original article

Hirsutism in Saudi females of reproductive age: a hospital-based study

Atallah D. Al-Ruhaily, Usman H. Malabu, Riad A. Sulimani

From the Department of Medicine, King Khalid University Hospital, Riyadh, Saudi Arabia

Correspondence and reprints: Dr. Atalla Al-Ruhaily · Department of Medicine (38) King Khalid University Hospital · PO Box 7805 Riyadh 11472 Saudi Arabia · aruhaily@gmail.com · Accepted for publication August 2007

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BACKGROUND: Hirsutism among women of fertile age is commonly seen in clinical practice, but the pattern of the disease in Saudi Arabs has not been studied. The aim of the study was to determine the clinical, biochemical and etiologic features of hirsutism in Saudi females.

METHODS: 101 Saudi Arab women presenting with hirsutism at King Khalid University Hospital, Riyadh, Saudi Arabia, from 1 January 2000 to 31 December 2005 were prospectively assessed using the recently approved diagnostic guidelines for hyperandrogenic women with hirsutism.

RESULTS: Polycystic ovary syndrome (PCOS) was the cause of hirsutism in 83 patients (82%) followed by idiopathic hirsutism (IH) in 11 patients (11%). Others causes of hirsutism included late onset congenital adrenal hyperplasia in 4 patients (4%), microprolactinoma in 2 (2%) and Cushing's syndrome in 1 (1%) patient. Age at presentation of PCOS was 24.5±6.6 years (mean±SD) and 51% of the subjects were obese. Furthermore, 74 (89%) of patients with PCOS had an oligo/anovulatory cycle while the remaining 9 patients (11%) maintained normal regular menstrual cycle. Luteinizing hormone and total testosterone were significantly higher in patients with PCOS than in those with IH ($P<.05$).

CONCLUSIONS: The present data show PCOS to be the commonest cause of hirsutism in our clinical practice and PCOS is prominent amongst young obese females. However, further studies on a larger scale are needed to verify our findings.

Hirsutism is a common endocrine disorder among women of fertile age.[1,2] Of the various etiologies of hirsutism, polycystic ovary syndrome (PCOS) is reported to be the commonest cause worldwide.[3,4] In Saudi Arabia, the prevalence of PCOS is still unknown but it is the authors' belief that it might be similar to other reports.[4] The lack of international consensus on the definition of PCOS prior to the year 2003 accounted for the widely variable prevalence in the world. For instance, using ultrasound according to European criteria, 91% of cases of hirsutism were due to PCOS in the United Arab Emirates[5] yet others reported a rate as low as 59% in the same region.[6] As far as we know, no study has been conducted using the recently approved consensus opinion on diagnostic criteria for diagnosis of PCOS[7] in Saudi patients. Furthermore, there is no study on the pattern of hirsutism in the local population despite it being commonly seen in clinical practice, with its associated infertility and metabolic syndrome.[8,9] The aim of the study therefore was to determine clinical, biochemical and etiologic features of hirsutism in Saudi females.

METHODS

We studied a consecutive series of 148 Arab Saudi women presenting with hirsutism to the endocrinology clinic at King Khalid University Hospital, Riyadh, Saudi Arabia from 1 January 2000 to 31 December 2005. Patients were examined for the severity of hirsutism according to modified Ferriman and Gallwey scale.[10] Women who scored 8 or more were included in the study. Using this scale, we assessed the growth of terminal hairs on the upper lip, sideburn area, chest, upper abdomen, and lower abdomen. Acne was also assessed. The presence of comedones on the face, neck, upper chest, upper back, or upper arms was classed as acne. Patients who were taking drugs that might interfere with the results (oral contraceptives, prolactin-lowering drugs, and any drug given for hirsutism) and those who failed to report at any scheduled follow-up visit were excluded from the study. Other exclusion criteria included pregnancy, breastfeeding, known liver or kidney

disease, alanine aminotransferase >60 IU/L, creatinine >130 µmol/L, and known alcohol abuse. Only 101 subjects were evaluable at the end of the study. The clinical evaluation consisted of a detailed history, including the rapidity of onset of symptoms, the presence of symptoms of virilization or other endocrinopathies or metabolic disorders, menstrual and reproductive history, and drug and family history. Subjects were assessed for the presence of other signs of hyperandrogenism and virilization and for stigmata of endocrinopathies, and abdominal masses. Height and weight were measured to calculate body mass index (BMI) in kg/m^2.

PCOS was diagnosed based on the presence of 2 out of 3 of the following: 1) oligo- or anovulation and exclusion of other etiologies (congenital adrenal hyperplasia, androgen secreting tumors, Cushing's syndrome), 2) clinical and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries as recommended by the 2003 consensus diagnostic criteria.[7] Ultrasonographic examinations were performed on average 4 weeks after the clinical evaluation. Patients were examined in a supine position with a 6-MHz probe, and a polycystic ovary was considered based on presence of 12 or more follicles in each ovary measuring 2-9 mm in diameter, and/or increased ovarian volume (>10 mL) according to the guideline.[7] A regular menstrual cycle was defined as one between 21 and 35 days with no more than a 4-day variation. Oligomenorrhea was defined as menstrual cycles >35 days in length and amenorrhea was defined as an absence of a menstrual period in more than 6 months. Without the presence of menstrual disturbances and any other signs or symptoms of hyperandrogenism, except hirsutism, the diagnosis of idiopathic hirsutism (IH) was made. Hyperandrogenemia plus hirsutism (HH) was defined by the presence of elevated androgen levels and hirsutism but normal ovulation.[11] Patients with evidence of ovulatory dysfunction underwent measurements of serum prolactin and thyroid-stimulating hormone levels to exclude a prolactin secreting adenoma and thyroid dysfunction, respectively. Screening for Cushing's syndrome was performed by either an overnight dexamethasone suppression test (i.e. measurement of a cortisol level the morning after the administration of 1 mg dexamethasone orally at bed time) or by measuring 24 hr urine free cortisol content. All patients had a 2-day laboratory evaluation on days 20-22 of the menstrual cycle (when applicable) in order to characterize ovulatory dysfunction and hormonal profile in the luteal phase. On day 1 a random blood sample was obtained for total testosterone, androstenedione (A), dehydroepiandrosterone sulphate (DHEAS), prolactin (PRL), progesterone (P), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), T3, and T4. 21-hydroxylase deficiency was excluded by a basal follicular phase 17-hydroxyprogesterone (17-OHPG) level <6.0 ng/mL. Subjects with a basal 17-OHPG level equal to or higher than 6.0 ng/mL underwent an acute ACTH stimulation test, in which 250 ug of cortrosyn (alpha 1-24 corticotrophin) was administered and 17-OHPG levels were determined immediately before and again after 30 and 60 minutes. ACTH stimulated 17-OHPG levels >10 ng/mL were considered the criteria for 21-hydroxylase deficient late onset congenital adrenal hyperplasia (LOCAH) while values > 30 ng/mL were the criteria for classical congenital adrenal hyperplasia.[12]

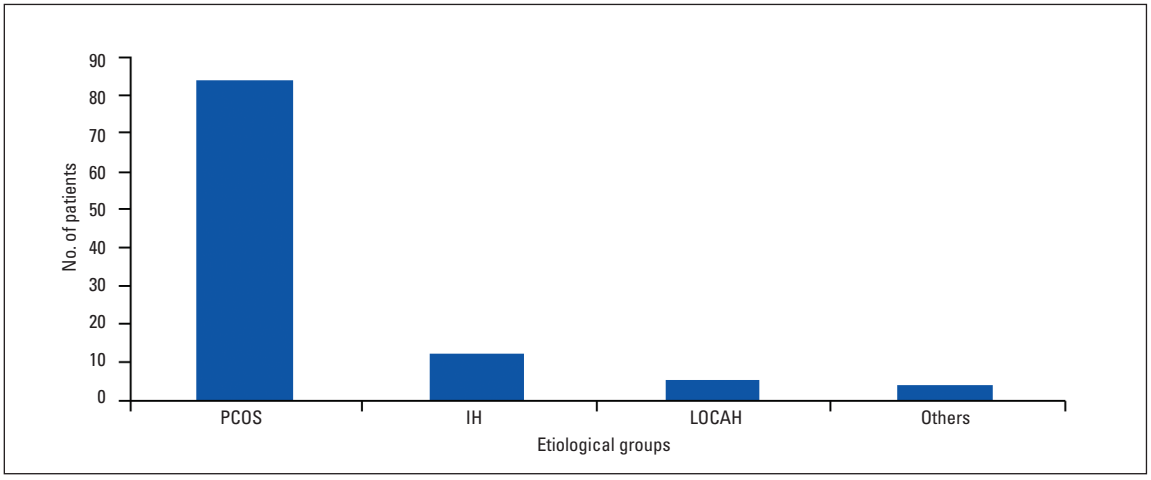

Figure 1. Etiology of hirsutism in the study population. Polycystic ovary syndrome (PCOS), idiopathic hirsutism (IH), late-onset congenital adrenal hyperplasia (LOCAH).

All statistical procedures were performed using SPSS. Values were reported as mean and standard deviation and when applicable, standard error of the mean. Differences between groups were evaluated with two tailed t-tests for independent samples or the Mann-Whitney z-test, where normality could not be assumed. Pearson correlation coefficients were calculated for correlation analyses. Two-tailed *P*-values <0.05 were considered significant. Simple linear regression analyses were formed for the investigation of linear trends.

RESULTS

PCOS was the cause of hirsutism in 83 patients (82%) followed by idiopathic hirsutism (IH) with 11 patients (11%) (Figure 1). Others causes of hirsutism in our study included late-onset congenital adrenal hyperplasia in 4 patients (4%). Of the miscellaneous causes, 2 patients (2%) had microprolactinoma and 1 patient (1%) had Cushing's syndrome. Of the two major groups identified, PCOS and IH, there were no significant differences between the groups in terms of age at presentation, distribution of hirsutism, body weight or BMI (Table 1). Overall, 51% of PCOS and 45% of IH patients were obese. Hirsutism scores were 20.1±7.8 in PCOS and 16.6±6.2 in patients with IH; the differences were not significant (Table 1). Seventy-four patients (89%) with PCOS had oligo/anovulatory cycle while the remaining 9 patients (11%) maintained normal regular menstrual cycle.

The distribution of BMI among patients with PCOS is shown in Table 2. Biochemical characteristics of the patients based on etiology are shown in Table 3.

Table 1. Clinical characteristics of the study population according to major etiologic groups.

Parameter	Polycystic ovary syndrome	Idiopathic hirsutism
Number	83	11
Age	24.5±6.6	28±8.2
Weight (kg)	76.0±19.6	73.9±17.3
Body mass index	30.9±8.1	30.7±8.0
Ferriman score	20.1±7.8	16.6±6.2
Family history	28%	29%
Acne	51%	55%
Frontal balding	22%	45%
Obesity	51%	45%
Oligo-ovulatory	89%	0%

Values are mean±standard deviation for age, weight, body mass index, and Ferriman score. PCOS, polycystic ovary syndrome; IH, idiopathic hirsutism.

There were no significant differences between groups for metabolic tests such as fasting blood glucose, 2-hour post-prandial blood glucose and cortisol. As would be expected, LH was higher in the PCOS group compared to the IH group, but the difference was not statistically significant. Furthermore, there was a significant difference in the LH-FSH gradient (serum LH level subtracted from serum FSH level) whereby the values were higher for the PCOS patients compared with the other two groups ($P<.05$). In contrast, IH subjects had significantly higher FSH levels when compared to PCOS ($P<.05$). Total testosterone was found to be significantly higher in PCOS patients compared to IH patients ($P<.0.05$). Serum levels of progesterone, estradiol, prolactin, androstenedione, and DHEAS did not differ between the two main etiologic groups. According to our diagnostic guideline for LOCAH,[12] four patients met the criteria for 21-hydroxylase deficiency.

DISCUSSION

We have reported our experience evaluating 101 Saudi Arab patients presenting to our endocrine clinic with hirsutism. Of the patients included in the study, 82% had hirsutism caused by PCOS. This is similar to large studies reported by others.[1,11,15] However, a close look at our data revealed that 75% of the subjects studied were less than 30 years of age at the time of their initial visit and 51% were obese (BMI ≥30 kg/m^2). Thus, the prevalence of obesity among our relatively young patients was higher than in the general population. For example, the Saudi National Survey indicated that the prevalence of obesity in women was 44%,[16] a higher prevalence than our PCOS subjects. In population studies, 10% to 38% of women with PCOS were obese.[17-20] Thus, the high prevalence of obesity in our PCOS patients may reflect an overall pattern of obesity in our general female population.[16]

Table 2. Distribution of body mass index in patients with polycystic ovary syndrome.

Body mass index in kg/m^2	Number (%)
<19 (underweight)	2 (2.7)
19-24.9 (normal weight)	13 (17.6)
25-29.9 (pre-obese)	19 (25.7)
30-34.9 (mildly obese)	18 (24.3)
35-39.9 (moderately obese)	12 (16.2)
>40 (severely obese)	10 (13.5)

According to 1998 World Health Organization and 1999 National Center for Health Statistics/Centers for Disease Control and Prevention criteria.[13,14]

Insulin resistance with compensatory hyperinsulinemia has been associated with PCOS and is thought to contribute to other features of the metabolic syndrome.[9] Hyperandrogenism has been found to manifest clinically by frontal balding, acne, hirsutism, and clitoromegaly. In our series, we found that over half of the patients in both PCOS and IH had acne, an observation similar to others.[6] Nevertheless, there were no differences in metabolic data amongst the groups, which was similar to the report by Taponen et al[21] but different from others.[22] This disparity might be due to a higher prevalence of metabolic syndrome in our study population.[23] The prominence of frontal balding in patients with IH as compared to PCOS is not explained. However, it might be due to the small sample size in the IH group. Further studies on a larger population are needed to characterize this finding.

In our series, 9% of patients diagnosed with PCOS had hirsutism in addition to biochemical hyperandrogenism, yet they maintained a normal menstrual cycle. Azziz et al reported and introduced a new term, hyperandrogenism plus hirsutism (HH), for the category of hirsute women with normal regular menses that are also hyperandrogenic.[11] The controversy over the disparity between the clinical manifestations of hyperandroginism including menstrual irregularity and the metabolic data suggestive of hyperandrogenism was settled in the recently reviewed international consensus on diagnostic criteria for PCOS.[7,15] Based on the new guideline we included the HH into PCOS. In retrospect, Gatee et al reported a higher prevalence of 26% of HH from the same racial group in the neighboring United Arab Emirates.[5]

Previously, most hirsute women were labeled as having 'idiopathic hirsutism', but up to 60% of these women do have some disturbances in androgen metabolism.[11,24] Furthermore, more than 90% of patients with IH were proved to have PCOS.[25,26] Lack of uniformity in agreeable guidelines for diagnosis of PCOS might account for the higher figure of IH in older series.[27,28] In an attempt to unify the diagnosis of PCOS, a joint European and American group came up with a consensus opinion on the diagnostic criteria we used in our study.[7] According to the new guideline, PCOS is diagnosed if two of the following three criteria are present, after the exclusion of other etiologies: 1) oligo- and/or anovulation, 2) clinical and/or biochemical signs of hyperandrogenism, and 3) polycystic ovaries on ultrasonography.[15]

Other etiologies of hirsutism were not common in our study group, which is reflected in the observations of others in the region.[5,6] Of the less common causes, LOCAH was found in 4% of patients, higher than the 1.6% reported in Whites, but lower than the 9.5% reported in patients of Mediterranean descent.[29] The relatively higher prevalence of LOCAH in this study may reflect the pattern of referrals received by our unit, which is a referral center for all of Saudi Arabia, and may differ from the prevalence in the community. However, the overall pattern of PCOS being the commonest is the same as seen all over the world.[3,5,11] Two patients had hyperprolactinemia, which may be part of the syndrome of PCOS.[30] However, these patients lacked the full-blown picture of PCOS, which includes biochemical hyperandrogenism and one patient did not have menstrual disturbances. Furthermore, the typical polycystic ovaries were lacking. Both were proven on pituitary MRI to have adenoma with a normal thyroid function test and both responded well to bromocriptine.

Thus, our data shows that PCOS is the commonest cause of hirsutism in our clinical practice and that it is prominent among young obese females, which reflects the worldwide pattern. Our findings call for an early intervention strategy to prevent or reduce metabolic syndrome in this subgroup of the population. Further prospective studies on a larger scale are needed, however, to verify our findings.

Table 3. Biochemical characteristics of the study population by diagnostic groups.

Biochemical Test	PCOS	IH
Fasting blood glucose (mmol/L)	6.0±2.4	6.5±4.0
2 hr postprandial blood glucose (mmol/L)	6.8±4.0	7.9±3.6
Total testosterone (nmol/L)	2.9±1.7	1.4±0.4**
Androstenedione (nmol/L)	3.2±2.3	1.6±1.0
DHEAS (ng/mL)	1365±1114	926±1188
LH (IU/L)	8.5±7.2	4.3±1.2
FSH (IU/L)	5.5 ±2.2	7.2±4.2**
LH/FSH	2.4±6.3	0.7±0.2
LH-FSH gradient (IU/L)	3.1±7.5	–2.8±3.8**
Progesterone (ng/mL)	2.0±4.5	0.6±0.3
Estradiol (pmol/L)	302±420	278±74
Prolactin (ng/mL)	403±303	378±190
Cortisol (nmol/L)	299±175	296±221

PCOS, polycystic ovary syndrome; IH, idiopathic hirsutism; DHEAS, dehydroepiandrosterone sulfate; LH, luteinizing hormone; FSH, follicle stimulating hormone; ** $P<0.05$ PCOS vs IH.

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