Review Article

Metformin use in women with polycystic ovary syndrome

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Abstract: Polycystic ovary syndrome (PCOS) is an endocrinopathy characterised by increased resistance to insulin. Metformin is one of the longest established oral insulin sensitising agents. For decades its use was restricted to management of type 2 diabetes. However, in the past two decades, its properties as an insulin sensitising agent have been explored in relation to its applicability for women with PCOS. Metformin is an effective ovulation induction agent for non-obese women with PCOS and offers some advantages over other first line treatments for anovulatory infertility such as clomiphene. For clomiphene-resistant women, metformin alone or in combination with clomiphene is an effective next step. Women with PCOS undergoing *in vitro* fertilisation should be offered metformin to reduce their risk of ovarian hyperstimulation syndrome. Limited evidence suggests that metformin may be a suitable alternative to the oral contraceptive pill (OCP) for treating hyperandrogenic symptoms of PCOS including hirsutism and acne. More research is required to define whether metformin has a role in improving long term health outcomes for women with PCOS, including the prevention of diabetes, cardiovascular disease and endometrial cancer.

Keywords: Anovulation; hirsutism; hyperandrogenism; infertility; insulin resistance; metformin; polycystic ovary syndrome (PCOS); randomized controlled trials (RCTs)

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Introduction

Polycystic ovary syndrome (PCOS) is the commonest endocrinopathy amongst young women, with approximately one in five women having ovaries with a polycystic appearance on ultrasound (1) and almost half of those with polycystic ovaries fulfilling the diagnostic criteria for PCOS (see below) (2).

Insulin resistance appears to be the fundamental common pathway to disease amongst women with PCOS. Women with PCOS have normal insulin molecules and the insulin receptor on cells appears to be normal. However it appears to be a post-receptor deficit, in relation to the downstream cellular effects of what happens after insulin binds to the insulin receptor, meaning that the molecular cascade of intracellular events has a level of impairment, leading to a post-receptor 'intracellular' resistance to insulin. Since there is relative insulin resistance, women with PCOS produce higher levels of insulin than they otherwise would have. These increased circulating levels of insulin have direct effects on the ovaries, and the increased insulin levels also release other factors—notably insulin-like growth factor 1 (IGF-1) from the liver—which, in turn, exerts an effect on the ovary. The impact of higher levels of insulin and IGF-1 on the ovary is for the ovary to release higher levels of testosterone. All of these hormones—including insulin, IGF-1 and testosterone—prevent the growth of ovarian follicles through to ovulation, leading to an accumulation of small ovarian follicles less than 10 mm diameter that do not progress through to ovulation.

It can be understood, therefore, how insulin resistance gives rise to the three key features, at least two of which must be present to fulfill the Rotterdam criteria for the diagnosis of PCOS (2):

- At least twelve small follicles 2-9 mm in at least one ovary;

- Symptoms or biochemical evidence of hyperandrogenism;
- Anovulation or oligo-ovulation with fewer than nine menstrual periods every 12 months.

Anovulation (or oligo-ovulation) in women with PCOS is one of the commonest causes of infertility (3). High circulating androgen levels results in women with PCOS experiencing hirsutism and acne. Other recognized associations of PCOS include acanthosis nigricans, increased tendency towards type 2 diabetes, hypertension, dyslipidaemia. It is debatable whether PCOS is a cause for weight gain, however it is certain that having a high body mass index (BMI) contributes to the pathogenesis of PCOS—women with a high BMI tend to suffer more from the anovulatory and hyperandrogenic consequences of PCOS.

Soon after the insulin resistance contribution to the pathogenesis of PCOS was recognized, it was speculated whether insulin sensitising agents such as metformin could be useful to treat the various consequences of the condition. Early studies and even small randomized controlled trials (RCTs) were promising and metformin seemed to be adopted into practice to some extent prematurely before its utility was proven (4). Anecdotal observation suggested that metformin could also be helpful to improve hyperandrogenic symptoms in some cases and might also promote weight loss. However, in 2009 the report of an international consensus group, who met in Thessaloniki, seemed to end the routine use of metformin for anovulatory infertility in favour of the more established first line treatment clomiphene, through the statement: "use of metformin should be restricted to those patients with glucose intolerance" (5). This recommendation was dominated by a very large and high quality American multi-centre trial, which showed clear benefit of clomiphene over metformin (6). This was widely accepted as definitive evidence that clomiphene should remain the first line treatment for anovulatory PCOS, with apparently no place for metformin first line. However no consideration seems to have been given to an Italian RCT involving non-obese women with PCOS that found significant benefit of metformin over clomiphene (7). Indeed others continued to question whether metformin should continue to have a more prominent role, especially where immediacy of achieving pregnancy is not paramount (8,9).

Evidence for the utility of metformin for other symptoms of PCOS has now also emerged. This paper aims to review the best available evidence for the use of metformin for women with PCOS and to define its place amongst the other recognised treatments for the various problems that women with PCOS can experience.

Metformin for anovulatory infertility in women with PCOS

Metformin as an ovulation induction agent

Metformin is effective as a treatment for anovulatory infertility amongst women with PCOS. A Cochrane review of seven RCTs involving 702 women found that the clinical pregnancy rate for metformin versus placebo was significantly increased [Peto odds ratio (OR) 2.31, 95% confidence interval (CI), 1.52 to 3.51] (10). However only three RCTs involving 115 women examined the outcome live birth, therefore this analysis was consequently underpowered and did not find a significant benefit (Peto OR 1.80, 95% CI, 0.52 to 6.16) (10).

Metformin versus clomiphene

Clomiphene has long been considered the first line treatment for women with ovulation dysfunction related to PCOS. It is clear that lifestyle intervention should be the mainstay of treatment for women with high BMI who are anovulatory in association with PCOS, a simple and healthy approach that yields a reasonable percentage of successful pregnancies without further intervention and through surprisingly modest weight reductions (11). Thus if anovulatory women with PCOS are obese (BMI >30)—and particularly if gross obesity is present (BMI >35)—the poor success rates and the pregnancy risks run by women in this group who do become pregnant mandate that lifestyle intervention to reduce weight should be the first line option. The RCT that found clomiphene to be superior to metformin as an ovulation induction agent [and that dominated the Thessaloniki consensus statement (5)], whilst an otherwise high quality and well powered multi-centre USA trial, recruited women with a mean BMI over 35—in other words, over half of the women on this trial were grossly obese (6).

However there are clear health risks that pregnancy poses to women with obesity (12,13) so that in most settings, the group of women considered for pharmacological intervention as a treatment for anovulatory PCOS is the non-obese group. A meta-analysis of RCTs (14) considered the world RCT literature for the non-obese group (women with BMI under 30—or in our New Zealand setting, we

recruited women with BMI up to 32, recognizing the Maori and Pacific Island ethnic groups have a different lean body mass to women of European women) and found three RCTs that met the criteria for inclusion (7,15,16). This meta-analysis of 285 women with anovulatory PCOS and BMI less than 30-32 kg/m^2 found no significant overall difference in clinical or viable pregnancy rate [relative risk (RR) 0.91, 95% CI, 0.35 to 2.35] or live birth rate (RR 0.83, 95% CI, 0.22 to 3.24) for metformin versus clomiphene given for 6 months to non-obese women with anovulatory infertility related to PCOS (14). The meta-analysis, in which there was significant statistical heterogeneity, found overall clinical pregnancy rates were 36.7% (52/142) for metformin and 35.7% (51/143) for clomiphene; live birth rates were 30.3% (43/142) for metformin and 30.8% (44/143) for clomiphene (14). A further RCT, from Iraq, that also included only non-obese women, was excluded from this meta-analysis because it presented no live birth data (17). There were four interventions in this trial protocol including metformin and clomiphene (but also combination therapy clomiphene plus metformin, and a group undergoing lifestyle intervention), and it is of note that the pregnancy rates of 14.4% (13/90) in the metformin group and 12.2% (11/90) in the clomiphene group were also very similar, consistent with the findings from the meta-analysis (14). The latest version of the Cochrane review has also included this important non-obese subgroup of women (women with a BMI under 30 or under 32) in a subgroup analysis, albeit that did not include the non-obese subgroup of women whose data were available from a supplementary data publication associated with the primary publication of the American trial (15), and reached a similar conclusion, that no difference was apparent between the effectiveness of metformin and clomiphene as monotherapy for ovulation induction in non-obese women with PCOS (10). For obese women, on the other hand, the pregnancy and live birth rate appeared to be overwhelmingly higher for clomiphene versus metformin (10), further supported by a Malaysian RCT (18) in which most of the women were obese and again, clomiphene was found to be superior to metformin for obese women with anovulatory PCOS.

In relation to the heterogeneity in the results of the three RCTs that examined metformin versus clomiphene in the non-obese group of women (14), it was surprising that such a marked variation in results between the Italian (7), American (15) and our New Zealand trial (16) was apparent in the outcome from metformin treatment [pregnancy rates of 62% (7), 12% (15) and 40% (16); live birth rates of 56% (7), 9% (15) and 29% (16) respectively]. The results from clomiphene treatment in these different trials were remarkably consistent [pregnancy rates of 32% (7), 37% (15) and 39% (16); live birth rates of 20% (7), 36% (15) and 36% (16) respectively], given that there is much more potential for variation in practice with clomiphene therapy (such as dose used, days of treatment, monitoring or otherwise and cycle stopping rules) than with metformin therapy (where patients are simply prescribed the drug, typically without cycle monitoring). Whether these marked differences in response to metformin relate to dose used, the failure to adjust dose to BMI, rapid release versus sustained release preparations, or whether there are fundamental differences in the patient populations that impact their response to metformin, remains unclear.

These data, amongst other datasets, are also raising the question as to whether women who become pregnant following ovulation induced by metformin should continue with metformin through early pregnancy. The trial protocols all employed a policy of stopping metformin once pregnancy has been diagnosed, however there appears to be a trend towards higher pregnancy loss rates in the metformin group compared to the clomiphene group (19).

What is becoming increasingly clear is that, contrary to the international consensus recommendation (5), metformin is a very suitable alternative to clomiphene as a first line ovulation induction treatment for non-obese women with anovulatory PCOS. In fact metformin carries some potential advantages over clomiphene, including no known adverse endometrial effect [whilst endometrial thinning could reduce embryo receptivity for some women using CC (20,21)], no known increase in multiple pregnancy rate (unlike that associated with CC) and thus no requirement for inconvenient and costly monitoring of ovulation induction cycles (that many fertility clinics insist upon for CC), and no concern over long term adverse effects on the ovaries [contrasting with the lingering concern over increased risk of ovarian cancer seen in some cohort studies of women using CC, particularly serous ovarian cancer (22) and amongst those using long treatment courses (23)]. My own view is that, owing to these many advantages of metformin over clomiphene, it should be metformin that is used first line for treatment of anovulatory infertility in non-obese women with PCOS. Recourse to other suitable treatments, such as clomiphene, letrozole, laparoscopic ovarian drilling, gonadotrophin injections and IVF, should be considered only for those women in whom metformin monotherapy

has been unsuccessful.

Whilst it has been traditional to recommend metformin for women with PCOS and raised BMI (24), there is a growing evidence base that metformin response is better in women with PCOS who have a lower BMI (16,25). There is no such important impact of higher BMI in attenuating the response to clomiphene therapy (6). It is feasible that the additional insulin resistance affecting women with obesity, on top of the insulin resistance that is a fundamental part of the pathophysiology of PCOS, may be too much for metformin (recognized as an insulin sensitizer of only moderate potency compared to, say, the glitazones) to overcome.

Dual therapy clomiphine plus metformin

It is logical to use monotherapy as first line treatment with either metformin alone or clomiphene alone. In spite of many RCTs examining the potential benefit of combined therapy, no clear benefit has been found in RCTs of dual therapy over monotherapy (4). The live birth rate was not improved amongst 907 women in a meta-analysis who were randomised to clomiphene plus metformin versus clomiphene alone (Peto OR 1.16, 95% CI, 0.85 to 1.56) (10). Although the clinical pregnancy rate was significantly higher in women receiving dual therapy versus clomiphene alone (Peto OR 1.51, 95% CI, 1.17 to 1.96, from meta-analysis of 1,208 women in RCTs who had this outcome assessed) (10), it is unclear to what extent these data were biased by inclusion of women with prior resistance to clomiphene.

Metformin versus aromatase inhibitors

Whilst there is emerging evidence that letrozole may be superior to clomiphene in terms of live births (26), there are few RCT data comparing metformin with aromatase inhibitors.

Metformin versus second line treatments for women with anovulatory PCOS

There are no consistent data comparing effectiveness of metformin versus either laparoscopic ovarian drilling or gonadotrophin injection therapy for women with anovulatory PCOS. However, given the tendency of metformin to improve responses in women who have proven to be resistant to clomiphene and other treatments, it seems reasonable for all women in these treatment categories to be offered metformin treatment until they have established a pregnancy, perhaps even to continue taking metformin into pregnancy, given that metformin's safety track record in pregnancy is now reassuring. Logically metformin should be considered prior to laparoscopic ovarian drilling or gonadotrophin injection therapy and whether synchronous administration of metformin improves outcomes from these treatments is meritworthy of further research.

Wider applications of metformin in assisted reproductive treatment

A systematic review of five RCTs of a total of 582 randomised women with PCOS found no evidence that metformin treatment before or during assisted reproductive technique (ART) cycles could improve live birth or clinical pregnancy rates (27). The Peto OR live birth rate (3 RCTs) was 0.77 (95% CI, 0.27 to 2.18) and for clinical pregnancy rate (5 RCTs) was 0.71 (95% CI, 0.39 to 1.28) (27). The risk of OHSS in women with PCOS and undergoing IVF or ICSI cycles was reduced with metformin (pooled OR 0.27, 95% CI, 0.16 to 0.47) (27).

Effectiveness of metformin for women with PCOS and repeat pregnancy loss remains speculative

Evidence is emerging that abruptly stopping metformin once pregnancy is diagnosed might predispose to pregnancy loss (19). It has long been debated whether PCOS is an independent risk factor in its own right that contributes to risk of recurrent pregnancy loss, or whether it is purely the association of PCOS with obesity that sees recurrent miscarriage over-represented in women with PCOS, with most authorities now favouring the latter theory of obesity as the cause for this association. Nonetheless early observational data were cited as 'evidence' that metformin may improve the chance of successful pregnancy amongst women with PCOS and recurrent miscarriage (28), although this remains unproven by RCTs.

Metformin for hyperandrogenic symptoms in women with PCOS

The logical extension of the use of metformin beyond reproductive indications was that for the other symptoms of PCOS. A systematic review of six RCTs, that assessed hyperandrogenic symptoms and other non-fertility

symptoms, compared metformin versus the combined oral contraceptive pill (OCP) (104 participants) and two RCTs compared OCP combined with metformin versus OCP alone (70 participants) (29). Limited data demonstrated no evidence of difference in effect between metformin and the OCP on hirsutism and acne (29). Metformin was less effective than OCP in reducing serum androgen levels [total testosterone: weighted mean difference (WMD) 0.54, 95% CI, 0.22 to 0.86; free androgen index: WMD 3.69, 95% CI, 2.56 to 4.83] (29). Metformin was less effective than OCP in improving menstrual pattern (Peto OR 0.08, 95% CI, 0.01 to 0.45) (29).

Metformin resulted in a higher incidence of gastrointestinal (Peto OR 7.75, 95% CI, 1.32 to 45.71), and a lower incidence of non-gastrointestinal (Peto OR 0.11, 95% CI, 0.03 to 0.39), severe adverse effects requiring stopping of medication (29).

Metformin for long term health maintenance in women with PCOS

Lifestyle intervention, through dietary improvement and exercise yielding weight loss, remains the cornerstone of effective long term health improvement for women with PCOS who are overweight or obese (30). Metformin was more effective than OCP in reducing fasting insulin (WMD –3.46, 95% CI, –5.39 to –1.52) and not increasing triglyceride (WMD –0.48, 95% CI, –0.86 to –0.09) levels, but there was insufficient evidence regarding comparative effects on reducing fasting glucose or cholesterol levels (29). There was either insufficient or no data on the relative efficacy of metformin or OCP (alone or in combination) for preventing the development of diabetes, cardiovascular disease, or endometrial cancer (29). Nonetheless if metformin restores cyclicity and ovulation for women with PCOS who would otherwise be anovulatory, this would be expected to have a protective effect from the increased risk of endometrial cancer amongst these women, and may be a very suitable treatment for women who are unable to use OCP.

Conclusions

The absence of evidence of superiority of either agent, metformin versus clomiphene, from available RCT data combined with the other advantages of metformin over clomiphene, means that metformin should be seriously considered as the most suitable first line treatment for anovulatory infertility for non-obese women with PCOS. For women who have proven to be resistant to clomiphene alone (when clomiphene is used as a first line agent), the use of metformin alone or in combination with clomiphene is a logical next step. Women with PCOS undergoing *in vitro* fertilisation should be offered metformin to reduce their risk of ovarian hyperstimulation syndrome. Consideration should be given to continuing metformin through the first trimester rather than stopping metformin abruptly once pregnancy has been diagnosed. Metformin may be a suitable alternative to the OCP for treating hyperandrogenic symptoms of PCOS including hirsutism and acne. More research is required to define whether metformin has a role in improving long term health outcomes for women with PCOS, including the prevention of diabetes, cardiovascular disease and endometrial cancer.

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