

## Chapter 2

# Polycystic Ovarian Syndrome: A Diagnosis of Exclusion

Jennifer Wolf, Courtney L. Barnes, and Mira Aubuchon

### Key Points

- Polycystic ovary syndrome presents with features that may overlap with multiple other endocrine disorders and clinical conditions.
- These conditions must be ruled out before the diagnosis of PCOS can be established.

### Introduction

Polycystic ovary syndrome (PCOS) is a common chronic condition with implications for morbidities, both in short-term (e.g., subfertility and pregnancy-related complications) and long-term risks (e.g., type 2 diabetes, cardiovascular disease, depression, poor quality of life, and overall mortality) [1]. A prompt diagnosis allows opportunities for early institution of preventive strategies for prevention of sequelae. However, diagnosing PCOS can be challenging, as the symptoms do overlap with a number of disorders that themselves require specific treatment. No single symptom,

---

J. Wolf, M.D.

Department of Obstetrics and Gynecology, University of Missouri Healthcare Women's and Children's Hospital, 500 North Keene Street, Suite 400, Columbia, MO 65201, USA  
e-mail: wolfje@health.missouri.edu

C.L. Barnes, M.P.H., M.D.

Department of Obstetrics and Gynecology, University of Missouri Women's and Children's Hospital, 2325 Smiley Lane, Columbia, MO 65202, USA  
e-mail: barnesc1@health.missouri.edu

M. Aubuchon, M.D. (✉)

Department of Obstetrics, Gynecology, and Women's Health, University of Missouri, 500 N Keene St, Suite 203, Columbia, MO 65202, USA  
e-mail: aubuchonm@health.missouri.edu

**Table 2.1** Differential diagnoses that may mimic or coexist with PCOS

Condition	Initial screening
Hypothyroidism	TSH
NCCAH	17-Hydroxyprogesterone
Hyperprolactinemia	Prolactin
Androgen-secreting tumor	Testosterone, DHEAS
Cushing's syndrome	Midnight serum/salivary cortisol, 24-h urine free-cortisol, or dexamethasone suppression test
Exogenous androgen exposure	History-taking
Hypothalamic hypogonadism	Estradiol, FSH, LH

examination finding, or laboratory data is diagnostic of this disorder. Rather, arriving at a diagnosis requires a systematic approach aimed at excluding the differential diagnoses that could account for the patient's presentation; the diagnosis of PCOS is thus one of systematic exclusion.

Table 2.1 lists the common alternative etiologies that could mimic PCOS. On occasion, patients may experience these conditions concurrently with PCOS.

## Prevalence and Epidemiology of PCOS

It is estimated that 2–18 % of women have PCOS, making PCOS the most common endocrine disorder among reproductive-aged women [2–4]. However, determination of exact prevalence is problematic owing to heterogeneity in the employed diagnostic criteria (see next section) and variability in presenting symptoms, laboratory values, and imaging studies across populations and over time.

## Diagnostic Criteria for PCOS (Laboratory and Imaging)

PCOS may include hyperandrogenism, chronic anovulation, and sonographic polycystic ovarian morphology, once other etiologies have been excluded. Hyperandrogenism, either clinical or biochemical, is required for diagnosis of PCOS by the 1990 National Institutes of Health criteria and the 2006 Androgen Excess-PCOS criteria, in contrast to the 2003 Rotterdam criteria, which allows for any two of three [5–7]. Although obesity, luteinizing-hormone elevations, and insulin resistance are common among PCOS, these are not required for diagnosis [1].

Clinical hyperandrogenism can manifest with hirsutism, defined as midline distributed terminal hair growth, acne, or male-pattern balding [1]. Biochemical hyperandrogenism may include elevations in total or bioavailable testosterone or dehydroepiandrosterone sulfate (DHEAS), although the assays may not be sensitive even in the presence of clinical hyperandrogenism [1]. The presence of virilization (rapidly progressing hirsutism/acne with clitoromegaly) should raise suspicion for malignancy [1].

Chronic anovulation is suggested by oligomenorrhea with nine or fewer menstrual cycles annually, although eumenorrhea with absent ovulation is present in 20 % of PCOS patients [6]. Transvaginal ultrasound is considered the best imaging modality, with polycystic ovaries defined as having either  $\geq 12$  follicles 2–9 mm in diameter or ovarian volume  $>10 \text{ cm}^3$  in at least one ovary in the absence of ovarian lesions [5].

Etiologies that must be excluded include pregnancy, thyroid dysfunction, hyperprolactinemia, congenital adrenal hyperplasia, ovarian insufficiency, androgen-secreting neoplasm, hypothalamic amenorrhea, and Cushing's syndrome [1].

## **Congenital Adrenal Hyperplasia**

Congenital adrenal hyperplasia (CAH), particularly nonclassical (NCAH), must be considered in any woman presenting with features of PCOS. Notably, symptoms of hirsutism, acne, alopecia, and menstrual dysfunction that are commonly attributed to PCOS can be seen in patients with CAH [8, 9].

CAH is an autosomal recessive disorder most commonly involving the mutations of the gene encoding the enzyme 21-hydroxylase and, less frequently, genes encoding 11 $\beta$ -hydroxylase and 3 $\beta$ -hydroxysteroid dehydrogenase, with phenotypes exhibiting wide variability depending on severity of mutations and number of alleles affected [9, 10]. All of these enzyme deficiencies lower production of cortisol and aldosterone by the adrenal cortex. This lowers the negative feedback of cortisol on the pituitary, prompting compensatory increased pituitary adrenocorticotrophic hormone (ACTH), leading to hyperplasia of the adrenal cortex [9]. Precursor hormones proximal to the deficient enzyme accumulate that are either themselves androgenic or are converted to androgenic products and thus promote androgenization and virilization [9]. For example, 17-hydroxyprogesterone that is elevated in 21-hydroxylase and 11 $\beta$ -hydroxylase deficiencies may be converted to androstenedione via 17, 20 lyase, and through an alternate pathway, to dihydrotestosterone [9].

NCAH presents in later childhood to early adulthood, affecting approximately 1 in 1,000 to 2 in 1,000 [8, 9] in the general population, but may be much more prevalent in certain ethnic groups such as Hispanics, Yugoslavs, and Eastern European Ashkenazi Jews [9, 10]. Classical CAH occurs in 1 in 5,000–15,000 live births [9] and manifests as neonatal ambiguous genitalia or virilization, but diagnosis is important because 75 % of cases have associated salt-wasting [10]. Subfertility and infertility are uncommon in NCAH but more prevalent with the classical type [11]. However, NCAH has been reportedly associated with higher rates of pregnancy loss that improved with glucocorticoid therapy [11]. Twenty-seven to seventy-six percent of NCAH are carriers of a severe loss-of-function mutation, which has particular importance during pregnancy in terms of female fetus virilization [11]. If the paternal status is unknown, the mother may be treated with dexamethasone to suppress fetal ACTH and minimize excessive fetal

androgen production until prenatal diagnosis can be achieved by either chorionic villus sampling or amniocentesis [10]. This strategy is recommended, particularly if there is a history of a child or first-degree relative with classical CAH, but concerns have been raised about adverse maternal and fetal effects as a result of dexamethasone exposure [10].

Clinically, it can be difficult to distinguish NCAH from PCOS [8, 12, 13], since both present with features of androgen excess. The androgen excess associated with CAH may lead to disruption of gonadotropin release from the pituitary and ovarian cysts, producing superimposed PCOS [10]. NCAH due to 11 $\beta$ -hydroxylase deficiency may be distinguished from PCOS by accompanying hypertension [14]. A morning basal 17-hydroxyprogesterone level >2 ng/mL during the follicular (preovulatory) stage of the menstrual cycle has 97 % sensitivity for screening the commonest variant of NCAH that due to 21-hydroxylase insufficiency [8]. However, 17-hydroxyprogesterone will be normal in cases of 3 $\beta$ -hydroxysteroid dehydrogenase deficiency [15].

Once NCAH is suspected based on initial screening, patient should undergo the diagnostic ACTH Stimulation Test. Exogenous acutely administered ACTH would be expected to increase accumulation of precursors proximal to the deficient enzyme. In the case of suspected 21-hydroxylase deficiency, 17-hydroxyprogesterone (sometimes accompanied by androstenedione) is drawn at both baseline and 30–60 min following intravenous administration of 250  $\mu$ g synthetic ACTH [9]. Testing should be done in the morning when endogenous ACTH is maximal [16] and during the follicular phase of the cycle to prevent false-positive progesterone elevations from ovulation. An overnight fast is preferred, given that food intake may affect the hypothalamic–pituitary–adrenal axis [17]. NCAH is diagnosed with a stimulated 17-hydroxyprogesterone level >10 ng/mL [12].

With 11 $\beta$ -hydroxylase deficiency, 11-deoxycortisol and 11-deoxycorticosterone increase in addition to 17-hydroxyprogesterone and androstenedione during the ACTH Stimulation Test [14]. Different hormone profiles will be seen for the rare HSD3B2 deficiency, whereby elevated 17-hydroxypregnenolone and DHEA levels are observed [15]. The clinical impression may be further refined with genotyping. CYP21A2 is encoded on the short arm of chromosome 6, and missense mutations resulting in NCAH with 20–60 % of enzyme activity preserved include P30L, V281L, R339H, and P453S [10].

Treatment of NCAH depends on the severity of symptoms and is individualized to the patient. Menstrual cyclicity can be reinstituted and hyperandrogenic features controlled through use of hormonal contraceptives and use of antiandrogens (individually or in concert). A judicious use of exogenous glucocorticoid by exerting negative feedback at the pituitary level and, hence, suppressing the ACTH-driven adrenal steroidogenic pathway, allows spontaneous resumption of ovulation without conferring additive risk of multiple pregnancy, and should be considered in anovulatory patients desirous of achieving pregnancy [9, 10]. As discussed earlier, a diagnosis of NCAH per se is not an indication for continuing glucocorticoid therapy during pregnancy [10, 18].

## Tumors

In women, androgen-secreting tumors can originate from the ovary or the adrenal gland. Rapidity of onset and symptom progression and evidence of virilization should alert one to the possibility of an androgen-secreting tumor as a mechanism for the PCO-like clinical picture. Tumors vary in the potency of androgens secreted, although weaker androgens may be converted into potent hormones in peripheral sites. Serum total testosterone  $>200$  ng/dL has been used as a threshold for alerting clinicians regarding the possibility of an underlying androgen-secreting tumor, and warrants further evaluation to rule out the possibility of an ovarian and/or adrenal tumor [19, 20]. At this specified threshold, the test has a high sensitivity and negative predictive value. However, because of the relatively low overall prevalence of androgen-secreting tumor/s, the positive predictive value of total testosterone for diagnosing an androgen-secreting ovarian or adrenal tumor is poor [20]. It is important to appreciate that total testosterone levels at  $\leq 200$  ng/dL do not necessarily exclude the possibility of an underlying tumor; additionally, tumor interpretation can be challenging because a standardized testosterone assay is not available [1]. Virilizing tumors of the adrenal glands are also extremely rare. Measurement of DHEAS has been recommended for screening of virilizing adrenal tumors given its exclusive production by the adrenal, with further workup at levels  $>600$ – $700$   $\mu$ g/dL, but it is difficult to assess positive predictive value because the prevalence of tumor is so low [20]. Levels that suppress to normal with dexamethasone administration suggest a non-neoplastic process [19].

Ultrasound is generally regarded as the initial imaging choice for evaluating the ovaries. However, sex cord-stromal tumors can be difficult to visualize by ultrasound given that a majority are isoechoic to the ovary [21]. When ultrasound imaging of the ovaries is inconclusive, additional imaging is warranted, preferably by magnetic resonance imaging (MRI) rather than computer tomography (CT). Even with advanced imaging, however, virilizing ovarian tumors can be difficult to localize [22]. When this occurs, the ovarian veins can be sampled bilaterally and testosterone levels can be measured to identify the laterality of ovarian source of excess androgen [22]. The ovarian vein with abnormally high androgen levels can identify on which side the tumor exists [22].

The treatment of androgen-secreting ovarian tumors depends on the stage at the time of diagnosis. Most are stage I, meaning that they are unilateral and localized to the ovary, and are treated with surgery [23, 24]. Surgery may involve unilateral or bilateral oophorectomy accompanied by hysterectomy, depending on the patient's fertility desires, along with staging [23, 24]. In contrast to the ovary, CT is a reasonable initial imaging modality for virilizing adrenal imaging tumors [19]. In the event of a suspected focal adrenal source of androgen excess, patients should be promptly referred for definitive management that will likely entail a surgical approach [19].

## Cushing's Syndrome

Cushing's syndrome is an uncommon but potentially life-threatening condition that can mimic PCOS. Caused by excessive exposure to cortisol, with an incidence of 0.7–2.4 per million population per year [25], the clinical presentation commonly overlaps that of PCOS, including progressive weight gain, menstrual abnormalities, and features of hyperandrogenism (acne and hirsutism) [25, 26]. Clinical stigmata include evidence of central adiposity, dorsal cervical fat accumulation, proximal muscle weakness, violaceous cutaneous striae, depression, hypertension, osteopenia, and glucose intolerance [25, 26]. Anterior pituitary corticotroph tumors leading to excessive ACTH production are responsible for 70 % of the cases of Cushing's syndrome, with the remainder being due to ectopic ACTH production [25]. Cushing's syndrome may be the presenting feature of an occult cancer presenting as a paraneoplastic syndrome, or it may result secondary to cortisol-secreting tumors or even follow exogenous exposure to glucocorticoids [25].

Screening for Cushing's syndrome may be accomplished by sampling cortisol in serum, saliva, or urine, either alone or in combination. Timing of sample takes into consideration diurnal changes of ACTH and cortisol, which peak in the morning and nadir at night [16]. Salivary cortisol assessed between 2,300 and midnight is used as a surrogate for midnight serum cortisol [26]. Falsely positive screening may be encountered in cases of depression, alcoholism, anorexia nervosa, and use of estrogen-containing contraceptives (within 6 weeks of testing), rifampin, antiepileptic drugs, or late pregnancy [25, 27]. Contraceptive use increases cortisol binding globulin and, thereby, total serum or salivary cortisol, but it does not affect free-cortisol levels in urine [27]. Renal dysfunction or severe illness may produce false-negative results [25, 27]. An abnormal result for 24 h urine free-cortisol is considered as  $>4$  times normal ( $<150$   $\mu\text{g}/24$  h, depending on the assay) [26–28]. A salivary cortisol level  $>8.6$  nmol/L (0.31  $\mu\text{g}/\text{dL}$ ) or repeatedly  $>4.3$  nmol/L (0.15  $\mu\text{g}/\text{dL}$ ) is highly suggestive of Cushing's syndrome, with sensitivity of 90–95 % and specificity of 90–100 %, but results may be compromised in patients with depression or for occupations with disrupted sleep–wake cycles [26, 27].

Suppression of normal pituitary ACTH release follows exposure to an exogenous glucocorticoid, thereby decreasing serum cortisol level. As a screening strategy for diagnosing overproduction of cortisol, the overnight dexamethasone suppression test (DST) utilizes administration of 1 mg dexamethasone at 2300 hours, followed by serum cortisol measurement in early morning, between 0800 and 0900 hours; serum cortisol level of  $<50$  nmol/L ( $<1.8$   $\mu\text{g}/\text{dL}$ ) is taken to reflect adequate adrenal suppression [25, 26]. An overnight fast is preferred, as serum cortisol levels during the DST may be affected by food intake [17]. Less commonly, a total of 4 mg dexamethasone is administered in divided doses of 0.5 mg every 6 h over 48 h, and serum cortisol is measured at 0900 hours at the start and end of the test [25]. The false-negative rate of the DST is reported to be 8 % [26].

Once a diagnosis of CS has been made, the patient should be referred to an endocrinologist for further management. While definitive management is beyond

the scope of reproductive endocrinology, the next steps focus on unraveling the underlying mechanism(s) for cortisol overproduction. Serum ACTH levels, if abnormally elevated, should prompt imaging studies to identify focal pituitary pathology and/or metastatic lesions that may account for ACTH overproduction. Alternatively, non-suppressible excess cortisol in the setting of low ACTH levels should direct one to imaging of the adrenals for evidence of an adrenal mass or hyperplasia. In the absence of evident adrenal asymmetry or mass, adrenal vein sampling may help establish a diagnosis of adrenal overproduction of cortisol; definitive surgical intervention can then follow, if indicated [25].

## **Exogenous Androgens**

Prior to making a diagnosis of PCOS, a hyperandrogenic patient should be queried as to exposure to agents with androgenic activity such as danazol, synthetic derivatives of testosterone for “performance enhancing,” and exogenous use of testosterone by the patient or her partner (symptoms of androgen excess have been reported from passive transfer through physical contact of transdermal testosterone gel being used by partner) [29]. Once exposure is discontinued, symptoms typically improve, although virilization with clitoromegaly, male-pattern balding, voice deepening, and hirsutism may persist [30].

## **Idiopathic Hyperandrogenism**

At least in one study, idiopathic hyperandrogenism accounted for approximately 15 % of cases of presumed androgen excess in premenopausal women of Italian origin [31]. The diagnosis is based on clinical and biochemical assessment. Ovulatory menstrual cycles, sonographically normal ovaries, and a normal androgen milieu despite clinical evidence of hyperandrogenism identify these cases as distinct from PCOS [31].

## **Hypothyroidism**

While menstrual disturbances are commonly encountered in the setting of thyroid dysfunction, the prevalence of menstrual dysfunction is much higher with hypothyroidism compared to hyperthyroidism [32]. Evaluation of thyroid function must be undertaken in any woman presenting with menstrual irregularities. Thyroid evaluation is typically performed by obtaining a serum thyroid-stimulating hormone (TSH) level, preferably in the morning when the level is at its nadir [33]. If the TSH is elevated, a thyroxine (T4) serum level can be obtained. In the case of overt

hypothyroidism, laboratory findings would demonstrate an elevated TSH level and a decreased free-T4 level [33]. Elevated TSH in the setting of normal free-T4 levels is consistent with subclinical hypothyroidism, which can progress to overt disease over time [33]. Less commonly, free T4 is low but TSH is normal or low, which suggests hypothalamic or pituitary dysfunction [33]. Patients having severe hypothyroidism with TSH >10 mIU/mL have significant menstrual disturbances (34 % vs. 23 % in controls), including irregular cycles, oligo-, poly-, and amenorrhea, but those with mild-moderate hypothyroidism were not significantly different [32]. The prevalence of TSH >4.5 mIU/mL in the United States among women age 12–49 is 3.1 % [34] but increases to 31.5 % at TSH of 4–4.5 mIU/mL [35]. Other laboratory findings of hypothyroidism include elevated low-density lipoprotein (LDL), high triglycerides, hyponatremia, normocytic anemia, proteinuria, hyperprolactinemia, and elevated C-reactive protein levels [33].

Patients with overt hypothyroidism are encouraged to start thyroid replacement therapy, which is typically continued for life [33]. This has particular importance for women of reproductive age, although evidence to support therapy in the setting of subclinical hypothyroidism is debated [36]. The thyroid gland makes thyroxine (T4) and the more biologically active triiodothyronine (T3) [33]. Twenty percent of T3 is synthesized from the thyroid gland, with the remainder derived from peripheral conversion of T4 by deiodinase enzymes [33]. T3 preparations have short half-lives and require more frequent daily dosing, so T4 in the form of levothyroxine is preferred [33]. After initiating pharmacologic treatment of hypothyroidism, TSH levels are followed until normalized [33].

Hashimoto's disease is the most common cause of hypothyroidism in the United States and is the result of autoimmune thyroid damage [33]. Other relatively uncommon etiologies for hypothyroidism include iodine deficiency, radioablation or surgery to treat hyperthyroidism, radiation to the neck, central dysfunction from a cranial mass, radiation to the head, or ischemia [33]. Certain medications can also result in hypothyroidism, such as lithium, amiodorone, interferon-alpha, and interleukin-2 [33].

## Hyperprolactinemia

Hyperprolactinemia is a relatively common endocrinopathy with an estimated prevalence at 15 % in women with isolated anovulation, and 43 % in those manifesting a combination of galactorrhea with anovulation [37]. While hyperprolactinemia may be asymptomatic, common clinical features include galactorrhea, oligo-amenorrhea, reduced libido, and subfertility [38].

Prolactin is synthesized and released by lactotroph cells in the anterior pituitary and is inhibited by dopamine from the hypothalamus via the pituitary portal circulation [37–39]. Diurnal variations in circulating levels of prolactin are evident, with the levels being highest during sleep and lowest during waking hours [39]. Normal serum levels of prolactin are 10–28 µg/L [37–39].



A spectrum of physiological, pathological, and pharmacological etiologies may underlie hyperprolactinemia. Physiologic causes of prolactin excess include pregnancy, lactation, breast stimulation, stress, sexual intercourse, and exercise [37–39]. Pathologic contributors to prolactin excess include pituitary and non-pituitary tumors, of which the most common are tumors of lactotrophs (prolactinoma) that account for about 30 % of all pituitary adenomas [37–39]. Iatrogenic causes of hyperprolactinemia are not uncommon; commonly used pharmacological agents that can cause hyperprolactinemia include verapamil, metoclopramide, methyldopa, phenothiazine, and reserpine [37–39]. Estrogen, thyrotropin-releasing hormone (TRH), epidermal growth factor, and dopamine receptor antagonists promote synthesis and secretion of prolactin [37–39]. In primary hypothyroidism, in which thyroid hormone secretion is low, compensatory increased TRH would increase both TSH and prolactin secretion [39].

Per the Endocrine Society, serum prolactin levels are accurate for diagnosing hyperprolactinemia, and dynamic testing (TRH, L-dopa, nomifensine, and domperidone) is not superior or necessary [38]. Despite diurnal variations [39], prolactin can be drawn at any time of day [38]. It is best to measure prolactin at least 1 h after awakening or eating [40]. It is preferable to draw prolactin levels prior to performing breast or pelvic examinations, though one study did not find that breast examinations affected prolactin levels in euprolactinemic women [41]. Prolactin levels persistently  $>25$ – $28$   $\mu\text{g/mL}$  need further evaluation. If the patient with moderately elevated prolactin level  $<150$   $\mu\text{g/mL}$  is asymptomatic or has less-typical presenting symptoms such as decreased libido in the setting of eumenorrhea, polyethylene glycol precipitation to identify macroprolactin forms, which have low bioactivity, can avoid further workup [38, 40]. Symptomatic patients should receive a gadolinium-enhanced MRI to evaluate the pituitary for an adenoma, particularly a macroadenoma with size  $>10$  mm [38, 40]. Although macroadenomas are associated with prolactin levels  $>250$   $\mu\text{g/mL}$ , tumor size does not always correlate with serum levels, so imaging is warranted even with low degrees of prolactin elevations [38, 40]. Symptoms of headaches, visual changes, features suggestive of cranial nerve palsy, and perturbations in pituitary hormones in addition to prolactin excess (such as concomitant thyroid and adrenal dysfunction) are concerning as mass effect phenomena secondary to a pituitary tumor, and merit expeditious evaluation with brain MRI and visual field testing [38].

If the patient with hyperprolactinemia is asymptomatic, does not have amenorrhea, and does not have a macroprolactinoma, treatment is not needed [38]. Treatment of hyperprolactinemia depends on the underlying mechanism and the individual patient's clinical profile. In medication-induced hyperprolactinemia, discontinuation of the offending agent may restore gonadal function, but may come at the expense of exacerbating other medical conditions, particularly psychiatric [38]. Restoration of functioning of the hypothalamic–pituitary–ovarian (HPO) axis through use of dopamine agonists allows resumption of spontaneous ovulation; this strategy is particularly meaningful for those desirous of fertility, and in those diagnosed with a pituitary macroadenoma wherein tumor shrinkage can be achieved in more than 90 % of patients through lactotroph suppression [37–39].

Dopamine agonists (such as bromocriptine, cabergoline, and quinagolide) are the mainstay of pharmacologic treatment in clinical practice; acting on the D2-type receptors on the pituitary lactotrophs, these agents decrease the synthesis and cellular release of prolactin [37–39]. Treatment with dopamine agonists restores ovulation in about 90 % of women with anovulatory infertility secondary to hyperprolactinemia [37–39]. Cabergoline is preferred for macroprolactinomas over bromocriptine, with magnitude of tumor shrinkage 90 % vs. 50 %, respectively [38].

Decreased bone mineral density and predisposition to skeletal fragility should be considered as a long-term risk relating to chronic hyperprolactinemia and premenopausal hypogonadism [38]. Dopamine agonist therapy should be considered as a strategy to normalize ovarian function in patients deemed at a lifetime risk for skeletal fragility, as correction of hypogonadism allows an opportunity for optimizing bone mass accrual [38].

However, dopamine agonist therapy may exacerbate psychiatric illness, and, therefore, may not be appropriate for some patients [38, 40]. Estrogen-containing hormonal contraceptives may be considered in hypogonadal women with a microprolactinoma not desiring pregnancy or those who are not good candidates for dopamine agonist therapy [38, 40].

## Hypothalamic Hypogonadism

Hypothalamic hypogonadism (HH) is the most common cause for menstrual irregularities in adolescents and must be considered in the differential diagnosis when evaluating for PCOS [42]. While oligo-amenorrhea dominates the clinical picture, subtle features suggestive of hyperandrogenemia may be apparent (e.g., acne and excess villous hair). Circulating levels of androgens are typically within normal range, although mild excess in free testosterone may be seen and can be attributed to suppressed serum sex hormone binding levels (a sequel to protracted hypoestrogenemia). Laboratory testing typically indicates low estradiol, while gonadotropin levels may be low or normal, and other etiologies relating to thyroid or prolactin disorders are excluded [42].

HH is categorized as functional, implying a correctable cause, and nonfunctional. In functional HH, pituitary follicle-stimulating hormone (FSH) and luteinizing hormone (LH) responsiveness to hypothalamic gonadotropin release hormone (GnRH) is intact, but the pulsatility of GnRH secretion is altered. Potentially reversal causes of functional HH include psychological stress, nutrition deficit, and exercise excess [42]. Stress (psychological as well as physical) is a recognized contributor to HH; stress-induced release of hypothalamic corticotropin release hormone (CRH) disrupts the pulsatile release of GnRH, thereby resulting in dysfunction of the pituitary gonadotrophs [42]. Anorexia nervosa (AN) is classically associated with HH. Combinations of extreme nutritional limitations, low percentage body fat mass, and concomitant leptin deficiency as well as ongoing psychological stress are

recognized as contributory to HH of patients diagnosed with AN; the latter explains the inconsistent recovery of the hypothalamic–pituitary–ovarian axis function, despite fat mass being regained through intervention in some patients diagnosed with AN [42]. Athletes endure combinations of extreme physical and psychological stresses as well as dietary restrictions that predispose them to HH [42]. Nonfunctional hypothalamic states as causes for HH are relatively uncommon and merit consideration in appropriate clinical settings; these include idiopathic HH, Kallmann’s syndrome, infection, and chronic illness [42]. Idiopathic HH presents as primary amenorrhea and absent pubertal development and is estimated at 1 in 50,000 females [43]. Kallmann’s syndrome is a rare condition caused by a genetic mutation and additionally presents with anosmia (apparent or covert) due to failure of olfactory neuron migration during embryonic development [42]. Infectious etiologies include tuberculosis, sarcoidosis, and syphilis [42].

Management considerations for HH are guided by underlying mechanisms and the patient’s unique clinical profile. Of particular concern is the long-term risk for skeletal fragility given that HH is a protracted state of hypoeurogenemia. For patients with HH not desirous of pregnancy, estrogen therapy (either as a hormonal contraceptive formulation or as menopausal hormonal regimen) offers skeletal benefit for all except those with AN [44]. For the latter, some success with normalization of the HPO-axis function, and skeletal protection may be achieved through combinations of targeted psychological support and therapy and through deliberate weight gain [42]. Additionally, bisphosphonate risedronate and low-dose testosterone, both used off-label, improved bone density in a trial involving premenopausal women with AN [44]. Exogenous leptin therapy has demonstrated therapeutic success in achieving normalization of the HPO functioning, albeit in research settings [45].

For patients with HH seeking fertility, correction of the underlying condition may restore GnRH pulsatility; more realistically, however, successful ovulation can be achieved either through use of exogenous gonadotropins (albeit at the cost of an increased risk for multiple pregnancy) or where access to pharmacological GnRH is available with use of exogenous GnRH administered in a physiological paradigm through a transcutaneous pump (a physiological approach that holds minimal risk for multiple ovulation) [42].

## **Hyperandrogenic Insulin Resistance with Acanthosis Nigricans (HAIR-AN) Syndrome**

Hyperandrogenic insulin resistance with acanthosis nigricans, or HAIR-AN, syndrome represents an extreme state of insulin resistance and can be identified in 1–3 % of women presenting with clinical features of hyperandrogenism [46]. Although there is no gold-standard test, a diagnosis is suggested based on markedly elevated basal or glucose-stimulated insulin levels (more than 3–5 times higher than the upper limit of normal range) [46]. It is quite plausible that rather than being a distinct entity, HAIR-AN may represent a more metabolically severe form

of PCOS [46, 47]. Despite the severe hyperinsulinemia, pancreatic  $\beta$  cells appear to be dysfunctional, such that the severity of hyperinsulinemia is disproportionate to the glycemic profile of these patients [47]. High circulating levels of insulin are recognized to drive androgen synthesis by the ovarian theca cells and, thus, are of pathophysiological relevance to the overall clinical picture. Management strategies aim at improving insulin sensitivity through a combination of lifestyle modifications and pharmacological therapy [46, 47].

## Hyperreactio Luteinalis

Hyperreactio luteinalis is an uncommon condition that occurs during pregnancy in the second or third trimester and produces severe virilization [48]. The etiology is unknown but may be due to increased ovarian sensitivity to hCG, thereby increasing androgen production by theca cells and causing large cystic ovaries [48]. The risk is increased in gestational trophoblastic disease [48]. Although the condition is unlikely to be mistaken for PCOS during pregnancy, it is possible that a provider may see the patient for the first time during the postpartum period.

## Coexisting with PCOS

Although related endocrinologic disorders are typically ruled out prior to establishing the diagnosis of PCOS, they may coexist. Hyperprolactinemia was present in 7 % of Spanish women with hyperandrogenism [49]. As half of those cases were associated with macroprolactin, which would point more toward PCOS as the primary etiology for the hyperandrogenism, it is unclear whether the association is coincidental and independent or somehow related [49].

Autoimmune hypothyroidism and thyroiditis are more prevalent among PCOS patients compared to controls, and may relate to increased humoral immunity in the setting of unopposed estrogen [50, 51]. Subclinical hypothyroidism (TSH 4.5–10 mIU/mL) was present in 11 % of Brazilian women with PCOS and was associated with higher LDL cholesterol and prolactin levels than those with normal TSH [52]. Women with PCOS and subclinical hypothyroidism also have higher triglycerides than euthyroid PCOS women [53]. This relationship is likely bidirectional, as metformin therapy for women with both PCOS and hypothyroidism reduced TSH levels [54], while thyroid hormone therapy for hypothyroid patients with polycystic ovaries decreased both ovarian size and serum androgen levels [55].

Superimposed PCOS can occur due to the hyperandrogenic state from NCAH [10], with the two coexisting in 10 % of NCAH-afflicted Greek women [13].

Among patients with functional hypothalamic amenorrhea, 30–50 % have sonographic polycystic ovary morphology [56]. Although these patients are not

**Table 2.2** Diagnostic paradigms for PCOS<sup>a</sup>

	Society consensus criteria		
	NIH 1990	Rotterdam 2003	AES 2006
	Oligomenorrhea + androgen excess	Any 2	Androgen excess + either anovulation or PCO
Signs/symptoms			
Oligomenorrhea or anovulation	+	+/-	+/-
Hyperandrogenism	+/-	+/-	+/-
Hyperandrogenemia	+/-	+/-	+/-
PCO on ultrasound	–	+/-	+/-

<sup>a</sup>Reprinted from Fertility and Sterility, 81/1, revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome, 19–25, Copyright 2004, with permission from Elsevier

**Table 2.3** Suggested workup for evaluation of PCOS

TSH
Prolactin
Androgens
DHEAS
Testosterone (total and free)
17-Hydroxy progesterone
Pelvic ultrasound
Miscellaneous
Glucose tolerance test or hemoglobin a1c
Lipids
24-h Urine-free cortisol

hyperandrogenic initially, they have higher stimulated serum androstenedione and testosterone levels than controls [57]. This exaggerated ovarian response to gonadotropins is similar to that found in PCOS; a normal unstimulated androgen status in a subgroup of women with HH may be a reflection of ovarian quiescence due to basal hypothalamic suppression, and recovery of HPO axis in this population may unmask a PCOS phenotype [57].

Summary

PCOS is the most common cause of hyperandrogenic anovulation among reproductive-aged women. Early diagnosis allows the opportunity of timely interventions aimed at reducing long-term morbidity in this population. A variety of potentially serious disorders can, however, mimic the clinical presentation of PCOS. Despite a patient meeting well-defined clinical criteria (Table 2.2), the diagnosis of PCOS is one of exclusion after systematic evaluation to rule out common endocrinopathies that can masquerade as PCOS (Table 2.3).

## References

1. ACOG Committee on Practice Bulletins—Gynecology. ACOG Practice Bulletin No. 108: Polycystic ovary syndrome. *Obstet Gynecol.* 2009;114(4):936–49.
2. Farah L, Lazenby AJ, Boots LR, Azziz R. Prevalence of polycystic ovary syndrome in women seeking treatment from community electrologists. Alabama Professional Electrology Association Study Group. *J Reprod Med.* 1999;44(10):870–4.
3. Knochenhauer ES, Key TJ, Kahsar-Miller M, Waggoner W, Boots LR, Azziz R. Prevalence of the polycystic ovary syndrome in unselected black and white women of the southeastern United States: a prospective study. *J Clin Endocrinol Metab.* 1998;83(9):3078–82.
4. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. *Hum Reprod (Oxford, UK).* 2010;25(2):544–51.
5. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. *Fertil Steril.* 2004;81(1):19–25.
6. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *J Clin Endocrinol Metab.* 2006;91(11):4237–45.
7. Dunaif A, Givens J, Haseltine F, Merriam G, editors. Polycystic ovary syndrome. Boston, MA: Blackwell Scientific Publications; 1992.
8. Pall M, Azziz R, Beires J, Pignatelli D. The phenotype of hirsute women: a comparison of polycystic ovary syndrome and 21-hydroxylase-deficient nonclassic adrenal hyperplasia. *Fertil Steril.* 2010;94(2):684–9.
9. Witchel SF, Azziz R. Congenital adrenal hyperplasia. *J Pediatr Adolesc Gynecol.* 2011;24(3):116–26.
10. Nimkarn S, Lin-Su K, New MI. Steroid 21-hydroxylase deficiency congenital adrenal hyperplasia. *Endocrinol Metab Clin North Am.* 2009;38(4):699–718.
11. Bidet M, Bellanne-Chantelot C, Galand-Portier MB, Golmard JL, Tardy V, Morel Y, et al. Fertility in women with nonclassical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab.* 2010;95(3):1182–90.
12. Moran C. Nonclassic adrenal hyperplasia. *Fertil Steril.* 2006;86 Suppl 1:S3.
13. Trakakis E, Rizos D, Loghis C, Chrysikopoulos A, Spyropoulou M, Salamalekis E, et al. The prevalence of non-classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency in Greek women with hirsutism and polycystic ovary syndrome. *Endocr J.* 2008;55(1):33–9.
14. Nimkarn S, New MI. Steroid 11beta-hydroxylase deficiency congenital adrenal hyperplasia. *Trends Endocrinol Metab.* 2008;19(3):96–9.
15. Mermejo LM, Elias LL, Marui S, Moreira AC, Mendonca BB, de Castro M. Refining hormonal diagnosis of type 2 3beta-hydroxysteroid dehydrogenase deficiency in patients with premature pubarche and hirsutism based on HSD3B2 genotyping. *J Clin Endocrinol Metab.* 2005;90(3):1287–93.
16. Spath-Schwalbe E, Scholler T, Kern W, Fehm HL, Born J. Nocturnal adrenocorticotropin and cortisol secretion depends on sleep duration and decreases in association with spontaneous awakening in the morning. *J Clin Endocrinol Metab.* 1992;75(6):1431–5.
17. Vicennati V, Ceroni L, Gagliardi L, Gambineri A, Pasquali R. Comment: response of the hypothalamic–pituitary–adrenocortical axis to high-protein/fat and high-carbohydrate meals in women with different obesity phenotypes. *J Clin Endocrinol Metab.* 2002;87(8):3984–8.
18. Speiser PW, Azziz R, Baskin LS, Ghizzoni L, Hensle TW, Merke DP, et al. Congenital adrenal hyperplasia due to steroid 21-hydroxylase deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;95(9):4133–60.
19. Derksen J, Nagesser SK, Meinders AE, Haak HR, van de Velde CJ. Identification of virilizing adrenal tumors in hirsute women. *N Engl J Med.* 1994;331(15):968–73.

20. Waggoner W, Boots LR, Azziz R. Total testosterone and DHEAS levels as predictors of androgen-secreting neoplasms: a populational study. *Gynecol Endocrinol*. 1999;13(6):394–400.
21. Outwater EK, Marchetto B, Wagner BJ. Virilizing tumors of the ovary: imaging features. *Ultrasound Obstet Gynecol*. 2000;15(5):365–71.
22. Dickerson RD, Putman MJ, Black ME, Pinto KR, Diamond NG, Marynick S, et al. Selective ovarian vein sampling to localize a Leydig cell tumor. *Fertil Steril*. 2005;84(1):218.
23. Brown J, Sood AK, Deavers MT, Milojevic L, Gershenson DM. Patterns of metastasis in sex cord-stromal tumors of the ovary: can routine staging lymphadenectomy be omitted? *Gynecol Oncol*. 2009;113(1):86–90.
24. Thrall MM, Paley P, Pizer E, Garcia R, Goff BA. Patterns of spread and recurrence of sex cord-stromal tumors of the ovary. *Gynecol Oncol*. 2011;122(2):242–5.
25. Newell-Price J, Bertagna X, Grossman AB, Nieman LK. Cushing's syndrome. *Lancet*. 2006;367(9522):1605–17.
26. Findling JW, Raff H. Cushing's syndrome: important issues in diagnosis and management. *J Clin Endocrinol Metab*. 2006;91(10):3746–53.
27. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2008;93(5):1526–40.
28. Boscaro M, Arnaldi G. Approach to the patient with possible Cushing's syndrome. *J Clin Endocrinol Metab*. 2009;94(9):3121–31.
29. Kathiresan AS, Carr BR, Attia GR. Virilization from partner's use of topical androgen in a reproductive-aged woman. *Am J Obstet Gynecol*. 2011;205(3):e3–4.
30. Merhi ZO, Santoro N. Postmenopausal virilization after spousal use of topical androgens. *Fertil Steril*. 2007;87(4):976 e13–5.
31. Carmina E, Rosato F, Janni A, Rizzo M, Longo RA. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. *J Clin Endocrinol Metab*. 2006;91(1):2–6.
32. Kakuno Y, Amino N, Kanoh M, Kawai M, Fujiwara M, Kimura M, et al. Menstrual disturbances in various thyroid diseases. *Endocr J*. 2010;57(12):1017–22.
33. Gaitonde DY, Rowley KD, Sweeney LB. Hypothyroidism: an update. *Am Fam Physician*. 2012;86(3):244–51.
34. Aoki Y, Belin RM, Clickner R, Jeffries R, Phillips L, Mahaffey KR. Serum TSH and total T4 in the United States population and their association with participant characteristics: National Health and Nutrition Examination Survey (NHANES 1999–2002). *Thyroid*. 2007;17(12):1211–23.
35. Asvold BO, Vatten LJ, Midthjell K, Bjoro T. Serum TSH within the reference range as a predictor of future hypothyroidism and hyperthyroidism: 11-year follow-up of the HUNT Study in Norway. *J Clin Endocrinol Metab*. 2012;97(1):93–9.
36. Vissenberg R, van den Boogaard E, van Wely M, van der Post JA, Fliers E, Bisschop PH, et al. Treatment of thyroid disorders before conception and in early pregnancy: a systematic review. *Hum Reprod Update*. 2012;18(4):360–73.
37. Crosignani PG. Current treatment issues in female hyperprolactinaemia. *Eur J Obstet Gynecol Reprod Biol*. 2006;125(2):152–64.
38. Melmed S, Casanueva FF, Hoffman AR, Kleinberg DL, Montori VM, Schlechte JA, et al. Diagnosis and treatment of hyperprolactinemia: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(2):273–88.
39. Prabhakar VK, Davis JR. Hyperprolactinaemia. *Best Pract Res Clin Obstet Gynaecol*. 2008;22(2):341–53.
40. Casanueva FF, Molitch ME, Schlechte JA, Abs R, Bonert V, Bronstein MD, et al. Guidelines of the Pituitary Society for the diagnosis and management of prolactinomas. *Clin Endocrinol*. 2006;65(2):265–73.
41. Hammond KR, Steinkampf MP, Boots LR, Blackwell RE. The effect of routine breast examination on serum prolactin levels. *Fertil Steril*. 1996;65(4):869–70.



42. Deligeorgiou E, Athanasopoulos N, Tsimaris P, Dimopoulos KD, Vrachnis N, Creatsas G. Evaluation and management of adolescent amenorrhea. *Ann N Y Acad Sci.* 2010; 1205:23–32.
43. Bhagavath B, Podolsky RH, Ozata M, Bolu E, Bick DP, Kulharya A, et al. Clinical and molecular characterization of a large sample of patients with hypogonadotropic hypogonadism. *Fertil Steril.* 2006;85(3):706–13.
44. Miller KK, Meenaghan E, Lawson EA, Misra M, Gleysteen S, Schoenfeld D, et al. Effects of risedronate and low-dose transdermal testosterone on bone mineral density in women with anorexia nervosa: a randomized, placebo-controlled study. *J Clin Endocrinol Metab.* 2011;96(7):2081–8.
45. Chou SH, Chamberland JP, Liu X, Matarese G, Gao C, Stefanakis R, et al. Leptin is an effective treatment for hypothalamic amenorrhea. *Proc Natl Acad Sci U S A.* 2011;108(16): 6585–90.
46. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, et al. Androgen excess in women: experience with over 1000 consecutive patients. *J Clin Endocrinol Metab.* 2004;89(2):453–62.
47. Rager KM, Omar HA. Androgen excess disorders in women: the severe insulin-resistant hyperandrogenic syndrome, HAIR-AN. *Sci World J.* 2006;6:116–21.
48. Amoah C, Yassin A, Cockayne E, Bird A. Hyperreactio luteinalis in pregnancy. *Fertil Steril.* 2011;95(7):2429 e1–3.
49. Escobar-Morreale HF. Macroprolactinemia in women presenting with hyperandrogenic symptoms: implications for the management of polycystic ovary syndrome. *Fertil Steril.* 2004;82(6): 1697–9.
50. Janssen OE, Mehlmauer N, Hahn S, Offner AH, Gartner R. High prevalence of autoimmune thyroiditis in patients with polycystic ovary syndrome. *Eur J Endocrinol.* 2004;150(3):363–9.
51. Ganie MA, Marwaha RK, Aggarwal R, Singh S. High prevalence of polycystic ovary syndrome characteristics in girls with euthyroid chronic lymphocytic thyroiditis: a case-control study. *Eur J Endocrinol.* 2010;162(6):1117–22.
52. Benetti-Pinto CL, Berini Piccolo VR, Garmes HM, Teatin Juliato CR. Subclinical hypothyroidism in young women with polycystic ovary syndrome: an analysis of clinical, hormonal, and metabolic parameters. *Fertil Steril.* 2013;99(2):588–92. doi:[10.1016/j.fertnstert.2012.10.006](https://doi.org/10.1016/j.fertnstert.2012.10.006).
53. Ganie MA, Laway BA, Wani TA, Zargar MA, Nisar S, Ahamed F, et al. Association of subclinical hypothyroidism and phenotype, insulin resistance, and lipid parameters in young women with polycystic ovary syndrome. *Fertil Steril.* 2011;95(6):2039–43.
54. Rotondi M, Cappelli C, Magri F, Botta R, Dionisio R, Iacobello C, et al. Thyroidal effect of metformin treatment in patients with polycystic ovary syndrome. *Clin Endocrinol.* 2011; 75(3):378–81.
55. Muderris II, Boztosun A, Oner G, Bayram F. Effect of thyroid hormone replacement therapy on ovarian volume and androgen hormones in patients with untreated primary hypothyroidism. *Ann Saudi Med.* 2011;31(2):145–51.
56. Robin G, Gallo C, Catteau-Jonard S, Lefebvre-Maunoury C, Pigny P, Duhamel A, et al. Polycystic ovary-like abnormalities (PCO-L) in women with functional hypothalamic amenorrhea. *J Clin Endocrinol Metab.* 2012;97(11):4236–43.
57. Wang JG, Lobo RA. The complex relationship between hypothalamic amenorrhea and polycystic ovary syndrome. *J Clin Endocrinol Metab.* 2008;93(4):1394–7.



Polycystic Ovary Syndrome

Current and Emerging Concepts

Pal, L. (Ed.)

2014, XVII, 340 p. 34 illus., 21 illus. in color., Hardcover

ISBN: 978-1-4614-8393-9