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Androgen plays an important role in polycystic ovarian syndrome (PCOS)

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Abstract
In 1935, Stein and Leventhal first described the association between amenorrhea and polycystic ovaries, which we now know as polycystic ovary syndrome (PCOS). In fact, PCOS appears to be one of the more common endocrine disorders, affecting approximately 4% of reproductive-aged women. This disorder is also associated with an increased risk of insulin resistance and hyperinsulinemia, type II diabetes mellitus, dyslipidemia, endometrial carcinoma, and psychosocial dysfunction.
An informal survey of conference participants indicated that for most women, the major criteria for PCOS "included (in order of importance): (i) hyperandrogenism and/or hyperandrogenemia, (ii) oligo-ovulation, [and] (iii) exclusion of other known disorders, such as Cushing's syndrome, hyperprolactinemia, or congenital [non-classic] adrenal hyperplasia." The presence of "polycystic ovaries on ultrasound" was also noted as a possible inclusion criterion, although this was felt to be particularly controversial.
In general, PCOS can be viewed as a heterogeneous disorder in which ovarian, and possibly adrenal, androgen excess is present, along with varying degrees of gonadotropic and metabolic abnormalities. We should, however, note that PCOS is a diagnosis of exclusion in which other causes of oligoovulation or hyperandrogenism are ruled out by the examining clinician.

Keywords: PCOS, androgen, oligo ovulation, and hyperadrenogenism

Introduction

Access to Androgen

Androgen Excess in PCOS While recent press announcements and research publications have suggested that most patients with PCOS have insulin resistance and secondary hyperinsulinemia, we should note that the universal and pervasive abnormality in PCOS is androgen excess. It is androgen excess, and not insulin resistance, that is directly responsible for the signs and symptoms we have come to recognize as PCOS, including hirsutism, acne, alopecia, and ovulatory dysfunction [1].
In fact, according to the diagnostic criteria generated by the 1990 National Institutes of Health-sponsored conference on the subject, patients with PCOS must have some element of androgen excess, either clinical (as in hirsutism, acne, or androgenic alopecia) or biochemical (i.e., hyperandrogenemia) or both to be considered as suffering from the disorder. It is true that in many patients with PCOS, the excess insulin levels resulting from the insulin resistance may, in part, be responsible for the hyperinsulinemia of these women and may actually directly affect hypothalamic-pituitary function to further impair ovulatory function [9].
The importance of androgens in producing the PCOS phenotype is highlighted by studies in female to male transsexuals, where androgen supplementation alone produces a polycystic ovarian morphology [15].
Hyperandrogenemia is also a common feature among those women with normal ovulatory function but polycystic ovarian morphology, which may represent an occult form of PCOS [3, 4]. Androgen levels have also been found to be one of the most predictable markers of inheritance in family studies of patients with PCOS. In addition, Escobar-Morreale and colleagues have recently constructed receiver-operating curves for the diagnosis of PCOS in an unselected general population and observed that androgen measures, including free T, DHEAS, and the free androgen index were highly effective as single analytical procedures for the detection of PCOS [7]. Androgen levels also predict therapeutic response. Fauser and colleagues studied 182 normogonadotropic oligomenorrhea infertile women to identify what endocrine screening characteristics could potentially predict which women would be resistant to induction of ovulation by clomiphene citrate [11].
The ability of insulin to predict patients who remained anovulatory after clomiphene citrate treatment disappeared when the free androgen index was included in the model, suggesting that markers for insulin sensitivity are associated with abnormal ovarian function through their correlation with androgens. These data indicate that androgen levels are perhaps the most important determinant of clinical symptoms in PCOS [13].

Androgen Levels "Normal" in Some Patients with PCOS, Why?

The fact that androgen excess is directly responsible for many of the symptoms of PCOS does not mean that patients with "normal" androgen levels cannot have this disorder. In fact, about 20% of patients with PCOS diagnosed by the criteria arising from the 1990 National Institutes of Health conference have normal androgen levels [12]. To understand this apparent contradiction we need to review a few peculiarities inherent in the

measurement and regulation of androgens in women. First, the measurement of androgens (e.g., T, free T, and androstenedione) in the blood is notoriously inexact, not surprising in view of the small size and significant similarity of many of these molecules (for example, T is a steroid that differs from E2 by only one double bond in the A ring and a methyl group on position 18). This requires that the assay used to measure androgens be very exact, almost always requiring serum extraction and chromatography to purify the steroid in question. However, most clinicians use commercial assays, which directly measure the androgen in unextracted serum. Unfortunately, when we recently tested nine different commercial assays for total T we observed significant between-kit variability, which was greatest for serum samples obtained from women [2].

This study strongly suggested that the measurement of total serum T using commercial kits might have limited utility, particularly for the detection of hyperandrogenemia in women. While we did not directly study assays for free T, it should be noted that the level of free T is only about 2% of the total and thus it is very unlikely that commercial kits are going to be better at detecting this even smaller amount of hormone. Second, most normal ranges for hormone levels, including androgens, are generally established by the kit manufacturers and not by the immediate commercial laboratory using the kits [14].

To establish a normal range, the kit manufacturers usually measure the blood levels of the hormone in question using their kit in 50 or so unselected women. No effort is generally made to document whether these women are actually normal. Since the normal ranges are defined as those hormonal values observed in 95%–97.5% of the population, by definition, "excessive levels of hormones" are observed in 5%–2.5% of the normal women studied [16]. Unfortunately, because the incidence of PCOS or hirsutism in the general population of reproductive-age women is about 4% and 7%, respectively, it is very possible that the upper normal limit established by the kit manufacturer may be excessively high if some of these women are inadvertently included in the normal population used to establish the normal range. If this range is later used to determine whether a patient actually has hyperandrogenemia, many patients with abnormal values will be classified as normal. [10, 17] Third, we should note that there is no tight endocrine regulation of androgen levels in women (or men for that matter). For example, as the level of free thyroxin goes up, the production of TSH goes down practically simultaneously, resulting in a lower overall production of total thyroxin by the thyroid and the maintenance of normal circulating levels of the free hormone. Alternatively, as observed in men, in menopausal women [8], or in patients with PCOS the circulating levels of androgens can increase by 100% or more, without a significant concomitant decrease in the circulating levels of LH and FSH (the pituitary hormones controlling ovarian androgens) [6, 5].

Conclusion

Androgen Excess Is the Key Element in PCOS Although many women with PCOS have insulin resistance and hyperinsulinemia, which may be the underlying factor in their disease process, androgen excess is the immediate culprit that determines these patients' endocrine symptoms, including their degree of irregular ovulation, hirsutism, acne, or alopecia. Androgen suppression continues to be the mainstay of treatment in patients with PCOS not desiring immediate fertility. However, because of the problems inherent in the measurement and interpretation of androgen levels clinically, androgen measurements are principally useful in the evaluation of the nonhirsute oligo-ovulatory woman. This approach will minimize the amount of confusion caused by patients with frank and obvious PCOS, but whose androgen levels are deemed normal, and avoid the classification of many women with obesity (and hyperinsulinemia) as having PCOS.

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Conflict of interest

No conflict of interest

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