Mini-Review

The Polycystic Ovary Morphology-Polycystic Ovary Syndrome Spectrum

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A B S T R A C T

Background: Polycystic ovary syndrome (PCOS) is the most common cause of chronic hyperandrogenic anovulation. Two-thirds of PCOS patients have functionally typical PCOS, with typical functional ovarian hyperandrogenism manifest as 17-hydroxyprogesterone hyperresponsiveness to gonadotropin stimulation. Most, but not all, of the remainder have atypical functional ovarian hyperandrogenism. Many asymptomatic volunteers with polycystic ovary morphology (PCOM) have similar abnormalities.

Objective: The objective of this paper is to review the relationship of biochemical ovarian function to the clinical spectrum observed in PCOS and in normal volunteers with PCOM.

Findings: Adolescents and adults with PCOS are similar clinically and biochemically. Ninety-five percent of functionally typical PCOS have classic PCOS, ie, hyperandrogenic anovulation with PCOM. In addition to having more severe hyperandrogenism and a greater prevalence of PCOM than other PCOS, they have a significantly greater prevalence of glucose intolerance although insulin resistance is similarly reduced. Half of normal-variant PCOM have PCOS-related steroidogenic dysfunction, which suggests a PCOS carrier state.

Conclusions: There is a spectrum of ovarian androgenic dysfunction that ranges from subclinical hyperandrogenemia in some normal-variant PCOM to severe ovarian hyperandrogenism in most classic PCOS. A minority of mild PCOS cases do not fall on this spectrum of ovarian androgenic dysfunction, but rather seem to have obesity as the basis of their hyperandrogenism, or, less often, isolated adrenal androgenic dysfunction. Half of normal-variant PCOM also do not fall on the PCOS spectrum, and some of these seem to have excessive folliculogenesis as a variant that may confer mild prolongation of the reproductive lifespan. Improved understanding of PCOM in young women is needed.

Key Words: Polycystic ovary, Polycystic ovary syndrome, Insulin resistance, Glucose intolerance, Obesity

Introduction

Polycystic ovary syndrome (PCOS) is the most common cause of chronic hyperandrogenic anovulation and the most common cause of female infertility.[1,2] Considerable evidence suggests that PCOS has diverse causes, arising as a complex trait with contributions from both heritable factors that affect ovarian steroidogenesis and congenital and acquired environmental factors, of which insulin-resistant hyperinsulinemia is the most common.[3–5]

Diagnostic criteria for PCOS have evolved considerably since the classic description of the syndrome by Stein and Leventhal.[6] Three international conferences over the past 25 years have developed diagnostic criteria for adults based on various combinations of otherwise unexplained hyperandrogenism, anovulation, and a polycystic ovary, all of which are encompassed by the Rotterdam consensus criteria.[7–9] These criteria generate 4 phenotypes,[10] which fall on a spectrum of decreasing specificity,[9,11–13] as listed in Table 1.

Decreasing phenotype specificity is paralleled by a spectrum of decreasing clinical severity. Hyperandrogenism severity decreases with decreasing phenotype specificity, as does, in most populations, the severity of insulin resistance, obesity, and luteinizing hormone elevation.[11–19] The hyperandrogenic phenotypes 1-3 have ovulatory dysfunction of successively lesser degree, whereas phenotype 4 is anovulatory but lacks evidence of hyperandrogenism. While insulin-resistance and obesity are common in PCOS, they are not recognized as diagnostic criteria.

Recent Endocrine Society clinical guidelines suggest that adolescent PCOS be diagnosed using the National Institutes of Health (NIH)-based criteria of hyperandrogenism and persistent anovulatory menstrual symptomatology.[20] Though the criteria for abnormal menses were not specified, criteria based on developmental stage and gynecologic age would seem appropriate.[21] While some have argued that ultrasonographic polycystic ovary morphology (PCOM) lends more specificity to the diagnosis of PCOS in adolescents,[22] the definition of PCOM in adolescents is problematic, as discussed later.

It is now clear that PCOS occupies 1 end of a clinical and biochemical spectrum that includes many apparently normal females who have PCOM.[23,24] The objective of this paper is to review the relationship of biochemical ovarian function to the major clinical features across the entire spectrum observed between normal and classic PCOS (Fig. 1).

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Table 1
Adult Diagnostic Criteria for Polycystic Ovary Syndrome*

1. Phenotype 1 ("Classic PCOS")†
   (a) Clinical and/or biochemical evidence of hyperandrogenism
   (b) Evidence of oligo-anovulation
   (c) Ultrasonographic evidence of a polycystic ovary
2. Phenotype 2 (Essential National Institutes of Health Criteria)†
   (a) Clinical and/or biochemical evidence of hyperandrogenism
   (b) Evidence of oligo-anovulation
3. Phenotype 3 ("Ovulatory PCOS")†
   (a) Clinical and/or biochemical evidence of hyperandrogenism
   (b) Ultrasonographic evidence of a polycystic ovary
4. Phenotype 4 (Non-hyperandrogenic PCOS)
   (a) Evidence of oligo-anovulation
   (b) Ultrasonographic evidence of a polycystic ovary

* Rotterdam criteria; all involve exclusion of other causes of hyperandrogenism and anovulation.
† Androgen Excess-PCOS Society recognizes only hyperandrogenic phenotypes.

Biochemical Phenotyping for PCOS Features

Thorough biochemical phenotyping for PCOS features involves testing ovarian and adrenal androgenic function status. This generates a functional categorization of PCOS (Table 2).[23] Functionally typical PCOS (PCOS-T) is defined as typical functional ovarian hyperandrogenism (FOH), that is, 17-hydroxyprogesterone (17OHP) hyperresponsiveness (in the absence of evidence of a steroidogenic block) to gonadotropins, which is determined by inducing gonadotropin release with a gonadotropin releasing hormone agonist (GnRHag, eg, leuprolide acetate) challenge test or by administering human chorionic gonadotropin.[25,26] Functionally atypical PCOS (PCOS-A) is defined as a normal 17OHP response to GnRHag.[23,25] An alternative indication of FOH is an elevated testosterone level after a short dexamethasone androgen-suppression test (SDAST). Functional adrenal hyperandrogenism is defined as an elevated dehydroepiandrosterone response to adrenocorticotropic hormone (ACTH) testing in the absence of a steroidogenic block.[23] Elevated baseline serum dehydroepiandrosterone sulfate (DHEAS) is a simple correlate of this adrenal androgenic dysfunction (r = 0.708). Functional adrenal hyperandrogenism appears to be due to a disturbance of adrenal steroidogenesis similar to that affecting the PCOS ovary and usually coincides with it.[3,23]

Biochemical phenotyping for the other major features involves determining PCOM status by pelvic ultrasonography, measuring serum anti-müllerian hormone (AMH) as an indicator of folliculogenesis, and assessing metabolic status by an oral glucose tolerance test.

Accordingly, we phenotyped over 100 PCOS patients and over 50 controls, 11-39 years of age.[23–25] They were recruited through pediatric, medical, and reproductive endocrinology clinics. PCOS patients had an elevated plasma free testosterone and anovulatory symptoms inappropriate for gynecologic age. Control subjects were healthy eumenorrheic volunteers who lacked clinical evidence of hyperandrogenism. The reference group for these studies was those volunteers with normal ovarian morphology (V-NOM n = 21, 24.5 ± 9.2, SD, y age). The other volunteers were entirely similar clinically except for having PCOM (V-PCOM, n = 32, 22.9 ± 7.9 y).[25] Approximately half of the study subjects were adolescents (11.0-17.9 years of age and ≥1 y post-menarcheal).

To understand the functional diversity of PCOS, we analyzed subsets of PCOS-T (n = 40) and PCOS-A (n = 20) that were age-matched to the controls. The data on ovarian and adrenal function have been detailed in 1 report,[23] and ovarian androgenic function was related to markers of folliculogenesis (PCOM and serum AMH) in another report.[24] This review provides some comparisons that were outside the scope of the original publications so as to provide an integrated overview of the entire clinical spectrum.[25]

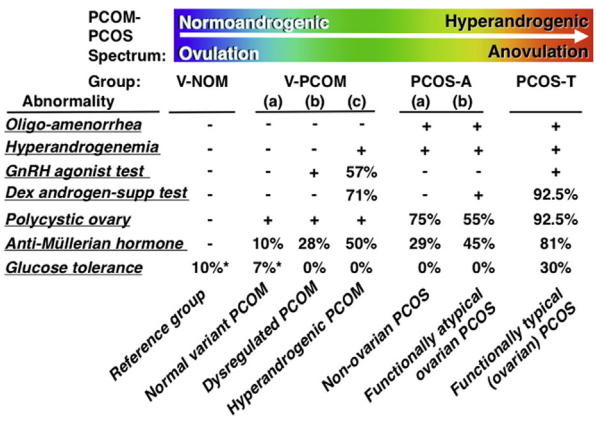

Fig. 1. The spectrum of ovarian androgenic function from normal to functionally typical PCOS. The position of study groups and subgroups along the spectrum is indicated schematically in relation to evidence of ovarian dysfunction. Study groups and subgroups as defined in the text: V-NOM (volunteers with ultrasonographically normal ovarian morphology), V-PCOM (volunteers with polycystic ovarian morphology, PCO), PCOS-A (functionally atypical PCOS), PCOS-T (functionally typical PCOS). Defining abnormality of group or subgroup: +, abnormal, –, normal. Experimental findings shown as % abnormal.[23,24] * Some normal volunteers had impaired glucose tolerance. GnRH, gonadotropin releasing hormone; Dex, dexamethasone; supp, suppression. Modified with permission from Rosenfield et al: Antimüllerian hormone levels are independently related to ovarian hyperandrogenism and polycystic ovaries. Fertil Steril 2012; 98:242.

The Biochemical and Clinical Spectrum of PCOS

Adolescent and adult PCOS patients had similar clinical, biochemical, and ovarian morphologic findings (Table 3).[21,25] Hirsutism was present in 57% of the adolescents, 51% of the adults; obesity in 74% and 70%, respectively.

Two-thirds of PCOS patients have a characteristic form of FOH that is indicated by 17-OHP hyper-responsiveness to a GnRHag test.[3,25] This typical FOH appears to be due to dysregulation of ovarian theca cell androgen formation[3] that is usually intrinsic[27]: high intraovarian androgen levels can account for all the major reproductive endocrine features of the syndrome.[3,28] Insulin-resistant hyperinsulinemia often aggravates this ovarian androgenic dysfunction and sometimes seems to be the primary cause of it.[29,30] The third of PCOS patients who lack this typical FOH have been shown to have diverse pathophysiology. We here review our biochemical studies to determine the source of androgen in the various types of PCOS.[23–25]

The biochemical spectrum of PCOS.[21,25] As noted above, two-thirds of PCOS had PCOS-T, that is, typical FOH by GnRHag test criteria (Fig. 2,A *(c)*).[23] The vast majority (92%) of PCOS-T also had an abnormal SDAST (Table 2). Coincidental adrenal hyperandogenism was present in 27.5%.