The Polycystic Ovary Morphology-Polycystic Ovary Syndrome Spectrum

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Abstract

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 hyper-responsiveness 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.

Keywords

Polycystic ovary; Polycystic ovary syndrome; Insulin resistance; Glucose intolerance; Obesity

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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).

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 adrenocorticotrophic 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

The Biochemical and Clinical Spectrum of PCOS

Adolescent and adult PCOS patients had similar clinical, biochemical, and ovarian morphologic findings (Table 3).^{21,25} 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 formation³ that is usually intrinsic²⁷: 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 hyperandrogenism was present in 27.5%.

The one-third of PCOS subjects who lacked 17OHP hyperresponsiveness to GnRHag (PCOS-A) proved to be functionally heterogeneous in the source of androgen excess (Table 2).²³ Most (60%) had an abnormal SDAST (Fig. 2, A (b)): this indicates a mild and atypical form of FOH (Table 2). This is the PCOS-A subgroup termed “atypical ovarian PCOS” in Figure 1. Functional adrenal hyperandrogenism coexisted with FOH in 25% of this subgroup. These data lead to the conclusion that the great majority (52/60, 87%) of PCOS had one or the other form of FOH.

The other 40% of PCOS-A (ie, 8/60, 13%) had no evidence of an ovarian source of androgen (Fig. 2 (a)); thus the subgroup is termed “non-ovarian PCOS” in Figure 1. Nonovarian PCOS itself is functionally heterogeneous (Table 2). Isolated functional adrenal hyperandrogenism was present in 3 of 8 (37.5%); most had an elevated baseline DHEAS level. On the other hand, evidence for a glandular source of androgen was lacking in 5 of 8 (62.5%). All in this subgroup were obese, and we have attributed their androgen excess to excessive peripheral testosterone formation by their excessive adipose tissue.²³

Relationship of the biochemical to the clinical PCOS spectrum. PCOS-T is the most clinically severe form of PCOS. They had the highest baseline testosterone levels ($P < .001$)²³ and almost uniformly (>90%) had “classic” PCOS, that is, ovarian hyperandrogenism with PCOM (Fig. 1).²⁴ The prevalence of PCOM was significantly higher (particularly by ovarian volume criteria, $P < .005$) in PCOS-T than in PCOS-A (Figs. 1, 2A(b,c)). Nevertheless, 65% of PCOS-A had PCOM, most (83%) by volume criteria, and thus had the classic phenotype. They differed more strikingly from PCOS-T in that AMH elevation was half as frequent (39%) and generally milder ($P < .05$) (Fig. 2, B (c–d)).

PCOS-T also had a significantly higher prevalence of glucose intolerance (30%, of whom one-quarter were diabetic) than did PCOS-A (in whom glucose intolerance was absent; Fig. 1).²³ However, insulin resistance, according to homeostatic metabolic assessment index and the insulin sensitivity index, was similar in the 2 PCOS groups, while significantly greater than in volunteers. This suggests that PCOS-T is specifically associated with early pancreatic beta-cell failure.

The 13% of PCOS patients with “non-ovarian PCOS” (Fig.1), that is, those who lack FOH (Fig. 2, A (a), Table 2), had the mildest hyperandrogenism: serum total testosterone was normal and free testosterone elevated ($P < .01$ vs the atypical ovarian PCOS-A subgroup). Only 2 (25%–29%) of this subgroup had enlarged ovaries and elevated AMH (Fig. 2, B (d)), although most met follicle count criteria for PCOM.

Discussion

These findings are consistent with the concept that ovarian androgen excess is ordinarily responsible for the major reproductive features of the syndrome.³ Ovarian hyperandrogenism not only accounts for the cutaneous manifestations, it can also account for all the histopathologic features of the polycystic ovary of PCOS^{31,32}: a high intraovarian androgen concentration not only enhances the recruitment of primordial follicles into the pool of growing small pre-antral and antral follicles,^{28,33} it impairs selection of the dominant

follicle,^{34,35} dual effects that can account for the polycystic appearance of the ovaries, ovarian enlargement, capsular thickening, and thecal/stromal hyperplasia and luteinization.^{36,37}

Anti-müllerian hormone, a product of the granulosa cells of growing follicles, is thought to regulate follicular growth and development by exerting a paracrine negative feedback effect on the recruitment of precursor (primordial) follicles.²⁴ AMH levels are increased in PCOS in proportion to its clinical severity, as reflected by their number of diagnostic features³⁸ and the antral follicle count.^{39,40} Disordered folliculogenesis that involves resistance to AMH action is suggested by an increase in the ratio of growing to resting follicles in polycystic ovaries.⁴¹ Although an intrinsic defect in folliculogenesis cannot be excluded,⁴² substantial evidence suggests that this increased AMH results from the stimulatory effect of androgens on early follicular growth.²⁸

The non-ovarian source of androgen excess in a small fraction of PCOS needs an explanation as to the pathophysiologic basis of their ovarian dysfunction. The cause of the ovarian dysfunction of the small subset with isolated functional adrenal hyperandrogenism is unclear. Heightened ovarian sensitivity to modest hyperandrogenemia may be the explanation in some. One postulated mechanism is that these patients possess androgen receptors encoded by short trinucleotide CAG repeats, which increase androgen receptor sensitivity to androgen.⁴³ On the other hand, it is possible that our tests are not sufficiently sensitive or accurate to detect a mild degree of the ovarian hyperandrogenism that is often associated with this type of adrenal dysfunction.

The largest subset of non-ovarian PCOS had only obesity as a potential source of androgen excess. Not only can excess adipose tissue itself generate androgen, obesity may also account for anovulation by a suppressive effect on gonadotropins.⁴⁴ Thus, the mechanisms of hyperandrogenic anovulation in simple obesity may have a different pathogenesis than that of ordinary PCOS, a concept that has unique treatment implications and that has led us to term this “pseudo-PCOS.”²³

In summary, adolescents and adults with PCOS have similar ovarian dysfunction. These data indicate that the spectrum of ovarian androgenic dysfunction in PCOS parallels the spectrum of clinical features seen across phenotypes. The cases with the most severe clinical manifestations have the most severe ovarian androgenic dysfunction, whereas the mildest seem to have none.

The Biochemical Spectrum in Normal Females with Polycystic-appearing Ovaries

Ultrasonographic PCOM is a common finding among healthy women. Many of these women have mild PCOS features, that is, irregular menstrual cycles and/or hirsutism.^{45,46} When care has been taken to exclude those with such symptoms, groups of apparently normal women with PCOM, including some with documented ovulatory cycles, have been shown to have subclinical androgenic ovarian dysfunction that is intermediate between that of women with normal ovaries and those with PCOS.^{11,25,47,48} Data vary as to whether insulin resistance is associated with PCOM in healthy adult volunteers.^{11,48,49}

AMH serum concentrations in normal subjects with PCOM, both adolescents and adults, are intermediate between those of women with normal ovarian morphology and those with PCOS.^{50–52} AMH elevation has been postulated to be an indicator of the stimulating effect of ovarian hyperandrogenism on folliculogenesis.²⁸ The AMH level also independently indicates the size of the follicular (“ovarian reserve”) pool.^{24,53} We here review our studies of the relationships among ovarian androgenic function, PCOM, and serum AMH levels in normal volunteers Table 3.²⁴

The biochemical spectrum of normal-variant PCOM. Healthy adolescent volunteers and adult volunteers had similar ovarian function and morphology, with the exception of slightly lower FSH and higher AMH in the adolescents.^{21,25} Normal volunteers with PCOM were found to have a spectrum of ovarian function (Fig. 1, Fig. 3, Table 4).²⁴ At 1 end of the V-PCOM spectrum was a subgroup of 40% with an extreme variation of normal size and morphology; they had theca and granulosa cell function like that of V-NOM (Fig. 2, C (a) and Fig. 2, D (a)). At the other end of the V-PCOM spectrum, was a subgroup of 22% with “hyperandrogenic PCOM” (V-PCOMh in Fig. 2, C (b–d)): they had baseline hyperandrogenemia, and so met the definition of “ovulatory PCOS” (Table 1, phenotype 3); all also had a positive SDAST and/or GnRHag test, which indicates subclinical FOH. They also had mildly increased adrenal androgenic function: DHEAS was 159 ± 58 , SD, $\mu\text{g/dl}$, significantly higher than that of V-NOM (81 ± 41 $\mu\text{g/dl}$) and both other V-PCOM subgroups (all $P < .01$), which had DHEAS levels similar to V-NOM; they also tended to have a higher dehydroepiandrosterone response to ACTH ($P = .15$). These test results were respectively elevated in 42% and 14% of this subgroup.

Between these extremes lie 2 different kinds of ovarian functional variants. On the normal side of the spectrum was a subgroup (10% of V-PCOM) with an isolated AMH elevation (V-PCOM in Fig. 2, D (d)) that indicates increased folliculogenesis. On the PCOS side of the spectrum were V-PCOM with “dysregulated PCOM”, that is, steroidogenic hyper-responsiveness to GnRHag (17OHP elevation without hyperandrogenemia) (V-PCOM in Fig. 2, C (d)). It seems probable that this dysregulation indicates a very mild and subclinical degree of intraovarian androgen excess. Dysregulated V-PCOM fell into 2 subgroups (Fig. 3, Table 4): in most (18% of all V-PCOM) it was isolated; in the remainder (10% of all V-PCOM) AMH was mildly elevated. Multiple regression analysis showed that serum AMH was independently related to ovarian hyperandrogenism and to the presence of PCOM.²⁴

Discussion

Based on these studies of age-matched subjects spanning the reproductive age group, the picture that emerges from this biochemical spectrum of differences in ovarian function among V-PCOM subjects is that half have no evidence of steroidogenic dysfunction and, thus, no relation to PCOS. On the other hand, half have subclinical evidence of a PCOS-related dysregulation of ovarian steroidogenesis. This includes some asymptomatic young women who meet criteria for ovulatory PCOS.

Most V-PCOM appear to be ovulatory and at low risk of developing symptomatic PCOS^{11,25,47,48,54} despite a substantial minority having dysregulated steroidogenic function

like PCOS. How is this to be interpreted? For one, it seems reasonable to suspect that this dysregulated subgroup represents a carrier state, or occasionally a risk factor, for PCOS,²⁵ though this remains to be established. For another, many of this subgroup have elevated AMH levels, which suggests that a very mild degree of intraovarian androgen excess is promoting folliculogenesis^{28,33} without interfering with ovulatory function. The subgroup of V-PCOM with isolated AMH elevation likewise seems to have an increased population of growing follicles. Thus, both subgroups can be expected to have a somewhat prolonged reproductive lifespan.⁵³

From an evolutionary perspective these considerations are consistent with the concept that PCOS evolved as a means of preserving anabolism and reproductive capacity in times of nutritional deprivation. In ancient eras of scarce nutrition, the higher androgen levels of such women would have been advantageous to reproduction as well as survival, though in current times of plenty this phenotype is disadvantageous.⁵⁵ The diversity of apparently unrelated gene variations that are associated with PCOS suggests that multiple mechanisms underpin this common phenotype.

Our studies,⁵⁶ like those of others,^{52,57} suggest that hyperandrogenemia and insulin resistance are less common in normal adolescents than in normal adults with PCOM. However, there are important caveats to all conclusions about PCOM. For one, the current international ultrasonographic criteria for adult PCOM (ovarian volume > 10 cc and antral follicle count ≥ 12) were developed based on expert opinion with the expectation that they would highly discriminate between PCOS and normal.⁵⁸ However, it has subsequently been shown that about half of normal young adults have PCOM by follicle count criteria.^{50,59,60} In part this is because the antral follicle number is normally up to 25 per ovary, twice that previously considered maximum normal, according to improved, high-definition imaging technology (≥ 8 MHz transducer frequency).⁶¹ In part this is because the antral follicle count decreases throughout the adult reproductive years, as does ovarian volume to a lesser degree.^{60–63}

Diverse criteria have been used for defining PCOM in adolescents,^{52,56,64–70} which has contributed to widely different estimates of PCOM prevalence in adolescents. It is now clear that current adult PCOM criteria are exceeded in about one-third of normal adolescents.⁶⁵ To some extent this is because the adolescent ovary may normally have a multifollicular appearance,^{58,71} but many meet current polycystic follicle count criteria.^{52,64,66–68} Furthermore, several studies indicate that ovarian volume during adolescence is larger than that of the normal adult: for example, the median for the normal upper limit of mean ovarian volume during adolescence according to studies to date approximates 12 cc (Table 5).^{52,56,66–70,72,73} Thus, application of adult criteria for PCOM to adolescents seems very problematic.

Conclusions

There is a spectrum of ovarian androgenic dysfunction that ranges from subclinical hyperandrogenemia in some normal females who have ultrasonographic PCOM to successively more severe functional ovarian hyperandrogenism in PCOS-A and PCOS-T.

PCOS-T, the most common form of PCOS, has a relatively homogeneous phenotype (hyperandrogenic anovulation with PCOM). A minority of mild PCOS-A cases do not fall on this spectrum of ovarian androgenic dysfunction, but rather seem to have an isolated adrenal androgenic dysfunction or, more often, obesity as the basis of their hyperandrogenism. Half of subjects with normal-variant PCOM do *not* fall on this spectrum, and some of these seem to have excessive folliculogenesis as a variant that may confer mild prolongation of the reproductive lifespan. On the other hand, those with normal-variant PCOM who fall on this spectrum because of subclinical evidence of steroidogenic dysregulation appear likely to be carriers for PCOS. There is need for data to improve the definition and understanding of the significance of the polycystic-appearing ovary in normal adolescents.

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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.

Fig. 2.

Scatterplots demonstrating relationships among tests for ovarian hyperandrogenism, polycystic ovarian morphology (PCOM), and serum AMH concentrations. Subjects are healthy eumenorrheic non-hirsute volunteers with normal or polycystic ovarian morphology ($n = 21$ V-NOM, $n = 32$ V-PCOM) and patients with PCOS identified by NIH criteria ($n = 20$ PCOS-A, $n = 40$ PCOS-T). This figure is an alternative display of published data in age-matched 11.1–39.9 year olds.^{23–25} Encircled PCOS cases have PCOM. Serum for AMH was available in 90% of subjects with tests of ovarian androgenic function. Dotted lines show the

95th percentile of normal for the V-NOM reference group; thus (a) quadrants show normal ranges. A, The relationship between the results of the short dexamethasone androgen-suppression test (SDAST) and the GnRHag test of androgenic ovarian function ($r = 0.671$, $P < .0001$) divides PCOS into 3 subgroups. Functionally typical PCOS (PCOS-T) is defined by an elevated 17OHP response to the GnRHag test (c). Functionally atypical PCOS (PCOS-A) lacks 17OHP elevation in response to GnRHag: DAST indicates that 60% of these PCOS-A cases have atypical FOH (b) and 40% of PCOS-A cases have normal ovarian androgenic function (a). B, SDAST relationship to baseline AMH levels. C, Twenty-two percent ($n = 7$) of healthy volunteers with PCOM have “hyperandrogenic PCOM” (V-PCOMh), defined as occult baseline hyperandrogenemia with FOH, as indicated by an abnormal SDAST or GnRHag test ($b-d$). Adolescent V-PCOM tended to have FOH less often (1/9) than adult V-PCOM (6/23). “Dysregulated” PCOM (V-PCOMd) is delineated by an abnormal 17OHP response to GnRHag in the absence of baseline hyperandrogenemia (d). This figure corrects a data entry error in the original publication that misclassified a V-PCOMd as V-PCOMh.²⁵ D, AMH elevation of a similar extent is found in normoandrogenic and hyperandrogenic normal volunteers who have PCOM. Adapted with permission from Rosenfield et al: Determination of the source of androgen excess in functionally atypical polycystic ovary syndrome by a short dexamethasone androgen-suppression test and a low-dose ACTH test. *Hum Reprod* 2011; 26:3138, and Rosenfield RL, et al: Antimüllerian hormone levels are independently related to ovarian hyperandrogenism and polycystic ovaries. *Fertil Steril* 2012; 98:242.

Fig. 3.

Schematic representation of the spectrum of ovarian function found in eumenorrheic non-hirsute healthy volunteers with PCOM (normal-variant PCOM, V-PCOM) in relation to the spectrum between normal and PCOS.^{23,24} Forty percent of V-PCOM have ovarian function like that of similar volunteers who lack PCOM. Another 10% of V-PCOM has elevated AMH in the absence of any evidence of ovarian steroidogenic dysfunction, which suggests an isolated increase in folliculogenesis. The remaining half of V-PCOM has some degree of PCOS-related steroidogenic dysregulation, often with mild AMH elevation (see Figs. 1, 2). Of those with ovarian steroidogenic dysfunction, nearly half (22% of the V-PCOM group) have biochemically hyperandrogenic PCOM, ie, subclinical FOH that meets the definition of “ovulatory PCOS.” The remainder have isolated dysregulation of ovarian function (ie, 17OHP hyper-responsiveness to GnRHag testing in the absence of hyperandrogenemia).

Table 1**Adult Diagnostic Criteria for Polycystic Ovary Syndrome^{*}**

1	Phenotype 1 ("Classic PCOS") [†]
	<ul style="list-style-type: none"> 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) [†]
	<ul style="list-style-type: none"> a. Clinical and/or biochemical evidence of hyperandrogenism b. Evidence of oligo-anovulation
3	Phenotype 3 ("Ovulatory PCOS") [†]
	<ul style="list-style-type: none"> a. Clinical and/or biochemical evidence of hyperandrogenism b. Ultrasonographic evidence of a polycystic ovary
4	Phenotype 4 (Non-hyperandrogenic PCOS)
	<ul style="list-style-type: none"> 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.

Table 2

Functional Classification of PCOS According to Source of Androgen Excess^{2,3}

PCOS Functional Type	Source of Androgen	GnRHag Test: 17OHP Response	DAST: Testosterone Response	ACTH test: DHEA Response	Prevalence among PCOS
Typical (PCOS-T)	Functional ovarian hyper-androgenism (FOH), typical	High	(High in 92%)	(High in 28%)	67%–69%
Atypical (PCOS-A)	Functional ovarian hyper-androgenism (FOH), atypical	Normal	High	(High in 30%)	20%
	Functional adrenal hyper-androgenism (FAH), isolated	Normal	Normal	High	5%
	Unknown (obesity?)	Normal	Normal	Normal	8%

“High” vs “normal” indicates defining characteristics; (percentages indicate experimentally determined prevalence of abnormality)

Table 3

Comparison of Normal Post-menarcheal and PCOS* Adolescents (Ages 11.1–17.9 yr) and Adults (Ages 18.0–39.9 yr). Mean $\pm$ SEM.

	Volunteers		PCOS		P Value
	Adolescent (n = 9)	Adult (n = 14)	Adolescent (n = 53)	Adult (n = 40)	
Baseline					
Age (yr)	14.5 ± 0.5	29.7 ± 1.7 [‡]	15.4 ± 0.2	25.0 ± 0.9 [‡]	<.05
Gynecologic age (yr)	2.5 ± 0.4	17.6 ± 1.7 [‡]	3.5 ± 0.2	12.6 ± 0.8 [‡]	<.05
Bone age (yr)	15.3 ± 0.7	N/A	16.5 ± 0.2	N/A	
Body mass index	24.5 ± 1.5	28.0 ± 2.3	34.9 ± 1.1	37.3 ± 1.9	<.001
Hirsutism score	1.2 ± 0.7	1.5 ± 0.7	8.5 ± 1.0	7.1 ± 1.0	<.001
PCOM prevalence (%)	0% (defined)	0% (defined)	67% §	83% §	<.001
Total testosterone (ng/dl)	26.9 ± 4.0	29 ± 3.6	67.5 ± 3.5	65.6 ± 4.0	<.001
Free testosterone (pg/ml)	6.3 ± 0.9	5.3 ± 0.5	22.4 ± 1.3	19.8 ± 1.7	<.001
SHBG (nM)	23.4 ± 3.7	31.0 ± 2.8	10.0 ± 1.1	17.1 ± 2.0 [‡]	<.001
AMH (ng/ml) [†]	3.9 ± 0.7	2.1 ± 0.5 [‡]	8.2 ± 0.9	9.8 ± 1.0	<.001
Dexamethasone short test					
Total testosterone (ng/dl)	15.2 ± 2.9	13.7 ± 1.4	51.7 ± 4.0	48.1 ± 2.9	<.001
GnRH agonist test [¶]					
LH 0 hr (U/L)	3.1 ± 0.5	4.0 ± 0.4	9.1 ± 0.7	6.6 ± 0.8	<.001
LH 1 hr (U/L)	18.4 ± 3.7	23.1 ± 3.9	38.2 ± 3.6	32.7 ± 3.1	<.05
FSH 0 hr (U/L)	4.8 ± 0.4	6.1 ± 0.5 [‡]	5.0 ± 0.2	4.7 ± 0.2	
FSH 4 hr (U/L)	28.2 ± 5.1	32.7 ± 2.9	17.7 ± 1.2	18.3 ± 1.5	<.001
Estradiol 0 hr (pg/ml)	36 ± 9.6	51 ± 5.5	52 ± 5.2	50 ± 2.7	
Estradiol 20–24 hr peak (pg/ml)	205 ± 19	158 ± 17	289 ± 19	287 ± 21	<.001
17OHP 0 hr (ng/dl)	<25	26	50 ± 4.3	43 ± 4.3	<.001
17OHP 20–24 hr peak (ng/dl)	101 ± 8.4	76.1 ± 8.5	240 ± 24	259 ± 37	<.001
Adrenal function tests					
DHEAS baseline	74 ± 11	89 ± 12	123 ± 8.0	148 ± 16	<.001
DHEA peak post-ACTH	541 ± 81	697 ± 64	831 ± 48	963 ± 63	<.002
DHEA, Dehydroepiandrosterone; 17OHP, 17-hydroxyprogesterone; SHBG, sex hormone binding globulin capacity					

Conversion multipliers to SI units: AMH 7.125 (pM), estradiol 3.61 (pM), DHEA 0.0347 (nM), DHEAS 0.0271 (μM), 17OHP 0.0303 (nM), testosterone free (3.47, pM) and total (0.0347, nM).

* Otherwise unexplained hyperandrogenemic abnormal uterine bleeding.

[†] Comparison of age-matched subsets of pooled adolescents and adults.

[‡] P <0.05 vs adolescents

[§] 79–82% of these met volume criteria (adolescents >10.8 cc) for PCOM.

[¶] GnRH agonist test, afternoon post-dexamethasone

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Classification of PCOM According to Ovarian Function^{2,3}

Table 4

Type of Ovarian Dysfunction	Testosterone Baseline Level	GnRHag Test 17OHP Response	SDAST Testosterone Response	Anti-Müllerian Hormone Level	Prevalence among volunteers (%)
None	Normal	Normal	Normal	Normal	40
AMH elevation, isolated	Normal	Normal	Normal	High	10
AMH elevated + dysregulated	Normal	High	Normal	High	10
Dysregulated, isolated	Normal	High	Normal	Normal	18
Hyperandrogenic	High	(High in 57%)	(High in 71%)	(High in 50%)	22

“High” vs “normal” indicates defining characteristics; (percentages indicate experimentally determined prevalence of abnormality). Reference: Rosenfield RL, Wroblewski K, Padmanabhan V, et al: Antimüllerian hormone levels are independently related to ovarian hyperandrogenism and polycystic ovaries. Fertil Steril 2012; 98:242.

Table 5Upper Limits of Ovarian Volume and Follicle Number in Eumenorrheic Adolescents^{*52,56,66–70,72,73}

Study Date, First Author	Ovarian Volume, Mean (cc) [†]	Ovarian Volume, Largest Ovary (cc) [†]	Antral Follicles (Number/Ovary) [†]	Comments
1995, Venturoli ⁶⁶	11.7 (97%)	n/a	10	Volunteers implied to lack clinical evidence of hyperandrogenism
2000, van Hoof ⁶⁷	11.8 (95%)	n/a	10	Schoolgirls; 0% hirsute, 9% serious acne
2001, Avvad ⁶⁸	10.0 (97%)	n/a	10	Volunteers with no clinical evidence of hyperandrogenism
2006, Mortensen ⁵⁶	15.5 (95%) [‡]	16.0 (95%) [‡]	< 10 (95%)	Volunteers with no clinical evidence of hyperandrogenism
2008, Chen ⁶⁹	8.4 (92%) [§]	11.0 (96%) [§]	n/a	Volunteers with no clinical evidence of hyperandrogenism
2011, Villarroel ⁵²	12.0 (95%)	15.1 (95%) [‡]	17 (95%)	Volunteers with no clinical evidence of hyperandrogenism; non-obese
2013, Brown ⁷⁰	13.5 (95%)	n/a	25 (95%)	Volunteers with no clinical evidence of hyperandrogenism; MRI
2013, Villa ⁷²	8.8 (97%) [§]	n/a	n/a	Volunteers implied to lack clinical evidence of hyperandrogenism
2014, Radivojevic ⁷³	12.5 (97%)	n/a	n/a	Ultrasonography patients lacking history of endocrinopathy, chronic illness, hormonal therapy
	Median 11.8	Median 15.1–16	Median ~17	

* Determined by ultrasonography unless specified as magnetic resonance imaging (MRI).

[†] 96% represents either percentile or specificity; 97% = mean + 2SD.

[‡] Unpublished data.

[§] Ovarian volumes corrected to prolate ellipsoid volume ($0.523 \times l \times w \times d$) n/a: not available.