Polycystic Ovary Syndrome

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ISSN: 1536-3619
12345/09876  CU072
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Objectives

This monograph is designed to enable the obstetrician–gynecologist to do the following:

• Understand the pathophysiology and clinical approaches for the prevention and management of polycystic ovary syndrome and its sequelae
• Recognize the clinical manifestations of polycystic ovary syndrome and screen patients accordingly
• Counsel patients about the diagnosis and lifestyle factors that decrease the risk of long-term sequelae
• Evaluate patients and initiate management or referral
• Provide long-term follow-up of patients

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Credit for Clinical Updates in Women’s Health Care: Polycystic Ovary Syndrome, Volume XV, Number 4, July 2016, is initially available through December 2019. During that year, the unit will be re-evaluated. If the content remains current, credit is extended for an additional 3 years.

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Polycystic ovary syndrome (PCOS) affects 6–12% of reproductive-aged women, placing obstetrician–gynecologists at the front line of recognizing the syndrome and managing the reproductive, metabolic, and psychologic consequences of this disorder. Furthermore, obstetrician–gynecologists play a particularly important role in guiding patients through the lifestyle modifications that are known to have a profound effect on the consequences of PCOS from puberty to the postmenopausal period. Obstetrician–gynecologists need to be well versed in diagnostic testing modalities and treatments available for PCOS and equipped to counsel patients regarding future fertility, pregnancy-associated complications, and risks of endometrial neoplasia, insulin resistance, obesity, obstructive sleep apnea, and cardiovascular disease. The primary clinical features of PCOS, such as abnormal uterine bleeding, hyperandrogenism, and infertility, are at the core of obstetrics and gynecology. However, a multidisciplinary approach to the other features, including obesity, diabetes mellitus, dyslipidemia, and other cardiovascular risks, often is required.

The authors of this monograph are both subspecialists in reproductive endocrinology and infertility and participate in cutting-edge research in this field. In this revised monograph, they review the most up-to-date understanding of the genetics and pathophysiology of PCOS and subsequently provide a succinct, but inclusive, guide for the practicing obstetrician–gynecologist to diagnose and manage the entire array of reproductive and metabolic consequences of this clinical disorder. Their focus is not only on the effects of PCOS in reproductive-aged women but also in women in their post-reproductive years. The authors also include tips for counseling patients and resources available for patient and physician education. This monograph will be useful for any women’s health professional.

Russell R. Snyder, MD
Editor
ABSTRACT. Polycystic ovary syndrome (PCOS) affects 6–12% of reproductive-aged women (1, 2). The condition is now recognized to have its beginnings in the perinatal period and may be exacerbated by environmental and lifestyle influences in the peripubertal timeframe. The consequences of PCOS extend beyond menopause. The paradigm of PCOS is one of a life-long condition with multiple effects at key developmental periods, requiring assessment and management in the primary care setting. The definition of PCOS has evolved over time but essentially includes assessment of ovulatory function, androgen status, and ovarian morphology. The pathophysiology of PCOS is still not entirely understood, and clinical presentations based on the diagnostic criteria encompass a wide spectrum. Evidence of familial inheritance of the syndrome exists, but genetic studies thus far have not isolated a susceptibility gene to explain the disease in most individuals. Increasing evidence points to the role of epigenetic factors in the intrauterine environment and postnatal environmental influences that may change the trajectory of PCOS. A primary characteristic of PCOS is hyperandrogenism, which, in most cases, is linked to hyperinsulinemia. Resultant metabolic changes include an increased risk of diabetes. Polycystic ovary syndrome alters gonadotropin dynamics, which results in ovulatory dysfunction and, in many cases, infertility. Obesity is a common finding in patients with PCOS, and the prevalence of PCOS increases when obesity is present in high frequency in the population. Diagnosis remains primarily a clinical one with elimination of other causes of oligo-ovulation or hyperandrogenism. The primary features of PCOS, including androgen excess, menstrual irregularity, and infertility, are best treated based on a symptomatic approach. Oral contraceptives remain the mainstay of management of androgen excess and menstrual irregularities. The association between PCOS and metabolic disorders has been recognized, and patients with PCOS should undergo screening for diabetes mellitus and cardiovascular risk factors. Prevention of these complications will be reviewed in this monograph. Lifestyle modification remains a mainstay of treatment, with metformin therapy useful for glucose intolerance and metabolic dysfunction. The best opportunities for intervention present when the condition is first recognized in the adolescent patient because this may represent the best chance for long-term benefit. A multidisciplinary approach often is helpful to address the concerns regarding obesity and hyperandrogenism with attention to the increased risk of depression and anxiety seen in patients with the condition.

In 1935, Stein and Leventhal first linked polycystic ovaries with amenorrhea, infertility, and occasional obesity and hirsutism (3). In providing care for a subset of women with these clinical characteristics, they noted bilateral ovarian enlargement based on gynecography (a combination of hysterosalpingography and pelvic pneumography). The finding of ovarian enlargement with associated amenorrhea was “usual enough to warrant
biopsies of the ovaries.” Through gross and microscopic observations, they described polycystic ovaries as two to four times the normal size and containing 20–100 follicular cysts that varied in size from 1 mm to 1.5 mm and were confined to the ovarian cortex. By applying strict diagnostic criteria based on clinical characteristics and gynecography, they successfully treated 93 of 96 women with Stein–Leventhal syndrome by wedge resection in the 20-year span after the initial case series (4).

**Definition**

Although the diagnostic criteria for polycystic ovary syndrome (PCOS) have evolved since the initial description, they are still based on clinical characteristics and imaging (Box 1). In 1990, the National Institutes of Health (NIH) convened an expert conference to create a standard definition of PCOS. The 1990 NIH criteria define PCOS as the presence of clinical or biochemical evidence of hyperandrogenism and ovarian dysfunction.

**Box 1. Different Diagnostic Criteria for the Diagnosis of Polycystic Ovary Syndrome**

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<thead>
<tr>
<th>National Institutes of Health: National Institute of Child Health and Development (1990)*</th>
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<td>• Clinical signs or biochemical evidence of hyperandrogenism</td>
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<td>• Evidence of oligoovulation</td>
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<td>• Exclusion of other androgen excess disorders</td>
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<th>European Society for Human Reproduction and Embryology and American Society for Reproductive Medicine: Rotterdam consensus (2003)†</th>
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<th>Androgen Excess and PCOS Society (2006)‡</th>
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*At the 2012 NIH Evidence-Based Methodology Workshop on Polycystic Ovary Syndrome, it was recommended to use the Rotterdam criteria for diagnosis.


†At least two of the three criteria must be present.

‡Clinical or biochemical evidence of hyperandrogenism plus at least one of the three additional criteria.
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(oligoovulation or anovulation) after exclusion of other etiologies (eg, congenital adrenal hyperplasia, androgen-secreting tumors, and Cushing syndrome) (5).

In 2003, the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine cosponsored an expert conference in Rotterdam that expanded the diagnostic criteria to include ultrasound evidence of polycystic ovaries (6). According to the expert panel, a polycystic ovary consists of 12 or more small follicles measuring between 2 mm and 9 mm in diameter, has an increased volume (greater than 10 cm³), or both. The 2003 Rotterdam criteria define PCOS as the presence of two of the following three features: 1) clinical or biochemical evidence of hyperandrogenism, 2) ovarian dysfunction (oligoovulation or anovulation), and 2) polycystic ovaries on ultrasonography, after exclusion of other etiologies (6).

In 2006, the Androgen Excess and PCOS Society emphasized hyperandrogenism as a required feature. The society’s 2006 criteria define PCOS as the presence of clinical or biochemical evidence of hyperandrogenism associated with ovarian dysfunction, polycystic ovaries on ultrasonography, or both, after exclusion of other etiologies (7).

In 2012, the European Society for Human Reproduction and Embryology and the American Society for Reproductive Medicine acknowledged that several characteristics of adult PCOS are transient findings in normal adolescents and defined the Amsterdam 2012 adolescent PCOS criteria as the presence of all of the following criteria: clinical and biochemical hyperandrogenism, ovulatory dysfunction (oligomenorrhea or amenorrhea, persisting 2 years after menarche or primary amenorrhea at age 16 years), and abdominal ultrasound result, demonstrating ovarian enlargement (greater than 10 cm³) (8).

Given the confusion created by the different diagnostic criteria, the NIH sponsored the Evidence-Based Methodology Workshop on Polycystic Ovary Syndrome in 2012 (9). The conference outlined the strengths and weaknesses of the proposed diagnostic criteria. A strength of the diagnostic criteria is that the major components, androgen excess, and ovulatory dysfunction are common clinical concerns for patients. Furthermore, recognition of polycystic ovarian morphology may identify women who are hypersensitive to ovarian stimulation. Limitations of the diagnostic criteria include lack of objective identification of androgen excess, ovulatory dysfunction, and polycystic ovaries. Identification of biochemical evidence of androgen excess is challenging because standardized assays and normative data are lacking. Furthermore, serum androgen levels may not reflect tissue sensitivity. Ovulatory dysfunction may be difficult to measure objectively and may vary over a woman’s reproductive life. Identification of polycystic ovarian morphology is limited by the lack of normative data for ovarian morphology during the menstrual cycle and for various age groups. The expert panel recommends application of the 2003 Rotterdam criteria while specifying the phenotype (androgen excess plus ovulatory dysfunction, androgen excess plus polycystic ovarian morphology, ovulatory dysfunction plus polycystic ovarian morphology, and androgen excess plus ovulatory dysfunction plus polycystic ovarian morphology). Given that polycystic ovarian morphology is not necessary or
sufficient for the diagnosis, the expert panel recommended that the disorder be renamed to reflect the complex metabolic, hypothalamic, pituitary, ovarian, and adrenal interactions that characterize the syndrome and their reproductive implications. To date, the name remains polycystic ovary syndrome.

**Prevalence and Ethnic Variability**

The prevalence of PCOS varies based on the diagnostic criteria and the population studied. The prevalence of PCOS ranges from 4% to 8% when the 1990 NIH criteria are applied to various populations (2, 10). The prevalence increases to 6.3–20.9% with the 2003 Rotterdam criteria and to 6–15.3% with the 2006 Androgen Excess and PCOS Society criteria (11). The prevalence of PCOS among white and black women appeared to be similar (4.8% vs 8%), but it was higher among Mexican Americans (13%) in community-based assessments (1, 12). The prevalence of PCOS has been reported to range from 12% to 21% of Australian reproductive-aged women, with increased prevalence in overweight women or those of indigenous background (2). Generally, the prevalence of PCOS is increased when using the Rotterdam criteria.

There is evidence of ethnic variability in phenotypic associations. Black and Hispanic women with PCOS are more likely to be obese than white women. Black women are more likely to exhibit hypertension and cardiovascular (CV) disease, whereas Hispanic women are prone to insulin resistance and diabetes mellitus (12, 13). Asian women are less likely to be obese but are more likely to have diabetes mellitus than white women (13). Among these women, South Asian women with PCOS (eg, Indian, Bangladeshi, Sri Lankan, and Pakistani) have a higher risk of insulin resistance compared with East Asian women (eg, Chinese and Japanese) (8). East Asian women tend to exhibit mild hirsutism and lower testosterone levels than white and African American women (14). Women of Middle Eastern and Mediterranean origin with PCOS tend to exhibit severe hirsutism (8).

**Clinical Significance**

Hirsutism and menstrual irregularity are common problems of patients with PCOS. However, the severity of the phenotype varies widely on an individual basis and over a woman’s lifetime. Clear diagnostic criteria for PCOS aid in identifying an etiology for these common problems and also identify women who are at a long-term risk of associated morbidities, such as anovulatory infertility, pregnancy complications, endometrial cancer, metabolic dysfunction, and mood disorders. Furthermore, an accurate diagnosis may have implications for family members because first-degree relatives of women with PCOS have an increased risk of developing PCOS and metabolic dysfunction.
Genetics

Familial clustering of PCOS supports a genetic basis for the syndrome. The strong concordance of PCOS observed among monozygotic twins suggests that 70% of the pathogenesis can be attributed to genetic factors (15). Further evidence of a genetic basis can be drawn from studies of first-degree relatives of women with PCOS. The prevalence of PCOS among sisters and mothers of women with PCOS is 20–40% (16, 17). Sisters and mothers of women with PCOS also are more likely to exhibit dyslipidemia and metabolic syndrome (18). Although brothers and fathers of women with PCOS do not exhibit a specific phenotype, they have an increased risk of obesity and metabolic syndrome (19).

Candidate gene association studies have identified several PCOS susceptibility genes, although these findings have been difficult to replicate given inadequate sample sizes and the heterogeneity of phenotypes in the populations studied (20). A genome-wide association study of Han Chinese women with PCOS identified three PCOS risk loci: 1) thyroid-adenoma–associated protein-coding gene (THADA), 2) DENN/MADD domain containing 1A (DENND1A), and 3) luteinizing hormone/choriogonadotropin receptor (LHCGR). Two of the loci (THADA and DENND1A) have been associated with PCOS in European women (21, 22). Evaluation of single nucleotide polymorphisms in DENND1A and THADA in Han Chinese women with PCOS has suggested that THADA contributes to lipid metabolic disorders and hypersecretion of testosterone and luteinizing hormone (LH), whereas DENND1A may contribute to insulin resistance in PCOS (23). Small sample sizes have limited the power of these studies, and larger population studies are necessary to advance this field of promising research.

Pathophysiology

Although genetic factors predispose individuals to PCOS and metabolic syndrome, environmental factors likely alter expression of the syndrome. Animal models suggest that in utero exposure to testosterone excess can program a PCOS-like phenotype in adulthood with reproductive and metabolic abnormalities (24). In a case–control study, mean testosterone levels were higher in the cord blood of newborns of women with PCOS compared with newborns of women without the syndrome, but long-term follow-up is needed to determine if this finding correlates with the development of a PCOS phenotype (25).

Women with PCOS demonstrate altered gonadotropin secretion with increased LH levels and low to normal follicle-stimulating hormone (FSH) levels (Fig. 1). Factors, such as hyperandrogenemia, chronic estrogen secretion, and the lack of progesterone negative feedback, likely alter hypothalamic gonadotropin-releasing hormone (GnRH) pulse frequency in a manner that favors LH secretion over FSH secretion. Luteinizing hormone hypersecretion contributes to the follicular arrest and anovulation commonly observed in patients with PCOS.
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Insulin resistance is a common finding in both lean and obese women with PCOS. Visceral fat, which releases cytokines associated with insulin resistance, is increased in both lean and obese women with PCOS. Insulin production, release, action, and clearance may be altered in the pancreas, adipose tissue, and hepatic tissue of women with PCOS (Fig. 1). Insulin resistance and the compensatory hyperinsulinemia contribute to androgen excess through two pathways: 1) insulin inhibits hepatic sex-hormone–binding globulin (SHBG) production, resulting in increased serum-free androgen levels and 2) insulin also directly stimulates theca cell androgen synthesis. Local androgen excess in the follicle may lead to follicular arrest by inhibiting aromatase activity and acquisition of LH receptors on granulosa cells. Follicular atresia contributes to the increased volume characteristic of a polycystic ovary, although increased total number of active follicles also is noted.

Adrenal androgen levels are increased in approximately one half of women with PCOS for reasons that are unclear. The increased production of adrenal androgens further contributes to androgen excess (Fig. 1).

**Risk Factors**

Early recognition of individuals at risk of PCOS may lead to early diagnosis and management of the reproductive and metabolic consequences of the disease. Risk factors for PCOS include family history of first-degree relatives with PCOS and early signs of insulin resistance and deregulated steroidogenesis (Box 2). Infants with intrauterine growth restriction and low birth weight are at a risk of postnatal insulin resistance (26), although
most women with PCOS do not have a history of low birth weight. However, the low birth weight population also may have a risk of premature pubarche and possibly PCOS as a consequence of early insulin resistance. Premature pubarche is associated with a 15–20% risk of developing PCOS, particularly among girls who exhibit exaggerated production of adrenal androgens \( (27) \). Obese girls who exhibit conditions related to insulin resistance, such as acanthosis nigricans or metabolic syndrome, appear to be at an increased risk of developing a PCOS phenotype after puberty (Box 2) \( (28) \).

**Box 2. Possible Risk Factors for Polycystic Ovary Syndrome**

- Family history of a first-degree relative with polycystic ovary syndrome
- History of premature pubarche, particularly if associated with a history of low birth weight
- Peripubertal obesity, resulting in insulin resistance

**Clinical Manifestations**

Women with PCOS typically report irregular bleeding, infertility, or symptoms of androgen excess, such as hirsutism or severe acne. The history of irregular bleeding often is present from menarche. Infertility usually is associated with chronic anovulation. These clinical presentations often cause women to seek care from obstetrician–gynecologists.

**Oligoovulation**

Oligoovulation, associated with irregular menses and PCOS, often begins at the time of menarche, which occasionally may be delayed in some adolescents despite otherwise normal pubertal development. Menstrual bleeding often is unpredictable, with regular menses noted for several months followed by stretches of amenorrhea. Bleeding may be protracted, which is characteristic of uncontrolled endometrial breakthrough bleeding caused by a long period of unopposed estrogen stimulation to the endometrium. Even the presence of relatively regular withdrawal bleeding is not always associated with an ovulatory cycle. If the presence of ovulation in a woman with the diagnosis of PCOS is in question, a serum progesterone level can be measured in the second half of the cycle to assess ovulation. Generally, luteal phase concentrations of progesterone greater than 5 ng/mL are consistent with ovulation.

It is helpful to assess the bleeding pattern so that the best course of therapy can be chosen. For individuals with long-term persistent amenorrhea without evidence of progestin effect, an endometrial biopsy may be indicated to rule out the presence of endometrial hyperplasia, particularly in the setting of occasional irregular spotting before ovulation induction therapy is initiated.
Androgen Excess

The most reliable sign of androgen excess in women with PCOS is hirsutism, or the presence of hair distribution in a male pattern (face, neck, back, chest, lower abdomen, and upper thighs). Other symptoms that can be associated with androgen excess include acne and male-pattern hair loss or alopecia. Signs of virilization, such as deepening of the voice, severe balding, increased muscle mass, and clitoromegaly, typically are not seen in patients with PCOS. If these signs are present, additional causes of androgen excess should be evaluated. If they are severe or present in rapid progression, assessment for an androgen-secreting tumor should be considered.

Hirsutism and Alopecia

Hirsutism is the presence of darkened, coarse (terminal) hair in a male pattern of distribution. Testosterone is converted to dihydrotestosterone at the hair follicle by means of the enzyme 5-alpha reductase. Dihydrotestosterone can act directly on the hair follicle to convert it from a vellus hair (light and fine) to a terminal one in androgen-sensitive areas. This is a nonreversible process. Weaker androgens, such as dehydroepiandrosterone and androstenedione, also can affect the dermal papillae to result in terminal hair differentiation. The pattern of male hair distribution includes hair growth on the facial, sideburn, and chin areas. Hair follicles located on the chest, upper back, and lower abdomen and thighs also respond to androgenic stimulation.

Assessment of the degree of hirsutism is challenging and few normal population standards have been established. The most common rating scale, the modified Ferriman–Gallwey scoring system, was originally published in 1961 and since then has been modified. Hair is assessed in nine areas, including the upper lip, chin, chest, upper and lower abdomen, upper thighs, upper arms, and upper and lower back. Hair growth is assigned a score from 0 (absence of terminal hair) to 4 (excessive terminal hair) in each of the nine areas (29). Generally, it is accepted that a score greater than 7 indicates hirsutism. However, different ethnic groups demonstrate different propensities toward terminal hair growth and there is variability by age of presentation, making a single cutoff point unreliable. Furthermore, the amount of distress that a woman may experience from any degree of hirsutism is not entirely correlated with the Ferriman–Gallwey score. Nonetheless, it is helpful to document type and amount of hair growth present at initial assessment to be able to monitor response to treatment.

Hair loss caused by androgen excess typically is seen in the frontal and bitemporal areas but also can be generalized to the top of the scalp. This type of hair loss is called androgenic alopecia, and it tends to be gradual and persistent (30). Also, it is highly heritable. This can be a distressing and difficult symptom to treat, similar to men. Antiandrogen treatments often offer modest benefits.
ACNE

The presence of acne in an adolescent by itself is not a demonstration of abnormal androgen excess because it affects most adolescents and spontaneously resolves in most cases (31). However, the sebaceous glands of the face, chest, and back are highly influenced by androgens, and, in the setting of significant androgen excess, acne can be severe and concerning to the patient. The degree and severity of acne is associated with circulating androgen concentrations. In a normal adolescent population, severe acne is present in less than 5% of girls and is associated with increased androgen concentrations and the presence of hirsutism (32, 33). Therefore, the presence of severe acne can be considered a clinical marker for hyperandrogenism.

Assessment of acne is challenging for the same reasons hirsutism scoring is challenging. Ethnic predispositions to acne present with varying expression. Several acne scoring scales are available that have evolved over time (34, 35). The grading of severity of lesions is difficult; therefore, the most common tool used for accuracy is counting total lesions. The section “Resources” provides a link to acne scoring systems.

ACANTHOSIS NIGRICANS

Acanthosis nigricans is a cutaneous manifestation of hyperinsulinemia. Although it is not a direct result of hyperandrogenism, it is commonly seen in patients with androgen excess conditions with associated hyperinsulinemia, such as PCOS. A hyperplasia of the basal layer of the epidermis is seen in patients with conditions of increased insulin, leading to development of a raised velvety hyperpigmented area typically on the back of the neck or axilla (Fig. 2) but also under the breast or upper thighs.

Fig. 2. Acanthosis nigricans.
These cutaneous lesions do not respond directly to antiandrogen therapy but do improve with reductions in insulin resistance, typically achieved with lifestyle changes or use of insulin sensitizers. Otherwise, there are few medical treatments known to be successful in eradicating these lesions.

**Ovarian Morphology**

**Diagnostic Criteria**

The morphology of the polycystic ovary reflects a specific pattern on ultrasonography. Numerous small subcapsular cysts that reflect the antral follicles at various stages of development define the classic polycystic ovary. These are not ovarian cysts in the traditional sense and are not generally felt by the patient, nor do they represent pathology. However, the ultrasound finding represents one of the key diagnostic features of PCOS (Fig. 3).

The diagnostic criteria by ultrasonography have been defined at the time of the Rotterdam consensus (36). The criteria include enlarged ovaries (volume greater than 10 cm³), with 12 or more follicles ranging in size from 2 mm to 9 mm. Only one ovary needs to meet these criteria to establish the diagnosis of a polycystic ovary. Although these criteria are relatively easy to define, it is recognized that the ovary is dynamic in imaging studies and if there is a large dominant follicle or cyst noted in the ovary, it is not possible to conclusively identify the morphology of that ovary.

**Concerns Regarding Age Groups and Technology**

Diagnostic technology to ascertain an increased number of follicles is now available and continues to evolve, and it is possible that the diagnostic criteria also may evolve (37).
Furthermore, the ovary is a dynamic organ that changes over the reproductive lifespan; therefore, the findings are not static. Normative standards are lacking across the menstrual cycle. Currently, a significant overlap is evident between the description of normal adolescent ovaries and the definition of polycystic ovaries. The incomplete definition combined with the potential use of transabdominal ultrasonography for the diagnosis of PCOS renders the current diagnostic criteria for adolescent patients generally unhelpful. Additionally, postmenopausal women will not demonstrate the typical findings of the polycystic morphology given the postmenopausal status of the ovary. Therefore, diagnostic criteria in this age group cannot include the ultrasound findings.

Clinical Phenotypes

Rotterdam Criteria

The National Institutes of Health Evidence-Based Methodology Workshop on Polycystic Ovary held in December 2012 concluded that the Rotterdam criteria are the broadest and most inclusionary in the diagnosis of PCOS (9). The 2003 Rotterdam criteria include both the classic NIH criteria and the Androgen Excess and PCOS Society criteria and expand the range of possible phenotypes (Table 1).

Correlation Between Phenotypes and Disease Risk

The importance of specifying the phenotype in PCOS is exemplified by discovering a correlation between the phenotype and metabolic risk (11); specifically, there appears to be an association between the degree of androgenic disturbance and the metabolic risk. The individuals with oligo-ovulation and polycystic ovaries but without the evidence of androgen excess have the lowest risk of diabetes mellitus in several studies (38, 39). The conclusions of the NIH conference recommend that the specific phenotype be recorded for clinical care (9).

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<th>Table 1. Possible Phenotypes by Clinical Manifestations in Polycystic Ovary Syndrome</th>
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Insulin Resistance and Diabetes Mellitus

Pathophysiology

Although PCOS primarily is an endocrine disorder, there is also evidence of metabolic dysfunction. However, the exact pathophysiology of PCOS is unclear. Several lines of evidence suggest that the etiology of PCOS is multifactorial, including genetic, epigenetic, and environmental factors (40). Peripheral insulin resistance has been demonstrated in most women with PCOS when studied intensively (41). This appears to be independent of obesity, although insulin resistance is clearly exacerbated by obesity. Women with PCOS may demonstrate hyperinsulinemia, but measurement of insulin resistance or insulin levels is neither required nor advised for the diagnosis or management of PCOS.

Incidence of Diabetes Mellitus

Women with PCOS have increased rates of diabetes mellitus across several observational studies (42–44), and PCOS is a recognized independent risk factor for diabetes. However, the magnitude of this risk is unclear with some studies indicating a prevalence of impaired glucose tolerance or diabetes mellitus in 40% of obese women with PCOS (45). Factors, such as obesity, family history, and lifestyle factors, all influence the prevalence of diabetes in a PCOS population. Large prevalence studies that use defined criteria are unavailable in PCOS populations. However, a meta-analysis of 35 articles demonstrated an increased risk of type 2 diabetes mellitus in women with PCOS with an odds ratio of 4 (1.97–8.1) in studies of patients matched for body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) (46). Also, it is clear that measurement of fasting plasma glucose levels alone is inadequate as a screening test for diabetes mellitus in women with PCOS (47). However, evidence supports the use of a formal 2-hr 75-g oral glucose tolerance test (OGTT). National and international organizations recommend screening all women with PCOS with an OGTT (48, 49). Known risk factors for diabetes mellitus, such as advancing age, ethnicity with high prevalence of diabetes mellitus, family history, history of gestational diabetes, physical inactivity, and waist circumference, should be considered in counseling the patient with PCOS regarding her diabetes risk.

Conversion Rates

Early onset of diabetes mellitus relative to the general population and rapid progression to diabetes mellitus have been described in patients with PCOS. A study of 67 Australian women monitored for an average of 6.2 years demonstrated a high rate of conversion to diabetes mellitus in the patients in that time frame (50). In those who demonstrated impaired glucose tolerance at baseline, 54% had developed type 2 diabetes mellitus at the conclusion of the follow-up period. Furthermore, 8% of those with normoglycemia at the outset of the study had progressed to diabetes mellitus in the same timeframe. These women had a mean age of 39 years at the outset of the study. The presence of obesity influences both the likelihood of finding a glucose abnormality at initial assessment and the possibility of progression of disease.
The significantly increased risk of diabetes mellitus in patients with PCOS clearly represents a major health burden of this disease. Therefore, establishing the diagnosis and assessment of glucose tolerance are an important part of the care of women with PCOS. For the best diagnostic potential, an OGTT is recommended as well as consideration of additional risk factors in deciding how frequently to screen women with PCOS. The recommendation of the Australian national guidelines is to screen women at high risk every 2 years based on the observed conversion rates (49).

**Cardiovascular Disease**

**Epidemiologic Data**

Cardiovascular disease is the number one cause of mortality in U.S. women (51). There are known identifiable CV risk factors that are likely modifiable through lifestyle change. Given the prevalence of PCOS in the population, identification of whether PCOS increases the possibility of CV disease has important public health implications. It is uncertain if PCOS is an independent risk factor for the development of CV disease although multiple lines of evidence suggest an increase in CV disease risk factors in young women with PCOS, including increased prevalence of metabolic syndrome, type 2 diabetes mellitus, dyslipidemia, hypertension, and increased waist circumference (8).

Up to 70% of women with PCOS have evidence of dyslipidemia, predominantly low high-density lipoprotein cholesterol levels and increased triglyceride concentrations (52, 53). This pattern is known to be associated with insulin resistance and found commonly in patients with type 2 diabetes. Other studies have shown increased levels of low-density lipoprotein cholesterol although not typically in high ranges. It is likely the lipid abnormalities seen in patients with PCOS are influenced by the presence of obesity and genetic and lifestyle factors.

The diagnosis of metabolic syndrome requires any three of the following five factors (54): 1) increased blood pressure (BP) (130 mm Hg or higher, systolic, and 85 mm Hg or higher, diastolic); 2) increased waist circumference (greater than 88 cm in women); 3) increased fasting plasma glucose level 100 mg/dL or greater); 4) decreased high-density lipoprotein cholesterol level (less than 50 mg/dL in women); and 5) increased triglyceride level (150 mg/dL or greater). The prevalence of metabolic syndrome is significantly increased by obesity, but after controlling for obesity, a somewhat increased prevalence of the condition remains in patients with PCOS. The presence of metabolic syndrome has been shown to increase the risk of CV disease in other populations (55, 56).

Markers of atherosclerosis appear to be increased in women with PCOS, including increased carotid intima media thickness and increased prevalence of coronary artery calcification. These findings appeared to be independent of age or BMI (57, 58). However, the studies to date are limited to small populations, and it is unclear if this finding is consistent in all populations of women with PCOS.
**Outcome Data**

Although most studies of CV disease markers show increased prevalence in women with PCOS, conflicting evidence exists for actual CV disease morbidity or mortality in patients with PCOS (53). Several initial epidemiologic studies did not show any increased risk of either fatal or nonfatal CV events, although they did suggest an increase in stroke risk. However, a more recent finding from the Women’s Ischemia Evaluation Study showed that women with PCOS had a larger number of CV events than women without PCOS (59). In this study, CV disease was observed in 32% of women with PCOS compared with 25% of women without PCOS (odds ratio, 1.7), which correlated with several factors, including increased serum androgen levels. Furthermore, the event-free survival (including fatal and nonfatal events) was significantly lower in women who had PCOS compared with women who did not have PCOS. The difference between the two groups was increased when cerebrovascular accidents were considered. Overall, this is the strongest evidence to date of an effect of PCOS on CV disease.

**Further Assessment**

The data on CV disease in patients with PCOS are challenged by the lack of large-scale prospective trials that would monitor women with PCOS through menopause to assess for CV disease development. Many of the studies are challenged by poorly defined PCOS and use of retrospective diagnosis based on reported cycles or history. There is evidence that different phenotypes exhibit various degrees of risk factor abnormality, including risk of type 2 diabetes mellitus, which is the strongest risk factor for CV disease. Therefore, the risk by phenotype for CV disease also is likely variable. Given the enormous public health considerations, additional well-designed trials in patients with PCOS are needed to assess the true risk of CV disease and the most appropriate way to identify those at the highest risk of developing CV disease.

**Screening, Evaluation, and Diagnosis**

Although PCOS is associated with a variety of symptoms, the diagnosis is straightforward when using the Rotterdam criteria. The diagnostic assessment includes obtaining a medical history, performing a physical examination, and ordering laboratory studies. The diagnostic algorithm is presented in Figure 4.

**History and Physical Examination**

Obtaining of focused medical history and performing a physical examination will identify most PCOS phenotypes as defined by the 2003 Rotterdam criteria. Key components of the medical history include the menstrual history, the onset and duration of signs of androgen excess, and family history of PCOS, metabolic dysfunction, or both. Menstrual cycles often vary over the reproductive lifespan of women with PCOS. Often, they are irregular or absent in adolescents and young women with PCOS and become regular as
women with PCOS approach menopause. Menstrual cycle intervals greater than 45 days are consistent with oligoovulation or anovulation. The absence of premenstrual molimina symptoms (eg, bloating, breast tenderness, and mood change) may aid in identifying women with normal cycle intervals who are anovulatory. Signs of androgen excess include hirsutism, acne, or androgenic alopecia (8). Hirsutism is a reliable marker of androgen excess, although it may vary by ethnicity and may be difficult to quantify objectively. Inquiring about hair removal practices may aid in gauging the extent of hirsutism. Isolated acne and androgenic alopecia are less reliable markers of hyperandrogenemia. Inquiring about treatment of adult acne may be helpful in identifying androgen excess because acne becomes less prevalent with age. Androgenic alopecia, or hair loss confined to the crown, is an uncommon presentation of androgen excess in women with PCOS. Rapid onset of androgen excess, signs consistent with virilization (eg, androgenic
alopecia, deepening voice, or clitoromegaly), or both should prompt consideration of androgen-secreting tumors.

The physical examination should aid in confirming the diagnosis of PCOS, excluding other disorders, and identifying metabolic dysfunction. Physical examination of the skin and hair (eg, upper lip, chin, chest, lower abdomen, and inner thighs) may provide clinical evidence of androgen excess, which aids in the diagnosis of PCOS and can serve as a baseline assessment to track the response to treatment. The presence of Cushing syndrome signs (eg, moon facies, buffalo hump, abdominal striae, centripetal fat distribution, easy bruising, and proximal muscle weakness) should prompt screening for this rare syndrome (60). Pelvic examination should include assessment for clitoromegaly if virilization is suspected. Bimanual examination may suggest other disorders that contribute to abnormal uterine bleeding, such as uterine leiomyomas or adenomyosis. Criteria associated with metabolic syndrome include increased BP (130 mm Hg or higher, systolic; 85 mm Hg or higher, diastolic) and increased waist circumference (greater than 88 cm) (54). The presence of acanthosis nigricans (ie, velvety, hyperpigmented skin at the base of the neck, on axillae, or under the breasts) should be noted as a marker for insulin resistance (Fig. 2).

Laboratory Studies

Similar to the physical examination, laboratory studies should aid in confirming the diagnosis of PCOS, excluding other disorders and identifying metabolic dysfunction. The Rotterdam phenotype of androgen excess plus ovulatory dysfunction can be identified based on a history of oligomenorrhea or amenorrhea and a physical examination revealing clinical evidence of androgen excess. If clinical evidence of androgen excess is absent, biochemical evidence of androgen excess may be evaluated through free and total testosterone levels. Free testosterone reflects bioactive testosterone that is unbound to SHBG. A free testosterone level can be calculated based on total testosterone levels, ideally obtained by liquid chromatography or mass spectrometry, and SHBG, obtained by an immune-based or competitive binding assay (60). Interpretation of increased free and total testosterone levels should be based on local laboratory ranges given the lack of a standardized testosterone assay. Limitations of diagnosing androgen excess based on increased serum testosterone levels include the lack of well-defined normative data, poor assay reliability at lower ranges, variation of levels with time of the day and age, and inability to assess tissue sensitivity (9).

Identification of Rotterdam phenotypes that include polycystic ovarian morphology (androgen excess plus polycystic ovarian morphology, ovulatory dysfunction plus polycystic ovarian morphology, and androgen excess plus ovulatory dysfunction plus polycystic ovarian morphology) requires transvaginal ultrasound assessment in women. Polycystic ovarian morphology is defined as at least one ovary with 12 or more small follicles (measuring between 2 mm and 9 mm in diameter), an increased ovarian volume
Clinical Updates: Polycystic Ovary Syndrome

(greater than 10 cm³), or both. Diagnosis of polycystic ovarian morphology is limited by a lack of normative standards during the menstrual cycle. If a follicle with the size greater than 10 mm in diameter is noted, the ultrasound evaluation should be repeated in the early follicular phase to calculate the ovarian volume accurately (60). As mentioned previously, normative standards based on age are lacking despite knowledge that ovarian morphology varies across the reproductive lifespan. In adolescents, transvaginal ultrasonography may be inappropriate and transabdominal ultrasonography may be preferred. Diagnosis of polycystic ovarian morphology in the adolescent is established when ovarian volume is greater than 10 cm³ on transabdominal ultrasonography. Assessment of follicular distribution is not used to diagnosis polycystic ovary morphology in the adolescent because resolution may be limited by transabdominal ultrasonography, and multifollicular ovaries are common in adolescents without PCOS.

Laboratory testing to exclude other disorders should be individualized. Women with ovulatory dysfunction should be screened for thyroid dysfunction and hyperprolactinemia with thyroid-stimulating hormone (TSH) and fasting prolactin levels. Mild increases in prolactin levels may be observed in women with PCOS, but significant increases should prompt evaluation for a prolactinoma with magnetic resonance imaging of the pituitary gland. Nonclassical or late-onset congenital adrenal hyperplasia (CAH) also may present as the androgen excess plus ovulatory dysfunction phenotype. Certain ethnic groups (eg, Ashkenazi Jews, Hispanics, Yugoslavs, Native American Inuits, and Italians) exhibit an increased prevalence of 21 hydroxylase deficiency (61). Women with the androgen excess plus ovulatory dysfunction phenotype who are at high risk of nonclassical CAH based on their ethnicity can be screened with a fasting 17α-hydroxyprogesterone level measurement (specimen should be obtained in the morning during the follicular phase). The fasting 17α-hydroxyprogesterone levels less than 2 ng/mL exclude nonclassical CAH, and increased values should be followed with an adrenocorticotropic hormone stimulation test (62). Women with androgen excess that has a rapid onset or is consistent with virilization should be screened for the presence of androgen secreting tumors with testosterone and dehydroepiandrosterone sulfate measurements. Significant increases in total testosterone levels should prompt evaluation for an ovarian tumor with transvaginal ultrasonography. Significant increases in dehydroepiandrosterone sulfate levels should prompt evaluation for an adrenal tumor with adrenal computed tomography imaging, although both tumors are exceedingly rare. Women with the androgen excess plus ovulatory dysfunction phenotype and signs of Cushing syndrome should be screened with either multiple late night salivary cortisol level test, a 24-hour urinary free cortisol excretion test, or a low-dose dexamethasone suppression tests (63).

Laboratory testing also can identify metabolic dysfunction in women with PCOS. Insulin resistance is increasingly prevalent among women with the androgen excess plus ovulatory dysfunction phenotype, Hispanic and South Asian women, obese women, women with an increased waist circumference, women with acanthosis nigricans, and women with a family history of diabetes mellitus (8). A 2-hour 75-g OGTT will identify
women with impaired glucose tolerance (fasting glucose level of 110–125 mg/dL, 2-hour glucose level of 140–199 mg/dL, or both) and diabetes mellitus (fasting glucose level greater than 126 mg/dL, 2-hour glucose level greater than 200 mg/dL, or both). Random glucose levels and hemoglobin A1c levels can be used to diagnose diabetes mellitus, but they will not detect impaired glucose tolerance. Insulin levels are not diagnostic of impaired glucose tolerance or diabetes mellitus. Dyslipidemia is increasingly prevalent among women with androgen excess, obesity, or both. Fasting lipid and lipoprotein levels will identify women with dyslipidemia (high-density lipoprotein cholesterol level less than 50 mg/dL or triglyceride level 150 mg/dL or greater). Metabolic syndrome can be diagnosed as per the discussion of epidemiologic data in the section “Cardiovascular Disease.”

CASE NO. 1. An 18-year-old college student is seen by her obstetrician–gynecologist for irregular periods and progressive hair growth on her upper lip, chin, and inner thighs. She reports irregular periods since menarche at age 13 years and estimates that she has three to four periods per year. She previously shaved her facial hair once or twice a week but now shaves her facial and body hair daily or every other day. Also, she is concerned about gaining 15 lb since starting college. Her BP is 110 mm Hg, systolic, and 70 mm Hg, diastolic; waist circumference is 30 in (76.2 cm); and BMI is 31 (calculated as weight in kilograms divided by height in meters squared). Physical examination reveals hirsutism of the upper lip, chin, lower abdomen, and inner thighs.

Given the persistence of oligomenorrhea for longer than 2 years after menarche and evidence of progressive hirsutism, this patient is likely presenting with PCOS. Additional evidence of PCOS in the adolescent would include biochemical evidence of androgen excess (increased free testosterone levels, total testosterone levels, or both) and an ultrasound result revealing an increased ovarian volume (greater than 10 cm³). Other disorders, such as thyroid dysfunction and hyperprolactinemia, should be excluded with a normal TSH level and fasting prolactin level. If the patient is at risk of nonclassical CAH based on her ethnicity, a fasting level of 17α-hydroxyprogesterone should be obtained in the morning during the follicular phase. Evaluation for metabolic dysfunction could include a 2-hr 75-g OGTT and a fasting lipid and lipoprotein panel.

Counseling: Establishing a Dialogue

Describing the Disorder

Given the reproductive, endocrinologic, and metabolic risks of PCOS, establishing a dialogue with the patient is an opportunity to begin a lifelong conversation about the proper steps to maintain reproductive and metabolic health. Patients seek care from obstetrician–gynecologists at different stages of life, and each visit presents unique challenges for the clinician to strike the proper tone and emphasis (Box 3).
The adolescent is likely to present for care at a time of self-identity development, which can represent a volatile stage in development. She may present with menstrual cycle concerns, unwanted hair growth or body weight and body image concerns that may significantly affect her self-concept. Emphasizing the management of the adolescent’s current physical state while setting the stage and awareness for the proper management of the long-term issues without compromising her self-concept is challenging for clinicians.

Reproductive-aged women are the most common group seen by obstetrician–gynecologists and often express conflicting desires to become pregnant and to manage the androgenic and menstrual symptoms of PCOS. Infertility is common in PCOS because of ovulatory dysfunction, and weight gain negatively affects the chances for success. The risks of diabetes mellitus, gestational diabetes, and preeclampsia also may present in this group of women but may be reduced by lifestyle management.

The perimenopausal and postmenopausal women with a history of PCOS may need additional discussion regarding the long-term risks and particular assessment for CV disease risks. Menstrual cycles may normalize before menopause, but androgenic symptoms can worsen during this time. Conditions, such as sleep apnea, may cause increasing fatigue and metabolic dysfunction in this group of women.

**Counseling for Risks**

**Infertility**

Infertility affects a significant portion of women with PCOS primarily through ovulatory dysfunction. Other causes of infertility in reproductive-aged women, such as tubal disease or male factor, appear to occur with equal frequency in women with PCOS and those without PCOS and need to be considered in women presenting with delayed fertility. However, it is important to emphasize in counseling that not all women with PCOS require treatment for infertility. However, if a woman desires pregnancy and is having infrequent menses, prompt medical assessment is advised.
**CARDIOVASCULAR DISEASE**

It is unclear whether the incidence of CV morbidity or mortality is increased in women with PCOS. However, risk factors for CV disease may present earlier in life in women with PCOS compared with women without PCOS; therefore, the affected population may require more frequent assessment. Taking into account the family history and lifestyle factors, such as tobacco use and increased weight, is very important.

**DIABETES MELLITUS**

The strongest association of metabolic disease with PCOS is through diabetes mellitus (the detailed discussion of this association is provided in the section “Insulin Resistance and Diabetes Mellitus”). Glucose intolerance can present even in adolescence; therefore, the discussion should be initiated early in the life span with an emphasis on preventive measures, including lifestyle change. Evidence of rapid progression of glucose intolerance in patients with PCOS exists (64), and the need for monitoring with an OGTT should be reviewed.

**OBSTRUCTIVE SLEEP APNEA**

It has been shown that insulin resistance is associated with an increased risk of obstructive sleep apnea that may be independent of degree of obesity (65). If snoring or daytime sleepiness is identified, careful assessment with a sleep study may be indicated. The presence of untreated sleep apnea may lead to an increased CV risk independently.

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**Management**

The treatment plan for a patient with PCOS will vary with the clinical presentation and desire of the patient. Often, it is best to consider each treatment goal individually to address the specific concern. Therapy should be focused on both the short-term features and long-term features. Figure 5 is an overview algorithm for treatment by specific problem. Some overlap in management recommendations has been noted. However, similar features may require different approaches based on the outcomes desired. For instance, a desire to normalize menstrual cycles may require different treatment than ovulation requirements for fertility purposes.

**Lifestyle Management**

Obesity or excess weight is a common finding in women with PCOS. Also, it is a major cause of disease in the United States. The most recent National Health and Nutrition Examination Survey data suggest that more than 60% of women in the United States are either overweight or obese, with an additional 8% who are extremely obese (BMI 40 or greater) (66). Evidence exists that women with PCOS may have higher rates of obesity
than those without PCOS, although this may be related to specific populations and vary geographically (67).

Obesity has a significant effect on the physical and metabolic features of PCOS. Evidence suggests increased rates of menstrual dysfunction and severity of androgenic symptoms with obesity (68). Obesity appears to increase the sex steroid abnormalities in patients with PCOS. Hyperandrogenism is strongly associated with insulin resistance as are decreased SHBG concentrations. Increased severity of menstrual dysfunction also has been noted in patients with PCOS complicated by obesity (68).

A large number of small, uncontrolled trials of weight reduction suggest success in lifestyle modification in reduction in androgen levels, insulin resistance, fertility, ovulation, and CV risk factors. For example, a modest weight reduction in the range of 5–10% of initial body weight has been shown to improve insulin resistance in patients with PCOS and this may be associated with improvement in the reproductive features (69). Large-scale controlled trials of lifestyle change in patients with PCOS specifically designed to examine improvement in the metabolic endocrine symptoms of these patients are lacking. However, results of randomized controlled trials in the general population do support reduction in metabolic risk with lifestyle change (70, 71). Prevention of additional weight gain is important across the life span, although the best strategy for accomplishing this is not clear.

It seems reasonable to target weight loss interventions to women with a BMI greater than 25. The prevention of weight gain also is important in those with a normal BMI but
likely would not involve intensive lifestyle advice. A treatment algorithm for lifestyle management is provided in Figure 6.

The best approach to weight reduction in a patient with PCOS is not clear because most diets show substantial regain of weight over extended time (72). No randomized trials to date have demonstrated the advantage of one type of diet over another in the management of weight reduction in patients with PCOS. The most recommended weight reduction strategy is an integrated behavioral program that includes both exercise and modest caloric restriction, although long-term comparative controlled trials on successful weight reduction in patients with PCOS are lacking. However, short-term trials demonstrate improved adherence to therapy with behavioral support. Long-term, large-scale trials of weight loss effect in patients with PCOS, which are not currently available, may ultimately not show significant improvement of symptoms; however, the short-term data are encouraging. Weight reduction plans may not work for every patient nor is every patient at a behavioral stage where she is able to make successful changes to lifestyle; therefore, sensitive counseling, encouragement, and emotional support are as important as clinical advice.

**Fig. 6.** Lifestyle management algorithm. 

*Body mass index is calculated as weight in kilograms divided by height in meters squared.*
CASE NO. 2. A 25-year-old woman sees her obstetrician–gynecologist for increasingly irregular menses, hirsutism, and acne. She is obese with a BMI of 35 (calculated as weight in kilograms divided by height in meters squared) and has a waist circumference of 46 in (116.8 cm). She states she has had irregular menses since adolescence and has intermittently used oral contraceptives (OCs) for treatment, but she has not used them in the past 2 years. Her weight has been steadily increasing and she feels her facial hair is getting worse. She does not regularly engage in exercise. She is sexually active but is not interested in getting pregnant currently, although she expressed the desire to conceive in 2 years.

This patient likely has substantial risk of metabolic disease given her central obesity and worsening clinical presentation. Obesity has been demonstrated to have a significant effect on insulin resistance. This is primarily manifested as an increased risk of glucose intolerance. In studies of obese women with PCOS compared with lean women with PCOS, rates of glucose intolerance were threefold higher in obese women. Diabetes rates were 7-fold to 10-fold higher (73).

Given the increasing obesity in this patient, lifestyle modification should be discussed as primary therapy. It is likely that her increasing menstrual irregularity also is related to obesity. She should have an oral glucose screening, and if she has impaired glucose tolerance, she would be a candidate for metformin therapy. In several studies, metformin therapy has been associated with modest weight reduction in patients without PCOS (74). However, metformin would not be expected to yield significant improvement in this patient when used alone, without lifestyle management. In this patient, PCOS management should focus on support and education, with an emphasis on healthy lifestyle and targeted medical therapy.

This patient also has expressed desire for a future pregnancy. The success of ovulation induction for pregnancy is markedly reduced in obese patients with PCOS. Therefore, attempting and maintaining a modest weight reduction before pregnancy should be expected to improve her success with therapy. Detailed discussion of ovulation induction is provided in the section “Infertility.”

Management of Irregular Bleeding

Erratic, heavy, or absent menses are frequent problems in women with PCOS. Initially, this symptom can be one of the most distressing. For many women, the use of a combined OC can be highly effective in managing this erratic bleeding (Fig. 7). Several clear advantages of this approach include regular withdrawal bleeding, reduction in the risk of endometrial hyperplasia, reduction in testosterone levels with increased SHBG levels, and associated improved hirsutism and acne (8). No specific OC is felt to be of superior benefit. Use of cyclic progestin therapy can achieve regulation of menses, but it does not result in a similar reduction in androgen levels or provide contraceptive benefits. However, no randomized trials of progestin treatment exist that can identify the most effective treatment regimen (75).

Oral contraceptives can be used safely even in adolescence, but contraindications should be carefully reviewed. In patients with contraindications to the use of combined OCs, an alternative for endometrial suppression includes the progestin intrauterine device. Although no large-scale trials exist on the use of the progestin intrauterine devices in
patients with PCOS, there is evidence of improved menstrual response and improved cost effectiveness over either combination oral contraceptives or progestins in patients with dysfunctional uterine bleeding (76).

Metformin also has been studied in the resumption of menstrual cycles and there is evidence of improved cycle regularity. However, in a head-to-head comparison, OCs demonstrated improved cycle control over metformin and better androgenic control. Metformin also had little benefit on hirsutism scores (77).

Management of Hirsutism and Acne

Hirsutism and acne are the most common clinical expressions of hyperandrogenism. The symptoms can be quite disturbing and associated with decreased quality of life. Direct blockade of androgen production or action is required to manage these symptoms effectively and can be accomplished with the use of combined OCs or antiandrogenic agents (8). Oral contraceptives suppress LH production from the pituitary gland, which reduces testosterone production from the ovary. Oral contraceptives also significantly increase SHBG production by the liver, which reduces the overall availability of free testosterone. There are no large-scale head-to-head comparisons of different formulations of OCs to either suppress androgen production or action or to manage hirsutism. Therefore, the obstetrician–gynecologist should consider adverse effects and tolerance to find an appropriate agent for each patient. Oral contraceptives also have been shown to decrease the severity of acne (78).

Antiandrogen therapy can be used alone or in combination with an OC to increase effectiveness of androgen suppression (79, 80). The most common antiandrogen used
in the United States is spironolactone (81). Spironolactone is an aldosterone antagonist that has shown benefit in the management of hirsutism, although as an off-label indication. Spironolactone competes with circulating androgen for the androgen receptor and reduces androgen synthesis. Effective doses are between 100 mg/d and 200 mg/d in divided doses. Adverse effects generally are mild and include polyuria, fatigue, and headache. Irregular bleeding also can be seen because of direct endometrial effects. Therefore, spironolactone can be used in combination with an OC, which will potentiate the androgen suppression and control the endometrial effects.

Other antiandrogen agents include flutamide and finasteride. Neither agent has been approved by the U.S. Food and Drug Administration (FDA) for the treatment for hirsutism. In rare cases, flutamide has been associated with hepatotoxicity and, although it appears to provide similar androgen suppression to spironolactone, it is generally not used for this indication because of the serious nature of the potential hepatotoxic risk. Finasteride is a 5α-reductase inhibitor with evidence for suppression of hirsutism. It is not commonly used for hirsutism in the United States and has no better suppression than spironolactone. All antiandrogen therapy is potentially teratogenic and should be used with effective contraception. In counseling the patient, it should be noted that the length of the hair cycle for facial hair effects the time required to see a change in hirsutism. Typically this is at least 6 months. It is important to set the appropriate expectation for treatment duration.

Generally, no medical treatment will reverse the growth of a terminal hair follicle. Therefore, most patients with hirsutism will require mechanical removal of terminal hair. Temporary techniques, such as waxing, plucking, shaving, bleaching, and the use of depilatories, are popular but require active use on a regular basis. Skin irritation, ingrown hairs, and folliculitis can result. Permanent destruction of the follicle with use of electrolysis or laser therapy has been shown to be more effective than the temporary techniques in long-term studies (82). Generally, laser therapy is more successful in individuals with fair skin and dark hair than in individuals with other skin and hair types, but new technologies offer successful hair removal for multiple skin types (83).

One medical therapy has been approved by the FDA for the removal of unwanted facial hair. Eflornithine hydrochloride is an irreversible inhibitor of l-ornithine decarboxylase, an enzyme that controls cell growth and division in the hair follicle. Growth is significantly slowed and thickness is reduced, usually within 8 weeks (84). Metformin therapy has been studied in patients with hirsutism but is generally less effective than other antiandrogens and OCs (85). Although weight reduction in women with PCOS does appear to reduce androgens, few data suggest significant improvement in hirsutism.
Infertility

Ovulation Induction

Restoration of regular ovulation can be achieved in women with PCOS who lose 5–10% of their weight (86). A randomized controlled trial indicated that cumulative ovulation rates increased after weight loss (87). If weight reduction does not restore ovulation or cannot be achieved despite diet, exercise, and behavioral modification, ovulation induction can be considered. Oral agents used for ovulation induction include clomiphene citrate or letrozole (Fig. 8). Clomiphene citrate is a selective estrogen receptor modulator approved by the FDA for ovulation induction. Clomiphene citrate typically is administered for 5 days starting on the fifth day after a spontaneous or progestin-induced menses. Letrozole is an aromatase inhibitor that is not approved by the FDA for ovulation induction. Typically, it is administered for 5 days starting on the third day after spontaneous or progestin-induced menses. The National Institutes of Health/The Eunice Kennedy Shriver National Institute of Child Health and Human Development Reproductive Medicine Network conducted two multicenter randomized double-blinded clinical trials (PPCOS I and PPCOS II) to determine which oral ovulation induction agent is more effective.
likely to result in live birth in women with PCOS and anovulatory infertility (88, 89). The PPCOS I trial randomized women with PCOS to receive clomiphene citrate plus placebo, extended-release metformin plus placebo, or a combination of clomiphene citrate plus metformin for 6 months. The cumulative live-birth rate was similar in the clomiphene citrate plus placebo group (22.5%) and the clomiphene citrate plus metformin group (26.8%) and was significantly higher than in the metformin plus placebo group (7.2%). The rate of multiple pregnancy was 6% in the clomiphene citrate plus placebo group, 3.1% in the clomiphene citrate plus metformin group, and 0% in the metformin plus placebo group. Given the increased live-birth rate with clomiphene citrate compared with metformin, clomiphene citrate is preferred over metformin for ovulation induction (88).

The PPCOS II trial randomized women with PCOS and anovulatory infertility to receive letrozole or clomiphene citrate for up to 5 treatment cycles (89). The cumulative live-birth rate was significantly higher in the letrozole group (27.5%) compared with the clomiphene citrate group (19.5%). The multiple pregnancy rate was similar between the groups (3.2% with letrozole and 7.4% with clomiphene citrate). Given the increased live-birth rate with letrozole, letrozole may be preferable to clomiphene citrate as the first-line therapy for ovulation induction.

Resistance to ovulation induction with clomiphene citrate is observed in 20% of women with PCOS (90). In an analysis of response to clomiphene citrate, 51% of patients were anovulatory after a 50-mg dose, and, overall, 22.5% did not ovulate when doses up to 150 mg were used. The best predictors of failure to respond were the free testosterone index and BMI (90). However, it is still advised to begin treatment with clomiphene citrate typically starting with 50-mg tablets for 5 days. The dosage can be increased by 50-mg-dose increments in subsequent cycles if ovulation is not observed (91). Although doses as high as 250 mg have been used to achieve ovulation induction, doses greater than 100 mg are not approved by the FDA for ovulation induction, and most practitioners limit the dose to 150 mg. Progestin-induced withdrawal bleeding may not be necessary before increasing the dose of clomiphene citrate and may be associated with lower live-birth rate (92). A higher dose of clomiphene citrate may be administered without inducing withdrawal bleeding if ovulation is not observed by day 21. As mentioned earlier, the starting dosage of clomiphene citrate (50 mg/d for 5 days) may be increased in 50-mg increments to 100 mg/d for 5 days and then to 150 mg/d for 5 days. A “stair-step protocol” leads to a decreased time to ovulation (93). Women who are resistant to increased doses of clomiphene citrate may respond to a longer duration of clomiphene citrate therapy (7–8 days) or adjunctive treatments, such as metformin, corticosteroids, or sequential clomiphene citrate–gonadotropin therapy (91). Letrozole also may induce ovulation in clomiphene citrate-resistant women.

If ovulation induction cannot be achieved with oral agents or pregnancy is not achieved with oral ovulation induction agents, second-line options may be used, including gonadotropins or laparoscopic ovarian drilling (60) (Fig. 8). Low-dose gonadotropin therapy should be used with the goal of monofollicular recruitment to reduce the risk of multiple
pregnancy. Laparoscopic ovarian drilling with laser or diathermy is an alternative to low-dose gonadotropin therapy and is associated with a similar rate of live birth and lower risk of multiple pregnancy (94). Risks include surgical complications, adhesions, and premature ovarian failure.

**IN VITRO FERTILIZATION**

If pregnancy is not achieved with first- or second-line options for ovulation induction, in vitro fertilization (IVF) is an option with high pregnancy rates and lower multiple pregnancy rates than observed with gonadotropin therapy (Fig. 8). Additionally, IVF may be preferred in couples with multifactorial infertility (anovulatory PCOS with tubal factor, severe male factor, or both). Women with PCOS treated with IVF achieve similar pregnancy and live-birth rates as matched controls and are candidates for single embryo transfer in appropriate selected cases (95). Women with PCOS are at risk of ovarian hyperstimulation syndrome and stimulation protocols can be tailored to minimize this risk. Gonadotropin-releasing hormone antagonists are used during controlled ovarian hyperstimulation to inhibit gonadotropin release directly and prevent a premature LH surge. The rate of ovarian hyperstimulation syndrome is 10% lower with GnRH antagonist protocols compared with GnRH agonist protocols in women with PCOS (96). The risk of ovarian hyperstimulation syndrome can be further reduced with GnRH antagonist protocols by inducing final oocyte maturation with a GnRH agonist instead of human chorionic gonadotropin (97). A single bolus of a GnRH agonist will induce a physiologic LH surge when given during a GnRH antagonist protocol, which leads to final oocyte maturation while eliminating the risk of early ovarian hyperstimulation syndrome. Gonadotropin-releasing hormone agonist triggers are associated with decreased pregnancy rates because of diminished luteal support unless aggressive luteal support with estradiol, progesterone, and low-dose human chorionic gonadotropin is implemented. Alternatively, cryopreserving embryos and performing a subsequent frozen–thawed transfer eliminates concerns regarding inadequate luteal support.

In vitro maturation is an experimental procedure that is an alternative to IVF for women with PCOS at risk of ovarian hyperstimulation syndrome (98) (Fig. 8). In vitro maturation minimizes or eliminates the need for gonadotropin stimulation by maturing immature oocytes in vitro in IVF media supplemented with gonadotropins. This approach eliminates the risk of ovarian hyperstimulation syndrome, but lower implantation rates are observed with embryos derived from in-vitro matured oocytes (5.5–21.6%) when compared with IVF (36%). Further research is necessary to optimize in vitro maturation protocols to achieve pregnancy rates that are similar to IVF.
CASE NO. 3. A 28-year-old Hispanic woman reports the inability to conceive for 3 years. She initiated therapy with combination OC pills at age 18 years for irregular periods and hirsutism. After stopping combination OCs at age 25 years, she reports infrequent menstrual periods and estimates that she has one or two menstrual periods per year. She and her partner engage in frequent intercourse. She does not have risk factors for tubal infertility, and her partner has proven fertility from a previous relationship. Her BP is 130 mm Hg, systolic, and 85 mm Hg, diastolic, waist circumference is 38 in (96.5 cm), and BMI is 36. Hirsutism is present on her upper lip and chin, and acanthosis nigricans is noted at the base of the neck. Pelvic examination yields normal results.

The diagnosis of PCOS can be established given that androgen excess and ovulatory dysfunction are apparent from this patient’s history and physical examination. Other disorders associated with ovulatory dysfunction (thyroid dysfunction, hyperprolactinemia, and nonclassical CAH) can be excluded with normal TSH, prolactin, and 17α-hydroxyprogesterone levels. Given her ethnicity, central obesity, and acanthosis nigricans, she should be screened for impaired glucose tolerance and diabetes mellitus with a 2-hr 75-g OGTT. The patient should be counseled that regular ovulation can be restored with a weight loss of 5–10%. In addition, she should be counseled regarding the risk of gestational diabetes, hypertensive disorders in pregnancy, the potential for cesarean delivery, and preterm birth. If she remains anovulatory despite weight loss, ovulation induction with oral agents, such as clomiphene citrate or letrozole, can be considered. She should be counseled regarding the risk of multiple pregnancy with oral ovulation induction agents.

Emotional Well-Being

Prevalence of depression and anxiety in women with PCOS in several studies exceeds 30% and is significantly higher than in the general population (99). Several contributing factors are present in women with PCOS, including an increased prevalence of overweight and obesity, the long-term nature of the condition, and the effect on self-image because of androgenic symptoms. The exact nature and extent that PCOS has on quality of life is controversial, but the effects are likely negative. Recognition of depression and anxiety in patients with PCOS remains low. Therefore, the assessment for depression, anxiety, or both is important and the presence of these conditions likely affects adherence to lifestyle regimens. No large studies have examined the effect of mood disorders on women with PCOS or the effect of treatment on the disease process. If a woman with PCOS has evidence of depression or anxiety, she should be referred for appropriate treatment.

Pregnancy Considerations

Women with PCOS who become pregnant are at a two–three-fold risk of developing gestational diabetes, pregnancy-induced hypertension, and preeclampsia compared with those without PCOS (100). Polycystic ovary syndrome appears to be an independent risk factor for these complications after controlling for confounding factors, such as obesity, multiple pregnancy, and low parity. Women with PCOS before pregnancy who have impaired glucose tolerance or a BMI greater than 30 are at an increased risk of
gestational diabetes and should be screened for gestational diabetes early in pregnancy. Obese women with PCOS have an increased risk of cesarean delivery. Neonates born to women with PCOS are at an increased risk of premature birth and neonatal intensive care unit admission likely caused by the increased rate of maternal morbidities observed in patients with PCOS and the increased multiple pregnancy rate associated with ovulation induction and IVF.

Women with PCOS who are planning a pregnancy should receive prepregnancy counseling regarding the risks of pregnancy. Risk counseling can be individualized by performing prepregnancy assessment of BMI, BP, and oral glucose tolerance and management of abnormal findings (48). Weight loss of 5–10% of current body weight may restore ovulation in women with anovulatory PCOS, but it is unclear if this degree of weight loss will reduce the risk of gestational diabetes and hypertensive disorders in women who become pregnant. Although data support reduced rates of gestational diabetes and hypertensive disorders in women who have undergone bariatric surgery before pregnancy, no data exist regarding the relationship of bariatric surgery and maternal morbidities in women with PCOS (101). Furthermore, only limited data support the use of metformin in pregnant women with PCOS to prevent pregnancy loss or improve obstetric outcomes (88). Data do not support continuing metformin therapy during pregnancy in the absence of preexisting diabetes mellitus, and conflicting evidence is available for a reduction in the incidence of miscarriage with its use.

Some studies have reported an increase in the risk of recurrent pregnancy loss in women with PCOS. It is unclear if the increase in risk is independently associated with PCOS or caused by the increased rate of impaired glucose tolerance or diabetes mellitus or an increased rate of obesity seen in the studies. Polycystic findings in the ovary alone, without endocrine dysfunction, are not associated with an increased risk of pregnancy loss (102).

**Special Concerns for Older Women**

Diagnostic criteria for PCOS specific to this age group are lacking (48). Women with PCOS may experience a decline in ovarian and adrenal androgen secretion and increased menstrual frequency in their mid to late reproductive years (103). Ovulation may be restored because of an increase in FSH levels in response to diminished ovarian reserve. Furthermore, ovarian volumes decrease secondary to a decrease in follicle number. Despite the decrease in androgen levels and ovarian volumes observed in women with PCOS as they age, these values remain increased compared with controls.

Although the reproductive dysfunction may improve in the mid to late reproductive years, metabolic dysfunction persists (Box 4). Patients who demonstrate impaired glucose tolerance should be counseled regarding a risk of developing type 2 diabetes mellitus.
and be screened annually with a 2-hr 75-g OGTT (53). By the fourth decade of life, up to 40% of overweight and obese women with PCOS will demonstrate abnormal glucose tolerance (104). Lifestyle modification to achieve weight loss is preferred over metformin therapy alone for the prevention of diabetes mellitus in high-risk individuals (70). Furthermore, those patients who demonstrate evidence of metabolic syndrome should be counseled regarding the risk of CV disease. Women with PCOS are four times more likely than controls to meet criteria for metabolic syndrome and demonstrate early subclinical atherosclerosis as measured by increased coronary artery and aortic calcification (105). Although women with PCOS develop metabolic dysfunction and atherosclerosis at a younger age than controls, it is unclear if early and prolonged exposure to these risk factors leads to an increase in CV morbidity and mortality in women with PCOS. A longitudinal study (106) and a retrospective cohort study (107) did not find an increased risk in myocardial infarction or death from CV disease in women with PCOS diagnosed during their reproductive years, although postmenopausal women with a history of oligo- menorrhea (108) and elevated androgens (59) appear to be at an increased risk of coronary heart disease and worsening CV event-free survival. These conflicting observations suggest that the subgroup of women with PCOS who do not demonstrate improved reproductive function (eg, decreased androgens and increased ovulation) with aging may be at risk of CV events after menopause, whereas the risk may normalize among women who demonstrate improved reproductive function in their mid to late reproductive years (103). Further prospective studies are needed to identify women with PCOS who are at the greatest risk of CV events.

Women with PCOS also may be at risk of developing endometrial cancer (Box 4) and they should be counseled regarding the importance of reporting changes in the menses. Women with PCOS share many of the risk factors associated with the development of endometrial cancer, including obesity, hyperinsulinism, diabetes mellitus, and abnormal uterine bleeding. Women with PCOS are at a two–three-fold risk of developing endometrial cancer given the risk factors of chronic anovulation, obesity, and type 2 diabetes mellitus (109). A meta-analysis that assessed the association between PCOS and endometrial cancer showed a borderline increased relative risk of developing endometrial cancer (relative risk, 2.7; 95% confidence interval, 1–7.29) (110). Reproductive-aged women with PCOS who present with prolonged episodes of unopposed estrogen use or fail to respond to medical therapy should be screened for endometrial cancer by performing

Box 4. Concerns for Women With Polycystic Ovary Syndrome in Mid to Late Reproductive Years

- Type 2 diabetes mellitus
- Metabolic syndrome
- Endometrial cancer
an endometrial biopsy for pathologic sampling (111). All women older than 45 years who present with suspected anovulatory bleeding should be evaluated with endometrial biopsy. Routine ultrasound screening for endometrium thickness is not recommended in women with PCOS (48).

CASE NO. 4. A 54-year-old woman, para 2, wishes to establish care and undergo an annual well-woman examination. At the initial visit, she recalls that her periods were irregular during adolescence and early adulthood and that she required clomiphene citrate to conceive her two children in her mid 20s. Her second pregnancy was complicated by gestational diabetes that resolved in the postpartum period. She used combination OCs for the management of irregular menses and hirsutism until her early 40s when she developed poorly controlled hypertension. She was surprised that her cycles were regular after she discontinued combination OCs until 2 years ago when her menstrual cycles ceased. On physical examination, her BP is 134 mm Hg, systolic, and 90 mm Hg, diastolic; waist circumference is 38 in (96.5 cm); and BMI is 42. The results of the clinical breast and pelvic examinations are normal. A fasting cholesterol and lipid panel and a 2-hr 75-g OGTT are performed. The results are listed as follows: total cholesterol level, 218 mg/dL; high-density lipoprotein cholesterol level, 39 mg/dL; low-density lipoprotein cholesterol level, 163 mg/dL; triglyceride level, 166 mg/dL; fasting glucose level, 96 mg/dL; and 2-hr glucose level, 162 mg/dL.

A presumptive diagnosis of PCOS can be established given that she is presenting in her late reproductive years with a history of ovulatory dysfunction and androgen excess. As mentioned earlier, women with PCOS may experience a decline in ovarian and adrenal androgen secretion and increased menstrual frequency in their mid to late reproductive years, which would explain this patient’s regular menses before the onset of menopause.

Given the evidence of impaired glucose tolerance, this patient should be counseled regarding her risk of developing type 2 diabetes mellitus and screened annually with a 2-hr 75-g OGTT. Lifestyle modification for weight loss should be recommended. Furthermore, she is demonstrating evidence of metabolic syndrome and should be counseled regarding the risk of CV disease.

Follow-up

Follow-up should be individualized based on management goals. Lifestyle management will address both reproductive and metabolic dysfunction in overweight and obese women with PCOS. Frequent follow-up may improve adherence to diet, exercise, and behavioral modification by providing objective measures of progress and physician support. A follow-up at 6 months should be considered when hormonal therapy is initiated to manage menstrual irregularity or hirsutism in order to assess adherence and satisfaction. A follow-up at 1–2 months should be considered after increasing the dose of metformin to assess for adverse effects and tolerance. It is important to screen for kidney disease because metformin should not be used if creatinine levels increase. Screening for impaired glucose tolerance and diabetes mellitus with a 2-hr 75 g OGTT should be
performed at diagnosis. If impaired glucose tolerance is detected, annual screening may be performed (53), otherwise screening can be performed every 3–5 years (48). More frequent screening may be considered in the case of an increased waist circumference or weight gain. A fasting serum lipid profile can be reassessed every 2 years or sooner if weight gain occurs (53). Ovulation induction with oral agents will require monthly monitoring to determine if ovulation and pregnancy are achieved. If pregnancy has not been achieved after 6 months of ovulation, follow-up is in order to determine if additional evaluation or second-line treatment options should be considered.

**Complementary and Alternative Medicine**

Often, women with PCOS are interested in alternatives to medical management of reproductive and metabolic dysfunction. Low-frequency electro-acupuncture has been shown to significantly reduce circulating androgen levels and improve menstrual frequency when compared with physical activity or no intervention (112). Some evidence exists that polycystic ovaries demonstrate increased sympathetic activity (113). This increased sympathetic nerve activity may be correlated with testosterone action and be associated with decreased ovulatory rates. Low-frequency electro-acupuncture may work through improved autonomic function or increase in β-endorphin levels. Currently, no large-scale randomized trials have been conducted to conclude effectiveness. Therefore, it is unclear if acupuncture increases the rate of ovulation, although small trials have suggested a benefit (114). Traditional Chinese supplements, particularly Di Long (Earth Dragon or earthworm) extract, have been used for ovulation induction, although inconsistencies and impurities in the preparation have raised safety concerns (115). Small or uncontrolled studies of vitamin D, vitamin B_{12}, folate, cinnamon extract, and myo-inositol use have demonstrated improved insulin resistance, although larger, controlled studies are needed (115, 116).

**Referral**

Common concerns of women with PCOS, including menstrual irregularity, hirsutism, and infertility, should be evaluated and treated by an obstetrician–gynecologist. If medical or family history, physical examination results, or screening test results suggest other disorders associated with anovulation and androgen excess (ie, nonclassical CAH, Cushing syndrome, and virilizing tumors), specialists, such as medical endocrinologists or reproductive endocrinologists, may assist in confirming the diagnosis and outlining an appropriate treatment plan. Metabolic dysfunction (ie, impaired glucose tolerance and dyslipidemia) can be addressed with lifestyle management, metformin therapy, or both. A primary care physician should manage metabolic dysfunction if weight loss, metformin
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use, or both are unsuccessful or if the condition progresses. If weight loss cannot be achieved with counseling and physician support, consideration should be given to referral to a weight loss program that can provide the multidisciplinary approach (ie, nutritionist, exercise physiologist, psychologist, and peer support) necessary to achieve and sustain weight loss. Bariatric surgery may be indicated for patients with extreme obesity. If ovulation induction cannot be achieved with oral agents or pregnancy is not achieved with an adequate trial of ovulation induction, referral to a reproductive endocrinologist is indicated.

Conclusions and Future Directions

Polycystic ovary syndrome remains a complex and incompletely understood condition that affects many women. The disease is characterized by a wide spectrum of conditions, and using the broadest definition of the disease, the Rotterdam criteria, has been proposed by experts in Europe, Australia, and the United States as a way to maintain consistency in the reporting and study of PCOS (6). The understanding of the effect of the variable phenotypes on the consequences of the condition poses significant challenges. Although it is clear that women who are most severely affected by androgen excess demonstrate the greatest metabolic risk, separating the effect of obesity from PCOS has been problematic. A significant portion of women with PCOS present with obesity. It is unknown if a predisposition to weight gain exists in this population, but it is clear that the severity of metabolic dysfunction is increased in obese women with PCOS, including a large number of women who progress to type 2 diabetes mellitus.

Insight into the origins of PCOS is emerging, but much is still unknown. Genetic studies have not yet led to a definitive genetic profile. However, the understanding of the epigenetic conditions that may predispose one to the development of PCOS is growing and this provides encouragement that interventions may be developed to help to either prevent the development or reduce the effect of the disease from the outset. A focus on the adolescent offers the unique opportunity to allow for more effective long-term treatment. Given the high prevalence of obesity in patients with PCOS, the effects of weight management, nutritional changes, and behavioral therapy on the progression of sequelae of PCOS require further study.

New ovulation agents and regimens, such as letrozole therapy, have been successfully introduced, demonstrating better response than the traditional use of clomiphene. As in vitro fertilization techniques continue to improve the singleton live-birth rate, they can assist with the significant problem of multiple birth seen with the use of ovulation induction regimens in women with PCOS who often have a robust stimulation response to gonadotropin therapy. Pregnancy complications in patients with PCOS remain a significant concern. These women should be carefully monitored during pregnancy for the development of gestational diabetes and preeclampsia.
The data on the long-term CV risks in patients with PCOS remain unclear. Clear evidence exists of increased metabolic dysfunction and increased CV risk factors in patients with PCOS, but the association of increased mortality from CV disease has not been determined, and further research is needed. It is important that obstetrician–gynecologists and primary health care providers screen patients appropriately to identify abnormalities for early intervention, which may require a multidisciplinary approach. Behavioral counseling and assessment for depression should be included in the management approach to women with PCOS. With the emerging understanding of this common condition and the availability of improved medical approaches, there is an opportunity to improve the quality of life for women with PCOS with an effect that may span across multiple generations.

As mentioned earlier, many areas of PCOS remain an object of further research, especially with respect to etiology, diagnosis, consequences, and best treatment strategies. At the NIH Evidence Based Methodology Workshop in Polycystic Ovary Syndrome held in December 2012, several key areas for research were identified. Specifically, the ability to measure serum androgens in women is limited because of the poor reliability of testosterone assays in women. Improvement in the standardization of this assay as well as establishment of normal ranges is of utmost importance.

The progress in imaging technology provides improved views of the ovary by means of office-based ultrasonography. Consequently, improved assessment of normal and abnormal morphology across age ranges and populations is expected.

With respect to the etiology of PCOS, additional research into the epigenetic causes is required as is an understanding of different ethnic populations and the development of PCOS. Also, the understanding of the role of glucose tolerance in pregnant patients is lacking. The effect of glucose tolerance on both pregnancy complications in women with PCOS and their offspring is another prospective area of research. The effect of PCOS on CV disease remains uncertain, and well-designed, adequately powered, long-term epidemiologic studies are needed to determine if the risk of CV mortality is increased in women with PCOS.

The optimal therapies for managing the most common concerns in PCOS, ie, hirsutism, menstrual irregularities, ovulation induction, and weight management, have not been fully developed and remain in need of further research. The effect and prevalence of obesity, as well as its contribution to the incidence of PCOS needs to be determined. The interpretation of the multitude of clinical findings from research to the public needs to be strengthened with health care provider awareness, public education, and implementation on a public health level. Much can be learned from the Australian national experience with PCOS. The authors are hopeful that algorithms based on the evidence available can be adapted to the U.S. health care system to improve the long-term quality of life of U.S. women with PCOS (49).
Polycystic ovary syndrome is a highly prevalent condition that has both reproductive and metabolic features. This condition is associated with high levels of burden for women and often is underdiagnosed. The following key points summarize information provided in this monograph:

- Diagnosis of PCOS should be established based on the Rotterdam criteria, identifying at least two out of three criteria.
- The syndrome is associated with a high prevalence of insulin resistance and impaired glucose metabolism, and women should be screened for glucose tolerance early in the disease and subsequently, particularly if they are overweight or obese.
- Overall attention to lifestyle factors, including nutritional concerns and sedentary behavior, should underscore additional treatment of the symptoms of PCOS.
- Pregnancy in women with PCOS is associated with a high risk of gestational diabetes, and prepregnancy counseling should include assessment of glucose abnormalities and dietary advice in overweight or obese women.
- A growing body of evidence indicates an association between PCOS and psychologic concerns, such as anxiety and depression.
- It is still unclear whether CV disease morbidity or mortality is increased in women with PCOS, but risk factors for CV disease should be addressed, if present.
American College of Obstetricians and Gynecologists’ Patient Education Pamphlet


Other Resources

*The following list is for information purposes only. Referral to these sources and web sites does not imply the endorsement of the American College of Obstetricians and Gynecologists. This list is not meant to be comprehensive. The exclusion of a source or web site does not reflect the quality of that source or web site. Please note that web sites are subject to change without notice.*

Patient Education


Professional Publications


Organizations

- American Academy of Dermatology
  930 E Woodfield Road
  Schaumburg, IL 60173
  Telephone: 847-240-1280 or 866-503-SKIN (7546)
  Web: www.aad.org

- Androgen Excess and PCOS Society
  12520 Magnolia Boulevard, Suite 212
  North Hollywood, CA 91607
  Web: www.ae-society.org

(continued)
Resources (continued)

PCOS Foundation
10901 Katy Freeway
Houston, TX 77079
Telephone: 713-487-7267
Web: www.pcosfoundation.org

The American Society for Reproductive Medicine
1209 Montgomery Highway
Birmingham, AL 35216-2809
Telephone: 205-978-5000
Web: www.asrm.org

The Endocrine Society
2055 L Street NW, Suite 600
Washington, DC 20036
Telephone: 202-971-3636 or 888-363-6274
Web: www.endocrine.org
Test Your Clinical Skills

Complete the answer sheet at www.clinicalupdates.org under “Test Your Clinical Skills” and receive 5 continuing medical education credits. The answers appear on page 47.

Directions: Select the one best answer or completion.

1. The ESHRE/ASRM 2012 conference criteria for diagnosis of PCOS in adolescents require oligomenorrhea or amenorrhea for how long after the onset of menarche?
   A. 12 months
   B. 24 months
   C. 3 years
   D. 5 years

2. Compared with white women, which group of women with PCOS has higher incidence of insulin resistance and diabetes mellitus?
   A. Black
   B. East Asian
   C. Hispanic
   D. South Asian

3. Which of the following conditions is a risk factor for subsequent development of PCOS?
   A. Premature menarche
   B. Delayed pubarche
   C. Intrauterine growth restriction
   D. Large-for-gestational-age birth weight

4. Acanthosis nigricans is a manifestation of
   A. hyperandrogenism
   B. hyperglycemia
   C. hyperinsulinemia
   D. obesity

5. Which of the following factors is not a criterion for ultrasound diagnosis of PCOS?
   A. Bilateral ovarian involvement
   B. Presence of 12 or more follicles
   C. Follicle size of 2–9 mm
   D. Ovarian volume greater than 10 cm²

6. Which of the following laboratory values is not part of the definition of metabolic syndrome?
   A. Fasting glucose level of 100 mg/dL
   B. High-density lipoprotein level of less than 50 mg/dL
   C. Low-density lipoprotein level greater than 150 mg/dL
   D. Triglyceride level greater than 150 mg/dL

7. Which of the following conditions has the weakest association with PCOS?
   A. Cardiovascular disease
   B. Diabetes mellitus
   C. Infertility
   D. Obstructive sleep apnea
8. Compared with lean women with PCOS, the rates of diabetes mellitus are increased how many times in obese women with PCOS?
   A. 1–2
   B. 3–4
   C. 5–6
   D. 7–10

9. In addition to oral contraceptives, the authors most strongly recommend which of the following drugs for treatment of hirsutism in patients with PCOS?
   A. Finasteride
   B. Flutamide
   C. Metformin
   D. Spironolactone

10. The PPCOS I and PPCOPS II trials found the highest live-birth rate in patients with PCOS treated with
    A. clomiphene citrate
    B. follicle-stimulating hormone–luteinizing hormone
    C. letrozole
    D. metformin

11. If there is no objective evidence of ovulation by day 21 after the administration of clomiphene citrate on day 5, the next step should be
    A. inducing a withdrawal bleeding with a progestin followed by an increased dose of clomiphene citrate for ovulation induction
    B. administering an increased dose of clomiphene citrate for ovulation induction without inducing withdrawal bleeding with a progestin
    C. waiting until day 45 to evaluate the patient further
    D. either option A or option B

12. Depression in women with PCOS occurs in at least what percentage of patients?
    A. 10%
    B. 20%
    C. 30%
    D. 50%

13. What percentage of obese and overweight women with PCOS will develop type 2 diabetes mellitus by the fourth decade of life?
    A. 10%
    B. 20%
    C. 30%
    D. 40%

14. Circulating androgens have been shown to be significantly reduced by which of the following complementary and alternative medicine treatments?
    A. Acupuncture
    B. Cinnamon extract
    C. Di Long
    D. Myo-inositol


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60. **Clinical Updates: Polycystic Ovary Syndrome**


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Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

I  Evidence obtained from at least one properly designed randomized controlled trial.
II-1 Evidence obtained from well-designed controlled trials without randomization.
II-2 Evidence obtained from well-designed cohort or case–control analytic studies, preferably from more than one center or research group.
II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Answers
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- **Metabolic Bone Disease (Volume XIV, April 2015)**
- **Benign Breast Disease (Volume XIV, July 2015)**
- **Hormone Therapy and Alternative Therapies for Menopause (Volume XIV, October 2015)**
- **Lower Gastrointestinal Tract Disorders (Volume XIV, November 2015)**
- **Hypertension (Vol XV, January 2016)**
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- **Elder Abuse**
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Reliable Take-Home Information for Your Patients

The American College of Obstetricians and Gynecologists’ Patient Education Pamphlets are designed to complement and supplement the information and advice you provide in the office. After you talk to your patients about polycystic ovary syndrome, ensure they have accurate information they can refer to and share with their families and friends when they are at home.

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