Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline

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Objective: The aim was to formulate practice guidelines for the diagnosis and treatment of polycystic ovary syndrome (PCOS).

Participants: An Endocrine Society-appointed Task Force of experts, a methodologist, and a medical writer developed the guideline.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe both the strength of recommendations and the quality of evidence.

Consensus Process: One group meeting, several conference calls, and e-mail communications enabled consensus. Committees and members of The Endocrine Society and the European Society of Endocrinology reviewed and commented on preliminary drafts of these guidelines. Two systematic reviews were conducted to summarize supporting evidence.

Conclusions: We suggest using the Rotterdam criteria for diagnosing PCOS (presence of two of the following criteria: androgen excess, ovulatory dysfunction, or polycystic ovaries). Establishing a diagnosis of PCOS is problematic in adolescents and menopausal women. Hyperandrogenism is central to the presentation in adolescents, whereas there is no consistent phenotype in postmenopausal women. Evaluation of women with PCOS should exclude alternate androgen-excess disorders and risk factors for endometrial cancer, mood disorders, obstructive sleep apnea, diabetes, and cardiovascular disease. Hormonal contraceptives are the first-line management for menstrual abnormalities and hirsutism/acne in PCOS. Clomiphene is currently the first-line therapy for infertility; metformin is beneficial for metabolic/glycemic abnormalities and for improving menstrual irregularities, but it has limited or no benefit in treating hirsutism, acne, or infertility. Hormonal contraceptives and metformin are the treatment options in adolescents with PCOS. The role of weight loss in improving PCOS status per se is uncertain, but lifestyle intervention is beneficial in overweight/obese patients for other health benefits. Thiazolidinediones have an unfavorable risk-benefit ratio overall, and statins require further study. **(*J Clin Endocrinol Metab* 98: 4565–4592, 2013)**

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Abbreviations: BMI, body mass index; CI, confidence interval; DM, diabetes mellitus; HC, hormonal contraceptive; HDL, high-density lipoprotein; HgbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; IR, insulin resistance; IVF, in vitro fertilization; LDL, low-density lipoprotein; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; OGTT, oral glucose tolerance test; 17-OHP, 17-hydroxyprogesterone; OHSS, ovarian hyperstimulation syndrome; OR, odds ratio; OSA, obstructive sleep apnea; PCO, polycystic ovary (or ovaries); PCOS, polycystic ovary syndrome; RR, relative risk; T2DM, type 2 DM.

Summary of Recommendations

1.0 Diagnosis of PCOS

Diagnosis in adults

1.1 We suggest that the diagnosis of polycystic ovary syndrome (PCOS) be made if two of the three following criteria are met: androgen excess, ovulatory dysfunction, or polycystic ovaries (PCO) (Tables 1 and 2), whereas disorders that mimic the clinical features of PCOS are excluded. These include, in all women: thyroid disease, hyperprolactinemia, and nonclassic congenital adrenal hyperplasia (primarily 21-hydroxylase deficiency by serum 17-hydroxyprogesterone [17-OHP]) (Table 3). In select women with amenorrhea and more severe phenotypes, we suggest more extensive evaluation excluding other causes (Table 4) (2|⊕⊕⊕◯).

Diagnosis in adolescents

1.2 We suggest that the diagnosis of PCOS in an adolescent girl be made based on the presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of persistent oligomenorrhea. Anovulatory symptoms and PCO morphology are not sufficient to make a diagnosis in adolescents, as they may be evident in normal stages in reproductive maturation (2|⊕⊕◯◯).

Diagnosis in perimenopause and menopause

1.3 Although there are currently no diagnostic criteria for PCOS in perimenopausal and menopausal women, we suggest that a presumptive diagnosis of PCOS can be based upon a well-documented long-term history of oligomenorrhea and hyperandrogenism during the reproductive years. The presence of PCO morphology on ultrasound would provide additional supportive evidence, although this is less likely in a menopausal woman (2|⊕⊕◯◯).

2.0 Associated morbidity and evaluation

Cutaneous manifestations

2.1 We recommend that a physical examination should document cutaneous manifestations of PCOS: terminal hair growth (see hirsutism guidelines, Ref. 1), acne, alopecia, acanthosis nigricans, and skin tags (1|⊕⊕⊕◯).

Infertility

2.2 Women with PCOS are at increased risk of anovulation and infertility; in the absence of anovulation, the risk of infertility is uncertain. We recommend screening ovulatory status using menstrual history in all women with PCOS seeking fertility. Some women with PCOS and a eumenorrheic menstrual history may still experience anovulation and a midluteal serum progesterone may be helpful as an additional screening test (1|⊕⊕◯◯).

2.3 We recommend excluding other causes of infertility, beyond anovulation, in couples where a woman has PCOS (1|⊕⊕◯◯).

Pregnancy complications

2.4 Because women with PCOS are at increased risk of pregnancy complications (gestational diabetes, preterm

Table 1. Summary of Proposed Diagnostic Criteria for PCOS in Adults

Category	Specific Abnormality	Recommended Test	NIH	Rotterdam (2 of 3 Met)	Androgen Excess PCOS Society (Hyper-Androgenism With 1 of 2 Remaining Criteria)
Androgen status	Clinical hyperandrogenism[a]	Clinical hyperandrogenism may include hirsutism (defined as excessive terminal hair that appears in a male pattern) (1, 295), acne, or androgenic alopecia.	XX	X	XX
			or	or	or
	Biochemical hyperandrogenism[a]	Biochemical hyperandrogenism refers to an elevated serum androgen level and typically includes an elevated total, bioavailable, or free serum T level. Given variability in T levels and the poor standardization of assays (31), it is difficult to define an absolute level that is diagnostic of PCOS or other causes of hyperandrogenism, and the Task Force recommends familiarity with local assays.	XX	X	XX
Menstrual history	Oligo- or anovulation	Anovulation may manifest as frequent bleeding at intervals <21 d or infrequent bleeding at intervals >35 d. Occasionally, bleeding may be anovulatory despite falling at a normal interval (25–35 d). A midluteal progesterone documenting anovulation may help with the diagnosis if bleeding intervals appear to suggest regular ovulation.	XX	X	X
Ovarian appearance	Ovarian size/morphology on ultrasound	The PCO morphology has been defined by the presence of 12 or more follicles 2–9 mm in diameter and/or an increased ovarian volume >10 mL (without a cyst or dominant follicle) in either ovary (78).		X	X

The Task Force suggests using the Rotterdam criteria for the diagnosis of PCOS, acknowledging the limitations of each of the three criteria (Table 2). All criteria require exclusion of other diagnoses (listed in Table 3) that cause the same symptoms and/or signs (6–9). X, may be present for diagnosis; XX, must be present for diagnosis.

[a] Clinical or biochemical hyperandrogenism is included as one criterion in all classification systems. If clinical hyperandrogenism is present with the absence of virilization, then serum androgens are not necessary for the diagnosis. Similarly, when a patient has signs of hyperandrogenism and ovulatory dysfunction, an ovarian ultrasound is not necessary.

Table 2. Diagnostic Strengths and Weaknesses of the Main Features of PCOS as Adapted from the NIH Evidence-Based Methodology Workshop on PCOS

Diagnostic Criteria	Strength	Limitation
Hyperandrogenism	Included as a component in all major classifications	Measurement is performed only in blood
	A major clinical concern for patients	Concentrations differ during time of day
	Animal models employing androgen excess resembling but not fully mimicking human disease	Concentrations differ with age Normative data are not clearly defined Assays are not standardized across laboratories Clinical hyperandrogenism is difficult to quantify and may vary by ethnic group, eg, low rates of hirsutism in women with PCOS from east Asia Tissue sensitivity is not assessed
Ovulatory dysfunction	Included as a component in all major classifications	Normal ovulation is poorly defined
	A major clinical concern for patients	Normal ovulation varies over a woman's lifetime
	Infertility a common clinical complaint	Ovulatory dysfunction is difficult to measure objectively Anovulatory cycles may have bleeding patterns that are interpreted as normal
PCO morphology	Historically associated with syndrome	Technique dependent
	May be associated with hypersensitivity to ovarian stimulation	Difficult to obtain standardized measurement Lack of normative standards across the menstrual cycle and lifespan (notably in adolescence) May be present in other disorders that mimic PCOS Technology required to accurately image not universally available Transvaginal imaging possibly inappropriate in certain circumstances (eg, adolescence) or certain cultures

delivery, and pre-eclampsia) exacerbated by obesity, we recommend preconceptual assessment of body mass index (BMI), blood pressure, and oral glucose tolerance (1|⊕⊕⊕◯).

Fetal origins

2.5 The evidence for intrauterine effects on development of PCOS is inconclusive. We suggest no specific interventions for prevention of PCOS in offspring of women with PCOS (2|⊕◯◯◯).

Endometrial cancer

2.6 Women with PCOS share many of the risk factors associated with the development of endometrial cancer including obesity, hyperinsulinism, diabetes, and abnormal uterine bleeding. However, we suggest against routine ultrasound screening for endometrial thickness in women with PCOS (2|⊕⊕⊕◯).

Obesity

2.7 Increased adiposity, particularly abdominal, is associated with hyperandrogenemia and increased metabolic risk (see cardiovascular disease prevention guidelines, Ref. 2). Therefore, we recommend screening adolescents and women with PCOS for increased adiposity, by BMI calculation and measurement of waist circumference (1|⊕⊕⊕◯).

Depression

2.8 We suggest screening women and adolescents with PCOS for depression and anxiety by history and, if identified, providing appropriate referral and/or treatment (2|⊕⊕◯◯).

Sleep-disordered breathing/obstructive sleep apnea (OSA)

2.9 We suggest screening overweight/obese adolescents and women with PCOS for symptoms suggestive of OSA and, when identified, obtaining a definitive diagnosis using polysomnography. If OSA is diagnosed, patients should be referred for institution of appropriate treatment (2|⊕⊕◯◯).

Nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH)

2.10 We suggest awareness of the possibility of NAFLD and NASH but recommend against routine screening (2|⊕⊕◯◯).

Table 3. Other Diagnoses to Exclude in All Women Before Making a Diagnosis of PCOS

Disorder	Test	Abnormal Values	Reference for Further Evaluation and Treatment of Abnormal Findings; First Author, Year (Ref.)
Thyroid disease	Serum TSH	TSH > the upper limit of normal suggests hypothyroidism; TSH < the lower limit, usually < 0.1 mIU/L, suggests hyperthyroidism	Ladenson, 2000 (10)
Prolactin excess	Serum prolactin	> Upper limit of normal for the assay	Melmed, 2011 (11)
Nonclassical congenital adrenal hyperplasia	Early morning (before 8 AM) serum 17-OHP	200–400 ng/dL depending on the assay (applicable to the early follicular phase of a normal menstrual cycle as levels rise with ovulation), but a cosyntropin stimulation test (250 μg) is needed if levels fall near the lower limit and should stimulate 17-OHP > 1000 ng/dL	Speiser, 2010 (12)

Table 4. Diagnoses to Consider Excluding in Select Women, Depending on Presentation

Other Diagnoses[a]	Suggestive Features in the Presentation	Tests to Assist in the Diagnosis	Reference for Further Evaluation and Treatment of Abnormal Findings; First Author, Year (Ref.)
Pregnancy	Amenorrhea (as opposed to oligomenorrhea), other signs and symptoms of pregnancy including breast fullness, uterine cramping, etc	Serum or urine hCG (positive)	Morse, 2011 (17)
HA including functional HA	Amenorrhea, clinical history of low body weight/BMI, excessive exercise, and a physical exam in which signs of androgen excess are lacking; multifollicular ovaries are sometimes present	Serum LH and FSH (both low to low normal), serum estradiol (low)	Wang, 2008 (18)
Primary ovarian insufficiency	Amenorrhea combined with symptoms of estrogen deficiency including hot flashes and urogenital symptoms	Serum FSH (elevated), serum estradiol (low)	Nelson, 2009 (296)
Androgen-secreting tumor	Virilization including change in voice, male pattern androgenic alopecia, and clitoromegaly; rapid onset of symptoms	Serum T and DHEAS levels (markedly elevated), ultrasound imaging of ovaries, MRI of adrenal glands (mass or tumor present)	Carmina, 2006 (16)
Cushing's syndrome	Many of the signs and symptoms of PCOS can overlap with Cushing's (ie, striae, obesity, dorsocervical fat (ie, buffalo hump, glucose intolerance); however, Cushing's is more likely to be present when a large number of signs and symptoms, especially those with high discriminatory index (eg, myopathy, plethora, violaceous striae, easy bruising) are present, and this presentation should lead to screening	24-h urinary collection for urinary free cortisol (elevated), late night salivary cortisol (elevated), overnight dexamethasone suppression test (failure to suppress morning serum cortisol level)	Nieman, 2008 (19)
Acromegaly	Oligomenorrhea and skin changes (thickening, tags, hirsutism, hyperhidrosis) may overlap with PCOS. However, headaches, peripheral vision loss, enlarged jaw (macrognathia), frontal bossing, macroglossia, increased shoe and glove size, etc, are indications for screening	Serum free IGF-1 level (elevated), MRI of pituitary (mass or tumor present)	Melmed, 2009 (20)

Abbreviations: DHEAS, dehydroepiandrosterone sulfate; HA, hypothalamic amenorrhea; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging.

[a] Additionally there are very rare causes of hyperandrogenic chronic anovulation that are not included in this table because they are so rare, but they must be considered in patients with an appropriate history. These include other forms of congenital adrenal hyperplasia (eg, 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase), related congenital disorders of adrenal steroid metabolism or action (eg, apparent/cortisone reductase deficiency, apparent DHEA sulfotransferase deficiency, glucocorticoid resistance), virilizing congenital adrenal hyperplasia (adrenal rests, poor control, fetal programming), syndromes of extreme IR, drugs, portohepatic shunting, and disorders of sex development.

Type 2 diabetes mellitus (T2DM)

2.11 We recommend the use of an oral glucose tolerance test (OGTT) (consisting of a fasting and 2-hour glucose level using a 75-g oral glucose load) to screen for impaired glucose tolerance (IGT) and T2DM in adolescents and adult women with PCOS because they are at high risk for such abnormalities (1|⊕⊕⊕◯). A hemoglobin A1c (HgbA1c) test may be considered if a patient is unable or unwilling to complete an OGTT (2|⊕⊕◯◯). Rescreening is suggested every 3–5 years, or more frequently if clinical factors such as central adiposity, substantial weight gain, and/or symptoms of diabetes develop (2|⊕⊕◯◯).

Table 5. Cardiovascular Risk Stratification in Women with PCOS

At risk—PCOS women with any of the following risk factors:
- Obesity (especially increased abdominal adiposity)
- Cigarette smoking
- Hypertension
- Dyslipidemia (increased LDL-cholesterol and/or non-HDL-cholesterol)
- Subclinical vascular disease
- Impaired glucose tolerance
- Family history of premature cardiovascular disease (<55 y of age in male relative; <65 y of age in female relative)

At high risk–PCOS women with:
- Metabolic syndrome
- T2DM
- Overt vascular or renal disease, cardiovascular diseases
- OSA

The Androgen Excess and Polycystic Ovary Syndrome Society relied upon evidence-based studies and concluded that women with PCOS be stratified as being either at risk or at high risk for cardiovascular disease using the criteria shown (167).

Cardiovascular risk

2.12 We recommend that adolescents and women with PCOS be screened for the following cardiovascular disease risk factors (Table 5): family history of early cardiovascular disease, cigarette smoking, IGT/T2DM, hypertension, dyslipidemia, OSA, and obesity (especially increased abdominal adiposity) (1|⊕⊕◯◯).

3.0 Treatment

Hormonal contraceptives (HCs): indications and screening

3.1 We recommend HCs (ie, oral contraceptives, patch, or vaginal ring) as first-line management for the menstrual abnormalities and hirsutism/acne of PCOS (refer to hirsutism guidelines in Ref. 1, recommendation 2.1.1), which treat these two problems concurrently (1|⊕⊕◯◯).

3.2 We recommend screening for contraindications to HC use via established criteria (see Table 6 and Ref. 3) (1|⊕⊕⊕◯). For women with PCOS, we do not suggest one HC formulation over another (2|⊕⊕◯◯).

Role of exercise in lifestyle therapy

3.3 We suggest the use of exercise therapy in the management of overweight and obesity in PCOS (2|⊕⊕◯◯).

Table 6. Considerations for Use of Combined HCs, Including Pill, Patch, and Vaginal Ring, in Women with PCOS Based on Relevant Conditions

		Conditions			
Criteria	**Further Classification**	**1**	**2**	**3**	**4**
		A condition for which there is no restriction for the use of the contraceptive method	A condition for which the advantages of using the method generally outweigh the theoretical or proven risks	A condition for which the theoretical or proven risks usually outweigh the advantages of using the method	A condition that represents an unacceptable health risk if the contraceptive method is used
Age	Menarche to <40 y	X			
	>40 y		X		
Smoking	Age ≥35 y		X		
	Age ≥35 y and smokes <15 cigarettes/d			X	
	Age ≥35 y and smokes ≥15 cigarettes/d				X
Obesity	BMI <30 kg/m^2		X		
	BMI ≥30 kg/m^2		X		
Hypertension	History of gestational hypertension	X			
	Adequately controlled hypertension			X	
	Elevated blood pressure levels (properly taken measurements): systolic, 140–159 mm Hg; or diastolic, 90–99 mm Hg			X	
	Elevated blood pressure levels (properly taken measurements): systolic, ≥160 mm Hg; or diastolic, ≥100 mm Hg				X
Dyslipidemia	Known hyperlipidemias		X	X	
Depression	Depressive disorders	X			
Unexplained vaginal bleeding (suspicious for serious condition)	Before evaluation[a]		X		
Diabetes	History of gestational diabetes		X		
	Nonvascular diabetes, insulin or non-insulin dependent		X		
	Vascular disease including neuropathy, retinopathy, nephropathy[b]			X	X
	Diabetes duration >20 y[b]			X	X

The boxes indicate the recommendation for the condition. The four possible recommendations are a spectrum ranging from condition 1, which favors the use of the pill, to condition 4, which discourages the use of the pill. [Adapted from: US Medical Eligibility Criteria for Contraceptive Use. *MMWR Recomm Rep*. 2010;59:1–86 (3), with permission. © Centers for Disease Control and Prevention.]

[a] If pregnancy or an underlying pathological condition (such as pelvic malignancy) is suspected, it must be evaluated and the category adjusted after evaluation.

[b] The category should be assessed according to the severity of the condition.

Although there are no large randomized trials of exercise in PCOS, exercise therapy, alone or in combination with dietary intervention, improves weight loss and reduces cardiovascular risk factors and diabetes risk in the general population.

Role of weight loss in lifestyle therapy

3.4 We suggest that weight loss strategies begin with calorie-restricted diets (with no evidence that one type of diet is superior) for adolescents and women with PCOS who are overweight or obese (2|⊕⊕◯◯). Weight loss is likely beneficial for both reproductive and metabolic dysfunction in this setting. Weight loss is likely insufficient as a treatment for PCOS in normal-weight women.

Use of metformin

3.5 We suggest against the use of metformin as a first-line treatment of cutaneous manifestations, for prevention of pregnancy complications, or for the treatment of obesity (2|⊕⊕◯◯).

3.6 We recommend metformin in women with PCOS who have T2DM or IGT who fail lifestyle modification (1|⊕⊕⊕◯). For women with PCOS with menstrual irregularity who cannot take or do not tolerate HCs, we suggest metformin as second-line therapy (2|⊕⊕⊕◯).

Treatment of infertility

3.7 We recommend clomiphene citrate (or comparable estrogen modulators such as letrozole) as the first-line treatment of anovulatory infertility in women with PCOS (1|⊕⊕⊕◯).

3.8 We suggest the use of metformin as an adjuvant therapy for infertility to prevent ovarian hyperstimulation syndrome (OHSS) in women with PCOS undergoing in vitro fertilization (IVF) (2|⊕⊕◯◯).

Use of other drugs

3.9 We recommend against the use of insulin sensitizers, such as inositols (due to lack of benefit) or thiazolidinediones (given safety concerns), for the treatment of PCOS (1|⊕⊕⊕◯).

3.10 We suggest against the use of statins for treatment of hyperandrogenism and anovulation in PCOS until additional studies demonstrate a favorable risk-benefit ratio

(2|⊕⊕◯◯). However, we suggest statins in women with PCOS who meet current indications for statin therapy (2|⊕⊕◯◯).

Treatment of adolescents

3.11 We suggest HCs as the first-line treatment in adolescents with suspected PCOS (if the therapeutic goal is to treat acne, hirsutism, or anovulatory symptoms, or to prevent pregnancy) (2|⊕⊕◯◯). We suggest that lifestyle therapy (calorie-restricted diet and exercise) with the objective of weight loss should also be first-line treatment in the presence of overweight/obesity (2|⊕⊕◯◯). We suggest metformin as a possible treatment if the goal is to treat IGT/metabolic syndrome (2|⊕⊕◯◯). The optimal duration of HC or metformin use has not yet been determined.

3.12 For premenarchal girls with clinical and biochemical evidence of hyperandrogenism in the presence of advanced pubertal development (ie, ≥ Tanner stage IV breast development), we suggest starting HCs (2|⊕⊕◯◯).

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee of The Endocrine Society deemed the diagnosis and treatment of PCOS a priority area in need of practice guidelines and appointed a Task Force to formulate evidence-based recommendations. The Task Force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group, an international group with expertise in development and implementation of evidence-based guidelines (4). A detailed description of the grading scheme has been published elsewhere (5). The Task Force used the best available research evidence to develop the recommendations. The Task Force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The Task Force has confidence that persons who receive care according to the strong recommendations will derive, on average, more good than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each *recommendation* is a description of the *evidence* and the *values* that panelists considered in making the recommendation; in some instances, there are *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the panelists and their values and preferences; therefore, these remarks are considered.

The Endocrine Society maintains a rigorous conflict of interest review process for the development of clinical practice guidelines. All Task Force members must declare any potential conflicts of interest, which are reviewed before they are approved to serve on the Task Force and periodically during the development of the guideline. The conflict of interest forms are vetted by the Clinical Guidelines Subcommittee (CGS) before the members are approved by the Society's Council to participate on the guideline Task Force. Participants in the guideline development must include a majority of individuals without conflict of interest in the matter under study. Participants with conflicts of interest may participate in the development of the guideline, but they must have disclosed all conflicts. The CGS and the Task Force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined by remuneration in any amount from the commercial interest(s) in the form of grants; research support; consulting fees; salary; ownership interest (eg, stocks, stock options, or ownership interest excluding diversified mutual funds); honoraria or other payments for participation in speakers' bureaus, advisory boards, or boards of directors; or other financial benefits. Completed forms are available through The Endocrine Society office.

Funding for this guideline was derived solely from The Endocrine Society, and thus the Task Force received no funding or remuneration from commercial or other entities.

1.0 Diagnosis of PCOS

Diagnosis in adults

1.1 We suggest that the diagnosis of PCOS be made if two of the three following criteria are met: androgen excess, ovulatory dysfunction, or PCO (Tables 1 and 2), whereas disorders that mimic the clinical features of PCOS are excluded. These include, in all women: thyroid disease, hyperprolactinemia, and nonclassic congenital adrenal hyperplasia (primarily 21-hydroxylase deficiency by serum 17-OHP) (Table 3). In select women with amenorrhea and more severe phenotypes, we suggest more extensive evaluation excluding other causes (Table 4) (2|⊕⊕⊕◯).

1.1 Evidence

PCOS is a common disorder with systemic metabolic manifestations. Its etiology is complex, heterogeneous, and poorly understood. There are three definitions for PCOS currently in use that variably rely on androgen excess, chronic anovulation, and PCO to make the diagnosis (Table 1). However, all criteria are consistent in that PCOS is considered a diagnosis of exclusion. All three sets of diagnostic criteria include hyperandrogenism, either clinical or biochemical, and anovulation (6–9). The Rotterdam criteria were the first to incorporate ovarian morphology on ultrasound as part of the diagnostic criteria (8, 9).

The panel from a recent National Institutes of Health (NIH)-sponsored Evidence-Based Methodology workshop on PCOS endorsed the Rotterdam criteria, although they identified the strengths and weaknesses of each of the three cardinal features (Table 2). These criteria allow the diagnosis to be made clinically (based upon a history of hyperandrogenic chronic anovulation) as well as biochemically with androgen assays or with ultrasound examination of the ovaries. We do not endorse the need for universal screening with androgen assays or ultrasound if patients already meet two of the three criteria clinically. It is recommended that the features leading to the diagnosis are documented. We recommend using the current definition of the Rotterdam criteria to document PCO morphology (at least one ovary with 12 follicles of 2–9 mm or a volume >10 mL in the absence of a dominant follicle >10 mm), in the absence of age-based criteria.

Disorders that mimic PCOS are comparatively easy to exclude; therefore, all women should be screened with a TSH, prolactin, and 17-OHP level (Table 3) (10–12). Hyperprolactinemia can present with amenorrhea or hirsutism (13, 14). Thyroid disease may present with irregular menstrual cycles. In women with hyperandrogenism, nonclassic congenital adrenal hyperplasia should be excluded because it can be found in 1.5–6.8% of patients presenting with androgen excess (15, 16). In select women who present with amenorrhea, virilization, or physical findings not associated with PCOS, such as proximal muscle weakness (Cushing's syndrome) or frontal bossing (acromegaly), other diagnoses should be considered and excluded (Table 4).

1.1 Values and preferences

In the absence of evidence-based diagnostic criteria, we have relied on the recommendations of the NIH Panel as noted above. The presence of specific phenotypic features may result in different risk and comorbidity profiles. For example, hyperandrogenism may be more highly associated with metabolic abnormalities, whereas irregular menses and PCO morphology may be more highly associated with infertility. When interpreting published research, clinicians should note that criteria different from their own may be used when performing research. The committee notes that the diagnosis of PCOS is problematic in women who are perimenarchal or perimenopausal because amenorrhea and oligomenorrhea are natural stages in reproductive maturation and senescence, as are changes in circulating androgens and ovarian morphology. Therefore, we discuss the diagnosis of PCOS separately in these groups. Finally, because there is evidence of a genetic component to PCOS and familial clustering of reproductive and metabolic abnormalities in male and female relatives, a careful family history should be taken, and further screening of first-degree relatives is a consideration.

Diagnosis in adolescents

1.2 We suggest that the diagnosis of PCOS in an adolescent girl be made based on the presence of clinical and/or biochemical evidence of hyperandrogenism (after exclusion of other pathologies) in the presence of persistent oligomenorrhea. Anovulatory symptoms and PCO morphology are not sufficient to make a diagnosis in adolescents because they may be evident in normal stages in reproductive maturation (2|⊕⊕○○).

1.2 Evidence

All PCOS diagnostic criteria were derived for adults (Table 1), not adolescents. Furthermore, normal adolescent physiology may mimic symptoms of PCOS. Oligomenorrhea is common after menarche during normal puberty and is therefore not specific to adolescents with PCOS. Anovulatory cycles comprise 85% of menstrual cycles in the first year after menarche, 59% in the third year, and 25% by the sixth year. Anovulatory cycles are associated with higher serum androgen and LH levels (21). Approximately two-thirds of adolescents with PCOS will have menstrual symptoms, and for one-third it will be the presenting symptom, with the spectrum from primary amenorrhea to frequent dysfunctional bleeding (22). Therefore, it is appropriate to evaluate persistent oligomenorrhea or amenorrhea as an early clinical sign of PCOS, especially when it persists 2 years beyond menarche (23).

Acne is common although transitory during adolescence (24); thus, it should not be used in isolation to define hyperandrogenism in adolescents (25). Hirsutism may develop slowly and thus be less severe in adolescents than in adults due to the shorter exposure to hyperandrogenism (26). However, hirsutism was a major symptom in about 60% of adolescents in one study (27) and may be suggestive of PCOS in adolescents (28). The Ferriman-Gallwey hirsutism score was standardized only in adult Caucasians and may have a lower cut-point in adolescents (29). An-

drogenic alopecia has not been studied in adolescents and should be viewed cautiously in diagnosing PCOS (25).

There is a lack of well-defined cutoff points for androgen levels during normal pubertal maturation (30), as well as the lack of T assay standardization (31). Furthermore, hyperandrogenemia appears to be exacerbated by obesity because a significant proportion of obese girls have elevated androgen levels across puberty compared with normal-weight girls (32). Hyperandrogenemia during puberty may be associated with infertility in later life (33), and adult cutoffs should be used until appropriate pubertal levels are defined.

Lastly, the Rotterdam ultrasound PCO criteria were not validated for adolescents. Recommending a transvaginal ovarian ultrasound in this group raises practical and ethical concerns. Transabdominal ultrasound, already limited in evaluating the ovaries, is rendered even less technically adequate with obesity, common in adolescent PCOS (34). In addition, multifollicular ovaries are a feature of normal puberty that subsides with onset of regular menstrual cycling (35) and may be difficult to distinguish from PCO morphology (20). It is possible that elevated anti-Mullerian hormone levels may serve as a noninvasive screening or diagnostic test for PCO in this population, although there are no well-defined cutoffs (36, 37).

In summary, the diagnosis of PCOS in adolescents should be based on a complete picture that includes clinical signs and symptoms of androgen excess, increased androgen levels, and exclusion of other causes of hyperandrogenemia in the setting of oligomenorrhea.

1.2 Values and preferences

In making this recommendation, the committee acknowledges that the diagnosis of PCOS in adolescents is less straightforward than in adults. A high index of awareness is needed to initiate a thorough medical and laboratory evaluation of adolescent girls with signs and symptoms of PCOS, including a family history of PCOS. Until higher quality evidence becomes available, this recommendation places a higher value in making an early diagnosis of PCOS in adolescents for timely initiation of therapy, which outweighs harms and burdens of misdiagnosis.

Diagnosis in perimenopause and menopause

1.3 Although there are currently no diagnostic criteria for PCOS in perimenopausal and menopausal women, we suggest that a presumptive diagnosis of PCOS can be based upon a well-documented long-term history of oligomenorrhea and hyperandrogenism during the reproductive years. The presence of PCO morphology on ultrasound would provide additional supportive evidence, although this is less likely in a menopausal woman (2|⊕⊕◯◯).

1.3 Evidence

The natural history of PCOS through perimenopause into menopause is poorly studied, but many aspects of the syndrome appear to improve. Ovarian size, follicle count, and anti-Mullerian hormone levels (a marker of antral follicle count) decrease with normal aging in women with and without PCOS (38–40). However, the decline in ovarian volume and follicle count may be less in women with PCOS than in normal women (39, 41, 42). Similarly, androgen levels decline with age in women with and without PCOS (serum T declines ~50% between the ages of 20 and 40 y) (43–45), with reports of improved menstrual frequency in PCOS (46, 47), although there is little evidence to support a decline in serum T associated with the menopause transition per se (43).

The diagnosis of PCOS in postmenopausal women is more problematic than in adolescents. There are no age-related T cutoffs for the diagnosis. Furthermore, T assays used to diagnose hyperandrogenemia in women are imprecise (31), even for assays utilizing tandem mass spectrometry technology (48). Nevertheless, supporting studies have shown that peri- and postmenopausal mothers of women with PCOS with a history of irregular menses tended to have features of PCOS as well as metabolic abnormalities, implying that aspects of the PCOS phenotype may persist with age (49). Very high T levels and/or virilization may suggest an androgen-producing tumor in postmenopausal women.

1.3 Values and preferences

We recognize that the diagnosis of PCOS in postmenopausal women is problematic but feel that it is unlikely that a woman can develop PCOS in the perimenopause or menopause if she has not had symptoms earlier. We recognize that there are few prospective studies to document the natural history of ovarian function with age in women with PCOS.

2.0 Associated morbidity and evaluation

Cutaneous manifestations

2.1 We recommend that a physical examination should document cutaneous manifestations of PCOS: terminal hair growth (see hirsutism guidelines, Ref. 1), acne, alopecia, acanthosis nigricans, and skin tags (1|⊕⊕⊕◯).

2.1 Evidence

The major clinical manifestations of hyperandrogenism include hirsutism, acne, and androgenic alopecia. The history of skin problems should assess the age at onset, the rate of progression, previous long-term treatments (including anabolic agents), any change with treatment or with fluctuations in body weight, and the nature of the

skin complaint relative to those of other family members. In rare instances, male pattern balding, increased muscle mass, deepening of the voice, or clitoromegaly may occur, suggesting virilizing androgen levels and a possible underlying ovarian or adrenal neoplasm or severe insulin-resistant states (9, 50) (Table 4). Notably, in obese, insulin-resistant women with PCOS, acanthosis nigricans is often present, as are skin tags (51).

Hirsutism

The prevalence of hirsutism in the general population ranges from 5–15%, with relevant differences according to ethnicity and geographic location (9). In a large study of patients with clinical hyperandrogenism, 72.1% of 950 patients were diagnosed with PCOS (16). Therefore, PCOS represents the major cause of hirsutism, but the presence of hirsutism does not fully predict ovulatory dysfunction. Overall, hirsutism is present in approximately 65–75% of patients with PCOS (although lower in Asian populations) (15, 52). Hirsutism may predict the metabolic sequelae of PCOS (53) or failure to conceive with infertility treatment (54). Hirsutism often tends to be more severe in abdominally obese patients (9). The most common method of visually assessing hirsutism is still the modified Ferriman-Gallwey score (1, 55).

Acne and alopecia

Acne is common in women with PCOS, particularly in the teenage years, and the prevalence varies (14–25%), with some difference in relation to ethnicity and patient age (56). The combined prevalence of acne with hirsutism in PCOS is still poorly defined, although there is clinical evidence that the prevalence of each of these features is higher than the combination of the two (57). Androgenic alopecia may be graded by well-known subjective methods, such as the Ludwig score (58). Androgenic alopecia is less frequent and presents later, but it remains a distressing complaint with significant psychopathological comorbidities (9). It may be associated with hirsutism and acne, although there is a poor correlation with biochemical hyperandrogenism. Some studies have demonstrated an association between androgenic alopecia with metabolic syndrome (59) and insulin resistance (IR) (60, 61). Some studies found that acne and androgenic alopecia are not good markers for hyperandrogenism in PCOS, compared with hirsutism (53, 62).

2.1 Values and preferences

Evaluating hirsutism, acne, and alopecia in women with PCOS depends on careful grading, but is subjective. We place value on recognizing these particularly stressful symptoms, even if they do not correlate with objective findings. Alopecia and acne may be related to hyperandrogenism and are distressing; therefore, our preference is to document and consider consultation with a dermatologist and to determine whether they are related to other etiologies in the case of alopecia or in the case of acne if unresponsive to HCs. More research is needed to quantify the relationship between cutaneous signs of hyperandrogenism and cardiovascular disease.

Infertility

2.2 Women with PCOS are at increased risk of anovulation and infertility; in the absence of anovulation, the risk of infertility is uncertain. We recommend screening ovulatory status using menstrual history in all women with PCOS seeking fertility. Some women with PCOS and a eumenorrheic menstrual history may still experience anovulation and a midluteal serum progesterone may be helpful as an additional screening test (1|⊕⊕◯◯).

2.3 We recommend excluding other causes of infertility, beyond anovulation, in couples where a woman has PCOS (1|⊕⊕◯◯).

2.2–2.3 Evidence

Infertility was one of the original symptoms of PCOS described by Stein and Leventhal (63) and is a common presenting complaint (64). Among a large series of women presenting with PCOS, close to 50% reported primary infertility, and 25% reported secondary infertility (65). Population-based studies of infertility have suggested that anovulatory infertility (encompassing PCOS) is common, accounting for 25–40% of cases (65, 66). Furthermore, PCOS is estimated to be the most common cause of ovulatory dysfunction, accounting for 70–90% of ovulatory disorders (67). Prolonged periods of anovulation are likely associated with increased infertility (68). Women with PCOS had a monthly spontaneous ovulation rate of 32% on placebo in a multicenter trial that randomly assigned subjects to placebo or troglitazone (69). Nevertheless, lifetime fecundity in Swedish women with PCOS was similar to controls, and almost three-fourths of women with PCOS conceived spontaneously (70).

Some women with PCOS and a eumenorrheic menstrual history may still experience anovulation, and a midluteal serum progesterone may be helpful as an additional screening test. Although the primary mechanism of infertility is presumed to be oligo- or anovulation, there are other potential factors including diminished oocyte competence (71, 72) and endometrial changes discouraging implantation (73, 74). Other factors associated with PCOS, such as obesity, have also been associated with subfertility and delayed conception (75). Male factor infertility or tubal occlusion must also be considered (one

study in PCOS found a nearly 10% rate of severe oligospermia and a 5% rate of bilateral tubal occlusion) (76).

2.2–2.3 Values and preferences

In making this recommendation, we emphasize the overall increased infertility burden among women with PCOS and ovulatory dysfunction, although there are spontaneous conceptions, which may increase with improved menstrual frequency and aging. The natural history of fertility in women with PCOS and the influence of milder phenotypes lacking ovulatory dysfunction are not well understood or described.

Pregnancy complications

2.4 Because women with PCOS are at increased risk of pregnancy complications (gestational diabetes, preterm delivery, and pre-eclampsia) exacerbated by obesity, we recommend preconceptual assessment of BMI, blood pressure, and oral glucose tolerance (1|⊕⊕⊕◯).

2.4 Evidence

There is a growing body of evidence that PCOS has implications for adverse pregnancy outcomes. Confounders include iatrogenic multiple pregnancy due to ovulation induction, higher complications in pregnancies resulting from infertility treatment per se, and higher rates of obesity in women with PCOS. Some studies have suggested increased early pregnancy loss in women with PCOS (77, 78). A meta-analysis of studies comparing IVF outcomes in women with and without PCOS demonstrated no significant difference in miscarriage rates between the two groups (odds ratio [OR], 1.0; 95% confidence interval [CI], 0.5–1.8) (79).

The link between PCOS and gestational diabetes was initially suggested by retrospective data (80). A study of 99 women with PCOS and 737 controls noted a higher rate of gestational diabetes, but it was largely explained by a higher prevalence of obesity in the PCOS group (81, 82). In contrast, a meta-analysis in which confounding factors such as BMI were taken into account demonstrated that PCOS was independently associated with an increased risk for gestational diabetes and hypertension (83). This meta-analysis demonstrated a small but significant association between premature singleton births (<37 wk gestation) and PCOS (OR, 1.75; 95% CI, 1.16–2.62), and between PCOS and pre-eclampsia (OR, 3.47; 95% CI, 1.95–6.17). Most studies reporting an association between hypertension or pre-eclampsia and pregnancy in PCOS are small and poorly controlled and show mixed results (82). In one of the largest studies, PCOS (n = 99) was not a significant predictor of pre-eclampsia compared with control pregnancies (n = 737), when controlled for nulliparity (more common in PCOS) (81). Although only a small absolute difference in gestational age was noted between cases and controls, increased neonatal morbidity was present (83).

2.4 Values and preferences

In making this recommendation, we believe that a priority should be placed on reducing the overall increased morbidity from pregnancy complications such as gestational diabetes, pre-eclampsia, and preterm delivery in women with PCOS. Whether these increased risks are due to PCOS itself or the features associated with PCOS such as IR or obesity requires further study.

Fetal origins

2.5 The evidence for intrauterine effects on development of PCOS is inconclusive. We suggest no specific interventions for prevention of PCOS in offspring of women with PCOS (2|⊕◯◯◯).

2.5 Evidence

Nonhuman primate models and sheep models suggest that androgen exposure in utero may program the fetus to express features characteristic of PCOS in adult life (84–86). Human data are limited, but there is evidence of fetal programming by androgens in girls with classic adrenal hyperplasia or with a mother with a virilizing tumor (87, 88). Androgen levels may be increased in pregnant women with PCOS (89). Nevertheless, an Australian study of 2900 pregnant women demonstrated no relationship between T levels at 18 and 34 weeks gestation and the presence of PCOS in 244 female offspring aged 14–17 years (90). The relationship between T levels during pregnancy in women with PCOS to outcomes remains to be determined using accurate assay methodology.

There is evidence that cardiovascular disease in humans is related to intrauterine events. Intrauterine growth restriction has been associated with increased rates of coronary heart disease, hypertension, and T2DM, providing evidence for fetal programming of adult diseases (91). There are limited data to suggest that intrauterine growth restriction may be associated with subsequent development of PCOS in some populations (92). In addition, a subset of girls born small for gestational age are at risk for developing premature adrenarche, IR, or PCOS (93, 94), although this has not been confirmed in longitudinal, population-based studies in northern Europe (95). Available data support the concept that rapid postnatal weight gain and subsequent adiposity can exacerbate metabolic abnormalities and PCOS symptoms (94, 96–98).

Endometrial cancer

2.6 Women with PCOS share many of the risk factors associated with the development of endometrial cancer including obesity, hyperinsulinism, diabetes, and abnormal uterine bleeding. However, we suggest against routine ultrasound screening for endometrial thickness in women with PCOS (2|⊕⊕⊕◯).

2.6 Evidence

An association between PCOS and endometrial cancer was first described in 1949 (99). There have been few studies with cohorts large enough to adequately assess the risk of endometrial cancer in women with PCOS. In a long-term follow-up of women with PCOS in the United Kingdom, morbidity data over 31 years were available on 319 compared with 1060 control women. Women with PCOS did not have a higher all-cause mortality but did show a 3.5 increased relative risk (RR) of development of endometrial cancer (100). A more recent meta-analysis assessing the association between PCOS and endometrial cancer suggested that women with PCOS had an increased risk of developing endometrial cancer (RR = 2.7; 95% CI, 1.0–7.29) (101), confirmed by a subsequent systematic review with a 3-fold increased risk (102).

Several factors in the epidemiology of endometrial cancer suggest a link to PCOS. Young women with endometrial cancer are more likely to be nulliparous and infertile, have higher rates of hirsutism, and have a slightly higher chance for oligomenorrhea (103). Obesity and T2DM, common in women with PCOS, are also endometrial cancer risk factors (104–107). In a woman with these risk factors, low physical activity scores further elevated the cancer risk (108).

There currently are no data supporting routine endometrial biopsy of asymptomatic women (109) or ultrasound screening of the endometrium (110). Ultrasound screening in women without abnormal bleeding shows poor diagnostic accuracy for diagnosing intrauterine pathology (110, 111). The American Cancer Society recommends against routine cancer screening for endometrial cancer in women at average or increased risk (with the exception of Lynch syndrome), but women should be counseled to report unexpected bleeding and spotting (112).

2.6 Values and preferences

In making this recommendation for increased awareness of endometrial cancer risk in women with PCOS, particularly those with abnormal uterine bleeding, prolonged amenorrhea, diabetes, and/or obesity, we believe that a priority should be placed on the consequences of development of endometrial cancer, and this priority offsets the limited data available for independent association with PCOS.

Obesity

2.7 Increased adiposity, particularly abdominal, is associated with hyperandrogenemia and increased metabolic risk (see cardiovascular disease prevention guidelines, Ref. 2). Therefore, we recommend screening adolescents and women with PCOS for increased adiposity by BMI calculation and measurement of waist circumference (1|⊕⊕⊕◯).

2.7 Evidence

Prevalence of obesity in PCOS

The prevalence of obesity varies greatly across the world; however, studies in different countries with significantly different background rates of obesity (30–70%) have yielded similar rates for the prevalence of PCOS (52, 113). Whether the incidence of PCOS may parallel the growing epidemic of obesity is unknown, although a modest but nonsignificant trend in the prevalence of PCOS with increasing BMI has been reported (114). Obesity may also cluster in PCOS families (97, 115), and referral bias to specialty clinics may also elevate the association of PCOS with obesity (116).

Impact of obesity on the phenotype of PCOS

Obesity in general and abdominal obesity in particular cause relative hyperandrogenemia, characterized by reduced levels of SHBG and increased bioavailable androgens delivered to target tissues (117, 118). Abdominal obesity is also associated with an increased T production rate and a non-SHBG-bound androgen production rate of dehydroepiandrosterone and androstenedione (119). Estrogen levels, particularly estrone, may also be higher in PCOS (120).

Menstrual disorders are frequent when the onset of excess weight occurs during puberty rather than during infancy (121). In adult overweight and obese women with PCOS, menstrual abnormalities and chronic oligoanovulation are more frequent than in normal-weight women (118). Obese women with PCOS exhibit a blunted responsiveness and lower pregnancy rates to pharmacological treatments for ovulation induction, such as clomiphene citrate, gonadotropins, or pulsatile GnRH (54, 68, 122).

Obesity increases the risk of the metabolic syndrome, IGT/diabetes mellitus (DM), dyslipidemia, and IR (118, 119, 123–128). Longitudinal studies have shown that IR may worsen over time (125). Consequently, obesity has a negative impact that may exceed that of the PCOS status per se.

2.7 Values and preferences

In making this recommendation, the committee believes that excess weight and obesity may have an important impact on the early development of PCOS and on the clinical presentation (93, 129, 130). Obesity may change in degree and possibly in distribution from adolescence to postmenopausal age, and these changes should be monitored.

Depression

2.8 We suggest screening women and adolescents with PCOS for depression and anxiety by history and, if identified, providing appropriate referral and/or treatment (2|⊕⊕◯◯).

2.8 Evidence

Small observational community- and patient-based case control studies consistently demonstrate an increased prevalence of depression in women with PCOS. In women with PCOS compared with non-BMI-matched controls, self-rated questionnaires demonstrate an increased rate of depressive symptoms (131–133). Similarly, in studies with direct psychiatric interviews, there was a higher lifetime incidence of a major depression episode and recurrent depression (OR, 3.8; 95% CI, 1.5–8.7; $P = .001$) and a history of suicide attempts that was seven times higher in PCOS cases vs controls (134). In a longitudinal study examining changes in depression scores, the incidence of depression was 19% in 1–2 years of follow-up (135). The increased prevalence of depression and depressive symptoms in women with PCOS appears to be independent of obesity, androgen levels, hirsutism, acne, and infertility (131–133, 135–137). Thus, studies of depression using different patient groups and methods of identification demonstrate an increased prevalence of depression in women with PCOS (138).

Community- and clinic-based case-control studies and studies using psychiatric interviews demonstrate higher rates of anxiety and panic disorders in women with PCOS (134, 137, 139). In addition, eating disorders are more common in women with PCOS (OR, 6.4; 95% CI, 1.3–31; $P = .01$) (132) and include binge-eating disorder (12.6 vs 1.9%; $P < .01$) (133). Although a history of depression or anxiety may be present in many women and adolescents with PCOS, for those without a prior diagnosis, a simple office screen using a two-item questionnaire such as the PHQ-2 may be helpful (140). Those identified with depression or anxiety should be referred for further therapy.

Sleep-disordered breathing/OSA

2.9 We suggest screening overweight/obese adolescents and women with PCOS for symptoms suggestive of OSA, and when identified, obtaining a definitive diagnosis using polysomnography. If OSA is diagnosed, patients should be referred for institution of appropriate treatment (2|⊕⊕◯◯).

2.9 Evidence

Women with PCOS develop OSA at rates that equal or exceed those in men. The high prevalence of OSA is thought to be a function of hyperandrogenism (a defining feature of PCOS) as well as obesity (common in PCOS) (141, 142), although these factors alone do not fully account for the finding. Even after controlling for BMI, women with PCOS were 30 times more likely to have sleep-disordered breathing and nine times more likely than controls to have daytime sleepiness (141). It also appeared that women with PCOS taking oral contraceptives were less likely to have sleep-disordered breathing (141), consistent with the lower likelihood of sleep-disordered breathing in postmenopausal women treated with hormone replacement therapy (143). Finally, women with PCOS had a significantly higher mean apnea-hypopnea index compared with weight-matched controls (22.5 ± 6.0 vs 6.7 ± 1.7; $P < .01$), with the difference most pronounced in rapid eye movement sleep (41.3 ± 7.5 vs 13.5 ± 3.3; $P < .01$) (143). Thus, the risk imparted by obesity is not sufficient to account for the high prevalence of sleep-disordered breathing in PCOS, suggesting that additional factors must be involved.

Continuous positive airway pressure treatment of OSA in patients with PCOS demonstrated modestly improved IR after controlling for BMI ($P = .013$) (144). In young obese women with PCOS, successful treatment of OSA improves insulin sensitivity, decreases sympathetic output, and reduces diastolic blood pressure. The magnitude of these beneficial effects is modulated by the hours of continuous positive airway pressure use and the degree of obesity.

2.9 Values and preferences

It is difficult to diagnose sleep abnormalities on the basis of a history and physical or by questionnaire. Polysomnography, when performed, should occur in a certified sleep laboratory with proper accreditation. The interpretation and recommendation(s) for treatment of sleep-disordered breathing/OSA should be made by a board-certified expert in sleep medicine.

NAFLD and NASH

2.10 We suggest awareness of the possibility of NAFLD and NASH but recommend against routine screening (2|⊕⊕◯◯).

2.10 Evidence

NAFLD is characterized by excessive fat accumulation in the liver (steatosis), whereas NASH defines a subgroup of NAFLD in which steatosis coexists with liver cell injury and inflammation (after exclusion of other causes of liver disease (viral, autoimmune, genetic, alcohol consumption, etc). Primary NAFLD/NASH is most commonly associated with IR and its phenotypic manifestations (145). The prevalence of ultrasound-documented NAFLD in the general population is 15–30% (146). Risk factors pertinent to PCOS include increasing age, ethnicity, and metabolic dysfunction (obesity, hypertension, dyslipidemia, diabetes). Because many women with PCOS have metabolic dysfunction, the association of PCOS with NAFLD is not surprising, but the available literature, especially in reference to the risk of NASH, is incomplete (147). Clinical studies report a 15–60% prevalence of NAFLD in the population, depending on the index used to define liver damage (increased serum alanine aminotransferase or ultrasound), the presence of obesity, and ethnicity (147–153). Whether androgen excess may be involved in the pathophysiology of NAFLD in women with PCOS is still unclear (153–155). Thus, women with PCOS and metabolic risk factors and/or IR may be screened using serum markers of liver dysfunction. If serum markers are elevated, noninvasive quantification of fibrosis by ultrasound and liver biopsy may be considered (156).

2.10 Values and preferences

In making this recommendation we believe that a priority should be placed on identifying this potentially major complication in women with PCOS with IR and/or metabolic syndrome. However, there is currently no simple and reliable screening test for NAFLD because elevated serum transaminases have low sensitivity and specificity. We also believe that investigating the true prevalence of NAFLD in collaboration with gastroenterologists and hepatologists who can identify and apply reliable markers of NASH should be a research priority for future recommendations. Finally, there is no approved drug to treat NAFLD, although lifestyle therapy, insulin sensitizers, and antioxidants are thought to be beneficial.

Type 2 diabetes mellitus

2.11 We recommend the use of an OGTT (consisting of a fasting and a 2-hour glucose level using a 75-g oral glucose load) to screen for IGT and T2DM in adolescents and adult women with PCOS because they are at high risk for such abnormalities (1|⊕⊕⊕◯). An HgbA1c may be considered if a patient is unable or unwilling to complete an OGTT (2|⊕⊕◯◯). Rescreening is suggested every 3–5 years, or more frequently if clinical factors such as central adiposity, substantial weight gain, and/or symptoms of diabetes develop (2|⊕⊕◯◯).

2.11 Evidence

Adolescents and adult women with PCOS are at increased risk for IGT and T2DM (125, 126, 157). A diagnosis of PCOS confers a 5- to 10-fold increased risk of developing T2DM (125, 126, 157). The overall prevalence of glucose intolerance among US women and adolescents with PCOS was 30–35%, and 3–10% had T2DM. Nonobese women with PCOS had a 10–15% prevalence of IGT and a 1–2% prevalence of T2DM (125, 126, 157). Limited studies have shown poor sensitivity of glycohemoglobin measure for detecting IGT (158, 159). Those with T2DM had a significantly higher prevalence of first-degree relatives with T2DM, confirming family history as an important risk factor. Multiple studies have also shown deterioration in glucose tolerance with follow-up (126, 158, 160).

Because of the high risk of IGT and T2DM in PCOS, periodic screening of patients to detect early abnormalities in glucose tolerance is recommended by several scientific organizations, although an interval for screening has not been specified (161–163).

2.11 Values and preferences

In making this recommendation, the committee believes in the strength of the evidence for a tight link between PCOS and diabetes and believes that reducing morbidity of IGT/diabetes through early diagnosis and treatment outweighs any unforeseen harm or burdens resulting from the screening. We have recommended an OGTT over an HgbA1c because of the potential increased association between IGT and cardiovascular disease in women (164, 165) and the potential to identify women at risk for gestational DM before pregnancy. Women with PCOS and IGT early in pregnancy are at greater risk for developing gestational DM (166), but there are currently insufficient data to recommend earlier screening for gestational DM in women with PCOS. Given the lack of evidence of the ideal period for rescreening, we have arbitrarily recommended a period of 3–5 years.

Cardiovascular risk

2.12 We recommend that adolescents and women with PCOS be screened for the following cardiovascular disease risk factors (Table 5): family history of early cardiovascular disease, cigarette smoking, IGT/T2DM, hypertension, dyslipidemia, OSA, and obesity (especially increased abdominal adiposity) (1|⊕⊕◯◯).

2.12 Evidence

Members of the Androgen Excess and Polycystic Ovary Syndrome Society conducted a systematic analysis and published a consensus statement regarding assessment of cardiovascular risk and prevention of cardiovascular disease in women with PCOS (167) (Table 5). In addition to elevations in triglycerides and decreases in high-density lipoprotein (HDL)-cholesterol, women with PCOS have higher low-density lipoprotein (LDL)-cholesterol and non-HDL-cholesterol, regardless of BMI (117, 167). Women with PCOS should have BMI and blood pressure measured at each clinic visit (and consider waist circumference if nonobese; $\geq$ 36 inches is abnormal), and upon diagnosis of PCOS, additional testing should include a complete fasting lipid profile (total cholesterol, LDL-cholesterol, non-HDL-cholesterol, HDL-cholesterol, and triglycerides).

Although hypertension has been an inconsistent finding, women with PCOS appear to be at risk, at least later in life (168–170). Although in many studies both systolic and diastolic blood pressures are normal (168–171), in others, mean arterial pressures and ambulatory systolic pressures are elevated in women with PCOS compared with controls (172). In addition, the nocturnal drop in mean arterial blood pressure is lower, a finding that has also been demonstrated in obese adolescents with PCOS (171, 173).

Anatomic evidence of early coronary and other vascular disease in PCOS has been documented using varied techniques. Increased carotid artery intima-media thickness, an independent predictor of stroke and myocardial infarction, has been noted in PCOS compared with age-matched control women (174). Another marker of atherosclerosis, coronary artery calcification, is more common in women with PCOS than in controls, even after adjusting for the effects of age and BMI (175–177). Echocardiography revealed both anatomic and functional differences between women with PCOS and controls including an increased left atrial size, increased left ventricular mass index, lower left ventricular ejection fraction (178), and diastolic dysfunction (179, 180). Of note, the left ventricular mass index was linearly related to the degree of IR (178).

Some, but not all, studies (181–183) demonstrate impaired endothelial function in women with PCOS, as reflected in reduced brachial artery reactivity to hyperemia (184, 185) and reduced vascular compliance, independent of obesity, IR, total T, or total cholesterol (186). Improved endothelial function has been documented when IR is attenuated with insulin-lowering medication or through weight loss (187–190). Discrepant findings between studies may be the result of the heterogeneous nature of the populations studied.

Despite the increased prevalence of cardiovascular risk factors in women with PCOS, there are limited longitudinal studies, and those are too small to detect differences in event rates (191). Nevertheless, epidemiological data consistently point to increased cardiovascular risk in women with stigmata of PCOS. The Nurses' Health Study noted an adjusted RR of 1.53 (95% CI, 1.24–1.90) for coronary heart disease in women with a history of irregular menstrual cycles (192). In addition, a case-control study based on data in the Women's Health Study database found that women who developed cardiovascular events had lower SHBG and higher calculated free androgen index (193). Among postmenopausal women evaluated for suspected ischemia, clinical features of PCOS were associated with more angiographic coronary artery disease and worsening cardiovascular event-free survival (194).

2.12 Values and preferences

We acknowledge that there is a paucity of studies identifying the rates of cardiovascular events and age of onset in women with PCOS; therefore, we have focused on cardiovascular disease risk factors. However, these may not necessarily equate with events or mortality.

3.0 Treatment

HCs: indications and screening

3.1 We recommend HCs (ie, oral contraceptives, patch, or vaginal ring) as first-line management for the menstrual abnormalities and hirsutism/acne of PCOS (refer to hirsutism guidelines in Ref. 1, recommendation 2.1.1), which treat these two problems concurrently (1|⊕⊕◯◯).

3.2 We recommend screening for contraindications to HC use via established criteria (see Table 6 and Ref. 3) (1|⊕⊕⊕◯). For women with PCOS, we do not suggest one HC formulation over another (2|⊕⊕◯◯).

3.1–3.2 Evidence

In women with PCOS, the progestin in HCs suppresses LH levels and thus ovarian androgen production, and the estrogen increases SHBG, thus reducing bioavailable androgen. In addition, some progestins have antiandrogenic properties, due to their antagonizing effects on the androgen receptor and/or to the inhibition of 5α-reductase activity (195), which have led to claims of increased efficacy for specific formulations without supporting level 1 clinical trial evidence. The choice of oral vs parenteral HC (ie, patch or vaginal ring) is uncertain, although risk-benefit ratios may vary among preparations and with different progestins in oral contraception. There is some evidence that extended-cycle HCs (vs cyclic therapy) offer greater

hormonal suppression and prevent rebound ovarian function during the pill-free interval (196).

HCs, insulin sensitivity, and glucose tolerance

The impact of HCs on carbohydrate metabolism in PCOS women is still in doubt because available studies are small and short-term, and they utilize varying methodologies assessing endpoints. Studies, mostly cross-sectional in healthy women, found decreased insulin sensitivity and increased glucose response to a glucose load during HC use, although these results varied according to the estrogen dose and the type of progestin used (197–202). The residual androgenic activity of the progestin contained in the HC formulation may influence glucose metabolism more than the dose of ethinyl estradiol (203–207). Some of these studies found that HCs had deleterious effects on glucose tolerance in obese, but not in lean, women with PCOS (208–210), but our systematic review did not confirm this (211).

No data are available assessing the long-term effect of HCs on glucose tolerance in nondiabetic and diabetic women with PCOS. A Cochrane meta-analysis concluded that HCs do not have a significant effect on glucose tolerance, although this conclusion was based on limited and low-quality evidence (203). On the other hand, long-term studies performed in healthy women are promising because HC use did not result in an increased incidence of T2DM either in the general population (202) or in women with a history of gestational DM (205, 206) and was not associated with an increased risk of complications in women with type 1 diabetes (205). Therefore, the American Diabetes Association along with the Centers for Disease Control and Prevention (CDC) concluded that HCs are not contraindicated in women with diabetes without vascular complications (3, 212).

HCs and lipids

As with glucose metabolism, the effect of HCs on lipid balance appears to be related to the formulation used. When estrogenic activity prevails, there is an increase in HDL-cholesterol and a decrease in LDL-cholesterol levels, whereas the opposite occurs when androgenic activity is higher (198, 202, 205, 213–215). However, lipids seem to be less sensitive to the residual androgenic properties of the progestins (198, 213, 216–218). The ability of HCs to increase HDL-cholesterol levels is the most favorable and promising metabolic effect in PCOS and may overcome the negative impact on triglycerides and LDL-cholesterol because low HDL-cholesterol may be the critical link between PCOS and the metabolic syndrome (208, 219–223).

HCs and body weight

The impact of HCs on body weight and fat distribution is similar between healthy women and women with PCOS. In particular, BMI and the waist-to-hip ratio were unchanged (209, 211, 220, 224–226) or occasionally improved, independent of coexistent obesity (227).

3.1–3.2 Values and preferences

In evaluating the benefits and risks of HC treatment in women with PCOS, we believed concerns related to untreated menstrual dysfunction and quality of life related to anovulatory bleeding and hirsutism to be the primary considerations. Screening recommendations follow the current World Health Organization and CDC medical eligibility guidelines (Table 6) (3, 228). In making these recommendations, the committee strongly believes that larger controlled studies should be performed to evaluate the risk of long-term HC use in women with PCOS, particularly in the presence of obesity, IR, and lipid disorders. There are insufficient data about whether women with PCOS face increased risk of thromboembolism on particular HC preparations, although preparations may vary with respect to thromboembolic risk in the general population. There are insufficient data to define the optimal duration of treatment with HCs. Women with severe hirsutism or contraindications to hormonal contraception may require other therapies such as antiandrogens (spironolactone, flutamide, finasteride, etc) or mechanical hair removal (laser, electrolysis, etc) (see hirsutism guidelines in Ref. 1).

Role of exercise in lifestyle therapy

3.3 We suggest the use of exercise therapy in the management of overweight and obesity in PCOS (2|⊕⊕◯◯). Although there are no large randomized trials of exercise in PCOS, exercise therapy, alone or in combination with dietary intervention, improves weight loss and reduces cardiovascular risk factors and diabetes risk in the general population.

3.3 Evidence

It is well recognized in the general population that cardiovascular fitness, as measured by maximal oxygen consumption during exercise, is an independent predictor of cardiovascular mortality (229). This remains significant after adjustment for age, smoking, cholesterol measures, diabetes, hypertension, and family history of cardiovascular disease. Overall, there is good evidence in the general population that metabolic status is improved with exercise alone, and this reduces the risk of diabetes (230). Thirty minutes per day of moderate to vigorous physical activity is effective in reducing the development of metabolic syn-

drome and diabetes (231, 232). There are few trials of exercise therapy targeting women with PCOS, and no large randomized trials are available (233), but there is a suggestion of weight loss, improved ovulation, and decreased IR (234–239).

3.3 Values and preferences

Despite the limited evidence in PCOS, we suggest that the benefits of exercise in improving metabolic disease are strong enough to favor its recommendation, despite a paucity of controlled trials available for review.

Role of weight loss in lifestyle therapy

3.4 We suggest that weight loss strategies begin with calorie-restricted diets (with no evidence that one type of diet is superior) for adolescents and women with PCOS who are overweight or obese (2|⊕⊕◯◯). Weight loss is likely beneficial for both reproductive and metabolic dysfunction in this setting. Weight loss is likely insufficient as a treatment for PCOS in normal-weight women.

3.4 Evidence

Weight loss is generally recommended as a first-line therapy for obese women with PCOS. Weight loss in PCOS has been accomplished via lifestyle modification, use of medications designed for weight loss, and bariatric surgery (239–242). Studies performed after sustained weight loss (up to 61% of initial weight) by bariatric surgery (241) or long-term dietary intervention (242) demonstrate that normalization of hyperandrogenemia can be achieved in obese women with PCOS. However, few data document subsequent improvements in hirsutism (243, 244). Menstrual function is improved in some women with as little as 5–10% reduction in body weight (243); however, there are no long-term data available to assess the sustainability of menstrual cycling and few data on pregnancy outcomes after weight reduction. In the short term, there is some evidence for improved pregnancy rates and a decreased requirement for use of ovulation induction or other fertility treatments in small uncontrolled trials of weight reduction (245, 246), although there are no randomized controlled trials supporting weight loss in the improvement of pregnancy rates. The response to weight loss is variable; not all individuals have restoration of ovulation or menses despite similar weight reduction (241, 242, 247, 248). Although improvements in reproductive and metabolic status in PCOS have been described with all weight loss methods, there are no long-term studies available in the literature for any of these approaches. Our own meta-analysis showed that weight loss had minimal effects on hirsutism and fertility, although there were significant improvements in some metabolic parameters (mainly glycemic effects related to improvements in fasting blood glucose and insulin levels) (249, 250).

3.4 Values and preferences

Taken together, the data in general populations and in our meta-analysis in women with PCOS support the role of lifestyle change for prevention and treatment of metabolic dysfunction. We found little evidence to support lifestyle change as an infertility treatment, although other reports (251) and national guidelines (252) have found a benefit. We attribute the failure to document additional benefits to the lack of well-designed studies in this area. Despite the relative lack of evidence that weight loss improves PCOS per se, we recommend lifestyle change in overweight and obese women with PCOS. There may also be some benefit in prevention of weight gain in women with PCOS who exercise regularly and eat sensibly.

Use of metformin in adults

3.5 We suggest against the use of metformin as a first-line treatment of cutaneous manifestations, for prevention of pregnancy complications, or for the treatment of obesity (2|⊕⊕◯◯).

3.6 We recommend metformin in women with PCOS who have T2DM or IGT who fail lifestyle modification (1|⊕⊕⊕◯). For women with PCOS with menstrual irregularity who cannot take or do not tolerate HCs, we suggest metformin as second-line therapy (2|⊕⊕⊕◯).

3.5–3.6 Evidence

Metformin use has been suggested for a number of comorbidities in women with PCOS. Some of these have been discussed in other guidelines including hirsutism (1) and treatment of cardiovascular risk factors in the primary prevention of cardiovascular disease and T2DM in patients at metabolic risk (2). We agree with the suggestion that metformin should not be used for hirsutism. Metformin studies have not been sufficiently powered to study acne (253, 254). We agree with the recommendation that lifestyle management be considered first-line therapy for women with PCOS at increased metabolic risk (2).

Metformin has been associated with weight loss in some trials (76, 230), but not in our meta-analysis (211). A systematic review and meta-analysis demonstrated that there was significant weight loss in trials using metformin compared with placebo in women with PCOS (255). The absolute weight lost was estimated to be 2.7 kg, equaling a 2.9% decrease in body weight, comparable to what occurs with orlistat treatment (256). However, metformin did not increase weight loss in patients using diet and exercise programs (255, 257). Taken together, when weight loss and lifestyle modifications are used to treat obesity, there is no

benefit to adding metformin. Therefore, diet and exercise, not metformin, should be the first line of therapy in obese women with PCOS. Metformin may remain a treatment consideration if the patient fails with diet and exercise.

One of the most important clinical outcomes demonstrated during metformin treatment was the improvement in menstrual cyclicity (258), leading to the possibility that metformin could be used to regulate menses (258). A systematic review and meta-analysis demonstrated an improvement in ovulation rate in women taking metformin (254). It is unknown whether ovulation occurs at a rate that is adequate to protect against endometrial carcinoma. Trials directly comparing metformin with oral contraceptives demonstrate that metformin is not as effective as oral contraceptives for menstrual cycle regulation (208, 259).

In patients with IGT, lifestyle modification with exercise and diet can decrease the progression to T2DM by 58% vs a 31% decrease with metformin (230). Furthermore, these benefits persist for up to 10 years after initiation, with lifestyle modification reducing diabetes incidence by 34% and metformin reducing it by 18% (230). However, intensive lifestyle modification, not metformin, was the only therapy that restored normal glucose tolerance in subjects with IGT (230, 260). Similar trials in women with PCOS and IGT are too small and limited in duration to determine whether metformin prevented T2DM or caused regression to normal glucose tolerance (259, 261). Metformin is recommended for prevention of diabetes in women with PCOS and IGT when lifestyle modification is not successful.

3.5–3.6 Values and preferences

The committee believes that a priority should be placed on effective treatment. Although the preferred treatment for prevention of T2DM is diet and lifestyle modification, there are a significant number of women who will fail this option. Although metformin treatment incurs expense and has the potential for side effects, the committee feels that metformin may provide an option for treatment of IGT in those women who fail lifestyle management.

Treatment of infertility

3.7 We recommend clomiphene citrate (or comparable estrogen modulators such as letrozole) as the first-line treatment of anovulatory infertility in women with PCOS (1|⊕⊕⊕◯).

3.8 We suggest the use of metformin as an adjuvant therapy for infertility to prevent OHSS in women with PCOS undergoing IVF (2|⊕⊕◯◯).

3.7–3.8 Evidence

Clomiphene and metformin have been studied extensively for infertility in PCOS with multiple large multicenter trials (76, 262–265). In almost all of these, clomiphene has had improved pregnancy rates vs metformin, as well as providing comparable rates to injectable gonadotropins (266). A recent meta-analysis of insulin sensitizers for the treatment of infertility in PCOS concluded that "the use of metformin for improving reproductive outcomes in women with PCOS appears to be limited" (254). In this review, there was no evidence that metformin improved live birth rates, whether it was used alone (pooled OR, 1.00; 95% CI, 0.16–6.39) or in combination with clomiphene (pooled OR, 1.05; 95% CI, 0.75–1.47) (254). Metformin has been recommended for use in infertility treatment partly because it is thought to be associated with monofollicular ovulation and lower multiple pregnancy rates. None of the trials have been adequately powered to detect differences in multiple pregnancy rates, although multiple pregnancies with metformin have been rare in these trials (≤5%) (76, 262–266) and more common (around 5%) with clomiphene. The benefit of multiple pregnancy reduction must be balanced against the substantially lower pregnancy rates and lower fecundity per ovulation with metformin alone (76).

Aromatase inhibitors have been proposed as oral agents, and although current cumulative evidence suggests an uncertain risk/benefit ratio to treat infertility (267), a recent large NIH-sponsored, multicenter, double-blind, randomized, clinical trial (n = 750 subjects) has been completed with a marked superiority in live birth rate of letrozole over clomiphene for the treatment of anovulatory infertility in women with PCOS (with a comparable safety and tolerance profile between drugs) (268). These results may alter recommendations for front-line treatment in subsequent revisions of this guideline. Although concerns about the relative teratogenicity of letrozole compared to clomiphene remain, this trial and other publications are reassuring (269). The relative success of two drugs that modulate estrogen action to achieve pregnancy further underscores this class of drugs as first-line treatment when compared with insulin sensitizers.

Metformin may have some use as an adjuvant agent for infertility in select women with PCOS, although it is likely to be more effective in obese women than nonobese women (74, 267, 270). A systematic review of metformin noted that in clomiphene-resistant women, metformin plus clomiphene led to higher live birth rates than clomiphene alone (RR, 6.4; 95% CI, 1.2–35); metformin also led to higher live birth rates than laparoscopic ovarian drilling (RR, 1.6; 95% CI, 1.1–2.5) (271). In addition, metformin may prevent the development of OHSS in women with PCOS receiving gonadotropin therapy for IVF (249, 272).

The routine use of metformin during pregnancy in women with PCOS is unwarranted, although it may be

useful to treat gestational diabetes (273). A meta-analysis of randomized, controlled trials demonstrated no effect of metformin on abortion rate (OR, 0.89; 95% CI, 0.59–1.75; $P = .9$) (238). A large, randomized, controlled trial demonstrated no difference in the prevalence of pre-eclampsia, preterm delivery, or gestational DM in women with PCOS treated with metformin during pregnancy (274). Metformin was associated with a significantly higher incidence of gastrointestinal disturbance, but no serious maternal or fetal adverse effects (76, 254, 274).

3.7–3.8 Values and preferences

The committee recognizes that the use of letrozole for the treatment of infertility in PCOS is promising. However, we believe, as with all recent discoveries, that publication of the finding and digestion, debate, and independent confirmation in other studies are necessary to establish letrozole as front-line infertility therapy. The committee also acknowledges that metformin may have some benefit as an adjuvant agent in the treatment of infertility in obese women, despite conflicting systematic reviews on the topic. Other national guidelines have favored metformin more than in the current guidelines (252). We recommend discontinuing metformin (when used to treat PCOS as opposed to T2DM) with a positive pregnancy test, given the lack of benefit associated with its routine use during pregnancy. In the face of resistance (anovulation) or failure (no conception despite ovulation) with front-line oral agents, referral to a subspecialist in infertility for further care is recommended.

Use of other drugs

3.9 We recommend against the use of insulin sensitizers, such as inositols (due to lack of benefit) or thiazolinediones (given safety concerns), for the treatment of PCOS (1|⊕⊕⊕◯).

3.10 We suggest against the use of statins for the treatment of hyperandrogenism and anovulation in PCOS until additional studies demonstrate a favorable risk-benefit ratio (2|⊕⊕◯◯). However, we suggest statins in women with PCOS who meet current indications for statin therapy (2|⊕⊕◯◯).

3.9–3.10 Evidence

Although a large phase II study sponsored by a pharmaceutical company provided evidence of a dose-response improvement in reproductive and metabolic abnormalities in PCOS with troglitazone (76), there have been no subsequent large randomized trials of thiazolidinediones in PCOS (254). The U.S. Food and Drug administration has removed troglitazone from the market due to hepatic toxiticity and restricted the use of rosiglitazone due to excess cardiovascular events. A recent FDA advisory linked pioglitazone to bladder cancer. The risk-benefit ratio may also be less favorable for infertility because animal studies suggest that thiazolidinediones may be associated with fetal loss (FDA Pregnancy Category C). Although there are no known serious adverse events related to D-chiro-inositol therapy, there are concerns about the formulation of the drug and limited evidence of its efficacy (275).

Dyslipidemia, including elevations in circulating LDL-cholesterol, the precursor to sex steroid biosynthesis, is common in women with PCOS. Statins have multiple actions that include inhibition of the enzyme hydroxymethylglutaryl coenzyme A reductase, which leads to decreased production of cholesterol (thus reducing circulating concentrations of cholesterol). In addition, there is some evidence that ovarian T production may be reduced by administration of statins (276, 277). This effect may be due, at least in part, to inhibition of theca cell growth and by decreasing the concentration of precursor for production of androstenedione (278). Furthermore, statins appear to have antioxidant properties. Clinical trials of statins alone or in combination with other medications among women with PCOS are limited in number, and conclusive evidence that statins ameliorate PCOS symptoms is lacking, although improvements in hyperandrogenemia have been noted (276, 279–281). Further recent data show that statin use may increase the risk for developing T2DM (282).

3.9–3.10 Values and preferences

There are few data to support the use of newer diabetes drugs that improve insulin action, such as the glucagon-like peptide-1 analogs or the dipeptidyl peptidase-4 inhibitors in women with PCOS. There are potential serious side effects to statins (myopathy and renal impairment), which may be more common in women then men, and these drugs are theoretically teratogenic (Pregnancy Category X), which merits caution in their use. Until additional studies demonstrate a clear risk-benefit ratio favoring statin therapy for other aspects of PCOS, statins should only be used in women with PCOS who meet current indications for statin treatment.

Treatment of adolescents

3.11 We suggest HCs as the first-line treatment in adolescents with suspected PCOS (if the therapeutic goal is to treat acne, hirsutism, or anovulatory symptoms or to prevent pregnancy) (2|⊕⊕◯◯). We suggest that lifestyle therapy (calorie-restricted diet and exercise) with the objective of weight loss should also be first-line treatment in the presence of overweight/obesity (2|⊕⊕◯◯). We suggest metformin as a possible treatment if the goal is to treat

IGT/metabolic syndrome (2|⊕⊕◯◯). The optimal duration of HC or metformin use has not yet been determined.

3.12 For premenarchal girls with clinical and biochemical evidence of hyperandrogenism in the presence of advanced pubertal development (ie, ≥Tanner stage IV breast development), we suggest starting HCs (2|⊕⊕◯◯).

3.11–3.12 Evidence

The treatment of PCOS in adolescents is controversial. Many support the symptom-driven approach, whereas others support an approach targeting the underlying reproductive/hormonal and metabolic abnormalities associated with PCOS (30). There are no adequately powered, randomized, double-blind, placebo-controlled trials in adolescents with PCOS. The dual goal of treating hyperandrogenism and providing contraception prompts the use of HCs as the mainstay of therapy for adolescents with PCOS (29, 283, 284). Additionally, benefits such as normal menses and decreased acne and hirsutism are typically of the greatest importance to an adolescent (285). Some of these can also be improved by lifestyle therapy and weight loss.

Nonetheless, the initiation of HCs in early adolescence is controversial, and few data exist to guide recommendations. After excluding other causes of primary amenorrhea, HCs could be considered in a patient with proven hyperandrogenism if the patient has achieved a sexual maturity of Tanner stage 4–5 when menarche should have occurred (286). The best HC for adolescents and the appropriate duration of therapy are uncertain (287). A longer duration of treatment with a combined HC may lead to a lower chance of developing signs of hyperandrogenism as an adult (23). Some authors suggest continuing with HC until the patient is gynecologically mature (defined by these authors as 5 years postmenarcheal) or has lost a substantial amount of weight (288).

Small, short-term studies demonstrate that metformin restores menstrual regularity and improves hyperandrogenemia, IR, and glucose intolerance in obese and nonobese adolescents with PCOS (289–291). Two sequential, randomized, placebo-controlled trials of metformin in adolescents with PCOS demonstrated improvements in hyperandrogenemia, ovulation, and dyslipidemia (223). These promising but limited data lead to the impression that metformin may be more beneficial for adolescents with PCOS than it is for adults with this condition (292, 293). The necessary duration of treatment is yet to be established, and the limited available data are conflicting. In one study, the beneficial effects of metformin on menstrual cycles persisted for 6 months after discontinuation of metformin (294), but in another study the effects were lost 3 months after discontinuing the medication (290). There is no literature regarding long-term use in adolescents.

Given the limited data, it is necessary to extrapolate from adult data in making adolescent treatment recommendations. Thus, lifestyle therapy should be recommended in overweight/obese adolescents. Metformin therapy may also be considered for treatment of PCOS based on the limited studies cited above. Because lifestyle change and/or metformin may increase ovulatory frequency and because cutaneous manifestations are common, appropriate contraception must be recommended to a sexually active teenager.

3.11–3.12 Values and preferences

In making these suggestions the committee recommends individualizing therapy of PCOS and weighing the pros and cons of one therapeutic approach against the other until such time when strong evidence from well-performed, long-term, randomized, controlled trials in adolescents becomes available. In recommending metformin in adolescents with PCOS, the committee believes that: 1) early treatment with metformin and/or lifestyle changes may yield promising and preventative results; 2) priority should be placed on treating PCOS not only as a hormonal/reproductive disorder, but also as a dysmetabolic syndrome characterized by IR; and 3) the safety of metformin and its reported outcomes outweigh the limited data. Because adolescents have higher user failure rates for hormonal contraception and because of the known teratogenicity of antiandrogens during pregnancy, we have avoided any specific recommendation of antiandrogens in this population; however, these agents may be beneficial in selected individuals. We note that our treatment recommendations in adolescents do not extend to girls with precocious pubarche, given the uncertain risk-benefit ratio in this age group.

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