The spectrum of androgen excess disorders

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A better understanding of the different phenotypes and of their endocrine and metabolic characteristics permits investigators to distinguish three main androgen excess disorders: classic polycystic ovary syndrome (PCOS), mild ovulatory PCOS, and idiopathic hyperandrogenism. These androgenic phenotypes differ more for the severity of the endocrine and metabolic alteration than for the etiopathogenetic mechanisms. The appearance of a particular androgenic phenotype is determined by a sum of genetic and environmental factors, but mostly by body weight. (Fertil Steril® 2006;85:1582–5. ©2006 by American Society for Reproductive Medicine.)

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THE CHANGING CLASSIFICATION OF ANDROGEN EXCESS DISORDERS

Influence of NIH Criteria for the Diagnosis of PCOS

During the last 15 years, a better understanding of the phenotypic heterogeneity of hyperandrogenic syndromes has modified the classification and the relative prevalence of the different androgen excess disorders. Until the 1980s, circulating hormone levels (i.e., an increase of the LH and/or LH/FSH ratio) and tests of blocking or stimulating adrenal or ovarian androgen secretion were used to distinguish between the different forms of androgen excess (1). However, these endocrine parameters showed little specificity, and in 1990, at a National Institutes of Health (NIH) meeting, a majority of experts agreed on making the diagnosis of polycystic ovary syndrome (PCOS) mostly on the basis of clinical data (i.e., clinical or biologic hyperandrogenism and chronic anovulation) (2). The study of the endocrine pattern was considered important only to exclude a few well-characterized hyperandrogenic syndromes (e.g., Cushing’s syndrome, androgen secreting tumors, nonclassic adrenal enzymatic deficiencies) (2). Using NIH criteria, PCOS is, by far, the most common form of androgen excess disorder. In a recent large study, 82% of patients with clinical hyperandrogenism were considered affected by PCOS, whereas the other most common androgen disorders (i.e., hyperandrogenism + ovulatory cycles and idiopathic hirsutism) were diagnosed in only 6.75% and 4.47% of the patients (3).

Influence of ESHRE/ASRM Criteria for Diagnosis of PCOS

Recently, at a European Society of Human Reproduction and Embryology/American Society for Reproductive Medicine (ESHRE/ASRM) meeting, new criteria for making the diagnosis of PCOS were proposed (4, 5). After exclusion of the same well-characterized but uncommon androgen excess disorders, PCOS may be diagnosed in patients presenting at least two of these three features: clinical or biologic hyperandrogenism, chronic anovulation, polycystic ovaries. Therefore, the diagnosis of PCOS may be assigned to patients presenting three different phenotypes:

1. Hyperandrogenism and chronic anovulation
2. Hyperandrogenism and polycystic ovaries but ovulatory cycles
3. Chronic anovulation and polycystic ovaries but no clinical or biochemical hyperandrogenism

Consequences of the New Guidelines on the Classification of Androgen Excess Disorders

Excluding the last phenotype (which by definition does not include hyperandrogenic patients), the new criteria for diagnosis of PCOS have determined important consequences on the classification of the androgen excess disorders. In fact, hyperandrogenic patients with ovulatory cycles but polycystic ovaries have to be separated from the group of hyperandrogenic patients with ovulatory cycles. It means that three main androgen excess disorders may be distinguished. We have used the following names to define these three disorders (6, 7):
1. Classic PCOS
2. Ovulatory PCOS
3. Idiopathic hyperandrogenism

Classic PCOS includes the patients with hyperandrogenism and chronic anovulation (NIH definition of PCOS). Ovulatory PCOS indicates patients who present hyperandrogenism and ovulatory cycles but polycystic ovaries, whereas idiopathic hyperandrogenism regroups hyperandrogenic patients with normal ovulatory cycles and normal ovaries. It is clear that these names are arbitrary and other experts may use different definitions. However, other authors have used similar names (8), and these different hyperandrogenic syndromes must be distinguished in some way.

New Criteria for Diagnosis of Idiopathic Hirsutism

The ESRHE/ASRM definition of PCOS has influenced even the criteria to make a diagnosis of idiopathic hirsutism. In fact, idiopathic hirsutism was previously diagnosed on the basis of clinical hyperandrogenism but normal ovulatory cycles and normal serum androgens, regardless of ovarian morphology (9). However, some of these patients may have polycystic ovaries and should be now considered affected by ovulatory PCOS.

Prevalence of the Different Forms of Androgen Excess Disorders

Using ESHRE/ASRM diagnostic criteria, we have recently assessed the relative prevalence of the different androgen excess disorders (7), and we have found that these three disorders include about 90% of hyperandrogenic patients (Fig. 1). This prevalence is similar to that reported by Azziz et al. (3) with the important difference that, in our experience, the mild androgenic disorders (i.e., ovulatory PCOS and idiopathic hyperandrogenism) affect about 30% of hyperandrogenic patients. The different setting of each study (Department of Obstetrics and Gynecology in the Azziz research (3) vs. Department of Endocrinology in our research (7)) probably explains the different prevalence. However, the problem of mild hyperandrogenism should not be undervalued. In fact, because classic PCOS is present in about 5% of young women (10), the prevalence of mild androgenic disorders may be calculated in 1%–2% of young adult women. Of course, only epidemiologic study may help to establish the real incidence of mild androgenic disorders.

Phenotypic Differences Between the Three Main Androgen Excess Disorders

Endocrine and Metabolic Differences. It is important to understand the endocrine and metabolic differences between the main forms of androgen excess disorders. In fact, it may help to understand the pathogenesis and the therapeutic approach to the different forms of hyperandrogenism.

Some help for this objective may come from the data that we have collected in 290 hyperandrogenic women (6). The results we have obtained are similar to the data recently presented by other authors (11) and may be summarized in this way:

1. **Gonadotropins**: An increased LH/FSH ratio (>1.5) may be found in 34% of patients with classic PCOS but also in 20% of patients with idiopathic hyperandrogenism and in 10% of patients with ovulatory PCOS.

2. **Serum androgens**: All groups have increased serum levels of testosterone and DHEAS with higher mean levels in patients with classic PCOS, intermediate levels in patients with ovulatory PCOS, and lower levels in patients with idiopathic hyperandrogenism.

3. **Body weight**: Increased only in patients with classic PCOS (Fig. 2).

4. **Serum insulin and insulin sensitivity**: All groups have increased serum insulin and reduced insulin sensitivity but in different degrees, with more severe alteration in patients with classic PCOS, intermediate alteration in patients with ovulatory PCOS, and milder alteration in patients with idiopathic hyperandrogenism (Fig. 3).

5. **Serum lipids**: Total and low-density lipoprotein (LDL)-cholesterol are increased (in a similar way) in classic and ovulatory PCOS, but not in patients with idiopathic hyperandrogenism. High-density lipoprotein (HDL)-cholesterol and
triglycerides are altered only in patients with classic PCOS (Fig. 4).

6. **Non-classic cardiovascular risk factors**: C-reactive protein is increased in patients with classic and ovulatory PCOS, but not in patients with idiopathic hyperandrogenism. Homocysteine is mildly increased only in patients with classic PCOS.

In summary, all these data suggest that the main hyperandrogenic syndromes overlap in many aspects. The distinction between the different disorders appears to reflect more the severity of endocrine and metabolic pattern than the differences in etiopathogenetic mechanisms. In fact, gonadotropin abnormalities, increased androgen secretion, and insulin resistance may be present in all hyperandrogenic syndromes, but with a scale of severity that goes from the milder phenotype (idiopathic hyperandrogenism) to the more severe phenotype (classic PCOS) (11). Increased cardiovascular risk is present only in hyperandrogenic patients with moderate or severe phenotypes (ovulatory PCOS and classic PCOS).

**Modifiers of the Severity of the Androgen Alteration: The Role of Obesity.** Factors that affect the severity of endocrine and metabolic alterations may influence the appearance of the different phenotypes. Both genetic and environmental factors probably play the role of phenotype modifiers.

Obesity is the most well-known factor that may modify the androgenic phenotype. In fact, obesity is a classic characteristic of PCOS (12) that worsens insulin resistance and hyperandrogenism (13). Although some patients with mild hyperandrogenic syndromes are obese, only patients with classic PCOS have a significant increase of prevalence of obesity when compared with the normal population (6). All these data suggest that obesity may modify the androgenic phenotype and transform a mild androgenic phenotype in
classic PCOS (12). It is confirmed by many data that the treatment of obesity may reverse the PCOS phenotype from the more severe anovulatory to the mild ovulatory (14).

Of course, obesity is not the only factor able to influence the androgenic phenotype. Many patients with classic PCOS have a normal body weight (15). In addition, obesity cannot explain the differences between ovulatory PCOS and idiopathic hyperandrogenism. In fact, these two mild androgen excess disorders have similar body weight but differences in terms of insulin resistance and cardiovascular risk (6). Other factors (e.g., fat distribution or genetically transmitted insulin resistance) must be involved in determining the phenotype of androgen excess disorders.

CONCLUSIONS

In the past, we have considered PCOS as a syndrome clearly distinguishable from other androgen excess disorders. However, a better understanding of the different phenotypes and their endocrine and metabolic characteristics appears to indicate that the main androgenic phenotypes differ more in the severity of the endocrine and metabolic alteration than in the etiopathogenetic mechanisms. A sum of genetic and environmental factors most likely influences the appearance of a particular androgenic phenotype, and some of these factors may be reversed by lifestyle changes.

REFERENCES