DEBATE

Should patients with polycystic ovarian syndrome be treated with metformin?

A note of cautious optimism

Roy Homburg

1Lis Maternity Hospital, Tel Aviv (Sourasky) Medical Centre, Tel Aviv 64239, Israel (affiliated to the Sackler School of Medicine, Tel Aviv University). E-mail: homburg@netvision.net.il

Hyperinsulinaemia has proved to be a key link in the enigmatic generation of the symptoms of polycystic ovarian syndrome (PCOS), i.e. anovulatory infertility and the skin stigmata induced by hyperandrogenism. Regression of these symptoms may be achieved by reducing the hyperinsulinaemia. As obesity exaggerates the expression of the symptoms induced by hyperinsulinaemia, a low calorie diet and lifestyle change resulting in loss of weight for obese women with PCOS is capable of reversing these symptoms. Insulin-sensitizing agents, predominately metformin, have been examined for their ability, in all patients with PCOS, to achieve similar beneficial changes to those induced by loss of weight in the obese. While the scientific value of many of these studies is questionable and solid evidence of efficiency and safety is not complete, the honourable intent of lowering high insulin levels in this way prompts the bottom line of this debate to strike a note of cautious optimism that insulin-sensitizing agents will be of some clinical usefulness both in the short-term aiding of infertility treatment and, possibly, in the prevention of the long-term sequelae for this troublesome and very prevalent condition.

Key words: hyperinsulinaemia/metformin/polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is a very common endocrine disorder occurring in 5–10% of the female population in the fertile age group (Franks, 1995). Although the symptoms and signs of PCOS are very heterogeneous, the syndrome usually presents with any combination of the following: menstrual irregularities (usually oligo- or amenorrhoea), signs of hyperandrogenism (hirsutism, acne, alopecia), a characteristic appearance of the ovaries on ultrasound examination and an endocrine disturbance often involving high serum concentrations of LH and androgens.

We are now also fully aware of a well established association between PCOS, insulin resistance and hyperinsulinemia. This association seems to be genetic in origin and the cellular and molecular mechanisms of insulin resistance in PCOS are distinct from those seen in other insulin-resistant conditions in that the problem appears to be in the post-insulin receptor domain, interfering with glucose transport (Dunaif, 1997). A possible defect in pancreatic β cell secretion of insulin has also been proposed (Holte et al., 1994).

Whatever the cause of the PCOS-associated hyperinsulinemia, there is little argument about the importance of its deleterious effects on the endocrine, reproductive and metabolic makeup of the patient regarding the degree of symptoms experienced. In women with PCOS and hyperinsulinemia, there is a correlation of raised fasting insulin concentrations with amenorrhoea (Robinson et al., 1993), serum androgen concentrations (Burghen et al., 1980) and a decrease of hepatic sex hormone binding globulin (SHBG) production (Poretsky et al., 1999), so increasing biologically available free testosterone concentrations in the circulation. Hyperinsulinaemia may also be involved in the hypersecretion of LH, but this has been difficult to establish due to the confounding effect of obesity. The endocrine manifestations of hyperinsulinemia are thus those of hyperandrogenemia, inducing consequent anovulation, reproductive failure and skin stigmata. In addition, hyperinsulinemia has been associated with metabolic defects such as an increased incidence of diabetes mellitus type 2, hypertension, increased low-density lipoprotein and decreased high-density lipoprotein cholesterol serum concentrations, all of which are risk factors for cardiovascular disease (Conway et al., 1992).

It is also now well established that excess body weight distributed in the waist region will exaggerate the expression and degree of symptoms of PCOS, further increasing insulin and consequently androgen serum concentrations in 80% of these women (Burghen et al., 1980; Conway et al., 1990; Robinson et al., 1993). It follows that a reversal of the cause of this exaggeration, i.e. loss of weight, is capable of reversing these signs and symptoms and this has been amply demonstrated in a number of studies (Kiddy et al., 1992; Clark et al., 1995).

However, there are two large subgroups of patients who need an alternative approach: (i) those who are obese but seem incapable of initiating and maintaining weight loss by dieting and exercise; and (ii) those who are of normal weight but who have hyperinsulinemia and are suffering from its consequences,
comprising some 30% of this normal weight group. Insulin-sensitizing drugs seemed the obvious approach for these women.

Metformin

Metformin is an oral biguanide, well established for the treatment of hyperglycaemia. It inhibits hepatic glucose production (Inzucchi et al., 1998), decreases intestinal absorption and promotes glucose uptake and utilization by peripheral tissues at the post-receptor level (Bailey and Puah, 1986). Metformin increases the number of insulin receptors but not insulin concentrations and therefore does not cause hypoglycaemia in normoglycaemic patients. The sum total of these actions is a decrease in insulin levels and, as a consequence, a lowering of circulating total and free androgen levels with a resulting improvement of the clinical sequelae of hyperandrogenism.

A large number of studies have been published on the effect of metformin in a dose of 1500–2000 mg/day in women with PCOS. The vast majority of these studies have demonstrated a significant improvement in insulin concentrations, insulin sensitivity and serum androgen concentrations accompanied by decreased LH and increased SHBG concentrations. Clinically, most have reported restoration of ovulation and regular menstruation.

Has this been a breakthrough in the treatment of PCOS? Doubters, of which there are many, have put forward several questions to contest the apparent efficiency of metformin in improving the lot of those afflicted.

Do we have the evidence?

Most of the available studies are observational, uncontrolled, with small numbers of patients not necessarily having been selected or tested for hyperinsulinaemia and are of short duration, including mostly obese women. Five randomized controlled trials (RCT) and six additional placebo controlled trials were traced and it is to the results of these trials that I will relate principally.

Does metformin exert its effect through weight loss?

In most of the published series, a loss of body weight and decrease in waist–hip ratio has been reported when using metformin. As the effects of weight loss and metformin in women with PCOS are well nigh identical, the metformin-induced weight loss has been cited by some as the real cause of improvement rather than direct actions of metformin. Whilst a reduction in body mass index (BMI) and waist–hip ratio can undoubtedly contribute to an amelioration, the fact is that hyperinsulinaemia and hyperandrogenism have been improved by metformin in obese women with PCOS who did not lose weight (Diamanti-Kandarakis et al., 1998), independently of changes in body weight (Moggetti et al., 2000) and in lean women with PCOS (Nestler and Jakubowicz, 1997) and improvement was comparable in women who did or did not lose weight (Glueck et al., 1999; Kolodziejczyk et al., 2000; Pasquali et al., 2000). In an RCT including 18 obese women with PCOS, all were put on a low calorie diet for 1 month before and during the trial of 6 months duration. Ten were treated with metformin and eight with placebo. When compared with the placebo group, metformin significantly improved hirsutism, menstrual cycle regularity, glucose-stimulated insulin secretion and testosterone concentrations (Pasquali et al., 2000). In a further trial in which all 24 patients with PCOS were given a low calorie diet for 26 weeks, compared with placebo metformin improved insulin sensitivity, lowered testosterone levels and improved ovulatory and menstrual disturbances (Casimirri et al., 1997). Although one placebo-controlled 16 week study did not demonstrate any additional effects of metformin over dieting (Crave et al., 1995) the subjects were very obese (BMI 35.2 kg/m²), were all hirsute and only 15 of the 24 women had ultrasound features of PCOS. They may represent a particularly difficult group to treat successfully. The balance of opinion seems to favour beneficial effects of metformin over and above those due to weight loss only.

Is metformin effective in the treatment of PCOS?

Soon after the publication of the pioneering work of Velazquez et al. (Velazquez et al., 1994), two studies failed to establish any biochemical or metabolic changes accountable to metformin after 10–12 weeks in very obese women with PCOS (Acbay and Gundogdu, 1996; Ehrmann et al., 1997) and initial enthusiasm was dampened. However, since then some 20 studies have demonstrated a beneficial effect of metformin on insulin metabolism and/or hormonal parameters.

Can metformin be of help for the restoration of ovulation?

The strong association between hyperinsulinaemia and anovulation would suggest that a reduction of insulin concentrations could be of great importance. This hypothesis has been substantiated by the restoration of regular menstrual cycles by metformin in the vast majority of published series and the reinstatement of ovulation in 78–96% of patients (Velazquez et al., 1997; Nestler et al., 1998; Moggetti et al., 2000; Ibanez et al., 2001). In an RCT performed on clomiphene-resistant infertile patients with PCOS, compared with placebo metformin markedly improved ovulation and pregnancy rates with clomiphene treatment (Vandermolen et al., 2001). In a large study, 46 anovulatory obese women with PCOS who did not ovulate on metformin or placebo for 35 days were given 50 mg of clomiphene daily for 5 days while continuing metformin or placebo. Of those on metformin, 19 of 21 ovulated compared with two of 25 on placebo (Nestler et al., 1998). In contrast, a similarly designed study did not demonstrate any superiority of metformin over placebo in the induction of ovulation in a group of women with clomiphene-resistant PCOS (Ng et al., 2001). The disparity of these results could be a matter of differences in patient selection, study design and dose of clomiphene used. When women with clomiphene-resistant PCOS were administered FSH with or without pretreatment with metformin for 1 month in an RCT, those receiving metformin developed significantly less large follicles, produced less estradiol and had fewer cycles cancelled due to excessive follicular development. The reduction of insulin concentrations induced by metformin seemed to favour a more orderly follicular growth in response to exogenous gonadotrophins for ovulation induction (De Leo et al., 1999). In the one published
study on the effects of metformin on clomiphene resistant patients undergoing IVF/ICSI, the results of cycles preceded by treatment with metformin were compared retrospectively with those in which metformin was not given. Those receiving metformin had a decreased total number of follicles but no difference in the mean number of oocytes retrieved. There were more mature oocytes, embryos cleaved, increased fertilization and clinical pregnancy rates (70 versus 30%) in the metformin group (Stadtmauer et al., 2001).

**Is metformin teratogenic?**

There is nowhere near enough data to provide a definite answer, but evidence so far looks reassuring. Women treated throughout their pregnancy with metformin for non-insulin dependent diabetes (NIDDM) did not seem to have a larger incidence of major congenital abnormalities compared with patients who had NIDDM but did not receive this treatment (Coetzee and Jackson, 1984). In a more recent study, not only did women receiving metformin (1.5–2.55 g/day) throughout their pregnancy not suffer any teratogenicity, but also benefited from an improved first trimester miscarriage rate (Glueck et al., 2001).

**Can metformin lessen the danger of adverse long-term consequences of insulin-resistant women with PCOS such as cardiovascular disease and type 2 diabetes?**

There is, at present, no evidence to this effect although the hypothesis sounds promising. In an interesting RCT, 32 obese women with PCOS were given either metformin or a combination of cyproterone acetate (2 mg) with ethinyl estradiol (35 μg) cyclically for 6 months. The hormonal combination significantly decreased testosterone and increased SHBG concentrations but slightly worsened glucose tolerance, whereas metformin significantly decreased waist–hip ratio, serum testosterone, fasting free fatty acid and insulin concentrations and improved menstrual cyclicity. The authors concluded that whereas the hormonal combination is highly efficient for the treatment of hyperandrogenism and hirsutism and as a contraceptive, metformin offers a useful alternative treatment for obese, anovulatory, infertile women with PCOS (Morin-Papuen et al., 2000). This may bode well for long-term prevention of unwanted sequelae in these patients.

**Do the unpleasant gastrointestinal side-effects of metformin preclude its use?**

While these effects will occur in a certain proportion of women during the initiation of therapy, drop out rates can be reduced by administering a small dose in the first week or so of treatment. Investigations studying the potential use of other insulin-sensitizing drugs such as glitazone rosiglitazone and D-chiro-inositol (INS-1) are still in the infant stage, but they may prove equally or even more effective than metformin without accompanying side-effects.

**Conclusions**

The treatment of the multiple clinical expressions of PCOS is necessarily symptomatic. Hyperinsulinaemia is instrumental in and/or exaggerates a large number of these symptoms including the sequelae of hyperandrogenism such as hirsutism and acne, anovulation and consequent infertility in the short-term. Its adverse metabolic effects seem to influence cardiovascular health and the prevalence of diabetes type 2 in the long-term. Metformin is the most thoroughly investigated drug studied to reverse the hyperinsulinaemia of PCOS and its clinical and metabolic expressions. The weight of evidence so far suggests that metformin is capable of reversing hyperinsulinaemia, correcting metabolic and biochemical stigmata of PCOS and restoring menstrual cyclicity. Hard evidence of its ability to improve results of ovulation induction is scanty but promising and evidence for its long-term effects on general health in women with PCOS is hypothetical at this stage, but has definite potential. As the likelihood of our ability to discern and influence the genetic make-up of PCOS seems fairly remote, common sense dictates an all out attack on one of the most important influential factors on the short- and long-term symptoms of such a very prevalent syndrome. While a sustained and maintained loss of weight in the obese will almost certainly produce very similar beneficial effects, many fail in this mission and they and patients of normal weight with insulin resistance need a solution. The promise afforded by the use of metformin and other newer insulin-sensitizing drugs must be followed up in randomized, controlled, larger studies to give us more complete assurance of their efficiency and safety. In the meantime, the well established safety and efficiency of metformin in the treatment of diabetes type 2 is reassuring and should allow its widespread but controlled use for the treatment of women with PCOS and insulin resistance.

**References**


855


