The role of metformin in ovulation induction: Current status

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Abstract To define the exact role of metformin in ovulation induction, it is crucial to distinguish three different indications: naïve PCOS, CC-resistant PCOS and ART. In naïve PCOS: metformin as compared to placebo has been shown to improve ovulation rates, but metformin did not exert significant advantage over CC with respect to cumulative ovulation, pregnancy or live-birth rates. The combined approach of metformin plus CC is not better than CC or metformin monotherapy in naïve PCOS. In CC-resistant patients: metformin has no benefit over placebo in ovulation, pregnancy, and live-birth rates as a single agent, but the combination of metformin and CC significantly improved ovulation and pregnancy rates when compared with CC alone. However, combined therapy did not improve the odds of live birth. Metformin pretreatment improves the efficacy of CC in PCOS patients with CC resistance. In PCOS patients scheduled for ART: metformin addition to gonadotropins reduces the duration of gonadotropins administration and the doses of gonadotropins required, and increases the rate of monoovulations, reducing the risk of cancelled cycles. Metformin co-administration to IVF treatment does not improve pregnancy or live-birth rates but reduces the risk of OHSS.

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1. Introduction

The polycystic ovary syndrome (PCOS) is a common endocrinopathy, affecting 6.8% of reproductive-aged women (1). Anovulation and androgen excess have been considered the hallmark diagnostic criteria of the syndrome. Insulin resistance (IR) has been identified as a significant contributor to the pathogenesis of PCOS. Metformin has been used alone or combined with CC in induction of ovulation. Its mechanism of action and role in ovulation induction will be discussed in three different indications: Naïve PCOS, CC-resistant PCOS and ART. Factors affecting response to metformin will be elaborated.

1.1. Insulin resistance

IR has been demonstrated to participate in the reproductive as well as metabolic abnormalities associated with PCOS (2). 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 signaling. IR and secondary hyperinsulinemia affect approximately 65–70% of women with PCOS (3).
Many of these women are also obese, which further exacerbates their IR. Insulin stimulates ovarian theca cell androgen production and secretion, and suppresses the hepatic production of sex hormone-binding globulin. The increased intraovarian androgens then disrupt folliculogenesis (4). Hyperinsulinemia may also directly cause premature follicular atresia and antral follicle arrest. The resulting anovulation also leads to unopposed estrogen production and endometrial proliferation in women with PCOS, leading to an increased risk of endometrial hyperplasia. Consistent with the high prevalence of IR and obesity, patients with PCOS demonstrate a greater prevalence of impaired glucose tolerance (IGT), type 2 DM, dyslipidemia, and chronic subclinical inflammation (5). Many patients with PCOS demonstrate features consistent with the metabolic (or dysmetabolic) syndrome. IR 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 IGT (6). Simple screening tests include an assessment of body mass index (BMI) and waist circumference. If the fasting blood glucose is <5.2 mmol/l the risk of IGT is low.

1.2. Metformin
Metformin is a biguanide currently used as an oral antihyperglycemic agent and is approved by the US Food and Drug Administration to manage type 2 DM. The benefits of metformin on insulin sensitivity have been demonstrated in non-DM women with PCOS. The use of metformin is associated with increased menstrual cyclicity, improved ovulation, and a reduction in circulating androgen levels (7). Metabolic benefits are enhanced in the presence of weight loss and weight loss itself may be enhanced in the presence of metformin (8).

1.2.1. Mechanism of action
Its primary clinical action is to inhibit hepatic glucose production, although it also decreases intestinal glucose uptake and increases insulin sensitivity in peripheral tissues (9). Metformin likely plays its role in improving ovulation induction in women with PCOS through a variety of actions, including reducing insulin levels and altering the effect of insulin on ovarian androgen biosynthesis, theca cell proliferation, and endometrial growth. Also, potentially through a direct effect, it inhibits ovarian glucose metabolism and thus reduces ovarian androgen production (10). Metformin has been shown to inhibit GnRH release by activation of hypothalamic AMPK, a crucial regulator of food intake in mammals, in a dose-dependent and time-dependent fashion (11).

2. Role of metformin in ovulation induction
Many studies involved small and phenotypically heterogeneous groups and did not draw any distinction between therapy-naive and clomiphene citrate (CC)-resistant women (12). To define the exact role of metformin in ovulation induction, it is crucial to distinguish three different indications: Naive PCOS, CC-resistant PCOS and ART.

2.1. Naive PCOS patients
2.1.1. As single agent
Metformin as compared to placebo has been shown to improve ovulation rates in women with PCOS in randomized controlled trials (RCTs), cohort studies, or uncontrolled descriptive studies. However, only few of them had pregnancy as a defined outcome measure (13). In a meta-analysis, metformin alone has been shown to have a significant benefit on inducing ovulation in women with PCOS, but there is limited evidence that it improves pregnancy rates (2).

Recently, a systematic review and meta-analysis of the head-to-head RCTs available in literature was conducted to better define the efficacy of CC and metformin, alone or in combination, as a first-step approach in treating anovulatory infertility in PCOS patients (14). Pooling the data obtained from the studies comparing metformin to CC (15–17), metformin did not exert significant advantage over CC with respect to cumulative ovulation, pregnancy or live-birth rates. However, the most interesting findings were the significant heterogeneity detected for all reproductive end-points. Great heterogeneity in the protocol used and in the populations studied was found (18).

2.1.2. Combined with CC
Three head-to-head RCTs (15,17,19) comparing reproductive efficacy of metformin plus CC combination vs. CC monotherapy in therapy-naive PCOS patients were available. Metformin plus CC was no more effective than CC alone in inducing ovulation in the study by Moll et al. (19) and by Zain et al. (17), whereas in the study by Legro et al. (15) the combination was significantly more effective than CC monotherapy. The pregnancy and live-birth rates were similar between metformin plus CC combination and CC monotherapy in the studies by Moll et al. (19), Legro et al. (15), and Zain et al. (17). When the data from these three studies were combined in a meta-analysis (14), the metformin plus CC association was shown to be no more effective than CC regarding rates of ovulation, pregnancy, or live births. A main drawback in the design of the RCTs that assessed the efficacy of combined CC plus metformin vs. CC (15,17,19) or metformin (15,17) alone was that metformin was started either concurrently with (15,17) or after only 1 month (19) of CC initiation. Metformin has a slower onset of action than CC; hence, the studies as such were unintentionally biased against demonstrating the value of the CC plus metformin combination.

In conclusion, in anovulatory infertile therapy-naive PCOS patients, the combined approach of metformin plus CC is not better than CC or metformin monotherapy.

2.2. CC-resistant PCOS patients
2.2.1. As single agent
In small RCT (18 infertile women) (21) found no benefit of metformin over placebo in ovulation, pregnancy, and live-birth rates as a single agent in CC-resistant patients. In a study by Vandermolen et al. a significant improvement on both ovulation and pregnancy rates were observed in women with CC-resistant PCOS who were treated with metformin alone. In RCT, Elnashar et al. demonstrated that metformin alone is an effective drug in inducing ovulation in CC-resistant PCOS, whereas N-acetyl cysteine alone is not (22).

Palomba et al. (23) compared metformin as a single treatment with laparoscopic ovarian diathermy (LOD) in CC-resistant PCOS patients. No difference was present between metformin and LOD in the ovulation rate but significantly higher pregnancy and live-birth rates were observed.
A successive meta-analysis (24) showed no evidence of difference in the clinical pregnancy rate, whereas the live-birth rate was still higher after metformin. However, metformin treatment was certainly not inferior to LOD and was about 20-fold less expensive than the surgical ovulation induction (23).

2.2.2. Combined with other treatment

2.2.2.1. With CC. The efficacy of metformin cotreatment in CC-resistant patients who received CC was evaluated in several studies (24–28). Two meta-analyses (25,26) agreed in demonstrating a significant benefit of metformin cotreatment in comparison with CC alone, even if a significant heterogeneity was observed between studies included in both meta-analyses. In particular, in CC-resistant PCOS women, the addition of metformin was demonstrated to be effective in inducing ovulation in the two meta-analyses by Lord et al. (25) and Kashyap et al. (26). In the same manner, significant benefits of the combination therapy on pregnancy rate were demonstrated in both studies.

A successive meta-analysis (27), designed to assess metformin coadministration as a second-step approach for CC-resistant PCOS patients, confirmed that metformin plus CC is significantly more effective than CC alone in terms of ovulations, even if a significant heterogeneity was demonstrated across studies, and no data were provided regarding the effect on pregnancy and live-birth rates.

Moll et al. (24) also compared metformin plus CC to CC alone in CC-resistant women and confirmed that metformin plus CC led to significantly higher clinical pregnancy and live-birth rates without significant heterogeneity in treatment effect across trials.

In a meta-analysis of placebo-controlled RCTs only, the combination of metformin and CC significantly improved ovulation and pregnancy rates when compared with CC alone (28). However, combined therapy did not improve the odds of live birth. Furthermore, a significant heterogeneity was detected between all studies included in the analysis. Conversely, metformin did not have any effect on live births and no significant heterogeneity data were present. The results suggested combination therapy (metformin plus CC) as the treatment of choice in CC-resistant women.

The combination of metformin plus CC was demonstrated to be more effective than LOD in CC-resistant PCOS patients with anovulatory infertility (29). In particular, metformin plus CC association was related to higher ovulation rates than LOD, even if no difference in the rates of pregnancies, live births and miscarriages were detected between two procedures (29). Despite the lack of convincing data that metformin improves live-birth rates, there may be value in attempting this treatment prior to proceeding to more expensive and invasive therapies, such as LOD or low-dose gonadotropins (21).

Metformin therapy would augment the induction of ovulation in CC-resistant women because of its favorable change in androgens, gonadotropins, and insulin, through mechanisms distinct from those of CC (21). It is plausible to assume that women with CC resistance receiving metformin have an increased response to CC secondary to an intrinsic alteration of the microenvironment of the follicle caused by the effect of metformin pretreatment on insulin and the insulin growth factor (IGF)-1 pathway in granulose cells (29). More specifically, Tosca et al. (31) reported that in bovine granulose cells, metformin decreases steroidogenesis and mitogen-activated protein kinase (MAPK)3/MAPK1 phosphorylation through AMPK activation.

2.2.2.2. With letrozole. Adding metformin to CC in clomiphene-resistant PCOS patients increases ovulatory response. However, because of anti-estrogenic effects of CC it may be associated with lower pregnancy rate, offsetting the ovulation rate benefit. Letrozole is an aromatase inhibitor which induces ovulation without anti-estrogenic effects. Small RCT was done by Sohrabvand et al. in 2006, (32) comparing addition of letrozole or CC to metformin clomiphene-resistant PCOS patients. After an initial 6–8 weeks of metformin, they received either letrozole (2.5 mg) or CC (100 mg) from day 3–7 of their menstrual cycle. No difference in mean number of mature follicles >18 mm and ovulation rate was found. However, endometrial thickness and full-term pregnancies were significantly higher in patients treated with metformin plus letrozole (32).

2.2.2.3. With LOD. In one trial (33) CC-resistant PCOS patients were randomized to LOD followed by metformin or LOD alone. Ovulation (86.1% vs. 44.6%) and pregnancy (47.6% vs. 19.1%) rates were significantly higher in patients who received metformin. Furthermore, a successive meta-analysis (24) demonstrated no significant benefit in clinical pregnancy rate for the metformin administration after LOD.

2.2.3. Metformin pretreatment

Several RCTs (34–39) evaluated the efficacy of metformin pretreatment before CC in CC-resistant PCOS patients. Even if these studies were very heterogeneous and were performed on small populations, most of them (34–37) suggest that metformin pretreatment improves the efficacy of CC in PCOS patients with CC resistance. In particular, one small RCT (38) showed no beneficial effect on ovulation and pregnancy rates after 3 months of metformin pretreatment, despite the improvement of IR and hyperandrogenemia.

On the contrary, other studies (34–37,39) demonstrated that metformin pretreatment, also when given in ultrashort protocols (37,39), improved CC response in terms of ovulation and pregnancy in CC-resistant PCOS patients. These findings support the idea that decreasing insulin secretion while administering metformin in PCOS patients facilitates the induction of ovulation by using CC (40).

2.3. PCOS patients scheduled for ART

2.3.1. Metformin, gonadotropins, and intrauterine insemination cycles

A meta-analysis done by Costello et al. demonstrated that the co-administration of metformin to gonadotropin does not significantly improve ovulation or pregnancy rates, whereas no RCT reporting live births as an outcome measure was identified (41). On the other hand, metformin was shown to be significantly efficient in reducing the length of time for ovarian stimulation while using gonadotropin and the total dose of FSH used.

Two RCTs (42,43) evaluating whether metformin changes ovarian responsiveness in controlled ovarian stimulation cycles were recently published. The first RCT (42) on 70 non obese insulin-resistant PCOS patients who received a low-dose step-up gonadotropin stimulation protocol followed by timed intercourse or intrauterine insemination demonstrated a
significant effect of metformin in increasing the rate of monoovulatory cycles and in reducing those of cancelled cycles. Furthermore, no effect of metformin pretreatment and coadministration was confirmed in ovulation, cycle cancellation, pregnancy, abortion, live births, multiple pregnancies, or OHSS. The latter study (43) showed that metformin improved the endocrine profile in insulin-resistant PCOS patients receiving gonadotropins in a step-up protocol and confirmed that it facilitated the monofollicular development during ovarian stimulation cycles.

Metformin may act on the regulation of ovarian response to exogenous gonadotropins improving insulin resistance. A reduction in serum testosterone and insulin levels in follicular fluid was observed after metformin treatment (44). Thus, the improvement of the hyperinsulinemic and hyperandrogenic ovarian environment might be crucial for a normal folliculogenesis, homogeneous development, and responsiveness of follicles and atresia of the small cohort of follicles (45).

A recent meta-analysis by Moll et al., on four RCTs demonstrated a pooled clinical pregnancy rate that was significantly higher when metformin was added to gonadotropins than with gonadotropins alone (46). However, no significant difference in live-birth rate could be proven. In addition, metformin was demonstrated to be effective in reducing multiple pregnancies, whereas no difference in OHSS was reported. The lack of an effect of metformin on this end-point was probably due to the low incidence of OHSS during ovarian stimulation with low-dose step-up gonadotropin protocols (47). On the other hand, the employment of a step-up low dose protocol tailoring the gonadotropin administration seems to be a pivotal factor more and more in PCOS patients who receive metformin because metformin coadministration has been shown to increase the incidence of multiple pregnancies in patients who receive gonadotropins (48).

In conclusion, in patients who received gonadotropins as treatment for anovulation, metformin addition reduces the duration of gonadotropins administration and the doses of gonadotropins required and increases the rate of monoovulations, reducing the risk of cancelled cycles.

### 2.3.2. Metformin and in vitro fertilization

A meta-analysis of RCT on the effects of metformin co-treatment in women with PCOS undergoing IVF, reported that a 28-day course of metformin during the IVF cycle improves the pregnancy outcome, higher rates of ongoing pregnancy per cycle and per transfer and reduces the risk of OHSS. It failed to improve the response to stimulation and the fertilization rate (49). This finding is supported by a case-controlled study that also reported an increase in the pregnancy rate and a highly significant increase of embryo quality with metformin (50). Addition of metformin to FSH treatment for CC-resistant patients with PCOS has been reported to reduce serum levels of vascular endothelial growth factor (VEGF), the number of preovulatory follicles and the peak level of E2 (51). VEGF through the stimulation of ovarian angiogenesis may be a key mediator of OHSS.

However, not all data support even this beneficial effect of metformin during IVF in patients with PCOS. Data obtained from two meta-analyses (41, 46) suggest that metformin did not improve the efficacy of gonadotropins when it was prescribed in the context of adjuvant treatment for IVF cycles. In particular, Costello et al. (41) analyzed four published RCTs and one trial published in abstract format only evaluating the effect of metformin addition to gonadotropins in women undergoing IVF cycles. Metformin was demonstrated to have no significant effect on the number of oocytes collected at IVF, length of ovarian stimulation, pregnancy and live-birth rates. A significant decrease in the total dose of gonadotropins used during IVF cycles and in OHSS risk was shown by Costello et al. (41). Pooling the data of the two trials that reported multiple pregnancies gave no evidence of a significant difference between the two groups on multiple pregnancies’ rates. On the basis of these results, some authors concluded that to date no adjuvant pretreatment in IVF cycles should be suggested in the clinical practice (52).

Metformin co-administration to IVF treatment does not improve pregnancy or live-birth rates but reduces the risk of OHSS. The OHSS is the most serious complication of IVF in women with PCOS and may lead to catastrophic complications and even death.

### 3. Factors affecting response to metformin

Reflecting the clinical and pathophysiologic heterogeneity of PCOS, treatment with metformin can elicit variable results, ranging from no response to moderate or significant improvement (53). Phenotypes of PCOS with distinct endocrine and metabolic features may be differentially affected by metformin therapy. However, the determinants of response to metformin therapy in women with PCOS remain enigmatic (7). Despite the lack of clear-cut evidence, clinical studies have attempted to identify predictors of response to metformin. Interestingly, favorable metabolic changes are often paralleled by reproductive improvement in treated patients. This observation is compatible with the fact that both the metabolic and the reproductive effects of metformin depend, to a large extent, on the alleviation of IR.

#### 3.1. Baseline BMI

Baseline BMI was confirmed as a major predictor of both ovulation and pregnancy under metformin treatment in women with PCOS. Higher BMIs appear to be associated with suboptimal therapeutic results of metformin regarding metabolic as well as reproductive abnormalities. It is commonly experienced that obese women, particularly those with morbid obesity, are refractory to metformin therapy (54). Obesity counteracts the attenuation of IR induced by metformin. This adverse interaction compromises the overall therapeutic efficacy of the drug, including both metabolic and reproductive aspects (2, 25). Advanced age and longer duration of infertility had an adverse impact on pregnancy response under metformin.

#### 3.2. Insulin-resistant PCOS

Insulin-resistant PCOS patients with low BMI were reported to be more likely to respond to metformin, whereas CC treatment was more effective in less hyperandrogenic and more insulin-sensitive patients with low BMI (56). However, previous studies did not confirm the predictive value of IR indices for ovulation induction by metformin (57). This discrepancy may reside in the use of surrogate mathematical indices for the assessment of IR. Alternatively, the dissociation between the improvement of insulin sensitivity and the restoration of
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ovulation implicates other mechanisms, independent of insulin, in the reproductive response to metformin. For example, metformin may be able to directly affect ovarian steroidogenesis (58). In addition, this drug could affect the central regulation of ovulation by modulating GnRH release through the activation of the hypothalamic AMPK (11). The degree of IR may be a factor in deciding whether or not to add metformin to the cycle regimen until the pregnancy test. Chang et al. (59) showed that the insulin levels and the degree of beta-cell function (as measured by homeostasis assessment model [HOMA] beta-cell percent) are highest in oligoovulatory women with PCOS who are both hirsute and hyperandrogenemic, as compared with patients with PCOS who are either hyperandrogenic or hirsute only. In this regard, a greater improvement in effectiveness (defined as decreases in luteinizing hormone [LH], estradiol, insulin, and C-peptide) was observed among women with PCOS who were both hyperandrogenic and hyperinsulinemic (60).

3.3. Androgen level

The degree of androgen excess may be another determinant of the reproductive efficacy of metformin. In studies evaluating the posttreatment ovulation rate (57), responders to metformin were less hyperandrogenic than nonresponders.

3.4. Genotype

The role of the genotype is also currently explored. In a prospective randomized trial, a specific polymorphism in STK11 (also known as LKB1), a kinase gene expressed in liver and implicated in metformin’s action, was associated with ovulatory response to treatment with metformin (61).

3.5. Menstrual abnormalities

Moghetti et al. (62) performed a logistic regression analysis of baseline characteristics in patients with PCOS who responded (i.e., had an improvement in menstrual bleeding frequency) or who did not respond to metformin treatment after receiving 1500 mg/day for 11.0 ± 1.3 months (open trial; range 4–26 months). The researchers observed that higher plasma insulin, lower serum androstenedione, and less severe menstrual abnormalities were independent predictors of clinical efficacy of metformin.

3.6. The length of metformin administration

In meta-analytic studies (13,24,26,28,63,27), the beneficial effect of metformin could be diluted in time with longer follow-up periods due to more time available for spontaneous ovulation in control group patients. On the other hand, short-course metformin (<4 weeks) could be a suboptimal pretreatment period before beginning CC. Unfortunately, there presently is no RCT assessing this aim, and there is insufficient data to determine whether long-course metformin pretreatment, before initiation of CC for ovulatory infertility treatment, is more effective than short-course pretreatment (64).

3.7. Specific subgroups

Although CC is recognized as the first-line agent in women with PCOS who desire immediate pregnancy, addition of metformin may be beneficial to specific subgroups:

(a) CC resistance (24) or those who are older and viscera1y obese (55). The ability of metformin to restore responsiveness to CC in obese women with PCOS and the low rates of multiparity and ovarian hyperstimulation syndrome (OHSS) are additional potential benefits of metformin therapy in the CC-resistant patient.

(b) Metformin appears to be a useful tool in women with longer timelines for achieving pregnancy (65). For those women with a short term but not immediate desire for pregnancy, consideration should be given to pretreatment with metformin before prescribing CC for ovulation induction. This option may allow metformin to develop its full reproductive and metabolic efficacy since its onset of action is known to be gradual. In these cases, pretreatment of obese patients with metformin combined with lifestyle modification may result in weight loss, which reduces the likelihood of clomiphene resistance and the risk for gestational or obstetrical complications (66).

(c) Glucose intolerance: the recent ‘Thessaloniki consensus paper’ recommended that metformin use in PCOS should be restricted to women with glucose intolerance (67).

4. Conclusion

(1) In naïve PCOS: metformin as compared to placebo has been shown to improve ovulation rates, but metformin did not exert significant advantage over CC with respect to cumulative ovulation, pregnancy or live-birth rates. The combined approach of metformin plus CC is not better than CC or metformin monotherapy.

(2) In CC-resistant patients: metformin has no benefit over placebo in ovulation, pregnancy, and live-birth rates as a single agent, but the combination of metformin and CC significantly improved ovulation and pregnancy rates when combined with CC alone. However, combined therapy did not improve the odds of live birth. Metformin pretreatment improves the efficacy of CC in PCOS patients with CC resistance.

(3) In PCOS patients scheduled for ART: metformin addition to gonadotropins reduces the duration of gonadotropins administration and the doses of gonadotropins required, and increases the rate of monoovulations, reducing the risk of cancelled cycles. Metformin co-administration to IVF treatment does not improve pregnancy or live-birth rates but reduces the risk of OHSS.

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