Chapter 2

Clinical Evaluation of PCOS

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Keywords: hyperandrogenism, insulin resistance, cardiovascular disease, infertility, cancer, reproduction

Polycystic ovary syndrome (PCOS) is a common endocrinopathy in women that in its simplest form consists of unexplained hyperandrogenic chronic anovulation, which affects ~7% of the US population [1]. Because its etiology and natural history are poorly understood, there is controversy about the diagnostic criteria and clinical evaluation of the syndrome. Its origins as a named disorder track back to its original description in the 1930s by Stein and Leventhal, a pair of gynecologists from Chicago, who described a complex of signs and symptoms including oligomenorrhea, enlarged polycystic ovaries, hirsutism, and obesity, and also pioneered the treatment of wedge resection of the ovaries which resulted in more regular menses and improved fertility [2]. Since that time, there has been debate as to what the cardinal features of the syndrome are or should be, but a guiding thread of consensus stemming from this original description has been that this is an ovarian disorder of hyperandrogenism (although whether this is primary or secondary is uncertain) and is most readily diagnosed in women of reproductive age [3,4].

1. FEATURES OF PCOS

The current controversy regarding the definition and criteria for PCOS was discussed in Chap. 1. Androgen excess may be manifested by either clinical signs, most commonly by disorders of the pilosebaceous unit such as acne, hirsutism, or androgenic alopecia, or by biochemical measures, most commonly elevated circulating total or free testosterone levels. Hirsutism is defined as excess body hair in a male pattern distribution (primarily in the midline), and many patients go to great lengths to remove such hair; thus it is important to both elicit the distribution of unwanted hair on history as well on clinical exam.

Peripheral hyperandrogenism is dependent on a number of factors, most likely genetic, given the racial differences in hair distribution (for instance, Asian individuals who demonstrate little midline body hair [5]). As such, many investigators prefer a more objective measure of hyperandrogenism, i.e., circulating hyperandrogenemia. However, assessment of biochemical evidence of androgen excess can also be somewhat problematic as most testosterone assays are geared toward measuring levels in the male range (> 200 ng/dL), which is above most levels in women with PCOS, as mean levels in PCOS are in the range of 60–80 ng/dL and are unlikely to exceed 150 ng/dL [6,7]. These levels are further confounded by age and reproductive stage [8], and by medications, such as oral contraceptives, which normalize the levels of circulating androgens in women with PCOS [9]. Despite the imprecision of testosterone assays in women, a movement toward their greater standardization [10] and the recognition of the role of female hyperandrogenemia and its association with metabolic abnormalities [11,12] recommends it routinely be measured in women with suspected PCOS [13].

A history of chronic anovulation is most commonly obtained by asking how many spontaneous menstrual cycles per year the subject has. Most clinical studies identify patients at some threshold such as 6, 8, or 9 or fewer per year [14–16] or with an intermenstrual interval of more than 35–40 days. However, because anovulation with androgen excess can present with unpredictable bleeding, thought to be due to prolonged unopposed estrogen exposure, affected women may also present with a history of frequent vaginal bleeding episodes [17].

Finally there is the characteristic appearance of the polycystic ovary on ultrasonography which contains multiple (> 10–12) small follicles (~2–9 mm in diameter) tightly spaced along the periphery of the ovary, what is known as "the pearl necklace sign," with increased central stroma (Fig. 1) [18,19]. Polycystic ovaries usually present bilaterally. The name polycystic ovary is a misnomer, because there are actually an absence of "cysts," i.e., no large (> 20 mm in diameter) dominant follicle or postovulatory corpus luteum cysts are present due to the chronic anovulation [20]. The name harkens from the pathologist's view of the microscopic enlargement of these small follicles (most likely arrested or atretretic follicles [21]) as "cysts."

The designation of an ovary as "polycystic" often summons up in the patient's mind a picture of a pathologically enlarged ovary full of large symptomatic cysts. In actuality, a polycystic ovary is only modestly enlarged in terms of volume compared to a cycling ovary in the early follicular phase (prior to the development of a physiologic cyst), with a mean volume of > 10 cm^3 in PCOS versus < 8 cm^3, respectively [19]. The polycystic ovary is usually not associated with any symptoms, other than those related to hyperandrogenic chronic anovulation.

It is difficult to make the diagnosis of PCOS when a woman is on hormonal contraception, such as oral contraceptive pills (OCPs), as this will normalize circulating androgen levels and can also significantly improve (especially

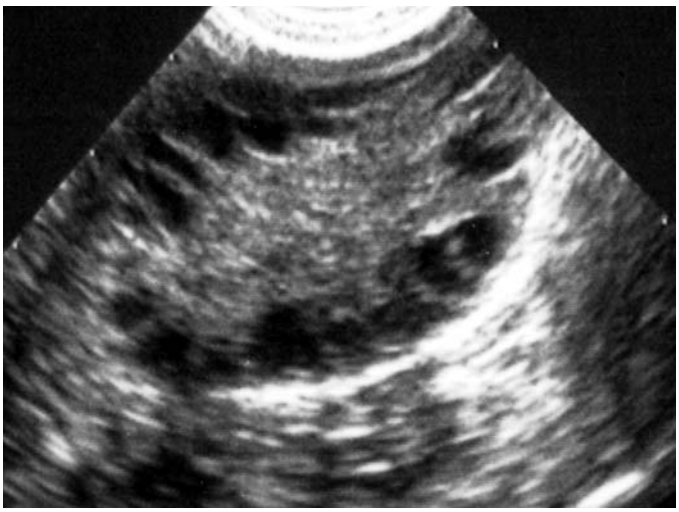

Fig. 1. Polycystic ovary on transvaginal ultrasound.

over 1–2 y periods) stigmata of hyperandrogenism, such as acne and hirsutism [22]. A recent study observed that discontinuing OCPs in women with PCOS for at least 8 weeks allows the return of all measured androgens and sex hormone-binding globulin (SHBG) levels to basal values [23].

Gonadotropins are also suppressed by hormonal contraception; however, while women with PCOS tend to display increased luteinizing hormone (LH) levels relative to follicle-stimulating hormone (FSH) [24], these are no longer included in any recommended diagnostic criteria [3,4]. There are many reasons for this. One is that the inherent pulsatility of gonadotropins [25], even with disordered secretion, can lead to a high percentage of false positives and negatives. Some investigators have recommended pooled collections to assess gonadotropins, but these are difficult to obtain in clinical practice [26]. Another confounding influence is the degree of obesity, which tends to be associated with blunted LH levels, although the same pattern of excess LH secretion can be elicited by dynamic challenge tests with GnRH [27]. Gonadotropins, therefore, have little utility in the diagnosis of PCOS, with the exception of diagnosing premature ovarian failure in which case a screening FSH would be obtained. It is worth noting that FSH levels, both basal and stimulated, tend to be normal in women with PCOS [24].

2. DIFFERENTIAL DIAGNOSIS OF PCOS

PCOS remains a diagnosis of exclusion, and it is useful to exclude other potential etiologies that can present with the triad of polycystic ovaries, hyperandrogenism, and chronic anovulation. It is important to note that the presence

of one of these signs or symptoms alone presents a much wider differential diagnosis. For instance, chronic anovulation alone may be due to failure or dysfunction of the hypothalamic–pituitary axis or to frank ovarian failure, states of steroid deficiency without androgen excess. In series of adult women presenting with amenorrhea alone, PCOS is present in about one-third of these patients [28], but rises to 70% or more when other symptoms such as hirsutism are considered [29].

Other than PCOS, other potentially serious causes of hyperandrogenism include such disorders as Cushing's syndrome and an androgen-secreting tumor [30]. These disorders are acquired and are often preceded by a period of normal menses without symptoms of hyperandrogenism. In contrast, PCOS presents in the postmenarche and tends to affect women throughout much of their reproductive life.

As Cushing's syndrome has an extremely low prevalence in the population (1–2 per million) and screening tests do not have 100% sensitivity/specificity, routine screening of all women with PCOS for Cushing's syndrome is not indicated [31]. Nonetheless, the presence of clinical signs more commonly found in Cushing's syndrome, such as ecchymoses, proximal muscle weakness, centripetal reddened striae, facial rubor and swelling, and perhaps hypertension and glucose intolerance, should signal the need for screening tests. Cortisol excess can be screened for with a 24-h urine collection for free cortisol.

Androgen secreting tumors are rare in this age group, are usually ovarian in origin, tend to have markedly elevated circulating androgen levels above the usual PCOS range, and are associated with a comparatively rapid onset of symptoms which frequently progress to frank virilization with clitoromegaly, breast atrophy, and voice changes [32,33]. Virilization is rarely, if ever, associated with PCOS, and this clinical presentation should always trigger a search for other causes, including anabolic steroid abuse.

A disorder that can present peripubertally in a similar indolent fashion as PCOS is 21-hydroxylase (21-OH) deficient nonclassic congenital adrenal hyperplasia (NCAH), also known as late-onset congenital adrenal hyperplasia. NCAH is a homozygous recessive disorder due to mutations in the *CYP21* gene, which results in an abnormal (or absent) 21-OH activity and a shift toward the overproduction of androgens. Overall, between 1 and 8% of women with androgen excess have *CYP21* deficient NCAH depending on ethnicity, with the highest rates reported in Ashkenazi Jewish populations [34]. Patients with NCAH may present with mild symptoms, many with only persistent acne or moderate degrees of hirsutism and oligoamenorrhea, and frank virilization or even severe hirsutism is relatively rare [35]. The levels of the exclusive adrenal androgen metabolite dehydroepiandrosterone sulfate (DHEAS) are not any higher in NCAH than in women with PCOS [35].

Although the frequency is relatively low, all patients with unexplained androgen excess should be screened for NCAH due to *CYP21* mutations, as

this diagnosis has a different prognosis, a different treatment regimen, and requires genetic counseling regarding the risks of congenital transmission [36,37]. The measurement of a basal 17α-hydroxyprogesterone (17-HP) in the follicular phase and in the morning can be used to screen for this disorder (normal < 2–4 ng/mL) [38]. This level is also unlikely to be affected by the concurrent use of oral contraceptives or glucocorticoids.

Other rare situations that may present with hyperandrogenic chronic anovulation are thyroid disease and hyperprolactinemia. Although the evidence linking thyroid disease to hyperandrogenism is weak, thyroid disease is common in women and merits detection. A TSH level is easily obtained, and thyroid abnormalities can readily be treated. The case for measuring prolactin is more complex. About 20–30% of women with PCOS have been reported to have mildly elevated prolactin levels [39]. In our lab, the normal prolactin level is 20 ng/mL, and we find many PCOS patients whose prolactin levels are in the range of 20–30 ng/mL. The mild elevations in prolactin probably reflect the hypothalamic–pituitary dysfunction associated with PCOS.

Polycystic ovaries on ultrasound are found in a wide variety of unrelated disorders with some syndromes having little overlap with hyperandrogenic chronic anovulation. For example, up to 30% of women with normal menses and normal circulating androgens may have polycystic ovaries [18,40,41]. There have been recent reports to suggest that polycystic ovaries per se may identify a group of women with some subtle stigmata of reproductive and metabolic abnormalities found in the endocrine syndrome of PCOS [42–44], and these data strengthened the position for incorporating the ultrasound morphology of the ovaries as part of the definition for PCOS [3,4,45]. However, clinical caution should be applied when a random ultrasound reveals polycystic ovaries in the absence of symptoms.

3. EVALUATION FOR INSULIN RESISTANCE IN PCOS

The etiology of PCOS remains unknown and the source of much speculation and research. It is the holy grail of female reproductive endocrinology, and religious-like fervor frequently accompanies the favored theories of the experts. Time and technology have shifted the focus from the ovary as the prime suspect [2] to the hypothalamic–pituitary axis [46], and currently on some primary defect in insulin action, as the primary instigator of the syndrome [47] (Fig. 2). There is clearly a vicious feedback loop in which disordered steroid feedback from the ovary (primarily androgen and weak peripherally aromatized estrogens) can lead to disordered hypothalamic–pituitary function and gonadotropin secretion (i.e., abnormal pulsatility with excess LH compared to normal FSH levels). More recently, it has been suggested that this feedback loop might have developed secondary to a systemic abnormality, such as the decreased glucose uptake in response to a given level of insulin (i.e., insulin resistant)

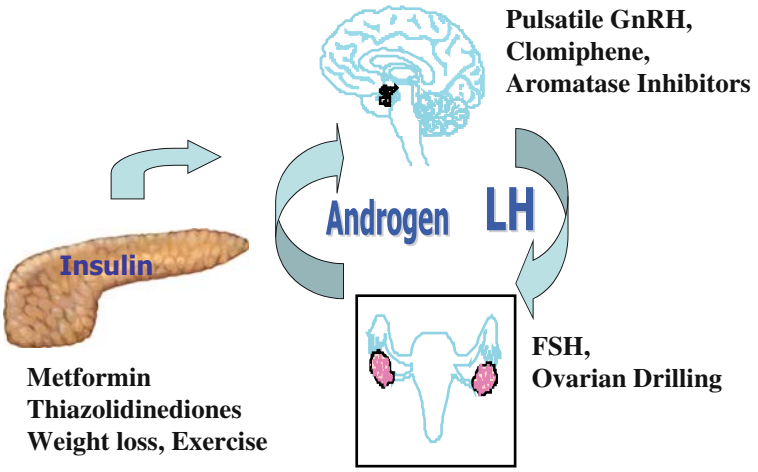

Fig. 2. Intervening in the vicious feedback cycle at many levels can restore ovulation in women with PCOS. Lowering androgens or gonadotropins, or insulin have all been reported as effective.

often observed in PCOS women [47]. Adding to the dilemma is that treatment of each one of these putative mechanisms can restore ovulation in many women with PCOS (Fig. 2).

This reconfiguration of PCOS as a metabolic syndrome with reproductive implications has led to extensive study of these women for signs and stigmata of insulin resistance. Women with PCOS appear to have a level of peripheral insulin resistance comparable to that of women with type 2 diabetes mellitus (DM) [48]. However, women with PCOS tend to demonstrate normal fasting glucose and normal glycohemoglobin levels, but tend to be glucose intolerant after glucose challenge. Consequently, about 40% of women with PCOS display impaired glucose tolerance or a 2-h glucose level ≥ 140 mg/dL after a standard 75 g oral glucose challenge after an overnight fast [49–51]. Women with PCOS often display both fasting and glucose challenged hyperinsulinemia, evidence for beta-cell compensation in response to the peripheral insulin resistance. However, the degree of compensation is inadequate for the degree of peripheral insulin resistance present, suggesting they are well on the road to developing type 2 DM [52,53].

Based on the prevalence of glucose intolerance in the larger population of US women ages 20–44 years (i.e., 7.8% impaired glucose tolerance and 1.0% undiagnosed diabetes) [54], the prevalence of glucose intolerance in PCOS (~40%) [49–51], and the prevalence of PCOS (~7%) [1], it can be extrapolatedthat PCOS contributes to approximately 30% of impaired glucose tolerance and 40–45% of type 2 DM among reproductive-aged women in the US. Risk factors for glucose intolerance in women with PCOS include a family history of diabetes, age, obesity, and especially, centripetal (android) body fat distribution [49–51].

In the US, obesity frequently accompanies PCOS. In the most comprehensive study of the prevalence of PCOS in an unselected population (i.e., women applying for work at a university hospital in Alabama), 24% were overweight (body mass index [BMI] 25.0–29.9 kg/M^2), and 42% were obese (BMI > 30 kg/M^2) [1]. Obesity further exacerbates metabolic and reproductive abnormalities in women with PCOS, worsening insulin resistance and the degree of hyperinsulinemia, and stimulates the expression of the PCOS phenotype in susceptible individuals as family studies suggest [55].

Overall, insulin resistance results in hyperinsulinemia, which, in turn, stimulates androgen secretion by theca cells [56,57] and suppresses the hepatic production of SHBG [58,59]. Thus, both obesity and insulin resistance lead to lower SHBG levels

Table 1. Suggested diagnostic evaluation for PCOS

Physical

(1) Blood pressure

(2) Body mass index (weight in kg divided by height in M^2) (BMI 25–30 = overweight, BMI > 30 = obese)

(3) Waist: measure to determine body fat distribution (value > 88 cm = abnormal)

(4) Presence of stigmata of hyperandrogenism/insulin resistance. Acne, hirsutism, androgenic alopecia, acanthosis nigricans

Laboratory

(1) Documentation of biochemical hyperandrogenemia. Total testosterone and/or bioavailable/free testosterone

(2) Exclusion of other causes of hyperandrogenism
- TSH (thyroid dysfunction)
- Prolactin (hyperprolactinemia)
- 17-Hydroxyprogesterone (nonclassical congential adrenal hyperplasia due to 21 hydroxylase deficiency), random normal: <3–4 ng/mL or fasting am <2 ng/mL
- Consider screening for Cushing's syndrome and other rare disorders such as acromegaly

(3) Evaluation for metabolic abnormalities
- 2-h OGTT (fasting glucose [<110 mg/dL = normal, 110–125 mg/dL = impaired fasting glucose, >126 mg/dL = type 2 diabetes) followed by 75 g oral glucose ingestion and then 2 h glucose level (<140 mg/dL = normal glucose tolerance, 140–199 mg/dL = impaired glucose tolerance, >200 mg/dL = type 2 diabetes)
- Fasting lipid and lipoprotein level (total cholesterol, HDL-C, triglycerides [LDL usually calculated by Friedewald equation])

(4) Optional tests to consider
- Ultrasound of ovaries for baseline evaluation/morphology prior to ovulation induction or in cases of virilization or rapid conversion to an androgen excess state
- Gonadotropin determinations to determine cause of amenorrhea
- Fasting insulin in younger women, those with severe stigmata of insulin resistance and hyperandrogenism, or those undergoing ovulation induction
- 24-Urine test for urinary free cortisol with late onset of PCOS symptoms or stigmata of Cushing's syndrome

OGTT is oral glucose tolerance test, 75 g.

and higher bioavailable levels of androgens [60]. In fact, SHBG may become a measure in the future that reflects both abnormalities in ovarian production and insulin resistance [61].

4. SUMMARY

PCOS is a disorder associated with hyperandrogenism, polycystic ovaries, and ovulatory dysfunction. The clinical evaluation discussed in this chapter has been summarized in Table 1. Because PCOS is a diagnosis of exclusion, other disorders should be excluded. Women with PCOS should be evaluated for both reproductive and metabolic abnormalities. Like the heterogeneity in the combination of reproductive signs and symptoms that characterize PCOS, metabolic risk factors are variably present in women with PCOS. Alternatively, there may be a publication bias toward linking PCOS with metabolic adversity. Further study of the long-term sequelae and the predictive role of surrogate markers will greatly aid the clinical evaluation of women with PCOS (see Chap. 8).

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