Metformin: Targeting Insulin Resistance in Polycystic Ovarian Syndrome

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Insulin resistance is a key feature in polycystic ovary syndrome (PCOS), a common endocrine and metabolic disorder characterised by oligomenorrhoea associated with chronic anovulatory cycles and features of hyperandrogenism. There is accumulating evidence that women with PCOS are at increased risk of developing type 2 diabetes and coronary heart disease. This is due to insulin resistance and its close association with multiple cardiovascular risk factors including diabetes mellitus, dyslipidaemia, visceral obesity and hypertension. Indeed, women with PCOS have an estimated 4 to 11-fold increased risk of CHD. The clinical features of this condition are heterogeneous which may result in difficulty in diagnosis. Furthermore, there are ethnic differences in its clinical presentation. In Caucasians, PCOS commonly presents with hirsutism and acne, whereas in Chinese, menstrual irregularity is more common. It is therefore not surprising that women with PCOS often present to the gynaecologists and the metabolic aspect of this condition is often overlooked. It has long been recognised that insulin resistance too plays an integral part in the pathogenesis of the syndrome, with hyperinsulinaemia having a direct effect in promoting ovarian androgen secretion leading to abnormal follicular development and hence giving rise to the endocrine features of the syndrome. Since insulin resistance plays a central role in PCOS, using insulin sensitisers to improve insulin sensitivity would be a logical approach in the management of PCOS. Although the effects of thiazolidinediones have been studied in PCOS, the vast majority of clinical trials focused on the use of metformin therapy.

Metformin: an old drug with a new indication?

Metformin is a biguanide antihyperglycaemic drug that has been used for 40 years in Europe for the treatment of type 2 diabetes. Its primary effect is on increasing peripheral glucose uptake in response to insulin, reduction in basal hepatic glucose production and in improving insulin sensitivity. It is recommended for use as a first-line therapy in overweight patients with type 2 diabetes. It has been shown that in women with PCOS, metformin improves insulin sensitivity and lowers the circulating androgen concentrations with improvement in menstrual cyclicity in PCOS. But do we have adequate clinical evidence for use of metformin in PCOS or is our clinical practice of prescribing metformin for PCOS ahead of the available evidence?

Effects on metabolic risk factors

Polycystic ovarian syndrome is not simply a reproductive endocrine disorder but also one which encompasses many of the components of the metabolic syndrome such as glucose intolerance, obesity, hypertension and dyslipidaemia. This results in an increased cardiovascular risk which is frequently overlooked in women with PCOS. Awareness of the association between PCOS and metabolic syndrome is important, for early recognition would lead to appropriate treatment to reduce cardiovascular risk. Clinically, insulin resistance is manifested by dyslipidaemia with noted elevated fasting serum triglyceride levels and low HDL-cholesterol levels, central adiposity with a high waist-to-hip ratio, glucose intolerance and occasionally acanthosis nigricans, a cutaneous marker of insulin resistance. Metformin has been shown to improve metabolic profile beyond glucose metabolism. Other beneficial effects include an improved lipoprotein profile, reduction of lipoprotein(a) and plasminogen activator inhibitor 1 (PAI-1). However, there is some evidence that these beneficial metabolic effects of metformin may not be as marked in women with PCOS.

Effects on menstrual cycle

Results from clinical trials of the use of metformin in regulating menstrual cycles were encouraging. However, most of these studies are limited by small sample size, short duration and study design (lack of a placebo group). The range of perceived benefits in uncontrolled trials varied widely with normal menstrual cycle being achieved in 16% to 90%.

Since metformin leads to restoration of normal menstrual cyclicity in only less than 50% of amenorrhoeic or oligomenorrhoeic women with PCOS, the first line option for women seeking cycle regulation and not pregnancy, is the combination estrogen-progestin contraceptive. Not only would this serve as an oral contraceptive, but it would also reduce ovarian androgen production by inhibiting gonadotrophin secretion leading to normalisation of menstrual cycles. Furthermore, chronic anovulation in PCOS is associated with increased risk of endometrial hyperplasia.
and carcinoma. Hence, daily exposure to progesterin would antagonise the endometrial effect of estrogen providing endometrial protection. However in a proportion of PCOS women with significant insulin resistance and obesity, the risk related to oral contraceptive use may outweigh the benefits. In such circumstances, metformin may be considered as an alternative treatment option.

Effect on hyperandrogenism

Current treatment for PCOS related acne and hirsutism include therapy for suppression of androgen (combined oral contraceptive pill) and anti-androgen therapy (cyproterone, spironolactone, flutamide, finasteride). The response to these drugs varies widely depending on the drug, the drug dosage and the individual response. Overall, the response is far from satisfactory. There is some evidence that metformin has an effect on the reduction of testosterone. Hence, there is a rationale for using metformin to treat features of hyperandrogenism in PCOS. However, current data are disappointing. Studies of the effect of metformin on hirsutism are largely disappointing. The effect of metformin on acne is also somewhat limited. Overall, metformin does not appear to have any major effects on features of hyperandrogenism. Fortunately, features of hyperandrogenism are not common in Hong Kong Chinese patients with PCOS and hence it does not pose a therapeutic problem.

Effect on fertility

Infertility may sometimes occur in PCOS. It has been shown that metformin pre-treatment followed by combined metformin and clomiphene therapy led to higher ovulation rates than those achieved by placebo and clomiphene alone. Pregnancy occurred in 6 of 11 women treated with metformin (1500mg daily) plus clomiphene but in only 1 of 14 women treated with placebo and clomiphene. This suggests that metformin pretreatment and subsequent cotreatment with clomiphene facilitates ovulation by sensitising follicles to follicle-stimulating hormone (FSH). This evidence opens up a new role for metformin for use in clomiphene-resistant women before considering surgery for ovulation induction. There is currently a large, multicentre trial in progress in the States on metformin use in women in PCOS addressing the issue of fertility and pregnancy outcome which may shed more light to alter our clinical practice in the near future. In addition to its benefit in fertility, metformin therapy in women with PCOS is associated with an improved first trimester miscarriage rate. Once pregnancy is confirmed, metformin should be discontinued although there are no reports of any teratogenicity associated with its use.

Administration of metformin in PCOS

The recommended metformin dosage is between 1500mg daily to 2000mg daily. Metformin may cause gastrointestinal upset and hence it should be taken with meals and start at a low dose of 500mg twice daily with gradual titration. As an insulin-sensitiser without any effect on insulin secretion, metformin does not cause hypoglycaemia in non-diabetic individuals. It has the additional benefit of reducing body weight which is a common problem in women with PCOS.

Although most women with PCOS are obese, non-obese women with PCOS may also be insulin resistant. Indeed, there is some evidence that metformin therapy is also effective in non-obese PCOS women.

Conclusion

In summary, women with PCOS are at risk of cardiovascular disease due to insulin resistance and associated metabolic risk factors. There is now growing evidence in the use of insulin-sensitisers, especially metformin, for PCOS. Current evidence supports the use of metformin which improves menstrual cyclicity, fertility as well as underlying metabolic derangement associated with PCOS. Most studies were carried out in Caucasian populations and there is a need for studies to be done in the Asian population whose metabolic response to medical therapy may differ. Furthermore, whether the improvement in insulin sensitivity and metabolic profile can be translated into clinical benefits will be the subject of future research.

References