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BRIEF REPORT

Hormonal Profile in Women with Polycystic Ovarian Syndrome with or without Type 1 Diabetes Mellitus

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Context: Anti-Müllerian hormone (AMH) levels are increased in polycystic ovarian syndrome (PCOS), but it is not known whether other forms of hyperandrogenism, such as PCOS observed in women with type 1 diabetes mellitus (DM1), are also associated with elevated AMH levels.

Objective: Our objective was to compare AMH and steroid levels in women with PCOS with and without DM1.

Design: We compared the clinical, hormonal, and ultrasonographic characteristics of 17 women with PCOS and DM1 (DM1+PCOS), 20 women with PCOS without DM1 (PCOS), and 35 normal women (control) in a cross-sectional study.

Results: The Ferriman-Gallwey score, serum testosterone, free androgen index, 17OH-progesterone, and ovarian volume were elevated in both groups of PCOS women compared with controls. Serum androstenedione, LH/FSH ratio, and follicle number, however, were higher and SHBG was lower in PCOS compared with DM1+PCOS and controls. AMH levels were higher in PCOS (76.0 ± 36.3 pmol/liter) than in DM1+PCOS (18.8 ± 7.4 pmol/liter) and controls (13.9 ± 8.3 pmol/liter). AMH levels correlated with follicle number in the three groups. Serum AMH/follicle number ratio was higher in PCOS than in DM1+PCOS and controls.

Conclusions: Women with DM1+PCOS have normal levels of AMH, inhibin B, estradiol, SHBG, and LH/FSH, suggesting that the pathophysiology of hyperandrogenism in PCOS patients with DM1 appears to be different from that in PCOS without DM1. However, hirsutism score and androgen levels were similar in both groups of women with PCOS. We postulate that insulin treatment acts as a co-gonadotropin increasing follicle recruitment, hence not increasing AMH levels. (*J Clin Endocrinol Metab* 92: 4742–4746, 2007)

A HIGH PREVALENCE of hyperandrogenism and polycystic ovarian syndrome (PCOS) has been described in adult women with type 1 diabetes mellitus (DM1) (1–3). Exogenous insulin treatment may be associated with the development of hyperandrogenism in these women. However, the pathophysiology of hyperandrogenism in DM1 has not been fully elucidated. Abnormal ovarian follicle development manifested by an increased number of small antral ovarian follicles and failure to recruit a dominant follicle is a central feature of PCOS (4, 5). Whether this also occurs in women with DM1 and hyperandrogenism is not known.

Anti-Müllerian hormone (AMH) is a homodimeric glycoprotein secreted by granulosa cells of small follicles (6, 7), which plays a key role in regulating follicle development (4). Serum AMH is clearly correlated with the number of small antral follicles (8–10). It has been postulated that serum AMH could be used as a surrogate marker for follicle number and possibly as a diagnostic tool for PCOS (11). We hypothesized that women with DM1 and PCOS, who have an elevated number of follicles (2), might also exhibit elevated AMH levels. To test our hypothesis we compared serum AMH, gonadotropins, and steroid levels in PCOS women with and without DM1.

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Abbreviations: AMH, Anti-Müllerian hormone; BMI, body mass index; DHEAS, dehydroepiandrosterone sulfate; DM1, diabetes mellitus type 1; FAI, free androgen index; LSD, least-significant difference; PCOS, polycystic ovary syndrome.

Subjects and Methods

Subjects

All the women with DM1 attending the diabetes clinic of Hospital San Borja-Arriarán, Santiago, who had experienced menarche at least 2.5 yr earlier, were invited to participate. This diabetes unit takes care of all the patients with DM1 in the Public Health System who live in central Santiago (2). Seventeen women fulfilled the Rotterdam criteria for PCOS, as previously described (2), and are included in this study (DM1+PCOS).

We also studied 20 nondiabetic women with PCOS followed at the Infertility Unit of the Institute of Maternal Research, University of Chile, between March 2004 and October 2006 for hyperandrogenism and/or infertility, who had not received treatment for PCOS during the previous 6 months. Diagnosis of PCOS was made according to the Rotterdam criteria (12). Diabetes was excluded with a normal oral glucose tolerance test.

As a control group, we also studied 35 healthy postmenarcheal women without a history of hyperandrogenism and who had regular

menstrual cycles, 24–34 d in length. The three groups of women were matched according to chronological age. Women were excluded from the study if they had been pregnant during the previous 6 months, used sex steroids, had abnormal thyroid function or prolactin levels, or presented chronic conditions such as genetic syndromes, celiac disease, renal, liver, or cardiac disease, or undernourishment.

Study protocol

We performed a complete physical examination in all the women who participated in this study. Hirsutism was evaluated by determining the presence of terminal hair using the modified Ferriman-Gallwey score (13). Weight was measured using a conventional Seca scale with a precision of 100 g, and height was measured with a Harpenden stadiometer. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height (meters). Waist circumference was measured to the nearest 0.5 cm, using a flexible measuring tape at the narrowest circumference between the lower costal margin and the iliac crest in the standing position. The hip circumference measurement was obtained at the maximum perimeter at the level of the femoral trochanters. Waist-to hip ratio was calculated as the ratio of these two circumferences.

An early morning blood sample was obtained during the follicular phase (d 1–7). In cases of oligo-/amenorrhea, blood sampling was done after the confirmation of the nonexistence of a dominant follicle (10 mm) or corpus luteum. Testosterone, androstenedione, 17OH-progesterone, dehydroepiandrosterone sulfate (DHEAS), and SHBG were measured as previously described (14–16). SHBG was measured in the basal sample, and free androgen index (FAI) was calculated from the formula 100 × testosterone (nmol/liter)/SHBG (nmol/liter) (17). Serum AMH was assayed using the AMH/MIS ELISA kit (Immunotech-Beckman, Marseilles, France) as previously described (18) The AMH assay had a sensitivity of 0.7 pmol/liter and intra- and interassay coefficients of variation of 5.3 and 8.7%, respectively.

Serum inhibin B was measured using specific two-site ELISAs (Diagnostic Systems Laboratories, Webster, TX). The assay sensitivity was 7 pg/ml, and intra- and interassay coefficients of variation were 4.8 and 7.1%, respectively (19).

Ultrasonography was performed as previously described (2). Whenever possible, the transvaginal exam was done. A similar proportion of subjects in the three groups were studied with transabdominal sonography. Mean ovarian volume and mean follicle numbers are reported. The protocol was approved by the institutional review board of the San Borja Arriarán Hospital. All patients older than 18 yr signed informed consents, and for younger patients, the consent was signed by their parents.

Statistical analysis

Clinical and laboratory data are shown as mean ± SD. Variables were tested for normal distribution using the Kolmogorov-Smirnov test. FAI and androstenedione were the only variables that failed the normality test. They were log transformed and analyzed with parametric tests. Differences between the three groups (DM1+PCOS, PCOS, and control) were assessed by one-way ANOVA, followed by the least-significant difference (LSD) test for multiple comparisons when applicable. Linear regression was used to adjust for BMI. Correlations between AMH levels and other clinical or laboratory findings were evaluated with the Pearson correlation test. All statistical calculations were run on SPSS for Windows version 11.5 (SPSS, Chicago, IL). A P value < 0.05 was considered statistically significant.

Results

The clinical characteristics of the patients are shown in Table 1. BMI and waist-to-hip ratio were higher in PCOS women than in DM1+PCOS and controls. Women with DM1+PCOS had higher waist-to-hip ratio than the control group, despite similar BMI. Ferriman-Gallwey score was similar in DM1+PCOS and PCOS women but higher than in the control group. The frequency of PCOS phenotypes differed between PCOS and PCOS+DM1 patients, with a higher prevalence of oligomenorrhea/amenorrhea in the PCOS group. A higher proportion of PCOS compared with DM1+PCOS patients fulfilled the National Institutes of Health criteria (90 *vs.* 29.4%, respectively, $P < 0.001$).

Serum testosterone, ovarian follicle count, and ovarian volume were higher in DM1+PCOS and PCOS than in con-

TABLE 1. Clinical and ultrasonographic findings in women with DM1+PCOS, PCOS, and controls

	Control (n = 35)	DM1+PCOS (n = 17)	PCOS (n = 20)
Age (yr)	26.4 ± 7.2	22.2 ± 5.6	24.5 ± 5.0
BMI (kg/m^2)	24.4 ± 3.3	24.9 ± 3.5	28.5[a] ± 6.6
Height (cm)	159.0 ± 5.8	157.1 ± 6.4	157.8 ± 5.4
Waist-to-hip ratio	0.77 ± 0.0	0.82[b] ± 0.1	0.86[c] ± 0.1
Ferriman-Gallwey score	0.9[d] ± 1.1	6.5 ± 4.6	7.5 ± 3.1
DM duration (yr)		10.5 ± 5.9	
HbA1c (%)		8.2 ± 1.4	
Insulin dose (U/kg·d)		1.2 ± 0.4	
PCOS			
Oligomenorrhea + hyperandrogenism + PCOM (%)		2 (11.8)	16 (80)[e]
Hyperandrogenism + oligomenorrhea (%)		3 (17.6)	2 (10)
Hyperandrogenism + PCOM (%)		10 (58.8)	2 (10)
Oligomenorrhea + PCOM (%)		2 (11.8)	0
Oligomenorrhea (%)		7 (41.2)	20 (100)[f]
No. of follicles	5.7 ± 2.8	10.4[g] ± 3.4	14.1[h] ± 4.6
Ovarian volume (ml)	6.0[i] ± 2.0	10.1 ± 3.1	11.9 ± 3.8

Data are shown as mean ± SD. Analysis was performed by ANOVA followed by the LSD test for multiple comparisons. HbA1c, Glycosylated hemoglobin; PCOM, polycystic ovarian morphology.

[a] $P < 0.05$ PCOS *vs.* DM1+PCOS and $P < 0.01$ PCOS *vs.* control.

[b] $P < 0.05$ DM1+PCOS *vs.* PCOS and $P < 0.05$ DM1+PCOS *vs.* control.

[c] $P < 0.001$ PCOS *vs.* control and $P < 0.05$ PCOS *vs.* DM1+PCOS.

[d] $P < 0.001$ DM1+PCOS *vs.* control and $P < 0.001$ PCOS *vs.* control.

[e] $P < 0.001$ for the proportion of different phenotypes in the two PCOS groups (Pearson's χ^2 test).

[f] $P < 0.001$.

[g] $P < 0.001$ PCOS+DM1 *vs.* control and $P < 0.01$ DM1+PCOS *vs.* PCOS

[h] $P < 0.0001$ PCOS *vs.* control and $P < 0.01$ PCOS and DM1+PCOS

[i] $P < 0.0001$ *vs.* control *vs.* DM1+PCOS and $P < 0.0001$ control *vs.* PCOS

trols. SHBG levels were normal in DM1+PCOS and decreased in PCOS, resulting in normal FAI in DM1+PCOS and elevated FAI in PCOS (Table 2). Similarly, LH/FSH ratio and androstenedione levels were higher in PCOS women than in the DM1+PCOS and control groups. However, lower DHEAS levels were observed in the PCOS group compared with the remaining groups. Differences between groups persisted after adjusting for BMI, except for estradiol. Inhibin B levels were similar in the three groups (ANOVA, $P = 0.094$).

AMH levels were elevated in PCOS patients (76.0 ± 36.3 pmol/liter), but they were not significantly different between DM1+PCOS patients (18.8 ± 7.4 pmol/liter) and controls (13.9 ± 8.3 pmol/liter, Fig. 1). Differences persisted after adjusting for BMI or androgens. Although the small numbers did not allow for statistical analyses, within each PCOS group, serum AMH seemed to be similar between the different PCOS phenotype subgroups (Fig. 1).

AMH levels correlated with follicle number in DM1+PCOS (r = 0.53; $P = 0.026$), PCOS (r = 0.6; $P = 0.018$), and control (r = 0.42; $P = 0.011$) women. In addition, AMH levels correlated with testosterone and androstenedione levels in control women only. No correlation was observed between insulin dose and AMH levels in DM1+PCOS women. The AMH/follicle number ratio was significantly increased in PCOS (6.6 ± 2.4 pmol/liter) but not in DM1+PCOS (1.9 ± 0.9 pmol/liter) and controls (2.9 ± 2.2 pmol/liter).

Discussion

The results of our study demonstrate significant differences in the phenotype and hormonal profile of patients with PCOS and DM1 compared with patients with PCOS alone, even after adjusting for BMI. Unexpectedly, AMH levels were normal in patients with PCOS+DM1. In nondiabetic patients with PCOS, the elevation of serum AMH is a typical feature; its high diagnostic value has led Pigny *et al.* (11) to postulate that it might replace ultrasonography. It appears that not all hyperandrogenic disorders exhibit the same abnormalities in follicular development and that some features may be observed exclusively in PCOS. In fact, apart from AMH, LH/FSH ratio, SHBG, androstenedione, DHEAS, and estradiol were also similar in PCOS+DM1 patients and age-matched controls. Milder endocrine and metabolic features have been described in a subset of PCOS patients according to the Rotterdam criteria: those with oligoanovulation and polycystic ovarian morphology but without hyperandrogenism (20). However, our DM1 patients do not represent this subset, because 88.2% were hyperandrogenic. Our observations suggest the existence of differences in the pathophysiology of hyperandrogenism between PCOS patients with and without DM1.

We demonstrated that AMH levels were normal in patients with PCOS and DM1, despite an elevated number of 2- to 9-mm follicles. In nondiabetic patients with PCOS, there is an increased serum AMH/follicle number ratio, which might be explained by an elevation of a nonvisible pool of follicles secreting AMH (4, 21) or by increased AMH secretion by each follicle (8, 22). The latter is supported by the observation that cultured granulosa cells obtained from PCOS patients exhibit increased AMH production *in vitro* (22). Our study shows that the serum AMH/follicle number ratio is normal in DM1 patients with PCOS. Although this finding does not allow us to draw firm conclusions on the underlying mechanism of hyperandrogenism in these patients, it suggests that follicles of DM1 patients with PCOS do not produce higher amounts of AMH. An alternative explanation might be that the increased follicle number observed by ultrasonography in DM1 patients compared with controls corresponds mostly to follicles larger than 5 mm, which produce limited amounts of AMH (4, 10). However, to support this hypothesis, we would need data on the diameter of each in patients with PCOS and DM1.

In PCOS patients, the ovary shows increased androgen

TABLE 2. Hormonal findings in women with DM1+PCOS, PCOS, and controls

	Control (n = 35)	DM1+PCOS (n = 17)	PCOS (n = 20)
LH (IU/liter)	8.4 ± 20.2	5.5 ± 3.3	9.3 ± 5.3
FSH (IU/liter)	5.9 ± 4.7	5.1 ± 1.8	5.3 ± 1.7
LH/FSH ratio	1.1 ± 0.6	1.2 ± 0.9	1.7[a] ± 0.7
Estradiol (pg/ml)	69.0 ± 27.4	66.1 ± 30.6	87.6[b] ± 21.1
Testosterone (ng/dl)	42.7[c] ± 15.6	68.1 ± 21.2	71.4 ± 27.9
FAI	5.1 ± 3.9	8.0 ± 5.2	11.8[d] ± 8.7
SHBG (nmol/liter)	45.8 ± 22.8	40.6 ± 19.5	25.9[e] ± 13.4
17OH-progesterone (ng/ml)	1.5 ± 0.5	2.0[f] ± 0.7	1.6 ± 1.0
DHEAS (ng/ml)	1278.4 ± 471.5	1639.6 ± 665.6	777.5[g] ± 1135.8
Androstenedione (ng/ml)	1.4 ± 0.5	2.1 ± 0.7	5.2[h] ± 4.3
Inhibin B (pg/ml)	128.1 ± 84.9	98.0 ± 47.1	88.6 ± 47.5

Data are shown as mean ± SD. Analysis was performed by ANOVA followed by the LSD test for multiple comparisons. To convert units to SI, for testosterone, ng/dl × 0.0347 = nmol/liter; androstenedione, ng/ml × 3.49 = nmol/liter; DHEAS, ng/ml × 0.0027 = nmol/liter; estradiol, pg/ml × 3.67 = pmol/liter; 17OH-progesterone, ng/ml × 3.03 = nmol/liter.

[a] $P < 0.05$ PCOS *vs.* DM1+PCOS and $P < 0.01$ PCOS *vs.* control.
[b] $P < 0.05$ PCOS *vs.* control and $P < 0.05$ PCOS *vs.* DM1+PCOS.
[c] $P < 0.001$ control *vs.* DM1+PCOS and $P < 0.001$ control *vs.* PCOS.
[d] $P < 0.001$ PCOS *vs.* control.
[e] $P < 0.01$ PCOS *vs.* control and $P < 0.05$ PCOS *vs.* DM1+PCOS.
[f] $P < 0.01$ DM1+PCOS *vs.* control.
[g] $P < 0.01$ PCOS *vs.* DM1+PCOS and $P < 0.05$ PCOS *vs.* control.
[h] $P < 0.001$ PCOS *vs.* DM1+PCOS *vs.* and $P < 0.001$ PCOS *vs.* control.

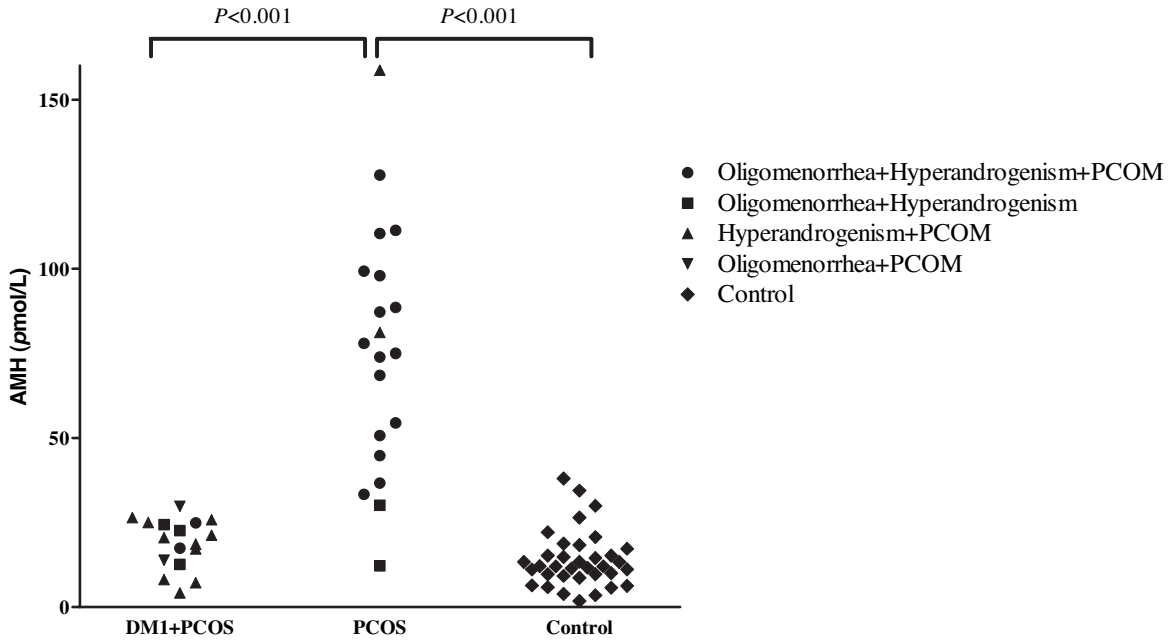

FIG. 1. Serum AMH levels in the three groups of women: DM1+PCOS, PCOS, and controls.

secretion by theca cells, even when these cells are propagated in culture (23), and altered follicle development (5). Evidence for an early onset of PCOS have been reported in children, including exaggerated adrenarche, a form of prepubertal hyperandrogenism that may frequently lead to PCOS later in life (24). In addition, we have previously shown that daughters of PCOS patients have elevated AMH levels during infancy, childhood, and puberty, suggesting the presence of an elevated growing follicle pool, even before the onset of puberty in these patients (25, 26).

The early onset of PCOS differs from what is observed in women with DM1, who may have only subtle manifestations of hyperandrogenism by the end of puberty (14) but who exhibit more marked hyperandrogenism at later stages of life (3). Studies evaluating the origin of the hyperandrogenism in women with DM1+PCOS have shown that the ovary is the main source of the elevated androgen levels (14, 27). It has been postulated that insulin, acting through the IGF-I and insulin receptors in the ovary, may stimulate androgen secretion (1, 28). In this group of women, the onset of hyperandrogenism is frequently associated with intensive insulin therapy (2, 3), especially if the disease developed before menarche (1). We postulate that the pathogenesis of hyperandrogenism in these women is related to the effect of insulin acting as a co-gonadotropin in the ovary stimulating steroid secretion and is not due to an increase in the small non-growing follicles. Likewise, insulin might be responsible for the increased number of cyclic follicles recruited. AMH is secreted mainly by small follicles before they are recruited by gonadotropin action; after recruitment by gonadotropin, follicle size increases and AMH secretion decreases. This might explain why this hormone is not elevated, even in the presence of an increased number of follicles, in DM1 patients receiving insulin treatment.

Inhibin B was not increased in either PCOS group. Previous studies have shown conflicting results regarding an elevation of this hormone in PCOS (29, 30). Inhibin B is chiefly produced by preovulatory follicles (31), which are not increased in PCOS, whereas AMH is synthesized by small preantral follicles.

Our results show that the degree of hirsutism in women with PCOS and DM1 and those with PCOS alone is mild in Chile, and its magnitude is similar in both groups. This finding is different from that reported by Roldan *et al.* (27) who described more severe hirsutism in PCOS than in hyperandrogenic diabetic women. In agreement with this report, our study confirms that total testosterone levels are similar in both groups of hyperandrogenic women but that diabetic women exhibit lower levels of androstenedione, LH/FSH, and follicle number than nondiabetic PCOS women. In addition, SHBG levels in women with PCOS and DM1 were within normal range.

We conclude that hyperandrogenic women with DM1 and PCOS exhibit normal serum AMH, estradiol, and LH/FSH levels, suggesting that the pathophysiology of hyperandrogenism is different from nondiabetic PCOS patients. More studies will be needed to clarify the mechanism of hyperandrogenism and increased follicle number that is not associated with an elevation in LH, AMH, and estradiol in DM1 patients with PCOS.

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