

Effect of combined metformin and oral contraceptive therapy on metabolic factors and endothelial function in overweight and obese women with polycystic ovary syndrome

BACKGROUND:

- Women with polycystic ovary syndrome (PCOS) are at risk for developing diabetes, dyslipidemia and endothelial dysfunction
- Historically, women with PCOS have been treated with oral contraceptives (OCs); however, OCs may cause worsened hyperinsulinemia, insulin resistance, and glucose tolerance.
- Metformin improves insulin resistance and hyperlipidemia, and may be a good treatment option in women with PCOS
- Few studies have compared OCs + metformin with OCs alone.

OBJECTIVE:

- To determine if combination metformin and oral contraceptive therapy would be more effective than oral contraceptive and placebo in improving insulin sensitivity, lipid profile, cardiovascular risk markers, and vascular endothelial function in women with PCOS.

METHODS

- **Design:** 3 month single-center, randomized, double blind, placebo-controlled trial
- **Inclusion Criteria:** PCOS, signs of hyperandrogenism, and at least one of the following: oligoovulation or anovulation or polycystic ovaries
- **Exclusion Criteria:** pregnant, diabetes, history of thromboembolism, use of tobacco within 6 months, use of OCs, treatment for diabetes/hyperlipidemia, or antiandrogens within 3 months
- **# patients enrolled:** 23
- **Drug regimens/dosages used:** metformin 500mg once daily for 1 week, then twice daily for one week, then 3 times daily for the remainder of the study; ethinyl estradiol (35mcg)/norgestimate (0.18mg/0.215mg/0.25mg)
- **Primary outcome measures:** change in insulin sensitivity
- **Secondary outcome measures:** changes in lipid profile, cardiovascular risk, vascular endothelial function, body size, blood pressure, and steroid concentrations
- **Power:** 22 participants needed to achieve a 90% power to detect a statistically significant difference in insulin sensitivity, assuming SD of 0.85 and α level of 0.05.
- **Data handling method:** per protocol

RESULTS

- Of the 23 women randomized, 4 were lost to follow up. 19 women completed the study, 10 randomized to receive OC + placebo and 9 randomized to receive OC+MET
- **Primary outcome measures:** none of the measures for insulin sensitivity were statistically significant between groups.
- **Secondary outcome measures:**
 - Cardiovascular risk, lipid profile, body size, blood pressure and steroid concentration: none of the measures were statistically significant between groups
 - Vascular endothelial function: Flow-mediated dilation was the only measure found to be statistically significant with 0.56 ± 0.83 in the OC group and 4.0 ± 0.88 in the OC+MET group ($p=0.01$)

- **Authors stated conclusions:** The combination of metformin and oral contraceptives may be of benefit in overweight women with PCOS because it improves vascular endothelial function to a greater extent than oral contraceptives alone. Larger studies of longer duration as well as studies using oral contraceptives with varying ethinyl estradiol and progestin levels are needed to clarify the impact of combination metformin and oral contraceptives on insulin sensitivity and serum cardiovascular inflammatory markers.

STRENGTHS

- Randomized, double-blind placebo controlled trial
- Use of most commonly prescribe oral contraceptive
- Use of an oral contraceptive containing a progestin with low androgenic activity

LIMITATIONS

- High likelihood of Type II error due to power not being achieved and having a small sample size
- Multiple parameters were used to detect differences between groups which increased the risk of Type I error
- By choosing a large effect size, the authors lowered the risk of detecting a significant difference by chance, which falsely elevated the power
- No restrictions on diet/exercise
- Short study duration
- Use of SEM rather than SD makes the data appear less variable
- Inappropriate use of a two-tailed ANOVA when there was only one independent variable in the study
- Potential for unblinding due to characteristics of metformin such as odor and side effects
- A1c is a standard measure for estimated average glucose over 3-months, and this measure was not used.

CONCLUSIONS

- The study objective and design are good; however, given the multiple limitations, the results of this study cannot be used to definitively rule in or out the use of metformin in combination with oral contraceptives in patients with PCOS. Further evaluation is needed in a larger number of patients for a longer duration to determine the true efficacy of the combination therapy.

Reference:

Essah PA, Arrowood JA, Cheang KI, Adawadkar SS, Stovall DW, Nestler JE. Effect of combined metformin and oral contraceptive therapy on metabolic factors and endothelial function in overweight and obese women with polycystic ovary syndrome. *Fertility and Sterility*. 2011; 96(2): 501-4.

Holly Kirk, Doctor of Pharmacy Candidate