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)

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; NASH, nonalcoholic fatty liver disease; 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 ovarian 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*                  | 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                                                                             |
|                                 | Biochemical hyperandrogenism*               | 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. | or    | or                     | or                                                                             |
| 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 sizemorphology 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                      | X                                                                              |

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

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.

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.

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.

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.

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.

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.

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                                                             | Clinical hyperandrogenism is difficult to quantify and may vary by ethnic group, e.g., low rates of hirsutism in women with PCOS from east Asia Tissue sensitivity is not assessed |
|                                       | Assays are not standardized across laboratories                                                     | Normal ovulation is poorly defined                                                               |
|                                       | Clinical hyperandrogenism is difficult to quantify and may vary by ethnic group, e.g., low rates of hirsutism in women with PCOS from east Asia Tissue sensitivity is not assessed |
|                                       | Anovulatory cycles may have bleeding patterns that are interpreted as normal                       | Normal ovulation varies over a woman’s lifetime                                                  |
|                                       | Technique dependent                                                                                  | Ovulatory dysfunction is difficult to measure objectively                                         |
|                                       | Difficult to obtain standardized measurement                                                        | Anovulatory cycles may have bleeding patterns that are interpreted as normal                    |
|                                       | Lack of normative standards across the menstrual cycle and lifespan (notably in adolescence)       | May be present in other disorders that mimic PCOS                                                |
|                                       | May be present in other disorders that mimic PCOS                                                    | Technology required to accurately image not universally available                               |
|                                       | Transvaginal imaging possibly inappropriate in certain circumstances (e.g., adolescence) or certain cultures |
| Ovulatory dysfunction                   | Included as a component in all major classifications                                               | Normal ovulation varies over a woman’s lifetime                                                  |
|                                       | A major clinical concern for patients                                                              | Ovulatory dysfunction is difficult to measure objectively                                         |
|                                       | Infertility a common clinical complaint                                                            | 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 (e.g., adolescence) or certain cultures |

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, TSH > 0.0040 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. | Ladenson, 2000 (10) |
| Prolactin excess              | Serum prolactin Early morning (before 8 am) serum 17-OHP |                                                                                                     | Melmed, 2011 (11) Speiser, 2010 (12) |
| Nonclassical congenital adrenal hyperplasia | Serum 17-OHP                |                                                                                                     |                                                                                               |
clinical factors such as central adiposity, substantial weight gain, and/or symptoms of diabetes develop (2|11021).

**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|9252).

### 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|11021).

3.2 We recommend screening for contraindications to HC use via established criteria (see Table 6 and Ref. 3) (1|11021). For women with PCOS, we do not suggest one HC formulation over another (2|11021).

**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|11021).
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). 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.

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

| Criteria                     | Further Classification | 1 | 2 | 3 | 4 |
|------------------------------|------------------------|---|---|---|---|
| Age                          | Menarche to <40 y      | X |   | X |   |
| Age                          | >40 y                  |   | X |   |   |
| Smoking                      | Age ≥35 y              | X |   |   |   |
| Obesity                      | BMI <30 kg/m²          | X |   |   |   |
| Hypertension                 | History of gestational hypertension | X |   |   |   |
| Depression                   | Depressive disorders   | X |   |   |   |
| Diabetes                     | History of gestational diabetes | X |   |   |   |
| Diabetes                     | Nonvascular diabetes, insulin or non-insulin dependent | X |   |   |   |
| Diabetes                     | Vascular disease including neuropathy, retinopathy, nephropathy | X |   |   |   |
| Diabetes                     | Diabetes duration >20 yb | 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.
broad evidence (2\circ\circ\circ\circ). However, we suggest statins in women with PCOS who meet current indications for statin therapy (2\circ\circ\circ\circ).

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\circ\circ\circ\circ). 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\circ\circ\circ\circ). We suggest metformin as a possible treatment if the goal is to treat IGT/metabolic syndrome (2\circ\circ\circ\circ). 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, \geq Tanner stage IV breast development), we suggest starting HCs (2\circ\circ\circ\circ).

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 \circ\circ\circ\circ denotes very low quality evidence; \circ\circ\circ\circ, low quality; \circ\circ\circ\circ\circ, moderate quality; and \circ\circ\circ\circ\circ\circ, 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\circ\circ\circ\circ).
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 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-
androgenic 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|8|8|8|).

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|8|8|8).

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|000).

2.3 We recommend excluding other causes of infertility, beyond anovulation, in couples where a woman has PCOS (1|000).

### 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 oligo-
spermia 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|\[\infty\infty\infty\infty\]).

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|\[\infty\infty\infty\infty\]).

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). 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 6.7 \( P < .01 \) (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. Polysonmography, 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 (157). An HgbA1c may be considered if a patient is unable or unwilling to complete an OGTT (256). 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 (258).

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) (157).
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; ≥ 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) (2) (3).

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

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 (227–229). 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[โดยเฉพาะ]). 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[โดยเฉพาะ]).

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

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 (1B⊙⊙⊙⊙).

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 multi-center 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
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 thiazolidinediones (given safety concerns), for the treatment of PCOS (1⃣⃣⃣⃣). 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 (2⃣⃣⃣⃣). However, we suggest statins in women with PCOS who meet current indications for statin therapy (2⃣⃣⃣⃣). 3.9–3.10 Evidence 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) (2⃣⃣⃣⃣). 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 (2⃣⃣⃣⃣). We suggest metformin as a possible treatment if the goal is to treat 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 ovariian 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 peptide-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) (2⃣⃣⃣⃣). 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 (2⃣⃣⃣⃣). We suggest metformin as a possible treatment if the goal is to treat 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).

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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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References

1. Martin KA, Chang RJ, Ehrmann DA, et al. Evaluation and treatment of hirsutism in premenopausal women: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93: 1105–1120.
2. Rosenzweig JL, Ferrannini E, Grundy SM, et al. Primary prevention of cardiovascular disease and type 2 diabetes in patients at metabolic risk: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2008;93:3671–3689.
3. Centers for Disease Control and Prevention. US medical eligibility criteria for contraceptive use. MMWR Recomm Rep. 2010;59:1–86.
4. Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490.
5. Swiglo BA, Murad MH, Schüenemann HJ, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab. 2008;93:666–673.
6. Zawadzki J, Dunai A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunai A, Givens J, Hasel-
son JA. The prevalence of upper lip hair in black and white girls during puberty: a new standard. J Pediatr. 2001;138:134–136.

27. Pfeifer SM, Kives S. Polycystic ovary syndrome in the adolescent. Obstet Gynecol Clin North Am. 2009;36:129–152.

28. Bexk MT, Connor EC, Allen DB. Characteristics of adolescents presenting to a multidisciplinary clinic for polycystic ovarian syndrome. J Pediatr Adolesc Gynecol. 2010;23:7–10.

29. Diamanti-Kandarakis E. PCOS in adolescents. Best Pract Res Clin Obstet Gynaecol. 2010;24:173–183.

30. Warren-Ulanch, Arslanian S. Treatment of PCOS in adolescence. Best Pract Res Clin Endocrinol Metab. 2006;20:311–330.

31. Rosner W, Aucius RJ, Azirz R, Sluss PM, Raff H. Position statement: utility, limitations, and pitfalls in measuring testosterone: an Endocrine Society position statement. J Clin Endocrinol Metab. 2007;92:405–413.

32. MacCartney CR, Blank SK, Prendergast KA, et al. Obesity and sex steroid changes across puberty: evidence for marked hyperandro- genemia in pre- and early pubertal obese girls. J Clin Endocrinol Metab. 2007;92:430–436.

33. Apter D, Vilko P. Endocrine determinants of fertility: serum androgen concentrations during follow-up of adolescents into the third decade of life. J Clin Endocrinol Metab. 1990;71:970–974.

34. Shaya R, Chang RJ. Reproductive endocrinology of adolescent polycystic ovary syndrome. BJOG. 2010;117:150–155.

35. Bridges NA, Cooke A, Healy MJ, Hindmarsh PC, Brook CG. Standards for ovarian volume in childhood and puberty. Fertil Steril. 1993;60:456–460.

36. Pawelczak M, Menigberg I, Milla S, Liu YH, Shah B. Elevated serum anti-Mullerian hormone in adolescents with polycystic ovary syndrome: relationship to ultrasound features. J Pediatr Endocrinol Metab. 2012;25:983–989.

37. Rosenfield RL, Wroblewski K, Padmanabhan V, Littlejohn E, Mortensen M, Ehrmann DA. Antimullerian hormone levels are independently related to ovarian hyperandrogenism and polycystic ovaries. Fertil Steril. 2012;98:242–249.

38. Johnstone EB, Rosen MP, Neril R, et al. The polycystic ovary post-Rotterdam: a common, age-dependent finding in ovari- lomales women without metabolic significance. J Clin Endocrinol Metab. 2010;95:4965–4972.

39. Alsamarai S, Adams JM, Murphy MK, et al. Criteria for polycystic ovarian morphology in polycystic ovary syndrome as a function of age. J Clin Endocrinol Metab. 2009;94:4961–4970.

40. Pigny P, Merlen E, Robert Y, et al. Elevated serum level of anti-mullerian hormone in patients with polycystic ovary syndrome: relationship to the ovarian follicle excess and to the follicular arrest. J Clin Endocrinol Metab. 2003;88:5957–5962.

41. Mulders AG, Laven JS, Eijkemans MJ, de Jong FH, Themmen AP, Fauser BC. Changes in anti-Mullerian hormone serum concentration over time suggest delayed ovarian ageing in normogonadotropic anovulatory infertility. Hum Reprod. 2004;19:2036–2042.

42. Piltonen T, Morin-Papunen L, Koivunen R, Perheentupa A, Ruokonen A, Tapanainen JS. Serum anti-Mullerian hormone levels remain high until late puberty in healthy girls and decrease during menformin therapy in women with polycystic ovary syndrome. Hum Reprod. 2005;20:1820–1826.

43. Aziz R, Carmina E, Dewaill D, et al. Positions statement: criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an Androgen Excess Society guideline. J Clin Endocrinol Metab. 2006;91:4237–4245.

44. Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab. 2005;90:3847–3853.

45. Winters SJ, Talbott E, Guezick DS, Zborowski J, McHugh KP. Serum testosterone levels decrease in middle age in women with the polycystic ovary syndrome. Fertil Steril. 2000;73:724–729.

46. Elting MW, Korsen TJ, Rekers-Mombarg LT, Schoemaker J. Women with polycystic ovary syndrome gain regular menstrual cycles when ageing. Hum Reprod. 2000;15:24–28.

47. Elting MW, Kwee J, Korsen TJ, Rekers-Mombarg LT, Schoemaker J. Aging women with polycystic ovary syndrome who achieve regular menstrual cycles have a smaller follicle cohort than those who continue to have irregular cycles. Fertil Steril. 2003;79:1154–1160.

48. Legro RS, Schlaff WD, Diamond MP, et al; Reproductive Medicine Network. Total testosterone assays in women with polycystic ovary syndrome: precision and correlation with hirsutism. J Clin Endocrinol Metab. 2010;95:5305–5313.

49. Sam S, Legro RS, Essah PA, Airdonidze T, Dunaif A. Evidence for metabolic and reproductive phenotypes in mothers of women with polycystic ovary syndrome. Proc Natl Acad Sci USA. 2006;103:7030–7035.

50. Semple RK, Savage DB, Halsall DJ, O’Rahilly S. Syndromes of severe insulin resistance and/or lipodystrophy. In: Weiss RE, Refetoff S, eds. Genetic Diagnosis of Endocrine Diseases. London, UK: Academic Press, Elsevier, Inc.; 2010:105–115.

51. Sari R, Akmun A, Alysoy E, Balci MK. The metabolic profile in patients with skin tags. Clin Exp Med. 2010;10:193–197.

52. Aziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab. 2004;89:2745–2749.

53. Ozdemir S, Ozdemir M, Gorkemli H, Kiyici A, Bodur S. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. Acta Obstet Gynecol Scand. 2010;89:199–204.

54. Rausch ME, Legro RS, Barnhart HX, et al; for the Cooperative MultiCenter Reproductive Medicine Network. Predictors of pregnancy in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2009;94:3458–3466.

55. Hatch R, Rosenfield RL, Kim MH, Tredway D. Hirsuitism: implications, etiology, and management. Am J Obstet Gynecol. 1981;140:815–830.

56. Lowenstein EJ. Diagnosis and management of the dermatologic manifestations of the polycystic ovary syndrome. Dermatol Ther. 2006;19:210–223.

57. Deplewski D, Rosenfield RL. Role of hormones in pilosebaceous unit development. Endocr Rev. 2000;21:363–392.

58. Ludwig E. Classification of the types of androgenetic alopecia (common baldness) occurring in the female sex. Br J Dermatol. 1977;97:247–254.

59. Arias-Santiago G, Gutierrez-Salmeron MT, Castellote-Caballero L, Buendia-Eisman A, Naranjo-Sintes R. Androgenetic alopecia and cardiovascular risk factors in men and women: a comparative study. J Am Acad Dermatol. 2010;63:420–429.

60. Matilainen V, Laasko M, Hirso P, Koskela P, Rajala U, Käininen-Kuukanen M. Hair loss, insulin resistance, and heredity in middle-aged women. A population-based study. J Cardiovasc Risk. 2003;10(3):227–231.

61. Ekemci TR, Ucak S, Basat O, Koslu A, Altunay T. The presence of insulin resistance and comparison of various insulin sensitivity indices in women with androgenetic alopecia. Eur J Dermatol. 2007;17(1):21–25.

62. Karrer-Voegeli S, Rey F, Reymond MJ, Meuwly JY, Gaillard RC, Gomez F. Androgen dependence of hirsutism, acne, and alopecia in women: retrospective analysis of 228 patients investigated for hyperandrogenism. Medicine (Baltimore). 2009;88:32–45.

63. Stein IF, Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol. 1935;29:181–191.

64. Goldzieher JW, Axelrod LR. Clinical and biochemical features of polycystic ovarian disease. Fertil Steril. 1963;14:631–653.

65. Balen AH, Conway GS, Kalsitas G, et al. Polycystic ovary syndrome: the spectrum of the disorder in 1741 patients. Hum Reprod. 1995;10:2107–2111.
66. Bhattacharya S, Porter M, Amalraj E, et al. The epidemiology of infertility in the North East of Scotland. *Hum Reprod*. 2009;24:3096–3107.

67. Hull MG. Epidemiology of infertility and polycystic ovarian disease: endocrinological and demographic studies. *Gyncol Endocrinol*. 1987;1:235–245.

68. Imani B, Eijkemans MJ, te Velde ER, Habbema JD, Fauser BC. Predictors of patients remaining anovulatory during clomiphene citrate induction of ovulation in normogonadotropic oligoamenorrheic infertility. *J Clin Endocrinol Metab*. 1998;83:2361–2365.

69. Azziz R, Ehrmann D, Legro RS, et al. Trogilitazone improves ovulation and hirsutism in the polycystic ovary syndrome: a multicenter, double blind, placebo-controlled trial. *J Clin Endocrinol Metab*. 2001;86:1626–1632.

70. Hudecova M, Holte J, Olovsson M, Sundström Poromaa I. Long-term follow-up of patients with polycystic ovary syndrome: reproductive outcome and ovarian reserve. *Hum Reprod*. 2009;24:1176–1183.

71. Trounson A, Wood C, Kausche A. In vitro maturation and the fertilization and developmental competence of oocytes recovered from untreated polycystic ovarian patients. *Fertil Steril*. 1994;62:353–362.

72. Wood JR, Dumesic DA, Abbott DH, Strauss JF 3rd. Molecular abnormalities in oocytes from women with polycystic ovary syndrome revealed by microarray analysis. *J Clin Endocrinol Metab*. 2007;92:705–713.

73. Apparao KB, Lovely LP, Gui Y, Lininger RA, Lessey BA. Elevated endometrial androgen receptor expression in women with polycystic ovarian syndrome. *Biol Reprod*. 2002;66:297–304.

74. Gregory CW, Wilson EM, Apparao KB, et al. Steroid receptor coactivator expression throughout the menstrual cycle in normal and abnormal endometrium. *J Clin Endocrinol Metab*. 2002;87:2960–2966.

75. Bolumar F, Olsen J, Rebagliato M, Sáez-Lloret I, Bisanti L. Body mass index and delayed conception: a European multicenter study on infertility and subfertility. *Am J Epidemiol*. 2000;151:1072–1079.

76. Legro RS, Barnhart HX, Schlaff WD, et al. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N Engl J Med*. 2007;356:551–566.

77. Homburg R, Berkowitz D, Levy T, Feldberg D, Ashkenazi J, Ben-Rafael Z. In vitro fertilization and embryo transfer for the treatment of infertility associated with polycystic ovary syndrome. *Fertil Steril*. 1993;60:833–863.

78. Balen AH, Laven JS, Tan SL, Dewailly D. Ultrasonic assessment of the polycystic ovary: international consensus definitions. *Hum Reprod Update*. 2003;9:505–514.

79. Heijnen EM, Eijkemans MJ, Hughes EG, Laven JS, Macklon NS, Fauser BC. A meta-analysis of outcomes of conventional IVF in women with polycystic ovary syndrome. *Hum Reprod*. 2006;12:13–21.

80. Holte J, Gennarelli G, Wide L, Lithell H, Berne C. High prevalence of polycystic ovaries and associated clinical, endocrine, and metabolic features in women with previous gestational diabetes mellitus. *J Clin Endocrinol Metab*. 1998;83:1143–1150.

81. Mikola M, Hiiusmaa V, Halttunen M, Suohon L, Tiiitinen A. Obstetric outcome in women with polycystic ovarian syndrome. *Hum Reprod*. 2001;16:226–229.

82. Haakova I, Cibula D, Rezabek K, Hill M, Fanta M, Zivy J. Pregnancy outcome in women with PCOS and in controls matched by age and weight. *Hum Reprod*. 2003;18:1438–1441.

83. Boomsma CM, Eijkemans MJ, Hughes EG, Visser GH, Fauser BC, Macklon NS. A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome. *Hum Reprod Update*. 2006;12:673–683.

84. Abbott DH, Zhou R, Bird IM, Dumesic DA, Conley AJ. Fetal programming of adrenal androgen excess: lessons from a nonhuman primate model of polycystic ovary syndrome. *Endocr Dev*. 2008;13:145–158.

85. Ortega HH, Rey F, Velazquez MM, Padmanaban V. Developmental programming: effect of prenatal steroid excess on intra-variety components of insulin signaling pathway and related proteins in sheep. *Biol Reprod*. 2010;82:1065–1075.

86. Recabarren SE, Padmanaban V, Codner E, et al. Postnatal developmental consequences of altered insulin sensitivity in female sheep treated prenatally with testosterone. *Am J Physiol Endocrinol Metab*. 2005;289:E801–E806.

87. Barnes RB, Rosenfield RL, Ehrmann DA, et al. Ovarian hyperandrogenism as a result of congenital adrenal virilizing disorders: evidence for perinatal masculinization of neuroendocrine function in women. *J Clin Endocrinol Metab*. 1994;79:1328–1333.

88. Ghizzone L, Virdis R, Vottero A, et al. Pituitary-ovarian responses to leuprolide acetate testing in patients with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *J Clin Endocrinol Metab*. 1996;81:601–606.

89. Sir-Petermann T, Maliqueo M, Angel B, Lara HE, Pérez-Bravo F, Recabarren SE. Maternal serum androgens in pregnant women with polycystic ovarian syndrome: possible implications in prenatal androgenization. *Hum Reprod*. 2002;17:2573–2579.

90. Hickey M, Sloboda DM, Atkinson HC, et al. The relationship between maternal and umbilical cord androgen levels and polycystic ovary syndrome in adolescence: a prospective cohort study. *J Clin Endocrinol Metab*. 2009;94:3714–3720.

91. Godfrey KM, Barker DJ. Fetal nutrition and adult disease. *Am J Clin Nutr*. 2000;71(suppl):1345S–1352S.

92. Sir-Petermann T, Hitchsfield C, Maliqueo M, et al. Birth weight in offspring of mothers with polycystic ovarian syndrome. *Hum Reprod*. 2005;20:2122–2126.

93. Ibáñez L, Potau N, Ferrer A, Rodriguez-Hierrro F, Marcos MV, De Zegher F. Anovulation in eumenorrheic, nonobese adolescent girls born small for gestational age: insulin sensitization induces ovulation, increases lean body mass, and reduces abdominal fat excess, dyslipidemia, and subclinical hyperandrogenism. *J Clin Endocrinol Metab*. 2002;87:5702–5705.

94. Diamanti-Kandarakis E, Christakou C, Palourea O, Kandarak E, Livadas S. Does polycystic ovarian syndrome start in childhood? *Pediatr Endocrinol Rev*. 2008;5:904–911.

95. Laitinen J, Taponen S, Martikainen H, et al. Body size from birth to adulthood as a predictor of self-reported polycystic ovary syndrome symptoms. *Int J Obes Relat Metab Disord*. 2003;27:710–715.

96. Ibáñez L, De Zegher F, Potau N. Anovulation after precocious pubarche: early markers and time course in adolescence. *J Clin Endocrinol Metab*. 1999;84:2691–2695.

97. Azziz R. Polycystic ovarian syndrome is a family affair. *J Clin Endocrinol Metab*. 2008;93:1579–1581.

98. Recabarren SE, Smith R, Rios R, et al. Metabolic profile in sons of women with polycystic ovary syndrome. *J Clin Endocrinol Metab*. 2008;93:1820–1826.

99. Speert H. Carcinoma of the endometrium in young women. *Surg Gynecol Obstet*. 1949;88:332–336.

100. Wild S, Pierpoint T, Jacobs H, McKeigue P. Long-term consequences of polycystic ovary syndrome: results of a 31 year follow-up study. *Hum Fertil (Camb)*. 2000;3:101–105.

101. Chittenden BG, Fullerton G, Maheshwari A, Bhattacharya S. Polycystic ovary syndrome and the risk of gynaecological cancer: a prospective follow-up study. *Hum Fertil (Camb)*. 2012;15:1327–1331.

102. Dahlgren E, Friberg LG, Johansson S, et al. Endometrial carcinoma; ovarian dysfunction—a risk factor in young women. *Eur J Obstet Gynecol Reprod Biol*. 1991;41:143–150.

103. Folsum AR, Kaye SA, Potter JD, Prinjes R. Association of incident carcinoma of the endometrium with body weight and fat distribu-
tion in older women: early findings of the Iowa Women’s Health Study. Cancer Res. 1989;49:6828–6831.

105. McCullough ML, Patel AV, Patel R, et al. Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev. 2008;17:73–79.

106. O’Mara BA, Byers T, Schoenfeld E. Diabetes mellitus and cancer risk: a multisite case-control study. J Chronic Dis. 1985;38:435–441.

107. Weiderpass E, Gridley G, Persson I, Nyrén O, Ekholm A, Adami HO. Risk of endometrial and breast cancer in patients with diabetes mellitus. Int J Cancer. 1997;71:360–363.

108. Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2007;16:276–280.

109. Koss LG, Schreiber K, Oberlander SG, Moussouris HF, Lesser M. Detection of endometrial carcinoma and hyperplasia in asymptomatic women. Obstet Gynecol. 1984;64:1–11.

110. Dreisler E, Sorensen SS, Ibsen PH, Lose G. Value of endometrial thickness measurement for diagnosing focal intrauterine pathology in women without abnormal uterine bleeding. Ultrasound Obstet Gynecol. 2009;33:344–348.

111. Timmermans A, Opmeer BC, Khan KS, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2010;116:160–167.

112. Smith RA, von Eschenbach AC, Wender R, et al; ACS Prostate Cancer Advisory Committee, ACS Colorectal Cancer Advisory Committee, ACS Endometrial Cancer Advisory Committee. American Cancer Society guidelines for the early detection of cancer: update of early detection guidelines for prostate, colorectal, and endometrial cancers. Also: update 2001–testing for early lung cancer detection. CA Cancer J Clin. 2001;51:38–75.

113. Ehrmann DA. Polycystic ovarian syndrome. N Engl J Med. 2005;352:1223–1236.

114. Yildiz BO, Knochenhauer ES, Azizz R. Impact of obesity on the risk for polycystic ovarian syndrome. J Clin Endocrinol Metab. 2008;93:162–168.

115. Sam S, Covinello AD, Sung YA, Legro RS, Dunai A. Metabolic phenotype in the brothers of women with polycystic ovarian syndrome. Diabetes Care. 2008;31:1237–1241.

116. Ezech U, Yildiz BO, Azizz R. Referral bias in defining the phenotype and prevalence of obesity in polycystic ovary syndrome. J Clin Endocrinol Metab. 2013;98:E1088–E1096.

117. Gambineri A, Pelusi C, Vicennati V, Pagotto U, Pasquali R. Obesity and the polycystic ovary syndrome. Int J Obes Relat Metab Disord. 2002;26:883–896.

118. Pasquali R, Gambineri A, Pagotto U. The impact of obesity on reproduction in women with polycystic ovary syndrome. BJOG. 2006;113:1148–1159.

119. Pasquali R. Obesity and androgens: facts and perspectives. Fertil Steril. 2006;85:1319–1340.

120. Stener-Victorin E, Holm G, Labrie F, Nilsson L, Janson PO, Olslson C. Are there any sensitive and specific sex steroid markers for polycystic ovary syndrome? J Clin Endocrinol Metab. 2010;95:810–819.

121. McCannery CR, Prendergast KA, Chhabra S, et al. The association of obesity and hyperandrogenism during the pubertal transition in girls: obesity as a potential factor in the genesis of postpubertal hyperandrogenism. J Clin Endocrinol Metab. 2006;91:1714–1722.

122. Nyboe Andersen A, Balen A, Plateau P, Devroey P, Helgaard L, Arce JC. Predicting the FSH threshold dose in women with WHO Group II anovulatory infertility failing to ovulate or conceive on clomiphene citrate. Hum Reprod. 2008;23:1424–1430.

123. Dunai A, Segal KR, Futterweit W, Dobrjansky A. Profound peripheral insulin resistance, independent of obesity, in polycystic ovary syndrome. Diabetes. 1989;38:1165–1174.

124. Morales AJ, Laughlin GA, Bützow T, Maheshwari H, Baumann G, Yen SS. Insulin, somatotropin, and luteinizing hormone axes in lean and obese women with polycystic ovary syndrome: common and distinct features. J Clin Endocrinol Metab. 1996;81:2854–2864.

125. Legro RS, Kunselman AR, Dodson WC, Dunai A. Prevalence and predictors of risk for type 2 diabetes mellitus and impaired glucose tolerance in polycystic ovary syndrome: a prospective, controlled study in 254 affected women. J Clin Endocrinol Metab. 1999;84:165–169.

126. Ehrmann DA, Barnes RB, Rosenfeld RL, Cavaghan MK, Imperial J. Prevalence of impaired glucose tolerance and diabetes in women with polycystic ovary syndrome. Diabetes Care. 1999;22:141–146.

127. Moran L, Misso ML, Wild RA, Norman RJ. Impaired glucose tolerance, type 2 diabetes and metabolic syndrome in polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2010;16:347–363.

128. Ehrmann DA, Liljenquist DR, Kasza K, Azizz R, Legro RS, Ghazzi MN; PCOS/Troglitazone Study Group. Prevalence and predictors of the metabolic syndrome in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91:48–53.

129. Eriksson JG, Forsén T, Tuomilehto J, Winter PD, Osmond C, Barker DJ. Catch-up growth in childhood and death from coronary heart disease: longitudinal study. BMJ. 1999;318:427–431.

130. Diamanti-Kandarakis E, Christakou CD, Kandarakis E, Alexandraki KI. Early onset adiposity: a pathway to polycystic ovary syndrome in adolescents? Hormones (Athens). 2007;6:210–217.

131. Weiner CL, Primeau M, Ehrmann DA. Androgens and mood dysfunction in women: comparison of women with polycystic ovarian syndrome to healthy controls. Psychosom Med. 2004;66:356–362.

132. Bhattacharya SM, Jha A. Prevalence and risk of depressive disorders in women with polycystic ovary syndrome (PCOS). Fertil Steril. 2010;94:357–359.

133. Hollinrake E, Abreu M, Mafield M, Van Voorhis BJ, Dokras A. Increased risk of depressive disorders in women with polycystic ovarian syndrome. Fertil Steril. 2007;87:1369–1376.

134. Månsso N, Holte J, Landin-Wiikens K, Dahlgren E, Johansson A, Landén M. Women with polycystic ovarian syndrome are often depressed or anxious—a case control study. Psychoneuroendocrinology. 2008;33:1132–1138.

135. Kirchner A, Lester W, Stuart SP, Dokras A. Risk of depression and other mental health disorders in women with polycystic ovarian syndrome: a longitudinal study. Fertil Steril. 2009;91:207–212.

136. Stunkard AJ, Faith MS, Allison KC. Depression and obesity. Biol Psychiatry. 2003;54:330–337.

137. Jedel E, Waern M, Gustafson D, et al. Anxiety and depression symptoms in women with polycystic ovary syndrome compared with controls matched for body mass index. Hum Reprod. 2010;25:450–456.

138. Dokras A, Clifton S, Futterweit W, Wild R. Increased risk for abnormal depression scores in women with polycystic ovary syndrome: a systematic review and meta-analysis. Obstet Gynecol. 2011;117:145–152.

139. Dokras A, Clifton S, Futterweit W, Wild R. Increased prevalence of anxiety symptoms in women with polycystic ovary syndrome: systematic review and meta-analysis. Fertil Steril. 2012;97:225–230.e2.

140. Gilbody S, Richards D, Brealey S, Hewitt C. Screening for depression in medical settings with the Patient Health Questionnaire (PHQ): a diagnostic meta-analysis. J Gen Intern Med. 2007;22:1596–1602.

141. Vgontzas AN, Legro RS, Bixler EO, Grayev A, Kales A, Chrousos GP. Polycystic ovary syndrome is associated with obstructive sleep apnea and daytime sleepiness: role of insulin resistance. J Clin Endocrinol Metab. 2001;86:517–520.

142. Gopal M, Duntley S, Uhles M, Attarain H. The role of obesity in the increased prevalence of obstructive sleep apnea syndrome in
patients with polycystic ovarian syndrome. Sleep Medicine. 2002;3:401–404.

143. Shahar E, Redline S, Young T, et al. Hormone replacement therapy and sleep-disordered breathing. Am J Respir Crit Care Med. 2003;167:1186–1192.

144. Tasali E, Chapotot F, Leproult R, Whitmore H, Ehrmann DA. Treatment of obstructive sleep apnea improves cardiometabolic function in young obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2011;96:365–374.

145. Ratziu V, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. J Hepatol. 2010;53:372–384.

146. Baumeister SE, Völzke H, Marschall P, et al. Impact of fatty liver disease on health care utilization and costs in a general population: a 5-year observation. Gastroenterology. 2008;134:85–94.

147. Setji TL, Holland ND, Sanders LL, Pereira KC, Diehl AM, Brown AJ. Nonalcoholic steatohepatitis and nonalcoholic fatty liver disease in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91:1741–1747.

148. Loria P, Carulli L, Bertolotti M, Lonardo A. Nonalcoholic fatty liver disease in women with polycystic ovary syndrome. J Hepatol. 2007;47:412–417.

149. Schwimmer JB, Khorram O, Chiu V, Schwimmer WB. Abnormal aminotransferase activity in women with polycystic ovary syndrome. Fertil Steril. 2005;83:494–497.

150. Gutierrez-Grobe Y, Ponciano-Rodriguez G, Ramos MH, Uribe M, Mendez-Sanchez N. Prevalence of non alcoholic fatty liver disease in premenopausal, postmenopausal and polycystic ovary syndrome women. The role of estrogens. Ann Hepatol. 2010;9:402–409.

151. Vassilatou E, Lafoyianni S, Vryonidou A, et al. Increased androgen bioavailability is associated with non-alcoholic fatty liver disease in women with polycystic ovary syndrome. Hum Reprod. 2010;25:212–220.

152. Mojiminiyi OA, Safar FH, Al Rumaith H, Diedova I. Variations in alanine aminotransferase levels within the normal range predict metabolic and androgenic phenotypes in women of reproductive age. Scand J Clin Lab Invest. 2010;70:554–560.

153. Kauffman RP, Baker TE, Baker V, Kauffman MM, CastracaneVD. Endocrine factors associated with non-alcoholic fatty liver disease in women with polycystic ovary syndrome: do androgens play a role? Gynecol Endocrinol. 2010;26:39–46.

154. de Ledinghen V, Ratziu V, Causse X, et al. Association Franaise pour l’Etude du Foie Groupe Epidemiologie et Evaluation: Association Nationale des Gastroenterologues des Hopitaux généraux de France. Diagnostic and predictive factors of significant liver fibrosis and minimal lesions in patients with persistent unexplained elevated transaminases. A prospective multicenter study. J Hepatol. 2006;45:592–599.

155. Palmert MR, Gordon CM, Kartashov AI, Legro RS, Emans SJ, Dunaif A. Screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome. J Clin Endocrinol Metab. 2002;87:1017–1023.

156. Legro RS, Gnatuk CL, Kuspelman AR, Dunaif A. Changes in glucose tolerance over time in women with polycystic ovary syndrome: a controlled study. J Clin Endocrinol Metab. 2005;90:3236–3242.

157. Velling Magnussen L, Mumm H, Andersen M, Glinborg D. Hemoglobin A1c as a tool for the diagnosis of type 2 diabetes in 208 premenopausal women with polycystic ovary syndrome. Fertil Steril. 2011;96:1275–1280.

158. Norman RJ, Masters L, Milner CR, Wang JX, Davies MJ. Relative risk of conversion from normoglycaemia to impaired glucose tolerance or non-insulin dependent diabetes mellitus in polycystic ovarian syndrome. Hum Reprod. 2001;16:1995–1998.

159. Alberti KG, Zimmet P, Shaw J. International Diabetes Federation: a consensus on type 2 diabetes prevention. Diabet Med. 2007;24:451–463.

160. American Association of Clinical Endocrinologists Polycystic Ovary Syndrome Writing Committee. American Association of Clinical Endocrinologists position statement on metabolic and cardiovascular consequences of polycystic ovary syndrome. Endocr Pract. 2005;11:126–134.

161. Salley KE, Wickham EP, Cheang KI, Essah PA, Karjane NW, Nester JE. Glucose intolerance in polycystic ovary syndrome–a position statement of the Androgen Excess Society. J Clin Endocrinol Metab. 2007;92:4546–4556.

162. Lundblad D, Eliasson M. Silent myocardial infarction in women with impaired glucose tolerance: the Northern Sweden MONICA study. Cardiovasc Diabetol. 2003;2:9.

163. Brohail G, Schmidt C, Behre CJ, Hulthe J, Wilkstrand J, Fagerberg B. Association between impaired glucose tolerance and carotid atherosclerosis: a study in 64-year-old women and a meta-analysis. Nutr Metab Cardiovasc Dis. 2009;19:327–333.

164. Dmitrovic R, Katcher HI, Kuselmann AR, Legro RS. Continuous glucose monitoring during pregnancy in women with polycystic ovary syndrome. Obstet Gynecol. 2011;118:878–885.

165. Wild RA, Carmina E, Diamanti-Kandarakis E, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab. 2010;95:2038–2049.

166. Zimmermann S, Phillips RA, Dunaif A, et al. Polycystic ovary syndrome: lack of hypertension despite profound insulin resistance. J Clin Endocrinol Metab. 1992;75:508–513.

167. Dahlgren E, Janson PO, Johansson S, Lapidus L, Odén A. Polycystic ovary syndrome and risk for myocardial infarction. Evaluated from a risk factor model based on a prospective population study of women. Acta Obset Gynecol Scand. 1992;71:599–604.

168. Dahlgren E, Johansson S, Lindstedt G, et al. Women with polycystic ovary syndrome wedge resected in 1956 to 1965: a long-term follow-up focusing on natural history and circulating hormones. Fertil Steril. 1992;57:505–513.

169. Wild RA, Vesely S, Beebe L, Whitsett T, Owen W. Ferriman Gallwey self-scoring I: performance assessment in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90:4112–4114.

170. Holte J, Gennarelli G, Berne C, Bergh T, Lithell H. Elevated ambulatory day-time blood pressure in women with polycystic ovary syndrome: a sign of a pre-hypertensive state? Hum Reprod. 1996;11:23–28.

171. Arslanian SA, Lewy VD, Danadian K. Glucose intolerance in obese adolescents with polycystic ovary syndrome: rules of insulin resistance and B-cell dysfunction and risk of cardiovascular disease. J Clin Endocrinol Metab. 2004;186:66–713.

172. Talbott EO, Zhorowski JV, Boudreaux MY, McHugh-Pemu KP, Sutton-Tyrrell K, Guzik DS. The relationship between C-reactive protein and carotid intima-media wall thickness in middle-aged women with polycystic ovarian syndrome. J Clin Endocrinol Metab. 2004;89:6061–6067.

173. Talbott EO, Zhorowski JV, Rager JR, Boudreaux MY, Edmundowicz DA, Guzik DS. Evidence for an association between metabolic cardiovascular syndrome and coronary and aortic calcification among women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2004;89:5434–5461.

174. Christian RC, Dumesic DA, Behrenbeck T, Oberg AL, Sherry PF 2nd, Fitzpatrick LA. Prevalence and predictors of coronary artery calcification in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88:2562–2568.
177. Shroff R, Kerchner A, Maifeld M, Van Beck EJ, Jagasia D, Dokras A. Young obese women with polycystic ovary syndrome have evidence of early coronary atherosclerosis. J Clin Endocrinol Metab. 2007;92:4609–4614.

178. Orio F Jr, Palomba S, Spinelli L, et al. The cardiovascular risk of young women with polycystic ovary syndrome: an observational, analytical, prospective case-control study. J Clin Endocrinol Metab. 2004;89:3696–3701.

179. Yarali H, Yildirir A, Aybar F, et al. Diastolic dysfunction and increased serum homocysteine concentrations may contribute to increased cardiovascular risk in patients with polycystic ovary syndrome. Fertil Steril. 2001;76:511–516.

180. Tiras MB, Yalcin R, Noyan V, et al. Alterations in cardiac flow parameters in patients with polycystic ovarian syndrome. Hum Reprod. 1999;14:1949–1952.

181. Kettel Jr, Stehouwer CD, Henry RM, et al. Greater arterial stiffness in polycystic ovary syndrome (PCOS) is an obesity—but not a PCOS-associated phenomenon. J Clin Endocrinol Metab. 2010;95:4566–4575.

182. Beckman JA, Goldfine AB, Dunaif A, Gerhard-Herman M, Creager MA. Endothelial function varies according to insulin resistance disease type. Diabetics Care. 2007;30:1226–1232.

183. Bickerton AS, Clark N, Meeking D, et al. Cardiovascular risk in women with polycystic ovarian syndrome (PCOS). J Clin Pathol. 2005;58:151–154.

184. Meyer C, McGrath BP, Teede HJ. Overweight women with polycystic ovary syndrome have evidence of subclinical cardiovascular disease. J Clin Endocrinol Metab. 2005;90:5711–5716.

185. Carmina E, Orio F, Palomba S, et al. Endothelial dysfunction in PCOS: role of obesity and adipose hormones. Am J Med. 2006;119:356.e1–e6.

186. Kravariti M, Naka KK, Kalantarioud SN, et al. Predictors of endothelial dysfunction in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2005;90:5088–5095.

187. Orio F Jr, Palomba S, Cascella T, et al. Improvement in endothelial structure and function after metformin treatment in young normal-weight women with polycystic ovary syndrome: results of a 6-month study. J Clin Endocrinol Metab. 2005;90:6072–6076.

188. Tarkun I, Cetinarslan B, Turemen E, Sahin T, Canturk Z, Komsooglu B. Effect of rosiglitazone on insulin resistance, C-reactive protein and endothelial function in non-obese young women with polycystic ovary syndrome. Eur J Endocrinol. 2005;153:115–121.

189. Diamanti-Kandarakis E, Spina G, Kouli C, Migdalis I. Increased endothelin-1 levels in women with polycystic ovary syndrome. JCEM. 2001;86:4666–4673.

190. Diamanti-Kandarakis E, Alexandraki K, Protogerou A, et al. Metformin administration improves endothelial function in women with polycystic ovary syndrome. Eur J Endocrinol. 2005;152:749–756.

191. Schmidt J, Landin-Wilhelmsen K, Brännström M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metabol. 2011;96:3794–3803.

192. Solomon CG, Hu FB, Dunaf A, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metabol. 2002;87:2013–2017.

193. Ruxorde KM, Manson JE, Lee IM, et al. Sex hormone levels and risk of cardiovascular events in postmenopausal women. Circulation. 2003;108:1688–1693.

194. Shaw LJ, Bailey Merz CN, Aziz R, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women’s Ischemia Syndrome Evaluation. J Clin Endocrinol Metabol. 2008;93:1276–1284.

195. Vrbikova J, Cibula D. Combined oral contraceptives in the treatment of polycystic ovary syndrome. Hum Reprod Update. 2005;11:277–291.

196. Legro RS, Pauli JG, Kunselman AR, et al. Effects of continuous versus cyclical oral contraception: a randomized controlled trial. J Clin Endocrinol Metabol. 2008;93:420–429.

197. Watanabe RM, Azen CG, Roy S, Perlman JA, Bergman RN. Defects in carbohydrate metabolism in oral contraceptive users without apparent metabolic risk factors. J Clin Endocrinol Metabol. 1994;79:1277–1283.

198. Cagnacci A, Ferrari S, Tirelli A, Zanin R, Volpe A. Insulin sensitivity and lipid metabolism with oral contraceptives containing chloromadinone acetate or desogestrel: a randomized trial. Contraception. 2009;79:111–116.

199. van der Vange N, Kloosterboer HJ, Hapsels AA. Effect of seven low-dose combined oral contraceptive preparations on carbohydrate metabolism. Am J Obstet Gynecol. 1987;156:918–922.

200. Simon D, Senan C, Garnier P, et al. Effects of oral contraceptives on carbohydrate and lipid metabolisms in a healthy population: the Telecom study. Am J Obstet Gynecol. 1990;163:382–387.

201. Godslad IF, Crook D, Worthington M, et al. Effects of a low-estrogen, desogestrel-containing oral contraceptive on lipid and carbohydrate metabolism. Contraception. 1993;48:217–227.

202. Crook D, Godslad IF, Worthington M, Felton CV, Proulder AJ, Stevenson JC. A comparative metabolic study of two low-estrogen-dose oral contraceptives containing desogestrel or gestodene progesterins. Am J Obstet Gynecol. 1993;169:1183–1189.

203. Lopez LM, Grimes DA, Schulz KF. Steroidal contraceptives: effect on carbohydrate metabolism in women without diabetes mellitus. Cochrane Database Syst Rev. 2009;4:CD006133.

204. Rimm EB, Manson JE, Stampfer MJ, et al. Oral contraceptive use and the risk of type 2 (non-insulin-dependent) diabetes mellitus in a large prospective study of women. Diabetologia. 2002;35:967–972.

205. Skouby SO, Endrikat J, Duesterberg B, et al. A 1-year randomized study to evaluate the effects of a dose reduction in oral contraceptives on lipids and carbohydrate metabolism: 20 microg ethinyl estradiol combined with 100 microg levonorgestrel. Contraception. 2005;71:111–117.

206. Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U, Buchanan TA. Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. JAMA. 1998;280:533–538.

207. Garg SK, Chase HP, Marshall G, Hoops SL, Holmes DL, Jackson WE. Oral contraceptives and renal and retinal complications in young women with insulin-dependent diabetes mellitus. JAMA. 1994;271:1099–1102.

208. Morin-Papunen L, Vauhkonen I, Koivunen R, Ruokonen A, Marron K, Lyytinen L, Lyytinen H. Changes in adipose tissue distribution and body composition and the beneficial effect of metformin therapy. JCEM. 2001;86:4666– 4673.

209. Diamanti-Kandarakis E, Alexandraki K, Protogerou A, et al. Metformin administration improves endothelial function in women with polycystic ovary syndrome. Eur J Endocrinol. 2005;152:749–756.

210. Schmidt J, Landin-Wilhelmsen K, Brännström M, Dahlgren E. Cardiovascular disease and risk factors in PCOS women of postmenopausal age: a 21-year controlled follow-up study. J Clin Endocrinol Metabol. 2011;96:3794–3803.

211. Solomon CG, Hu FB, Dunaf A, et al. Menstrual cycle irregularity and risk for future cardiovascular disease. J Clin Endocrinol Metabol. 2002;87:2013–2017.

212. Rexrode KM, Manson JE, Lee IM, et al. Sex hormone levels and risk of cardiovascular events in postmenopausal women. Circulation. 2003;108:1688–1693.

213. Shaw LJ, Bailey Merz CN, Aziz R, et al. Postmenopausal women with a history of irregular menses and elevated androgen measurements at high risk for worsening cardiovascular event-free survival: results from the National Institutes of Health–National Heart, Lung, and Blood Institute sponsored Women’s Ischemia Syndrome Evaluation. J Clin Endocrinol Metabol. 2008;93:1276–1284.
type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.
231. Hu G, Lakka TA, Kiipiäläinen TO, Tuomilehto J. Epidemiological studies of exercise in diabetes prevention. Appl Physiol Nutr Metab. 2007;32:583–595.
232. Lakka TA, Laaksonen DE. Physical activity in prevention and treatment of the metabolic syndrome. Appl Physiol Nutr Metab. 2007;32:76–88.
233. Harrison CI, Lombard CB, Moran LJ, Teede HJ. Exercise therapy in polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2011;17:171–183.
234. Orio F Jr, Galliurria F, Palomba S, et al. Cardiopulmonary impairment in young women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2006;91:2967–2971.
235. Thomson RL, Buckley JD, Moran LJ, et al. Comparison of aerobic exercise capacity and muscle strength in overweight women with and without polycystic ovary syndrome. BJOG. 2009;116:1242–1250.
236. Stener-Victorin E, Jede E, Janson PO, Sverrisdottr YB. Low-frequency electroacupuncture and physical exercise decrease high muscle sympathetic nerve activity in polycystic ovary syndrome. Am J Physiol Regul Integr Comp Physiol. 2007;297:R387–R395.
237. Moro C, Pasarica M, Elkind-Hirsch K, Redman LM. Aerobic exercise training improves atrial natriuretic peptide and catecholamine-mediated lipolysis in obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2009;94:2579–2586.
238. Palomba S, Falbo A, Orio F Jr, Zullo F. Effect of preconceptional metformin on abortion risk in polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2009;92:1646–1658.
239. Thomson RL., Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008;93:3373–3380.
240. Florakis D, Diamanti-Kandarakis E, Katsikis I, et al. Effect of hypocaloric diet plus sibutramine treatment on hormonal and metabolic features in overweight and obese women with polycystic ovary syndrome: a randomized, 24-week study. Int J Obes (Lond). 2008;32:692–699.
241. Escobar-Morreale HF, Botella-Carretero JI, Alvarez-Blasco F, Sancho J, San Millán JL. The polycystic ovary syndrome associated with morbid obesity may resolve after weight loss induced by bariatric surgery. J Clin Endocrinol Metab. 2005;90:6364–6369.
242. Pasquali R, Gambineri A, Cavazza C, et al. Heterogeneity in the responsiveness to long-term lifestyle intervention and predictability in obese women with polycystic ovary syndrome. Eur J Endocrinol. 2011;164:53–60.
243. Kiddy DS, Hamilton-Fairley D, Bush A, et al. Improvement in endocrine and ovarian function during dietary treatment of obese women with polycystic ovary syndrome. Clin Endocrinol (Oxf). 1992;36:105–111.
244. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Gallytch C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88:812–819.
245. Clark AM, Thomley B, Tomlinson L, Gallytch C, Norman RJ. Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Hum Reprod. 1998;13:1502–1505.
246. Crosignani PG, Colombo M, Veggetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod. 2003;18:1928–1932.
247. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic
ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab. 1999;84:1470–1474.

248. Tang T, Glanville J, Hayden CJ, White D, Barth JH, Balen AH. Combined lifestyle modification and metformin in obese patients with polycystic ovary syndrome. A randomized, placebo-controlled, double-blind multicentre study. Hum Reprod. 2006;21:80–89.

249. Tang T, Glanville J, Orsi N, Barth JH, Balen AH. The use of metformin for women with PCOS undergoing IVF treatment. Hum Reprod. 2006;21:1416–1425.

250. Domecq JP, Brutsky G, Mullan R, et al. Adverse effects of common treatments for polycystic ovary syndrome: a systematic review and meta-analysis [published online ahead of print October 3, 2013]. J Clin Endocrinol Metab. doi:10.1210/jc.2013-2374.

251. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2011;7:CD007506.

252. Teede HJ, Misso ML, Deeks AA. Assessment and management of polycystic ovary syndrome: summary of an evidence-based guideline. Med J Australia. 2011;195:S65–S112.

253. Harbome L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. J Clin Endocrinol Metab. 2003;88:4116–4123.

254. Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH. Insulin-sensitising drugs (metformin, rosiglitazone, pioglitazone, D-chiro-inositol) for women with polycystic ovary syndrome, oligoamenorrhea and subfertility. Cochrane Database Syst Rev. 2010;1:CD003053.

255. Nieuwenhuis-Ruifrok AE, Kuchenbecker WK, Hoek A, Middleton P, Norman RJ. Insulin sensitising drugs for weight loss in women of reproductive age who are overweight or obese: systematic review and meta-analysis. Hum Reprod Update. 2009;15:57–68.

256. Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. Int J Obes Relat Metab Disord. 2003;27:1437–1446.

257. Ladson G, Dodson WC, Sweet SD, et al. The effects of metformin with lifestyle therapy in polycystic ovary syndrome: a randomized double-blind study. Fertil Steril. 2011;95:1059–1066.e1-e7.

258. Nestler JE, Jakubowicz DJ, Evans WS, Pasquale R. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med. 1998;338:1876–1880.

259. Morin-Papunen L, Vauhkonen I, Koivunen RM, Ruokonen A, Nestler JE, Jakubowicz DJ, Evans WS, Pasquale R. Metformin improves pregnancy and live-birth rates in women with polycystic ovary syndrome (PCOS): a multicenter, double-blind, placebo-controlled randomized trial. J Clin Endocrinol Metab. 2012;97:1492–1500.

260. Moll E, van der Veen F, van Wely M. The role of metformin in polycystic ovary syndrome: a systematic review. Hum Reprod Update. 2007;13:527–537.

261. Tso LO, Costello MF, Albuquerque LE, Andriolo RB, Freitas V. Metformin treatment before and during IVF or ICSI in women with polycystic ovary syndrome. Cochrane Database Syst Rev. 2009;2:CD006105.

262. Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. N Engl J Med. 2008;358:2003–2015.

263. Vanky E, Stridsklev S, Heimstad R, et al. Metformin versus placebo from first trimester to delivery in polycystic ovary syndrome: a randomized, controlled multicenter study. J Clin Endocrinol Metab. 2010;95:E448–E455.

264. Galazis N, Galazi M, Atiomo W. D-Chiro-inositol and its significance in polycystic ovary syndrome: a systematic review. Gynecol Endocrinol. 2011;27:256–262.

265. Banaszewska B, Pawelczyk I, Spaczynski RZ, Duleba AJ. Comparison of simvastatin and metformin in treatment of polycystic ovary syndrome: prospective randomized trial. J Clin Endocrinol Metab. 2009;94:4938–4949.

266. Izquierdo D, Foyouzi N, Kwintkiewicz J, Duleba AJ. Mevastatin inhibits ovarian theca-interstitial cell proliferation and steroidogenesis. Fertil Steril. 2004;82(Suppl 3):1193–1197.

267. Sokalska A, Piotrowski PC, Rzepczynska IJ, Cress A, Duleba AJ. Statins inhibit growth of human theca-interstitial cells in PCOS and non-PCOS tissues independently of cholesterol availability. J Clin Endocrinol Metab. 2010;95:5390–5394.

268. Sathyapalan T, Kilpatrick ES, Coady AM, Atkin SL. The effect of atorvastatin in patients with polycystic ovary syndrome: a randomized double-blind placebo-controlled study. J Clin Endocrinol Metab. 2009;94:103–108.

269. Raja-Khan N, Kunselman AR, Hogeman CS, Stetter CM, Demers LM, Legro RS. Effects of atorvastatin on vascular function, inflammation, and androgens in women with polycystic ovary syndrome: a double-blind, randomized, placebo-controlled trial. Fertil Steril. 2011;95:1849–1852.

270. Raval AD, Hunter T, Stukey B, Hart RJ. Statins for women with polycystic ovary syndrome not actively trying to conceive. Cochrane Database Syst Rev. 2011;10:CD008563.
282. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011;305:2556–2564.

283. Guttmann-Bauman I. Approach to adolescent polycystic ovary syndrome (PCOS) in the pediatric endocrine community in the U.S.A. J Pediatr Endocrinol Metab. 2005;18:499–506.

284. Hillard PJ. Oral contraceptives and the management of hyperandrogenism-polycystic ovary syndrome in adolescents. Endocrinol Metab Clin North Am. 2005;34:707–723, x.

285. Cedars MI. Polycystic ovary syndrome: what is it and how should we treat it? J Pediatr. 2004;144:4–6.

286. Tanner JM. Growth and endocrinology of the adolescent. In: Gardner LI, ed. Endocrine and Genetic Diseases of Childhood and Adolescents. 2nd ed. Philadelphia, PA: WB Saunders: 1975:14.

287. Pfeifer SM, Dayal M. Treatment of the adolescent patient with polycystic ovary syndrome. Obstet Gynecol Clin North Am. 2003;30:337–352.

288. Buggs C, Rosenfield RL. Polycystic ovary syndrome in adolescence. Endocrinol Metab Clin North Am. 2003;34:677–705, x.

289. Ibáñez L, Valls C, Ferrer A, Marcos MV, de Zegher F. Sensitization to insulin induces ovulation in nonobese adolescents with anovulatory hyperandrogenism. J Clin Endocrinol Metab. 2001;86:3595–3598.

290. Ibáñez L, Valls C, Potau N, Marcos MV, de Zegher F. Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. J Clin Endocrinol Metab. 2000;85:3526–3530.

291. Arslanian SA, Lewy V, Danadian K, Saad R. Metformin therapy in obese adolescents with polycystic ovary syndrome and impaired glucose tolerance: amelioration of exaggerated adrenal response to adrenocorticotropic with reduction of insulinemia/insulin resistance. J Clin Endocrinol Metab. 2002;87:1555–1559.

292. Harwood K, Vuguin P, DiMartino-Nardi J. Current approaches to the diagnosis and treatment of polycystic ovary syndrome in youth. Horm Res. 2007;68:209–217.

293. Ladson G, Dodson WC, Sweet SD, et al. Effects of metformin in adolescents with polycystic ovary syndrome undertaking lifestyle therapy: a pilot randomized double-blind study. Fertil Steril. 2011;95:2595–2598.e1;e6.

294. De Leo V, Musacchio MC, Morgante G, Piomboni P, Petraglia F. Metformin treatment is effective in obese teenage girls with PCOS. Hum Reprod. 2006;21:2252–2256.

295. Rosenfield RL. Clinical practice. Hirsutism. N Engl J Med. 2005;353:2578–2588.

296. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med. 2009;360:606–614.