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

This is the second edition of this paper, previously published in December 2008 with the same title.

1. Background

Although many women who have polycystic ovaries do not have polycystic ovary syndrome (PCOS), it is a common endocrine disorder affecting 4–12% of women.[1,2] The diagnostic criteria of PCOS[2] are widely accepted, with two of the following being required:

- Oligo-ovulation and/or anovulation (menstrual irregularity and/or anovulatory infertility), i.e. menstrual disturbance.
- Clinical and/or biochemical signs of hyperandrogenism (hirsutism, acne, alopecia).
- Polycystic ovaries on ultrasound scan.

The World Health Organisation defines normal weight for adults as a body mass index (BMI) of 18.5–24.99 kg/m^2, overweight with a BMI of 25 kg/m^2 or more, and obese with a BMI of 30 kg/m^2 or more.[3] The consensus definition of PCOS[2] recognises obesity as an association and not a diagnostic criterion, as only 40–50% of women with PCOS are overweight. Other causes of menstrual disturbance and hyperandrogenism must be excluded by appropriate endocrine investigations.

Ovarian hyperandrogenism is driven primarily by luteinising hormone in women of normal weight, while in the overweight, insulin may augment the effects of luteinising hormone by amplifying the secretion of androgens by the ovaries.[2] Insulin also suppresses the secretion of sex hormone-binding globulin by the liver, leading to increased levels of free circulating testosterone. Women with PCOS are more insulin resistant than weight-matched women who do not have the syndrome. Insulin resistance (IR) is seen in approximately 10–15% of slim and 20–40% of obese women with PCOS, and women with PCOS are at increased risk of developing type II diabetes.[4,5] The more overweight an individual the greater the degree of IR. Maternal weight can have a profound effect on both natural and assisted conception, influencing the chance of becoming pregnant and the likelihood of a healthy pregnancy.[1] Studies have demonstrated higher rates of preterm birth, miscarriages and low birthweight in babies born to obese versus normal weight women with PCOS.[6,7]

The purpose of this paper is to clarify some of the advice published about the use of metformin therapy for the management of infertility in women with PCOS.

2. Insulin resistance (IR)

IR 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. In the ovary, high levels of circulating

insulin are thought to contribute to excess androgen production and to anovulation. A prospective study[5] of women with PCOS and normal glucose tolerance found the annual rate of developing IR was 4.5% compared with 0.9% in the control population. The annual rate for developing diabetes in women with PCOS who had existing IR was 10.4%.[5]

IR is a common feature independent of obesity;[8] although not all women with PCOS have increased IR.[4] Since IR is also influenced by age and ethnicity,[9,10] it would be difficult to have a universally agreed cut-off level for IR. Therefore, measuring IR is not included in the diagnostic criteria of PCOS.

IR can be measured by a number of expensive and complex tests, but in clinical practice it is more important to check for impaired glucose tolerance (IGT).[11] Simple screening tests include assessing BMI, waist circumference, and measuring fasting blood glucose. If the fasting blood glucose is less than 5.2 mmol/l, the risk of IGT is low. The 2-hour 75 g oral glucose tolerance test (OGTT) remains the gold standard investigation,[12] and may be conducted in those at high risk (BMI greater than 30 kg/m^2 in Caucasian women, or greater than 25 kg/m^2 in women from certain ethnic populations, such as those from South Asia, who are more prone to a greater degree of IR at a lower body weight).[2,12] In women with impaired fasting glucose (fasting plasma glucose level 6.1–6.9 mmol/l) or IGT (plasma glucose 7.8 mmol/l or more, but less than 11.1 mmol/l after a 2-hour 75 g OGTT), an OGTT should be performed annually.[13] An assessment of glycosylated haemoglobin (HbA1c) may be performed if women are unable to complete an OGTT and may be used for annual screening.[1]

3. Metformin therapy for PCOS

Metformin inhibits the production of hepatic glucose, decreases lipid synthesis, increases fatty acid oxidation and inhibits gluconeogenesis resulting in a decrease in circulating insulin and glucose.[14] Metformin enhances insulin sensitivity at the cellular level and also appears to have direct effects within the ovary.[15] Therefore, it would seem logical to anticipate that insulin lowering and insulin-sensitising treatments, such as metformin, should improve symptoms and reproductive outcomes for women with PCOS.

Most of the early studies of metformin in the management of PCOS were observational or had small sample sizes.[16] Initial results suggested that metformin, when compared with placebo, had a significant effect on lowering serum androgen levels, restoring menstrual cyclicity and was effective in achieving ovulation either alone or when combined with clomiphene citrate. Subsequent larger randomised trials[16] have found conflicting results and therefore, have not substantiated these early positive findings.

The latest Cochrane Review[17] included 40 studies, with a total of 3848 women, in which the median daily dose of metformin was 1500 mg and duration of the studies ranged from 4 weeks to 60 weeks. There was no consensus on the dose and duration of metformin therapy.

3.1 Metformin and body weight

While some studies have suggested that metformin therapy may achieve weight reduction, most large randomised controlled trials have failed to confirm this.[17] A large prospective randomised, double-blind, placebo-controlled study trial[18] evaluated the combined effects of lifestyle modification and metformin (850 mg twice daily), by studying 143 anovulatory women in the UK with a mean BMI of 38 kg/m^2. All subjects had an assessment by a dietician and were given a customised diet with the aim of reducing their daily energy intake by 500 kcal. As a result, the metformin and placebo groups managed to lose weight, but the percentage of weight

loss between the two groups was not significant (3.98% versus 4.41%; $P = 0.554$). An increase in menstrual cyclicity was observed in those who lost weight, but again was not significantly different between the two arms of the study. More recently, a subgroup analysis in a systematic review[19] also indicated that metformin therapy combined with lifestyle modification achieved limited impact in obese women with PCOS. Furthermore, metformin alone does not improve weight loss compared to placebo or no treatment.[17] Therefore, lifestyle improvement and supporting women with individualised assessment, setting goals and using a combination of diet and exercise remains the first-line approach.[12]

3.2 Metformin and ovulation induction

A high-quality multicentre Finnish randomised study[20] comparing metformin with placebo in 320 women with PCOS found significantly higher live birth rates in the metformin group (41.9% versus 28.8%; $P = 0.014$). This effect persisted when removing women undergoing assisted reproductive treatment and a subgroup analysis by BMI. However, when this study was included in the meta-analysis of the Cochrane review[17] with three other smaller studies, it was found that compared with placebo, the effect of metformin on live birth rate just reached statistical significance (OR 1.59, 95% CI 1.00–2.51), suggesting a marginal benefit only.

A limited number of studies have compared metformin with clomiphene citrate. Legro et al. enrolled 626 women for six cycles or 30 weeks, randomised to three treatment arms (metformin 1000 mg twice daily plus placebo, clomiphene citrate plus placebo, or metformin plus clomiphene citrate).[21] Overall, live birth rates were 7.2% (15/208), 22.5% (47/209) and 26.8% (56/209), respectively, with the metformin alone group being significantly lower than the other two groups. Higher rates of ovulation and clinical pregnancy were also found with clomiphene citrate rather than metformin, an effect that persisted when stratified by BMI. It was therefore 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 clomiphene citrate alone.[17,21] Furthermore, metformin does not improve metabolic parameters, such as fasting insulin, glucose, testosterone and lipid profiles.[17]

In a Dutch study,[22] 228 women with PCOS were treated with clomiphene citrate plus metformin or clomiphene citrate plus placebo. There were no significant differences in rates of ovulation (64% versus 72%), continuing pregnancy (40% versus 46%) or live birth rate (19% versus 27%). Taken together with the findings from Legro et al.,[21] this suggests that the combination of metformin and clomiphene citrate produces no significant benefit on reproductive outcomes. However, a subgroup analysis of women with a BMI greater than 35 kg/m^2 and of those with clomiphene citrate resistance did suggest a potential benefit from the combined use of metformin with clomiphene citrate.[21] A number of other small studies have suggested that metformin plus clomiphene citrate may improve ovulation rates when women are resistant to clomiphene citrate therapy (OR 4.89, 95% CI 2.62–9.13; six studies; n = 83), although there is no evidence of a difference in live birth rate.[17]

Moll et al.[22] reported higher miscarriage rates in the metformin alone group, but this finding is in contrast to the majority of studies that report no significant difference in pregnancy loss.[17,21] Metformin appears to be safe in pregnancy, however the usual advice is to discontinue post conception with the exception of those with diabetes. The results of a meta-analysis[23] comparing metformin to clomiphene in women with a BMI under 32 kg/m^2 reported no difference between metformin and clomiphene citrate in terms of ovulation, pregnancy, live birth, miscarriage and multiple pregnancy rates.

The use of metformin is consistently associated with more adverse effects compared with clomiphene citrate or placebo, particularly nausea, vomiting and other gastrointestinal disturbances.[17] Moll et al.[22] found a significantly

larger proportion of women in the metformin group discontinued treatment because of adverse effects (16% versus 5%). The use of long-acting preparations may help to reduce gastrointestinal adverse effects. However, the optimal regimen for metformin has not been determined; doses of between 500 mg/day and 3000 mg/day have been used, with the most common regimens being 500 mg three times daily or 850 mg twice daily. It is also not clear whether the dose should be adjusted for body weight or other factors.

Women with PCOS who have not responded to clomiphene citrate may be offered one of following second-line treatments:

- laparoscopic ovarian drilling
- combined treatment with clomiphene citrate and metformin, if this has not already been given as a first-line treatment, or
- gonadotrophins.

3.3 Metformin and in vitro fertilisation

It has been suggested that co-treatment with metformin may improve the response to exogenous gonadotrophins or the outcome of assisted reproduction. There is a dearth of evidence on the effect of metformin on oocyte or embryo quality and egg yield. A Cochrane review[24] including 816 women across nine studies compared metformin with placebo or no treatment, before or during assisted reproductive technology cycles. Clinical pregnancy rates were improved in the metformin group (OR 1.52, 95% CI 1.07–2.15; five studies; n = 551). However, the number of events dropped from 775 for the pregnancy rates to 551 for the live birth rates (live birth rates are not reported in some studies), which may have weakened the power of the meta-analysis with regards to live birth rates. There was no effect on the miscarriage rate. Women given metformin were, however, at significantly reduced risk of ovarian hyperstimulation syndrome (OHSS) when a long gonadotrophin-releasing hormone (GnRH) agonist protocol was used. Metformin decreased the risk of OHSS in these patients, probably by modulating the ovarian response to the stimulation. However, currently, the short GnRH antagonist protocol is recommended for women at risk of OHSS, for which the role of metformin is unclear.[1]

3.4 Metformin and pregnancy

A Finnish study[20] of 320 women who received metformin (1500–2000 mg/day) or placebo for 3 months prior to fertility treatment, and for a further 9 months during treatment and up to 12 weeks of gestation, demonstrated an increase in pregnancy rate from 40.4% to 53.6% (OR 1.61, 95% CI 1.13–2.29), with obese women experiencing the greatest benefit. Furthermore, the live birth rate was increased in those who received metformin (41.9% versus 28.8%; $P = 0.014$). Taking these results and those from further studies,[17] obesity seems to have the greatest impact on the risk of miscarriage and metformin appears to reduce miscarriage in obese women.

Women with PCOS are at increased risk of pregnancy-related complications, including gestational diabetes, pregnancy-induced hypertension, pre-eclampsia and neonatal morbidity.[6] In view of the favourable effects of metformin on metabolic, cardiovascular and thrombotic events in the diabetic population, it would seem feasible that outcomes could be improved in PCOS pregnancies with metformin. Unfortunately, a large Norwegian multicentre randomised controlled trial[25] found no improvement in these complications with continued use of metformin throughout pregnancy, although there appeared to be a nonsignificant trend toward reductions in late miscarriage

and preterm delivery rates, which is now the subject of a large ongoing randomised controlled trial. Metformin has a good safety profile in pregnancy, with no evidence of teratogenicity.

4. Other insulin-sensitising drugs

There is insufficient evidence to recommend the use of other insulin sensitisers, such as thiazolidinediones (glitazones), d-chiro-inositol and myo-inositol, in the treatment of anovulatory PCOS. A large study of 305 women evaluating the use of an insulin-sensitising agent (troglitazone) for PCOS has shown a dose-dependent increase in ovulation rate with risk of liver toxicity.[26] Smaller studies using rosiglitazone therapy in obese[27] and non-obese women[28] demonstrated restored regular ovulatory cycles. However, these studies lacked placebo-control arms and were not controlled. Newer insulin-sensitising agents, such as glucagon-like peptide 1 (GLP-1) analogues (e.g. exenatide and liraglutide), are currently under investigation.[29]

5. Opinion

Metformin appears to have a limited role in improving reproductive outcomes in women with PCOS, although there may be a benefit to using metformin in specific patient groups, for example in obese women when combined with clomiphene citrate, those with clomiphene citrate resistance, and those who have been found to have either IGT or type II diabetes. Metformin use can lead to unpleasant adverse effects such as nausea, vomiting, abdominal pain, diarrhoea, dizziness and unusual tiredness. Furthermore, despite evidence of a reduction in the development of diabetes in high-risk women who do not have PCOS, the long-term use of metformin in improving metabolic parameters is questionable.[30] Thus, lifestyle advice with appropriate attention to diet and exercise remains the mainstay for young women with PCOS.

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