Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in females, with a high prevalence. The etiology of this heterogeneous condition remains obscure, and its phenotype expression varies. Two widely cited previous ESHRE/ASRM sponsored PCOS consensus workshops focused on diagnosis (published in 2004) and infertility management (published in 2008), respectively. The present third PCOS consensus report summarizes current knowledge and identifies knowledge gaps regarding various women's health aspects of PCOS. Relevant topics addressed—all dealt with in a systematic fashion—include adolescence, hirsutism and acne, contraception, menstrual cycle abnormalities, quality of life, ethnicity, pregnancy complications, long-term metabolic and cardiovascular health, and finally cancer risk. Additional, comprehensive background information is provided separately in an extended online publication. (Fertil Steril® 2012;97:28–38. ©2012 by American Society for Reproductive Medicine.)

Key Words: Polycystic ovary syndrome, hirsutism, contraception, pregnancy complications, quality of life, insulin resistance, type 2 diabetes, metabolic syndrome, cardiovascular disease, cancer

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Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women, with a prevalence between 6% and 10% based on the U.S. National Institutes of Health (NIH) criteria and as high as 15% when the broader Rotterdam criteria are applied. Typically, PCOS is first identified during the early reproductive years. The clinical expression varies but commonly includes oligo-ovulation or anovulation, hyperandrogenism (either clinical or biochemical), and the presence of polycystic ovaries. The etiology of the syndrome remains obscure, and the variability in phenotype expression continues to render the clinical care

and research concerning this heterogeneous condition challenging.

Two ESHRE/ASRM-sponsored PCOS consensus workshops have previously been organized. The first one in Rotterdam, the Netherlands, in 2003 focused on diagnostic criteria for PCOS (1, 2); the second in Thessaloniki, Greece, in 2007 dealt with infertility management in PCOS (3, 4). The conclusions of these meetings were subsequently jointly published simultaneously in both *Human Reproduction* and *Fertility and Sterility*. These papers are highly cited, suggesting a great interest in this area and underlining the value of such consensus contributions.

A third PCOS consensus workshop—the focus of the present report—took place in Amsterdam, the Netherlands, in October 2010 and attempted to summarize current knowledge and to identify gaps in knowledge regarding various women's health aspects of PCOS. Diverse aspects of care during the reproductive and postreproductive years were addressed, including adolescence, hirsutism and acne, contraception, menstrual cycle abnormalities, quality of life and sexual health, ethnicity, pregnancy complications, long-term (metabolic) cardiovascular health, and cancer risk (Fig. 1). Due to the complexity of the many issues discussed, this contribution will address each topic separately in a fixed format: a brief introduction, concluding statements (where there was agreement), a summary of areas of disagreement (if any) and knowledge gaps, with recommended directions for future research. These concluding statements in relation to each specific topic mentioned are published in the journals (maximum of 5 references per paragraph). An extended version of this article is available online with Supplemental Material that provides comprehensive background information.

The hierarchy of the evidence available in the literature assessed for this conference was graded as follows:

Level A requires at least one randomized, controlled trial (RCT) as part of a body of literature of overall good quality and consistency that addresses the specific recommendation.

Level B requires the availability of well-controlled clinical studies, but no RCTs on the topics of recommendation.

Level C requires evidence obtained from expert committee reports of opinions and/or clinical experiences of respected authorities, which indicates an absence of directly applicable clinical studies of good quality.

Good practice points (GPP) are also addressed.

ADOLESCENCE

There is no overall agreement as to how to diagnose PCOS in adolescence. Acne is common during the adolescent years, whether or not PCOS is present, whereas hirsutism—associated with PCOS—typically develops over time. Hyperandrogenemia may be a more consistent marker for PCOS during the teenage years (5). In all young women, irregular menses are common in the years immediately after menarche. As many as 85% of menstrual cycles are anovulatory during the first year after menarche, and up to 59% are still anovulatory during the third year after menarche (6). In one study, persisting oligomenorrhea was not predicted by increased androgens, polycystic ovaries on ultrasound, or increased serum luteinizing hormone (LH) levels (7). Increased body mass index (BMI), however, was the major risk factor for persistent anovulation.

Only approximately 40% of adolescent women with menstrual irregularity have polycystic ovaries on ultrasound (8). These considerations have led to the suggestion that all three elements of the Rotterdam criteria should be present in teenagers to make the diagnosis of PCOS (9). These investigators suggest that oligomenorrhea or amenorrhea should be present for at least 2 years after menarche (or primary amenorrhea at age 16 yrs), the diagnosis of polycystic ovaries on ultrasound should include increased ovarian size (>10 cm^3), and hyperandrogenemia rather than just signs of androgen excess should be documented.

Conclusions (Agreement)

- Criteria for the diagnosis of PCOS in adolescents differ from those used for older women of reproductive age (level B).
- Groups at risk (e.g., obese, hirsute, irregular menses) should be identified, but physicians should be cautious of overdiagnosing PCOS (level B).
- Individual PCOS manifestations in adolescents (e.g., obesity, hirsutism, irregular menses) (level B) should be treated.

Knowledge Gaps/Recommended Future Research

- Absence of longitudinal studies through adolescence.
- Absence of specific diagnostic criteria for identifying PCOS early in adolescence.
- Absence of normative values for a number of biochemical markers during adolescence.
- Assessment of value of intervention in PCOS early in adolescence.
- Lack of clarity as to whether the severity of symptoms during adolescence predicts the extent of the disorder in later life.

HIRSUTISM/ACNE/ALOPECIA

Hirsutism is a good marker for hyperandrogenism even when considering ethnic differences and systemic factors such as obesity. Hirsutism is present in approximately 70% of women with PCOS, but hyperandrogenemia should be evaluated biochemically in all women suspected of having PCOS. By comparison, acne and alopecia are not commonly associated with hyperandrogenemia and therefore should not be regarded as evidence of hyperandrogenemia.

For women with PCOS in whom hirsutism is a major concern, treatment is focused on reduction of androgen production, decreasing the fraction of circulating free testosterone (T), and limiting androgen bioactivity to hair follicles. In those women with PCOS who have acne vulgaris, clinical benefit may be derived from many systemic therapeutic modalities. Because terminal hair turnover occurs slowly, at least 6 months of treatment is generally considered the minimal interval to see a response.

The main therapeutic emphasis has focused on inhibition of ovarian steroid production and decreased bioavailability through augmentation of sex hormone–binding globulin (SHBG) levels with the use of oral contraceptive pills (OCPs). Often OCPs are prescribed in combination with an antiandrogen to block androgen action at the hair follicles. Antiandrogens include spironolactone (an aldosterone-antagonist diuretic), flutamide (an androgen receptor antagonist), and finasteride (a 5α-reductase type 2 inhibitor). In general, the addition of an antiandrogen to OCPs has not appeared to increase the overall treatment benefit. Each of these agents have been shown to reduce hirsutism, and all appear (without head-to-head comparisons) to have equivalent efficacy (10–12). Notably, antiandrogens should not be used without effective contraception (given their potential fetal toxicity). Flutamide is of limited value because of associated hepatotoxicity. In addition, drospirenone is not antiandrogenic in the dosage used as a component of some OCPs. Insulin-sensitizing agents, such as metformin and pioglitazone, have little effect on hirsutism or acne (13, 14). Physical approaches to remove unwanted hair, including electrolysis and laser treatments, may be acceptable to many patients.

In severe acne, isotretinoin can be beneficial, but individual responses vary. It is not effective for hirsutism and occasionally may lead to alopecia. Physical approaches to remove unwanted hair, including electrolysis and laser treatments, may be acceptable to many patients. Topical treatment with eflornithine hydrochloride, an inhibitor of ornithine decarboxylase, limits cell division and has been shown to be effective for decreasing the development of new unwanted facial hair (15). No effective pharmacologic treatment for alopecia exists.

Conclusions (Agreement)

- Hirsutism, considering ethnic differences, is a good marker for hyperandrogenism (level B).
- Isolated acne and alopecia are not necessarily related to and are not good markers for hyperandrogenism (level B).
- Hirsutism should be evaluated biochemically (level B).
- Prolonged (>6 months) medical therapy for hirsutism is necessary to document effectiveness (level B).
- Many drugs used for the treatment of hirsutism are not approved by the U.S. Food and Drug Administration (FDA) for this indication (GPP).
- No effective treatment for alopecia is known (level B).
- Antiandrogens should not be used without effective contraception (level B).
- Flutamide is of limited value because of its dose-dependent hepatotoxicity (level B).
- Drospirenone in the dosage used in some OCPs is not antiandrogenic (level B).

Knowledge Gaps/Recommended Future Research

- Unclear what is the best medical therapy for hirsutism.
- Unclear how long therapy should be continued.
- Unclear how best to evaluate hirsutism clinically.
- Measurement of serum androgens fraught with error but the best estimate we have for hyperandrogenism.

MENSTRUAL IRREGULARITY

Although cycle abnormalities are common during the reproductive years, women with PCOS may ovulate spontaneously. How frequently this occurs is unknown (16), but ovulations have been reported in up to 32% of "cycles." Women with oligomenorrhea or amenorrhea have about a 90% chance of being diagnosed with PCOS, and up to 95% of affected adults have oligomenorrhea or amenorrhea (17). The definition used to establish the diagnosis of PCOS affects the proportion of women included with menstrual irregularities (18).

Amenorrheic women with PCOS usually have the most severe hyperandrogenism and higher antral follicle counts as compared with women presenting with oligomenorrhea or regular menstrual cycles. Menstrual cycles in women with PCOS become more regular as they approach menopause (19, 20). Obesity rather than the menstrual cycle pattern or the size of the follicular cohort determines hyperinsulinemia, dyslipidemia, and hypertension in aging women with PCOS (20).

Conclusions (Agreement)

- Both amenorrheic and oligomenorrheic women may occasionally ovulate (level B).
- Menstrual cycles in women with PCOS may become more regular later in life (level B).
- Irregular menses are associated with increased metabolic risk (level B).
- The greater the menstrual irregularity, the more severe the PCOS phenotype (level B).

Disagreement

- The time needed before regular menstrual cycles occur in young women.
- The extent to which irregular menses (especially amenorrhea) are a source of psychological morbidity and/or decreased quality of life.

Knowledge Gaps/Recommended Future Research

- It is unclear to what extent the severity of the menstrual disturbance is associated with the severity of the PCOS phenotype.
- The natural history and progression of menstrual irregularity in PCOS are not well understood.
- It remains unclear whether PCOS patients have a longer reproductive life span.
- How often do oligomenorrheic or amenorrheic women ovulate?

CONTRACEPTION

Women with PCOS who do not desire pregnancy need contraception. No contraceptive methods are contraindicated in PCOS. However, some of the features associated with PCOS

(such as obesity and insulin resistance) may represent a relative contraindication to the use of combined OCPs. Cycle control is usually achieved by the use of OCP in women with PCOS.

Oral contraceptives suppress LH secretion and lead to a decrease in ovarian androgen production. The estrogenic component increases the levels of sex hormone–binding globulin (SHBG), which, in turn, results in a decrease in circulating free T levels. The progestin in the pill can compete for 5α-reductase at the level of the androgen receptor. Oral contraception also decreases adrenal androgen production by a mechanism yet unclear, possibly due to a decrease in adrenocorticotropin hormone (ACTH) production.

There are few randomized double-blind studies comparing the metabolic effects of a combination of two OCPs, or combined with an insulin sensitizer (21). A Cochrane review, based on limited evidence, concluded that OCP use does not increase metabolic risk (22). Findings from a few small studies suggest that insulin resistance worsens during the natural course of PCOS, but long-term OCP use either does not change or improves cardiometabolic risk parameters, including insulin resistance, lipoprotein profile, and possibly body fat distribution.

Conclusions (Agreement)

- Overall, the benefits of OCPs outweigh the risks in most patients with PCOS (level B).
- Women with PCOS are more likely to have contraindications for OCP use than normal women (level C).
- In the absence of other risk factors, there is no evidence that women with PCOS are at increased risk with OCPs compared with normal women (level C).
- There is no evidence for differences in effectiveness and risk among the various progestogens and when used in combination with a 20 versus a 30 μg daily dose of estrogen (level B).
- Subsequent fertility is not negatively affected by OCPs (level C).
- There is no definitive evidence that the type of OCP determines efficacy of hirsutism control (level C).

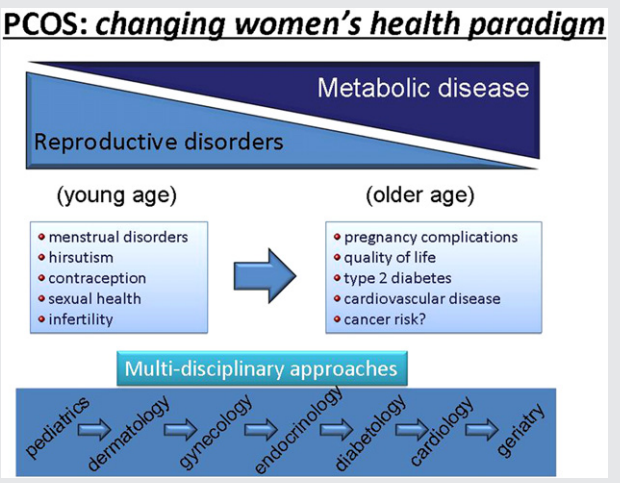
Knowledge Gaps/Recommended Future Research

- Head-to-head blinded trials comparing different OCP strategies are lacking.
- There is a lack of longitudinal follow-up studies after a course of OCPs.

QUALITY OF LIFE

Patients with PCOS are an at-risk group for psychological and behavioral disorders and reduced quality-of-life (QOL) (23–25). Studies in this area have been hampered by the existence of only one validated disease-specific questionnaire, the QOL Questionnaire for Women with PCOS (PCOSQ) (26). A review of generic and specific quality-of-life studies in women with PCOS concluded that (1) PCOS has a significant detrimental effect on QOL compared with controls, (2) weight issues are most apt to affect quality of life, (3) few studies include an instrument specific for PCOS in their assessment, and (4) very few studies include QOL instruments in their assessment of the benefits of the investigated treatment (24).

FIGURE 1



Schematic representation of the change in emphasis from early age reproductive disorders to long-term metabolic and cardiovascular health.

Fauser. ESHRE/ASRM PCOS Consensus. Fertil Steril 2012.

The PCOSQ cannot be used to evaluate the prevalence of emotional and other disorders (e.g., sexual or eating disorders). However, from other validated measures, it appears that patients with PCOS are at higher risk for developing significant psychological difficulties (i.e., depression, anxiety) compared with healthy and other controls and may also be at risk for eating disorders and sexual and relational dysfunction, though this evidence is inconsistent (23). It has been suggested that women with PCOS should undergo psychological screening to improve their long-term prognosis. However, until it is possible to disentangle potential features of the disorder from reactions to it, recommending psychological screening is premature.

Conclusions (Agreement)

- There is evidence of increased prevalence of psychological disorders in women with PCOS (level B).
- Psychological issues should be considered in all women with PCOS because of evidence suggesting increased prevalence and associated comorbidities (level C).
- It is unclear if this increased prevalence is due to the disorder itself or its manifestations (e.g., obesity, hirsutism, irregular menses, infertility) (level C).
- Based on the consultation and the patient's perception of her problems, appropriate counseling and intervention should be offered (level C).

Knowledge Gaps/Recommended Future Research

- Evaluation of the validity of existing instruments for psychopathology as screening tools in PCOS.

- Determination of the prevalence of psychological disorders using appropriate instruments.
- Development of appropriate screening instruments and interventions (level C).
- Determination whether disease, its manifestations, or its consequences lead to psychological disorders.

PREGNANCY

Women with PCOS may be subfertile. This may be explained by the effects of obesity and/or metabolic, inflammatory, and endocrine abnormalities on ovulatory function, oocyte quality, and endometrial receptivity. Ovarian hyperandrogenism and hyperinsulinemia may promote premature granulosa cell luteinization, and paracrine dysregulation of growth factors may disrupt the intrafollicular environment and impair cytoplasmic and/or nuclear maturation of oocytes (27). These features are not universal, and oocyte quality, fertilization, and implantation rates in an individual woman with PCOS can be normal (28).

During early pregnancy, the embryo may be exposed to androgen excess in utero. This may have long-term effects, particularly on female offspring. Fetal hyperandrogenism may disturb epigenetic programming, in particular those genes regulating reproduction and metabolism. Data in relation to the risk of miscarriage in women with PCOS are conflicting, although miscarriage rates are generally thought to be comparable with other subfertile populations (29, 30). When pregnancy occurs in women with PCOS, there is a higher incidence of gestational diabetes (GDM) (40% to 50%) and associated fetal macrosomia, gestational hypertensive disorders (such as preeclampsia and pregnancy-induced hypertension) (5%), and birth of small-for-gestational-age (SGA) babies (10% to 15%) (31). The use of metformin for women with anovulatory PCOS has no benefit with respect to enhancing either fertility or live-birth rates, and its routine use is not recommended.

Conclusions (Agreement)

- Women with PCOS who desire a pregnancy may be at increased risk for adverse pregnancy outcomes, and this may be exacerbated by obesity and/or insulin resistance (level B).
- Health should be optimized before conception, with advice about smoking cessation, lifestyle, diet, and appropriate vitamin supplementation (e.g., folic acid) (GPP).
- Miscarriage rates are not increased in natural conceptions in women with PCOS, independent of obesity. Miscarriage rates after induction of ovulation mirror those found in other infertile populations (level A).
- Women with PCOS should be observed closely during pregnancy as they may be at increased risk for the development of GDM, gestational hypertension, and associated complications (level B).
- Pregnancy-associated risks are greater in women diagnosed by more classic (NIH) criteria as opposed to nonhyperandrogenic women (level B).
- Babies born from women with PCOS may have increased morbidity and mortality (level B).
- There is no evidence for improved live-birth rates or decreased pregnancy complications with the use of metformin either before conception or during pregnancy (level A).

Knowledge Gaps/Recommended Future Directions for Research

- Is there any value to specific periconceptional diets for women with PCOS?
- Should pregnancies of women with PCOS have increased antenatal monitoring, including earlier screening for GDM and additional Doppler studies?
- What is the long-term outcome of children born from women with PCOS?
- What is the long-term outcome for women with PCOS who develop gestational hypertension and GDM compared with women with PCOS who do not conceive?

ETHNIC DIFFERENCES IN THE PHENOTYPE

There is considerable ethnic variation in the expression of PCOS, including the prevalence and severity of obesity, metabolic disturbances, and their correlates. There are differences in psychosocial aspects affecting QOL and health-seeking behaviors (32). For example, Asian women are generally shorter, have a lower BMI, and a milder hyperandrogenic phenotype. South Asians in particular have a high prevalence of the metabolic syndrome (MetS) and are at risk for type 2 diabetes (T2D), with central obesity more than BMI reflecting their metabolic risk (33). A common clinical indicator of greater metabolic risk is acanthosis nigricans.

African American and Hispanic women are more often obese and more prone to metabolic problems; women of African descent are particularly prone to hypertension and cardiovascular disease, whereas Hispanic women are more at risk for MetS and T2D (34). There is a strikingly high prevalence of hirsutism among women of Middle Eastern and Mediterranean origin. Nevertheless, abnormal glucose tolerance in southern and eastern Europeans is far less common than in South Asians and Hispanics (33, 35). Geographic location, ethnic origin, and cultural/social practices are likely contributors to the differing manifestations of PCOS and should be recognized in routine clinical practice.

Conclusions (Agreement)

- Ethnic origin and culture contribute to the differing manifestations of PCOS (level B).
- Ethnically appropriate thresholds are required for identifying anthropometric cutoffs for appropriate metabolic screening in high-risk ethnic groups (level B).

Knowledge Gaps/Future Directions for Research

- Effects of migration and rapid economic development for different ethnic groups for long-term cardiovascular and metabolic risk.
- Population-based prevalence of PCOS in all ethnicities.

- Best management for manifestations by ethnicity, and the role of genetic and environmental factors to explain ethnic variances.
- Effects of insulin sensitizers in different ethnic groups.

OBESITY

There is widespread variability in the prevalence of overweight (BMI 25 to 30 kg/m^2) and obese (BMI >30 kg/m^2) women in PCOS populations across different countries. The proportion of women with PCOS who are overweight but not obese ranges from 10% in Italy to 37% in Kuwait. The highest prevalence of obesity is reported in studies conducted in the United States and Australia, with 61% to 76% of women with PCOS considered obese (36, 37).

Women with PCOS are more likely to have upper-body fat distribution compared with weight-matched controls. Greater abdominal or visceral adiposity is associated with greater insulin resistance, which could exacerbate the reproductive and metabolic abnormalities in PCOS (38). It is known that obesity is associated with PCOS, but its causal role in this condition has yet to be determined. Very few studies report the association of BMI with menstrual irregularity. Few randomized controlled studies have been performed on lifestyle interventions, but these suggest substantial reproductive and metabolic benefits (39, 40).

Conclusions (Agreement)

- The prevalence of obesity is increasing and has an important bearing on the phenotype of PCOS (level B).
- Some studies suggest that higher BMI is associated with a greater prevalence of menstrual irregularity, hyperandrogenemia, and hirsutism, but more studies are required to confirm this (level B).
- Increased BMI and visceral adiposity are associated with greater insulin resistance as in the general population, but its effect on menstrual irregularity and hirsutism remain unclear (level B).
- Lifestyle management results in weight loss and improves surrogate markers of metabolic disease/syndrome (level A).

Knowledge Gaps/Recommended Future Directions for Research

- Mechanistic studies are necessary to understand the evolution of obesity and PCOS. Does PCOS predispose to obesity, and does obesity unmask latent PCOS?
- More studies are required of the type and duration of exercise specifically for women with PCOS.
- Further research is required on determinants of increasing participation and compliance in lifestyle programs as well as the effects of these interventions on primary outcomes such as live birth, perinatal morbidity, and diabetes prevention.
- Research is required on the role of bariatric surgery for all aspects of PCOS and on the offspring of women with PCOS conceived after such surgery.
- Research is required to optimize lifestyle interventions, maximizing weight loss and minimizing dropouts among participating women.

INSULIN RESISTANCE AND THE METABOLIC SYNDROME (METS)

Insulin resistance is a prevalent finding in the obese in general, and in women with PCOS (41). It is most prevalent and severe in those with the classic NIH PCOS phenotype involving hyperandrogenism and chronic anovulation. Women with PCOS assessed by the Rotterdam criteria yet with regular cycles are metabolically less abnormal (40, 42, 43).

The cellular and molecular mechanisms of insulin resistance in PCOS differ from those in other common insulin-resistant states such as obesity and T2D. In vivo insulin action is profoundly decreased in skeletal muscle secondary to signaling defects, but hepatic insulin resistance is present only in obese women with PCOS. There is a synergistic negative effect of having both PCOS and obesity on insulin action. Pancreatic β-cell dysfunction is also present in PCOS but may be more related to T2D risk factors as this dysfunction is most severe in women with a first-degree relative who has T2D (44).

Extensive evidence indicates that hyperinsulinemia contributes directly to reproductive dysfunction in PCOS (41). Women with classic NIH PCOS have significantly increased rates of the MetS compared with reproductively normal women of similar age and weight.

Conclusions (Agreement)

- Metabolic disorders associated with PCOS are major predictors of prediabetes, diabetes, and MetS in reproductive-age women (level B).
- Patients with MetS are an important clinical subset of women with PCOS (level B).
- Not all PCOS phenotypes have similar metabolic risk. The combination of hyperandrogenemia and oligomenorrhea signifies the most at-risk group (level B).
- It is critical for public health and for optimum design of long-term studies to stratify women with PCOS according to metabolic risk. This goal would be greatly facilitated by using a specific name for this high metabolic risk PCOS subset (GPP).

Knowledge Gaps/Recommended Future Directions for Research

- Long-term prospective studies to define metabolic outcomes and cardiovascular disease (CVD) risk in PCOS.
- Research on the role of androgens in the spectrum of MetS risk in women.
- Further definition of the importance of adipocyte pathophysiology, in particular in the visceral adipose depot, in the evolution of insulin resistance and MetS in PCOS.

TYPE 2 DIABETES (T2D)

Insulin resistance is a prominent feature of PCOS. There is now compelling evidence from epidemiologic data (45) that PCOS is

associated with increased risk of impaired glucose tolerance (IGT), GDM, and T2D (31, 40, 41). Biochemical screening in the form of an oral glucose tolerance test (OGTT) is indicated in obese women with PCOS, and/or those with increased visceral adiposity, as measured by waist circumference. Risk of IGT or diabetes is highest in women who have both oligo-ovulation or anovulation and hyperandrogenism, and the risk is further amplified by obesity (46).

Management of women at risk for T2D should include diet and lifestyle improvement as the first-line treatment. Metformin treatment is indicated in those with IGT who do not respond adequately to calorie restriction and lifestyle changes. In those with frank diabetes, metformin is safe and effective whereas there is concern about the use of thiazolidinediones and glucagonlike peptide-1 analogues in women of reproductive age (47).

Conclusions (Agreement)

- PCOS is a major risk factor for developing IGT and T2D (level A).
- Obesity (by amplifying insulin resistance) is an exacerbating factor in the development of IGT and T2D in PCOS (level A).
- The increasing prevalence of obesity in the population suggests that a further increase in diabetes in PCOS is to be expected (level B).
- Screening for IGT and T2D should be performed by OGTT (75 g, 0- and 2-hour values). There is no utility for measuring insulin in most cases (level C).
- Screening should be performed in the following conditions: hyperandrogenism with anovulation, acanthosis nigricans, obesity (BMI >30 kg/m^2, or >25 in Asian populations), in women with a family history of T2D or GDM (level C).
- Diet and lifestyle are first choice for improving fertility and prevention of diabetes (level B).
- Metformin may be used for IGT and T2D (level A). Avoid use of other insulin sensitizing agents such as thiazolidinediones (GPP).

Knowledge Gaps/Recommended Future Research

- Identification of genetic factors contributing to diabetes risk in PCOS.
- Clear definition of the interaction of obesity and body fat distribution with PCOS in development of IGT and T2D.
- Definition of the prevalence of GDM in a large cohort of women with PCOS.
- Collection of good longitudinal data on progression from IGT to T2D.
- Data on efficacy and safety of newer drugs for treatment of T2D in PCOS (including GLP-1 agonists).
- Better assessment of the efficacy of bariatric surgery and its long-term effect.

CARDIOVASCULAR DISEASE MARKERS

Metabolic dysfunction in women with PCOS leads to exaggerated risk for cardiovascular disease (CVD) with aging. Markers for CVD risk reflect the metabolic dysfunction. Changes can occur without obesity and are magnified with obesity. More android central obesity occurs in nonobese women with PCOS. Severity of insulin resistance is related to the amount of abdominal obesity even in women with a normal BMI. This is likely to contribute to the abnormalities in the classic markers for CVD risk (IGT, metabolic syndrome, T2DM, dyslipidemia).

The odds for these CVD risk indicators are approximately three times higher in women with PCOS compared with women without PCOS, and in BMI-matched studies the odds are approximately double. The prevalence of these increased CVD risk markers differs by geographic region (48). The more severe PCOS phenotypes are associated with a greater magnitude of CVD risk, and this has been found in obese and nonobese women (49, 25).

Triglyceride, low density lipoprotein (LDL), and non–high density lipoprotein (HDL) cholesterol changes are higher compared with women who do not have PCOS. This reflects more atherogenic apolipoprotein B (ApoB)/ApoA ratios. Differences are greater when PCOS is diagnosed using NIH rather than Rotterdam criteria. Assessing waist circumference and non-HDL-cholesterol appear to be the most useful clinical indicators of this metabolic disturbance. Systemic inflammation associated with endothelial vascular dysfunction and metabolic disturbance is commonly present in women with PCOS. Numerous biochemical inflammatory and thrombotic markers of CVD risk circulate in excess in women with PCOS. Some of these markers correlate with insulin resistance. It remains unclear if increased levels of markers of inflammation and thrombotic risk CVD risk provide additional predictive power beyond assessment using classic CVD risk factor estimates for estimating individual of CVD.

Conclusions (Agreement)

- PCOS at any age is characterized by greater odds for elevated CVD risk markers. Elevated markers occur without obesity and are magnified with obesity (level B).
- Dyslipidemia, IGT, and T2D (classic risk indicators of atherosclerosis and CVD) are more prevalent in women with PCOS, even when weight matched with normal control women (level B).
- Altered levels of triglycerides, HDL, LDL, and non-HDL (reflecting altered ApoB/ApoA metabolism) are prevalent in women with PCOS and are more severe in hyperandrogenic women (level B).
- Non-HDL cholesterol and waist measurement appear to be the best clinical indicators of elevated CVD risk (level C).
- All markers reflect a greater magnitude of risk when women are diagnosed using NIH criteria (including hyperandrogenism) compared with the Rotterdam criteria (level B).
- Depression and anxiety, major risk factors for CVD, are common in women with PCOS (level B).
- The recommended CVD risk assessment at any age is for psychosocial stress, blood pressure, glucose, lipid profile (cholesterol, triglycerides, HDL, LDL, and non-HDL

cholesterol), waist circumference, physical activity, nutrition, and smoking (level C).
- Because CVD risk increases with age and accompanying additive environmental insults, periodic reassessment for CVD risk is recommended (GPP).

Knowledge Gaps/Recommended Future Research

- How often should CVD risk assessment be repeated in women with PCOS with or without elevated risk indicators?
- What are optimal specific recommendations in various races or ethnicities?
- Which novel CVD risk markers provide added benefit beyond the classic CVD risk indicators?
- Longitudinal studies associating surrogate markers with CVD events are needed for precise CVD risk prediction.

CARDIOVASCULAR DISEASE OUTCOMES

Life-long metabolic dysfunction in women with PCOS exaggerates the risk for CVD with aging, particularly after menopause. This metabolic dysfunction is based upon insulin resistance, which occurs in most women with PCOS and is independent of and additive with obesity. Consequently, beginning in adolescence, IGT and T2D are highly prevalent in PCOS (odds ratio (OR) of approximately 4:1) and occur in about 40% of women with PCOS by the fourth decade of life, with age and weight gain worsening glycemic control. Insulin-resistant women with PCOS have vascular dysfunction, which is associated with total and abdominal adiposity. Women with PCOS also have more subclinical vascular disease than normal women. The severity of carotid-intima media thickening, coronary artery calcification, and to a lesser extent aortic calcification are greater in women with PCOS (by NIH criteria) than controls, independent of age and BMI.

Nevertheless, evidence for increased CVD morbidity and mortality in women with PCOS, based upon Rotterdam and/or NIH criteria, remains inconclusive (20, 50–52). It is not possible to properly diagnose PCOS after menopause. Nevertheless, postmenopausal women with existent hyperandrogenemia and premenopausal menstrual irregularity have a larger number of cardiovascular events than controls, despite technical challenges in accurately measuring low circulating androgen levels in this age group (53). Among nondiabetic postmenopausal women with intact ovaries, moreover, atherosclerotic CVD is associated with features of PCOS, including premenopausal menstrual irregularity, hirsutism, and postmenopausal biochemical hyperandrogenism (54).

Conclusions (Agreement)

- Life-long metabolic dysfunction in women with PCOS exaggerates CVD risk, causing a possible increase in CVD events with age, especially after menopause (level B).
- All surrogate markers of cardiovascular risk are higher in PCOS (adjusted for age and BMI), but the association of these markers with cardiovascular events in PCOS remains unclear (level B).
- Endothelial dysfunction in PCOS is related to abdominal obesity and insulin resistance (level B).
- Coronary artery calcification and carotid intima media wall thickness are also increased in women with PCOS compared with matched controls (level B).
- Among nondiabetic postmenopausal women with intact ovaries, atherosclerotic CVD is associated with features of PCOS, such as relative androgen excess and a recalled history of irregular menses (level B).

Disagreement

- Uncertainty exists as to whether PCOS status per se increases cardiovascular mortality.

Knowledge Gaps/Recommended Future Research

- Data are lacking regarding ethnic and racial differences in the set point for vascular damage associated with PCOS.
- Precision of cardiovascular surrogate markers is unknown.
- Association between cardiovascular surrogate markers and cardiovascular events is unclear.
- Longitudinal studies are needed to associate cardiovascular markers with vascular events.
- Longitudinal studies are lacking regarding the effects of various PCOS phenotypes on cardiovascular events.
- The role of sex steroids on regional adipogenesis and its impact on total and abdominal obesity is uncertain.
- It is uncertain whether PCOS phenotypic expression varies over lifetime and modulates cardiovascular risk.
- It is uncertain whether hyperandrogenemia per se has its own independent effects on atherosclerosis.
- The optimum multifaceted approach to women with PCOS that reduces and prevents CVD has yet to be determined.

CANCER RISK

Polycystic ovary syndrome is a common reproductive disorder resulting in a disruption of normal reproductive physiology. This condition may be associated with increased risk of the development of cancer of the endometrium, ovary, and/or breast, either directly or mediated by its associated reproductive-metabolic alterations. There is a small to moderate amount of literature assessing the association of PCOS with the development of cancer of the reproductive organs.

Estimates of the strength of association are likely to be sensitive to a number of factors including limitations in the definition of PCOS, limitations in comparison with various populations, and the small number of studies assessing each cancer type (50, 52, 55, 56).

Conclusions (Agreement)

- There are moderate quality data to support that women with PCOS have a 2.7-fold (95% confidence interval [CI], 1.0–7.3) increased risk for endometrial cancer. Most endometrial cancers are well differentiated and have a good prognosis (level B).
- Limited data exist that do not support the conclusion that women with PCOS are at increased risk for ovarian cancer (level B).

- Limited data exist that do not support the conclusion that women with PCOS are at increased risk for breast cancer (level B).

Disagreement

- There is no agreement on the optimal modality or timing of how to monitor women for the presence of endometrial cancer or precursor endometrial changes using ultrasound and/or endometrial biopsy. The decision to assess for the presence of endometrial cancer should be based on clinical factors including length of amenorrhea, presence of abnormal uterine bleeding, thickness and appearance of the endometrium on imaging, and the age of the patient (GPP).

Knowledge Gaps/Recommended Future Research

- There is insufficient evidence to evaluate any association of PCOS with vaginal, vulvar, or cervical cancer.
- Cancer risk with PCOS is difficult to separate from other recognized risk factors such as nulliparity, infertility and its treatment, anovulation, and obesity.
- There is a lack of precision in the estimate of the risk of endometrial cancer in PCOS, especially in subgroups with and without risk factors.
- There is limited confidence in the association of PCOS and ovarian cancer.
- Cancer studies in PCOS should involve more patients, with more clarity on the phenotypic variation in the diagnosis of PCOS.
- Comparison population studies should be conducted and improved.

MENOPAUSE, GENERAL HEALTH

The transition of women with PCOS into menopause and whether there is a specific phenotype for PCOS after menopause is poorly understood. There is evidence that women with PCOS have a larger cohort of primary follicles than age-matched control women before menopause. Serum T levels decrease as women age from the third to fifth decades. Additionally, women with PCOS often develop improved menstrual regularity with age. These factors may all contribute to improvement in reproductive functioning with age before menopause. Menopausal PCOS phenotype is poorly defined. The polycystic ovary criterion is likely not useful after menopause.

It is not definitively known what the general health status of postmenopausal women with PCOS is, or what are optimum therapies. It is suspected that women with PCOS who have transitioned through menopause will have increased rates of obesity, diabetes, and cardiovascular events. Most reports tend to show normal or increased bone mineral density in women with PCOS. The natural history of hirsutism and/or alopecia in postmenopausal women with PCOS is unknown. It is difficult from the existing data to know whether the mortality rate is different in women with PCOS. Retrospective data in women with polycystic ovaries suggest mortality occurs at a similar rate as in the general population and presumably at the same age (19, 57–61). Alternative data suggest they have higher rates of stroke and CVD.

Conclusions (Agreement)

- Age may improve many manifestations of PCOS, including normalizing ovarian size and morphology, T levels, and oligo-ovulation before menopause (level B).

Knowledge Gaps/Recommended Future Research

- There are little data on long-term fecundity and precise age of menopause in women with PCOS.
- The long-term risk for morbidity and mortality among postmenopausal women with a history of PCOS is uncertain.
- There is no established phenotype for PCOS after menopause.
- Most clinical assays are not precise for determining T levels in postmenopausal women.
- Long-term, multicenter cohort studies are needed where the following issues should be assessed: menopausal phenotype, cardiovascular events, cancer, and other causes of morbidity/mortality.
- Genomewide association studies should be used to identify new genes/pathways involved in ovarian dysfunction related to age of menopause and polycystic ovaries.

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