

Outlook

Metformin use in infertile patients with polycystic ovary syndrome: an evidence-based overview



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Abstract

Metformin is an insulin sensitizer currently used for treating type-2 diabetes mellitus and recently administered for inducing ovulatory menstrual cycles in oligo-amenorrhoeic patients with polycystic ovary syndrome (PCOS). The aim of the present review is to describe the efficacy of metformin as an ovulation inducer on the basis of the most important evidence-based medicine supported data, including meta-analyses and randomized controlled trials. Specifically, we reviewed the uses of metformin as first- and second-step treatment for PCOS related anovulatory infertility and as co-treatment in infertile PCOS patients who receive gonadotrophins. To date, there is evidence that metformin is effective for restoring normal menstrual cycles in anovulatory PCOS patients, and that it is more effective and cheaper than laparoscopic ovarian drilling as the second therapeutic step in PCOS patients previously defined as resistant to clomiphene citrate. Co-administration of metformin in PCOS patients treated with gonadotrophin improves the mono-ovulation rate and can prevent ovarian hyperstimulation syndrome in patients treated with gonadotrophins for IVF cycles.

Keywords: anovulation, fertility, insulin, metformin, ovulation induction, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disease affecting about 5–10% of women of reproductive age (Knochenhauer *et al.*, 1998; Diamanti-Kandarakis *et al.*, 1999). One of the most important and newly discovered features of the syndrome is insulin resistance (IR), which is constantly accompanied by compensatory hyperinsulinaemia. Despite the frequent presence of obesity in PCOS patients and the well-established relation between obesity and IR, a specific mechanism of IR in PCOS, independent of obesity and consisting of a specific post-receptor defect, has been demonstrated. Specifically, IR in PCOS women is due to a reduction of the auto-phosphorylation of tyrosine residues and to an increase in phosphorylation of serine residues on the insulin receptor (Dunaif *et al.*, 1989). The rationale to use insulin sensitizers for ovulation induction in infertile PCOS patients is based on these findings.

The first study showing the beneficial effects of insulin sensitizers on ovarian function was published in 1994 by Velasquez and co-workers (Velasquez *et al.*, 1994). They demonstrated that metformin at doses of 1500 mg daily is effective in reducing body weight, improving menstrual cycles and fertility in PCOS women. Following this study, there was a dramatic increase in the number of publications concerning the use of insulin-sensitizers and PCOS. In particular, during the last 5 years there has been a marked increase in the number of clinical trials, randomized controlled trials (RCT), and meta-analyses. As a result almost all that is known regarding the clinical efficacy of insulin sensitizers is very recent and up-to-date.

Moreover, the scientific literature focuses on a single drug, metformin. In fact about 90% of the scientific studies have

considered the reproductive effects of metformin. In addition more than 10 meta-analyses on metformin administration are currently available (Lord *et al.*, 2003a,b; Kahyap *et al.*, 2004; Beck *et al.*, 2005; Levri *et al.*, 2005; Costello *et al.*, 2006, 2007a,b; Siebert *et al.*, 2006; Gibert *et al.*, 2006). In contrast, the scientific literature offers only one systematic review with meta-analysis regarding the use of other insulin sensitizers (Lord *et al.*, 2003b). Thus, to date, the potential evidence-based medicine (EBM) recommendations are limited to metformin use in PCOS rather than other insulin sensitizers.

The current review aimed to describe, firstly, the relationships between IR, hyperinsulinaemia and ovarian dysfunction and, secondly, the role of metformin administration in improving fertility in infertile PCOS patients. The latter aim was approached using the last systematic reviews with meta-analysis actually available and updating these with the most recent RCT.

Insulin resistance, hyperinsulinaemia, and PCOS-related ovarian dysfunction

Ovarian dysfunction in PCOS consists of abnormal folliculogenesis with follicular arrest at the early development stages (Ehrmann, 2005). In comparison with healthy women, the ovarian tissue of PCOS patients, contains an increased number of primary, secondary and small antral follicles (Ehrmann *et al.*, 2005). Several mechanisms have been proposed to explain the deleterious effects of IR on PCOS-related ovarian dysfunction (**Figure 1**). All suggested mechanisms are potential and may act independently or combined.

IR seems to have a role in the pathogenesis of PCOS-related ovarian dysfunction via hyperandrogenism and worsening the already abnormal androgen signalling at the ovarian level (Dunaif, 1997; Nestler *et al.*, 1998a; Prior *et al.*, 2000; Arslanian *et al.*, 2002). High serum concentrations of insulin result in increased ovarian androgen biosynthesis and in decreased hepatic production of sex hormone-binding globulin (SHBG) (Plymate *et al.*, 1988), leading to a greater bioavailability of free androgens. The excess of local ovarian androgen production, augmented by hyperinsulinaemia, is the cause of premature follicular atresia and anovulation. In this regard, in PCOS populations a significant relationship between androgen concentration and follicle number has been demonstrated (Pache *et al.*, 1993; Welt *et al.*, 2006). In animal models, androgen administration induces a PCOS-like morphology, including increased ovarian volume and increased follicle number, suggesting a direct action of androgens on ovarian cells (Vendola *et al.*, 1998). On the other hand, the use of anti-androgen flutamide has been shown to improve ovarian dysfunction (De Leo *et al.*, 1998).

It has also been postulated that hyperinsulinaemia may influence ovarian function by altering pituitary hormone patterns (Poretsky and Kalin, 1987) with subsequent oligo-amenorrhoea for premature luteinization of the granulosa cells (Willis *et al.*, 1998). Specifically, hyperinsulinaemia would act via two mechanisms: either with a direct effect on the hypothalamus and/or pituitary gland increasing serum LH (and FSH) concentrations (Adashi *et al.*, 1981) or indirectly increasing LH-independent ovarian androgen biosynthesis, probably resulting in altered regulation of

the pituitary-ovarian axis. Despite the undeniable interest in this idea, it remains controversial. In particular, the influence of IR and compensatory hyperinsulinaemia at the central level is not relevant in all PCOS women. A recent study (Ulloa-Aguirre *et al.*, 2006), showed that metformin administration restored the neuroendocrine abnormalities in a proportion of PCOS women who received the drug.

The last mechanism postulated for explaining the cause-effect relationship between hyperinsulinaemia and anovulation is a direct effect of the action of hyperinsulinaemia on folliculogenesis (Franks *et al.*, 1998). High levels of insulin could directly arrest the growth of antral follicles after they have reached a diameter of 5–8 mm; however, this effect has not yet been proven. Furthermore, a local hyperinsulinaemia at the ovarian level due to selective alteration in insulin signalling on granulosa cells of PCOS patients has also been postulated. In particular, granulosa cells of PCOS subjects could have an impaired insulin-stimulated glucose metabolism and a normal insulin-stimulated steroidogenesis (Wu *et al.*, 2003; Rice *et al.*, 2005). The impaired glucose metabolism could cause a deficient energy mobilization and, then, abnormal folliculogenesis (Wu *et al.*, 2003; Rice *et al.*, 2005).

Metformin for treating infertility in PCOS patients

Metformin is an oral biguanide drug currently used for the treatment of type-2 diabetes mellitus and belonging to the Food and Drug Administration (FDA) pregnancy category B classification. The clinical effects of metformin administration include decrease in peripheral insulin resistance, and in serum insulin and glucose concentrations.

Metformin seems to act by several mechanisms (**Figure 2**). Specifically, metformin exerts its action principally on the liver, inhibiting gluconeogenesis and reducing hepatic glucose output (Stumvoll *et al.*, 1995; Bailey and Turner, 1996). In addition, in-vitro (Matthaei *et al.*, 1991; Pryor *et al.*, 2000) and in-vivo (Pryor *et al.*, 2000) data suggest that metformin restores peripheral insulin sensitivity augmenting insulin-mediated glucose uptake in skeletal muscle. Furthermore, the exact mechanism for explaining these actions still remains only partially understood. Metformin seems to increase the translocation of glucose transporters from the intracellular pool to plasma membranes in rat adipocytes (Matthaei *et al.*, 1991) and the binding of insulin to its receptor (Fantus and Brausseau, 1986). In this regard, metformin has been shown to regulate the phosphorylation of the insulin receptor β -subunit and phosphoinositol (PI) 3-kinase and Akt activities in adipocytes exposed to a hyperinsulinaemic environment for a long time (Pryor *et al.*, 2000).

To date, metformin administration is employed not only as first- and/or second-step treatment for inducing ovulation in infertile PCOS patients but also in infertile PCOS patients who receive gonadotrophins. This review will analyse, with an EBM approach, the reproductive effects of metformin when administrated for these specific cases.

Use of metformin as first-step treatment

For establishing the efficacy of metformin as the first-line agent for ovulation induction it is necessary to address three potential clinical issues. Specifically, the following three questions need to be answered: (i) Is metformin effective for treating ovulatory infertility? (ii) Is it the gold standard for anovulatory PCOS patients? and (iii) Does metformin improve the standard first-step approach for treating anovulation in PCOS patients? **Table 1** shows the results of the main meta-analyses of these issues.

Efficacy of metformin for treating anovulatory infertility

The answer to the first question requires a demonstration that metformin administration is more effective than either placebo or no treatment. EBM data in this sense comes from two meta-analyses, published by two independent groups of researchers, and, thus, without any selection biases (Lord *et al.*, 2003a; Kashyap *et al.*, 2004). These two meta-analyses are

in agreement in defining metformin as an effective drug for restoring normal menstrual cycles and for inducing ovulatory cycles in anovulatory PCOS patients, even if conclusive data on its role in terms of fertility improvement are lacking. The analysis by Lord *et al.* (2003a) concludes that there is a significant effect of metformin compared with placebo on ovulation induction, showing an odds ratio (OR) of 3.88 [95% confidence interval (CI) 2.25, 6.69]. In particular, ovulation was achieved in 46% of women who received metformin alone compared with 24% of those receiving placebo, with a number needed to treat (NNT) of 4.4. In contrast, the comparison in terms of clinical pregnancy rate, reported by five trials, did not show any evidence of benefit of metformin in comparison with placebo (OR 2.76, CI 0.85, 8.98). Kashyap *et al.* (2004), in a more recent meta-analysis, confirm that metformin is 50% better than placebo for inducing ovulation in infertile PCOS patients [relative risk (RR) 1.50; 95% CI 1.13, 1.99] and that its benefit versus placebo for pregnancy achievement is not demonstrated (RR 1.07; 95% CI 0.20, 5.74).

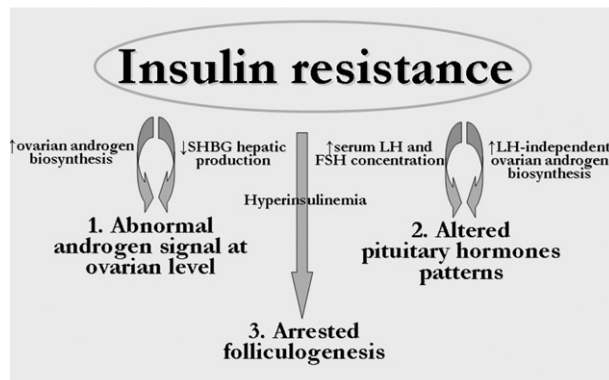


Figure 1. Mechanisms of insulin-related ovarian dysfunction. SHBG = sex hormone-binding globulin.

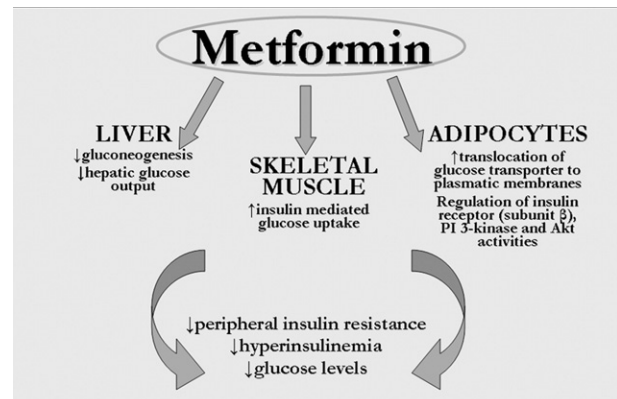


Figure 2. Mechanisms and sites of action of metformin. PI3-kinase = phosphoinositide 3-kinase.

Table 1. Metformin use as the first-step treatment in infertile anovulatory polycystic ovary syndrome patients: level of evidence 1a.

Treatment	Ovulation rate	Pregnancy rate	Live birth rate
Metformin versus placebo			
Lord <i>et al.</i> , 2003a	OR 3.88; 2.25, 6.69 ^a	OR 2.76; 0.85, 8.98	—
Kashyap <i>et al.</i> , 2004	RR 1.50; 1.13, 1.99 ^a	RR 1.07; 0.20, 5.74	—
Metformin versus CC			
Palomba <i>et al.</i> , unpublished data	RR 0.62; 0.04, 10.67	RR 0.87; 0.07, 10.95	RR 0.82; 0.04, 16.66
Metformin plus CC versus CC			
Palomba <i>et al.</i> , unpublished data	RR 0.92; 0.40, 2.16	RR 0.86; 0.62, 1.19	RR 1.01; 0.70, 1.44

Values are given as odds ratio (OR) or relative risk (RR); 95% confidence interval. CC = clomiphene citrate.

^a*P* < 0.05.

Efficacy of metformin as gold standard treatment

The second question to analyse is whether metformin may be considered the gold standard therapy for anovulatory PCOS patients. Thus, it is necessary to demonstrate, if possible, the superiority of metformin versus clomiphene citrate (CC), the treatment that is currently considered to be the gold standard ovulation inducer for PCOS patients (Hughes *et al.*, 2000).

To date, only two head to head RCTs evaluating this issue are available in the literature (Palomba *et al.*, 2005a; Legro *et al.*, 2007). Combining their results, metformin administration was not more effective than CC in terms of ovulation (RR 0.62, 95% CI 0.04, 10.67), pregnancy (RR 0.87, 95% CI 0.07, 10.95), and live birth rates (RR 0.82, 95% CI 0.04, 16.66) (Palomba *et al.*, unpublished data). Moreover, for all three primary endpoints a significant heterogeneity was observed between the two studies (Palomba *et al.*, 2005a; Legro *et al.*, 2007) making these results inconclusive.

Efficacy of metformin co-treatment in patients who receive clomiphene citrate

The third question regards the potential efficacy of associating metformin with the current gold standard treatment. In other words, can metformin improve the reproductive outcomes in patients who receive CC as first-step treatment? To address this question it is necessary to select the head to head RCT comparing the efficacy of CC plus metformin with CC administered alone, with or without placebo (Legro *et al.*, 2007; Moll *et al.*, 2006). In the same way as the combined data of these two RCT demonstrated that metformin does not improve the efficacy of CC as first-line therapy in terms of ovulation (RR 0.92, 95% CI 0.40, 2.16), pregnancy (RR 0.86, 95% CI 0.62, 1.19), and live birth (RR 1.01, 95% CI 0.70, 1.44) rates. A significant data heterogeneity was observed only for ovulation rate, thus the conclusion regarding pregnancy and live birth rates may be considered quite robust (Legro *et al.*, 2007; Moll *et al.*, 2006).

Use of metformin as second-step treatment

Standard practice is to administer CC for 5 days from the second or third day of the menstrual cycle, starting with 50 mg/day and increasing to 250 mg/day (Palomba and Zullo, 2006). When ovulation does not occur under CC administration at the maximum dose, a patient is classically defined as CC-resistant (Palomba and Zullo, 2006). To date, several studies consider a PCOS woman as CC-resistant when ovulation is not achieved after 3 cycles of CC at 100 or 150 mg/day, since 'managed care' data have shown that the most effective dose is 100 or 150 mg/day, and over 75% of ovulations occur with a dose of 100 mg/day (Palomba and Zullo, 2004).

In CC-resistant PCOS patients, metformin has been used as a second-line agent for inducing ovulation. In order to demonstrate the efficacy of metformin as a second-step approach, the efficacy of the drug in CC-resistant PCOS patients when added to CC in a combined administration (metformin co-treatment), as single treatment (metformin

treatment), and before use of CC (metformin pre-treatment) has to be evaluated.

In addition, to demonstrate the clinical efficacy of metformin these three therapeutic protocols should be compared not with CC re-administration with or without placebo but with other well-standardized second-line treatments such as laparoscopic ovarian diathermy (LOD) or ovarian stimulation with gonadotrophins. In fact, the efficacy of repeated CC treatment in PCOS patients previously defined as CC resistant is very low. Specifically, only 11% of CC-resistant patients will ovulate if CC is repeated (Branigan and Estes, 2003).

Efficacy of metformin co-treatment in clomiphene citrate-resistant patients who receive clomiphene citrate

Table 2 summarizes the results of the meta-analyses available (Lord *et al.*, 2003a; Kashyap *et al.*, 2004; Siebert *et al.*, 2006). In the meta-analysis by Lord *et al.* (2003a), the authors observed a significant effect of metformin co-administration with CC in comparison with CC alone in terms of ovulation (OR 9.34, 95% CI 3.97, 21.97) and pregnancy (OR 4.4, 95% CI 1.96, 9.85) rates. The meta-analysis by Kashyap *et al.* (2004) confirmed that metformin plus CC may be superior to CC alone or with placebo with regards to ovulation (RR 1.07, 95% CI 1.13, 1.99) and pregnancy (RR 1.07, 95% CI 0.20, 5.74).

Recently, a meta-analysis (Siebert *et al.*, 2006) that aimed to evaluate metformin as a second-step approach to induce ovulation in CC-resistant PCOS patients, has been published. That study (Siebert *et al.*, 2006) demonstrated metformin efficacy on ovulation in this subset of PCOS patients with an OR of 6.82 (95% CI, 3.59, 12.96). Unfortunately, no results were given regarding the cumulative effect on pregnancy and live birth rates.

Updating the meta-analyses (Lord *et al.*, 2003a; Kashyap *et al.*, 2004; Siebert *et al.*, 2006) from January 2005, two RCT can be identified (Khorram *et al.*, 2006; Rouzi and Ardawi, 2006). These RCT did not change the conclusions of the previously described meta-analyses. In particular, the first study (Khorram *et al.*, 2006) showed that in obese PCOS patients, 2 weeks of metformin treatment, administered starting from a progesterone-induced bleeding, significantly improved the ovulation rate in CC-resistant PCOS patients who received CC (44 versus 6.7%). The authors suggested that this regimen may be beneficial in noncompliant patients or in those intolerant to side effects associated with metformin administration. The latter RCT (Rouzi and Ardawi, 2006) compared the efficacy of rosiglitazone plus CC with metformin plus CC in CC-resistant PCOS women, demonstrating that short-term use of rosiglitazone plus CC is more efficacious than the association metformin-CC for inducing ovulation (64.3 versus 36.4%) but not for improving fertility (50.0 versus 38.5%) in CC-resistant PCOS patients.

Table 2. Metformin use as co-treatment with clomiphene citrate (CC) in CC-resistant patients: level of evidence 1a.

Reference	Ovulation rate	Pregnancy rate	Live birth rate
Lord <i>et al.</i> , 2003a	OR 9.34; 3.97, 21.97 ^a	OR 4.40; 1.96, 9.85 ^a	–
Kashyap <i>et al.</i> , 2004	RR 3.04; 1.77, 5.24 ^a	RR 3.65; 1.11, 11.99 ^a	–
Siebert <i>et al.</i> , 2006	OR 6.82; 3.59, 12.96 ^a	–	–

Values are given as odds ratio (OR) or relative risk (RR); 95% confidence interval.

^a*P* < 0.05.

Efficacy of metformin single treatment in clomiphene citrate-resistant patients who receive clomiphene citrate

The second point to address is the efficacy of insulin sensitizers as single treatment in CC-resistant PCOS patients. To date, only one RCT is available in the literature (Palomba *et al.*, 2004). This trial was conducted on a population of 120 PCOS CC-resistant patients who were randomized to receive LOD or diagnostic laparoscopy followed by placebo or metformin administration, respectively. The aim of the study (Palomba *et al.*, 2004) was to compare the efficacy of 6 months of metformin treatment to that of LOD in improving fertility in CC-resistant patients. The study confirmed that both treatments were similarly effective in inducing regular ovulatory cycles (54.8 versus 53.2%), but higher pregnancy (21.8 versus 13.4%) and live birth (86.0 versus 64.5%) rates were observed in women treated with metformin. The cost-analysis of the two approaches showed that metformin treatment was less expensive than drilling by about 20-fold.

Efficacy of metformin administered prior and during clomiphene citrate treatment in clomiphene citrate-resistant patients

The last issue relates to the use of metformin as an insulin sensitizing pre-treatment prior to CC administration in CC-resistant PCOS patients. The scientific literature does not include any meta-analysis on this issue. Despite this lack, several published RCT are available (Nestler *et al.*, 1998b; George *et al.*, 2003; Palomba *et al.*, 2005b; Hwu *et al.*, 2005), albeit performed on small samples and with very heterogeneous study designs, which seem to indicate that metformin pre-treatment could sensitize PCOS patients, previously defined CC-resistant, to CC treatment. However, data from small studies (Sturrock *et al.*, 2002; Sahin *et al.*, 2004) do not demonstrate the efficacy of metformin in this sense.

The RCT by Nestler *et al.* (1998b) shows the highest ovulation rate of CC resistant PCOS women pre-treated with metformin. In particular, the administration of 1500 mg/day of metformin for 35 days and later 50 mg/day of CC for 5

days resulted in an ovulation rate of 90%, although no data on fertility were reported. The authors postulated that the beneficial effects of metformin could be related to its ability to decrease serum insulin in women with PCOS.

These data were confirmed by other workers in a sub-analysis of a RCT (Palomba *et al.*, 2004, 2005b). In this last study (Palomba *et al.*, 2005b), it was demonstrated that, in overweight CC-resistant PCOS women who remain anovulatory after metformin, subsequent CC administration was effective in inducing ovulation with an ovulation rate of about 30%. Moreover, when administered in an ultra-short regimen, metformin is able to improve the ovarian responsiveness to CC. Specifically, this regimen was associated with an ovulation rate of 42.5% (Hwu *et al.*, 2005), and can be employed in non-compliant patients or in those with intolerance to the drug side effects. In addition, sequential treatment with metformin and CC is as effective as gonadotrophins in inducing ovulation, with a significantly lower drop-out rate and lower costs (George *et al.*, 2003). The results of the previous studies (George *et al.*, 2003; Hwu *et al.*, 2005; Palomba *et al.*, 2005b) on fertility are all in agreement, showing a pregnancy rate of about 15%.

On the other hand, two small studies (Sturrock *et al.*, 2002; Sahin *et al.*, 2004) disagreed with the above findings, showing that metformin pre-treatment does not increase ovulation and pregnancy rates and does not enhance ovulation induction in CC-resistant women with PCOS, despite improved insulin resistance and reduced androgen concentrations.

Despite the common use of the term 'pre-treatment' for this specific use of metformin, it should be noted that in all studies considered (Nestler *et al.*, 1998b; Sturrock *et al.*, 2002; George *et al.*, 2003; Sahin *et al.*, 2004; Hwu *et al.*, 2005; Palomba *et al.*, 2005b) metformin, given prior to inducing ovulation with CC, was continued during CC administration.

The results of the previously considered RCT are shown in **Table 3** (Nestler *et al.*, 1998b; Sturrock *et al.*, 2002; George *et al.*, 2003; Sahin *et al.*, 2004; Hwu *et al.*, 2005; Palomba *et al.*, 2005b).

Use of metformin in patients who receive gonadotrophins

The benefits of administering insulin sensitizers with gonadotrophins should be evaluated considering two main categories of patients: those who receive ovarian stimulation for inducing mono-ovulatory cycles as a last step for treating anovulation in PCOS women, and those treated with ovarian stimulation for inducing multiple follicular development for IVF cycles. Only one meta-analysis is available in the literature on this issue (Costello *et al.*, 2006). As regards women treated with gonadotrophins for inducing mono-ovulatory cycles, it has been demonstrated that the association of metformin with gonadotrophins gives no improvement either in terms of ovulation (OR 3.27, 95% CI 0.31, 34.72) or pregnancy (OR 3.46, 95% CI 0.98, 12.2) rate. However, it should be noted that a positive trend towards an improvement in pregnancy rate obtained with metformin co-administration (28 versus 10%) has been observed (Costello *et al.*, 2006). Unfortunately, no conclusion can be made about the live birth rate because no trial compared metformin combined with gonadotrophin versus gonadotrophin and placebo or no treatment in terms of live birth as an outcome measure.

It is interesting to evaluate how metformin co-administration influences the therapy with gonadotrophins. Metformin significantly reduces the length of ovarian stimulation with gonadotrophin [weighted mean difference (WMD) -4.14 days, 95% CI -6.36, 1.93], the total dose of FSH used during the treatment cycle (WMD -425.05 IU, 95% CI -507.08, 343.03) and the serum oestradiol concentration on the day of human chorionic gonadotrophin (HCG) trigger (WMD -1.24 nmol/l, 95% CI -1.5, 0.98) (Costello, 2006). Data from any RCT on ovarian hyperstimulation syndrome (OHSS) are lacking.

Infertile PCOS patients receiving ovarian stimulation with gonadotrophins seem to benefit from metformin administration in terms of reduction of OHSS risk (Khattab *et al.*, 2006), although no or poor explanations of this phenomenon have been offered. One of the possible mechanisms of action could be related to the improvement in insulin sensitivity due to metformin with consequent lowering of insulin concentrations. PCOS women who are hyperinsulinaemic, in fact, present higher levels of oestradiol and incidence of OHSS in response to ovarian stimulation with FSH compared with those with normoinsulinaemia (Fulghesu *et al.*, 1997). Moreover, insulin increases vascular endothelial growth factor (VEGF) expression in vascular smooth muscle cells (Doronzo *et al.*, 2004), and VEGF has emerged as one of the factors most likely to be involved in the pathophysiology of OHSS (Practice Committee of the American Society for Reproductive Medicine, 2003).

As regards the effects of metformin co-administration in patients treated with gonadotrophins to induce the multiple follicular development in IVF cycles, the same meta-analysis (Costello *et al.*, 2006) demonstrated that metformin co-administration does not improve pregnancy rates (34 versus 29%; OR 1.29, 95% CI 0.84 to 1.98). Data analysis included five RCT, only one of which showed an improvement in pregnancy rates with metformin (Tang *et al.*, 2005). Two RCT (Kjøtrød *et al.*, 2004; Tang *et al.*, 2005) assessed the effect of metformin co-administration during ovarian stimulation for IVF on live birth rates in PCOS women. Despite one of these (Tang *et al.*, 2005) showing a significant improvement in live birth rates with metformin, the meta-analysis (Costello *et al.*, 2006) of the combined data showed a non-significant improvement in live birth rates in patients taking metformin (36 versus 22%; OR 2.02, 95% CI 0.98, 4.14).

Table 3. Metformin use as pre-treatment in clomiphene citrate (CC)-resistant patients before CC administration: level of evidence 1b.

Treatment	Ovulation rate	Pregnancy rate	Live birth rate
Metformin pre-treatment before CC versus placebo pre-treatment before CC			
Nestler <i>et al.</i> , 1998b	90.0% versus 8.0% ^a	–	–
Hwu <i>et al.</i> , 2005	42.5% versus 12.5% ^a	15.0% versus 0.0% ^a	–
Sturrock <i>et al.</i> , 2002	41.7% versus 28.6%	25.0% versus 14.3%	–
Sahin <i>et al.</i> , 2004	74.4% versus 61.8%	45.5% versus 30.0%	–
Metformin pre-treatment before CC versus HMG			
George <i>et al.</i> , 2003	40.0% versus 46.7% ^a	16.7% versus 23.3%	–
Metformin pre-treatment before CC versus LOD pre-treatment before CC			
Palomba <i>et al.</i> , 2005b	30.6% versus 31.1%	16.7% versus 16.2%	66.7% versus 58.3%

^aP < 0.05; CC = clomiphene citrate; HMG = human menopausal gonadotrophin; LOD = laparoscopic ovarian drilling.

No effect of metformin co-administration on the ovarian stimulation length (WMD -0.09 days, 95% CI $-0.49, 0.31$) was observed, whereas metformin plus gonadotrophin treatment significantly decreased the total dose of FSH used (WMD -290.42 IU, 95% CI $-450.34, -130.51$). No effect was observed on the number of oocytes collected (WMD 0.44 , 95% CI $-0.98, 1.86$), whereas inconclusive results regarding serum oestradiol concentrations on the day of HCG trigger (WMD -3.53 nmol/l, 95% CI $-9.24, 2.18$) were detected because of a strong statistical heterogeneity observed between studies as a result of great variability in the treatment effects. However, the main finding is that metformin significantly reduces the risk of OHSS in IVF treatment (5.6 versus 21.0%; OR 0.21 , 95% CI $0.11, 0.41$) as shown by cumulative analysis of four RCT (Costello *et al.*, 2006).

The systematic search performed by Costello and co-authors stopped in August 2005 (Costello *et al.*, 2006). To date, several other papers are published in the literature on this issue, even if only three RCT are available (Palomba *et al.*, 2005c; van Santbrink *et al.*, 2005; Tang *et al.*, 2006).

Two studies (Palomba *et al.*, 2005c; van Santbrink *et al.*, 2005) analyse the use of metformin in PCOS patients who received gonadotrophins for mono-ovulation induction, and one (Tang *et al.*, 2006) for multiple-ovulation induction in IVF cycles. This last study (Tang *et al.*, 2006) should be considered as a duplicate publication and should replace, as a full text paper, the previous abstract of the same group included in Costello's meta-analysis (Costello *et al.*, 2006). Thus, this new study did not modify the meta-analysis conclusions on metformin effects in IVF cycles.

On the other hand, the two studies performed in patients who received gonadotrophins for mono-ovulation induction (Palomba *et al.*, 2005c; van Santbrink *et al.*, 2005) confirmed the absence of any effect induced by metformin administration on the ovulation, pregnancy, and live birth rates. Moreover, a significant beneficial effect on the number of mono-ovulatory cycles was observed in patients who received gonadotrophins plus metformin, despite a duration of stimulation and a number of vials used significantly higher in patients taking metformin (Palomba *et al.*, 2005c; van Santbrink *et al.*, 2005). Unfortunately, the beneficial effect of metformin in increasing mono-ovulatory cycles did not translate into a beneficial effect in reducing the multiple pregnancy rate. This result is probably due to the small sample size or to the already very low rate of multiple pregnancies observed in patients treated with low dose or very-low-dose step-up protocols.

Conclusions

Metformin administration is an effective first-treatment for PCOS patients with anovulatory infertility, but it does not improve the efficacy of CC. In addition, comparative data on the single best first-step treatment are inconclusive.

In CC-resistant PCOS patients, the association of metformin with CC has a beneficial effect, whereas studies controlled for gonadotrophin or laparoscopic ovarian drilling arm are lacking. In these patients, metformin alone is more effective and cheaper than LOD. At the moment, data on the efficacy of

metformin pre-treatment before CC in CC-resistant patients are controversial and inconclusive.

In PCOS patients taking metformin, given as second-step treatment, alone or in combination with CC, metformin should be continued during gonadotrophin stimulation in order to increase the rate of mono-ovulation, even if data on FSH doses and treatment length are again inconclusive. In infertile PCOS patients who receive gonadotrophins for inducing multiple follicular development for IVF cycles, metformin co-treatment reduces the risk of OHSS and, thus, its use should be planned for patients at high-risk for OHSS.

Finally, few recommendations can be given at present, mainly because there are many clinical trials in the literature but few experimental studies aimed at solving the problems of metformin use. In particular, it will be necessary to design experimental studies to define potential predictors, such as insulin resistance or body mass index, for tailoring the best treatment to each particular PCOS patient.

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