Metabolic Profile in Sons of Women with Polycystic Ovary Syndrome

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Context: Polycystic ovary syndrome (PCOS) is a common endocrine-metabolic disorder with strong familial aggregation. It has been demonstrated that parents and brothers of PCOS women exhibit insulin resistance and related metabolic defects. However, metabolic phenotypes in sons of PCOS women have not been described.

Objective: Our objective was to assess the metabolic profiles in sons of women with PCOS during different stages of life: early infancy, childhood, and adulthood.

Design: Eighty sons of women with PCOS ($PCOS_S$) and 56 sons of control women without hyperandrogenism (C_S), matched for age, were studied. In early infancy, glucose and insulin were determined in the basal sample. In children and adults, a 2-h oral glucose tolerance test was performed with measurements of glucose and insulin. Adiponectin, leptin, C-reactive protein, SHBG, and serum lipids were determined in the basal sample during the three periods.

Results: During early infancy, $PCOS_S$ showed higher weight ($P = 0.038$) and weight SD score ($P = 0.031$) than C_S. During childhood, weight ($P = 0.003$), body mass index (BMI) ($P < 0.001$), BMI SD score ($P < 0.001$), waist circumference ($P = 0.001$), total cholesterol ($P = 0.007$), and low-density lipoprotein cholesterol ($P = 0.022$) were higher in $PCOS_S$ compared with C_S, but after adjusting for BMI, these differences were nonsignificant. During adulthood, $PCOS_S$ exhibited higher weight ($P = 0.022$), BMI ($P = 0.046$), and waist circumference ($P = 0.028$) than C_S. Fasting insulin ($P = 0.030$), homeostasis model assessment for insulin resistance ($P = 0.034$), total cholesterol ($P = 0.043$), low-density lipoprotein cholesterol ($P = 0.034$), and 2-h insulin ($P = 0.006$) were also significantly higher and insulin sensitivity index composite significantly lower in $PCOS_S$ than in C_S ($P = 0.003$). After adjusting for BMI, only 2-h insulin and insulin sensitivity index composite remained significantly different.

Conclusions: This study indicates that sons of PCOS women exhibit higher body weight from early infancy. In addition, insulin resistance became evident as the subjects got older, which may place them at risk for the development of type 2 diabetes and cardiovascular disease. **(*J Clin Endocrinol Metab* 93: 1820–1826, 2008)**

Polycystic ovary syndrome (PCOS) is a familial endocrine-metabolic disorder, affecting approximately 5–8% of reproductive-aged women (1–3), characterized by irregular menses, chronic anovulation, infertility, and hyperandrogenism. Approximately 50% of the PCOS women are overweight or obese, and most of them exhibit excess abdominal fat distribution (4, 5). In addition, women with PCOS may also have other metabolic abnormalities such as insulin resistance (6, 7),

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Abbreviations: CRP, C-reactive protein; C_S, control sons; HOMA-IR, homeostatic model assessment for insulin resistance; ISI, insulin sensitivity index; PCOS, polycystic ovary syndrome; $PCOS_S$, PCOS sons; SDS, SD score.

glucose intolerance, type 2 diabetes (4, 8–10), and an increased prevalence of lipid-related abnormalities (11–14).

In view of the high prevalence of affected individuals within families of PCOS women, a genetic basis for this syndrome has been suggested (15). This has been evaluated in different populations (16) through phenotypic and family aggregation studies. These studies have demonstrated that a significant number of female relatives are affected with this condition (17–24). However, the male phenotype of PCOS is not well defined, so it has been difficult to establish whether male relatives are also affected. Multiple possible phenotypes have been proposed including increased hair growth (15), abnormalities in male hair distribution such as premature male balding (18, 25), and metabolic abnormalities such as insulin resistance (26, 27). Insulin resistance appears to have a genetic basis, because the abnormality is perpetuated in tissue culture (26, 28). Therefore, it is possible that a proportion of the males in an affected family with PCOS might also manifest insulin resistance.

In previous studies, we demonstrated that parents and brothers of PCOS women exhibit insulin resistance and related metabolic defects more often than control subjects (29, 30). Recently, Yildiz *et al.* (31) reported that first-degree relatives of women with PCOS have more insulin resistance and glucose intolerance than control subjects. On the other hand, it has been proposed that PCOS has an environmental component and that intrauterine life, as an environmental factor, is implicated in the origin of PCOS (32, 33). Therefore, intrauterine life may affect the endocrine/metabolic function of a child born to a PCOS mother, independent of genetic inheritance and sex. However, no studies have evaluated the metabolic characteristics of sons of women with PCOS from the early stages of sexual development into adulthood to establish whether metabolic abnormalities are present and, if so, the stage of life at which they develop.

Therefore, the aim of the present study was to assess the metabolic profiles in sons of women with PCOS during three different stages of life: early infancy (2–3 months), childhood (4–7 yr), and adulthood (18–30 yr).

Subjects and Methods

Subjects

We studied 80 boys (20 infants, 31 children, and 29 adults) born to PCOS mothers [PCOS sons ($PCOS_S$]. As a control group, we included 56 boys (20 infants, 17 children, and 19 adults) born to mothers with regular menses and without hyperandrogenism [control sons (C_S)]. The $PCOS_S$ and C_S were matched for age.

PCOS mothers were recruited from patients attending the Unit of Endocrinology and Reproductive Medicine at the University of Chile. This group of PCOS mothers is part of an unselected group of patients that has attended our clinic because they were diagnosed with PCOS. Diagnosis of PCOS was made according to the National Institutes of Health consensus criteria (34). PCOS women were evaluated before pregnancy, and they exhibited chronic oligomenorrhea or amenorrhea, hirsutism, serum testosterone more than 0.6 ng/ml and/or free androgen index more than 5.0, and androstenedione more than 3.0 ng/ml. In addition, PCOS women showed the characteristic ovarian morphology of PCO on ultrasound, based on the criteria described by Adams *et al.* (35). PCOS women were normoglycemic, with varying degrees of hyperinsulinemia that were evaluated by an oral glucose tolerance test. All patients had an elevated waist-to-hip ratio, greater than 0.85. We excluded patients with hyperprolactinemia, androgen-secreting neoplasms, Cushing's syndrome, and late-onset 21-hydroxylase deficiency as well as thyroid disease.

All $PCOS_S$ were born at term after spontaneous conceptions that led to singleton pregnancies. The prevalence of gestational diabetes for PCOS mothers, according to the World Health Organization criteria (36), was 17.5%, and the incidence of pregnancy-induced hypertension was 13.6%. In addition, 57.5% of PCOS patients and 42.8 of control mothers were primiparous.

As control mothers, we selected 56 women of similar socioeconomic level as the PCOS patients, with a history of singleton pregnancies, regular 28- to 32-d menstrual cycles, absence of hirsutism and other manifestations of hyperandrogenism, and no history of infertility or pregnancy complications.

There were no siblings included in the groups studied.

The protocol was approved by the institutional review boards of the San Juan de Dios and San Borja Arriarán Hospitals and the University of Chile. All parents and boys older than 8 yr signed an informed consent before entering the study.

Study protocol

Infants and children were admitted with their mothers to the pediatric unit of our Clinical Research Center at approximately 0830 h. We performed a complete physical examination on each boy, including anthropometric measurements [weight, height, waist, hip, BMI, and BMI SD score (SDS) calculated by the Growth Analyzer Program using the U.S. Growth Charts BMI for age). Adult males were admitted to our Clinical Research Center at approximately 0830 h, and we obtained a clinical history and performed a complete physical examination, including anthropometric measurements.

In children and adults, after a 12-h overnight fast, an oral glucose tolerance test (1.75 g/kg, up to a maximum of 75 g glucose in 250 ml water) was performed. In children, blood samples (5 ml) were obtained at baseline and 120 min after glucose administration. In adults, blood was withdrawn before and 30, 60, 90, and 120 min after the glucose load. In infants, a blood sample (3 ml) was obtained in the fasting state. Serum glucose and insulin were determined in each sample. Circulating concentrations of adiponectin, leptin, C-reactive protein (CRP), SHBG, and serum lipids were determined in the fasting sample.

Assays

Serum glucose was determined by the glucose oxidase method (Photometric Instrument 4010; Roche, Basel, Switzerland). The intraassay coefficient of variation of this method was less than 2.0%. The lipid profile was determined by standard colorimetric assays (Photometric Instrument 4010). Serum low-density lipoprotein (LDL)-cholesterol concentration was calculated by Friedewald's formula [LDL-cholesterol = total cholesterol − high-density lipoprotein (HDL)-cholesterol − (triglycerides/5)].

Serum adiponectin was assayed by RIA (Linco Research Inc., St. Charles, MO) with a sensitivity of 1.0 ng/ml and intra- and interassay coefficients of variation of 1.8 and 9.0%, respectively. Leptin concentrations were measured by RIA (Linco) with a sensitivity of 0.5 ng/ml and intra- and interassay coefficients of variation of 3.9 and 4.7%, respectively. CRP concentrations were determined by an ultrasensitive immunoturbidimetric assay (CRP Latex HS; Roche Diagnostics, Mannheim, Germany) with a sensitivity of 0.03 mg/liter and intra- and interassay coefficients of variation of 1.3 and 5.7%, respectively. Serum insulin was assayed by RIA (Diagnostic Systems Laboratories, Inc., Webster, TX). The intra- and interassay coefficients of variation were 5 and 8%, respectively. SHBG was determined by radioimmunometric assay (Diagnostic Products Corp., Los Angeles, CA) with intra- and interassay coefficients of variation of 3.8 and 7.9%, respectively.

Data analysis

The measurements derived from the oral glucose tolerance test included the following: 1) serum fasting glucose, serum fasting insulin, and homeostatic model assessment for insulin resistance (HOMA-IR) (37); 2) serum 2-h glucose and insulin; 3) whole-body insulin sensitivity index (ISI) composite (38); 4) serum lipid profile, total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol; and 5) serum adiponectin, leptin, CRP, and SHBG.

Statistical evaluation

Data are expressed as median and range. Normal distribution was assessed by the Kolmogorov-Smirnov test. Differences between study groups were assessed with the Student's *t* test when data were normally distributed or Mann-Whitney *U* test when not normally distributed. The effect of body weight or BMI on continuous variables was evaluated using multivariate analysis (multiple linear regression techniques). Spearman correlations analysis was used to evaluate the relationship among the variables of interest. Statistical analysis was performed with STATA 7.0 package. A P value of <0.05 was considered to be statistically significant.

Results

The clinical characteristics of control mothers and PCOS mothers during the study and the clinical characteristics of the newborns are given in Table 1. Control mothers were comparable in age with PCOS mothers in the three study periods. At the time when their sons were evaluated, PCOS mothers were more obese than control mothers of infants and children. Regarding pregnancy history, gravity and parity were similar between control mothers and PCOS mothers. BMI at term of pregnancy was significantly higher in PCOS mothers of children compared with control mothers. Gestational age and birth weight were similar between newborns of PCOS mothers and of control mothers in the three groups studied. There were no small for gestational age newborns (<2.0 SD of weight) in the PCOS groups or the control groups. However, a small number of large for gestational age children (>2.0 SD of weight) was observed only in the PCOS groups (two in the infant group; two in the childhood group, and one in the adult group). The correlation between the weight of the mothers at term of pregnancy and the weight of their sons at time of study was evaluated. A positive correlation between the weight of the PCOS mothers at term of pregnancy and the weight of the sons was observed during childhood ($r = 0.440$; $P = 0.02$) and adulthood ($r = 0.637$; $P = 0.001$). Moreover, during childhood, there was a positive correlation between BMI of the mothers and BMI of their sons in the PCOS group ($r = 0.425$; $P = 0.02$).

The clinical and metabolic characteristics during infancy in $PCOS_S$ and C_S are presented in Table 2. During early infancy, $PCOS_S$ showed a greater weight ($P = 0.038$) and weight SDS ($P = 0.031$) than C_S. Serum glucose, insulin, HOMA-IR, and lipids were similar in both groups. Adiponectin, leptin, SHBG, and CRP protein serum concentration were also similar in both groups.

During childhood, weight ($P = 0.003$), weight SDS ($P = 0.001$), BMI ($P < 0.001$), BMI SDS ($P < 0.001$), and waist circumference ($P = 0.001$) were higher in $PCOS_S$ compared with C_S. Total cholesterol ($P = 0.007$) and LDL-cholesterol ($P = 0.022$) were also higher in $PCOS_S$ compared with C_S, but after adjusting for BMI, these differences were nonsignificant (Table 3). Adiponectin, leptin, CRP serum concentration, and SHBG were not different between groups.

During adulthood, $PCOS_S$ exhibited higher weight ($P = 0.022$), BMI ($P = 0.046$), and waist circumference ($P = 0.028$) than C_S. Fasting insulin ($P = 0.030$), HOMA-IR ($P = 0.034$), total cholesterol ($P = 0.043$), LDL-cholesterol ($P = 0.034$), and 2-h insulin ($P = 0.006$) were also significantly higher. ISI composite was significantly lower than in C_S ($P = 0.003$). After adjusting for BMI, only 2-h insulin and ISI composite remained significantly different (Table 4). Adiponectin, leptin, and CRP serum concentration were not different between groups. SHBG serum concentrations tended to be lower in $PCOS_S$ compared with C_S ($P = 0.067$).

In a simple linear regression analysis, BMI was positively correlated with leptin ($r = 0.749$; $P = 0.001$), 2-h insulin ($r = 0.531$; $P = 0.002$), and triglycerides ($r = 0.409$; $P = 0.02$) in $PCOS_S$ during childhood. In addition, BMI was positively correlated with leptin ($r = 0.822$; $P = 0.001$), 2-h insulin ($r = 0.711$; $P = 0.001$), HOMA-IR ($r = 0.733$; $P = 0.01$), and triglycerides ($r = 0.453$; $P = 0.01$) in $PCOS_S$ during adulthood. BMI was inversely

TABLE 1. Clinical characteristics of control mothers and PCOS mothers during the study and clinical characteristics of the newborns

	Infancy		Childhood		Adulthood	
	Control mothers (n = 20)	PCOS mothers (n = 20)	Control mothers (n = 17)	PCOS mothers (n = 31)	Control mothers (n = 19)	PCOS mothers (n = 29)
Age at study (yr)	28.0 (22.0–38.0)	31.0 (21.0–38.0)	32.0 (26.0–46.9)	33.0 (23.0–46.0)	49.0 (43.0–64.0)	51.0 (45.0–59.0)
BMI at study (kg/m^2)	28.3 (21.1–33.6)	30.6 (23.3–42.0)[a]	24.2 (20.5–25.8)	30.1 (21.2–31.6)[a]	25.4 (22.3–26.4)	25.2 (21.8–33.3)
Gestations (n)	1.0 (1.0–3.0)	1.0 (1.0–4.0)	2.0 (1.0–4.0)	1.0 (1.0–4.0)	3.0 (1.0–4.0)	3.0 (2.0–4.0)
Parities (n)	1.0 (1.0–3.0)	1.0 (1.0–4.0)	2.0 (1.0–4.0)	1.0 (1.0–4.0)	3.0 (1.0–4.0)	3.0 (2.0–4.0)
Weight at term of pregnancy (kg)	77.0 (60.0–90.0)	79.5 (63.0–115.8)	68.0 (57.0–76.0)	86.0 (67.0–120.0)[a]	70.0 (65.0–75.0)	71.0 (66.0–89.0)
Birth weight (kg)	3.5 (2.7–4.1)	3.7 (2.6–4.3)	3.3 (3.0–3.5)	3.5 (3.1–4.4)	3.5 (3.1–4.1)	3.4 (3.0–4.2)
Gestational age (wk)	39.0 (37.0–41.0)	39.0 (38.0–41.0)	38.0 (37.0–41.0)	40.0 (37.0–40.0)	40.0 (38.0–40.0)	39.5 (38.0–40.0)
SDS weight at birth	0.3 (−1.8–1.6)	0.7 (−1.7–2.2)	−0.2 (−0.9–0.7)	0.4 (−1.4–2.7)[a]	0.1 (−1.2–1.9)	−0.1 (−1.9–2.4)

Values are median (range).

[a] $P < 0.05$ between control mothers and PCOS mothers.

TABLE 2. Clinical and metabolic characteristics during infancy in C_S and $PCOS_S$

	C_S (n = 20)	$PCOS_S$ (n = 20)	*P*, unadjusted	*P*, adjusted
Age (months)	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.582	
Weight (kg)	5.6 (5.0–7.5)	6.1 (4.9–8.4)	0.038	
Height (cm)	58.3 (56.0–61.0)	59.5 (53.0–67.0)	0.273	
Weight SDS	0.3 (-0.8–2.0)	0.5 (−0.9–3.0)	0.031	
Fasting				
Glucose (mg/dl)	100.0 (88.0–119.0)	102.5 (87.0–117.0)	0.577	0.691
Insulin (μIU/ml)	4.7 (4.0–14.7)	5.3 (4.0–24.4)	0.091	0.103
HOMA-IR	1.2 (0.9–4.0)	1.4 (0.9–6.7)	0.110	0.126
Triglycerides (mg/dl)	149.0 (75.0–258.0)	121.5 (70.0–239.0)	0.208	0.357
Cholesterol (mg/dl)	155.7 (89.0–224.0)	145.1 (103.0–183.0)	0.072	0.152
HDL-cholesterol (mg/dl)	51.6 (35.6–67.5)	55.1 (33.6–68.1)	0.110	0.184
LDL-cholesterol (mg/dl)	66.6 (20.3–152.1)	57.8 (9.9–101.7)	0.110	0.184
SHBG (nmol/liter)	113.9 (48.3–173.2)	95.6 (30.3–164.3)	0.115	0.117
Adiponectin (μg/ml)	57.4 (49.9–69.8)	58.1 (34.9–74.4)	0.540	0.836
Leptin (ng/ml)	7.4 (1.6–15.0)	8.1 (2.6–19.3)	0.470	0.233
CRP (mg/ml)	0.4 (0.3–8.9)	0.3 (0.3–10.8)	0.936	0.237

Values are median (range). *P* values were adjusted by weight.

correlated with ISI composite ($r = -0.524$; $P = 0.004$) in $PCOS_S$ during adulthood.

Discussion

In this study, we evaluated metabolic parameters during different stages of life in sons of women with PCOS. We observed that $PCOS_S$ exhibited a higher body weight than C_S at all stages. In addition, insulin resistance independent of body weight became evident during adulthood.

In the present study, $PCOS_S$ exhibited a higher body weight than C_S. During early infancy and childhood, $PCOS_S$ showed higher weight and weight SDS than C_S but no other metabolic changes were observed after the data were corrected by BMI. Finally, during adulthood, insulin resistance was present independent of body weight, indicating that sons of PCOS women showed an abnormal metabolic profile that was more evident as the subjects became older.

Interestingly, an increased body weight during infancy was the earliest sign that was observed in our $PCOS_S$ and persisted during the different stages of life. This may represent an important finding that may underscore the crucial role of early excess weight gain in the development of metabolic changes in these boys. As mentioned previously, approximately 50% of PCOS women are overweight or obese, and most of them exhibit an abdominal phenotype (4, 5). It has been proposed that obesity may play a pathogenetic role in the development of this syn-

TABLE 3. Clinical and metabolic characteristics during childhood in C_S and $PCOS_S$

	C_S (n = 17)	$PCOS_S$ (n = 31)	*P*, unadjusted	*P*, adjusted
Age (yr)	5.1 (4.0–7.0)	6.0 (4.0–7.5)	0.340	
Weight (kg)	19.4 (14.5–24.0)	23.0 (14.3–38.7)	0.003	
Height (cm)	111.0 (97.0–125.0)	116.0 (96.0–132.0)	0.129	
BMI (kg/m^2)	15.1 (13.8–18.8)	17.4 (14.9–24.7)	<0.001	
Weight SDS	−0.3 (−1.6–1.6)	1.0 (−1.3–2.8)	0.001	
BMI SDS	−0.2 (−1.9–2.1)	1.2 (−0.7–2.9)	<0.001	
Waist circumference (cm)	51.0 (46.0–61.5)	57.5 (47.0–70.0)	0.001	0.219
Fasting				
Glucose (mg/dl)	85.0 (64.0–109.2)	90.2 (59.0–115.0)	0.157	0.529
Insulin (μIU/ml)	5.4 (4.0–12.3)	5.8 (4.0–18.0)	0.488	0.498
HOMA-IR	1.0 (0.5–2.6)	1.3 (0.7–4.3)	0.335	0.426
Triglycerides (mg/dl)	86.0 (59.0–130.0)	101.0 (63.0–174.0)	0.340	0.492
Cholesterol (mg/dl)	155.0 (110.0–199.0)	171.0 (129.0–262.0)	0.007	0.153
HDL-cholesterol (mg/dl)	41.5 (31.6–73.6)	44.2 (29.8–58.3)	0.253	0.310
LDL-cholesterol (mg/dl)	94.0 (60.4–142.5)	106.8 (52.6–224.3)	0.022	0.321
SHBG (nmol/liter)	97.5 (59.1–128.1)	87.3 (53.9–129.8)	0.527	0.563
Adiponectin (μg/ml)	22.1 (13.9–39.0)	21.8 (9.3–61.1)	0.397	0.429
Leptin (ng/ml)	3.4 (0.7–9.1)	4.3 (0.9–10.1)	0.123	0.143
CRP (mg/ml)	0.3 (0.3–7.0)	0.3 (0.3–5.8)	0.551	0.584
2-h				
Glucose (mg/dl)	91.4 (65.0–121.0)	100.5 (69.0–139.0)	0.051	0.285
Insulin (μIU/ml)	8.6 (4.0–47.3)	19.7 (4.0–61.1)	0.224	0.483

Values are median (range). *P* values were adjusted by BMI.

TABLE 4. Clinical and metabolic characteristics during adulthood in C_S and $PCOS_S$

	C_S (n = 19)	$PCOS_S$ (n = 29)	*P*, unadjusted	*P*, adjusted
Age (yr)	22.0 (19.0–29.0)	22.0 (18.0–29.0)	0.597	
Weight (kg)	72.5 (54.0–86.0)	78.0 (56.2–139.0)	0.022	
Height (cm)	175.0 (165.0–184.0)	176.0 (163.0–190.0)	0.399	
BMI (kg/m^2)	22.9 (19.4–29.1)	25.1 (20.0–45.4)	0.046	
Waist circumference (cm)	82.0 (71.0–95.0)	87.0 (65.0–129.0)	0.028	0.222
Fasting				
Glucose (mg/dl)	86.3 (65.6–108.6)	85.4 (65.9–105.4)	0.945	0.696
Insulin (μIU/ml)	7.0 (4.0–49.8)	10.4 (4.0–59.4)	0.030	0.560
HOMA-IR	1.3 (0.8–13.4)	2.3 (0.7–14.5)	0.034	0.729
Triglycerides (mg/dl)	117.5 (69.0–345.0)	112.0 (69.0–340.0)	0.663	0.367
Cholesterol (mg/dl)	163.0 (106.0–208.0)	182.0 (102.0–240.0)	0.043	0.148
HDL-cholesterol (mg/dl)	41.9 (28.7–64.1)	41.3 (29.1–64.9)	0.548	0.399
LDL-cholesterol (mg/dl)	97.2 (84.1–185.5)	114.5 (39.6–169.2)	0.034	0.108
SHBG (nmol/liter)	26.3 (13.3–46.8)	23.1 (10.2–44.7)	0.067	0.121
Adiponectin (μg/ml)	10.5 (5.1–15.7)	11.5 (2.1–36.8)	0.194	0.121
Leptin (ng/ml)	3.2 (2.4–7.7)	6.1 (1.0–56.8)	0.364	0.317
CRP (mg/ml)	0.7 (0.3–11.7)	0.7 (0.3–9.2)	0.513	0.237
2-h				
Glucose (mg/dl)	79.6 (54.9–105.5)	89.2 (57.0–155.0)	0.058	0.210
Insulin (μIU/ml)	18.2 (4.0–63.0)	55.3 (24.0–394.2)	0.006	0.043
ISI composite	8.3 (2.1–17.0)	4.6 (0.7–10.3)	0.003	0.010

Values are median (range). *P* values were adjusted by BMI.

drome in susceptible individuals (4, 39, 40). It is possible that a similar phenomenon occurs in the sons of PCOS women.

The origin of obesity in these boys is probably the consequence of several factors, which include genetic susceptibility, environmental factors, and eating habits. In this regard, it is interesting to point out that PCOS mothers were more obese than control mothers at the time when these boys were evaluated. In addition, we have demonstrated that during pregnancy, PCOS mothers are more obese and exhibit an altered metabolic profile with high insulin and low adiponectin levels (41). Moreover, in the present study, a positive correlation between the weight of the PCOS mother at term of pregnancy and the weight of their sons was observed in children and adults Therefore, prenatal environmental factors and/or abnormal eating habits of the mother may be important for promoting weight gain. On the other hand, sisters of PCOS patients have higher BMI than sisters of normal women, suggesting a genetic component for PCOS-associated obesity in these subjects (22).

Considering that numerous studies confirm that childhood obesity is associated with insulin resistance, hyperinsulinemia, and an increased risk of developing diabetes, $PCOS_S$ constitute a high risk group for metabolic abnormalities. Interventions aimed at reducing body fat through dietary modifications and exercise are likely to improve insulin resistance, reducing the risk of developing type 2 diabetes and cardiovascular disease, similar to what has been proposed for women with PCOS (42).

Several studies have reported a high prevalence of insulin resistance in PCOS women. Few studies, however, have systematically examined possible metabolic abnormalities in male relatives of PCOS women, and none have included a concurrently studied control group. The present study demonstrates for the first time that adult sons of women with PCOS exhibit insulin resistance according to ISI composite values, independent of body weight. Several methods have been proposed to evaluate insulin sensitivity from data obtained by the oral glucose tolerance test. Most of them rely on the ratio of plasma glucose to insulin concentrations during the oral glucose tolerance test. In the present study, we chose two methods, HOMA-IR (37) and ISI composite (38). Fasting plasma glucose, fasting plasma insulin, and HOMA-IR index are poor predictors of insulin resistance and glucose intolerance in young subjects or in studies where a small number of subjects are included (43, 44). In the case of the ISI composite, basal and poststimulated values of glucose and insulin are integrated, differing from HOMA-IR, which considers only the fasting values of glucose and insulin. Therefore, ISI composite offers more advantages than HOMA-IR and is a better method to assess individual insulin resistance in young subjects (45). After the data were adjusted by BMI, ISI composite was the only measurement of insulin resistance that persisted as significantly different between control and $PCOS_S$ during adulthood. However, we were not able to assess insulin resistance by more sensitive methods to establish whether insulin resistance is present since childhood, because multiple blood sampling at this age was not possible.

The presence of insulin resistance in adult sons of PCOS women is a novel finding, which suggests that insulin resistance may constitute part of the male PCOS phenotype, as previously proposed (27). Our findings confirm the results of Norman *et al.* (26), who proposed that hyperinsulinemia may be an important marker of the condition in family members of PCOS patients. Insulin resistance is central to the pathogenesis of both type 2 diabetes and PCOS, with a strong genetic basis and important implications for the management of both disorders. Insulin resistance and hyperinsulinemia are common precursors of impaired glucose tolerance and type 2 diabetes (46, 47). In this context, the presence of insulin resistance in early-adulthood sons of women with PCOS could be the first step in the development of type 2 diabetes. Therefore, its detection and the em-

ployment of therapeutic tools might be useful for the prevention of this disorder.

It is difficult, however, to establish whether insulin resistance in $PCOS_S$ is a genetic trait, the result of fetal programming, or both. There are relatively few studies studying this hypothesis in males. Recently, we have demonstrated that female sheep treated prenatally with testosterone exhibited reduced birth weight and impaired insulin sensitivity in early postnatal life (48). In adult male rhesus monkeys treated prenatally with testosterone, a similar phenomenon was observed (49). On the other hand, in humans, we demonstrated a significant increase in androgen concentrations during pregnancy in PCOS women, suggesting that these androgens could provide a potential source of androgen excess for the fetus (50). In sum, it is possible that prenatal androgen excess may influence insulin sensitivity in the offspring of PCOS mothers, which may act in concert with an inherited genetic predisposition for a reduced insulin sensitivity in these patients.

Other metabolic variables measured in the present study, such as leptin, adiponectin, CRP, and SHBG, were similar in both groups. Recently, we observed that normal weight prepubertal daughters of PCOS women showed significantly lower concentrations of adiponectin and higher levels of poststimulated insulin compared with control daughters (51). Normal-weight pubertal PCOS daughters exhibited higher levels of triglycerides and poststimulated insulin and lower levels of SHBG compared with controls, suggesting that some metabolic features of PCOS are also present in these girls (51). However, in comparison with the data of the present study, some interesting differences were observed. The boys were relatively more obese than the girls, and surrogate markers of insulin resistance such as circulating concentrations of adiponectin and SHBG were affected in girls but not in boys. It is possible that gender differences and body weight may partly explain these differences. However, based on our studies, we should point out that both daughters and sons of PCOS women appear to constitute high-risk groups for possible metabolic derangements.

In conclusion, our results suggest that some of the metabolic alterations described in PCOS women are present in their sons. In addition, sons of PCOS women exhibit higher body weight since early life. In addition, insulin resistance became evident as the subjects got older. We propose that insulin resistance may be part of the male PCOS phenotype and that this metabolic feature should be investigated in males born to PCOS mothers.

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References

1. **Franks S** 1995 Polycystic ovary syndrome. N Engl J Med 333:853–861
2. **Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF** 2000 A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 85:2434–2438
3. **Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO** 2004 The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 89:2745–2749
4. **Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R** 2002 Obesity and the polycystic ovary syndrome. Int J Obes Relat Metab Disord 26:883–896
5. **Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX** 2004 Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update 10:267–280
6. **Holte J** 1996 Disturbances in insulin secretion and sensitivity in women with the polycystic ovary syndrome. Baillieres Clin Endocrinol Metab 10:221–247
7. **Dunaif A** 1997 Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 18:774–800
8. **Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J** 1999 Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care 22:141–146
9. **Legro RS, Kunselman AR, Dodson WC, Dunaif A** 1999 Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab 84:165–169
10. **Sir-Petermann T** 2005 Polycystic ovary syndrome, a pathway to type 2 diabetes. Nutrition 21:1160–1163
11. **Wild RA** 1997 Cardiovascular and lipoprotein abnormalities in androgen excess. In Azziz R, Nestler JE, Dewailly D eds. Androgen excess disorders in women. Philadelphia: Lippincott-Raven; 681–688
12. **Legro RS, Kunselman AR, Dunaif A** 2001 Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. Am J Med 111:607–613
13. **Cenk Sayin N, Yardim T** 2003 Insulin resistance and lipid profile in women with polycystic appearing ovaries: implications with regard to polycystic ovary syndrome. Gynecol Endocrinol 17:387–396
14. **Banaszewska B, Duleba AJ, Spaczynski RZ, Pawelczyk L** 2006 Lipids in polycystic ovary syndrome: role of hyperinsulinemia and effects of metformin. Am J Obstet Gynecol 94:1266–1272
15. **Cooper H, Spellacy W, Prem K, Cohen W** 1968 Hereditary factors in the Stein-Leventhal syndrome. Am J Obstet Gynecol 100:371–387
16. **Crosignani PG, Nicolosi AE** 2001 Polycystic ovarian disease: heritability and heterogeneity. Hum Reprod Update 7:3–7
17. **Lunde O, Magnus P, Sandvik L, Hoglo S** 1989 Familial clustering in the polycystic ovarian syndrome. Gynecol Obstet Invest 28:23–30
18. **Carey AH, Chan KL, Short F, White D, Williamson R, Franks S** 1993 Evidence for a single gene effect causing polycystic ovaries and male pattern baldness. Clin Endocrinol (Oxf) 38:653–658
19. **Lander ES, Schork NJ** 1994 Genetic dissection of complex traits. Science 265:2037–2048
20. **Jahanfar S, Eden JA, Warren P, Seppala M, Nguyen TV** 1995 A twin study of polycystic ovary syndrome. Fertil Steril 63:478–486
21. **Franks S, Gharani N, Waterworth D, Batty S, White D, Williamson R, McCarthy M** 1997 The genetic basis of polycystic ovary syndrome. Hum Reprod 12:2641–2648
22. **Legro RS, Spielman R, Urbanek M, Driscoll D, Strauss JF 3rd, Dunaif A** 1998 Phenotype and genotype in polycystic ovary syndrome. Recent Prog Horm Res 53:217–256
23. **Legro RS, Driscoll D, Strauss 3rd JF, Fox J, Dunaif A** 1998 Evidence for a genetic basis for hyperandrogenemia in polycystic ovary syndrome. Proc Natl Acad Sci USA 95:14956–14960
24. **Kahsar-Miller MD, Nixon C, Boots LR, Go RC, Azziz R** 2001 Prevalence of polycystic ovary syndrome (PCOS) in first-degree relatives of patients with PCOS. Fertil Steril 75:53–58
25. **Govind A, Obhrai MS, Clayton RN** 1999 Polycystic ovaries are inherited as an autosomal dominant trait: analysis of 29 polycystic ovary syndrome and 10 control families. J Clin Endocrinol Metab 84:38–43

26. **Norman RJ, Masters S, Hague W** 1996 Hyperinsulinemia is common in family members of women with polycystic ovary syndrome. Fertil Steril 66:942–947
27. **Legro RS** 2000 Is there a male phenotype in polycystic ovary syndrome families? J Pediatr Endocrinol Metab 13(Suppl 5):1307–1309
28. **Dunaif A, Xia J, Book CB, Schenker E, Tang Z** 1995 Excessive insulin receptor serine phosphorylation in cultured fibroblasts and in skeletal muscle. A potential mechanism for insulin resistance in the polycystic ovary syndrome. J Clin Invest 96:801–810
29. **Sir-Petermann T, Angel B, Maliqueo M, Carvajal F, Santos JL, Perez-Bravo F** 2002 Prevalence of type II diabetes mellitus and insulin resistance in parents of women with polycystic ovary syndrome. Diabetologia 45:959–964
30. **Sir-Petermann T, Cartes A, Maliqueo M, Vantman D, Gutierrez C, Toloza H, Echiburu B, Recabarren SE** 2004 Patterns of hormonal response to the GnRH agonist leuprolide in brothers of women with polycystic ovary syndrome: a pilot study. Hum Reprod 19:2742–2747
31. **Yildiz BO, Yarali H, Oguz H, Bayraktar M** 2003 Glucose intolerance, insulin resistance, and hyperandrogenemia in first degree relatives of women with polycystic ovary syndrome. J Clin Endocrinol Metab 88:2031–2036
32. **Abbott DH, Dumesic DA, Eisner JR, Colman RJ, Kemnitz JW** 1998 Insights into the development of polycystic ovary syndrome (PCOS) from studies of prenatally androgenized female Rhesus monkeys. Trends Endocrinol Metab 9:62–67
33. **Xita N, Tsatsoulis A** 2006 Review: fetal programming of polycystic ovary syndrome by androgen excess: evidence from experimental, clinical, and genetic association studies. J Clin Endocrinol Metab 91:1660–1666
34. **Zawadzky JK, Dunaif A** 1992 Diagnosis criteria: Towards a rational approach. In: Hershmann JM, ed. Current issues in endocrinology and metabolism. Boston: Blackwell Scientific; 377–384
35. **Adams J, Polson DW, Franks S** 1986 Prevalence of polycystic ovaries in women with anovulation and idiopathic hirsutism. Br Med J (Clin Res Ed) 293:355–359
36. **World Health Organization Department of Noncommunicable Disease Surveillance** 1999 Definition, diagnosis and classification of diabetes mellitus and its complications. Part I: diagnosis and classification of diabetes mellitus. Geneva: World Health Organization
37. **Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC** 1985 Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 28:412–419
38. **Matsuda M, DeFronzo RA** 1999 Insulin sensitivity indices obtained from oral glucose tolerance testing: comparison with the euglycemic insulin clamp. Diabetes Care 22:1462–1470
39. **Pasquali R, Pelusi C, Genghini S, Cacciari M, Gambineri A** 2003 Obesity and reproductive disorders in women. Hum Reprod Update 9:359–372
40. **McCartney CR, Prendergast KA, Chhabra S, Eagleson CA, Yoo R, Chang RJ, Foster CM, Marshall JC** 2006 The association of obesity and hyperandrogenemia during the pubertal transition in girls: obesity as a potential factor in the genesis of postpubertal hyperandrogenism. J Clin Endocrinol Metab 91:1714–1722
41. **Sir-Petermann T, Echiburu B, Maliqueo M, Crisosto N, Sanchez F, Hitschfeld C, Carcamo M, Amigo P, Perez-Bravo F** 2007 Serum adiponectin and lipid concentrations in pregnant women with polycystic ovary syndrome. Hum Reprod 22:1830–1836
42. **Norman RJ, Davies MJ, Lord J, Moran LJ** 2002 The role of lifestyle modification in polycystic ovary syndrome. Trends Endocrinol Metab 13:251–257
43. **Palmert MR, Gordon CM, Kartashov AI, Legro RS, Emans SJ, Dunaif A** 2002 Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. J Clin Endocrinol Metab 87:1017–1023
44. **Arslanian SA, Lewy VD, Danadian K** 2001 Glucose intolerance in obese adolescents with polycystic ovary syndrome: roles of insulin resistance and β-cell dysfunction and risk of cardiovascular disease. J Clin Endocrinol Metab 86:66–71
45. **Carnevale Schianca GP, Sainaghi PP, Castello L, Rapetti R, Limoncini AM, Bartoli E** 2006 Comparison between HOMA-IR and ISI-gly in detecting subjects with the metabolic syndrome. Diabetes Metab Res Rev 22:111–117
46. **Haffner SM, Stern MP, Miettinen H, Gingerich R, Bowsher RR** 1995 Higher proinsulin and specific insulin are both associated with a parental history of diabetes in nondiabetic Mexican-American subjects. Diabetes 44:1156–1160
47. **Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA** 2001 Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 86:1930–1935
48. **Recabarren SE, Padmanabhan V, Codner E, Lobos A, Duran C, Vidal M, Foster DL, Sir-Petermann T** 2005 Postnatal developmental consequences of altered insulin sensitivity in female sheep treated prenatally with testosterone. Am J Physiol Endocrinol Metab 289:E801–E806
49. **Bruns CM, Baum ST, Colman RJ, Eisner JR, Kemnitz JW, Weindruch R, Abbott DH** 2004 Insulin resistance and impaired insulin secretion in prenatally androgenized male rhesus monkeys. J Clin Endocrinol Metab 89:6218–6223
50. **Sir-Petermann T, Maliqueo M, Angel B, Lara HE, Perez-Bravo F, Recabarren SE** 2002 Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. Hum Reprod 17:2573–2579
51. **Sir-Petermann T, Maliqueo M, Codner E, Echiburú B, Crisosto N, Pérez V, Pérez-Bravo F, Cassorla F** 2007 Early metabolic derangements in daughters of women with polycystic ovary syndrome (PCOS). J Clin Endocrinol Metab 92:4636–4642