

Mini Review

The Current Role of Metformin in the Treatment of Infertility in PCOS: A Mini-Review

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Abstract

The role for metformin in the treatment of an ovulatory infertility in PCOS is currently limited. Metformin alone is not recommended as first line medical ovulation induction treatment in an ovulatory PCOS women as letrozole and clomiphene citrate are more effective in terms of ovulation, pregnancy and live-birth rates. However, metformin alone may be considered if medical facilities are not available to monitor the more effective therapies of clomiphene citrate and letrozole.

On the other hand, metformin may be used as an adjunct therapy in the second line treatment of an ovulatory woman with PCOS. Metformin combined with clomiphene citrate improves fertility outcomes in clomiphene citrate resistant and/or obese PCOS an ovulatory women. In addition, recent preliminary RCT evidence suggests that metformin may increase the live birth rate among clomiphene citrate resistant PCOS women undergoing gonadotrophin ovulation induction with timed intercourse or intra-uterine insemination. The use of metformin as an adjuvant therapy in PCOS women undergoing GnRH agonist long protocol IVF/ICSI may also be recommended in order to reduce the risk of developing ovarian hyper stimulation syndrome. However, it is currently recommended that metformin be stopped with the diagnosis of pregnancy due to the lack of benefit associated with its routine use in reducing pregnancy complications.

Keywords

- Metformin
- PCOS
- Infertility
- Live-birth
- Pregnancy

ABBREVIATIONS

PCOS: Polycystic Ovary Syndrome; RCT: Randomized Controlled Trial

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, with prevalence between 6% and 10% based on the U.S. National Institutes of Health (NIH) criteria and as high as 15% when the broader Rotterdam criteria are applied [1]. A diagnosis of PCOS is based on features of oligo-ovulation and/or an ovulation, clinical or biochemical hyperandrogenism and polycystic ovaries [2]. Infertility is a prevalent presenting feature of PCOS with approximately 75% of these women suffering infertility due to an ovulation, making PCOS by far the most common cause of an ovulatory infertility [3].

The aetiological hypotheses of PCOS are continually developing with the understanding and incorporation of the evolving evidence of the syndrome, which appears to be both multifactorial and polygenic and includes hypothalamic-pituitary-ovarian and adrenal axis contributions, ovarian thecal

cell steroidogenesis dysfunction, and insulin resistance with compensatory hyperinsulinemia [4]. Based on the association between insulin resistance and an ovulation in both lean and obese PCOS women, insulin-sensitising drugs, such as metformin, have been added as a promising therapy to restore ovulation and enhance pregnancy in PCOS [5].

Metformin is a biguanide and the preferred and most cost-effective first-line oral therapy for the treatment of type 2 diabetes as an anti-hyperglycemic agent. Metformin reduces hepatic glucose production by reducing hepatic gluconeogenesis, improves insulin sensitivity by increasing insulin mediated glucose uptake by skeletal muscle / liver / adipose tissue, reduces intestinal absorption of glucose, reduces lipogenesis and increases fatty acid oxidation in skeletal muscle / liver / adipose tissue, and reduces ovarian androgen production both directly by a reduction in CYP17 enzyme activity and indirectly via a reduction in hyperinsulinemia. It is estimated that 10-15% of its efficacy in type 2 diabetes is due to peripheral improvement in insulin sensitivity, primarily in skeletal muscle. Thus, metformin is not primarily an insulin-sensitizing drug, although it is often labeled as such in the treatment of women with [6-8].

The first published report on the use of metformin in PCOS was in 1994 [9]. This observational study reported that metformin at a dose of 1500mg daily reduced hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy in a case series of 26 women with PCOS. It was not until almost a decade later that the first systematic review on the use of metformin in PCOS was published [10]. At that stage limited data consisting of 12 randomized controlled trials (RCTs), two cohort studies, and 16 uncontrolled descriptive studies on predominately obese PCOS patients demonstrated that metformin alone improved both restoration of regular menses and spontaneous ovulation, but there was no data supporting an improvement in pregnancy rate. The addition of metformin to clomiphene citrate resulted in an improved ovulation and pregnancy rate in both unselected and clomiphene citrate-resistant PCOS women. There was insufficient data to make any conclusions on the effect of metformin on FSH ovulation induction or IVF.

METFORMIN ALONE AS FIRST LINE OVULATION INDUCTION TREATMENT

A Cochrane systematic review and pair-wise meta-analysis of RCTs comparing metformin with placebo or no treatment in PCOS women showed that metformin improves ovulation rate (OR = 1.81; 95% CI, 1.13–2.93; 16 RCTs; 1208 women) and clinical pregnancy rate (OR = 2.31; 95% CI, 1.52–3.51; 8 RCTs; 707 women) but not live-birth rate (OR = 1.80; 95% CI, 0.52–6.16; 3 RCTs; 115 women) per woman [11]. In the first ever systematic review and network meta-analysis on ovulation induction in WHO Group 2 (including PCOS) an ovulation published in 2017, metformin was also demonstrated to be more effective than placebo or no treatment in terms of ovulation (OR = 4.10; 95% CI 6.23–31.42) and pregnancy (OR = 3.58; 95% CI 1.93–6.63) rates but there was again no evidence of a difference in live-birth rate (OR = 2.87 favouring metformin; 95% CI 0.40–20.77) with findings on the latter outcome inconclusive due to the wide 95% confidence intervals [12].

Recent guidelines or consensus statements reporting on the treatment of infertility in PCOS recommend either clomiphene citrate (selective estrogen receptor modulator or SERM) or letrozole (aromatase inhibitor) as first line medical ovulation induction treatment in an ovulatory PCOS women [13–17].

Metformin has been compared in a head to head manner to clomiphene citrate in a number of recent systematic reviews and pair-wise meta-analyses of RCTs [11,18–19]. Clomiphene citrate is superior to metformin in terms of live-birth rates for all an ovulatory PCOS women (OR = 0.48; 95% CI, 0.31–0.73; 4 RCTs; 612 women) but there was significant statistical heterogeneity and therefore caution is required in interpreting these results [18]. In obese an ovulatory PCOS women, clomiphene citrate is superior to metformin in terms of live-birth rates (OR = 0.30; 95% CI, 0.17–0.52; 2 RCTs; 500 women) without statistical heterogeneity [11]. However, there is no evidence of a difference in live-birth rate between clomiphene citrate and metformin in PCOS women with a BMI less than 30–32 Kg/m² (OR = 0.84 in favour of clomiphene citrate; 95% CI, 0.12–5.94; 3 RCTs; 285 women) although one is unable to exclude an important difference in favour of either

clomiphene citrate or metformin [19]. In the largest single RCT (and adequately powered to assess live-birth rates) published to date comparing metformin with clomiphene citrate over 6 months of treatment in over 600 women with PCOS, clomiphene citrate was demonstrated to be superior to metformin for the following outcomes: live-birth (22.5% versus 7.2%) and clinical pregnancy (23.9% versus 8.7%) rates per woman at end of 6 months; ovulation (49% versus 29%), pregnancy (5.3% versus 1.8%) and live-birth (5.0% versus 1.5%) rates per cycle; and pregnancy (13.4% versus 8.4%) and live-birth (10.2% versus 5.1%) rates per ovulatory cycle [20].

In the first ever systematic review and network meta-analysis on ovulation induction published in 2017, there was no evidence of a difference in live-birth rate between metformin and clomiphene citrate (OR = 1.06; 95% CI 0.75–1.50) but letrozole was more effective than metformin in terms of live-birth rate (OR = 0.54; 95% CI 0.29–0.98) [12]. The latest published guideline commenting on the treatment of infertility in PCOS has concluded that metformin has a limited role in the treatment for an ovulatory infertility in PCOS and recommended that metformin alone could be used to improve ovulation and pregnancy rates if facilities are not available to monitor the more effective therapies of clomiphene citrate and letrozole [17].

METFORMIN AS AN ADJUNCT TREATMENT TO CLOMIPHENE CITRATE AS SECOND LINE OVULATION INDUCTION TREATMENT

The addition of metformin to clomiphene citrate is beneficial in improving ovulation, pregnancy and live-birth rates in clomiphene citrate resistant (failure to ovulate on standard doses of clomiphene citrate) PCOS women rather than persisting with more cycles of clomiphene citrate alone treatment [17,21–23]. Fertility outcomes in terms of ovulation rate and pregnancy rate, but not live-birth rate, are also improved with the addition of clomiphene citrate to metformin compared to metformin alone in obese (BMI >30 kg/m²) PCOS women [21,23]. This evidence has led to a number of published guidelines commenting on the treatment of infertility in PCOS to recommend the use of metformin as a combination treatment with clomiphene citrate in clomiphene citrate resistant and/or obese PCOS an ovulatory women [13,15–17].

Ovulation induction with a combination of metformin with clomiphene citrate is inferior to gonadotrophins for the outcomes of ovulation (OR = 0.25; 95% CI, 0.15–0.41; 3 RCTs; 323 women), pregnancy (OR = 0.45; 95% CI, 0.27–0.75; 3 RCTs; 323 women) and live-birth (OR = 0.33; 95% CI, 0.13–0.85; 2 RCTs; 170 women) rates in clomiphene citrate resistant PCOS women as demonstrated by Abu Hashim and colleagues in a systematic review and meta-analysis of RCTs [24].

METFORMIN AS AN ADJUNCT TREATMENT TO LETROZOLE AS SECOND LINE OVULATION INDUCTION TREATMENT

The efficacy of combined metformin and letrozole in infertile PCOS women has been assessed in 2 RCTs [25,26]. Both RCTs were conducted in Iran and compared combined metformin and letrozole to combined metformin and clomiphene citrate

in clomiphene citrate resistant PCOS women with a mean BMI around 30 kg/m² undergoing either timed intercourse [25] or intra-uterine insemination [26] and who had an initial 6-8 weeks of metformin therapy alone before the combination therapy. Both RCTs found a significantly lower estradiol level but significantly greater endometrial thickness in the combined metformin and letrozole groups. Sohrabvand and colleagues demonstrated a higher live-birth rate per patient (OR = 4.05; 95% CI, 1.96–16.94, 59 randomized women) in the combined metformin and letrozole patients but no evidence of a difference in pregnancy rate per patient or miscarriage rate per pregnancy between the 2 groups over 2 treatment cycles [25]. Davar et al., showed no evidence of a difference in either biochemical or clinical pregnancy rate per woman between the 2 groups over 3 treatment cycles in 100 randomized women [26].

METFORMIN AS AN ADJUNCT TREATMENT TO FSH AS SECOND LINE OVULATION INDUCTION TREATMENT

Bordewijk et al., in a systematic review and meta-analysis of RCTs published earlier in 2017, found that the addition of metformin to gonadotrophins improved the clinical pregnancy (OR = 2.51; 95% CI, 1.46–4.31; 5 RCTs; 264 women), ongoing pregnancy (OR = 2.46; 95% CI, 1.36–4.46; 4 RCTs; 232 women) and live-birth (OR = 2.31; 95% CI, 1.23–4.34; 2 RCTs; 180 women) rates per woman based on low quality evidence with no evidence of a difference in ovarian hyper stimulation syndrome (OR = 0.32 in favour of no metformin; 95% CI, 0.01–8.23; 1 RCT; 180 women) rates in PCOS women with clomiphene citrate resistance undergoing gonadotrophin ovulation induction with timed intercourse or intra-uterine insemination [27]. The authors concluded that preliminary evidence suggests that metformin may increase the live birth rate among women undergoing ovulation induction with gonadotrophins but additional trials are necessary before one can provide further conclusions that may affect clinical practice.

METFORMIN AS AN ADJUNCT TREATMENT IN IVF

Metformin administration before and/or during long GnRH agonist long protocol IVF or ICSI treatment increased clinical pregnancy rates (OR = 1.52; 95% CI 1.07 to 2.15; 8 RCTs, 775 women, moderate-quality evidence) and decreased the risk of ovarian hyper stimulation syndrome (OR = 0.29; 95% CI 0.16 to 0.51, 7 RCTs, 758 women, moderate-quality evidence) in an ovulatory women with PCOS, with or without another cause of couple infertility, in a recently updated Cochrane systematic review and meta-analysis of RCTs [28,29]. However, there was no evidence of a benefit in live birth rates (OR = 1.39, 95% CI 0.81 to 2.40, 5 RCTs, 551 women, low-quality evidence). Based on these findings, recently published guidelines addressing the treatment of infertility in PCOS have recommended the use of metformin as an adjuvant therapy in PCOS women undergoing GnRH agonist long protocol IVF in order to prevent or reduce the risk of ovarian hyper stimulation syndrome [15,17].

METFORMIN AND PREGNANCY COMPLICATIONS

There have been a number of published systematic reviews and meta-analyses of RCTs demonstrating no evidence that

pre-conceptional metformin reduces the risk of miscarriage in women with PCOS [11,12,27,28,30]. Metformin intake during the first trimester of pregnancy in PCOS women has not been shown to reduce miscarriage rates based on 2 RCTs [31,32]. Metformin taken during the pregnancy from the first trimester of pregnancy until delivery did not reduce the prevalence of pregnancy complications (gestational diabetes, pre-eclampsia or preterm delivery, or a composite of the three outcomes) in a multicenter, double blind, placebo controlled RCT of 274 singleton pregnancies in women with PCOS [33].

The Endocrine Society and NICE Guidelines on PCOS state that the routine use of metformin during pregnancy in women with PCOS is unwarranted, although it may be useful to treat gestational diabetes, and therefore recommended against the use of metformin for the prevention of pregnancy complications [15,34].

CONCLUSION

The current role for metformin in the treatment of an ovulatory infertility in PCOS is limited. Metformin alone is not recommended as first line medical ovulation induction treatment in an ovulatory PCOS woman but may be used in a second line treatment as adjunct therapy to clomiphene citrate and gonadotrophin ovulation induction in clomiphene citrate resistant and/or obese PCOS an ovulatory women. Metformin may also be recommended as an adjunct therapy in PCOS women undergoing GnRH agonist long protocol IVF/ICSI in order to reduce the risk of developing ovarian hyper stimulation syndrome. However, it is currently recommended that metformin be stopped with the diagnosis of pregnancy due to the lack of benefit associated with its routine use in reducing pregnancy complications.

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