming et al., 2002</td>
<td>Prospective, Randomized, placebo-controlled</td>
<td>Oligo/amenorrhea, US criteria</td>
<td>92</td>
<td>28.9</td>
<td>14 wk</td>
<td>↓</td>
<td>↓</td>
<td>↑ BMI, ↑ HDL, ↑ LDL, ↑ TG</td>
<td>30% of treatment group resumed regular cycles compared with 18% in placebo group</td>
<td>NA</td>
</tr>
</tbody>
</table>

PCOS = polycystic ovarian syndrome; n = number of patients evaluated; BMI = body mass index (kg/m²); ↓ = decreased with treatment; ↑ = increased with treatment; [–] = unchanged with treatment; NA = not applicable; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglycerides; SBP = systolic blood pressure; DBP = diastolic blood pressure.
Should patients with polycystic ovarian syndrome be treated with metformin?

In this study, patients were selected based on the presence of hirsutism and it is not clear whether all patients had PCOS. Another prospective randomized trial showed no improvement in ovulatory rate with metformin treatment in lean, clomiphene-resistant women diagnosed with PCOS based on ultrasonographic criteria (Ng et al., 2001). However, most of the subjects did not have clinical or laboratory hyperandrogenism and some had regular menstrual cycles, limiting the validity of this study. Ehrmann et al. failed to show any effect of metformin in morbidly obese women with PCOS (BMI as high as 50 kg/m²) (Ehrmann et al., 1997), suggesting that women with extreme obesity and insulin resistance may not respond to conventional doses of metformin therapy. This is consistent with the findings of Fleming et al. who showed that women with PCOS and a BMI >37 kg/m² are less likely to respond to metformin therapy (Fleming et al., 2002). Whether this can be overcome by using higher doses of metformin remains to be determined.

Several reports have shown that metformin is beneficial in combination with other forms of ovulation induction. Nestler et al. treated 61 moderately obese women with PCOS with metformin or placebo for 5 weeks and subsequently used clomiphene citrate in both groups (50 mg daily for 5 days). When compared with placebo, metformin therapy resulted in an 8-fold increase in spontaneous ovulation during the pretreatment period and >10-fold increase in clomiphene-induced ovulation (Nestler et al., 1998). Others evaluated the effect of metformin in women with PCOS who previously failed clomiphene citrate treatment. Vandermolen et al. studied 27 women with PCOS who previously failed to ovulate in response to 1500 mg/day of clomiphene citrate for 5 days. Following 7 weeks of metformin or placebo treatment, up to six cycles of ovulation induction were attempted using clomiphene citrate at an initial dose of 50 mg/day and increasing this dose as required. In the metformin and placebo groups, 75 and 27% of participants ovulated and 55 and 7% conceived respectively (Vandermolen et al., 2001). The above data demonstrate that metformin augments the effects of clomiphene citrate on ovulatory function and ultimately improves pregnancy rates. The optimal timing and duration of metformin pretreatment remains to be established.

Metformin is also beneficial in women resistant to high doses of clomiphene citrate and undergoing treatment with gonadotrophins (De Leo et al., 1999). In clomiphene-resistant women, metformin treatment for a month prior to ovulation induction with FSH resulted in lowering of the number of ovarian follicles >15 mm on the day of hCG administration and lowering the level of plasma estradiol. These findings indicated that metformin reduced the risk of ovarian hyperstimulation in these patients (De Leo et al., 1999). Metformin also improves the fertilization and clinical pregnancy rates in women with PCOS undergoing IVF (Stadtmueller et al., 2001).

An important complaint of many women with PCOS is hirsutism. The effect of metformin treatment on hirsutism is not well established. Most of the studies summarized above evaluated the effect of metformin on metabolic and hormonal parameters, as well as ovulatory function, during a short period of time. Those who studied the effect of metformin on hirsutism reported conflicting results (Ibanez et al., 2000; Moghetti et al., 2000). Large randomized prospective trials with appropriate patient selection and long-term follow-up are necessary to establish the effect of metformin on hirsutism.

Patients starting metformin therapy should be advised that they might suffer from gastrointestinal side-effects. These may include diarrhoea, abdominal discomfort, anorexia, nausea, and rarely, a metallic taste in the mouth. The symptoms are dose-related and remit if the dose is reduced, and sometimes an increase in the dose can later be tolerated. More than half of patients can tolerate the maximal dose, but ~5% cannot tolerate any dose of metformin (Bailey and Turner, 1996). Metformin also causes a small increase in basal and postprandial blood lactate concentrations, typically within the normal range. The increased blood lactate concentrations are probably caused by metformin-induced conversion of glucose to lactate by intestinal mucosa. In patients with hepatic or renal impairment, cardiac or respiratory insufficiency, severe infection or alcoholism there is an increased risk of lactic acidosis, and metformin is contraindicated. Lactic acidosis is thought to occur in <0.01–0.08 cases per 1000 patient-years; however, when it occurs it has a reported mortality of 50%. Should a patient develop lactic acidosis attributable to metformin, the drug can be removed by haemodialysis (Bailey and Turner, 1996).

In conclusion, there is convincing evidence that metformin improves the regularity of menstrual cycles in women with PCOS. Furthermore, metformin is effective in ovulation induction, either alone or in combination with other fertility enhancing medications. However, these beneficial effects have only been demonstrated in women with insulin resistance (lean and obese) and at present there is no systematic published report examining the use of metformin in women with PCOS who are not insulin resistant.

Protection from pregnancy losses

Early pregnancy loss is a major complication of pregnancy in women with PCOS. It is estimated that 30–50% of pregnancies in women with PCOS end with spontaneous miscarriage during the first trimester (Jakubowicz et al., 2002). This represents a 3-fold higher rate than that of 10–15% reported in retrospective studies of healthy women (Regan et al., 1989). Moreover, in women with recurrent miscarriages, the prevalence of ultrasonographically detected polycystic ovaries is four times higher (Sagle et al., 1988). It has been proposed that the use of metformin to lower insulin levels in women with PCOS during ovulation induction and early pregnancy may improve endometrial function, implantation and pregnancy outcome.

Metformin is a pregnancy category B medication. There are no adequate and well-controlled studies evaluating the effects of metformin in pregnant women. Metformin is not teratogenic in rats or rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits respectively. In humans, metformin treatment during pregnancy for non-insulin dependent diabetes (NIDDM) did not appear to lead to a
higher incidence of major congenital abnormalities when compared with untreated pregnant women with NIDDM (Coetzee and Jackson, 1984). The results of this study should be accepted with caution due to the fact that most of the patients started metformin after the beginning of pregnancy.

Recently, two studies investigated the effect of metformin on first trimester spontaneous miscarriages in women with PCOS. First, Glueck et al. evaluated the effects of metformin treatment (1,500–2,550 mg/day) in 19 women with PCOS who conceived while being treated with metformin and continued the treatment during the pregnancy. Ten of these women had 22 previous pregnancies with a 73% miscarriage rate. While using metformin, these women had a spontaneous miscarriage rate of only 10%. Patients had no adverse side effects and there were no birth defects (Glueck et al., 2001). More recently, a retrospective cohort study evaluated the effect of metformin in 96 women with PCOS (Jakubowicz et al., 2002). Women who conceived while taking metformin and who continued taking metformin at a dose of 1000–2000 mg daily during pregnancy were compared with a control group of women who did not use metformin before or after conception. The early pregnancy loss rate in the metformin group was 8.8%, while in the control group it was 41.9%. Metformin was not associated with any fetal abnormalities (Jakubowicz et al., 2002).

In summary, currently available data suggest that metformin improves pregnancy outcome by decreasing early spontaneous miscarriages in women with PCOS. If this finding is confirmed by randomized, prospective, placebo-controlled trials, metformin will be established as the only known treatment for recurrent spontaneous miscarriage (Talbott et al., 1994; Talbott et al., 2000b). Recently, Talbott et al. reported that PAI-1 is higher in women with PCOS even when controlled for obesity or hyperinsulinaemia, which are independently associated with elevations of PAI-1 (Talbott et al., 2000b).

Another cardiovascular risk factor that has been associated with PCOS is hypertension. As a group, women with PCOS would be expected to be prone to hypertension due to the tendency towards obesity and hyperinsulinaemia. In a retrospective cohort study, Dahlgren et al. reported an increased prevalence of hypertension in 33 women with a mean age of 50 years and a history of PCOS treated with wedge resection 22–31 years previously compared with 132 age-matched controls (Dahlgren et al., 1992). More recently, Talbott et al. reported that mean systolic, but not diastolic, blood pressure levels were greater in women with PCOS compared with age and race-matched controls. On the other hand, when they applied multiple regression analysis to adjust for other cardiovascular risk factors such as BMI, fasting insulin and age, there were no significant differences in blood pressure (Talbott et al., 1995). Zimmerman et al. also failed to show an increase in blood pressure in women with PCOS compared with age-, race- and BMI-matched controls and questioned the suggested association between syndrome X and PCOS (Zimmermann et al., 1992).

While there is little doubt that women with PCOS cluster risk factors for cardiovascular disease, it is not clear whether they have higher cardiovascular morbidity and mortality. PCOS is generally diagnosed in a woman’s reproductive years, when it is too early to detect the accumulative effects of risk factors. For this reason, most studies evaluated surrogate endpoints (Wild, 2002). Atherosclerosis is the principal pathology underlying cardiovascular disorders, and subclinical atherosclerosis has been investigated as a surrogate endpoint in women with PCOS. Carotid intima-media thickness, as measured non-invasively by carotid ultrasound, is an established measure of general atherosclerosis. Using carotid ultrasound, Talbott et al. found that carotid intima-media thickness is significantly higher in women >45 years old with PCOS compared with age-matched controls. Moreover, the difference persists even when the results are adjusted for BMI, LDL cholesterol, triglycerides, and systolic and diastolic blood pressure in multiple regression analyses (Talbott et al., 2000a). On the other hand, in a large retrospective cohort study, Wild et al. did not find an increase in cardiovascular morbidity and mortality at long-term follow-up in women diagnosed with PCOS based on histopathologic criteria compared with age-matched controls (Wild et al., 2000).

In summary, women with PCOS display a higher prevalence of cardiovascular risk factors such as obesity, hyperinsulinemia, dyslipidaemia and hypertension, and seem to be at high risk for developing early onset coronary heart disease. On the other hand, a direct association of PCOS with increased cardiovascular morbidity and mortality is, as yet, uncertain.

The use of metformin in diabetes has been shown to decrease the risk of cardiovascular complications (Anonymous, 1995; Anonymous, 1998). Currently, there are no data regarding the effect of metformin on cardiovascular morbidity or mortality in women with PCOS. On the other hand, metformin treatment has been shown to improve cardiovascular
risk factors in women with PCOS. In our recent study, the use of metformin in hyperinsulinaemic women with PCOS led to an improvement of lipid profile, including a decrease of total cholesterol, LDL and triglycerides (Kolodziejczyk et al., 1999). These findings are consistent with the results of two recent randomized prospective trials (Moghetti et al., 2000; Fleming et al., 2002). Moreover, in some reports metformin treatment has also been associated with a decrease in BMI (Velazquez et al., 1994, 1997a; Glueck et al., 1999; Kolodziejczyk et al., 2000) and serum PAI-1 levels (Velazquez et al., 1997b). Studies with appropriate control groups and long-term follow-up are necessary in order to determine whether PCOS is associated with an increase in cardiovascular events and whether modification of risk factors is beneficial.

PCOS is also associated with an increased risk of type 2 diabetes (Dahlgren et al., 1992). Multiple factors contribute to diabetes risk in women with PCOS, including obesity, insulin resistance, family history of type 2 diabetes and dyslipidaemia (Legro, 2001). Recently, the results of a large randomized prospective trial conducted by The Diabetes Prevention Program Research Group became available. In this trial, 3234 non-diabetic subjects with elevated fasting and post-load plasma glucose concentrations were treated with placebo, metformin (850 mg twice daily), or a lifestyle-modification programme with the goals of at least a 7% weight loss and 150 min of physical activity per week. The average follow-up was 2.8 years. Metformin reduced the incidence of type 2 diabetes by 31% (7.8 versus 11.0 cases per 100 person-years). The lifestyle intervention was even more effective than metformin (Anonymous, 2002). More recently, metformin therapy (2550 mg per day) throughout pregnancy was associated with a 10-fold decrease in the development of gestational diabetes in non-diabetic women with PCOS (Glueck et al., 2002).

In summary, preliminary evidence indicates that the use of metformin by women with PCOS may improve their cardiovascular risk and delay or even prevent the onset of overt type 2 diabetes.

Conclusions

The accumulated evidence supports the use of metformin in the treatment of PCOS-related anovulation. Preliminary and encouraging evidence indicates that metformin may also be effective in decreasing the risk of early spontaneous miscarriage. Metformin also appears to induce cardioprotective effects on serum lipids as well as PAI-1, although the actual protection from cardiovascular mortality and morbidity has yet to be demonstrated. Furthermore, it is possible that the use of metformin may delay or prevent the onset of type 2 diabetes. This highly promising therapeutic profile of metformin is related to the role of this agent in controlling an important aetiologic factor of PCOS: hyperinsulinaemia.

However, PCOS is a heterogeneous group of disorders, each responding differently to individual treatments. Therefore, one of the greatest challenges ahead will be the identification of optimal therapies addressing the specific endocrine and metabolic profiles of individual subgroups. Metformin, like other therapeutic agents, will ultimately find its place in treatment of some, but not all, patients with PCOS.

References


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