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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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ABSTRACT: 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). The present third PCOS consensus paper 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.

Key words: PCOS / hirsutism / contraception / quality of life / pregnancy / type 2 diabetes / cardiovascular disease / insulin resistance / cancer / menopause

Introduction

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women with a prevalence between 6 and 10% based on the National Institute of Health criteria and as high as 15% when the broader Rotterdam criteria are applied. PCOS is typically first identified during the early reproductive years. The clinical expression varies but commonly includes oligo- 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 (The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2004a,b); the second in Thessaloniki, Greece, in 2007, dealt with infertility management in PCOS (The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group, 2008a,b). The conclusions of these meetings have subsequently been 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—which is the focus of the present paper—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 post-reproductive 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 above are published in the journals (maximum of five references per paragraph). Comprehensive background information will be provided in the initial working document published online.

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

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‡ The members of The Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group is listed in the Appendix section.

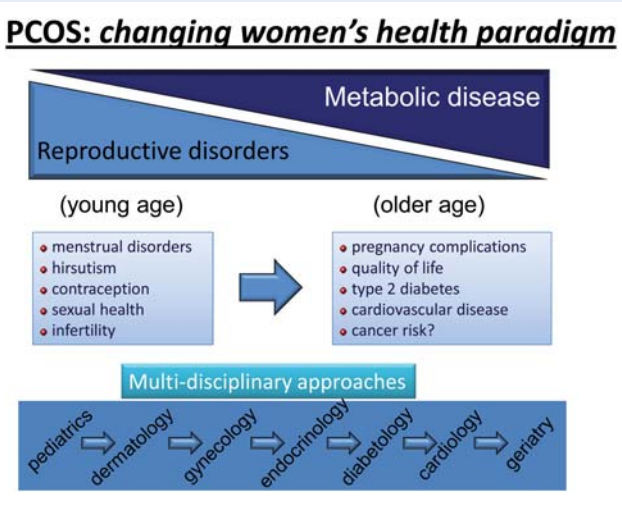

Figure 1 Schematic representation of the change in emphasize from early age reproductive disorders to long-term metabolic and cardiovascular health.

Level A requires at least one randomized controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation.

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

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

GPP, good practice points.

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 (Blank *et al.*, 2008). In all young women, irregular menses are common in the years immediately following menarche. As many as 85% of menstrual cycles are anovulatory during the first year after menarche, while up to 59% are still anovulatory during the third year following menarche (Apter, 1998). In one study, persisting oligomenorrhea was not predicted by increased androgens, polycystic ovaries on ultrasound or increased serum LH levels (van Hooff *et al.*, 2004). Increased BMI, however, was the major risk factor for persistent anovulation.

Only around 40% of adolescent women with menstrual irregularity have polycystic ovaries on ultrasound (Venturoli *et al.*, 1995). These considerations have led to the suggestion that all three elements of the Rotterdam criteria should be present in teenagers in order to make the diagnosis of PCOS (Carmina *et al.*, 2010). These investigators suggest that oligomenorrhea or amenorrhea should be present for at least 2 years after menarch (or primary amenorrhea at age 16 years), 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 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.
- Value of intervention in PCOS early in adolescence should be assessed.
- Unclear if 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 ~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 in 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). OCPs are often prescribed in combination with an anti-androgen to block androgen action at the hair follicles. Anti-androgens 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 anti-androgen to OCPs has not appeared to increase 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 (O'Brien *et al.*, 1991; Erenus *et al.*, 1997; Moghetti *et al.*, 2000). Notably, anti-androgens should not be used without effective contraception (given potential fetal toxicity). Flutamide is of limited value because of associated hepatotoxicity. In addition, drospirenone in the dose used as a component of some OCPs is not anti-

androgenic. Insulin-sensitizing agents, such as metformin and pioglitazone, have little effect on hirsutism or acne (Harborne *et al.*, 2003; Cosma *et al.*, 2008). Physical approaches, to remove unwanted hair, including electrolysis and laser, may be acceptable to many patients.

In severe acne, isoretinoin can be beneficial, but individual responses vary. It is not effective for hirsutism and occasionally may lead to alopecia. Topical treatment with eflornithine hydrochloride, an inhibitor of ornithine decarboxylase limits cell division, has been shown effective for decreasing the development of new unwanted facial hair (Balfour and McClellan, 2001). No effective pharmacological 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 FDA approved for this indication (GPP).
- No effective treatment for alopecia is known (Level B).
- Anti-androgens 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 OCs is not anti-androgenic (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 is fraught with error but is 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 (Laven *et al.*, 2002), but ovulations have been reported in up to 32% of 'cycles'. Women with oligo- or amenorrhea have about a 90% chance of being diagnosed with PCOS and up to 95% of affected adults have oligo- or amenorrhea (Kumarapeli *et al.*, 2008). The definition used to establish the diagnosis of PCOS affects the proportion of women included with menstrual irregularities (Vutyavanich *et al.*, 2007).

Amenorrheic women with PCOS usually have the most severe hyperandrogenism and higher antral follicle counts when compared with women presenting with oligomenorrhea or regular menstrual cycles. Menstrual cycles in women with PCOS become more regular as they approach menopause (Dahlgren *et al.*, 1992; Elting *et al.*, 2001). One large study reported that obesity rather than the menstrual cycle pattern or the size of the follicular cohort determines hyperinsulinemia, dyslipidemia and hypertension in aging women with PCOS (Elting *et al.*, 2001).

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) represent a source of psychological morbidity and/or decreased quality of life.

Knowledge gaps/recommended future research

- 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 oligo- 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 [obesity, insulin resistance (IR) etc.] may represent a relative contraindication to the use of combined OCPs. Cycle control is usually achieved by the use of OCPs in women with PCOS.

OCPs suppress LH secretion and lead to a decrease in ovarian androgen production. The estrogenic component increases the levels of 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 production.

There are few randomized double-blind studies comparing the metabolic effects of a combination of two OCPs, or combined with an insulin sensitizer (Yildiz, 2008). A Cochrane review, based on limited evidence, concluded that OCP use does not increase metabolic risk (Costello *et al.*, 2007). Findings from few small studies suggest that IR worsens during the natural course of PCOS, while long-term OCP use either does not change or improves cardiometabolic risk parameters, including IR, lipoprotein profile and possibly body fat distribution.

Conclusions

- 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 of cardiovascular disease (CVD) with OCP treatment 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).
- OCPs do not negatively affect subsequent fertility (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.
- 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) (*Himelein and Thatcher, 2006*; Jones *et al.*, 2008; Dokras *et al.*, 2011). 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) (Cronin *et al.*, 1998). A review of generic and specific QoL studies in women with PCOS concluded: (i) PCOS has a significant detrimental effect on QoL compared with controls, (ii) weight issues were most apt to affect QoL, (iii) few studies included an instrument specific for PCOS in their assessment and (iv) very few studies included QoL instruments in their assessment of the benefits of the investigated treatment (Jones *et al.*, 2008).

The PCOSQ cannot be used to evaluate the prevalence of emotional and other disorders (e.g. sexual and 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 (Himelein and Thatcher, 2006). It has been suggested that women with PCOS should undergo psychological screening to improve 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 co-morbidities (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 etc.) (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.
- Appropriate screening instruments and interventions remain to be developed (Level C).
- Determine if it is the disease, its manifestations or consequences that lead to psychological disorders.

Pregnancy

Women with PCOS may be subfertile. This may be explained by the effects of obesity, 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 (Dumesic *et al.*, 2008). These features are not universal, and oocyte quality, fertilization and implantation rates in an individual woman with PCOS can be normal (Weghofer *et al.*, 2007).

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 (Tang *et al.*, 2010; Vanky *et al.*, 2010). When pregnancy occurs in women with PCOS, there is a higher incidence of gestational diabetes (GDM) (40–50%) and associated fetal macrosomia, gestational hypertensive disorders (such as pre-eclampsia and pregnancy-induced hypertension) (5%), and birth of small-for-gestational-age babies (10–15%) (Boomsma *et al.*, 2006). 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. This may be exacerbated by obesity and/or IR (Level B).
- Health should be optimized prior to 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 followed 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 non-hyperandrogenic 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 of specific periconceptional diets for women with PCOS?
- Should pregnancies of women with PCOS have increased antenatal monitoring, including earlier screening for GDM, additional Doppler studies etc.?
- Long-term outcome of children born from women with PCOS.
- Long-term outcome for women with PCOS who develop gestational hypertension and GDM, compared with women with PCOS who do no't conceive.

Ethnic differences in the phenotype

There is considerable ethnic variation in the expression of PCOS, including prevalence and severity of obesity, metabolic disturbance and their correlates. There are differences in psycho-social aspects affecting QoL and health-seeking behaviors (Goodarzi *et al.*, 2005). 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 risk for type 2 diabetes (T2D), with central obesity more than BMI reflecting metabolic risk (Wijeyaratne *et al.*, 2011). 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; African descendents are particularly prone to hypertension and CVD, while Hispanic women are more at risk for MetS and T2D (Lo *et al.*, 2006). There is a strikingly high prevalence of hirsutism among women from the Middle East and those of Mediterranean origin. Nevertheless, abnormal glucose tolerance in Southern Europeans and East Europeans is far less common than in South Asians and Hispanics (Kalra *et al.*, 2009; Wijeyaratne *et al.*, 2011). The geographic location, ethnic origin and cultural/social practices are likely contributors to the differing manifestation of PCOS and should be recognized in routine clinical practice.

Conclusions (agreement)

- Ethnic origin and culture contribute to the differing manifestation of PCOS (Level B).
- Ethnically appropriate thresholds are required for identifying anthropometric cut-offs 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 managements for manifestations by ethnicity. 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 25–30 kg/m^2) and obese (BMI $>$ 30 kg/m^2) women in PCOS populations across different countries. The proportion of PCOS women 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 USA and Australia, with 61–76% of PCOS women considered obese (Glueck *et al.*, 2005; Ching *et al.*, 2007).

PCOS women are more likely to have upper body fat distribution compared with weight-matched controls. Greater abdominal or visceral adiposity is associated with greater IR, which could exacerbate the reproductive and metabolic abnormalities in PCOS (Lord *et al.*, 2006). 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 associations of BMI with menstrual irregularity. Only a few randomized controlled studies on lifestyle interventions exist, but these suggest substantial reproductive and metabolic benefit (Moran *et al.*, 2009, 2010).

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 IR as in the general population, but its effect on menstrual irregularity and hirsutism remains 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 into the type and duration of exercise beneficial to 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, diabetes prevention etc.
- Research is required on the role of bariatric surgery for all aspects of PCOS and the off-spring of women with PCOS conceived after such surgery.
- Research is required to optimize lifestyle interventions, maximizing weight loss and minimizing drop-outs of participating women.

IR and MetS

IR is a prevalent finding in women with PCOS (Dunaif, 1997). It is most prevalent and severe in those with the classic NIH PCOS phenotype involving hyperandrogenism and chronic anovulation. Women with PCOS assessed by Rotterdam criteria yet with regular cycles are metabolically less abnormal (*Legro et al., 2005*; Johnstone *et al.*, 2010; Moran *et al.*, 2010).

The cellular and molecular mechanisms of IR in PCOS differ from those in other common IR states such as obesity and T2D. *In vivo* insulin action is profoundly decreased in skeletal muscle secondary to signaling defects, but hepatic IR 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 since this dysfunction is most severe in women with a first-degree relative who have T2D (Ehrmann *et al.*, 1995).

Extensive evidence indicates that hyperinsulinemia contributes directly to reproductive dysfunction in PCOS (Dunaif, 1997). Women with classic NIH PCOS have significantly increased rates of the MetS compared with reproductively normal women of similar age and weight.

Conclusions (agreement)

- PCOS-associated metabolic disorders 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 CVD risk in PCOS.
- The role of androgens in the spectrum of MetS risk in women.
- Further, define the importance of adipocyte pathophysiology, in particular in the visceral adipose depot, in the evolution of IR and MetS in PCOS.

Type 2 diabetes

IR is a prominent feature of PCOS. There is now compelling evidence from epidemiological data (Solomon *et al.*, 2001) that PCOS is associated with increased risk of impaired glucose tolerance (IGT), GDM and T2D (Dunaif, 1997; Boomsma *et al.*, 2006; Moran *et al.*, 2010). 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/anovulation and hyperandrogenism, and the risk is further amplified by obesity (Barber *et al.*, 2007).

Management of women at risk for T2D should include diet and lifestyle improvement as 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 glucagon-like peptide-1 analogs in women of reproductive age (Franks, 2011).

Conclusions (agreement)

- PCOS is a major risk factor for developing IGT and T2D (Level A).
- Obesity (by amplifying IR) 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 h 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 in 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 the development of IGT and T2D.
- Need to define the prevalence of GDM in a large cohort of women with PCOS.
- Need for collection of good longitudinal data on progression from IGT to T2D.
- Need to gather data on efficacy and safety of newer drugs for treatment of T2D in PCOS (including GLP-1 agonists).
- Need to better assess the efficacy of bariatric surgery and its long-term effect.

CVD markers

Metabolic dysfunction in women with PCOS leads to exaggerated risk for 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 non-obese women with PCOS. Severity of IR is related to the amount of abdominal obesity even in women with normal BMI. This is likely to contribute to the abnormalities in the classic markers for CVD risk (IGT, MetS and T2DM and dyslipidemia).

The odds for these CVD risk indicators are ~3 times higher in women with PCOS compared with those without PCOS, and in BMI-matched studies, the odds are approximately double. The prevalence of these increased CVD risk markers differs by geographical region (Chen *et al.*, 2010). The more severe PCOS phenotypes are associated with greater magnitude of CVD risk and this has been found in obese and non-obese women (Zhao *et al.*, 2010; Dokras *et al.*, 2011).

Triglyceride, low-density lipoprotein (LDL) and non-high-density lipoprotein (HDL) cholesterol changes are higher compared with non-PCOS women. This reflects more atherogenic 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 IR. 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).
- Recommended CVD risk assessment at any age: assessment 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.

CVD 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 IR, which occurs in most women with PCOS, being independent and additive with that of obesity. Consequently, beginning in adolescence, IGT and T2D are highly prevalent in PCOS [odds ratio (OR) of ~4:1] and occur in ~40% of PCOS women 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 is 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 (*Pierpoint et al., 1998*; Cibula *et al.*, 2000; Wild *et al.*, 2000; Elting *et al.*, 2001). It is not possible to properly diagnose PCOS after menopause. Nevertheless, post-menopausal 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 (Shaw *et al.*, 2008). Among non-diabetic post-menopausal women with intact ovaries, moreover, atherosclerotic CVD is associated with features of PCOS, including premenopausal menstrual irregularity, hirsutism and post-menopausal biochemical hyperandrogenism (Krentz *et al.*, 2007).

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 CV events in PCOS remains unclear (Level B).
- Endothelial dysfunction in PCOS is related to abdominal obesity and IR (Level B).

- Coronary artery calcification and carotid intima-media wall thickness are also increased in women with PCOS compared with matched controls (Level B).
- Amongst non-diabetic post-menopausal 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 CV 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 CV surrogate markers is unknown.
- Association between CV surrogate markers and CV events is unclear.
- Longitudinal studies are needed to associate CV markers with vascular events.
- Longitudinal studies are lacking regarding the effects of various PCOS phenotypes on CVD events.
- The role of sex steroids on regional adipogenesis and its impact on total and abdominal obesity is uncertain.
- Does PCOS phenotypic expression vary over lifetime and modulate CV risk?
- Does hyperandrogenemia *per se* have its own independent effects on atherosclerosis?
- Determine the optimum multi-faceted approach to PCOS women that reduces and prevents CVD.

Cancer risk

PCOS disrupts normal reproductive physiology. The 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 (*Schildkraut et al., 1996*; Pierpoint *et al.*, 1998; Wild *et al.*, 2000; Chittenden *et al.*, 2009).

Conclusions (agreement)

- There are moderate quality data to support that women with PCOS have a 2.7-fold (95% confidence interval 1.0–7.3) increased risk for endometrial cancer. Most endometrial cancers are well differentiated and have a good prognosis (Level B).
- Limited data suggest that PCOS women are not at increased risk for ovarian cancer (Level B).
- Limited data suggest that PCOS women are not 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

- Insufficient evidence to evaluate any association of PCOS with vaginal, vulvar or cervical cancer.
- Difficulty in separating PCOS cancer risk from other recognized risk factors such as nulliparity, infertility and its treatment, anovulation and obesity.
- Lack of precision in the estimate of the risk of endometrial cancer in PCOS, especially in subgroups with and without risk factors.
- Limited confidence in the association of PCOS and ovarian cancer.
- Cancer studies in PCOS should involve more subjects, 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 prior to menopause. Menopausal PCOS phenotype is poorly defined. The polycystic ovary criterion is likely not useful in post-menopause.

It is not definitively known what the general health status of post-menopausal 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 post-menopausal 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 (*Dahlgren et al., 1992*; Mulders *et al.*, 2004; Davison *et al.*, 2005; Alsamarai *et al.*, 2009; Hudecova *et al.*, 2009; Tehrani *et al.*, 2010).

Alternative data suggest that 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 prior to 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.
- Long-term risk for morbidity and mortality among post-menopausal 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 post-menopausal women
- Long-term, multi-center cohort studies are needed where the following issues should be assessed: menopausal phenotype, cardiovascular events, cancer and other causes of morbidity/mortality.
- Utilize genome-wide association studies to identify new genes/pathways involved in ovarian dysfunction related to age of menopause and polycystic ovaries.

Supplementary Information

An extended supplementary document containing comprehensive background information is provided online at http://humrep.oxfordjournals.org/.

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Conflict of interest

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Appendix

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