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

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Abstract

In this randomized, double-blind, placebo controlled study, 19 overweight women with PCOS were randomized to a 3-month course of either metformin plus combined hormonal oral contraceptive (OC) (n=9) or OC and matched placebo (n=10). After 3 months, both treatments had similar effects on androgen levels, lipid profile, insulin sensitivity and serum inflammatory markers, but flow-mediated dilatation increased by 69.0% in the metformin-OC group (p=0.01) while it remained unchanged in the OC group.

Keywords

metformin; oral contraceptives; endothelial function; insulin sensitivity

Insulin resistance increases the risk for diabetes, dyslipidemia, and endothelial dysfunction in women with polycystic ovary syndrome (PCOS) (1–3). Although oral contraceptive pills (OCs) have been used for decades to treat PCOS, they may worsen hyperinsulinemia, insulin

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resistance, and glucose tolerance (4–6). Conversely, metformin improves insulin sensitivity and dyslipidemia (7).

Few studies have evaluated the effects of combined metformin and OC compared to OC alone in PCOS. Therefore, we conducted a study to determine whether combination metformin and OC therapy, compared to OC and placebo, would more effectively improve insulin sensitivity as measured by modified frequently sampled intravenous glucose tolerance test (FSIVGTT), a method highly correlated with the euglycemic hyperinsulinemic clamp technique (8), lipid profile, cardiovascular risk markers, and vascular endothelial function as measured by flow-mediated dilatation (FMD).

This was a single-center randomized, double-blind, placebo-controlled trial with evaluations performed at baseline and after 3 months of treatment. PCOS was defined using modified Rotterdam criteria, after exclusion of other endocrine disorders (9): (i) presence of clinical and/or biochemical signs of hyperandrogenism and ii) at least one of the following: oligo- or anovulation or polycystic ovaries. All subjects had hyperandrogenemia.

Subjects were excluded if they were pregnant; had diabetes or history of thromboembolism; tobacco use within prior 6 months; or use of OCs, diabetes/hyperlipidemia medications, and anti-androgens within prior 3 months. All participants provided signed, informed consent. The study was approved by the VCU Institutional Review Board and was registered at clinicaltrials.gov (NCT00682890).

Subjects presented after 12-hour overnight fasts for 2 consecutive days of testing both at baseline and after 3 months of treatment. All evaluations were performed in the follicular phase of the menstrual cycle, confirmed by serum progesterone <2 ng/mL (6.4 nmol/L). On day 1, fasting labs were drawn for lipids, androgen levels, and cardiovascular risk markers (C-reactive protein [hsCRP], soluble vascular cell adhesion molecule-1 [sVCAM-1], soluble intercellular adhesion molecule-1 [sICAM-1], adiponectin, plasminogen activator inhibitor-1 [PAI-1], interleukin-6 [IL-6], and monocyte chemoattractant protein-1 [MCP-1]). A 2-hr OGTT was performed with determinations of fasting glucose and insulin every 15 minutes after a 75gm glucose load. On day 2, subjects underwent FMD followed by 3-hour FSIVGTT.

Participants were randomized to either: 1) OC and metformin 500 mg orally three times daily or 2) OC and metformin-matched placebo orally three times daily. The OC used was ethinyl estradiol 35mcg /norgestimate 0.18/0.215/0.25 mg (Ortho-McNeil Janssen Pharmaceuticals, , Raritan, NJ), because it was the most commonly prescribed OCs in the U.S. Metformin was given in a dose of 500mg once daily for 1 week, twice daily for 1 week, and three times daily for the remainder of the study period. The VCU Investigational Pharmacy prepared metformin and matched placebo capsules randomized subjects with a computerized random number generator using a 1:1 allocation ratio with blocks of random size (3 and 4 subjects in a block), and concealed allocation. Medication adherence was assessed by interview and pill count.

Insulin sensitivity was determined by modified FSIVGTT as previously described (10,11). Data analysis was performed with Minimal Model Identification Software (MINIMOD,

version 6.02, Los Angeles, CA) (12), which yields quantitative determinations of insulin sensitivity (SI), acute insulin response to glucose (AIRg), disposition index (DI), and glucose effectiveness (Sg).

FMD was measured by B-mode ultrasound images of the brachial artery (ATL CV 500 Phillips Medical Systems, Andover, MA). Endothelial-dependent and independent vasodilatation were measured using standard methods (13, see Supplemental Data). The same trained investigator (P.A.E) and ultrasound technician conducted all the studies, and one cardiologist (J.A.A.), blinded to treatment assignment, evaluated all images. The intraclass correlation coefficient (ICC) between the pre- and posttreatment images was 0.99, (95% CI, 0.98–0.99).

Serum and plasma were stored at -70°C until assayed. Determinations were made in duplicate. Serum glucose was measured by glucose oxidative method; serum insulin and steroids by radioimmunoassay and hsCRP by ELISA immunoassay (ALPCO, Salem, NH); total PAI-1, sVCAM, sICAM, and adiponectin by Human CVD Panel 1 Lincoplex kit (Linco Research, St. Charles, MI); and IL-6 and MCP-1 by ELISA Quantikine kit (R and D Systems, Minneapolis, MN). The inter- and intra-assay CV $<10\%$ for all assays.

The primary endpoint was change in insulin sensitivity. Sample size calculations were based on a 3-month study that reported a three-fold improvement in insulin sensitivity with metformin therapy (14). Power analysis revealed that 22 subjects were needed to detect a significant difference in insulin sensitivity, assuming an estimated SD of 0.85, power of 90%, and alpha level of 0.05.

Data are presented as mean $\pm$ SE. Baseline comparison between groups was performed using t-tests. Change at 3 months from baseline within and between groups was analyzed using two-way repeated measures ANOVA or analysis of covariance if there was significant baseline difference between groups. Non-parametric or logarithmic transformation was used when appropriate. Post-hoc comparisons of individual pairs included t-tests with Bonferroni correction. Statistical analysis was performed using JMP 9.0 (SAS Institute Inc., Cary, NC). P values <0.05 were considered statistically significant.

Of 98 subjects screened, 23 were randomized to OC and placebo (OC group) or metformin and OC (Met-OC group). Two subjects were lost to follow-up due to loss of interest (one from each group), one from moving (Met-OC), and one from heavy menstrual bleeding (OC). Of the remaining 19 subjects, 10 were randomized to OC and 9 to Met-OC. In total, 26% of the women were overweight and 74% were obese, evenly distributed by group. Six women (31.6%) had glucose intolerance, with 3 in the combination metformin-OC group and 3 in the OC monotherapy group. No subjects experienced serious adverse effects.

Most baseline parameters did not differ between the groups (Table 1 and Supplemental Table 1). The Met-OC group had somewhat higher blood pressure compared to the OC group. Likewise, the OC group had slightly higher mean triglyceride and LDL-C levels than the Met-OC group. There were no differences in baseline FMD.

After 3 months, the Met-OC group showed a 1.9 % decrease in BMI ($p=0.006$) (Supplemental Table 1). Change in waist circumference and waist-to-hip ratio did not differ within or between groups. In contrast to the Met-OC group, the OC group increased total cholesterol by 7.3% after 3 months ($p=0.03$). Both groups increased mean triglyceride levels. Only the Met-OC group showed a significant decrease in free testosterone ($p=0.01$) and a significant increase in SHBG ($p=0.001$). Total testosterone, androstenedione, and estradiol did not change in either group. ISI, SI, AIRg, DI, and Sg did not differ between groups. FMD increased by 69.0% in the Met-OC group after 3 months ($p=0.004$) but did not change in the OC group ($p=0.45$) (Table 1), with a significant difference between groups ($p=0.01$).

In summary, we demonstrated that after 3-months: 1) Met-OC, but not OC, reduces BMI and free testosterone, 2) Met-OC and OC affect insulin sensitivity, lipid profile, and serum inflammatory markers similarly, and 3) Met-OC is superior to OC monotherapy in improving endothelial function.

We found no change in weight with OC monotherapy, consistent with other studies (15). Although Elter et al. (16) described a decrease in BMI with combination Met-OC after 3 months, other studies reported no changes after 4–6 months (17,18). Indeed, the literature has been inconsistent on the effects of metformin on weight in PCOS (19) likely due to varying doses, tolerability, and duration. Only women in the Met-OC group had a significant reduction in free testosterone and increase in SHBG, consistent with another study (16).

Neither Met-OC nor OC monotherapy significantly changed insulin sensitivity after 3 months, similar to studies of Met-OC therapy in obese and nonobese PCOS women assessed by glucose to insulin ratio (17) and in obese PCOS women measured by AUC insulin (8). A possible explanation for the lack of Met-OC on lipid profile and inflammatory markers in the present study is that the OC mitigated some effects of metformin. Perhaps a higher dose or longer duration of metformin was needed with Met-OC to fully observe its effects on these parameters.

Met-OC therapy, but not OC monotherapy, significantly improved endothelial function. Two of three published studies (20–22) reported that OCs impair endothelial function. One study (21) found that healthy women on OCs had significantly lower endothelial function compared with women who had not used OCs for at least 12 months. It is unknown, however, if OCs containing lower ethinyl estradiol doses or varying progestins may have had alternate metabolic effects. Unlike OCs, metformin has been reported to improve endothelial function as measured by FMD (23–27) although the mechanism remains unclear.

There are limitations to this study. Despite intensive recruitment effort, the study was underpowered for the primary outcome. The study duration was relatively brief, the groups were not tightly controlled in regards to diet and physical activity, and the administration of metformin was not maximized to reduce risk of gastrointestinal side effects. Furthermore, some baseline differences were observed despite randomization. However, statistical analysis did take these baseline differences into account.

In summary, we report that combination Met-OC may be of benefit in overweight women with PCOS because it improves vascular endothelial function to a greater extent than OC alone. This finding has significant clinical implications for the long-term pharmacological management of women with PCOS. Larger studies of longer duration as well as studies using OCs of 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Changes in Insulin Sensitivity, Cardiovascular Risk Markers, and Flow-Mediated Dilatation After 3 months (n=19)

Table 1

Parameter	OC (n=10)				P	Baseline	Met-OC (n=9)			OC vs. Met-OC P
	Baseline	Month 3	Change vs. Baseline	Month 3			Change vs. Baseline	P		
Fasting glucose (mmol/l)	4.9 ± 0.11	4.9 ± 0.18	-0.03 ± 0.15	0.64	5.0 ± 0.12	5.2 ± 0.19	0.21 ± 0.15	0.16	0.22	
Fasting insulin (pmol/l)	68.7 ± 15.2	66.0 ± 17.1	-2.6 ± 20.3	0.10	68.2 ± 16.0	77.3 ± 18.1	9.1 ± 21.4	0.58	0.12	
AUC glucose (mg·min·dl ⁻¹)	14842.1 ± 2707.6	26,338.3 ± 6478.5	11,496.3 ± 6185.1	0.20	13924.0 ± 2698.4	15,851.8 ± 6828.9	1927.7 ± 6519.6	0.21	0.30	
AUC insulin (μU·min·ml ⁻¹)	9987.4 ± 5327.6	8268.5 ± 1255.2	-1719.0 ± 1378.8	0.26	7828.8 ± 3918.8	7517.2 ± 1323.1	-311.5 ± 1453.4	0.83	0.49	
ISI	4.7 ± 1.6	4.4 ± 0.96	-0.3±1.1	0.63	7.3 ± 1.7	5.9 ± 1.0	-1.4 ± 1.2	0.42	0.50	
AIRg (μU·L ⁻¹ ·min)	997.0 ± 173.7	947.7 ± 192.8	-49.3 ± 73.1	0.52	610 ± 179.5	730 ± 192.3	119.9 ± 21.7	0.001^a	0.89	
DI (AIRg·SI)	1914.4 ± 390.6	1881 ± 509.3	-33.7 ± 618.6	0.96	1459.9 ± 196.6	1186 ± 213.6	-274.2 ± 187.6	0.18	0.84	
SI (min ⁻¹ /μU/L)	2.26 ± 0.48	2.8 ± 0.87	0.544 ± 0.79	0.51	3.83 ± 0.78	2.11 ± 0.44	-1.72 ± 0.61	0.03	0.48	
Sg (min ⁻¹)	0.02 ± 0.003	0.02 ± 0.005	-0.01 ± 0.005	0.85	0.02 ± 0.004	0.01 ± 0.002	-0.006 ± 0.004	0.19	0.94	
hsCRP (mg/l)	4.9 ± 1.4	5.6 ± 2.1	0.70 ± 1.9	0.28	3.5 ± 1.5	8.9 ± 2.3	5.4 ± 2.0	0.02^a	0.11	
sVCAM (ng/ml)	1202.4 ± 66.7	1179.4 ± 75.2	-23.0 ± 57.0	0.73	1169.6 ± 70.3	1111.8 ± 79.3	-57.8 ± 60.1	0.28	0.68	
sICAM (ng/ml)	246.6 ± 16.6	232.0 ± 15.3	-14.7 ± 9.3	0.13	196.2 ± 17.5	185.8 ± 16.1	-10.4 ± 9.8	0.34	0.75	
Adiponectin (μg/ml)	6.96 ± 1.78	7.81 ± 1.85	0.86 ± 0.60	0.04^a	10.56 ± 1.88	11.70 ± 1.95	1.13 ± 0.63	0.09	0.76	
PAI-1 (ng/ml)	81.2 ± 8.9	76.5 ± 7.9	-4.7 ± 6.8	0.52	74.7 ± 9.4	68.3 ± 8.3	-6.4 ± 7.1	0.38	0.87	
IL-6 (pg/ml)	2.1 ± 0.95	1.6 ± 0.59	-0.48 ± 0.48	0.06	2.2 ± 1.63	1.7 ± 0.57	-0.52 ± 1.61	0.69	0.81	
MCP-1 (pg/ml)	116.6 ± 47.3	118.5 ± 59.8	1.9 ± 33.5	0.79	141.7 ± 58.9	123.1 ± 44.8	-18.6 ± 37.1	0.15	0.36	
FMD (%)	5.9 ± 1.3	6.5 ± 1.1	0.56 ± 0.83	0.45	5.8 ± 1.3	9.8 ± 1.1	4.0 ± 0.88	0.004^a	0.01^a	
NMD (%)	14.0 ± .090	13.8 ± 1.2	-0.20 ± 1.6	0.81	15.9 ± 0.94	14.1 ± 1.3	-1.8 ± 1.7	0.46	0.51	

ISI = insulin sensitivity index, AIRg = acute insulin response to glucose, DI = disposition index, SI = insulin sensitivity, Sg = glucose effectiveness, FMD = flow-mediated dilatation, and NMD = nitroglycerin-mediated dilatation

To convert from mmol/l to mg/dl, divide by 0.0259 for total cholesterol, LDL-C, and HDL-C, by 0.0113 for triglycerides, and by 0.0555 for glucose. To convert insulin from pmol/l to μU/ml, divide by 6.945. To convert from nmol/l to ng/dl, divide by 0.0347 for total testosterone and by 0.0349 for androstenedione. To convert from nmol/l to pg/ml, divide by 3.47 for free testosterone and by 3.671 for estradiol.

^ap < .05