Metformin Therapy for the Management of Infertility in Women with Polycystic Ovary Syndrome

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1. Introduction

The key clinical features of polycystic ovary syndrome (PCOS) are hyperandrogenism (hirsutism, acne, alopecia) and menstrual irregularity with associated anovulatory infertility.⁰ The consensus definition of PCOS recognises obesity as an association and not a diagnostic criterion¹ as only 40–50% of women with PCOS are overweight. Ovarian hyperandrogenism is driven primarily by luteinising hormone (LH) in slim women, while in the overweight insulin may augment the effects of LH.¹ Women with polycystic ovaries are more insulin resistant than weight-matched women with normal ovaries. Insulin resistance is seen in 10–15% of slim and 20–40% of obese women with PCOS and women with PCOS are at increased risk of developing type 2 diabetes.²

2. Insulin resistance

Insulin resistance is defined as a reduced glucose response to a given amount of insulin and usually results from faults within the insulin receptor and post-receptor signalling. As a result circulating insulin levels rise. Insulin resistance does not affect all actions of insulin and, in the ovary, high levels of circulating insulin are thought to contribute both to excess androgen production and to anovulation. Insulin resistance can be measured by a number of expensive and complex tests but in clinical practice it is not necessary to measure it routinely; it is more important to check for impaired glucose tolerance.² Simple screening tests include an assessment of body mass index (BMI) and waist circumference. If the fasting blood glucose is less than 5.2 mmol/l the risk of impaired glucose tolerance is low. The 2-hour standard 75 g oral glucose tolerance test (OGTT) may be conducted in those at high risk (BMI greater than 30 kg/m² in white women or greater than 25 kg/m² in women from South Asia, who have a greater degree of insulin resistance at a lower body weight).¹,²

3. Metformin therapy for PCOS

Obesity has a profound effect on both natural and assisted conception, influencing the chance of becoming pregnant and the likelihood of a healthy pregnancy.³ Increasing obesity is associated with greater insulin resistance. Metformin inhibits the production of hepatic glucose, enhances insulin sensitivity at the cellular level and also appears to have direct effects on ovarian function. It is logical to consider, therefore, that insulin lowering and insulin sensitising treatments such as metformin and the thiazolidinediones (rosiglitazone, pioglitazone) should improve the symptoms and reproductive outcome for women with PCOS.⁴

Most of the initial studies of metformin in the management of PCOS were observational. Initial systematic reviews, in which the majority of studies had a small sample size and did not include a power calculation for the proposed effect, suggested that metformin when compared with placebo, had a significant effect on lowering serum androgen levels and restoring menstrual cyclicity and was effective in achieving ovulation either alone or when combined with clomifene.⁵ Subsequent larger randomised trials, however, have not substantiated these early positive findings. Furthermore, while some studies suggested that metformin therapy may achieve weight reduction,⁶ the large randomized controlled trials and systematic reviews have failed to confirm this.⁵,⁷,¹¹

Metformin appears to be less effective in those who are significantly obese (BMI greater than 35 kg/m²),⁴,⁷ although there is no agreement on predictors for response or the appropriate dose and whether dose should be adjusted for body weight or other factors. Doses of between 500–3000 mg/day have been used and the most common dose regimens are 500 mg three times daily or 850 mg twice a day. Long-acting preparations are associated with fewer gastrointestinal adverse effects. Metformin appears to be safe in
pregnancy, although usual advice is to discontinue once a pregnancy occurs. There is no firm evidence that metformin reduces the risk of either miscarriage or gestational diabetes.

The largest prospective randomised, double blind, placebo-controlled study trial to evaluate the combined effects of lifestyle modification and metformin (850 mg twice daily) studied 143 anovulatory women in the UK with a mean BMI of 38 kg/m.27 All subjects had an individualised assessment by a dietician in order to set a realistic goal that could be sustained with an average reduction of energy intake of 500 kcal per day. As a result, both the metformin-treated and placebo groups managed to lose weight but the amount of weight reduction did not differ between the two groups. An increase in menstrual cyclicity was observed in those who lost weight, but again did not differ between the two arms of the study.7

In a Dutch trial, 228 women with PCOS were treated either with clomifene citrate (CC) plus metformin or CC plus placebo.8 There were no significant differences in either rates of ovulation (64% versus 72%), continuing pregnancy (40% versus 46%) or rate of spontaneous miscarriage (12% versus 11%). A significantly larger proportion of women in the metformin group discontinued treatment because of adverse effects (16% versus 5%). The US Pregnancy in Polycystic Ovary Syndrome (PPCOS) trial9 enrolled 676 women for six cycles or 30 weeks, randomised to three treatment arms (metformin 1000 mg twice daily plus placebo, clomifene citrate plus placebo or metformin plus clomifene citrate). Overall, live birth rates were 7% (5/208), 23% (47/209) and 27% (56/209), respectively, with the metformin alone group being significantly lower than the other two groups. Miscarriage rates tended to be higher in the metformin alone group (40% versus 23% and 26%, respectively). Thus, it was concluded that as first-line therapy for the treatment of women who are anovulatory and infertile with PCOS, metformin alone was significantly less effective than clomifene citrate alone and that the addition of metformin to clomifene citrate produced no significant benefit.9 Subgroup analysis of women with a BMI greater than 35 kg/m2 and in those with clomifene resistance did, however, suggest a potential benefit from the combined use of metformin with clomifene citrate.9

It has been suggested that co-treatment with metformin may improve the response to exogenous gonadotropins or the outcome of assisted reproduction therapy. Indeed, the largest study to date has shown an increase in continuing pregnancy rates in women with polycystic ovaries and a mean BMI of 28 kg/m2 treated with metformin (850 mg twice daily) for only 4 weeks during an IVF cycle.10 In this study, 101 women were randomised to receive metformin or placebo. Both the clinical pregnancy rates beyond 12 weeks of gestation per cycle started (39% versus 16%; P = 0.023) and per embryo transfer (44% versus 19%; P = 0.022) were significantly higher in those treated with metformin. Furthermore, a significant decrease in the incidence of severe ovarian hyperstimulation syndrome was observed (4% versus 20%; p=0.023) despite the higher pregnancy rate in the metformin arm of the study.10 These results are promising but further studies are required to confirm these observations before the place of metformin in assisted reproductive techniques can be clearly assessed.

The updated Cochrane review concluded that the benefit of using therapy to lower insulin levels such as metformin is limited in terms of improvement in reproductive outcome and metabolic parameters.11 In particular, the use of metformin either alone or in combination with drugs to induce ovulation such as clomifene citrate did not increase the chance of having a livebirth. Furthermore, despite evidence of a reduction in development of diabetes in a high risk non-PCOS population12 the long-term use of metformin in reducing the risk of developing metabolic syndrome is questionable.11 Lifestyle advice with appropriate attention to diet and exercise has to be the mainstay for young women with PCOS.

4. Opinion

While initial studies appeared to be promising, more recent large randomised controlled trials have not observed beneficial effects of metformin either as first-line therapy or combined with clomifene citrate for the treatment of the anovulatory woman with PCOS. Most work has been undertaken in the
management of anovulatory infertility and there are no good data from randomised controlled trials on the use of metformin in the management of other manifestations of PCOS. It is clear that the first aim for women with PCOS who are overweight is to make lifestyle changes with a combination of diet and exercise in order to lose weight and improve ovarian function. The European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine consensus on infertility treatment for PCOS concluded that there is no clear role for insulin sensitising and insulin lowering drugs in the management of PCOS, and should be restricted to those patients with glucose intolerance or type 2 diabetes rather than those with just insulin resistance. Therefore, on current evidence metformin is not a first line treatment of choice in the management of PCOS.

References

The review process will commence in December 2011 unless otherwise indicated.