The Use of Metformin in the Polycystic Ovary Syndrome

There is increasing interest in the use of Metformin in women with PCOS. This information sheet outlines the current state of knowlegdge regarding its use in this condition.

Background

The polycystic ovary syndrome (PCOS) is one of the most common disorders affecting women. It has been estimated that 20% of women have polycystic ovaries as detected by ultrasonography and that 10% of all women experience a symptom of PCOS. The most common symptoms associated with PCOS are unwanted hair growth, irregular periods and a failure to ovulate. About half of women with this syndrome are overweight and one third become diabetic at some time in their lives. In general, as a women with PCOS gains weight so the symptoms get worse and the risk of diabetes rises.

The most typical hormone changes associated with PCOS are raised concentrations in the blood of testosterone, luteinising hormone (LH) and insulin. One third of women, however, will show no hormone abnormality. The simplest picture that explains the syndrome is that the ovary makes an excess of testosterone by one of two mechanisms. The ovary might be over active in its testosterone production spontaneously with no external drive, or the ovary might be driven to produce excess testosterone by the action of either LH or insulin.

Conventional treatment for PCOS aims to suppress ovarian testosterone production using the combined oral contraceptive pill. In some women 'the pill' is not appropriate treatment. For instance, one of the side effects of the pill is to increase the risk of a blood clot - a thrombosis - and this risk exaggerated in obese women. Also, in some women the use of the pill coincides with weight gain and this might make the symptoms of PCOS worse in the long run. For these reasons alternative treatments are increasingly being tested to good effect. The focus of these new approaches to treatment is the insulin axis.

The main role of insulin in the body is in regulating the level of glucose in the blood. In some individuals, high concentrations of insulin are required in order to maintain normal glucose levels - insulin resistance. When insulin fails in this effort, glucose levels rise and diabetes ensues. Raised insulin concentrations have a side effect in the body of stimulating the ovary to produce more testosterone. Reducing insulin by diet, weight loss or drugs results in a lowering of testosterone and improved symptoms of PCOS. All women with PCOS who are over weight would benefit from a regime of diet reform and exercise. The only drug currently available in the UK which reliably reduces insulin concentrations is Metformin. Metformin has been used for over 30 years to treat maturity onset diabetes mellitus. It acts by making the body more sensitive to insulin.

The use of Metformin in women with PCOS

Several studies have recorded the use of Metformin in women with PCOS. Metformin is effective in reducing testosterone levels and in making the menstrual cycle more regular. While Metformin starts to improve the prospects for fertility in few weeks, a reduction in unwanted hair growth would be expected to take some months and be slower than conventional treatment. Women can find weight loss easier when taking Metformin even though it is not a traditional weight reducing agent. One placebo-controlled trail has shown that Metformin is better than placebo in inducing ovulation in women with PCOS. The effectiveness of Metformin has been best demonstrated in obese women and it is likely that women of normal weight would benefit very little from this drug.

Serious side effects to Metformin treatment are very rare. In particular, Metformin does not cause hypoglycaemia. In the first week of taking Metformin, an upset stomach or diarrhoea is common and this side effect can be reduced by taking it after food and by starting with a very low dose (250 mg) and to increase slowly by 250 mg per week until the full dose of 1700 mg is achieved (850 mg twice per day). Women who have kidney damage are at an increased risk of a very rare side effect of Metformin therapy called lactic acidosis. The drug should be given cautiously, if at all, in this instance. While safety during pregnancy has not yet been established, many women over the years have inadvertently taken Metformin when pregnant and no adverse effects have been reported. Indeed, one group has reported the intentional use of Metformin to treat diabetes throughout pregnancy.

Criteria for the use of Metformin

1. Established diagnosis of PCOS. 2. Body mass index over 30 km/m^2 or BMI < 30 and gaining weight.

Metformin comes in two sizes of tablet 500 and 850 mg. Take tablets after food - if side effects are encountered then stop the increase in dosage at the last acceptable level. Metformin works much better if combined with a strict regime of diet and exercise. Diet should be at least three light meals per day which are low in sugar and fat and high in fruit, fresh vegetables and salad. Light sustained exercise such as walking, cycling or swimming for at least an hour at a time several times per week.

Daily dose – slow route to avoid side effects

week 1	250 mg once	week 4	500 mg twice
week 2	250 mg twice	week 5	850 mg + 500 mg
week 3	500 mg + 250 mg	week 6	850 mg twice

Daily dose – fast route if stomach can take it

week 1	500 mg twice	week 3	850 mg twice

Monitoring the use of Metformin

Tests at the start of Metformin and every 2 months thereafter
Menstrual cycle diary for 6 months (recall), Weight, Urinalysis
LH, FSH, Testosterone, Glucose, HbA1c, U&E, Cholesterol, triglycerides, HDL, LDL – fasting insulin is optional.

Stop taking Metformin if pregnancy occurs.
There is no particular time limit for the use of Metformin - if no effect is seen in six months then there is no point in continuing. After one year the goals of future treatment should be reviewed.

The long term place of Metformin in PCOS is not clear. It is strongly recommended that the use of Metformin is monitored either in an official trail or as a formal audit in a specialist unit in order that the effectiveness of this treatment can be clearly documented.

Combination treatment

For those women who do not wish to get pregnant but for whom unwanted hair growth is the main concern then the addition of Spironolactone 50 mg twice daily is suitable.

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