Metformin Treatment for Improving Outcomes Related to Infertility in Polycystic Ovary Syndrome (PCOS) – A Bayesian Analysis

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Abstract

OBJECTIVE: To determine the effectiveness of metformin therapy in improving outcomes related to infertility (ovulation, pregnancy) in women with PCOS by updating the aforementioned meta-analysis.

1. To determine the effectiveness of metformin, clomiphene citrate and their combination for the different fertility related outcomes.

Methods

This 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 ovary”, “metformin” and “clomiphene”

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
- There was no significant difference between metformin + CC and CC alone: median OR=2.2 with 95% [CrI] 0.4–55.5

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

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).

Discussion

This meta-analysis and MTC indicated 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. 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 randomized metformin plus 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 distinct 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 studies1,6, both of these studies have been included in this analysis.

References

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