

Abstract

OBJECTIVE:

This study was conducted to determine the usefulness of metformin therapy in improving outcomes related to infertility in patients with polycystic ovary syndrome (PCOS). A Bayesian meta-analytic and mixed treatment comparison (MTC) approach was used.

METHODS:

A literature search was performed using PubMed and the Cochrane Central Register of Controlled Trials to identify randomized controlled trials that reported at least one of the outcomes of interest – ovulation, pregnancy and live birth in PCOS patients randomized to treatment with either metformin, clomiphene citrate (CC) or combination of these drugs, which included a comparison with either placebo or each other. Reference lists of meta-analyses and reviews were hand searched to identify any additional articles. Bayesian meta-analyses were conducted for each outcome separately and for different therapeutic comparisons with metformin. Additionally, Bayesian MTCs were also conducted for each outcome. Analyses were performed using random effects models.

RESULTS:

A total of 27 RCTs were identified and 24 studies reported outcomes in a usable form for inclusion in the analysis. The total number of patients was 2217. The meta-analyses revealed that metformin was superior to placebo for ovulation induction (median OR=2.9 with 95 %CrI] 1.6–6.0). Comparison of metformin and CC to CC alone revealed that combination therapy was superior in both ovulation induction (median OR=4.2 with 95 %CrI] 1.5–12.3) and pregnancy (median OR=5.0 with 95 %CrI] 1.7–22.4). When live birth was considered there was no significant difference between combination therapy and CC alone (median OR=2.2 with 95 %CrI] 0.4–55.5). In the MTC, the efficacy of the therapeutic comparisons for ovulation and pregnancy in descending ranking order was combination therapy, CC alone, metformin alone and placebo.

CONCLUSIONS:

Combination therapy with metformin and CC is more effective than CC alone in ovulation and pregnancy outcomes in women with PCOS.

Background

- Polycystic ovary syndrome (PCOS) is a common endocrinopathy affecting 5 – 10 % of women of reproductive age.
- The treatment of the disease is controversial and there have been recent attempts at a consensus based on available scientific evidence.¹
- In 1994 an observational study indicated menstrual and ovulatory cycle regularity in patients with PCOS subsequent to metformin therapy.²
- Since then, use of metformin as a pharmacologic therapy in the treatment of PCOS, and related infertility has become widespread.
- Metformin is an insulin-sensitizing drug, and its mode of action is to directly target insulin resistance, an underlying feature of PCOS. Decreasing circulating insulin induces ovulation through an indirect mechanism.
- However, the consensus statement from the European Society of Reproduction and Embryology (EHSRE) and the American Society of Reproductive Medicine (ASRM) sponsored workshop in 2007, recommended the restriction of metformin use to women with glucose intolerance.¹
- Clomiphene citrate, a fertility drug used for ovulation induction, was recommended as first line therapy.¹
- Numerous rigorously conducted trials have indicated the benefits of metformin either alone or in combination with clomiphene citrate in achieving fertility related outcomes, and a recent meta-analysis has also indicated its benefits.³

Objectives

- To determine the effectiveness of metformin therapy in improving outcomes related to infertility (ovulation, pregnancy, live birth) in patients with PCOS by updating the aforementioned meta-analysis.
- Rank the effectiveness of metformin, clomiphene citrate and their combination for the different fertility related outcomes.

Methods

- This study was a Bayesian meta-analysis and a mixed treatment comparison (MTC) of published studies evaluating metformin in PCOS.
- Randomized clinical trials (RCT) were included with any of the following comparisons;
 - metformin vs placebo
 - metformin + Clomiphene citrate (CC) vs CC
 - metformin vs CC
 - metformin + CC vs metformin
- Study identification;
 - The Cochrane central register of controlled trials and PubMed database were searched for relevant studies.
 - Search terms used were “polycystic ovar*”, “metformin” and “clomiphene”
 - Relevant meta-analyses and systematic reviews were identified using the search terms listed above on both PubMed and the Cochrane Database of Systematic Reviews. These were hand-searched to identify additional articles not revealed through the primary search.
- Search was conducted on 29th December, 2008, using studies published from 1990 onwards to date of the search
- The search was restricted to studies conducted in human females and published in English
- Inclusion criteria;
 - Reported original data from RCTs
 - Measured at least one of the outcomes of interest – ovulation, pregnancy, and live birth.
 - Pregnancy and live birth were considered only if the study included patients who were seeking to conceive, were infertile, or recruited from infertility clinics
 - Subjects were diagnosed as having polycystic ovary syndrome (PCOS)
- A Bayesian meta-analytic and mixed treatment comparison (MTC) approach was used for the analysis. Random effects model was used in the analysis.
- All analyses were conducted using WinBUGS Bayesian software.

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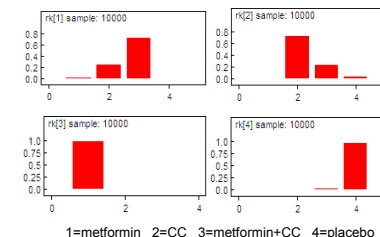
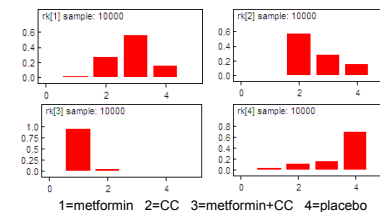
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Results

- 27 RCTs were identified with 24 studies having outcomes in a usable form for inclusion in the analysis, and a total of 2217 patients were included in the analysis.
- Ovulation
 - Metformin was significantly more effective than placebo: median OR=2.9 with 95 % credible interval [CrI] 1.6–6.0
 - Metformin + CC was significantly more effective than CC alone: median OR=4.2 with 95 %CrI] 1.5–12.3
- Pregnancy
 - Metformin + CC was significantly more effective than CC alone: median OR=5.0 with 95 %CrI] 1.7–22.4
- Live birth
 - There was no significant difference between metformin+CC and CC alone: median OR=2.2 with 95 %CrI] 0.4–55.5
- In the rank order analysis from the MTC, metformin + CC (comparison 3) had the highest probability of being the best treatment for both ovulation (Figure 1) and pregnancy (Figure 2), followed by CC (comparison 2), and subsequently metformin (comparison 1).
- The rank order analysis for the outcome live birth was less clear (results not shown).

Figure 1 – Rank order analysis of treatments to achieve ovulation

Figure 2 – Rank order analysis of treatments for pregnancy


Discussion

- This meta-analysis and MTC indicates that combined therapy with metformin + CC is more effective than CC alone in ovulation and pregnancy outcomes in women with PCOS.
- The superiority of metformin+CC over CC alone was not evident for live births. A definitive conclusion about this most important fertility related outcome is more difficult to ascertain due to the limited number of trials that examine this outcome as a study endpoint.
- The comparisons of metformin vs CC, and metformin+CC vs metformin alone, had comparisons of 3 and 2 studies respectively, which may contribute to the non significant results.
- In spite of the EHSRE/ASRM sponsored workshop recommendation on metformin¹, a recent editorial maintained the debate on the role of metformin in the treatment of infertility in PCOS patients.⁴ Metformin has a slower onset of action than CC, thus requiring a longer duration (i.e. at least 6 months) of therapy before its beneficial effects can be observed. Not all studies in the analysis fulfilled this criterion for duration.
- A limitation is the considerable heterogeneity of the studies included in the analysis. Some of these were: different study designs, patient characteristics, varying follow-up times, and possible influences of other infertility treatments.
- Additionally, some studies with the comparison of metformin+CC vs CC alone were nested within a study where CC was administered only if ovulation was not induced within a stipulated time period following initial randomization to metformin and placebo. This second phase of the study was not randomized and is a possible source of bias.
- There are studies and subgroup analysis conducted indicating that different treatments have distinctive benefits in patients with certain characteristics (i.e. obese, clomiphene resistant), and further research is required to establish the role of metformin in these patient subgroups before broad-based recommendations can be made.

Conclusion

- This analysis indicated that metformin, especially combined with CC may have a role to play in the treatment of infertility in women with PCOS
- The results contrasts with the consensus recommendations by the EHSRE/ASRM sponsored workshop, which were based on two large randomized controlled studies^{5,6}, both of these studies have been included in this analysis.

References

- Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group 2008 Consensus on infertility treatment related to polycystic ovary syndrome. Fertil Steril 89:505–522
- Velazquez EM, Mendoza S, Hamer T, Sosa F, Glueck CJ 1994 Metformin therapy in polycystic ovary syndrome reduces hyperinsulinemia, insulin resistance, hyperandrogenemia, and systolic blood pressure, while facilitating normal menses and pregnancy. Metabolism 43:647–654
- Creanga AA, Bradley HM, McCormick C, Wilkop CT 2008 Use of metformin in polycystic ovary syndrome: a meta-analysis. Obstet Gynecol 111:959–968
- Nestler JE 2008 Metformin in the treatment of infertility in polycystic ovarian syndrome: an alternative perspective. Fertil Steril 90:14–16
- Mail E, Bossuyt FM, Korevaar JC, Lambalk CB, van der Veen F 2006 Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. BMJ 332:1485
- Legro RS, Barnhart HX, Schaff WD, Carr BR, Diamond MP, Carson SA, Steinkamp MP, Coulfaris C, McGovern PG, Abtahi ND, Gosman GJ, Nestler JE, Giudice LC, Lappert PC, Myers ER, Cooperie Multicenter Reproductive Medicine Network 2007 Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. N Engl J Med 356:551–566