

Review Article

Long-Term Health Risks of Polycystic Ovary Syndrome

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Abstract

Polycystic Ovary Syndrome (PCOS) is a gynecologic endocrinologic disorder that causes systematic hormonal imbalances and is estimated to affect approximately 10% of women at their reproductive age. The current literature shows that women with PCOS have higher risk factors for premature morbidity and mortality. PCOS seems to have increased the prevalence of cardiovascular risk, hypertension, insulin resistance, and uterine pathology.

The endocrinopathy associated with PCOS prevails most commonly as anovulation, hyperandrogenism, obesity and acanthosis nigricans. In order for a patient to be diagnosed with PCOS according to the new Rotterdam criteria formulated by the European Society of Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM), at least two out of three set criteria, anovulation, excess of androgen and polycystic over morphology, must be met. Chronic anovulation makes women predisposed to endometrial cancer. PCOS has also increasingly been associated with breast and ovarian cancer.

The purpose of this review is to provide clinicians up-to-date information on PCOS based on clinical findings, to provide practical advice, and to provide insight in to associated health risks.

INTRODUCTION

PCOS is the most common endocrine abnormality in women of reproductive age and may be associated with an ovulation, infertility, and hyperandrogenism [1,2]. Diagnosis is dependent on identifying at least two of the following three features, as per the Rotterdam criteria, [3] agreed by ESHRE and ASRM.

(1) Polycystic ovaries (either 12 or more peripheral antral follicles or increased ovarian volume).

(2) Oligomenorrhea or an ovulation.

(3) Clinical and/or biochemical signs of hyperandrogenism.

It should be noted here that the patients' conditions should not be over-diagnosed as PCOS and diagnosis should be in accordance with the current international criteria listed above. To prevent over-diagnosis, AMH values may contribute to accurate PCOS diagnosis wherein high values of AMH may indicate PCOS [4].

Problems may arise if the focus of the treatment is solely on the patients' complaints, which may include, alongside other symptoms, irregular menstruation, infertility, and problems of being overweight. This can lead to suboptimal scanning because focusing only on the symptoms dictated by the patient could overlook associated health problems.

Women with PCOS should be screened for diabetes, hypertension, abnormal cholesterol/triglycerides, and abnormal uterine bleeding to gauge any consequential health risks.

The following sections will outline the cause and effect relationships that are caused by PCOS.

Infertility or sub fertility

Many women do not realize they have PCOS until they consult a doctor to determine reasons for why they cannot get pregnant. The cause of infertility in these cases is the imbalance of hormones, including an excessive production of testosterone by the ovaries. On the other hand, there are women that can get pregnant without any infertility treatments yet at the same time they are affected by PCOS.

Endometrial carcinoma

Long-term anovulation, which characterizes PCOS, is considered to be the main mechanism responsible for sustained undesired estrogen secretion which then increases the risk of endometrial carcinoma [5,6]. Other known factors that increase the risk of developing endometrial cancer include obesity, long-term use of unexpected estrogens, nulliparity, infertility, hypertension and diabetes [7,8]. It is known that many of these factors are also related to, and may be caused by PCOS at the same time.

Women with PCOS experience monthly growth of the endometrial lining and do not shed enough of the endometrium because they have rare or nonexistent menstrual periods. Thus, the endometrial lining continues to develop and may increase endometrial cancer risk. In women with PCOS, intervals between menstruation of more than three months may be associated with

endometrial hyperplasia and later carcinoma [5,6]. The data obtained from a large study involving 1270 women with chronic anovulation was found to be 3.1 in the risk of extreme endometrial cancer (95% CI, 1.1-7.3) [9]. However, a more recent assessment of the relationship between PCOS and endometrial cancer has failed to provide direct correlation [10], therefore leaving the actual risk of endometrial carcinoma in women diagnosed with PCOS not yet fully defined.

Ovarian cancer

Evidence suggests a link between PCOS and risk of ovarian cancer [11]. The risk appears to be increased in nulliparous women with early menarche and late menopause. It may be that inducing multiple ovulations in women with infertility may increase the risk. Multifollicular ovulation, which creates an imbalance for the risk of ovarian cancer in the treatment of expectant ovulation induction treatments and low-risk groups for women with PCOS, reduces the lifetime ovulation rate. There are several studies addressing the possibility that polycystic ovaries and ovarian cancer are linked to conflicting evidence.

Comprehensive studies in Denmark show that infertility increases the risk of invasive and borderline ovarian tumors [12,13]. Another study linking clomiphene and ovarian cancer suggests that the relative risk of ovarian cancer for women with PCOS is 4.1 compared to the control group [14]. A study in the United Kingdom concluded that the standardized mortality rate for ovarian cancer was a low mark of 0.39 (95% CI 0.01-2.17) [15].

However, more recent evidence on the relationship between polycystic over syndrome and ovarian cancer is still contradictory [16]. There are significant debate and concern around the risk of ovarian cancer in women with anovulation, especially because of the widespread use of drugs for ovulation induction in PCOS.

Breast cancer

Obesity, hyperandrogenism, and infertility are widely known to be associated with breast cancer development. However, studies do not show a significant increase in the risk of breast cancer in women with PCOS (RR1.2;95% CI0.7-2.0) [5,17].

Impaired glucose tolerance and diabetes

Women with PCOS, especially those who are overweight (BMI > 30 kg / m²), are at increased risk of impaired glucose tolerance, Type 2 Diabetes and metabolic syndrome [18].

Fasting glucose levels are poor predictors of glucose intolerance risk in women with PCOS and therefore the screening for IGT should be against a 2-hour oral glucose tolerance test (OGTT) [9].

The central distribution of fat is not dependent on BMI and is in fact associated with higher concentrations of insulin. The presence of an insulin action defect that enhances androgen secretion induced by LH from calcium cells is well established [19,20].

It has been reported that more than 20% of obese women with PCOS will have impaired glucose tolerance after the age of 30 [21]. Evidence also suggests that the prevalence of type 2 diabetes in women who are diagnosed with PCOS is seven times

greater than the control group (15% to 2% respectively) [7,21]. Abdominal obesity with insulin resistance suggests that the prevalence of type 2 diabetes is higher in PCOS [11,22,23]. However, the risk of developing type 2 diabetes is also increasing in women with non-obese PCOS [17,24]. PCOS is an independent risk factor for middle-aged type 2 diabetes [5,22]. The majority of women under 45 with type 2 diabetes are diagnosed with PCOS [20,23]. Women with PCOS, who are obese at the same time and needing ovulation induction, are thought to have more risk [24]. Also, women with gestational diabetes have been found with a high prevalence of PCOS after pregnancy [8,23].

Insulin resistance or impaired glucose tolerance has been associated with PCOS. Moreover, high-level insulin stimulates testosterone production, which aggravates PCOS [25].

Cardiovascular disease and hypertension and lipid abnormalities

Hyperandrogenism may cause a negative lipid profile in women with PCOS. This means that a woman with PCOS may have high negative fat content in the bloodstream. In some women, the blood lipid profile may show high-density lipoproteins at low levels, and low-density lipoproteins at high levels. This imbalance increases the risk for cardiovascular disease.

The main cause of increased cardiovascular risk in women with PCOS has appeared hyperinsulinemia. In the absence of impaired glucose tolerance, there is a pancreatic β cell dysfunction inversely proportional to SHBG (sex hormone binding globulin) concentration leading to hyperandrogenism and chronic unopposed estrogen secretion. There are two mechanisms by which insulin resistance in PCOS contributes significantly to the higher incidence of cardiovascular disease in these women [17]. Women with PCOS appear to have wider coronary artery disease with angiography [19]. Impaired glucose tolerance and diabetes caused by PCOS have known risk factors for cardiovascular disease. In women with polycystic ovaries, the lipoprotein profile is markedly impaired. They usually have high concentrations of serum triglycerides and total and low-density lipoprotein cholesterol [26]. On the other hand, high-density lipoprotein (HDL) levels and especially the HDL2 subfraction are suppressed [27,28]. In addition, serum plasminogen activator inhibitor-I concentrations are also elevated [8]. The latter can lead to impaired fibrinolysis and thus directly affect vascular tissue, leading to changes in coronary heart disease. Evidence suggests that the risk of developing cardiovascular disease really increases in women with PCOS. Regarding hypertension, there appears to be a direct relationship between insulin plasma levels and blood pressure [29,30]. Compared to the control group in women with PCOS, the prevalence of hypertension treated between the ages of 40-59 is three times higher [30]. It appears that the major risk factors for atherosclerosis, hypertension and myocardial infarction are earlier than women without PCOS [31].

Obstructive sleep apnea

Studies confirm that obstructive sleep apnea is high in women with PCOS [32]. Increased body weight contributes to this risk for women with PCOS [33]. High testosterone levels in women with PCOS seem to play a role in the development of sleep apnea [32]. Treatment of PCOS reduces the severity of sleep apnea.

Emotional and quality of life issues

The majority of PCOS studies have shown effects of depression, anxiety, and deterioration in the quality of life. Clinicians must investigate the presence and severity of mental distress and address this in their treatment plan. Long-term health impacts of impaired life quality have been asserted but not strictly measured [34].

Lifestyle intervention and PCOS Prevention Lifestyle intervention through diet and exercise are the key treatments for reducing PCOS [35]. It is recommended that women who are non-obese and have PCOS should keep their BMI in the normal range.

Modest weight loss (5-10%) is associated with a significant improvement in metabolic indexes [36]. Dietary advice should focus on total calorific intake, and most evidence suggests that low glycemic index diets are preferred [37]. Regular exercise (30 minutes of aerobic exercise/day) has been shown to decrease central obesity and increase insulin sensitivity so is strongly recommended [37].

CONCLUSION

The diagnosis for PCOS should be made according to the internationally set criteria to prevent over-diagnosis. A more holistic diagnosis can be attained if the treatment does not simply focus on the patients' complaints, but rather takes into account other possible long-term health risks that can be caused by PCOS.

In relation to this, research indicates a correlation between the presence of PCOS and the risk of endometrial carcinoma, ovarian cancer, developing obstructive sleep apnea, impaired glucose tolerance. No direct link has been observed between PCOS and breast cancer.

Women with PCOS should be screened for diabetes, hypertension, abnormal cholesterol/triglycerides, and abnormal uterine bleeding to gauge any consequential health risks. Clinicians must also investigate for mental distress and address this in the treatment plan. Regular exercise is strongly recommended.

Women with PCOS should be informed about this condition and its long-term health risks. Furthermore, recommendations should be made on how they can reduce this risk.

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