Effects of Medical Therapy on Insulin Resistance and the Cardiovascular System in Polycystic Ovary Syndrome

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OBJECTIVE — We aimed to determine the impact of medical therapy for symptom management on insulin resistance, metabolic profiles, and surrogate markers of cardiovascular disease in polycystic ovary syndrome (PCOS), an insulin-resistant pre-diabetes condition.

RESEARCH DESIGN AND METHODS — One hundred overweight women (BMI >27 kg/m^2), average age 31 years, who were nonsmokers, were not pregnant, did not have diabetes, and were off relevant medications for 3 months completed this 6-month open-label controlled trial. Randomization was to a control group (higher-dose oral contraceptive [OCP] 35 μg ethinyl estradiol [EE]/2 mg cyproterone acetate, metformin [1 g b.d.] or low-dose OCP [20 μg EE/100 μg levonorgestrel + aldactone 50 mg b.d.]). Primary outcome measures were insulin resistance (area under curve on oral glucose tolerance test) and surrogate markers of cardiovascular disease including arterial stiffness (pulse wave velocity [PWV]) and endothelial function.

RESULTS — All treatments similarly and significantly improved symptoms including hirsutism and menstrual cycle length. Insulin resistance was improved by metformin and worsened by the high-dose OCP. Arterial stiffness worsened in the higher-dose OCP group (PWV 7.46 vs. 8.03 m/s, $P < 0.05$), related primarily to the increased insulin resistance.

CONCLUSIONS — In overweight women with PCOS, metformin and low- and high-dose OCP preparations have similar efficacy but differential effects on insulin resistance and arterial function. These findings suggest that a low-dose OCP preparation may be preferable if contraception is needed and that metformin should be considered for symptomatic management, particularly in women with additional metabolic and cardiovascular risk factors.

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It is well recognized that polycystic ovary syndrome (PCOS) has both reproductive and metabolic features. Insulin resistance (IR), the primary underlying abnormality, affects the majority of women with PCOS (1,2). In general populations, IR independently predicts cardiovascular risk (3,4), underlies the metabolic syndrome, and increases the risk of type 2 diabetes (1,2). Type 2 diabetes also potently increases cardiovascular risk, especially in women. Furthermore, treating IR improves the metabolic profile, reduces progression to type 2 diabetes, and decreases cardiovascular risk in general populations. In PCOS, IR is increased, cardiovascular risk factors are elevated, type 2 diabetes risk is increased four- to sevenfold, and the risk of cardiovascular disease is also likely to be increased (2,5). We postulate that IR per se is an important target in the treatment of this condition, especially when considering long-term health implications in PCOS.

Lifestyle modification is first-line therapy for IR in PCOS, and a loss of 5–10% of body weight improves IR and increases ovulation (6,7). As long-term weight loss is not feasible or sustainable in the majority (8), additional medical therapy is usually required. The oral contraceptive (OCP) is first-line medical therapy in PCOS, when fertility is not desired, in regulating cycles and controlling hyperandrogenism. Yet, in both PCOS and non-PCOS populations, the OCP increases IR, albeit inconsistently (1,9–12). The increased IR appears to be estrogen dose related (13,14). The metabolic effects of OCP preparations have not been adequately studied in PCOS, and optimal preparations and doses remain unclear.

Alternatively, medical therapy can directly target IR in PCOS. Glitazones are considered inappropriate in reproductive-age women until concerns over teratogenicity are clarified (1). Metformin, supported by a Cochrane review (15), has a legitimate adjuvant role with lifestyle for those with PCOS seeking fertility. The role of metformin in targeting symptoms in PCOS (cycle irregularity or hirsutism) remains controversial (2,16).

This randomized, controlled, 6-month study examined the comparative clinical efficacy and metabolic and cardiovascular effects of differential doses of OCPs and metformin, in addition to lifestyle, in overweight women with PCOS. The control group received high-dose OCP (35 μg ethinyl estradiol [EE]/2 mg cyproterone acetate) as the most commonly prescribed OCP in PCOS in Australia. Comparator groups received either metformin (1 g b.d.) or a low-estrogen dose OCP (20 μg EE/100 μg levonorgestrel) combined with an anti-androgen (spironolactone 50 mg b.d.), as no OCP contained variable-dose estrogen and identical progestins. The primary end point was IR based on area under the curve (AUC) insulin with an oral glucose tolerance test (OGTT), previously vali-

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Abbreviations: AUC, area under the curve; DHEAS, dehydroepiandrosterone; EE, ethinyl estradiol; FAI, free androgen index; FMD, flow-mediated vasodilation; HOMA, homeostasis model assessment; IR, insulin resistance; OCP, oral contraceptive; OGTT, oral glucose tolerance test; PCOS, polycystic ovary syndrome; PWV, pulse wave velocity; SHBG, sex hormone–binding globulin; WHR, waist-to-hip ratio.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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dated in this population. The euglycemic clamp, although considered the gold standard, has poor reproducibility and is impractical for larger trials. Secondary end points were arterial functional markers including pulse wave velocity (PWV), an index of arterial stiffness, and brachial arterial flow-mediated vasodilation (FMD), an index of endothelial function. These markers correlate with cardiovascular risk factors, predict cardiovascular events, and are impaired in women with PCOS (1,2,5).

RESEARCH DESIGN AND METHODS

— Overweight women (BMI >27 kg/m^2) with PCOS were recruited from community advertisements, and 110 women were studied between 2003 and 2005. PCOS diagnosis was based on perimenarchal onset of irregular cycles (<21 days or >35 days) and clinical manifestations of hyperandrogenism (hirsutism or acne) or biochemical hyperandrogenism with elevation of at least one circulating ovarian androgen (according to 1990 National Institutes of Health criteria [1]). Secondary causes of amenorrhea and hyperandrogenism were excluded with clinical screening and early follicular 17-hydroxyprogesterone levels. Diabetes was excluded on OGTTs (according to World Health Organization criteria [available at http://www.staff.ncl.ac.uk/philip.home/who_dmg.pdf]). Pregnancy tests were negative before enrollment. The Southern Health Research Advisory and Ethics Committee approved the study, and all participants gave written informed consent.

If potentially eligible after telephone screening (by C.M.), after an overnight fast participants underwent detailed medical evaluation at the Monash University Vascular Medicine Department at Dandenong Hospital (by C.M.)

At screening, standard diet and lifestyle advice was delivered according to National Heart Foundation of Australia recommendations (www.heartfoundation.com.au), and medications affecting IR, including all OCPs, were ceased 3 months before randomization.

At randomization, 110 subjects were allocated to one of three groups based on computer-generated random numbers: *1*) metformin 1 g b.d. with dose titrated up over 4 weeks starting at 500 mg b.d., *2*) high-dose OCP (35 μg EE/2 mg cyproterone acetate), or *3*) low-dose OCP (20 μg EE/100 μg levonorgestrel) combined with an anti-androgen (spironolactone 50 mg b.d.). This was an open-label study. The high-dose OCP was selected as a commonly prescribed OCP in PCOS in both Australia and Europe. The lowest available EE-dose OCP (20 μg) was selected, with the limitation that it is unavailable with identical anti-androgenic progestins. The 30 μg EE + drospirenone preparation was not used, with a 25% deterioration in glucose tolerance already documented in non-PCOS populations (17). Spironolactone use reflected clinical practice to increase anti-androgenic efficacy.

Participants were reviewed by the same investigator (C.M.) at screenings conducted at baseline and 3 and 6 months after commencing medications. End point data collection was completed by the research nurse, who was blinded to treatment allocation. Prospective menstrual dairies and hirsutism scores (Ferriman-Gallwey score >7 indicates hirsutism) were collected at each visit (18). BMI was calculated and waist and hip circumferences measured at the umbilicus and greater trochanter, respectively. The waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Fasting blood samples were taken for endocrine and metabolic variables, an OGTT was performed, and PWV and FMD were measured at randomization and 6 months.

IR measures

IR was measured by homeostasis model assesment (HOMA) and a 75-g OGTT (glucose and insulin at 0, 30, 60, and 120 min). The HOMA score was calculated as fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (19). AUC glucose and insulin were calculated using the trapezoidal rule.

Noninvasive arterial parameters

Arterial parameters were measured after a 12-h caffeine-free fast by an experienced research assistant in a dark, quiet laboratory following supine rest. Published internal repeatability data (20) demonstrate the accuracy and repeatability of these parameters.

Arterial stiffness

PWV was determined from recorded pressure waveforms over the aortofemoral arterial segments (20). Pulse transit time was defined as the time between the foot of simultaneously recorded pressure waves, occurring at the end of diastole and the beginning of systole, averaged over 10 cardiac cycles. Velocity was derived from computer-generated pulse transit times and measured distances between the two recording sites, as previously described. PWV was calculated as follows: PWV = $D/\Delta t$ (m/s), where D = distance and Δt = time interval.

Endothelial function

Brachial artery diameter was measured from B-mode ultrasound images captured on a Diasonics DRF-400 machine (Diasonics, Milpitas, CA) using a 10-MHz transducer, while an electrocardiogram trace was simultaneously recorded. Longitudinal scanning identified the brachial artery above the elbow with continuous scanning for 30 s prior and 4 min after ischemia, induced via a pneumatic tourniquet inflated around the upper arm to 40 mmHg above systolic pressure for 4 min. Vessel diameter was measured during systole and diastole and averaged over five cardiac cycles. FMD was determined as the percentage of change from baseline to 60 s postischemia, the point of maximal dilation (20).

Assays

Dehydroepiandrosterone (DHEAS) and sex hormone–binding globulin (SHBG) were analyzed by immunoassay using an Immulite 1000 (EURO/DPC, Gwynedd, U.K.). The internal intra- and interassay coefficients of variation (CVs) were 7.6 and 8.1%, respectively, for DHEAS and 4.1 and 5.8%, respectively, for SHBG. Testosterone was analyzed using a chemiluminescent immunoassay (Beckman Coulter, Fullerton, CA). The intra- and interassay CVs were 1.7 and 4.8%, respectively. The free androgen index (FAI) was calculated from FAI = (testosterone/SHBG) × 100.

Total cholesterol (CV 1.5–3.1%) and triglycerides (CV 2.3–5.3%) were measured using enzymatic reagents (DADE Diagnostics, Brisbane, Australia). HDL cholesterol (CV 2.5–2.8%) was measured by homogeneous assay techniques (HDLC-Plus; DADE Diagnostics) adapted to a DADE Dimension RXL chemistry analyzer. LDL cholesterol was calculated using the Friedewald equation [LDL cholesterol = (total cholesterol − HDL cholesterol) − (triglycerides/2.2)], adapted to S.I. units. The insulin assay used was the AxSYM assay based on the microparticle enzyme immunoassay technology. The sensitivity of the assay was 1.0 μU insulin/ml, the cross-reactivity with proinsulin was 0.016%, and there

Table 1—*Clinical symptoms, hormonal parameters, measures of insulin resistance, lipid profiles, and arterial function over 6 months*

	Group 1: metformin (n = 36)			Group 2: high-dose OCP (n = 31)			Group 3: low-dose OCP/spironolactone (n = 33)		
	Baseline	6 months	Mean change (95% CI)	Baseline	6 months	Mean change (95% CI)	Baseline	6 months	Mean change (95% CI)
Systolic blood pressure (mmHg)	121	118	−2.6 (−5.1 to 10.3)	114	122	6.9 (−2.6 to 16.3)	115	112	−2.9 (−4.5 to 10.3)
BMI (kg/m^2)	36.3	35.9	−0.5 (−2.4 to 4.0)	36.5	36.8	0.3 (−0.9 to 0.3)	35.5	35.2	−0.3 (−0.4 to 0.9)
WHR	0.87	0.89	0.18 (−0.03 to 0.01)	0.84	0.85	0.01 (−0.03 to 0.01)	0.86	0.88	0.02 (−0.01 to 0.04)
Symptoms/androgens									
Menstrual cycle (days)	112	65*	−47.1 (−1.5 to −93)	75	32*	−44 (−18 to −69)	101	39*	−61.8 (−27.3 to −96)
Ferriman-Gallwey	8.80	6.1*	−2.7 (−1.5 to −3.9)	6.7	4.6*	−2.0 (−0.9 to −3.2)	6.4	4.3*	−2.0 (−0.7 to −3.4)
Testosterone (nmol/l)	2.50	2.38	−0.2 (−0.3 to 0.6)	2.10	1.65*	−0.47 (−0.1 to −0.8)	2.76	2.00*	−0.7 (−0.4 to −1.2)
DHEAS (μmol/l)	5.49	5.10	−0.37 (−1.0 to 0.2)†	4.89	3.53*	−1.4 (−0.7 to −2.1)	4.29	3.62*	−0.7 (−0.2 to −1.1)
SHBG (nmol/l)	30.1	37.4	7.4 (−4.6 to 19.4)†	33.9	148*	115 (143 to 87)‡	33.5	78.5*	44.7 (60 to 29)§
FAI	10.3	8.2	−2.1 (−3.1 to 3.2)†	8.3	1.5*	−6.8 (−9.4 to −4.2)‡	9.8	3.5*	−6.3 (−8.1 to −4.4)
IR									
Fasting insulin (units/l)	20.4	14.5	−6.0 (−12.6 to 0.4)	20.2	21.5	1.15 (−4.2 to 6.5)	18.3	16.6	−1.67 (−2.3 to 5.6)
HOMA	4.42	3.29*	−1.13 (−0.6 to −2.8)	4.10	4.16	0.10 (−1.3 to 1.1)	3.70	3.58	−0.22 (−1.14 to 0.7)
AUC insulin	11,909	7,878*	−4,030 (−1,489 to −6,571)†	8,950	1,1195*	2,246 (931 to 3,561)‡	10,806	10,779	−34 (−1,942 to 2,011)
Lipid profiles (mmol/l)									
Total cholesterol	5.28	5.12	−0.17 (−0.4 to 0.1)	5.10	4.99	−0.12 (−0.2 to 0.4)	5.07	5.27	0.19 (−0.1 to 0.5)
HDL cholesterol	1.24	1.14*	−0.1 (−0.03 to −0.2)†	1.36	1.46	0.10 (−0.1 to 0.20)	1.22	1.22	0.01 (−0.1 to 0.1)
LDL cholesterol	3.37	3.33	−0.04 (−0.2 to 0.3)	3.18	2.78*	−0.40 (−0.1 to −0.7)	3.21	3.28	0.06 (−0.3 to 0.2)§
Triglycerides	1.52	1.58	0.06 (−0.4 to 0.23)	1.25	1.66*	0.4 (0.1 to 0.7)	1.45	1.57	0.13 (−0.1 to 0.3)
Arterial markers									
Central PWV (m/s)	7.47	7.46	−0.01 (−0.2 to 0.2)†	7.46	8.03*	0.56 (0.1 to 1.0)	7.13	7.31	0.18 (−0.1 to 0.4)
FMD (% of change)	10.84	12.58	1.66 (−0.4 to 3.7)	11.65	11.08	−0.57 (−1.7 to 2.9)	12.78	12.44	−0.34 (−1.2 to 1.8)

Mean change = change from baseline to 6 months ±95% CI. Within-group change, *$P < 0.05$, comparing 0 and 6 months. Between groups, $P < 0.05$. †Comparison between groups 1 and 2, ‡comparison between groups 1 and 3, §comparison between group 2 and 3.

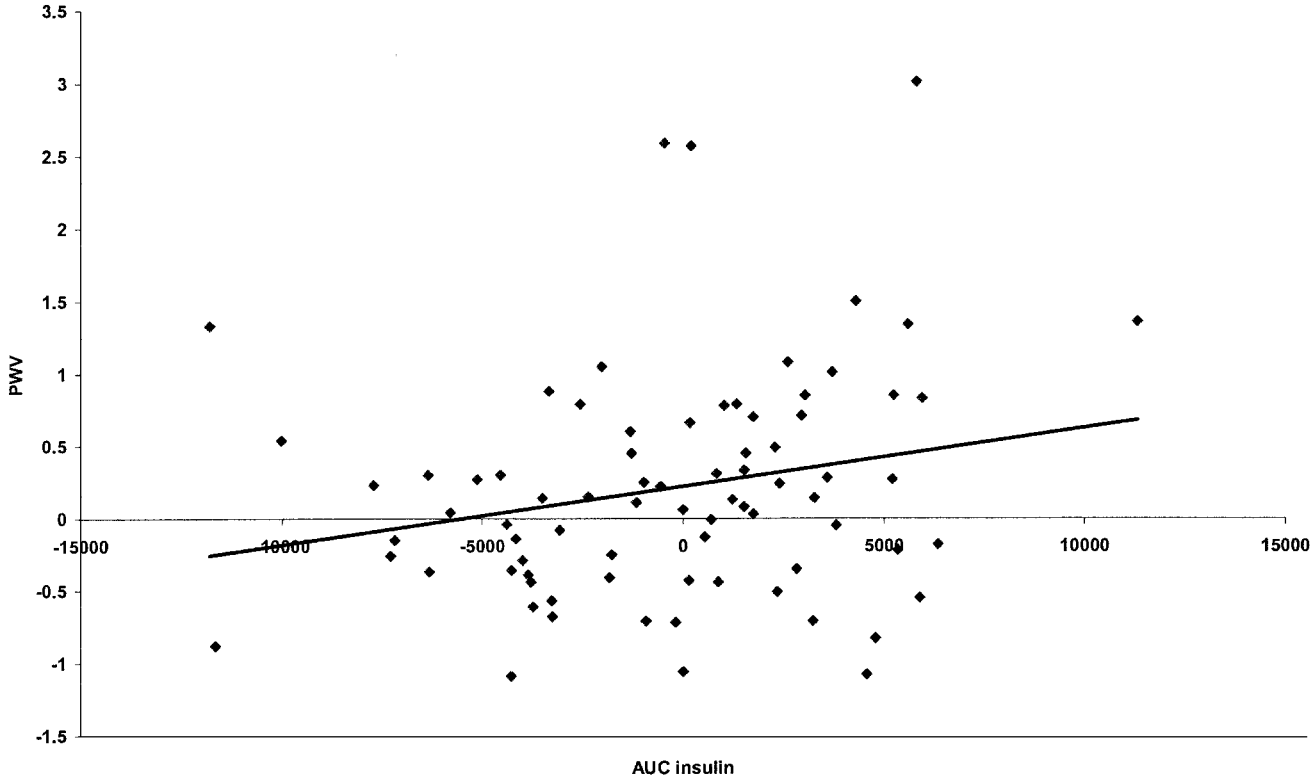

Figure 1—*Relationship between change in PWV and AUC insulin.*

was no cross-reactivity with C-peptide. Plasma glucose was determined with the glucose oxidase method.

Statistics

Power calculations were performed based on the sensitivity of the insulin assay and the degree of change in IR detected in similar studies (12). We used the interactive program nQueryAdvisor version 5 (Statistical Solutions, Boston, MA). Based on AUC insulin from an OGTT, for a 10% change in insulin sensitivity with 90% power, 25 subjects were required in each group for two-sided $P = 0.01$. We allowed for a drop-out rate of 20%, with 30 in each group.

Including 25 subjects in each group also powered the study for secondary end points, including a 20% difference in FMD and a 3–4% difference in PWV. No interim analysis was conducted. Analysis was performed on the 100 subjects who completed the trial. Baseline results are shown as means ± SE. One-way ANOVA was used to detect any differences between groups at baseline.

Within-group comparisons. Paired Student's *t* tests were used to compare changes from baseline to 6 months within groups with data presented as change in parameters (±95% CI).

Between-group comparisons. One-way ANOVA was used to examine the mean change between groups from baseline to 6 months for each parameter.

Simple linear regression analysis was performed to assess the underlying mechanisms of change in central PWV. Statistical significance was accepted at the level of $P < 0.05$, and statistical calculations were performed in association with a statistician using the SPSS statistical package, version 11 (SPSS, Chicago, IL).

RESULTS

— All 110 subjects who were eligible after screening completed the 3-month run-in, and 37 women were randomized to metformin, 35 to the higher-dose OCP, and 38 to the low-dose OCP/spironolactone. Ten women withdrew, of whom one was on metformin, four were on the higher-dose OCP, and five were on the low-dose OCP/spironolactone. Most withdrawals (8 of 10) were for personal reasons, while 1 woman withdrew from each OCP group because of mood swings. After the withdrawals, there were 36 subjects on metformin, 31 on the higher-dose OCP, and 33 on the low-dose OCP/spironolactone. Data analysis is based on the 100 women completing the study.

Clinical features

Following lifestyle change in the 3-month run-in, during the intervention period, dietary composition, quantity, daily activity, and exercise levels remained stable according to self-reporting on a National Heart Foundation questionnaire. Baseline clinical, anthropometric, and endocrine characteristics are listed in Table 1. Groups were well matched at baseline except for Ferriman-Gallwey score (8.8 ± 0.8 vs. 6.7 ± −0.7 vs. 6.4 ± 0.7, $P <$ 0.05) and testosterone levels (2.5 ± 0.1 vs. 2.1 ± 0.1 vs. 2.76 ± 0.2) in the metformin and high- and low-dose OCP groups, respectively.

Within groups, all three treatments significantly improved symptoms, with shorter menstrual cycle length and decreased hirsutism (Ferriman-Gallwey score) (Table 1). The three treatments had similar beneficial clinical effects on between-group analysis (Table 1, Fig. 1). BMI and WHR remained stable in all groups (Table 1).

Effects on sex steroids

Both OCP preparations reduced testosterone and DHEAS, whereas androgens did not change significantly with metformin (Table 1). SHBG increased in both OCP

groups, with concomitant reductions in FAI.

Effects on IR

IR improved with metformin, with a reduction in HOMA and a 34% reduction in AUC insulin (Table 1). In the higher-dose OCP group, the AUC insulin increased 25%, whereas there were no changes in IR with low-dose OCP/spironolactone (Table 1). Small changes in lipids were noted, primarily in the higher-dose OCP group (Table 1).

Effects on arterial function

Blood pressure was stable in all groups (Table 1). PWV increased by 7% in the higher-dose OCP group, with no significant change in FMD. Neither parameter changed in either of the other groups (Table 1). The change in PWV was significantly different between metformin-treated and higher-dose OCP groups (Table 1). In a linear regression model, deterioration in arterial stiffness was related to deterioration in IR (AUC insulin), with change in AUC insulin significantly predicting change in PWV ($r^2 = 0.05$, $P < 0.05$) (Fig. 2).

CONCLUSIONS — In women with PCOS, we have demonstrated that in addition to healthy lifestyle advice, metformin and the low-dose OCP/spironolactone have efficacy (regulating cycles and reducing hirsutism) similar to that of the high-dose OCP. Despite similar efficacy, differential metabolic effects were observed, with metformin reducing IR by 34% and the high-dose OCP increasing IR by 25%. The increased IR in the high-dose OCP group was associated with an increase in arterial stiffness (PWV), as a predictor of cardiovascular risk (21,22), supporting a reevaluation of current medical therapy in PCOS including consideration of metabolic effects.

The role of metformin in the symptomatic management of PCOS remains controversial (2). Symptomatic management includes cycle regulation for fertility and prevention of endometrial carcinoma (23). Consistent with previous studies in PCOS, metformin improved menstrual cyclicity in the current study. While the effect of metformin and the OCPs on cycle duration was not statistically different, cycles in the metformin group were longer in duration. Frequency was, however, more than four cycles per year, as per clinical recommendations for endometrial protection (2,15,24). Metformin significantly improved hirsutism in the current study, similar to both OCP groups, despite differential effects on androgen levels. One previous controlled study (2,25) reported the effects of metformin on hirsutism, demonstrating greater efficacy with metformin than with high-dose OCP. Potential mechanisms of action include improved IR and/or IGF-I activity, each of which are affected by metformin and involved in hair growth (25). These results, combined with extensive safety data over five decades in non-PCOS populations (2,26), suggest a legitimate role for metformin in the symptomatic management of women with PCOS.

While clinical efficacy of the interventions were similar, the effects on IR were significantly different, based on the more accurate measure of IR, AUC insulin. Metformin improved IR consistent with previous studies (2,12), whereas the higher-dose OCP increased IR, and low-dose OCP/spironolactone had no effect. This is the first direct comparison of commonly available contraceptive preparations focusing on IR in PCOS. Prior studies (1,2) noted increased IR with higher-dose EE preparations; however, results have been inconsistent. In non-PCOS subjects, higher doses of estrogen (50 μg) have reduced glucose clearance while lower doses (20 μg) have not (27). Current findings (10,12) significantly support prior small, largely uncontrolled, shorter-duration studies suggesting that high-dose OCPs increase IR in PCOS. IR should now be considered when selecting medical therapy in overweight women with PCOS.

The mechanisms by which OCPs affect IR are not clear. In the current trial, it was unrelated to changes in weight, as BMI and WHR remained stable in all groups. This is consistent with current literature on the effects of OCPs on BMI (12,28,29). The effects of metformin remain controversial, with reductions in BMI and WHR reported (12,30) while others report reductions in IR with no change in adiposity (2,31,32). Mechanisms may include differential effects on free fatty acid concentrations affecting both glucose disposal and IR (33).

IR has been associated with increased arterial stiffness in both diabetic and nondiabetic subjects (34,35). Our group has previously shown (5) that overweight women with PCOS have stiffer arteries associated with IR compared with weight-matched control subjects. A novel finding here was the further deterioration in PWV noted with the high-dose OCP that was unrelated to blood pressure and primarily related to a deterioration in IR (Fig. 2). The clinical relevance of the observed 7% increase in PWV is important to explore. PWV is predictive of cardiovascular mortality in population studies (22,36). In a renal failure population, a 1-m/s increase in PWV was associated with a 39% increase in mortality over 72 months (37), while in IR subjects, a 1-m/s increase in PWV was associated with an 8% increase in mortality (38). In general population studies (39) of healthy older subjects, increases in PWV are associated with increasing relative risk for all-cause and cardiovascular mortality with a threshold effect between the first and second quartile of PWV. Even among healthy younger subjects, increases in PWV of 1 SD predict a composite of cardiovascular outcomes above and beyond traditional cardiovascular risk factors (40). The increase in the current study was 0.56 m/s over 6 months in the high-dose OCP group and is likely to be clinically relevant.

Large observational studies have shown that, compared with weight-matched control subjects, women with PCOS have impaired endothelial function related to IR (5,41). Small, uncontrolled, interventional studies have demonstrated improvements in FMD after metformin and rosiglitazone (42,43). However, this larger controlled study suggests that improving IR with 6 months of metformin does not improve FMD. This may relate to inadequate repeatability inherent in FMD methodology (20), highlighting the need for research with other endothelial functional markers.

There are limitations of the current study. Although longer than most PCOS trials, long-term follow-up is still needed. Furthermore, the specific effects of the individual OCP components cannot be ascertained from this study. These preparations allowed clinically relevant comparisons of high- and low-dose EE OCPs in common use. Progestins differed by necessity because of the lack of variable EE doses with identical progestins. Studies on progestins and IR have yielded inconsistent results (44–46); yet, progestins are a critical component of the OCP, and differentiating between estrogenic and progestogenic effects does not alter the net effect of the OCP on IR. Likewise, the isolated effects of spironolactone on IR cannot be elucidated from the current study. One study has demonstrated no effect of hyperaldosteronism on insulin ac-

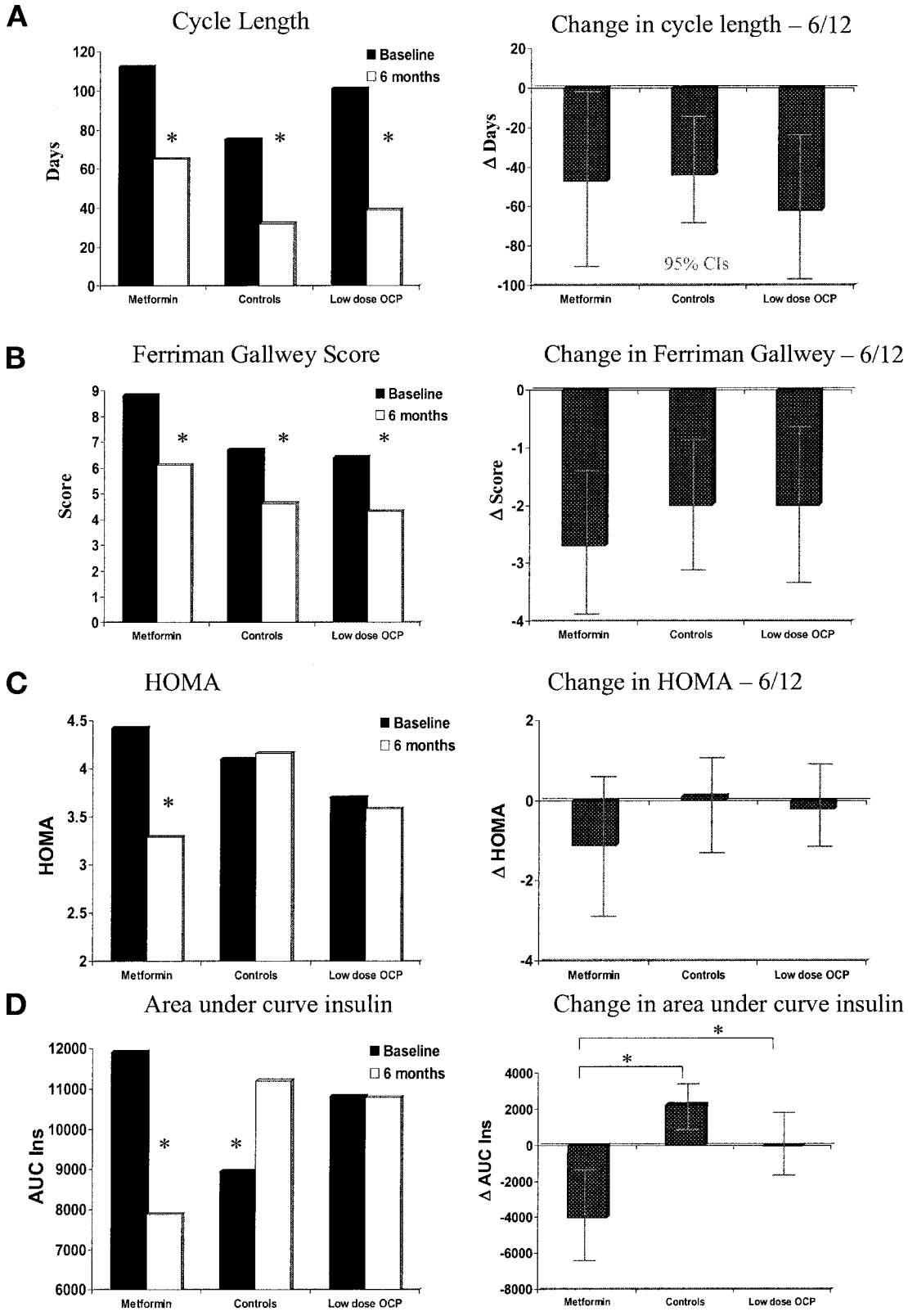

Figure 2—*Change in menstrual cycle length and hirsutism score (A and B) and HOMA of IR and AUC insulin (C and D) in the three treatment groups. Metformin significantly improved both measures of insulin resistance. The higher-dose OCP worsened the AUC insulin. All three treatments significantly improved hirsutism and mentrual cycle length. There was no significant difference between groups.* *$P < 0.05$.

tion (47), while another study in type 2 diabetes found that spironolactone had adverse endothelial effects potentially mediated through deterioration in glycemic control (48). This is an area that requires further research.

In this randomized, controlled, 6-month study in overweight women with IR and PCOS, we have demonstrated

similar clinical efficacy yet differential metabolic and cardiovascular effects of the OCP and metformin in addition to lifestyle advice. Metformin decreased IR, the low-dose OCP/spironolactone had a neutral effect, and the higher-dose OCP increased IR. In association with increased IR in the high-dose OCP group, we report a significant increase in arterial stiffness as a predictor of cardiovascular risk. While further long-term studies are required, this data supports a reevaluation of medical therapy in PCOS. A low-dose estrogen preparation may be preferable if contraception is required. Along with mounting evidence, this data suggests that targeting IR, through lifestyle modification combined with metformin, is a legitimate therapy in PCOS, improving symptoms and fertility and having metabolic advantages most relevant in those with IR and increased risk of type 2 diabetes.

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