Influence of adrenal hyperandrogenism on the clinical and metabolic phenotype of women with polycystic ovary syndrome

Macarena Alpañés, M.D., Manuel Luque-Ramírez, M.D., Ph.D., M. Ángeles Martínez-García, Ph.D., Elena Fernández-Durán, B.S., Francisco Álvarez-Blasco, M.D., Ph.D., and Héctor Francisco Escobar-Morreale, M.D., Ph.D.

Diabetes, Obesity and Human Reproduction Research Group, Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Instituto Ramón y Cajal de Investigación Sanitaria IRYCIS, and Centro de Investigación Biomédica en Red Diabetes y Enfermedades Metabólicas Asociadas (CIBERDEM), Madrid, Spain

Objective: To study the impact of adrenal hyperandrogenism (AH; defined as DHEAS concentration >95th percentile of a healthy female control population) on cardiometabolic risk factors associated with polycystic ovary syndrome (PCOS).
Design: Cross-sectional study.
Setting: Academic hospital.
Patient(s): Two-hundred ninety-eight consecutive women with PCOS, of whom 120 were obese (body mass index [BMI] ≥ 30 kg/m^2) and 178 nonobese (BMI <30 kg/m^2).
Intervention(s): None.
Main Outcome Measure(s): Comprehensive evaluation of cardiovascular risk factors, including 75-g oral glucose tolerance test, office blood pressure, lipid profile, and low-grade inflammatory markers.
Result(s): Patients with AH (AH-PCOS) had higher insulin circulating levels and lower insulin sensitivity than their counterparts without AH (non-AH-PCOS). Obesity, but not AH, was the main contributor to the presence of glucose tolerance disorders. Both obesity and AH increased the prevalence of prehypertension and hypertension. AH diminished high-density lipoprotein (HDL) levels in nonobese PCOS women in parallel with a decrease in total cholesterol levels, leading to a total to HDL cholesterol ratio similar to that of nonobese non-AH-PCOS patients. Furthermore, AH blunted the deleterious effect of obesity on the total cholesterol/HDL ratio, with the ratio of obese AH-PCOS patients being similar to that of nonobese PCOS patients with or without AH.
Conclusion(s): The presence of AH in women with PCOS is associated with reduced insulin sensitivity and increased blood pressure but may have beneficial impact on the lipid profile. Obesity is the main determinant of the clustering of cardiovascular risk factors in PCOS women. (Fertil Steril® 2015;■:■–■. ©2015 by American Society for Reproductive Medicine.)
Key Words: Androgen excess, dehydroepiandrosterone sulfate, glucose tolerance, insulin sensitivity, insulin resistance, obesity

Discuss: You can discuss this article with its authors and with other ASRM members at http://fertstertforum.com/alpanesm-adrenal-hyperandrogenism-phenotype-pcos/

Use your smartphone to scan this QR code and connect to the discussion forum for this article now.*

* Download a free QR code scanner by searching for "QR scanner" in your smartphone's app store or app marketplace.

Received October 26, 2014; revised December 5, 2014; accepted December 9, 2014.
M.A. has nothing to disclose. M.L.-R. has nothing to disclose. M.A.M.-G. has nothing to disclose. E.F.-D. has nothing to disclose. F.A.-B. has nothing to disclose. H.F.E.-M. has nothing to disclose.
M.A. and M.L.-R. should be considered similar in author order.
Supported by grant PI1100357 from Instituto de Salud Carlos III, Spanish Ministry of Economy and Competitiveness. Centro de Investigación Biomédica en Red Diabetes y Enfermedades Metabólicas Asociadas is also an initiative of Instituto de Salud Carlos III. Supported in part by funds from Fondo Europeo de Desarrollo Regional (European Union).
Reprint requests: Héctor Francisco Escobar-Morreale, M.D., Ph.D., Department of Endocrinology and Nutrition, Hospital Universitario Ramón y Cajal, Carretera de Colmenar km 9, 1, E-28034 Madrid, Spain (E-mail: hectorfrancisco.escobar@salud.madrid.org).

Fertility and Sterility® Vol. ■, No. ■, ■ 2015 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2014.12.105

Hyperandrogenism is a key feature of polycystic ovary syndrome (PCOS) that may lead to hirsutism, ovulatory or menstrual dysfunction, and even polycystic ovarian morphology on ultrasound (1). Even though the ovaries are the main source of androgen excess in PCOS, the adrenal glands also contribute to androgen excess in these patients. The prevalence of adrenal hyperandrogenism (AH) reported in earlier studies of

patients with PCOS ranged from 20% to 65% (2–5) depending on the definition used (6) and the age (5), body mass index (BMI) (5, 7), and race (5) of the participants.

Hyperandrogenemia, mainly increased concentrations of total testosterone (T) and/or free testosterone (FT), has been linked to adverse metabolic outcomes in women with PCOS (8, 9) including obesity and abdominal adiposity (9, 10), an increased prevalence of abnormalities of glucose tolerance, the metabolic syndrome (11, 12), and increased epicardial fat thickness (13).

However, the possible influence of adrenal androgen excess on the unfavorable cardiovascular profile of women with PCOS is uncertain. Some authors have even postulated a protective effect of elevated levels of DHEA and its sulfated form, DHEAS, on insulin resistance (7, 14), abdominal obesity (15), hypercholesterolemia (16), and early cardiovascular disease (17), yet the reports are conflicting and a convincing explanation for these putative protective effects is lacking. This association may be spurious, derived from the fact that DHEAS concentrations are inversely correlated with age and that young people usually have fewer cardiovascular risk factors, but the possibility also exists that elevated insulin or glucose levels may inhibit the synthesis of DHEAS (7).

In the present study, we aimed to provide new insights into the possible impact of adrenal androgen excess on the clinical and metabolic phenotype of women with PCOS.

PATIENTS AND METHODS

Subjects

We recruited 298 consecutive premenopausal women with PCOS attending the Reproductive Endocrinology clinic of two of the authors (H.F.E-M. and M.L-R.) for this and other studies. Contemporarily with the recruitment of patients, we included 147 women to serve as control subjects, aiming to obtain a reference group that was similar to the PCOS group in terms of BMI and prevalence of obesity. Therefore, the control group included healthy female volunteers recruited from the hospital's staff and overweight or obese women seeking medical attention in our department. None of these control subjects had any signs or symptoms of hyperandrogenism or menstrual dysfunction, or had a history of infertility, ovariectomy, or hysterectomy (Supplemental Table 1, available online at www.fertstert.org). The same study protocol was applied to patients and control subjects.

Because ovarian ultrasound is not performed routinely in our clinic, we included only patients presenting with the classic definition of the PCOS. Therefore, all patients included here had clinical and/or biochemical hyperandrogenism together with ovulatory dysfunction, regardless of the ultrasound appearance of the ovaries (18). Secondary causes of hirsutism or oligomenorrhea, such as hyperprolactinemia, congenital adrenal hyperplasia, Cushing syndrome, or androgen-secreting tumors, were excluded by means of either clinical exam or appropriate laboratory testing. We classified the subjects according to their BMI into obese (BMI $\geq$30 kg/m^2; n = 120) and nonobese (BMI $<$30 kg/m^2; n = 178) subgroups.

Because DHEAS is considered to be the main circulating adrenal androgen in humans (19), we defined AH by the presence of elevated DHEAS concentrations, using as cutoff value the 95th percentile (9.1 nmol/L) of the 147 healthy control women.

Before enrollment, none of the women included here had earlier diagnosis of hypertension, diabetes, or cardiovascular events, or had received treatment with oral contraceptives or antiandrogenic, antidiabetic, or antihypertensive drugs during the 6 preceding months.

All patients and control subjects provided informed consents allowing us to include their data in a database for research purposes, and the local Ethics Committee approved the study.

Study Protocol

We performed a comprehensive clinical history and physical evaluation that included BMI, waist circumference, and waist-to-hip ratio (WHR) in all 298 subjects. Office blood pressure (BP) was determined as the mean of two manual sphygmomanometer readings in the sitting position by trained operators (20). To define prehypertension and hypertension, we considered the normative data derived from the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure for office BP (20).

We obtained blood samples after an overnight fast during the follicular phase of a spontaneous or a progestin-induced cycle or at random in amenorrheic patients. Serum T and E_2, SHBG, cortisol (F), 11-deoxycortisol (S), 17-hydroxyprogesterone (17OH-P), Δ^4-androstenedione (Δ^4-A), DHEAS, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides (TG), and high-sensitivity C-reactive protein (hsCRP) concentrations were assessed. The FT concentrations were calculated from T and SHBG concentrations (21).

Then a standard 75-g oral glucose tolerance test (oGTT) was performed and samples were obtained at 0, 30, 60, 90, and 120 minutes to determine serum insulin and plasma glucose. The composite insulin sensitivity index (ISI) was determined from glucose and insulin levels during the oGTT (22). The areas under the curve (AUCs) of glucose and insulin during the oGTT were determined according to the trapezoidal rule. The disorders of glucose tolerance were defined by the clinical recommendations of the American Diabetes Association (23).

Right after performing the oGTT test, we injected a 250 μg intravenous bolus of 1–24 ACTH (Synacthen; Novartis) and blood samples were obtained after 30 minutes for measurement of F, S, 17OH-P and Δ^4-A. We calculated the Δ^4-A/F ratio, where an increment suggests a relative shift of adrenal steroidogenesis toward the synthesis of Δ^4-A instead of the normal pathway favoring F synthesis.

Samples were immediately centrifuged, and serum and plasma were separated and frozen at −30°C until assayed.