Effects of metformin versus ethinyl-estradiol plus cyproterone acetate on ambulatory blood pressure monitoring and carotid intima media thickness in women with the polycystic ovary syndrome

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Objective: To compare the effects of metformin versus an antiandrogenic contraceptive pill on ambulatory blood pressure monitoring (ABPM) and carotid intima media thickness (CIMT) in women with polycystic ovary syndrome (PCOS).
Design: Clinical randomized trial.
Setting: Academic hospital.
Patient(s): Thirty-four consecutive PCOS patients.
Intervention(s): PCOS patients randomized to oral treatment with metformin (n = 19) or with Diane[35] Diario pill (n = 15) for 24 weeks.
Main Outcome Measure(s): ABPM recordings and ultrasound measurements of CIMT as marker of subclinical atherosclerosis obtained at baseline and after treatment.
Result(s): Metformin resulted in reductions in daytime and 24-hour average systolic and diastolic blood pressure whereas Diane[35] Diario induced a slight increase in these parameters. Compared with a nonhyperandrogenic control group, the increased CIMT values of PCOS patients decreased to the normal range after treatment with either metformin or Diane[35] Diario.
Conclusion(s): Metformin treatment decreased daytime ABPM recordings whereas Diane[35] Diario exerted the opposite effect. The safer blood pressure profile of metformin should be considered in PCOS patients who present with a history of hypertension or who are at risk for this disorder. Treatment with either Diane[35] Diario or metformin improved CIMT mean values. (Fertil Steril® 2009;91:2527–36. ©2009 by American Society for Reproductive Medicine.)

Key Words: Androgens, insulin resistance, hypertension, metformin, oral contraceptives, atherosclerosis

Polycystic ovary syndrome (PCOS) is associated with classic and nonclassic cardiovascular risk markers (1). Obesity and insulin resistance play a major role in the clustering of cardiovascular risk factors in the PCOS patient, including hypertension and abnormalities in the regulation of blood pressure (2); an increased prevalence of glucose intolerance (3), type 2 diabetes (3), and dyslipidemia (4); and an association with chronic low-grade inflammation (5). Androgen excess also contributes to the association of PCOS with cardiovascular risk factors, independent of insulin resistance and obesity. On the one hand, PCOS is characteristically associated with the loss of the physiologic nocturnal decrease in blood pressure in adults and adolescents (2, 6). On the other hand, hyperandrogenemia, not obesity or insulin resistance, is the major determinant of the increased carotid intima-media thickness (CIMT, an early marker of atherosclerosis) found in women with PCOS (7).

Lifestyle recommendations and diet in women with weight excess are essential for cardiovascular disease prevention in PCOS patients (8). But, aside from therapeutic strategies directed toward restoration of fertility, chronic pharmacologic treatment of PCOS is based on the use of two families of drugs: oral contraceptives containing a progestin of low androgenicity or even antiandrogenic properties, or insulin sensitizers. Because oral contraceptives might adversely influence insulin resistance and glucose tolerance in nonhyperandrogenic women, the possible worsening of the already unfavorable cardiovascular risk profile of PCOS patients by the administration of oral contraceptives has been raised by

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reputed investigators in the field (9), who advocate the use of the metabolically safer insulin-sensitizing drugs (10). However, this recommendation is not supported by scientifically convincing evidence (11).

We report the results of a randomized clinical trial on the effects on the ambulatory blood pressure monitoring (ABPM) recordings and CIMT of an antiandrogenic low-dose oral contraceptive pill compared with the insulin sensitizer metformin in PCOS patients.

MATERIALS AND METHODS

Our study was derived from a more ample randomized, controlled, open-label clinical trial that addressed the effects of treatment with an antiandrogenic oral contraceptive compared with the insulin sensitizer metformin on classic and nonclassic cardiovascular risk factors ClinicalTrials.gov Identifier NCT00428311). The precise description of the clinical trial as well as the results regarding the effects of these treatments on hyperandrogenism, insulin resistance, glucose tolerance, and the lipid profile were reported previously elsewhere (12).

In brief, 34 consecutive PCOS patients were recruited. The diagnosis of PCOS was based on the presence of clinical and/or biochemical hyperandrogenism, oligo-ovulation, and exclusion of secondary etiologies (13). The methods used to evaluate each particular criterion have been described in detail elsewhere (12).

None of the patients had a personal history of hypertension, diabetes mellitus, or cardiovascular events, or had received treatment with oral contraceptives, antiandrogens, insulin sensitizers, or drugs that might interfere with blood pressure regulation for the previous 6 months. Family history of hypertension or cardiovascular events in first-degree relatives was collected. Written informed consent was obtained from all the participants, and the study was approved by the local ethics committee and by the Spanish Agency of Medicines.

After giving informed consent, the 34 patients were randomized to receive an antiandrogenic oral contraceptive containing 35 μg of ethinyl-estradiol plus 2 mg of cyproterone acetate (Diane^{35} Diario; Schering España S.A., Madrid, Spain) or 850 mg of metformin (Dianben; Merck Farma y Química S.A., Mollet del Vallés, Spain) twice daily for 24 weeks. Simple randomization was conducted using blocks of 10 sealed opaque envelopes assigning five patients to receive Diane^{35} Diario and five patients to receive metformin. Randomization allocated 15 patients to Diane^{35} Diario and 19 patients to metformin.

Treatment was started the first day of a spontaneous menstrual cycle, or, in women with amenorrhea, after excluding pregnancy by proper testing. Patients were instructed to maintain a diet containing 25 to 30 kcal per kg of body weight per day and continue to perform moderate physical activity throughout the trial. Patients were given a complete evaluation at baseline and after 12 and 24 weeks of treatment that included anthropometric and laboratory measurements (12), and several tests of cardiovascular performance. The ABPM profiles and CIMT measurements were performed at baseline and at the end of the study.

Ambulatory Blood Pressure Monitoring

Twenty-four hour recordings were obtained in the 15 patients allocated to the Diane^{35} Diario group. Recordings were performed for 18 of the 19 patients allocated to the metformin group because the baseline recordings of one patient were erased by a malfunction of the A&D TM2430EX oscillometric device (A&D Company, Ltd., Tokyo, Japan). The cuff (12 $\times$ 22 cm for lean patients, and 14 $\times$ 30 cm for overweight or obese patients) was placed on the nondominant arm in every woman. The period from 07:00 to 23:00 was considered daytime, and from 23:00 until 07:00 the next day was considered nighttime, reflecting the usual sleeping habits of Spaniards. Systolic, diastolic, and mean blood pressure as well as heart rate were measured every 20 minutes during daytime and every 30 minutes during nighttime. The nocturnal decreases in systolic and diastolic blood pressure were calculated using this equation: [(Mean of diurnal blood pressure $-$ Mean of nocturnal blood pressure)/Mean of diurnal blood pressure] $\times$ 100. Nondippers were defined as those patients who did not show a reduction in mean systolic and diastolic blood pressures by $\geq$10% from day to night; the remaining patients were considered dippers. For ABPM, we used the normative data for women in the 25 to 44 years age range derived from the PAMELA study (14). Women presenting with average 24-hour systolic and/or diastolic blood pressure values at or above the 95th percentile of the reference population were considered hypertensive, but the presence of isolated daytime or nighttime hypertension (values at or above the 95th percentile only during these periods, but not during the 24-hour period) were also noted. Systolic and diastolic blood pressure loads were defined as the percentage of blood pressure determinations above or equal to a reference range of 140/90 mm Hg and 125/75 mm Hg for daytime and nighttime periods, respectively.

Carotid Intima-Media Thickness Measurements

In all the patients, carotid imaging was obtained as previously reported elsewhere (7) by the same trained operator (C.M-A.) using a high-resolution 7.5-MHz phased-array transducer (Imagepoint-Hx; Hewlett-Packard, Andover, MA), according to the method described by Pignoli et al. (15).

The intraobserver coefficient of variation was 10.8%. The normal CIMT range was defined by the mean $\pm$ 2 standard deviations (0.17–0.49) of the CIMT measurements of 20 nonhyperandrogenic women in the same age and body mass index range of the PCOS patients studied here (7).

Statistical Analysis

Data are shown as mean $\pm$ standard deviation and raw numbers (percentages) unless otherwise stated. The sample size analysis for the clinical trial indicated adequate 0.80 power to detect differences in surrogates indexes of insulin resistance (the primary outcome of the clinical trial) with a total