INVITED COMMENTARY

Insulin sensitizing agents and polycystic ovary syndromeRenato Pasquali and Marco Filicori¹*Division of Endocrinology, Department of Internal Medicine, University of Bologna, Italy and ¹Reproductive Endocrinology Center, Department of Obstetrics and Gynecology, University of Bologna, Italy**(Correspondence should be addressed to M Filicori, Reproductive Endocrinology Center, Department of Obstetrics and Gynecology, University of Bologna, Via Massarenti 13, I-40138 Bologna, Italy)*

Insulin resistance and compensatory hyperinsulinemia are prominent features of many women with polycystic ovary syndrome (PCOS) (1). Increased insulin concentrations appear to play a role in the pathophysiology of hyperandrogenism of PCOS since they can stimulate ovarian androgen production and decrease the synthesis of sex hormone binding globulin (SHBG) by the liver (2). Obesity, which is commonly associated with PCOS, can amplify these disorders and may worsen further both hyperandrogenism and its related clinical signs (3). In addition, both hyperinsulinemia and obesity appear to adversely affect ovulation and fertility after both clomiphene and pulsatile gonadotropin releasing hormone (GnRH) administration (4).

The hypothesis that hyperinsulinemia may contribute to hyperandrogenism and infertility in women with PCOS, particularly when they are obese, has stimulated several studies on the efficacy of both dietary-induced weight loss and treatment with insulin lowering drugs. Results so far accrued suggest that body weight reduction with low calorie diets ameliorates insulin action in the target tissues and reduces insulin concentrations in PCOS, thus resulting in both hormonal and metabolic improvements and enhancement of fertility (3). Furthermore, previous studies by Nestler and coworkers (5) showed that suppression of insulin by diazoxide without changes in body weight can reduce testosterone and increase SHBG concentrations in hyperandrogenic women with obesity and PCOS, but not in normal weight controls. Therefore, it is possible that clinical improvements can be achieved in these women merely by reducing serum insulin levels.

Metformin is a biguanide that has been extensively used in Europe and Canada for several years in the management of type II diabetes. More recently, use of this drug has also been adopted in the United States. The mechanisms of action of metformin include a reduction in hepatic glucose production and an increase in the sensitivity of peripheral tissues to insulin, without significant effects on β -cell insulin production (6). Therefore, metformin can reduce peripheral insulin concentrations and improve glucose tolerance and metabolism.

Several recent studies have demonstrated that metformin may be effective in reducing androgen

levels and increasing SHBG concentrations in women with obesity and PCOS (7, 8). There is evidence that many women with PCOS have increased ovarian cytochrome P450c15 α activity, resulting in excessive ovarian androgen production; this abnormality is associated with increased 17 α -hydroxyprogesterone (OHP) response to stimulation by GnRH agonists (9). The hypothesis that hyperinsulinemia may stimulate ovarian cytochrome P450c15 α activity has recently been tested by Nestler and Jakubowicz (8) who found that administration of metformin (1500 mg daily) reduced insulin levels as well as the OHP and luteinizing hormone responses to leuprolide. This finding suggests that decreasing insulin levels may reduce ovarian cytochrome P450c15 α activity, thereby ameliorating hyperandrogenism. These effects were also seen after dietary-induced weight loss (10). The study by Diamanti-Kandarakis *et al.* (11) reported in this issue was performed in obese women with PCOS and yields further evidence of insulin's role in inducing hyperandrogenism. Although this study lacks a control group, its findings are comparable to those reported by others (7) in similarly uncontrolled studies. Although no significant difference was found in either fasting or glucose-stimulated insulin levels, the authors found that metformin caused a weight-independent increase in glucose utilization rate (measured during a two-step euglycemic hyperinsulinemic clamp technique) which indicates an amelioration of the insulin resistant state. However, these findings were not in agreement with previous results reported by Ehrmann *et al.* (12) who failed to detect any significant difference in androgen levels and insulin sensitivity (measured by the frequently sampled i.v. glucose tolerance test) in a group of PCOS and obese women treated with metformin for three months.

Another class of insulin sensitizing agents, the thiazolidinediones, have recently become available for the treatment of insulin resistant states. One of these agents, troglitazone, was shown to improve glucose metabolism and insulin sensitivity in patients with type II diabetes, regardless of body weight changes (13). In two separate studies (14, 15) it was found that administration of this compound (400 mg daily) improved total body insulin sensitivity, lowered circulating insulin levels,

and ameliorated the metabolic and hormonal derangements in obese PCOS women. Correction of excessive testosterone levels and of triglycerides and plasminogen activator inhibitor type I may reduce the risk of long-term complications such as cardiovascular disease.

Available data thus support the hypothesis that several benefits can be achieved in women with obesity and PCOS by decreasing hyperinsulinemia. This finding could be of great clinical relevance, since these women are susceptible to developing diabetes and cardiovascular disease (such as hypertension and myocardial infarction) later in life, particularly in the postmenopausal (16). Both epidemiological and clinical studies suggest that these disorders can be partially prevented by improving insulin sensitivity and hyperinsulinemia.

In summary, the use of insulin sensitizing agents seems to open a new era in the management of women with PCOS, since they can ameliorate hyperandrogenism and possibly fertility. Further studies are needed to assess if this therapeutic strategy may also be helpful in the prevention of metabolic and cardiovascular disease.

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