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Management of Polycystic Ovary Syndrome in the Non-Infertility Patient

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Learning Objectives: *After participating in this activity, the obstetrician/gynecologist should be better able to:*

1. *Describe the pathophysiology that underlies polycystic ovary syndrome.*
2. *Diagnose and treat polycystic ovary syndrome in a setting of a woman who does not desire pregnancy at the current time.*
3. *Counsel patients with polycystic ovary syndrome regarding the long-term health implications of their diagnosis.*

Polycystic ovary syndrome (PCOS) is the most common female endocrinopathy in reproductive-aged women, affecting an estimated 6% to 8% of women in this age group.[1-3] The hallmark of PCOS is chronic hyperandrogenism and chronic anovulation, with polycystic ovaries frequently associated with the syndrome but not necessary for diagnosis. PCOS was first described 75 years ago by Stein and Leventhal,[4] who reported 7 women with amenorrhea and polycystic ovaries, with the majority also having obesity and hirsutism.[4]

Women with PCOS typically present with symptoms of irregular menstrual cycles, hirsutism, and/or infertility. When fertility is not a concern, the focus of treatment is usually managing symptomatic androgen excess and regulating menstrual cycles. In addition, substantial research indicates that the diagnosis of PCOS has important long-term health implications for women, including an increased risk of type 2 diabetes mellitus (T2DM), metabolic syndrome, chronic hypertension, heart disease, and dyslipidemia. Thus, it is imperative that long-term management of patients with PCOS targets risk reduction of these important health issues. Although general obstetrician-gynecologists are usually comfortable treating infertility in patients with PCOS, there is a gap in the understanding of how to address the medical implications of the syndrome in those women who do not intend to become pregnant. The purpose of this article is to address this gap by reviewing the management of PCOS in patients who do not currently desire pregnancy.

Pathophysiology

The pathophysiology of PCOS is complex and is not completely understood. Two key factors that play a major role in the pathologic pathway of PCOS include inappropriate gonadotropin secretion and insulin resistance with resulting hyperinsulinemia. Hyperandrogenism has been detected in 60% to 80% of PCOS cases and insulin resistance in 50% to 80% of women with PCOS.[5] Hyperinsulinemia results in decreased sex hormone binding globulin (SHBG) levels, which lead to increased levels of free androgens, most notably testosterone.

At the level of the pituitary and hypothalamus, there is an increase in frequency and amplitude of luteinizing hormone (LH) pulses, often resulting in an LH-to-follicle-stimulating hormone (FSH) ratio greater than 2. Hyperinsulinemia and increased LH work synergistically to stimulate the ovaries to secrete excess androgens: LH by the hormone's action on the theca cells of the ovary, and hyperinsulinemia by stimulating androgen secretion from both the ovaries and adrenal glands. It is theorized that insulin contributes to the hyperandrogenic state by activating insulin receptors within the ovary or acting on insulin-like growth factor receptors.

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The authors have disclosed that the use of oral contraceptives for treatment of hirsutism and spironolactone for treatment of hyperandrogenism as discussed in this article has not been approved by the U.S. Food and Drug Administration.

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At the level of the ovary, increased androgen levels and hyperinsulinemia impair ovarian follicular development. Women with PCOS have disordered follicular development with most cycles failing to result in the emergence of a dominant follicle; instead, the ovarian cortex becomes occupied by numerous small follicles. Because of decreased levels of FSH relative to LH, ovarian granulosa cells cannot aromatize the androgens to estrogens, leading to hyperandrogenism and anovulatory cycles. The high levels of androgens can be aromatized peripherally in adipose cells and lead to high levels of estrone, a relatively weak but nevertheless bioactive estrogen when present in high and constant amounts. About 25% to 33% of women with oligo amenorrhea or menstrual dysfunction have PCOS.[6]

Clinical manifestations of PCOS include those attributable to androgen excess and insulin resistance. Hyperandrogenism results in hirsutism, acne, and, in some cases, alopecia. *Hirsutism* is the presence of terminal hair in a male pattern and reflects androgen excess. Androgens can directly transform vellus hair to terminal hair, and the result is not reversible. Male hair pattern includes hair on the face, chest, upper back, thighs, and abdomen. Testosterone, the main circulating androgen, is converted to the more potent dihydrotestosterone by 5-alpha-reductase at the hair follicle. Dihydrotestosterone then converts a vellus hair into a terminal hair. Acne can also be a result of hyperandrogenism because of the influence of androgens on sebaceous glands. The effects of insulin resistance on the skin can be seen by the development of acanthosis nigricans. Increased insulin leads to hyperplasia of the basal layer of epidermis, leading to velvety hyperpigmented skin lesions most often seen on the back of the neck or axillary regions.

The genetic basis of PCOS is unclear at the current time as there are not clearly identified genes. There is, however, a clear familial pattern of PCOS with affected mothers and daughters, which implies a role for genetic factors. In women with PCOS, about 35% of their mothers and 40% of their sisters are also reported to have the syndrome.[7] However, identifying causative genes remains a challenge due to phenotypic heterogeneity within the same family and lack of a male phenotype, making linkage studies difficult. Current evidence implies that PCOS is a multifactorial polygenic disorder with likely heterogeneity within both the phenotype and the genotype.[6]

Diagnosis

There is no clear consensus regarding the official diagnostic criteria for PCOS. In 1990, the National Institute of Child Health and Development stated that women can be classified as having PCOS if they have chronic oligoanovulation and evidence of androgen excess for which there is no other cause.[8] The 2003 Rotterdam criteria, developed at an international consensus workshop sponsored by the American Society for Reproductive Medicine and the European Society for Human Reproduction and Embryology, further expanded the diagnostic scope of PCOS. The Rotterdam criteria included patients with 2 of the following: (1) chronic anovulation; (2) clinical and/or biochemical evidence of hyperandrogenism; and (3) polycystic-appearing ovaries on sonogram.[9]

The Rotterdam criteria broadened the PCOS phenotypic spectrum, now suggesting that a woman did not necessarily need to manifest

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both anovulation and hyperandrogenism to be diagnosed with PCOS. A woman with hyperandrogenism and polycystic ovaries but regular menstrual cycles could now have PCOS, as could a woman with anovulation and polycystic ovaries but no signs of androgen excess. The inclusion of these more mild phenotypes has received criticism as complicating treatment recommendations. As 25% of young women have polycystic ovaries, the inclusion of polycystic ovaries in the diagnostic criteria has increased the prevalence of PCOS using the Rotterdam criteria.[10] Polycystic ovaries are defined as 12 or more follicles in each ovary measuring 2 to 9 mm and/or an increased ovarian volume of more than 10 mL.[11] Because of the common finding of many follicles in the ovaries of normal young women, some have suggested that this criterion should be modified to require that the 12 or more follicles must be seen in a single plane. The Rotterdam definition of polycystic ovaries cannot be used when the patient is on oral contraceptive pills (OCPs), as these modify ovarian morphology.[12]

In 2006, the Androgen Excess Society proposed PCOS criteria that specified hyperandrogenism as a necessary diagnostic factor, in combination with other symptoms of the syndrome.[13] Table 1 reviews the diagnostic criteria for PCOS. Although insulin resistance is often associated with PCOS, it is not part of the diagnostic criteria. Polycystic ovaries should be noted to be a nonspecific finding and can be seen in women who do not have a diagnosis of PCOS.

PCOS remains a diagnosis of exclusion. It is critical to rule out alternative causes of androgen excess such as late-onset congenital adrenal hyperplasia and androgen-secreting tumors. Signs of virilization, such as lowered voice tone, temporal balding, increased muscle mass, and clitoromegaly, should prompt evaluation for an androgen-secreting tumor of the adrenal gland or ovary. Laboratory studies in patients with suspected PCOS are ordered to document hyperandrogenism biochemically and rule out nonclassic adrenal hyperplasia. A serum 17-hydroxyprogesterone level less than 200 ng/dL will effectively exclude nonclassic adrenal hyperplasia. If the 17-hydroxyprogesterone level exceeds 200 ng/dL, an adrenocorticotropic hormone stimulation test is the next step and a level more than 1000 ng/dL confirms the diagnosis. Laboratory tests to document hyperandrogenism include total and free testosterone and dehydroepiandrosterone sulfate . A patient with clinical stigmata of Cushing syndrome should be screened with a 24-hour urinary free cortisol test. Finally, the syndrome of hyperandrogenism, insulin resistance, and acanthosis nigricans can be associated with severe symptoms of hirsutism. Idiopathic hirsutism can be determined with normal ovulatory cycles and normal-appearing ovaries.[14]

Table 1. Diagnostic Criteria for Polycystic Ovary Syndrome

1990 National Institute of Child Health & Human Development criteria*
Chronic anovulation
Clinical and/or biochemical evidence of hyperandrogenism
Exclusion of other known etiologies
2003 Rotterdam criteria†
Chronic anovulation or oligoanovulation
Clinical and/or biochemical evidence of hyperandrogenism
Polycystic ovaries
Exclusion of other known etiologies
2006 Androgen Excess Society*
Clinical or biochemical signs of androgen excess
Ovarian dysfunction, as reflected by oligoanovulation or polycystic ovaries
Exclusion of other known etiologies

*Three required for diagnosis.

†Two of the first 3 required.

Clinical Management of PCOS

Management of Androgen Excess

Clinically, androgen excess presents with hirsutism, acne, and male pattern alopecia. *Hirsutism,* in women, is defined as male pattern terminal hair distribution and can be qualified using the standardized Ferriman-Gallwey scale, with a score of 6 to 8 consistent with hirsutism. It should be noted that androgen suppression will not alter previous hair growth patterns. The prevalence of hirsutism among women with PCOS will vary according to the race and ethnicity of the patients. For instance, there is a lower prevalence of hirsutism among East Asian women with PCOS.[13] There are few data to support the use of Glucophage (metformin) or other insulin-sensitizing agents for the treatment of hirsutism alone in patients with PCOS.[14]

Oral Contraceptive Pills

OCPs are considered first-line treatment of hirsutism in women with PCOS, although no specific OCP has been approved by the FDA for treatment of hirsutism.[14,15] Combined OCPs function by increasing levels of SHBG, thus reducing free circulating androgen levels. OCPs also decrease LH secretion, thus reducing ovarian androgen production.[14,16] An oral contraceptive containing ethinyl estradiol and a progestin with minimal androgenic activity, such as norgestimate, norethindrone, or desogestrel, is most beneficial.

Spironolactone

Spironolactone is often considered a second-line therapy for PCOS, especially in the setting of those patients who cannot take OCPS or who have suboptimal results from treatment with OCPs alone after at least 6 months of treatment.[15] Spironolactone is an aldosterone antagonist that inhibits dihydrotestosterone binding, directly inhibits 5-alpha-reductase, and decreases androgen synthesis. The drug should be used together with contraception in sexually active women because of potential adverse effects on the genitalia of male fetuses. The usual starting dose of spironolactone is 25 to 100 mg twice daily, and the dose is titrated to achieve the desired effect. Adverse effects of spironolactone include headaches, fatigue, gastritis, and increased urination. Because it can exacerbate hyperkalemia, spironolactone should not be used in women with

impaired renal function.[14] Spironolactone is not approved by the FDA for treatment of hyperandrogenism in women with PCOS.

Flutamide and Finasteride

Flutamide and finasteride are 2 antiandrogens that are sometimes used in severe cases of hirsutism. Neither medication is approved by the FDA for this indication. Flutamide is an androgen-receptor blocker that has produced improvement in hirsutism in small trials. Flutamide has been linked to hepatitis in rare cases, and its most common side effect is dry skin. Because it is a known teratogen, contraception is necessary for patients on this therapy. A typical starting dose for flutamide is 125 to 250 mg daily. Finasteride, a 5-alpha-reductase inhibitor, has minimal effects and toxicity. It is available as a 1-mg tablet for the treatment of male alopecia. As it can feminize male fetuses, adequate contraception should be used.[14]

Eflornithine

Topical eflornithine has been approved by the FDA for treating female hirsutism. Its mechanism of action involves the inhibition of the enzyme ornithine decarboxylase. A randomized, double-blind trial analyzed the use of topical eflornithine for treatment of female facial hair; in 60% of women, the condition improved after 6 months of treatment. The cream is applied topically twice daily to affected facial areas with side effects including local stinging, burning, and erythema.[14,17]

Additional Cosmetic Therapies

Mechanical measures of hair removal such as waxing, electrolysis, and laser treatment are increasingly in use to treat hirsutism. Laser therapy has been reported in studies to be an effective treatment of hirsutism secondary to PCOS. In laser therapy, follicular melanin absorbs the laser wavelengths, selectively thermal-damaging the hair follicle. Medical management to decrease circulating androgen levels is recommended to prevent vellus hair from differentiating into terminal hair.[14,18]

Management of Anovulation or Oligoanovulation

Most patients with PCOS present with ovulatory dysfunction, with 70% to 80% of women presenting with oligomenorrhea or amenorrhea.[19] Menstrual irregularity may be masked by OCP use. Menorrhagia can occur because of unopposed estrogen and can be further exacerbated by the increase in estrogen associated with obesity. It is critical to regulate menstrual cycles to prevent endometrial hyperplasia and, therefore, the risk of endometrial adenocarcinoma in this group of patients.

Endometrial Protection

Although anovulation is extremely common in patients with PCOS, the ovaries continue to secrete low levels of estrogen, which is significantly exacerbated by peripheral conversion of androgens. With a lack of cyclic estrogen and progesterone withdrawal over time, unopposed estrogen can lead to abnormal proliferation of the endometrium and ultimately endometrial hyperplasia. Because endometrial hyperplasia is a well-known risk factor for endometrial cancer, it is imperative that patients with PCOS have regular withdrawal bleeds or another means of endometrial protection.

Combined OCPs is the most commonly used method of endometrial protection for women with PCOS. If combination OCPs are contraindicated or not desired, cyclic progestin therapy may be prescribed monthly or every alternate month to induce a withdrawal bleed and decrease the patient's risk of menorrhagia and endometrial hyperplasia. A recommended dose is 10 mg of medroxyprogesterone acetate for 10 to 12 days every 6 to 8 weeks to induce a regular withdrawal bleed. Patients using this regimen should be counseled that pregnancy is possible using this method unless contraception is used. An additional option for endometrial protection for women with PCOS is the levonorgestrel-releasing intrauterine device, as its suppression of the endometrial lining provides protection against endometrial hyperplasia.[20] Endometrial biopsy should be considered in selected patients to determine whether endometrial hyperplasia is preexisting, such as those with prolonged history of menorrhagia and/or dysfunctional uterine bleeding.

Management of Metabolic Sequelae and Long-Term Health Implications

Obesity and Weight Loss

Obesity is a common comorbid condition in patients with PCOS, but it is not a diagnostic requirement. In fact, 20% of women with PCOS are not obese. Obesity is a key factor in exacerbating the reproductive and metabolic abnormalities in women with PCOS. Studies have shown that weight loss can benefit women with PCOS by lowering circulating androgen levels, decreasing hirsutism, and improving glucose and lipid profiles.[16,21,22] The Androgen Excess and Polycystic Ovary Syndrome Society recommends lifestyle management as the primary therapy in overweight and obese women with PCOS for the treatment of metabolic complications.[23]

Insulin Resistance and T2DM

Insulin resistance occurs in approximately 50% to 80% of women with PCOS, according to the National Institutes of Health diagnostic criteria.[24] The etiology of the insulin resistance is complex and multifactorial and affected by genetic and environmental factors. Although obesity is a key modulator of the insulin resistance, it is not the only factor involved. For instance, lean women with PCOS often have abnormalities in insulin secretion compared with weight-matched controls.[25] Compared with age- and weight-matched controls, women with PCOS are at increased risk of developing impaired glucose tolerance and T2DM.[24] Approximately 10% of women with PCOS have T2DM, and 30% to 40% of women with PCOS have impaired glucose tolerance by the age of 40 years.[24,26]

Several organizations have recommended screening for impaired glucose tolerance and T2DM in patients with PCOS. This article will focus on the most recent guidelines from the American Diabetes Association (ADA) that include the addition of the hemoglobin A_{1c} (HbA_{1c}) measurement in screening those at risk for diabetes. HbA_{1c} is a widely used marker of chronic hyperglycemia, reflecting average blood glucose levels over a 2- to 3-month period. Although HbA_{1c} has been used for some time to monitor glycemic control for patients with T2DM, for the first time, the 2010 guidelines include HbA_{1c} as a means to diagnose impaired glucose control and T2DM. The ADA recommends testing for T2DM to assess future risk for the disease in individuals who are overweight or obese (body mass index ≥25 kg/m^2) and have 1 or more additional risk factors, with PCOS included as a risk factor. If test results are normal, repeat testing is recommended at a minimum of 3-year intervals. Tests deemed appropriate by the ADA include an HbA_{1c}, fasting plasma glucose, or a 2-hour oral glucose tolerance test.[27] Please refer to Table 2 for criteria for those with "prediabetes" and Table 3 for diagnostic criteria for those with T2DM.

Per the 2010 ADA guidelines, female patients who meet criteria for impaired glucose tolerance or impaired fasting glucose or have an HbA_{1c} level of 5.7% to 6.4% are considered "prediabetic" and should be referred to a program for weight loss. Weight loss of 5% to 10% of body weight and an increase in physical activity to at least 150 min/wk of moderate activity, such as walking, should be encouraged. Metformin may be considered in those who are at high risk for developing diabetes (combined impaired fasting glucose and impaired glucose tolerance plus other risk factors such as HbA_{1c} >6%, hypertension, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, obesity, or a strong family history of diabetes). For patients with prediabetes, testing for diabetes should be performed annually.[28]

Metformin, a biguanide, is the most widely used drug worldwide for the treatment of T2DM. Its primary action is to increase peripheral insulin sensitivity and inhibit hepatic glucose production. Metformin is used in combination with diet and exercise for women with PCOS. Common side effects include gastrointestinal symptoms such as diarrhea, nausea, abdominal bloating, flatulence, and anorexia. Metformin also carries a small risk of lactic acidosis, usually associated with impaired renal function. Metformin is usually started at a small dose and then titrated to 1500 to 2000 mg daily in divided doses.[14]

Table 2. 2010 American Diabetes Association Criteria for Increased Risk of Diabetes

Impaired fasting glucose	Fasting plasma glucose: 100–125 mg/dL
Impaired glucose tolerance	2-h plasma glucose after 75-g glucose load: 140–199 mg/dL
Borderline HbA_{1C}	HbA_{1C} value: 5.7%–6.4%

Table 3. 2010 American Diabetes Association Diagnostic Criteria for Diabetes Mellitus*

Test	Value	Comments
1. HbA_{1C}	≥6.5%	Test should be performed in a laboratory
2. Fasting plasma glucose	≥126 mg/dL	*Fasting* is defined as no caloric intake for at least 8 h
3. 2-h oral glucose tolerance test	≥200 mg/dL	Test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water
4. Random plasma glucose	≥200 mg/dL	In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis

*In the absence of unequivocal hyperglycemia, criteria 1–3 should be confirmed by repeat testing.

Metabolic Syndrome

Metabolic syndrome is a common disorder associated with insulin resistance, and women with PCOS are at risk for this important disorder as well. To date, no study has looked at the prevalence of PCOS among women with metabolic syndrome or T2DM. The presence of metabolic syndrome predicts an increased risk for cardiovascular disease. The hallmarks of metabolic syndrome include visceral obesity, hypertension, dyslipidemia, insulin resistance, and glucose intolerance. The diagnostic criteria for metabolic syndrome were established by the Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults and include having 3 of 5 diagnostic criteria as outlined in Table 4.[29] The 2003 Rotterdam consensus includes screening for metabolic syndrome for management of patients with PCOS. Specifically, women with PCOS should be screened for metabolic syndrome, which includes serum cholesterol (HDL) and triglycerides, blood pressure screening, and appropriate diabetes screening, as reviewed in the previous section.[9]

Long-Term Health Consequences

The clinical significance of PCOS extends past the immediate problems that may bring a patient to the office, usually anovulation, hirsutism, and infertility. Notably, the diagnosis of PCOS implies an increased risk of T2DM and metabolic syndrome. As a consequence of these disorders, women with PCOS are at increased risk for cardiovascular disease due to their frequent findings of hyperinsulinemia, glucose intolerance, dyslipidemia, and hypertension. Anovulation is also associated with unopposed estrogen, which can lead to endometrial hyperplasia, an important precursor to endometrial cancer. There is also an increased identification of depression and other mood disturbances among women with PCOS.[30] Dyslipidemia is more prevalent in patients with PCOS than in weight-matched controls, with

Table 4. Metabolic Syndrome Diagnostic Criteria*

Criterion	Values/Requirements
Elevated blood pressure	≥130 systolic blood pressure or ≥85 diastolic blood pressure or drug treatment of hypertension
Waist circumference	≥35 in or ≥88 cm for women
Reduced HDL cholesterol level	≤50 mg/dL or drug treatment of reduced HDL
Elevated fasting glucose level	≥100 mg/dL or drug treatment of elevated glucose level
Elevated triglyceride level	≥150/dL or drug treatment of elevated triglycerides

*Three required for diagnosis. HDL, high-density lipoprotein.

higher triglycerides and lower HDL cholesterol. Although the dyslipidemia is independent of body mass index, there is a negative effect on lipid profile caused by obesity. The etiology of dyslipidemia in patients with PCOS is unclear but likely multifactorial, with insulin resistance suspected to play a major role.[31,32]

Conclusion

PCOS is a common endocrinopathy in women and, given the heterogeneity and wide spectrum of clinical features in the PCOS phenotype, presentation can vary across the life cycle. The manifestations of PCOS often change over time, from menstrual irregularity and hirsutism to infertility and then to metabolic complications such as T2DM and metabolic syndrome. Obesity is an important contributor to the medical complications of PCOS. Diagnosing a woman with PCOS has significant medical consequences as it implies an increased risk for infertility, dysfunctional uterine bleeding, endometrial cancer, depression, T2DM, and metabolic syndrome with its associated dyslipidemia, hypertension, and risk of cardiovascular disease.

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CME QUIZ: Volume 31, Number 11

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1. Which one of the following statements associated with the pathophysiology of PCOS is *true?*
- **A.** The FSH:LH ratio is less than 2.
- **B.** There is a decrease in the frequency and amplitude of LH pulses.
- **C.** Hyperinsulinemia stimulates androgen secretion from the adrenal glands but not the ovaries.
- **D.** Hyperinsulinemia reduces SHBG and raises free testosterone levels.
- **E.** Androgens can directly transform vellus hair to terminal hair, but the result is reversible.

2. Which one of the following statements regarding the use of spironolactone for PCOS is *false*?
- **A.** Adverse effects include diuresis, hyperkalemia, fatigue, and headaches.
- **B.** Spironolactone can have potential adverse effects on genitalia of male fetuses if taken during pregnancy.
- **C.** Spironolactone directly inhibits 5-alpha-reductase activity.
- **D.** Spironolactone is an aldosterone antagonist.
- **E.** Women taking spironolactone should also take potassium supplements.

3. Which one of the following statements describing the mechanism of action of OCPs as used to treat PCOS is *true?*
- **A.** OCPs increase circulating gonadotropin levels.
- **B.** OCPs increase SHBG levels.
- **C.** OCPs increase free testosterone.
- **D.** OCPs directly inhibit peripheral conversion of androgens to estrone.
- **E.** OCPs increase the activity of 5-alpha-reductase.

4. Which one of the following statements to describe flutamide in the treatment of women with hirsutism and PCOS is *true?*
- **A.** Flutamide can cause adverse fetal effects, so concurrent contraception is required.
- **B.** Flutamide exerts its effects by inhibiting 5-alpha-reductase.
- **C.** Renal toxicity is a rare but reversible side effect of flutamide.
- **D.** Flutamide should be considered one of the first pharmacologic agents to begin in these patients.
- **E.** The FDA has approved flutamide for this use.

5. Which one of the following statements *most* accurately describes the appearance of polycystic ovaries on ultrasound?
- **A.** Ovarian volume greater than 5 mL
- **B.** More than 1 dominant follicle larger than 18 mm in each ovary
- **C.** 12 or more follicles in each ovary measuring 2 to 9 mm
- **D.** The greatest diameter of each ovary measures at least 4 cm
- **E.** At least 20 follicles identified in each ovary

6. Which one of the following is *not* part of the diagnostic criteria for metabolic syndrome?
- **A.** Elevated blood pressure (≥130/85 mm Hg)
- **B.** Increased waist circumference (≥35 in)
- **C.** Elevated fasting glucose levels (≥100 mg/dL)
- **D.** Reduced high-density lipoprotein cholesterol level (≤50 mg/dL)
- **E.** Reduced triglyceride levels (≤100/dL)

7. Which one of the following health conditions is *not* associated with PCOS?
- **A.** Endometrial adenocarcinoma
- **B.** Type 2 diabetes mellitus
- **C.** Metabolic syndrome
- **D.** Chronic hypertension
- **E.** Pelvic pain

8. Which one of the following statements regarding current understanding of the genetic basis of PCOS is *true?*
- **A.** There is a consistent male phenotype, which makes linkage analysis convenient.
- **B.** One specific gene mutation has been identified as the causative genetic defect in PCOS.
- **C.** Current evidence implies that PCOS is a multifactorial polygenic disorder with likely heterogeneity within both the phenotype and the genotype.
- **D.** The PCOS phenotype is consistent among patients diagnosed, aiding in ability to locate genetic mutations.
- **E.** There is not a clear familial component seen in PCOS; thus, a genetic basis is unlikely.

9. Which one of the following statements regarding the use of metformin in patients with PCOS is *true?*
- **A.** Metformin should be considered a first-line treatment for all women with PCOS.
- **B.** Metformin is generally well tolerated with minimal side effects.
- **C.** Metformin is considered safe for women with renal impairment.
- **D.** A biguanide, metformin has no effective on peripheral insulin resistance.
- **E.** In a patient with impaired fasting glucose, PCOS, and obesity, the ADA supports the use of metformin.

10. Which one of the following would be the best first-line treatment for a 20-year woman with PCOS who has irregular menstrual periods every 6 months, chronic hyperandrogenism, and hirsutism, and does not desire to become pregnant at the current time?
- **A.** OCPs
- **B.** Metformin 500 mg twice daily
- **C.** Finasteride
- **D.** Spironolactone
- **E.** Depo-Provera