Clinical Presentation and Etiologic Factors of Hirsutism in Premenopausal Iranian Women

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Background: Hirsutism is a common clinical condition with different etiologies. Many of these patients have frank or subclinical abnormalities in the adrenal and ovarian steroidogenesis. The disease may be associated with other clinical signs of hyperandrogenism. The objective of this study was to investigate the clinical features of hirsutism and its etiologic factors in premenopausal Iranian women.

Methods: In a cross-sectional study, 790 consecutive premenopausal women referred to the dermatology Clinics of Hazrat-e Rasool and Firoozgar University Hospitals and three private dermatology clinics during 2001 – 2003 with the clinical diagnosis of hirsutism were studied. All patients underwent detailed clinical assessment and transabdominal ultrasonography of the ovaries. Endocrinologic work-up was performed for 285 patients.

Results: Hirsutism was mild in 65%, moderate in 32.5%, and severe in 2.5% of the patients. Positive family history was found in 56.2%. Hormonal studies revealed some abnormalities in 35.2% of the patients. Coexisting medical conditions included acne in 70% of the patients, menstrual irregularity in 38.6%, androgenic alopecia in 21.3%, obesity in 6.5%, acanthosis nigricans in 4.9%, and diabetes in 0.6% of the patients. Etiology of hirsutism was identified as polycystic ovary syndrome (62.53%), idiopathic (35.19%), congenital adrenal hyperplasia (0.38%), prolactinoma (0.13%), and undetermined (1.77%). Polycystic ovary syndrome was diagnosed more frequently in women with menstrual irregularity than eumenorrheic patients (97.70% vs. 40.41%, P < 0.001).

Conclusion: Hirsute patients frequently have either elevated androgen levels or clinical conditions associated with hyperandrogenemia. Eumenorrhea does not rule out endocrine abnormality and particularly polycystic ovary syndrome which is a common cause of hirsutism. We recommend performing endocrinologic work up, investigation of coexisting hyperandrogenic states, and evaluation of polycystic ovary syndrome in all patients with hirsutism.

Keywords: Androgens • hirsutism, endocrine diseases • polycystic ovary syndrome

Introduction

Hirsutism is defined as the abnormal growth of terminal hair in an androgen-dependent pattern in women. The involved sites include face, chest, areolae, lower abdomen, and crural area. In severe cases shoulder area, lower back, upper abdomen, and upper arms are also affected. Patients may show clinical signs of virilization such as frontoparietal (male-pattern) hair loss, acne, amenorrhea, and sometimes masculinization of the muscle mass, hypertrophy of vocal cords, or clitoromegaly.1,2 Hirsutism may be associated with obesity, insulin resistance, diabetes, polycystic ovary syndrome (PCOS), hypertension, infertility, and menstrual irregularities.1,3

The threshold level for acceptable amount of excessive hair varies in different cultures. Some women with minimal degrees of hirsutism may be psychologically devastated, while others accept...
more severe forms without much concern.²

The prevalence of hirsutism is higher in Mediterranean and South Americans than Indians and Mongoloids.¹ ³ Some families are affected more than the others. The prevalence of hirsutism has been reported 8% in the United States and 10.5% in Kashmir, India.¹ It should be mentioned that the affected areas most concern to the patients include upper lip, chin, chest, and areola.³ The degree of hirsutism in different parts of the body is assessed by the Ferriman and Gallwey score.⁵

Stress has been proposed as a contributing factor in hirsutism.² The number of hirsute patients referred to dermatology clinics in Iran has increased dramatically over the last two decades. Whether this can be attributed to stress and psychologic trauma of eight years of war between Iran and Iraq, or the changing lifestyle and nutritional habits needs further investigation. The objective of this study was to investigate the clinical features of hirsutism and its etiologic factors in premenopausal Iranian women.

**Patients and Methods**

In this cross-sectional study, 790 consecutive Iranian hirsute patients aged between 10 and 45 years referred to the Dermatology Clinics of Hazrat-e Rasool and Firoozgar University Hospitals and three private dermatology clinics during 2001 – 2003 were investigated. None of the patients suffered from any chronic or acute diseases. Women who were pregnant or lactating, those who received oral contraceptive pills or other drugs that could interfere with the hormonal and metabolic studies, and postmenopausal women were excluded from the study. Informed consent was obtained from each patient, and the study protocol was approved by Iran University of Medical Sciences’ Review Board.

Personal medical history was obtained from each patient using a questionnaire including age, age at onset of the disease, marital status, parity, personal history of diabetes mellitus, hypertension and history of drug use or any kind of hormonal contraception. Menstrual cycle history included age at menarche and a detailed recall of the last 2 – 3 years, to detect age at menarche and the presence of menstrual irregularities. The menstrual patterns were defined as regular cycles, if length of cycle was between 22 and 40 days. The cycle was considered irregular if the patient had either oligomenorrhea (bleeding at intervals of greater than 40 days), polymenorrhea (bleeding at intervals of less than 22 days), or amenorrhea (absence of menstruation for 12 months or more).⁶ A careful family history of hirsutism was obtained.

Body mass index (BMI; weight/height²) was also measured. Obesity was defined as a BMI ≥ 25 kg/m². Three dermatologists examined the patients for clinical evidence of acne, androgenic alopecia, acanthosis nigricans (AN), and galactorrhea. The degree of hirsutism was assessed using the Ferriman and Gallwey score in the face (chin, upper lip), areola and chest, upper back, lower back, upper abdomen, lower abdomen, thighs, and upper arms. The overall score in all of the affected parts was also assessed. Hirsutism was classified as mild (score 8 – 16), moderate (score 17 – 24), and severe (score >24).³ ⁵

A transabdominal ultrasonography was done for all patients in the early follicular phase (5 – 9th days of the menstrual cycle) and PCO was defined as the presence of bilaterally normal or enlarged ovaries containing at least 10 microcysts (2 – 8 mm in diameter) on ultrasonography.⁷ – ¹⁰ Hormonal profile was assessed in all patients with severe hirsutism (n = 20). Of women with mild and moderate hirsutism, 265 patients were selected through a stratified random sampling — i.e., one from every three consecutive patients in each group — for blood survey. Blood sampling was done in the early follicular phase of spontaneous or induced (by medroxyprogesterone acetate [MPA] 10 mg/day for 7 days) menstrual cycles (day 5 – 9). After overnight fasting for 10 – 12 hours, blood samples were collected around 8 – 9 AM to measure serum levels of follicular stimulating hormone (FSH), luteinizing hormone (LH), prolactin (PRL), total testosterone (Test), dehydroepiandrosterone sulfate (DHEA-S), 17-alpha-hydroxyprogesterone (17-OH-P), and fasting plasma glucose (FPS). All hormone assays were performed with commercial radioimmunoassay kits (Immunotech, Marseille, France) at a reference laboratory, so that the results could be comparable between groups. Plasma glucose concentrations were determined by the glucose oxidase technique with a glucose analyzer (Beckam, Fullerton, CA, USA). The patients then underwent an oral glucose tolerance test (OGTT). Diabetes was defined in accordance with the criteria of the World Health Organization (WHO) by an FPS ≥ 126 mg/dL or a plasma glucose level of 200 mg/dL or more two hours after ingestion of 75 g glucose dissolved in 150 mL water. If serum 17-OH-P level was 300 –
800 ng/dL, an adrenocorticotropic hormone (ACTH) stimulation test (250 µg IV, Synachten; Ciba-Geigy, Basel, Switzerland) was performed to detect the late-onset congenital adrenal hyperplasia (CAH). According to the 2003 international consensus,7 PCO was defined as the presence of at least two of the following signs after exclusion of other causes of androgen excess: 1) oligoovulation or anovulation which usually manifested as oligomenorrhea or amenorrhea; 2) elevated levels of circulating androgens (hyperandrogenemia) or clinical manifestations of androgen excess (hyperandrogenism); and 3) PCOs in ultrasonography.

Statistical analyses were done by SPSS® version 10.5. The $\chi^2$ test was used for comparison between categoric variables and the Student’s $t$-test for comparison of means between two continuous variables. $P < 0.05$ was considered significant.

**Results**

**Clinical features**

Seven hundred and ninety hirsute patients with the mean age of 20.9 (range: 10 – 45) years were studied. Most of the patients (86.6%) were 16 to 35 years old at the time of the first diagnosis (Figure 1). There were 212 married patients (26.8%), among whom only 44 (5.6% of the patients) had children. Overall, 444 patients (56.2%) had a positive family history of hirsutism.

According to Ferriman and Gallwey score, hirsutism was mild in 65% moderate in 32.5%, and severe in 2.5% of the patients. The involved sites in the order of decreasing frequency included face in 709 (89.7%), lower abdomen in 595 (75.3%), areola in 518 (65.4%), inguinal region and upper thighs in 509 (64.4%), and chest in 413 (52.3%) patients. In 295 (37.3%) women, all of the above-mentioned sites were affected. Involvement of the upper abdomen, shoulders, lower back, and upper arms was rare.

None of the patients had signs or symptoms of severe virilism. Acne was the most frequent (70%) sign of hyperandrogenism in our patients, followed by menstrual irregularity (38.6%) and androgenic alopecia (21.3%).

Fifty-one patients had a BMI $\geq$ 25 kg/m² and, thus, were considered obese. They had a mean score of hirsutism (16.2) significantly ($P < 0.05$; nonpaired Student’s $t$-test) higher than those with normal weight (14.1). AN was found in 39 patients, 29 (74.4%) of whom were obese. The prevalence of AN was significantly ($P < 0.001$; $\chi^2$ test) higher (56.9%) in obese hirsute women than hirsute patients with BMI $< 25$ kg/m² (1.4%). Overt diabetes was diagnosed in only five patients.

Assessment of menstrual cycle revealed that most of the patients (75.1%) had their first menstrual cycle at the age of 12 – 14 years, which is in accordance with the national demographic data. Menstrual cycle was regular in 485 (61.4%)
patients, while 305 (38.6%) women had irregular menses including oligomenorrhea (28.4%), amenorrhea (8.8%), or polymenorrhea (1.4%). The majority (97.7%) of the 305 women with both hirsutism and menstrual irregularity had PCOS. Four out of 305 patients had minor hormonal dysregulations, which could not be classified; two were diagnosed to have CAH and one had prolactinoma. It is noteworthy that among patients with normal menstrual cycle, 196 (40.4%) patients had PCOS, one had CAH, and only 278 (57.3%) patients had idiopathic hirsutism.

**Etiologic aspects**

The results of endocrine work-ups are shown in Table 1. Hormonal abnormalities were found in 185 (64.9%) of the 285 patients studied. Mild to moderate elevation of androgens consistent with levels observed in PCOS was the most encountered abnormality. Only one patient had prolactinoma with a serum prolactin level of 890 ng/dL. Serum level of 17-OH-P was >300 ng/dL in three patients who were subsequently diagnosed to have CAH. Two patients with CAH had moderate hirsutism and abnormal menses; one of them, nonetheless, had apparently normal menses, mild hirsutism, and none of the other symptoms of hyperandrogenism.

The relative frequency of different etiologies of hirsutism observed in our patients is shown in Table 2. Among different diagnoses, PCOS ranked first with 494 (62.5%) patients being affected. PCOS was significantly more frequent in women with irregular menses (97.7%) than eumenorrheic patients (40.4%). Among patients with PCOS, 74.9% had PCOs detected by abdominal ultrasonography, and 60.3% had irregular menses.

Idiopathic hirsutism, defined as hirsutism in association with regular menses and normal hormonal levels, was the next frequent (35.2%) diagnosis made. Fourteen patients had irregular menses or minor hormonal irregularities but none fulfilled the diagnostic criteria for PCOS or other endocrinopathies and, thus, were categorized as hirsutism of undetermined origin.

Comparison of the mean hirsutism score among different etiologic groups with one-way ANOVA revealed no statistically significant differences.

Table 3 shows the prevalence of coexisting conditions among different groups of patients with hirsutism. Compared to idiopathic hirsutism, hirsute women with PCOS had a significantly higher frequency of acne ($P < 0.001; \chi^2$ test), androgenic alopecia ($P = 0.002; \chi^2$ test), and AN ($P = 0.001; \chi^2$ test); while frequency of obesity ($P = 0.286; \chi^2$ test) and diabetes was not significantly different ($P = 0.926; \chi^2$ test) between the two groups.

**Discussion**

Hirsutism is a common clinical condition that usually has a benign course. In rare cases, however, it may be the presenting feature of a serious underlying disease which needs diagnosis and aggressive treatment. It should be differentiated from hypertrichosis, which is defined as the excessive growth of hair independent of androgens and is usually of vellus type.1 The intensity of hirsutism in particular areas of the body varies in different patients and depends on the rate of androgen excess, or increased sensitivity of hair follicles to normal levels of androgens in the serum. The most frequently involved sites are face, periumbilical and lower abdomen, areola, upper thighs, and chest, as shown in the literature.10–12

There are several probable etiologies for the disease. It can occur idiopathically, or due to ovarian disorders (e.g., PCOS, hyperthecosis, and ovarian tumors), adrenal causes (e.g., classic or late-onset CAH, adrenal tumors, and Cushing’s syndrome), prolactinoma, pregnancy, or postmenopausal state. Some cases are iatrogenic.1 Excessive production of androgens from adrenals or ovaries accounts for 60 – 80% of cases of

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**Table 1. Frequency of hormonal abnormalities in patients with hirsutism ($n = 285$).**

<table>
<thead>
<tr>
<th>Hormonal abnormality</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone</td>
<td>58 (20.4)</td>
</tr>
<tr>
<td>LH</td>
<td>49 (17.2)</td>
</tr>
<tr>
<td>DHEA-S</td>
<td>47 (16.5)</td>
</tr>
<tr>
<td>LH/FSH ratio</td>
<td>30 (10.5)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>10 (3.5)</td>
</tr>
<tr>
<td>17-OH-P</td>
<td>7 (2.5)</td>
</tr>
</tbody>
</table>

**Table 2. Characteristics of different etiologic groups in hirsute women.**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n (%)</th>
<th>Mean ± SD hirsutism score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>494 (62.5)</td>
<td>14.3 ± 4.1</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>278 (35.2)</td>
<td>14.1 ± 3.9</td>
</tr>
<tr>
<td>CAH</td>
<td>3 (0.4)</td>
<td>9.2 ± 6.1</td>
</tr>
<tr>
<td>Prolactinoma</td>
<td>1 (0.1)</td>
<td>13</td>
</tr>
<tr>
<td>Undetermined</td>
<td>14 (1.8)</td>
<td>12.8 ± 8.3</td>
</tr>
</tbody>
</table>

CAH = congenital adrenal hyperplasia; PCOS: Polycystic ovary syndrome.
hirsutism in different studies. In our study, we found hyperandrogenemia in 46.7% of the patients.

One of the most common causes of hirsutism is PCOS, which was diagnosed in 62.5% of our patients. PCOS is the most common endocrine abnormality affecting women in the reproductive age group with an estimated prevalence of 5 – 10%. In Northern Finland Birth Cohort of 1966, PCO morphology was detected in 18.4% of the patients who reported only hirsutism, in 47.9% of those reporting only oligomenorrhea, and in 70.4% of those reporting both symptoms. gate et al reported the presence of PCO in 91% of 102 hirsute patients in the United Arab Emirates. In a study of 60 hirsute patients in India by Mithal et al PCO was found in 75% of the cases. In similar studies, Zargar et al found an incidence of 37.3% of 150 patients in Kashmir, India. Moran et al reported PCO in 53% of 250 Mexican hirsute patients. Erkkola and Ruutiaien studied 229 patients in Finland and found evidence of PCO in 33%. In England, an incidence of 60% has been reported. The corresponding figure in the United States has been near 70 – 78%. In a previous study, Farnaghi and Seyrafi evaluated 110 Iranian hirsute patients and found 49% of them with evidences of PCO. One of the important findings in our study is that history of normal menstrual cycle does not rule out the diagnosis of PCOS, as we found evidence of this syndrome in 40.4% of hirsute women with normal menses. Early detection of PCOS is of paramount importance because of the substantial risk for the development of metabolic and cardiovascular abnormalities similar to those that make up the metabolic syndrome. So, we recommend close follow-up of all hirsute patients, even those with normal menses, for clinical and laboratory signs of PCOS.

17-OH-P is a hormone, which might be mildly elevated in patients with PCO, or more significantly increased in patients with CAH. The finding of mild elevation of 17-OH-P in 2.4% of our patients is in accordance with the findings of Zargar et al. Most of these cases were due to PCO; yet, we found significant elevations of this hormone, which is indicative of CAH in three cases. The clinical presentation of late-onset CAH is indistinguishable from that of other hyperandrogenic states causing hirsutism. ACTH stimulation test is the only way to diagnose this entity. As patients might have normal menses and only mild degrees of hirsutism (as one of our patients), the probability of CAH should be kept in mind in any patients with hirsutism and/or other manifestations of hyperandrogenemia.

Often, hirsutism occurs in a familial basis. This is due to the familial clustering of some of its underlying diseases (e.g., CAH or PCOS). It has been shown that 35% of mothers and 40% of sisters of patients with PCOS are affected by PCOS, themselves. A positive family history of hirsutism was found in 56.2% of our patients. So, obtaining a family history might be useful in finding the etiology of excessive growth of hair.

Hirsutism might be associated with other clinical signs of hyperandrogenism, metabolic, or endocrine disturbances. One of the contributing factors to hyperandrogenemia is increased adiposity, particularly visceral adiposity that is reflected by an elevated waist circumference (>88 cm). Other possible consequences of obesity are insulin resistance, glucose intolerance, and dyslipidemia. The prevalence of obesity in patients with PCOS or hirsutism is different in various populations. We found obesity (BMI ≥ 25 kg/m²) in 6.4% of our patients. This is similar to the reported figure of 7% in Finland. The prevalence among hirsute Mexicans was higher (18%), which might be explained by the higher prevalence of obesity in Mexico for the genetic susceptibility or environmental factors.

Hirsute patients have a high risk for development of diabetes, although this could be due to the higher number of overweight patients among this population. In a retrospective study of

### Table 3. Frequency of coexisting conditions in two major groups of hirsutism.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>PCOS</th>
<th>Idiopathic</th>
<th>All groups</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acne</td>
<td>336 (68.0)</td>
<td>212 (76.3)</td>
<td>553 (70.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Menstrual irregularity</td>
<td>298 (60.3)</td>
<td>51 (6.5)</td>
<td>349 (9.1)</td>
<td>0.286</td>
</tr>
<tr>
<td>Androgenic alopecia</td>
<td>124 (25.1)</td>
<td>40 (14.4)</td>
<td>168 (21.3)</td>
<td>0.002</td>
</tr>
<tr>
<td>Obesity</td>
<td>29 (5.9)</td>
<td>22 (7.9)</td>
<td>51 (6.5)</td>
<td>0.026</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>35 (7.1)</td>
<td>4 (1.4)</td>
<td>39 (4.9)</td>
<td>0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>3 (0.6)</td>
<td>2 (0.7)</td>
<td>5 (0.6)</td>
<td>0.926</td>
</tr>
</tbody>
</table>

*χ² test, comparison between PCOS and Idiopathic groups; †Idiopathic hirsutism was defined as hirsutism with normal menses and laboratory tests.
hirsute patients, 4.9% had previously-undiagnosed diabetes and 50% had hyperinsulinemia. Insulin resistance is a major event in the pathogenesis of PCOS and as many as 10% of PCO patients have type 2 diabetes by their fourth decade of life. However, we found no significant differences in diabetes prevalence between idiopathic hirsutism and patients with PCOS. This finding is consistent with some previous studies. One possible explanation could be that women with idiopathic hirsutism have subclinical hormonal imbalances which are responsible for abnormalities in the glucose metabolism but are not severe enough to cause menstrual irregularities or other signs of hyperandrogenism.

AN is a cutaneous marker of hyperinsulinemia which frequently accompanies hyperandrogenemia. In a study of hyperandrogenic women with impaired glucose tolerance (IGT) and/or hyperinsulinemia, AN was found in up to 29% of hirsute patients. This high prevalence might be due to the selection of patients with IGT which have a strong correlation with AN. We found AN in 4.9% of our patients; from these patients, 89.7% had PCOS. On the basis of this finding, we would recommend careful investigation for PCOS in hirsute woman with AN.

Idiopathic hirsutism was the final diagnosis made in 35.2% of our patients. The corresponding figure has been 5% in the United Arab Emirates, 15% in the USA, 17% in India, 25% in Mexico, and 38% in Finland and England. The difference between these figures reflects the variable extent of hormonal and metabolic studies which have been performed before assigning the label of “idiopathic hirsutism” to a patient. The diagnosis of idiopathic hirsutism should be applied only to hirsute patients with normal ovulatory function and circulating androgen levels. It is noteworthy that a history of regular menses is not sufficient to exclude ovulatory dysfunction, since 57.3% of eumenorrheic hirsute women in our study had idiopathic hirsutism. This is similar to the previous study by Azziz et al who have shown evidence of anovulation in up to 40% of eumenorrheic hirsute women. Some authors question the existence of “idiopathic hirsutism” and believe that all patients with hirsutism will show some metabolic or endocrine disturbances if exhaustive investigations are performed. It has been suggested that idiopathic hirsutism is associated with insulin resistance and an increased prevalence of IGT in obese patients. Further, idiopathic hirsute women with normo-androgenemia show an increased ovarian secretion of 17-OH-P and a minimally elevated adrenal delta 4-17, 20-lyase activity, suggesting that mild forms of ovarian and adrenal functional hyperandrogenism may be present in these patients. Therefore, patients with the so-called “idiopathic hirsutism” may experience several metabolic disturbances and need careful evaluation and long-term follow-up.

This study further highlights the need for a careful study of hyperandrogenemia and its associated conditions in patients with hirsutism to detect the possible associated abnormalities in an early and curable stage and to prevent the development of further metabolic complications.

References


