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Position of alternatives: insulin sensitizers and others

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Abstract. The association between the polycystic ovary syndrome (PCOS) and insulin resistance has led to the use of insulin-sensitizing drugs to induce ovulations. Metformin was shown to lower insulin levels effectively, and metformin alone, as well as in combination with clomiphene citrate (CC), has been shown to enhance ovulation in PCOS patients. However, insulin-sensitizing medications have considerable side-effects, and lifestyle improvements (weight reduction and increased exercise) should be considered as first-line treatments in overweight women with PCOS. At present, metformin may best be used as an adjuvant therapy in CC-refractory PCOS patients.

Keywords: Anovulation; Polycystic ovary syndrome; Ovulation induction; Insulin-sensitizing drug; Metformin

1. Introduction

The main characteristics of polycystic ovary syndrome (PCOS) are anovulation or oligo-ovulation, elevated levels of androgens, and insulin resistance, resulting in the clinical manifestations of amenorrhoea or irregular menstrual cycles, subfertility, hirsutism, or acne.

A major feature of PCOS is insulin resistance, which leads to compensatory elevated blood insulin levels, by which normal glucose levels are maintained. Hyperinsulinaemia is more common in overweight women with PCOS (50–100%), but may also be present in lean PCOS patients (about 20%). Hyperinsulinaemia is associated with an increased risk for developing cardiovascular disease and type 2 diabetes mellitus.

2. Insulin-sensitizing drugs

Insulin-sensitizing drugs such as metformin may be effective in restoring ovulation and may also have long-term benefits for health. Metformin is a biguanide that has been used

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for more than 40 years for the treatment of non-insulin dependent diabetes mellitus (NIDDM). Biguanides do not have a hypoglycaemic effect in non-diabetic people and do not stimulate insulin release.

Insulin sensitizers improve insulin action by increasing insulin sensitivity, resulting in a decrease of hyperinsulinaemia. As the increased ovarian androgen production in PCOS is thought to be caused by increased insulin levels, a reduction in androgens may be expected, resulting in normalization of the cycle and also improvement of hirsutism or acne.

Adverse effects of metformin, principally of gastrointestinal origin, are reported to occur in 20–30% of NIDDM patients. The most common adverse effects are diarrhoea, nausea, vomiting, abdominal bloating, abdominal cramping or pain, flatulence, and anorexia. Also headache, agitation, dizziness, and tiredness have been observed. The safety of long-term use of metformin in young women is still unknown. Metformin appears to be safe for use during pregnancy, lacking evidence of teratogenicity. However, widespread use in ovulation induction would mean that rare effects on early pregnancy might become apparent.

3. Review of the literature and recommendations

A Cochrane review [6] addresses the effectiveness of metformin in short-term and long-term treatment of women with PCOS. In this meta-analysis, randomized controlled trials (RCTs) were included in which treatments with insulin-sensitizing drugs were compared with placebo, no treatment, or treatment with an ovulation induction agent such as clomiphene citrate or gonadotrophin. Also, the use of metformin, in combination with an ovulation induction treatment, was considered. Studies that combined treatment with insulin-sensitising drugs with dietary intervention or exercise were included because such complementary therapies are potential confounders.

Fifteen studies randomizing a total of 997 women were included in the meta-analysis. In 13 of these, metformin was investigated (543 women); in one study, troglitazone, and in another study D-chiro-inositol was used. It was difficult to draw conclusions concerning live birth rates or pregnancy rates because in none of the trials was live birth rate defined as outcome measure, and no trial had pregnancy as a primary endpoint. Moreover, only three of the nine trials reporting pregnancy rates lasted more than 4 months.

4. Results

The *clinical pregnancy rate* was reported in five trials comparing metformin with placebo. No evidence of benefit was apparent (odds ratio (OR) 2.76; 95% confidence interval (CI) 0.85–8.98). Three trials compared the combination of clomiphene citrate (CC) with metformin versus CC alone. These trials showed a significant effect for metformin (OR 4.4; CI 1.96–9.85). In these trials, women who were previously resistant to CC were included. This means that also CC-resistant PCOS patients may benefit from the combination of CC with metformin.

On *ovulation rate* (seven trials included), metformin performed significantly better than placebo (OR 3.88; CI 2.25–6.69). Ovulation was achieved in 46% of the patients with metformin, compared with 24% on placebo (number needed to treat: 4.4, which means

that, on average, treatment with metformin in 4.4 women will result in ovulation in one of them). The combination of metformin and CC versus CC alone was also beneficial, as had been addressed in three trials (OR 4.41; CI 2.37–8.22). Seventy-six percent of women receiving metformin plus CC ovulated, versus 42% receiving CC alone (number needed to treat: 3.0). This favourable result was observed in two of the three studies, in which patients who were previously resistant to CC were included [5,8]. The third study, however, did not select the CC-resistant patients before entering the study, and found no benefit of metformin with CC compared with CC alone. In this trial, the patients had high ovulation rates (64%) on placebo or CC [2].

The *menstrual pattern* was investigated in one study [9] and showed an improvement by metformin versus placebo or no treatment (OR 12.88; CI 1.85–89.61).

There was no significant effect on *body weight*, *body mass index* (*BMI*), *waist circumference*, or *waist/hip ratio*. Effects on *hirsutism* or *blood pressure* were conflicting, probably due to a very limited number of patients.

4.1. Biochemical measures

Total and free testosterone appeared only to be lowered by metformin in one study [3]; androstenedione levels decreased significantly by metformin, as was reported by seven trials (weighted mean difference (WMD) −1.21; CI −1.79 to −0.62). An effect on sex hormone binding globulin (SHBG) could not be demonstrated. Insulin levels (fasting and area-under-the-curve) decreased significantly by metformin (WMD −5.37; CI −8.11 to −2.63); however, glucose values (fasting and area-under-the-curve) showed no significant treatment effect. On lipids, metformin significantly reduced LDL cholesterol, with no effect on total cholesterol, HDL cholesterol, or fasting triglycerides. Obesity (BMI≥30 kg/m^2) appeared to have no influence on the actions of metformin as to clinical pregnancy rate, ovulation rate, and biochemical markers.

4.2. Dose

In most trials, a regime of 500 mg three times daily was used; in some, 850 mg twice daily. No differences on the outcomes were apparent between these regimens.

Summarizing, this meta-analysis showed that metformin induces ovulation in women with PCOS (46% vs. 24% with placebo) as well as combined with CC (76% vs. 42% with CC alone). Independently, another meta-analysis had been conducted in the same time period by Kashyap et al. [4], who came to very similar conclusions.

Because metformin has small but beneficial effects on some aspects of the metabolic syndrome (i.e., on fasting insulin, blood pressure, and possibly on low density lipoprotein cholesterol), some authors recommend its use as a first-line treatment for anovulation in PCOS [7]. With the present knowledge a more conservative and maybe more prudent approach is to apply metformin as an adjuvant therapy in CC-refractory patients.

It must be considered, however, that equal or even higher ovulation rates have been found to result from lifestyle improvements consisting of weight reduction and increased exercise [1], and that metformin is not a “weight loss” drug. Clark et al. [1] conducted a prospective, although not randomized study in which obese (BMI≥30 kg/m^2) anovulatory women underwent a weekly programme during 6 months, including guided exercise, diet, and seminars on weight-related topics. Of the 67 women, 60 resumed ovulation without

further treatment, with 18 achieving a spontaneous pregnancy. In total, 52 patients became pregnant; 34 of them, however, did so following adjuvant treatment. It is apparent that a loss of only 5–1% of body weight is sufficient to observe resumption of ovulation in most women. Weight reduction, although demanding, is cost-effective and safe. In conclusion, lifestyle improvements must be advocated before any medication is used for ovulation induction in especially overweight PCOS patients.

5. Future research

Future research should include live birth, or at least pregnancy, as a primary outcome. A long-term prospective RCT should compare the use of metformin with lifestyle improvement, the combined use of metformin and lifestyle improvement, and placebo. Also direct comparisons with CC as a first-line treatment, as well as with gonadotrophins and laparoscopic ovarian diathermy [10], are needed. From such studies could also be learnt which patients would benefit most from metformin treatment (for instance the more hyperinsulinaemic women, or those with the highest androgen levels).

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