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What do we know about metabolic syndrome in adolescents with PCOS?

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Abstract

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive-aged women that manifests itself with a variety of features. For this reason, three different diagnostic criteria have been introduced. For adults, the National Institutes of Health Conference (NIH) criteria, which consists of hyperandrogenism and oligo-anovulation, is the most widely used. Symptoms of PCOS usually start with puberty and may overlap with normal pubertal development. Hormonal fluctuations during this period make the diagnosis of PCOS more difficult. Until now, there is no validated diagnostic criteria for PCOS in adolescents. Although menstrual disorders and cosmetic problems are the most common complaints of adolescents with PCOS, patients should also be evaluated for the potential risk for insulin resistance, obesity, subclinical atherosclerosis, diabetes, metabolic syndrome and cardiovascular disease. Obesity is the most prominent predictor of metabolic syndrome. As the incidence of obesity is increasing both in childhood and adolescence, governments will be faced with a social and economic burden in the future. Adolescents with PCOS are more obese than normal adolescents and have an increased risk of metabolic syndrome. It is suggested that abdominal adiposity increases the risk of metabolic syndrome by inducing various cytokine secretions. Although there is no consensus on metabolic syndrome criteria in the adolescent period, International Diabetes Federation (IDF) criteria may be used for children older than 10 years. Various clinical and metabolic markers are investigated for the prediction of metabolic syndrome in the literature. Waist circumference, serum triglycerides and androgens are the suspected predictors of metabolic syndrome. The prevention of abdominal adiposity and the early diagnosis of PCOS in adolescence should be the main target for the prevention of metabolic syndrome. Clinicians should investigate adolescents with PCOS for metabolic and cardiovascular risks and take preventive action. A Mediterranean diet, low in fat and high in fruits and vegetables, along with moderate-intensity exercise and smoking cessation are the recommended interventions for especially obese adolescents with PCOS. Metformin may be the treatment of choice when lifestyle modifications are ineffective.

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Definition of Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) was first described by Stein and Leventhal in 1935 (1). The combination of polycystic ovaries and amenorrhoea, with variable hirsutism, were the clinical features of the syndrome. PCOS is a heterogeneous disease that manifests itself with a variety of features; therefore, various definitions are proposed by different working groups. Nowadays, three different diagnostic criteria are currently used for PCOS diagnosis; these are listed in Table 1. According to the Rotterdam Criteria, four phenotypes of PCOS are defined and the groups showed different metabolic characteristics (2). Polycystic ovary was accepted to be an alternative to ovarian dysfunction with the presence of hyperandrogenism, according to the Androgen excess society (AES) criteria; however, a combination of anovulation and polycystic ovaries without hyperandrogenism was not accepted as PCOS (3).

Until now, there is no validated diagnostic criteria for PCOS in adolescents. The Endocrine Society suggested that the diagnosis of PCOS can be made with the presence of persistent oligomenorrhoea and hyperandrogenism (clinical or biochemical) after excluding other pathologies in adolescents (4). Although the National Institutes of Health (NIH) criteria for diagnosis of PCOS is frequently preferred, unexplained hyperandrogenism accompanied by the presence of ovulatory dysfunction is the diagnostic criteria for adolescent PCOS in most cases. However, there is some debate on merely using the Rotterdam-AES criteria (5). The presence of polycystic ovaries in normally ovulating women is a common finding. PCOS can be over-diagnosed in adolescents as the AES criteria accepts the polycystic appearance of the ovaries as evidence of ovulatory dysfunction.

The diagnostic challenge in adolescents may result from many reasons like the higher rate of physiologic anovulatory cycles, irregular menses during the first 2 years following menarche, and the presence of acne at this age group and

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Table 1. Definitions of PCOS

Working Group	Date	Definition
NIH (56)	1990	Chronic anovulation & clinical or biochemical hyperandrogenism & exclusion of other diseases
ESHRE-ASRM / Rotterdam (57)	2003	Presence of at least two of the three criteria: Clinical or biochemical hyperandrogenism, Oligo-anovulation, Polycystic ovaries
AES (3)	2009	Hyperandrogenism (hyperandrogenaemia and/or hirsutism) & ovarian dysfunction (oligo-anovulation & polycystic ovaries) & exclusion of other diseases

PCOS: Polycystic ovary syndrome; NIH: National Institutes of Health Conference; ESHRE: European Society of Human Reproduction and Embryology; ASRM: America Society of Reproductive Medicine; AES: Androgen Excess Society

even in "normal" adolescents. Hyperandrogenaemia is thought to be a more reliable diagnostic criteria for the diagnosis of adolescent PCOS after ruling out other causes of hyperandrogenaemia such as late-onset adrenal hyperplasia and Cushing's Syndrome. Moreover, the clinical heterogeneity of the patients who often present with hirsutism without anovulation or anovulation without hirsutism, and the disagreement over whether the polycystic ovarian morphology without hyperandrogenism represents a subgroup of PCOS, leading to a lack of consensus on the diagnostic criteria, especially for adolescents.

Prevalence of PCOS in the Adolescent Population

Polycystic ovary syndrome (PCOS) is the most common endocrinopathy of reproductive-aged women. While the prevalence of PCOS is given as approximately 7% by the NIH (6), it is not easy to estimate the prevalence in adolescents due to the diversity among the experts in this field about the diagnostic criteria and the fact that many symptoms and signs of PCOS may overlap with normal puberty (7, 8). Under-diagnosis of PCOS may lead to more serious clinical presentations; for example, women with a diagnosis of PCOS were found to have a 2-fold increased risk of metabolic syndrome in a cross-sectional study from Turkey that reported the prevalence of PCOS under NIH and Androgen Excess Society criteria as 6.1% and 15.3%, respectively (9).

Onset of Clinical Manifestation in PCOS

Although clinical manifestations of PCOS usually occur during puberty with the onset of maturation of the hypothalamic-pituitary-ovarian axis, the female foetus might be programmed to develop PCOS in adult life due to exposure to an excess of androgen in foetal life because of the genetic or environmental factors or a combination of them (10, 11).

Genetically-determined hypersecretion of the androgens from the ovary is proposed to be the primary event that leads to the development of PCOS by favouring excess luteinising hormone (LH) secretion and insulin resistance (12). However, insulin resistance with or without a genetic mutation may be the initiator, followed by hyperandrogenism, as is seen in hyperandrogenism-insulin resistance-acanthosis nigricans (HAIR-AN) syndrome (13, 14). Insulin resistance is an important contributing factor to abnormal steroidogenesis in PCOS. Insulin acts with LH to increase androgen production and promotes LH binding to the receptors. Hyperinsulinaemia stimulates insulin like growth factor-I (IGF-I) pathway in theca cells of the ovary by cross-reacting with the receptors for IGF. This state blocks the down-regulation of androgens by LH surge and leads to the hyperandrogenic environment in the ovary. Treatments include weight loss, which lowers insulin levels, restores ovulation and lowers the ovarian androgen levels (15).

Genetic Factors Related to PCOS

No consistent abnormality was detected in the chromosomal studies of the patients with PCOS but genetic studies of the families of the affected women showed a high incidence of affected relatives, indicating both X-linked and autosomal dominant inheritance (16). Moreover, there are data implying the linkage of adolescent PCOS with paternal metabolic syndrome (17).

In order to identify the genetic factors resulting in the hereditary nature of PCOS, genes encoding enzymes involved in androgen synthesis (serine hyperphosphorylation of P450c17, 21hydroxylase (CYP21) mutation), or protein transducers of insulin signals (excessive phosphorylation of IR-beta, insulin receptor substrate (IRS) proteins, IRS-1 (Gly(972)Arg) and IRS-2 (Gly(1057) Asp) have been analysed (18, 19). However, the role of genetic polymorphisms or mutations in the pathogenesis of PCOS is still under investigation and further research is required.

Metabolic Manifestations of PCOS

In the past, PCOS was considered only a hyperandrogenic disorder which can lead to infertility. Current data show that the diagnosis of PCOS is related to an increased risk of metabolic disturbances like insulin resistance (IR), hyperinsulinism (HI), impaired glucose intolerance, increased risk of type 2 diabetes in later life due to HI and IR, obesity, subclinical atherosclerosis, vascular dysfunction, metabolic syndrome and cardiovascular disease. Because central obesity is associated with hyperandrogenism and cardiovascular diseases, the Endocrine Society also recommends screening adolescents with PCOS for central obesity by body mass index (BMI) and waist circumference measurements (4).

For this reason, primary care for metabolic and cardiovascular risks and defining preventive methods in women with PCOS are the definite goals of the treatment of PCOS (20).

The American Heart Association categorised the cardiovascular risks of women with PCOS. Patients with obesity, especially

abdominal adiposity, hypertension, dyslipidaemia, subclinical vasculopathy, impaired glucose tolerance, a family history of familial cardiovascular disease (<55 years of age in a male relative and <65 years of age in a female relative) and cigarette smoking were categorised as at risk for PCOS-related cardiovascular disease. Those who had metabolic syndrome, type 2 diabetes, and overt renal and vascular disease were categorised as the high-risk population according to American Heart Association criteria (21).

Metabolic Markers of Metabolic Syndrome in PCOS

In a recent study, the relationship of activins and follistatins with metabolic markers in PCOS was investigated (22). Serum follistatin levels were found to be elevated in PCOS patients, independent of age and BMI. Activin levels were found to be similar in both groups with and without PCOS. In this study, follistatin was related to markers of adiposity and lipids in both women with and without PCOS. Activins A and B have various reproductive and metabolic actions in females. They stimulate follicular growth and also inhibit androgen production in the theca cells of the ovary (23). On the other hand, follistatin neutralises activin activity, and inhibits follicle stimulating hormone (FSH) secretion and folliculogenesis. Follistatin is also a promoter in the inflammation process, which has been shown to initiate insulin resistance and diabetes (24). For this reason, the increased levels of follistatin might inhibit folliculogenesis by increasing ovarian androgen production. In order to understand the possible role of follistatin in the pathogenesis of PCOS, further research is necessary.

Women with PCOS usually have abdominal adiposity and an increased risk of metabolic syndrome. Central obesity leads to the secretion of various adipocyte-derived peptide hormones, named adipocytokines. Adiponectin is the major adipocytokine that is secreted from the visceral fat cells. The presence of adiponectin impairs glucose tolerance and is an important predictor of metabolic syndrome (25). Ghrelin is also another peptide hormone which has a role in energy metabolism and low levels were reported to be associated with insulin resistance and diabetes (26). Adiponectin and ghrelin levels were negatively correlated with androgen levels in some trials, thus supporting the relationship between the hyperandrogenaemic state of PCOS and metabolic risk factors (27). In this study, obese hirsute women with PCOS were found to have lower adiponectin levels than obese controls and women with PCOS also had lower ghrelin levels than weight-matched controls. Panidis et al. (28) reported an inverse correlation between ghrelin levels and androgen levels. They found ghrelin levels to be lower in women with PCOS and also lower still in patients with hyperandrogenaemia.

Ersan et al. (29) investigated the relationship between adipocytokines and metabolic syndrome in pre-menopausal women with PCOS; adiponectin was found to be significantly lower and leptin was significantly higher in patients with PCOS and metabolic syndrome.

However, in a recent study, the levels of metabolic risk markers like adiponectin, leptin and ghrelin were measured in obese adolescents with and without PCOS; all were found to be similar in both groups (30). The investigators concluded that the presence of PCOS alone does not result in a higher risk of metabolic syndrome in adolescents. As expected, adiponectin levels were negatively correlated and leptin positively correlated with BMI.

Prevalence of Metabolic Syndrome in Adolescents with PCOS

After the first description of metabolic syndrome by Reaven in 1988, many organisations like the National Cholesterol Education Program (NCEP), the International Disease Federation (IDF), the World Health Organisation (WHO), and the European Group for the Study of Insulin Resistance published the diagnostic criteria for syndrome (31). Among these, the 2001 Third Report of NCEP's Adult Treatment Panel is the most widely accepted definition as all risk factors can be easily and routinely measured using diagnostic criteria. However, the WHO and European Group for the Study of Insulin Resistance definition includes routinely unmeasured criteria like insulin resistance and microalbuminaemia. According to the NCEP criteria, the presence of any three criteria defines metabolic syndrome. Those criteria are denoted as follows: Central obesity (waist circumference ≥88 cm in women), serum triglycerides ≥150 mg/dL, serum HDL concentration <50 mg/dL in women, systemic hypertension ≥130/85 mmHg, and fasting plasma glucose level ≥100 mg/dL (32).

In Turkey, Çalışkan et al. (33) investigated the frequency of metabolic syndrome according to different diagnostic criteria in women with PCOS. All criteria used identified higher metabolic syndrome in patients with PCOS than in controls. However, the highest prevalence (26%) was demonstrated by using IDF criteria due to the lower cut-off values for waist circumference and fasting glucose levels in these definitions.

In a U.S. population survey, the overall presence of metabolic syndrome was identified as 22% and gradually increased with age. The prevalence of metabolic syndrome in the US population was determined as 6.7% in the twenties, increasing to 43.5% in the sixties (34). Aging increases the visceral fat deposition, which worsens the glucose and lipid metabolism. Contrary to US data, the prevalence of metabolic syndrome in Italy was determined as 2.4% in general population in the 20s and this was found to increase to nearly 5% in the 40s. This is probably due to the lower incidence of obesity in Italy. However, the prevalence was 3-fold higher in young women with PCOS (35).

There is an ongoing debate regarding the definition of metabolic syndrome in adolescents in the literature. Hormonal fluctuations which lead to metabolic changes during transition to adolescence may mimic the features of metabolic syndrome. In one study of 1098 adolescents, nearly half of the adolescents initially diagnosed as metabolic syndrome lost this diagnosis during the three years observation period (36). The reason for this change might be due to the lack of objective and consistent criteria for identifying metabolic syndrome in adolescents. In 2007, Jolliffe et al. (37) reported the age-specific metabolic syndrome criteria for adolescents by linking them to the NCEP and

ITP adult criteria with growth chart modelling. Similar to the growth charts used to monitor height and weight in children, the growth curve method is used to easily identify metabolic syndrome. Growth curves for waist circumference, blood pressure, serum high-density lipoprotein (HDL) and triglyceride (TG) concentrations were defined, but no growth curve was set for fasting glucose level due to the constant level (100 mg/dL) from 12 to 20 years of age in this study.

The International Diabetes Federation put forward a new definition to identify children and adolescents with metabolic syndrome in 2007. The definition is easily applicable in clinical practice and categorised according to the age group (32). The IDF suggests that the diagnosis of metabolic syndrome should not be used for children younger than 10 years of age. If the waist circumference is ≥90 percentile in the children younger than 10 years of age, weight reduction is recommended. For children aged between 10 and 16, the presence of abdominal obesity according to waist circumference percentiles with any two clinical features (elevated TG, low levels of HDL, elevated blood pressure, elevated fasting glucose) is sufficient for the diagnosis of metabolic syndrome. For children aged 16 years and older, it is recommended to use the adult criteria.

In a study conducted on Iranian adolescents with PCOS, the presence of metabolic syndrome was nearly three-fold higher than the control group (33.3% and 11.2%, respectively) (38). The frequency of metabolic syndrome components like hypercholesterolemia, hypertriglyceridemia and elevated blood pressure was significantly higher in obese adolescents with PCOS. However, there was no significant difference among metabolic parameters between the non-obese adolescents with or without PCOS.

The National Heart, Lung, and Blood Institute Growth and Health Study (NGHS) identified predisposing factors for developing metabolic syndrome in childhood. After 10 years follow-up, waist circumference and serum triglycerides were identified as predictive factors of metabolic syndrome in girls aged 9 and 10 years. For every 1 cm increase in waist circumference at year 2, the metabolic syndrome risk increased by 7.4% and for every increase of 1 mg/dl in triglycerides level, the metabolic syndrome risk increased by 1.3% (39). In one cohort study with a 25 year follow-up, it was found that self-reported cardiovascular disease was observed more often (19.4%) in adults who had clinical features of metabolic syndrome as children than in those who did not (1.5%) (40).

Pathogenesis of Metabolic Syndrome in Adolescent PCOS Women

Obesity is an important predictor of metabolic syndrome. Even normal weight females with PCOS are found to have a 50% greater body fat level than normal weight females (41). In a study of 205 adolescents (≤20 years), the presence of metabolic risk factors and metabolic syndrome was investigated. The prevalence of being overweight or obese was significantly higher in adolescents with PCOS compared with those without (60% vs. 18%) (42).

The relationship between features of PCOS and features of metabolic syndrome were investigated in a cohort study of adolescent Australian girls; neither menstrual disturbances nor PCO morphology were found to be related to insulin resistance. BMI is the most prominent factor for the presence of IR. When it is estimated independent of obesity, an elevated free testosterone level is the most prominent indicator for the presence of the insulin resistance. Nearly one third of the adolescents with PCOS (35.3%) were found to be at risk of metabolic syndrome, whereas only 15.5% of adolescents without PCOS had this risk (43).

In a study of 469 South Asian women with PCOS, the relationship between different phenotypes of PCOS and metabolic syndrome was investigated. Although normal cycling hyperandrogenic women (Hyperandrogenism and PCO morphology) had a significantly lower incidence of obesity than the other phenotypes, the prevalence of metabolic syndrome was similar in all phenotypes. In contrast to a large USA study, the data of which reported a two-fold increased risk of metabolic syndrome in hyperandrogenic women, this study did not reveal any link between plasma testosterone and the occurrence of metabolic syndrome (44).

In a recent study, we analysed the endocrine and cardiovascular risk profile differences between 139 women with main PCOS phenotypes in Turkey. Among 4 PCOS phenotypes, patients with hyperandrogenism and PCOS (HA&PCOS) had the lowest carotid intima thickness; low-density lipoprotein cholesterol (LDL-C), total cholesterol and BMI were also found to be lower in this group. For this reason, this phenotype is said to have the lowest cardiovascular risk compared to other phenotypes (2).

Amato et al. (45) conducted a study in order to verify a method for distinguishing the metabolic health of women of reproductive age with PCOS. The visceral adiposity index is suggested as an easy and successful method for the assessment of metabolically unhealthy women and the detection of cardiometabolic risk factors. The visceral adiposity index (VAI) is calculated by a formula using waist circumference (WC), BMI, TG and HDL levels.

BMI is the most important variables which precludes the presence of metabolic syndrome. In a cross-sectional study of overweight and obese adolescents, the presence of PCOS did not add any weight to the presence of the features of metabolic syndrome. In this study, 53% of PCOS and 55% of the control group obese adolescents met the diagnostic criteria of metabolic syndrome (46).

Management of PCOS in Adolescents

In an internet survey that questioned specialists about their clinical approaches to PCOS in North America, the percentage of the respondent's patients with PCOS who were <18 years was found to be 53% and the percentage of respondent's PCOS patients who were obese was found to be 65% (7). The percentage of specific tests used for the initial diagnosis was highly variable; nearly 80% of the specialists evaluated thyroid stimulating hormone (TSH) and prolactin (PRL), whereas 17% of them evaluated sex hormone binding globulin (SHBG). For the evaluation of metabolic syndrome features, nearly 60% of specialists searched lipid profile and fasting glucose level, 41%

investigated fasting insulin levels and 25% assessed haemoglobin A1C. In a large cohort of normal weight women with PCOS in Austria, the efficiency of diabetes screening tests like HbA1c and fasting glucose level were evaluated. The true incidence of diabetes was 12.8%, which was determined by using oral glucose tolerance testing (OGTT); in contrast, when using only HbA1C and fasting glucose levels, only 3.2% and 5.2% of patients, respectively, had a diagnosis of pre-diabetes. In conclusion, the authors stated that although the OGTT is time consuming, neither fasting glucose nor HbA1c can be used as an alternative screening test for pre-diabetes in PCOS (47).

Weight loss with a low-fat and low-carbohydrate diet has improved menstrual function in obese adolescents with PCOS in a recent study (48). Marsh et al. (49) compared the low glycaemic index diet and conventional healthy diet in patients with polycystic ovary syndrome; after similar weight losses, women who consumed the low glycaemic diet showed more regular menstrual cycles. In a cohort study, the presence of insulin resistance in lean women with PCOS is investigated; none of the lean PCOS women were found to have insulin resistance and, as a conclusion, the routine performance of OGTT in lean women with PCOS is not recommended (50). The most recent guideline of the Endocrine Society also recommends exercise therapy in overweight and obese adolescents in order to reduce the cardiovascular risk. However, in normal weight women with PCOS, exercise therapy alone is not sufficient for treatment (4).

In our recent study, obesity was found to be negatively correlated to health-related quality of life in patients with PCOS. We analysed the health quality profiles of infertile women according to different PCOS phenotypes in this study (51). PCOS phenotype 1 patients (Hyperandrogenism and anovulation) had significantly higher BMI and hirsutism scores in comparison to other phenotypes and also showed significantly lower health-related quality of life scores.

Studies have demonstrated higher rates of many psychiatric disorders like anxiety, depression and eating disorders in adults and adolescents with PCOS (4, 52). The impact of hirsutism on the development of psychiatric problems are debatable (53). Given the high prevalence of anxiety and depression in women with PCOS, adolescents with PCOS should also be screened for these in their history and should be referred to psychiatrists for treatment.

Sleep disturbances like obstructive sleep apnoea appear to be a common complaint in women with PCOS. Sleep disordered breathing and daytime sleepiness were also more common in women with PCOS than in controls (54). In particular, the presence of hyperandrogenism and obesity are the suspected contributing factors for sleep disorders. Given the high prevalence of obstructive sleep apnoea in women with PCOS, especially overweight and obese adolescents should be evaluated for possible obstructive sleep apnoea symptoms and referred for polysomnography when suspected (4).

Management of Metabolic Syndrome in Adolescents

The prevention of adiposity, especially abdominal adiposity, is the primary target for the prevention of metabolic syndrome. For weight loss, lifestyle modifications like a restricted calorie diet and exercise are recommended as the first-line treatment by the recently published Endocrine Society guideline. There is no evidence that supports the superiority of one type of diet (4). The Mediterranean low fat diet that is high in fruit and vegetables has been found to improve glucose intolerance, insulin resistance, vascular endothelial function and lipid metabolism (55). The current recommended exercise program is a daily minimum of 30 minutes of moderate-intensity physical activity. Weight loss of about 5 to 10% of baseline weight is recommended in order to correct the abnormal glucose metabolism, but a cut-off level of fasting glucose has not yet been determined in patients with metabolic syndrome without diabetes.

Currently, studies in the literature investigating metabolic syndrome in children and adolescents with PCOS are quite limited; for this reason, it is difficult to define the long-term risk of cardiovascular disease and diabetes. Two randomised controlled studies demonstrated that the use of metformin improves the ovulation, hyperandrogenisim and abnormal lipid profile in adolescents with PCOS. Based on these data, the Endocrine Society recommended the use of metformin for the treatment of metabolic syndrome (4). However, early intervention with lifestyle changes such as increased physical activity, diet and smoking cessation may ameliorate these features in especially overweight and obese adolescents with PCOS. Metformin may be a choice of treatment when lifestyle modification is ineffective in obese adolescents.

Conclusion

The diagnosis of PCOS in adolescents is not easy due to a variety of diagnostic criteria and overlapping symptoms of pubertal development. However, the early diagnosis of PCOS is also important for identifying potential metabolic and cardiovascular risks during this period. Sleep disorders and psychiatric disease may also be diagnosed and treated earlier during the adolescence period. We know that especially obese adolescents with PCOS have an increased risk of metabolic syndrome. Although there is debate on the diagnostic criteria of metabolic syndrome during adolescence, abdominal obesity is the most prominent predictor of metabolic syndrome during childhood and adolescence. Therefore, early interventions with a Mediterranean diet, increased physical activity and smoking cessation are recommended in order to prevent metabolic syndrome, especially in obese adolescents with PCOS.

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