

# ACOG PRACTICE BULLETIN



CLINICAL MANAGEMENT GUIDELINES FOR OBSTETRICIAN—GYNECOLOGISTS

NUMBER 108, OCTOBER 2009

(Replaces Practice Bulletin Number 41, December 2002)

## Polycystic Ovary Syndrome

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Richard S. Legro, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.

*Polycystic ovary syndrome (PCOS) is a disorder characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries. Its etiology remains unknown, and treatment is largely symptom based and empirical. PCOS has the potential to cause substantial metabolic sequelae, including an increased risk of diabetes and cardiovascular disease, and these factors should be considered when determining long-term treatment. The purpose of this document is to examine the best available evidence for the diagnosis and clinical management of PCOS.*

### Background

#### ***Incidence, Definition, and Diagnostic Criteria***

There is no universally accepted definition of PCOS and expert generated diagnostic criteria have proliferated in recent years (see Table 1). The Rotterdam criteria, which supplanted the National Institutes of Health (NIH) diagnostic criteria (1), incorporated the appearance of the ovary based on ultrasound examination into the schema (2). Ultrasound criteria for the diagnosis of polycystic ovaries were decided by expert consensus (see Box 1) (3). These criteria have been criticized for including more mild phenotypes, which increases the prevalence of PCOS and may complicate treatment decisions. The Androgen Excess Society (AES) criteria recognizes hyperandrogenism as a necessary diagnostic factor, in combination with other symptoms of the syndrome (4). Hyperandrogenism can be established on the basis of clinical findings (eg, hirsutism or acne) or serum hormone measurement. All diagnostic approaches recommend that secondary causes (such as adult-onset congenital adrenal hyperplasia, hyperprolactinemia, and androgen-secreting neoplasms) should first be excluded. All diagnostic schemes also require more than one sign or symptom (Table 1, Box 3). Polycystic ovaries alone, for example, are a nonspecific finding and also are frequently noted in women with no endocrine or metabolic abnormalities.

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**Table 1. Recommended Diagnostic Schemes for Polycystic Ovary Syndrome by Varying Expert Groups**

Signs and Symptoms*	National Institutes of Health Criteria <sup>†</sup> 1990 (both are required for diagnosis)	Rotterdam Consensus Criteria <sup>‡</sup> 2003 (two out of three are required for diagnosis )	Androgen Excess Society <sup>§</sup> 2006 (hyperandrogenism plus one out of remaining two are required for diagnosis )
Hyperandrogenism <sup>  </sup>	R	NR	R
Oligoamenorrhea or amenorrhea	R	NR	NR
Polycystic ovaries by ultrasound diagnosis		NR	NR

Abbreviations: R, required for diagnosis; NR, possible diagnostic criteria but not required to be present

\*All criteria recommend excluding other possible etiologies of these signs and symptoms and more than one of the factors present to make a diagnosis.

<sup>†</sup>Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. Polycystic ovary syndrome. Boston (MA): Blackwell Scientific Publications; 1992.

<sup>‡</sup>Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. *Fertil Steril* 2004;81:19–25.

<sup>§</sup>Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *Androgen Excess Society. J Clin Endocrinol Metab* 2006;91:4237–45.

<sup>||</sup>Hyperandrogenism may be either the presence of hirsutism or biochemical hyperandrogenemia.

Insulin resistance has been noted consistently among many women with PCOS, especially in those with hyperandrogenism, but it is not included in any of the diagnostic criteria (5).

The incidence of PCOS varies according to the diagnostic criteria. Women with hyperandrogenic chronic anovulation (ie, NIH criteria) make up approximately 7% of reproductive-aged women. There are no significant differences in the prevalence of hirsutism or elevated circulating androgen levels between white and black women (6). The broader Rotterdam criteria increases the prevalence of PCOS in women with normogonadotropic anovulation to 91% from 55% using the NIH criteria (7). The prevalence according to the AES criteria will fall between these values (4).

## Etiology

The genetic contribution to PCOS remains uncertain, and there is currently no recommended genetic screening test. No specific environmental substance has been identified as causing PCOS. Insulin resistance may be central to the etiology of the syndrome (5). Obesity is a comorbidity that may amplify the effects of PCOS. However, obesity is not a diagnostic criterion for PCOS, and approximately 20% of women with PCOS are not obese. Obesity is more prevalent in the United States than in other countries and, therefore, the PCOS phenotype may be different. Compensatory hyperinsulinemia may result in decreased levels of sex hormone-binding globulin (SHBG) and, thus, more bioavailable circulating androgen and serve as a trophic stimulus to androgen production in the adrenal gland and ovary. Insulin also may have direct hypothalamic effects, such as abnormal appetite

### Box 1: Suggested Evaluation for Patients With Polycystic Ovary Syndrome

#### Physical

- Blood pressure
- BMI (weight in kg divided by height in m<sup>2</sup>)
  - 25–30 = overweight, greater than 30 = obese
- Waist circumference to determine body fat distribution
  - Value greater than 35 inches = abnormal
- Presence of stigmata of hyperandrogenism and insulin resistance
  - Acne, hirsutism, androgenic alopecia, acanthosis nigricans

#### Laboratory

- Documentation of biochemical hyperandrogenemia
  - Total testosterone and sex hormone-binding globulin or bioavailable and free testosterone
- Exclusion of other causes of hyperandrogenism
  - Thyroid-stimulating hormone levels (thyroid dysfunction)
  - Prolactin (hyperprolactinemia)
  - 17-hydroxyprogesterone (nonclassical congenital adrenal hyperplasia due to 21 hydroxylase deficiency)
    - Random normal level less than 4 ng/mL or morning fasting level less than 2 ng/mL
  - Consider screening for Cushing syndrome and other rare disorders such as acromegaly

(continued)

### **Box 1: Suggested Evaluation for Patients With Polycystic Ovary Syndrome (continued)**

#### **Laboratory (continued)**

- Evaluation for metabolic abnormalities
  - 2-hour oral glucose tolerance test (fasting glucose less than 110 mg/dL = normal, 110–125 mg/dL = impaired, greater than 126 mg/dL = type 2 diabetes) followed by 75 g oral glucose ingestion and then 2-hour glucose level (less than 140 mg/dL = normal glucose tolerance, 140–199 mg/dL = impaired glucose tolerance, greater than 200 mg/dL = type 2 diabetes)
- Fasting lipid and lipoprotein level (total cholesterol, high density lipoproteins less than 50 mg/dL abnormal, triglycerides greater than 150 mg/dL abnormal, [low density lipoproteins usually calculated by Friedewald equation])

#### **Ultrasound Examination**

- Determination of polycystic ovaries: in one or both ovaries, either 12 or more follicles measuring 2–9 mm in diameter, or increased ovarian volume (greater than 10 cm<sup>3</sup>). If there is a follicle greater than 10 mm in diameter, the scan should be repeated at a time of ovarian quiescence in order to calculate volume and area. The presence of one polycystic ovary is sufficient to provide the diagnosis.
- Identification of endometrial abnormalities

#### **Optional Tests to Consider**

- Gonadotropin determinations to determine cause of amenorrhea
- Fasting insulin levels in younger women, those with severe stigmata of insulin resistance and hyperandrogenism, or those undergoing ovulation induction
- 24-hour urinary free-cortisol excretion test or a low dose dexamethasone suppression test in women with late onset of polycystic ovary syndrome symptoms or stigmata of Cushing syndrome

stimulation and gonadotropin secretion. Hyperandrogenism, although central to the syndrome, may have multiple etiologies, some not related to insulin resistance.

### **Clinical Manifestations**

Women with PCOS commonly present with menstrual disorders (from amenorrhea to menorrhagia) and infertility. For this reason, much attention has been focused on the risks of ovulation induction among women with PCOS because they are at increased risk for ovarian

hyperstimulation syndrome and multifetal pregnancy. In addition, women with PCOS appear to be at increased risk for complications of pregnancy, including gestational diabetes, and hypertensive disorders (8). The risk of complications is further exacerbated by iatrogenic multiple pregnancy from infertility treatment.

Skin disorders, especially those due to peripheral androgen excess such as hirsutism and acne, and to a lesser degree androgenic alopecia, are common in women with PCOS (9). Women with PCOS are at increased risk of insulin resistance and its associated conditions, such as the metabolic syndrome (see Box 2) (10), nonalcoholic fatty liver disease (11), and obesity-related disorders such as sleep apnea (12). In turn, all of these conditions are risk factors for long-term metabolic sequelae, such as type 2 diabetes and cardiovascular disease. Women with PCOS also have multiple risk factors for endometrial cancer, including chronic anovulation, centripetal obesity, and diabetes, although the strength of the association with PCOS per se is debated (13). In recent years, there has been increased recognition of mood disturbances and depression among women with PCOS (14).

### **Differential Diagnosis of PCOS**

The differential diagnosis of PCOS includes other causes of androgen excess (see Box 3). The essential components of the history and physical examination necessary to diagnose the underlying cause of the disorder are described in Box 1. The history should focus on the onset and duration of the various signs of androgen excess, the menstrual history, and concomitant medications, including the use of exogenous androgens. A family history of diabetes and cardiovascular disease (especially first-degree relatives with premature onset of cardiovascular

### **Box 2: Metabolic Syndrome**

The metabolic syndrome in women most commonly is diagnosed by the updated Adult Treatment Panel III criteria of an elevated blood pressure level (greater than or equal to 130/85), increased waist circumference (greater than or equal to 35 inches), elevated fasting glucose levels (greater than or equal to 100 mg/dL), reduced high-density lipoprotein cholesterol level (less than or equal to 50 mg/dL), and elevated triglyceride levels (greater than or equal to 150 mg/dL).

Grundey SM, Cleeman JJ, Daniels SR, Donato KA, Eckel RH, Franklin BA, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute scientific statement: executive summary. *Circulation* 2005;112:e285–e290.

### **Box 3: Factors to Consider in the Differential Diagnosis of Polycystic Ovary Syndrome**

- Androgen secreting tumor
- Exogenous androgens
- Cushing syndrome
- Nonclassical congenital adrenal hyperplasia
- Acromegaly
- Genetic defects in insulin action
- Primary hypothalamic amenorrhea
- Primary ovarian failure
- Thyroid disease
- Prolactin disorders

disease [male younger than 55 years and female younger than 65 years]) is important.

The physical examination should include evaluation of balding, acne, clitoromegaly, and body hair distribution, as well as pelvic examination to look for ovarian enlargement. The presence and severity of acne should be noted. Signs of insulin resistance such as hypertension, obesity, centripetal fat distribution, and the presence of acanthosis nigricans should be recorded. Acanthosis nigricans is a dermatologic condition marked by velvety, mossy, verrucous, hyperpigmented skin. It has been noted on the back of the neck, in the axillae, underneath the breasts, and even on the vulva. The presence of acanthosis nigricans appears to be more a sign of insulin resistance or medication reaction than a distinct disease unto itself. Other pathologic conditions rarely associated with acanthosis nigricans should be considered, such as insulinoma and malignant disease, especially adenocarcinoma of the stomach. Clitoromegaly is rarely associated with PCOS, and its presence should elicit a search for other causes.

Because Cushing syndrome is extremely rare (1 in 1,000,000 individuals) and screening tests are not 100% sensitive or specific (15), routine screening for Cushing syndrome in all women with hyperandrogenic chronic anovulation is not indicated. Those who have coexisting signs of Cushing syndrome, including a moon facies, buffalo hump, abdominal striae, centripetal fat distribution, or hypertension, should be screened (see Box 1). Proximal myopathies and easy bruising, not typically present in women with PCOS, also may help identify patients with Cushing syndrome.

Androgen-secreting tumors of the ovary or adrenal gland are invariably accompanied by elevated circulating

androgen levels. However, there is no absolute level that is pathognomonic for a tumor, just as there is no minimum androgen level that excludes a tumor. In the past, testosterone levels above 2 ng/mL and dehydroepiandrosterone sulfate (DHEAS) levels greater than 700 micrograms/dL were regarded as suspicious for a tumor of ovarian and adrenal etiology, respectively, but these cut-off levels have poor sensitivity and specificity (16).

The best measurement of circulating androgens to document unexplained androgen excess is uncertain. The present recommendation by the AES is to measure free testosterone concentration either directly by equilibrium dialysis, or to calculate the free testosterone based on the total testosterone measured accurately (eg, by radioimmunoassay using column chromatography, or by mass spectrometry) and SHBG (eg, measured using competitive binding or a high quality immune-based assay). Each clinician should be familiar with the analytical performance and the normal ranges of local laboratories because there is no standardized testosterone assay in the United States and the sensitivity and reliability in the female ranges are often poor (17). Evaluation of DHEAS levels may be useful in cases of rapid virilization (as a marker of adrenal origin), but its utility in assessing common hirsutism is questionable.

Both the adrenal glands and ovaries contribute to the circulating androgen pool in women. The adrenal gland preferentially secretes weak androgens such as dehydroepiandrosterone (DHEA) or DHEAS (up to 90% of adrenal origin). These hormones, in addition to androstenedione, may serve as prohormones for more potent androgens such as testosterone or dihydrotestosterone. The ovary is the primary source of testosterone, and it is estimated that 75% of circulating testosterone originates from the ovary (mainly through peripheral conversion of prohormones by liver, fat, and skin, but also through direct secretion). Androstenedione, largely of ovarian origin, is the only circulating androgen that is higher in premenopausal women than men, yet its androgenic potency is only 10% of testosterone. Dihydrotestosterone is the most potent androgen, although it circulates in negligible quantities and results primarily from the intracellular 5- $\alpha$ -reduction of testosterone.

Mild elevations in prolactin are common in women with PCOS (18). A prolactin level can identify prolactinomas that secrete large amounts of prolactin and that may stimulate ovarian androgen production, but this is an extremely rare cause of hyperandrogenic chronic anovulation. Evaluating serum levels of thyroid-stimulating hormone also is useful given the protean manifestations and frequency of thyroid disease in women with menstrual disorders.

## Clinical Considerations and Recommendations

### ► *Who should be screened for nonclassical congenital adrenal hyperplasia, and how should screening be performed?*

Nonclassical congenital adrenal hyperplasia, often referred to as late-onset congenital adrenal hyperplasia, can present in adult women with anovulation and hirsutism and is almost exclusively due to genetic defects in the steroidogenic enzyme, 21 hydroxylase (CYP21). In Europe and the United States, congenital adrenal hyperplasia occurs with the highest prevalence among Ashkenazi Jews, followed by Hispanics, Yugoslavs, Native American Inuits in Alaska, and Italians (19). Women in groups at higher risk for nonclassical congenital adrenal hyperplasia and a suspected diagnosis of PCOS should be screened with a 17-hydroxyprogesterone value.

To screen for nonclassical congenital adrenal hyperplasia due to CYP21 mutations, a fasting level of 17-hydroxyprogesterone should be obtained in the morning. A value less than 2 ng/mL is considered normal. If the sample is obtained in the morning and during the follicular phase, some investigators have proposed cutoffs as high as 4 ng/mL (20). Specificity decreases if the sample is obtained in the luteal phase. High levels of 17-hydroxyprogesterone should prompt an adrenocorticotrophic hormone (ACTH) stimulation test.

### ► *In obese women with PCOS, does weight loss improve ovarian function?*

Obesity contributes substantially to reproductive and metabolic abnormalities in women with PCOS. Multiple studies have shown that weight loss can improve the fundamental aspects of the endocrine syndrome of PCOS by lowering circulating androgen levels and causing spontaneous resumption of menses. Reduction in body weight has been associated with improved pregnancy rates and decreased hirsutism, as well as improvements in glucose and lipid levels (21–24). Studies using pharmacologic weight loss agents, such as orlistat, an intestinal inhibitor of lipid absorption, and sibutramine, an anorexic agent, in women with PCOS have shown similar improvement in ovarian function (25, 26). Morbidly obese women with PCOS who undergo gastric bypass surgery experience near normalization of their reproductive and metabolic abnormalities (27). These changes have been reported with weight loss as little as 5% of the initial weight (28). The decrease in unbound testosterone levels after weight loss may be largely mediated through increases in SHBG (28). The effects of weight loss in normal weight women with PCOS are unknown.

### ► *Does PCOS increase the risk of developing type 2 diabetes, and who should be screened?*

Women with a diagnosis of PCOS should be screened for type 2 diabetes and impaired glucose tolerance with a fasting glucose level followed by a 2-hour glucose level after a 75-g glucose load (29) (see Box 1). Retrospective studies of women with PCOS have noted a twofold to fivefold increased risk of diabetes in women with PCOS when compared with a control population (30, 31). In a prospective, cohort study, 11.9% of women older than 30 years with PCOS had a physician's diagnosis of type 2 diabetes, compared with only 1.4% of controls (32). Other cohort studies have suggested as many as 40% of U.S. women with PCOS demonstrate glucose intolerance when the less stringent World Health Organization criteria are applied (2-hour glucose levels greater than or equal to 140 mg/dL) (33, 34), although the prevalence is lower in a thinner European population (35). Undiagnosed diabetes ranges from 3–10% in these PCOS cohorts. The risk factors associated with glucose intolerance in women with PCOS—age, high body mass index (BMI) high waist-hip ratios, and family history of diabetes—are identical to those in other populations.

There is no recommended screening test for insulin resistance. Instead, there has been increasing recognition of the metabolic syndrome, a clinical phenotype of insulin resistance with increased diabetes and cardiovascular disease risk (see Box 2). The metabolic syndrome is common among women with PCOS, affecting 33% of women participating in a large multicenter trial (10).

Fasting glucose levels are poor predictors of glucose intolerance risk in women with PCOS and, thus, some groups recommend adding an oral glucose tolerance test to screening for the metabolic syndrome. This finding has taken on new significance with the findings of the Diabetes Prevention Program and other diabetes prevention trials that both lifestyle interventions and the use of antidiabetic drugs such as metformin significantly reduce the risk of developing diabetes in women with impaired glucose tolerance (36).

There is little utility to routine testing of insulin levels in women with PCOS. Insulin level assessment has not been shown to identify women who will respond to therapy.

### ► *Does PCOS have a long-term effect on the development of cardiovascular disease and who should be screened?*

Women with PCOS should be screened for cardiovascular risk by determination of BMI, fasting lipid and lipoprotein levels, and metabolic syndrome risk factors (see Box 2 and Box 3). Women with PCOS should be rescreened periodically for cardiovascular disease risk

factors because conversion to impaired glucose tolerance approaches 20% per year (37), although low-density lipoprotein (LDL) levels have tended to persist and plateau over time (38). Regular exercise and weight control are proven methods to reduce cardiovascular morbidity and mortality. These modalities should be considered before prescription drugs are used.

Dyslipidemia is a common metabolic abnormality among women with PCOS. The prevalence of borderline or high lipid levels according to National Cholesterol Education Program guidelines approaches 70% in women with PCOS (39). Low-density lipoprotein levels are disproportionately elevated in women with PCOS (38, 39).

An increased risk and early onset of cardiovascular disease in women with PCOS is strongly suspected but less well documented. No prospective studies have documented an increased risk of cardiovascular events in women with PCOS. However a number of cohort studies, including the Nurse's Health Study, have suggested an increased dose–response risk of cardiovascular disease or events in the presence of increasing oligomenorrhea (40) or with more symptoms of PCOS in a menopausal population (41, 42). Studies in premenopausal women with PCOS have detected an increased prevalence of subclinical atherosclerosis compared with controls (ranging from less than 10% in women with PCOS and increased carotid intimal medial thickness to 40% in those with PCOS and coronary artery calcification) (43–45).

► ***In a woman with PCOS who is not attempting to conceive, what is the best medical maintenance therapy to treat menstrual disorders?***

**Combination Hormonal Contraceptives**

There are several options to treat menstrual disorders associated with PCOS. Combination low-dose hormonal contraceptives are most frequently used for long-term management and are recommended as the primary treatment of menstrual disorders. Although there are few well designed trials in women with PCOS, in general, combined hormonal contraceptives offer benefits through a variety of mechanisms, including suppression of pituitary luteinizing hormone secretion, suppression of ovarian androgen secretion, and increased circulating SHBG. Individual preparations may have different doses and drug combinations and thus have varying risk–benefit ratios. For instance, various progestins have been shown to have different effects on circulating SHBG levels (46), but whether that results in a clinical benefit is uncertain. There is insufficient evidence to determine the most effective combination hormonal contraceptive for women with PCOS to treat menstrual disorders.

**Progestin**

No studies have addressed the long-term use of depot medroxyprogesterone acetate and intermittent oral medroxyprogesterone acetate to treat hirsutism. The regimen of cyclic oral progestin therapy or progestin-containing intrauterine devices that most effectively prevent endometrial cancer in women with PCOS is unknown. Progestin-only contraceptives or progestin-containing intrauterine devices are an alternative for endometrial protection, but they are associated with abnormal bleeding patterns in 50–89% of users (47).

**Insulin-Sensitizing Agents**

Drugs initially developed to treat type 2 diabetes also have been used to treat PCOS. Most studies initially focused on agents that improve peripheral insulin sensitivity by lowering circulating insulin levels. These agents include biguanides (ie, metformin) and thiazolidinediones (ie, pioglitazone and rosiglitazone) (48, 49). They are rarely associated with hypoglycemia. These drugs are often referred to as insulin-sensitizing agents, but their individual effects and risk–benefit ratios vary. There are class differences, for example, biguanides tend to decrease weight and thiazolidinediones tend to increase weight. Within a class there also can be significant differences in the risk–benefit ratio (50). These effects have diminished interest in the use of thiazolidinediones to treat PCOS. Nonetheless, improving insulin sensitivity with these agents is associated with a decrease in circulating androgen levels, improved ovulation rate, and improved glucose tolerance (51, 52).

Because ovulation rates will likely improve with treatment, it is important to discuss contraceptive options. It is difficult to separate the effects of improving insulin sensitivity from those of lowering serum androgens because any improvement in insulin sensitivity can raise SHBG and, thus, lower bioavailable androgen.

None of the antidiabetic agents noted are currently approved by the U.S. Food and Drug Administration (FDA) for treatment of PCOS-related menstrual dysfunction, although metformin appears to have the safest risk–benefit ratio. There are no randomized controlled studies of treatment for 1 year or more with these agents in women, children, or adolescents with PCOS. The effects of these drugs on preventing endometrial hyperplasia or endometrial neoplasia in women with PCOS are largely unknown.

► ***In a woman with PCOS who is not attempting to conceive, what is the best medical maintenance therapy to reduce the risks of cardiovascular disease and diabetes?***

Lifestyle modifications are the best approach to modifying risks for cardiovascular disease and diabetes. Insulin-sensitizing drugs and statins also can be considered.

### **Lifestyle Modification**

An increase in exercise combined with dietary change has consistently been shown to reduce diabetes risk comparable to or better than medication (36). Weight loss may improve metabolic abnormalities associated with PCOS. In terms of weight loss, caloric restriction rather than the composition of the diet is the key factor (53), and smaller trials in women with PCOS have shown no other advantage to a particular hypocaloric diet (54). Thus, there is no ideal dietary modification for women with PCOS beyond caloric restriction.

### **Insulin-Sensitizing Agents**

The Diabetes Prevention Program demonstrated that metformin can delay the development of diabetes in high-risk populations (eg, those with impaired glucose tolerance) (36), and this result has been replicated for a number of antidiabetic drugs in individuals at high risk. Among women with PCOS who use metformin, glucose tolerance improves or stays steady over time (55). Metformin also may be associated with weight loss, but results are inconsistent (52). Metformin is often used in conjunction with lifestyle therapy to treat PCOS. Recent studies suggest that there is little benefit to the addition of metformin above lifestyle therapy alone (56, 57).

Metformin carries a small risk of lactic acidosis, most commonly among women with poorly controlled diabetes and impaired renal function. Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common adverse reactions and may be ameliorated by starting at a small dose and gradually increasing the dose or by using the sustained-release version now available in the United States. The dose most commonly used to treat women with PCOS is 1,500–2,000 mg per day given in divided doses.

Currently, data are insufficient to recommend insulin-sensitizing agents prophylactically to prevent diabetes in women with PCOS. However, results of diabetes prevention trials may favor more aggressive management when impaired glucose tolerance or metabolic syndrome is present to prevent diabetes.

### **Statins**

Another area where there is emerging support in the literature for a cardiovascular and endocrine benefit in women with PCOS, is the use of statins (58). However, their long-term effects in preventing cardiovascular disease in young women, especially adolescent girls, with PCOS, is unknown.

### **Combined Hormonal Contraceptives and Progestins**

There is no convincing evidence to demonstrate an increased risk of adverse effects of combined hormonal contraceptives and progestins on diabetes and cardiovascular risk in women with PCOS and, therefore, these agents may be considered. In the general population, hormonal contraceptive use has not been associated with an increased risk of developing type 2 diabetes (59). The use of hormonal contraceptives does not appear to contribute to the risk of diabetes in women with PCOS, although there are often adverse effects on insulin sensitivity that may be dose dependent (60, 61). Therefore, a low-dose hormonal contraceptive pill is recommended. Oral contraceptives also may be associated with a significant elevation in circulating triglycerides as well as in high-density lipoprotein (HDL) levels, although these do not appear to progress over time (62). There is no evidence to suggest that women with PCOS experience more cardiovascular events than the general population when they use oral contraceptives, although risk factors for adverse events such as hypertension, obesity, clotting history, and smoking must be considered. The effect of progestins alone on metabolic risk factors varies and is not well understood.

#### **► *In women with PCOS who are attempting to conceive, which methods of ovulation induction are effective?***

There is no evidence-based schema to guide the initial and subsequent choices of ovulation induction methods in women with PCOS. A recent American Society for Reproductive Medicine and European Society of Human Reproduction and Embryology (ASRM/ESHRE) sponsored conference recommended that before any intervention is initiated, preconception counseling should emphasize the importance of lifestyle, especially weight reduction and exercise in overweight women, smoking cessation, and reducing alcohol consumption.

The recommended first-line treatment for ovulation induction remains the antiestrogen clomiphene citrate. If clomiphene citrate use fails to result in pregnancy, the recommended second-line intervention is either exogenous gonadotropins or laparoscopic ovarian surgery (63).

All ovulation induction drugs are associated with an increase in multiple births and related obstetric and neonatal risks such as preterm birth and hypertensive disorders. There is a 10% increased risk of twin gestations with the use of clomiphene citrate and a significantly greater risk with the use of exogenous gonadotropins (63). These rates may be even higher in women with PCOS undergoing ovulation induction (63).

### **Clomiphene Citrate**

Clomiphene citrate has traditionally been the first-line treatment agent for anovulatory women, including those with PCOS, and several multicenter randomized controlled trials have upheld the use of clomiphene as first-line treatment. Six-month live birth rates range from 20–40% depending on the population (64–66). One half of all women who are going to conceive using clomiphene will do so at the 50-mg starting dose, and another 20% will do so at the 100-mg per day dose (67). Most pregnancies will occur within the first six ovulatory cycles, although a constant monthly pregnancy rate was noted suggesting there may continued benefit to longer use (65).

Alternative clomiphene regimens have been developed, including prolonging the period of administration (68), pretreating with oral contraceptives (69), and adding dexamethasone. Dexamethasone as adjunctive therapy with clomiphene citrate has been shown to increase ovulation and pregnancy rates in clomiphene resistant women with PCOS (70).

### **Gonadotropins**

Gonadotropins are frequently used to induce ovulation in women with PCOS for whom clomiphene treatment has failed. Low-dose therapy with gonadotropins offers a higher rate of ovulation and monofollicular development, with a significantly lower risk of ovarian hyperstimulation syndrome (71). This low-dose regimen is recommended when using gonadotropins in women with PCOS (63).

### **Ovarian Drilling**

The value of laparoscopic ovarian drilling with laser or diathermy as a primary treatment for subfertile women with anovulation and PCOS is undetermined (72), and it is primarily recommended as second-line therapy. Neither drilling by laser nor diathermy has any obvious advantage, and there is insufficient evidence to suggest a difference in ovulation or pregnancy rates when drilling is compared with gonadotropin therapy as a secondary treatment (72). Multiple pregnancy rates are reduced in those women who conceive following laparoscopic drilling. In some cases, the fertility benefits of ovarian drilling may be temporary, and adjuvant therapy after drilling with clomiphene or gonadotropins may be necessary (73). The long-term effects of laparoscopic ovarian drilling on ovarian function are unclear. Ovarian drilling does not appear to improve metabolic abnormalities in women with PCOS (74).

### **Aromatase Inhibitors**

Aromatase inhibitors such as letrozole and anastrozole have been proposed as both primary and secondary treatment for ovulation induction and results appear com-

parable to clomiphene from small trials (75). Proposed benefits include oral administration, a shorter half-life than clomiphene, potentially higher implantation rates, and lower multiple pregnancy rates due to monofollicular ovulation. Further study of these agents is needed to verify these claims, and fetal effects need to be more completely monitored. These agents are not approved by the FDA for ovulation induction.

### **Insulin-Sensitizing Agents**

#### ***Metformin***

The use of metformin alone as first-line infertility therapy has not been supported by randomized trials. Clomiphene is approximately three times more effective at achieving live birth compared with metformin. Meta-analysis has suggested there may be an increase in pregnancy rates by adding clomiphene to metformin, particularly in obese women with PCOS compared with use of clomiphene alone (OR, 2.67; 95% CI, 1.45–4.94; number needed to treat, 4.6) (76). Metformin has no known human teratogenic risk or embryonic lethality in humans and appears safe in pregnancy (it is also classified as Pregnancy Category B). There is no solid evidence that metformin use early in pregnancy prevents pregnancy loss, and the randomized trials that stopped drug use after a positive pregnancy test result have shown similar miscarriage rates with metformin as with clomiphene.

#### **► *How effective are the various medical agents in treating hirsutism in women with PCOS?***

Although medical methods improve hirsutism, they do not produce the dramatic results women desire, and treatment is often palliative rather than curative. Laser therapy is increasingly used. In general, combination therapies appear to produce better results than single-agent approaches. Clinical trials of hirsutism, with the exception of eflornithine HCl facial cream, tend to be small, single center, with incomplete assessment of clinical and patient response to treatment. Therefore, there is no clear primary treatment for hirsutism in PCOS.

### **Combined Hormonal Contraceptives**

No combined hormonal contraceptive has been approved by the FDA for the treatment of hirsutism. A number of observational or nonrandomized studies have noted improvement in hirsutism in women with PCOS who use oral contraceptives, but no studies of adequate power confirm their benefit in improving hirsutism in PCOS (77). Few studies have compared outcomes of different types of combined hormonal contraceptives, and no one type of pill has been shown to be superior in treating hir-



sutism in women with PCOS. A number of studies have found additive benefit when oral contraceptives are combined with other treatment modalities, most commonly spironolactone. If a combination hormonal contraceptive is used that contains drospirenone, a progestin with antimineralocorticoid properties, it may be necessary to reduce the dose of spironolactone if used as additional therapy, and evaluate the woman's potassium levels.

### **Antiandrogens**

None of the antiandrogen agents were developed to treat hyperandrogenism in women or are approved by the FDA for that indication. They have been used empirically in women with PCOS. The quality of trials examining hirsutism has been poor. A recent meta-analysis could only include 12 out of 348 eligible trials (78), and found these agents are mildly effective. These compounds primarily antagonize the binding of testosterone and other androgens to the androgen receptor. Androgen antagonism may result in improvements in other metabolic variables such as improvements in body composition and circulating lipid levels (79). All appear to offer some benefit, although the best choice for hirsutism in PCOS is unknown. As a class, antiandrogens are teratogenic and pose a risk of feminization of the external genitalia in a male fetus (ambiguous genitalia) should the patient conceive. Therefore, they are frequently used in combination with oral contraceptives.

### **Spironolactone**

Spironolactone, a diuretic and aldosterone antagonist, also binds to the androgen receptor as an antagonist. It has other mechanisms of action, including inhibition of ovarian and adrenal steroidogenesis, competition for androgen receptors in hair follicles, and direct inhibition of 5- $\alpha$ -reductase activity. The usual dosage is 25–100 mg, twice a day, and the dose is titrated to balance efficacy while avoiding side effects such as orthostatic hypotension. A full clinical effect may take 6 months or more. Approximately 20% of women using spironolactone will experience increased menstrual frequency (80). Because it can cause and exacerbate hyperkalemia, spironolactone should be used cautiously in women with renal impairment. Rarely, exposure has resulted in ambiguous genitalia in male infants.

### **Flutamide**

Flutamide, an androgen-receptor agonist, is another non-steroidal antiandrogen that has been shown to be effective against hirsutism in smaller trials. The most common side effect is dry skin, but its use has been associated with hepatitis in rare cases. The common dosage is 125–250 mg/d. The risk of teratogenicity with this compound is signifi-

cant, and contraception should be used. Flutamide also has been combined with lifestyle and metformin therapy for treatment of PCOS and may have additive effects (79).

### **Finasteride**

Finasteride inhibits both forms of the enzyme 5- $\alpha$ -reductase (type 1, predominantly found in the skin, and type 2, predominantly found in the prostate and reproductive tissues). It is available as a 5-mg tablet for the treatment of prostate cancer and a 1-mg tablet for the treatment of male alopecia. Finasteride is better tolerated than other antiandrogens, with minimal hepatic and renal toxicity; however, it has a well-documented risk for teratogenicity in male fetuses, and adequate contraception should be used.

### **Insulin-Sensitizing Agents**

There are few data to support the efficacy of metformin in the treatment of hirsutism (77). In a proof of concept 44-week study of an insulin sensitizer, only the highest dose of troglitazone (a thiazolidinedione now removed from the market) was found to significantly—although only modestly—improve hirsutism in women with PCOS (51). Studies with better precision and longer duration are needed to detect differences between classes of insulin-sensitizing agents and their long-term benefits. Currently, there is little or no clear benefit to the use of insulin-sensitizing agents (81).

### **Eflornithine**

An inhibitor of the enzyme ornithine decarboxylase, topical eflornithine has been approved by the FDA for treating female facial hirsutism. After 6 months of treatment, approximately 60% of women improved with treatment and one third were considered a clinical success. Success rates did not appear to have been affected by age and prior hair removal techniques, although a higher success rate was observed in white people than other populations (37% versus 22%), although black people did benefit from treatment. The cream is applied twice a day to affected facial areas. Side effects were primarily local with stinging, burning, erythema, and rarely a rash (82).

### **► Is there a role for adjuvant cosmetic management of hirsutism?**

Mechanical hair removal (shaving, plucking, waxing, depilatory creams, electrolysis, and laser vaporization) is often the front line of treatment used by women. There is no evidence that shaving can increase hair follicle density or size of the hair shaft. Plucking can be helpful if tolerated, but care must be taken to avoid folliculitis, pigmentation, and scarring.

Laser treatment has received more formal study than electrolysis as the primary mechanical method for removing excess hair and has been found to be an effective treatment in PCOS (83). Treatment removes hair because follicular melanin absorbs the laser wavelengths of light, which selectively thermally damage the target without damaging surrounding tissue. Women with dark hair and light skin are better candidates, and the approach appears to be most effective during anagen. Because of the skew of hair follicles among varying segments of the hair growth cycle, repeat treatments over time may be necessary (84). Concomitant medical management directed at decreasing androgen levels usually is recommended for excess androgen states, otherwise new vellus hairs will differentiate into terminal hairs, causing recurrence of hirsutism. The addition of eflornithine to laser treatment is superior in the treatment of hirsutism than laser alone (85).

## Summary of Recommendations and Conclusions

*The following recommendations and conclusions are based on good and consistent scientific evidence (Level A):*

- ▶ An increase in exercise combined with dietary change has consistently been shown to reduce diabetes risk comparable to or better than medication.
- ▶ Improving insulin sensitivity with insulin-sensitizing agents is associated with a decrease in circulating androgen levels, improved ovulation rate, and improved glucose tolerance.
- ▶ The recommended first-line treatment for ovulation induction remains the antiestrogen clomiphene citrate.
- ▶ The addition of eflornithine to laser treatment is superior in the treatment of hirsutism than laser alone.

*The following recommendations and conclusions are based on limited and inconsistent scientific evidence (Level B):*

- ▶ Women with a diagnosis of PCOS should be screened for type 2 diabetes and impaired glucose tolerance with a fasting glucose level followed by a 2-hour glucose level after a 75-g glucose load.
- ▶ Women with PCOS should be screened for cardiovascular risk by determination of BMI, fasting lipid

and lipoprotein levels, and metabolic syndrome risk factors.

- ▶ Reduction in body weight has been associated with improved pregnancy rates and decreased hirsutism, as well as improvements in glucose tolerance and lipid levels.
- ▶ There may be an increase in pregnancy rates by adding clomiphene to metformin, particularly in obese women with PCOS.
- ▶ If clomiphene citrate use fails to result in pregnancy, the recommended second-line intervention is either exogenous gonadotropins or laparoscopic ovarian surgery.

*The following recommendations and conclusions are based primarily on consensus and expert opinion (Level C):*

- ▶ Combination low-dose hormonal contraceptives are most frequently used for long-term management and are recommended as the primary treatment of menstrual disorders.
- ▶ Women in groups at higher risk for nonclassical congenital adrenal hyperplasia and a suspected diagnosis of PCOS should be screened to assess the 17-hydroxyprogesterone value.
- ▶ A low-dose regimen is recommended when using gonadotropins in women with PCOS.
- ▶ There is no clear primary treatment for hirsutism in PCOS.

## References

1. Dunaif A, Givens JR, Haseltine FP, Merriam GR, editors. Polycystic ovary syndrome. Boston (MA): Blackwell Scientific Publications; 1992. (Level III)
2. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. *Fertil Steril* 2004;81:19–25. (Level III)
3. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasound assessment of the polycystic ovary: international consensus definitions. *Hum Reprod Update* 2003;9:505–14. (Level III)
4. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. *Androgen Excess Society. J Clin Endocrinol Metab* 2006;91:4237–45. (Level III)
5. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. *Endocr Rev* 1997;18:774–800. (Level III)

6. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. *J Clin Endocrinol Metab* 2004;89:2745–9. (Level II-3)
7. Broekmans FJ, Knauff EA, Valkenburg O, Laven JS, Eijkemans MJ, Fauser BC. PCOS according to the Rotterdam consensus criteria: change in prevalence among WHO-II anovulation and association with metabolic factors. *BJOG* 2006;113:1210–7. (Level III)
8. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update* 2006;12:673–83. (meta-analysis)
9. Lobo RA, Goebelsmann U, Horton R. Evidence for the importance of peripheral tissue events in the development of hirsutism in polycystic ovary syndrome. *J Clin Endocrinol Metab* 1983;57:393–7. (Level II-2)
10. Ehrmann DA, Liljenquist DR, Kasza K, Azziz R, Legro RS, Ghazzi MN. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. PCOS/Troglitazone Study Group. *J Clin Endocrinol Metab* 2006;91:48–53. (Level II-3)
11. Setji TL, Holland ND, Sanders LL, Pereira KC, Diehl AM, Brown AJ. Nonalcoholic steatohepatitis and nonalcoholic fatty liver disease in young women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2006;91: 1741–7. (Level III)
12. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. *J Clin Endocrinol Metab* 2001;86: 517–20. (Level II-2)
13. Hardiman P, Pillay OC, Atiomo W. Polycystic ovary syndrome and endometrial carcinoma [published erratum appears in *Lancet* 2003;362:1082]. *Lancet* 2003;361: 1810–2. (Level III)
14. Jones GL, Hall JM, Balen AH, Ledger WL. Health-related quality of life measurement in women with polycystic ovary syndrome: a systematic review. *Hum Reprod Update* 2008;14:15–25. (Level III)
15. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice guideline. *J Clin Endocrinol Metab* 2008;93:1526–40. (Level III)
16. Waggoner W, Boots LR, Azziz R. Total testosterone and DHEAS levels as predictors of androgen-secreting neoplasms: a populational study. *Gynecol Endocrinol* 1999; 13:394–400. (Level II-3)
17. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. *J Clin Endocrinol Metab* 2007;92:405–13. (Level III)
18. Robinson S, Rodin DA, Deacon A, Wheeler MJ, Clayton RN. Which hormone tests for the diagnosis of polycystic ovary syndrome? *Br J Obstet Gynaecol* 1992; 99:232–8. (Level II-2)
19. New MI, Lorenzen F, Lerner AJ, Kohn B, Oberfield SE, Pollack MS, et al. Genotyping steroid 21-hydroxylase deficiency: hormonal reference data. *J Clin Endocrinol Metab* 1983;57:320–6. (Level III)
20. Azziz R, Hincapie LA, Knochenhauer ES, Dewailly D, Fox L, Boots LR. Screening for 21-hydroxylase-deficient nonclassic adrenal hyperplasia among hyperandrogenic women: a prospective study. *Fertil Steril* 1999;72:915–25. (Level II-2)
21. Pasquali R, Antenucci D, Casimirri F, Venturoli S, Paradisi R, Fabbri R, et al. Clinical and hormonal characteristics of obese amenorrheic hyperandrogenic women before and after weight loss. *J Clin Endocrinol Metab* 1989;68:173–9. (Level II-3)
22. Guzick DS, Wing R, Smith D, Berga SL, Winters SJ. Endocrine consequences of weight loss in obese, hyperandrogenic, anovulatory women. *Fertil Steril* 1994;61: 598–604. (Level I)
23. Clark AM, Thornley B, Tomlinson L, Galletley C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. *Hum Reprod* 1998;13:1502–5. (Level II-3)
24. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. *J Clin Endocrinol Metab* 1999;84:1470–4. (Level II-2)
25. Lindholm A, Bixo M, Bjorn I, Wolner-Hanssen P, Eliasson M, Larsson A, et al. Effect of sibutramine on weight reduction in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial. *Fertil Steril* 2008;89:1221–8. (Level I)
26. Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL. Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. *J Clin Endocrinol Metab* 2005;90:729–33. (Level III)
27. Escobar-Morreale HF, Botella-Carretero JJ, Alvarez-Blasco F, Sancho J, San Millan JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. *J Clin Endocrinol Metab* 2005;90:6364–9. (Level II-3)
28. Kiddy DS, Hamilton-Fairley D, Bush A, Short F, Anyaoku V, Reed MJ, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. *Clin Endocrinol* 1992;36: 105–11. (Level II-2)
29. Harris MI, Eastman RC, Cowie CC, Flegal KM, Eberhardt MS. Comparison of diabetes diagnostic categories in the U.S. population according to the 1997 American Diabetes Association and 1980–1985 World Health Organization diagnostic criteria. *Diabetes Care* 1997;20:1859–62. (Level II-2)
30. Cibula D, Cifkova R, Fanta M, Poledne R, Zivny J, Skibova J. Increased risk of non-insulin dependent diabetes mellitus, arterial hypertension and coronary artery disease in perimenopausal women with a history of the polycystic ovary syndrome. *Hum Reprod* 2000;15:785–9. (Level II-2)

31. Wild S, Pierpoint T, McKeigue P, Jacobs H. Cardiovascular disease in women with polycystic ovary syndrome at long-term follow-up: a retrospective cohort study. *Clin Endocrinol* 2000;52:595–600. (Level II-2)
32. Talbott EO, Zborowski JV, Sutton-Tyrrell K, McHugh-Pemu KP, Guzick DS. Cardiovascular risk in women with polycystic ovary syndrome. *Obstet Gynecol Clin North Am* 2001;28:111–33, vii. (Level III)
33. Legro RS, Kunselman AR, Dodson WC, Dunaif A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. *J Clin Endocrinol Metab* 1999;84:165–9. (Level II-2)
34. Ehrmann DA, Barnes RB, Rosenfield RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. *Diabetes Care* 1999;22:141–6. (Level II-3)
35. Gambineri A, Pelusi C, Manicardi E, Vicennati V, Cacciari M, Morselli-Labate AM, et al. Glucose intolerance in a large cohort of mediterranean women with polycystic ovary syndrome: phenotype and associated factors. *Diabetes* 2004;53:2353–8. (Level II-3)
36. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. Diabetes Prevention Program Research Group. *N Engl J Med* 2002;346:393–403. (Level I)
37. Legro RS, Gnatuk CL, Kunselman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. *J Clin Endocrinol Metab* 2005;90:3236–42. (Level II-2)
38. Talbott E, Clerici A, Berga SL, Kuller L, Guzick D, Detre K, et al. Adverse lipid and coronary heart disease risk profiles in young women with polycystic ovary syndrome: results of a case-control study. *J Clin Epidemiol* 1998; 51:415–22. (Level II-2)
39. Legro RS, Kunselman AR, Dunaif A. Prevalence and predictors of dyslipidemia in women with polycystic ovary syndrome. *Am J Med* 2001;111:607–13. (Level II-2)
40. Solomon CG, Hu FB, Dunaif A, Rich-Edwards J, Willett WC, Hunter DJ, et al. Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. *JAMA* 2001;286:2421–6. (Level II-2)
41. Krentz AJ, von Muhlen D, Barrett-Connor E. Searching for polycystic ovary syndrome in postmenopausal women: evidence of a dose-effect association with prevalent cardiovascular disease. *Menopause* 2007;14:284–92. (Level II-3)
42. Shaw LJ, Bairey Merz CN, Azziz R, Stanczyk FZ, Sopko G, Braunstein GD, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health—National Heart, Lung, and Blood Institute sponsored Women's Ischemia Syndrome Evaluation. *J Clin Endocrinol Metab* 2008;93:1276–84. (Level II-2)
43. Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. *Arterioscler Thromb Vasc Biol* 2000;20:2414–21. (Level II-2)
44. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sheedy PF 2nd, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88: 2562–8. (Level II-3)
45. Talbott EO, Zborowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzick DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2004; 89:5454–61. (Level II-2)
46. Vessey MP, Painter R. Endometrial and ovarian cancer and oral contraceptives—findings in a large cohort study. *Br J Cancer* 1995;71:1340–2. (Level II-2)
47. Hohmann H, Creinin MD. The contraceptive implant. *Clin Obstet Gynecol* 2007;50:907–17. (Level III)
48. Nestler JE, Jakubowicz DJ. Lean women with polycystic ovary syndrome respond to insulin reduction with decreases in ovarian p450c17 alpha activity and serum androgens. *J Clin Endocrinol Metab* 1997;82:4075–9. (Level II-2)
49. Nestler JE, Jakubowicz DJ, Evans WS, Pasquali R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. *N Engl J Med* 1998;338:1876–80. (Level II-1)
50. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published erratum appears in *N Engl J Med* 2007;357:100]. *N Engl J Med* 2007;356:2457–71. (meta-analysis)
51. Azziz R, Ehrmann D, Legro RS, Whitcomb RW, Hanley R, Fereshetian AG, et al. Troglitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double-blind, placebo-controlled trial. PCOS/Troglitazone Study Group. *J Clin Endocrinol Metab* 2001; 86:1626–32. (Level I)
52. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. *BMJ* 2003;327:951–3. (meta-analysis)
53. Shai I, Schwarzfuchs D, Henkin Y, Shahar DR, Witkow S, Greenberg I, et al. Weight loss with a low-carbohydrate, Mediterranean, or low-fat diet. Dietary Intervention Randomized Controlled Trial (DIRECT) Group. *N Engl J Med* 2008;359:229–41. (Level I)
54. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2003;88:812–9. (Level I)
55. Moghetti P, Castello R, Negri C, Tosi F, Perrone F, Caputo M, et al. Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J Clin Endocrinol Metab* 2000;85: 139–46. (Level I)

56. Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. *Hum Reprod* 2006;21:80–9. (Level I)
57. Hoeger K, Davidson K, Kochman L, Cherry T, Kopin L, Guzick DS. The impact of metformin, oral contraceptives, and lifestyle modification on polycystic ovary syndrome in obese adolescent women in two randomized, placebo-controlled clinical trials. *J Clin Endocrinol Metab* 2008;93:4299–306. (Level I)
58. Banaszewska B, Pawelczyk L, Spaczynski RZ, Dziura J, Duleba AJ. Effects of simvastatin and oral contraceptive agent on polycystic ovary syndrome: prospective, randomized, crossover trial. *J Clin Endocrinol Metab* 2007;92:456–61. (Level II-3)
59. Chasan-Taber L, Willett WC, Stampfer MJ, Hunter DJ, Colditz GA, Spiegelman D, et al. A prospective study of oral contraceptives and NIDDM among U.S. women. *Diabetes Care* 1997;20:330–5. (Level II-2)
60. Korytkowski MT, Mookan M, Horwitz MJ, Berga SL. Metabolic effects of oral contraceptives in women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 1995;80:3327–34. (Level II-3)
61. Meyer C, McGrath BP, Teede HJ. Effects of medical therapy on insulin resistance and the cardiovascular system in polycystic ovary syndrome. *Diabetes Care* 2007;30:471–8. (Level I)
62. Falsetti L, Pasinetti E. Effects of long-term administration of an oral contraceptive containing ethinylestradiol and cyproterone acetate on lipid metabolism in women with polycystic ovary syndrome. *Acta Obstet Gynecol Scand* 1995;74:56–60. (Level II-2)
63. Consensus on infertility treatment related to polycystic ovary syndrome. Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group. *Hum Reprod* 2008;23:462–77. (Level III)
64. Moll E, Bossuyt PM, Korevaar JC, Lambalk CB, van der Veen F. Effect of clomifene citrate plus metformin and clomifene citrate plus placebo on induction of ovulation in women with newly diagnosed polycystic ovary syndrome: randomised double blind clinical trial. *BMJ* 2006;332:1485. (Level I)
65. Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. Cooperative Multicenter Reproductive Medicine Network. *N Engl J Med* 2007;356:551–66. (Level I)
66. Zain MM, Jamaluddin R, Ibrahim A, Norman RJ. Comparison of clomiphene citrate, metformin, or the combination of both for first-line ovulation induction, achievement of pregnancy, and live birth in Asian women with polycystic ovary syndrome: a randomized controlled trial. *Fertil Steril* 2009;91:514–21. (Level I)
67. Gysler M, March CM, Mishell DR Jr, Bailey EJ. A decade's experience with an individualized clomiphene treatment regimen including its effect on the postcoital test. *Fertil Steril* 1982;37:161–7. (Level II-3)
68. Lobo RA, Granger LR, Davajan V, Mishell DR Jr. An extended regimen of clomiphene citrate in women unresponsive to standard therapy. *Fertil Steril* 1982;37:762–6. (Level II-3)
69. Branigan EF, Estes MA. A randomized clinical trial of treatment of clomiphene citrate-resistant anovulation with the use of oral contraceptive pill suppression and repeat clomiphene citrate treatment. *Am J Obstet Gynecol* 2003;188:1424–8; discussion 1429–30. (Level I)
70. Elnashar A, Abdelmageed E, Fayed M, Sharaf M. Clomiphene citrate and dexamethazone in treatment of clomiphene citrate-resistant polycystic ovary syndrome: a prospective placebo-controlled study. *Hum Reprod* 2006;21:1805–8. (Level I)
71. Christin-Maitre S, Hugues JN. A comparative randomized multicentric study comparing the step-up versus step-down protocol in polycystic ovary syndrome. Recombinant FSH Study Group. *Hum Reprod* 2003;18:1626–31. (Level I)
72. Farquhar C, Lilford R, Marjoribanks J, Vanderkerckhove P. Laparoscopic 'drilling' by diathermy or laser for ovulation induction in anovulatory polycystic ovary syndrome. *Cochrane Database of Systematic Reviews* 2007, Issue 3. Art. No.: CD001122. DOI: 10.1002/14651858.CD001122.pub3. (meta-analysis)
73. Bayram N, van Wely M, Kaaijk EM, Bossuyt PM, van der Veen F. Using an electrocautery strategy or recombinant follicle stimulating hormone to induce ovulation in polycystic ovary syndrome: randomised controlled trial. *BMJ* 2004;328:192. (Level I)
74. Lemieux S, Lewis GF, Ben-Chetrit A, Steiner G, Greenblatt EM. Correction of hyperandrogenemia by laparoscopic ovarian cautery in women with polycystic ovarian syndrome is not accompanied by improved insulin sensitivity or lipid-lipoprotein levels. *J Clin Endocrinol Metab* 1999;84:4278–82. (Level II-2)
75. Casper RF. Letrozole versus clomiphene citrate: which is better for ovulation induction? *Fertil Steril* 2007;DOI: 10.1016/j.fertnstert.2007.03.094. (Level III)
76. Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of metformin in polycystic ovary syndrome: a meta-analysis. *Obstet Gynecol* 2008;111:959–68. (meta-analysis)
77. Costello MF, Shrestha B, Eden J, Johnson NP, Sjoblom P. Metformin versus oral contraceptive pill in polycystic ovary syndrome: a Cochrane review. *Hum Reprod* 2007;22:1200–9. (meta-analysis)
78. Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, et al. Clinical review: antiandrogens for the treatment of hirsutism: a systematic review and meta-analyses of randomized controlled trials. *J Clin Endocrinol Metab* 2008;93:1153–60. (meta-analysis)
79. Gambineri A, Patton L, Vaccina A, Cacciari M, Morselli-Labate AM, Cavazza C, et al. Treatment with flutamide, metformin, and their combination added to a hypocaloric diet in overweight-obese women with polycystic ovary syndrome: a randomized, 12-month, placebo-controlled study. *J Clin Endocrinol Metab* 2006;91:3970–80. (Level I)

80. Helfer EL, Miller JL, Rose LI. Side-effects of spironolactone therapy in the hirsute woman. *J Clin Endocrinol Metab* 1988;66:208–11. (Level III)
81. Cosma M, Swiglo BA, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, et al. Clinical review: insulin sensitizers for the treatment of hirsutism: a systematic review and meta-analyses of randomized controlled trials. *J Clin Endocrinol Metab* 2008;93:1135–42. (meta-analysis)
82. Wolf JE Jr, Shander D, Huber F, Jackson J, Lin CS, Mathes BM, et al. Randomized, double-blind clinical evaluation of the efficacy and safety of topical eflornithine HCl 13.9% cream in the treatment of women with facial hair. Eflornithine HCl Study Group. *Int J Dermatol* 2007;46:94–8. (Level III)
83. Clayton WJ, Lipton M, Elford J, Rustin M, Sherr L. A randomized controlled trial of laser treatment among hirsute women with polycystic ovary syndrome. *Br J Dermatol* 2005;152:986–92. (Level I)
84. Sanchez LA, Perez M, Azziz R. Laser hair reduction in the hirsute patient: a critical assessment. *Hum Reprod Update* 2002;8:169–81. (Level III)
85. Smith SR, Piacquadio DJ, Beger B, Littler C. Eflornithine cream combined with laser therapy in the management of unwanted facial hair growth in women: a randomized trial. *Dermatol Surg* 2006;32:1237–43. (Level I)

The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and February 2009. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician–gynecologists were used.

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.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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**The American College of Obstetricians and Gynecologists**  
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Polycystic ovary syndrome. ACOG Practice Bulletin No. 108. American College of Obstetricians and Gynecologists. *Obstet Gynecol* 2009;114:936–49.