

The Role of Metformin in the Treatment of Polycystic Ovary Syndrome (PCOS)

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Hyperinsulinemia is believed to be a key link in the enigmatic generation of the symptoms of polycystic ovarian syndrome (PCOS), which include anovulatory infertility and the skin stigmata induced by hyperandrogenism. Regression of these symptoms may be achieved by reducing the hyperinsulinemia. Metformin, an insulin-sensitizing agent, has been proven to be of clinical usefulness both in the short-term aiding of infertility treatments and, potentially, in the prevention of the long-term sequelae for patients with PCOS. (*Chang Gung Med J* 2006;29:445-7)

Key words: polycystic ovary syndrome (PCOS), insulin resistance, metformin.

Polycystic ovary syndrome (PCOS), characterized by hyperinsulinemic hyperandrogenism with anovulation, is the most frequent androgen disorder of ovarian function, and it affects 5%-10% of all women. Clinically, PCOS is made up of three characteristics: hyperandrogenic state, anovulation and insulin resistance.^(1,2) The accompanying insulin resistance and hyperinsulinemia mark PCOS as a pre-diabetic state, with high incidence of impaired glucose tolerance, gestational diabetes, and overt diabetes. In patients with PCOS, other metabolic and biochemical changes, such as hypertension and dyslipidemia, increase the risk of cardiovascular disease.

The traditional pharmacological therapy for patients with PCOS mainly addresses correction of the hyperandrogenic state and anovulation, but always neglects the associated long-term metabolic risks (i.e. insulin resistance). Recently, the increasing evidence has shown that insulin resistance has an important implication in the pathogenesis of PCOS and the use of insulin-sensitizing drugs is an effective therapeutic approach.

Effects of metformin on the increase in insulin sensitivity

Insulin resistance with resultant hyperinsulinemia, irrespective of excess weight or frank obesity, has been reported in patients with PCOS.⁽²⁾ A growing body of evidence has suggested that hyperinsulinemia contributes to the excess ovarian androgen secretion observed in women with PCOS.⁽³⁾ As insulin has a direct effect on ovarian androgen production *in vitro*, insulin resistance may play a crucial role in the pathophysiology of PCOS. The recognition of insulin resistance as a principal factor in the pathogenesis of PCOS has led to the use of insulin-sensitizing drugs for treatment.

Metformin, a biguanide antihyperglycemic drug, has been shown to improve hyperandrogenism, hyperinsulinemia, and menstrual cyclicality, most likely through its positive effects on insulin clearance and abdominal adiposity, in both obese and non-obese PCOS patients.⁽⁴⁻⁶⁾ Recent evidence also suggests that one of the modes of action of metformin may be through phosphorylation of the insulin receptor and insulin receptor substrates.⁽⁷⁾ In addition, metformin appears to induce cardioprotective effects on serum lipids as well as the plasminogen activator inhibitor (PAI)-1 and may decrease the risk of development of type 2 diabetes.⁽⁸⁾ Collectively, in PCOS

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Received: Sep. 5, 2005; Accepted: Mar. 15, 2006

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patients, metformin has improved metabolic disorders as a consequence of insulin resistance and subsequent chronic sequelae, such as dyslipidemia, diabetes, hypertension and cardiovascular disease.

Effects of metformin on reduction of androgens

The primary goal of the treatment of hyperandrogenism is central or peripheral androgen suppression using three groups of drugs: inhibitors of androgen production (oral contraceptives), peripheral androgen blockers (cyproterone acetate, flutamide, finasteride and spironolactone), and insulin-sensitizing agents (metformin). In both obese and non-obese PCOS patients, hyperandrogenism was effectively treated by reducing hyperinsulinemia using metformin.^(4,5,8,9) In ovarian theca cells, metformin inhibited androstenedione production with no effect on progesterone.^(10,11) Clinically, metformin therapy resulted in a significant decrease in the total serum testosterone.^(4,7,11) Moreover, metformin corrected not only ovarian hyperandrogenism but also functional adrenal hyperandrogenism in adolescents with PCOS.⁽¹²⁾

Antiandrogens as sole treatment or combined with metformin have been proven effective treatments for the manifestations of hyperandrogenemia.^(9,13) Specifically, clinical improvement of hyperandrogenemia was observed more effectively using combined therapy than using a single agent.

Effects of metformin on ovulation, menstrual cycles and conception

In women with PCOS, elevation of circulating insulin and insulin-like growth factor-I (IGF-I) levels results in overproduction of androgens in ovarian theca cells.⁽¹⁴⁾ Metformin inhibits production of androgens in the theca cells, in part through reducing pituitary secretion of LH, leading to ovulation and regular menstrual cycles.^(10,15) Clinically, metformin is effective for ovulation induction, menstrual-cycle regulation and pregnancy in both obese and non-obese patients with PCOS.^(5,6,8,15,16) Previously, researchers demonstrated excellent efficacy of metformin on induction of ovulation and pregnancy in Asian women with clomiphene citrate (CC)-resistant PCOS.⁽¹⁷⁾

Although metformin has been shown to be effective in the treatment of anovulation in women with PCOS, clomiphene citrate (CC) is still consid-

ered to be the drug of choice to induce ovulation in these patients.⁽¹⁸⁾ In addition, metformin plus CC appears to be very effective for the achievement of pregnancy compared with CC alone.⁽¹⁶⁾

During pregnancy, metformin therapy has been reported to be not teratogenic and safely associated with the reduction in spontaneous abortion and gestational diabetes in women with PCOS.^(19,20) The efficacy of metformin used during pregnancy has encouraged the continued use of the drug after conception. Nevertheless, the use of metformin during pregnancy should be performed with great caution because of the limited availability of clinical data.

Conclusions

The overall aims of treatment for patients with PCOS are to induce ovulation for women desiring to conceive, to reduce androgen levels, to reduce body weight and to reduce long-term health risks of diabetes mellitus and cardiovascular disease. Metformin alone or combined with CC or antiandrogens may improve the disorders caused by PCOS to a significant extent including amelioration of dyslipidemia and prevention of cardiovascular disease. However, the effect of weight loss has not been achieved using metformin. Changes in lifestyle and a low calorie diet are effective in reducing excess weight.

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