SHEILA BALAKRISHNAN
Department of Obstetrics and Gynaecology,
SAT Hospital, Government Medical College, Trivandrum – 695011, Kerala, India
Correspondence to: drsheilabal@gmail.com

Abstract
Polycystic Ovary Syndrome (PCOS) is the most frequent endocrinopathy in women and is now being increasingly met with in adolescents. It is characterised by irregular cycles or amenorrhoea along with features of hyperandrogenism. This review focuses on the different definitions used and also describes the conclusions of the recent Amsterdam consensus workshop on adolescent PCOS. Insulin resistance and compensatory hyperinsulinaemia are seen in most cases of polycystic ovary syndrome and this close association with the metabolic syndrome is responsible for the public health importance of the problem. The importance of screening for PCOS in adolescence with a view to preventing future problems is highlighted. The review also includes the different modalities to be used in diagnosis and the management strategies to be followed in adolescent PCOS.
hyperandrogenism. Polycystic ovaries may also be present on ultrasound. Most of these girls are obese and have insulin resistance. The prevalence of Polycystic Ovary Syndrome (PCOS) has been shown to be 5-10% in women of reproductive age.\(^1\) The disorder was initially described by Stein and Leventhal in 1935.\(^2\) PCOS traditionally thought of as a triad of oligomenorrhea, hirsutism, and obesity, is now recognized as a heterogeneous disorder that results in overproduction of androgens, primarily from the ovary, and is associated with insulin resistance.

**Definition**

Defining the syndrome has been a matter of debate since a long time. There is little disagreement that PCOS should be considered a syndrome, *i.e.* a collection of signs and features, in which no single test is diagnostic. In essence, the whole (or global assessment) is greater than the sum of the individual features. However, establishing a clear, contemporaneous, and evidence based definition for this syndrome has important clinical and investigational implications.

**NIH criteria**

Initially the National Institute of Child Health and Human development criteria (1990) were used which consisted of the presence of oligomenorrhea, clinical or biochemical features of hyperandrogenism and the exclusion of other diseases that may mimic PCOS such as non classical congenital adrenal hyperplasia, virilising tumours or Cushing’s syndrome.\(^3\) The presence of a morphological picture of polycystic ovaries (PCO) was not required for establishment of the diagnosis.

**Rotterdam criteria**

However, most of the European gynecological endocrinologists still stressed the presence of polycystic ovaries as an important diagnostic feature. Since 1990, it has been also recognized that the syndrome encompasses a broader spectrum of signs and symptoms than those defined in the original NIH diagnostic criteria. Thus, a transatlantic consensual conference was held in Rotterdam in 2003 under the auspices of both prestigious professional gynaecological societies; the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). The meeting proceedings recommended that PCOS be defined when at least two of the following three features were present; irregular menses (IM), clinical and/or biochemical signs of hyperandrogenism (HA) and polycystic ovaries on ultrasound (PCO). All these should be in the absence of another disorder
that can cause the same symptoms or signs. Using these Rotterdam criteria, there are four possible diagnostic subcategories or phenotypes of PCOS, i.e. IM/HA with or without PCO, HA/PCO, and IM/PCO. This definition allowed for the inclusion of girls and women with regular menses who manifest the morphologic changes of polycystic ovaries on ultrasonography. The latter was not accepted as a diagnostic criterion in the aforementioned 1990 criteria.

**Androgen Excess Society guidelines**

More recently, a Phenotype Task Force of the Androgen Excess Society published their Guidelines stressing the importance of hyperandrogenism as the cardinal feature of PCOS, while accepting the major guidelines of the 1990 Conference consensus report.

**Limitations of the Rotterdam criteria**

The Rotterdam criteria are most widely accepted and used today. But there are a few limitations. There has been some debate about the Rotterdam criteria because they include girls and women with polycystic ovaries and anovulation, but no clinical or biochemical evidence of hyperandrogenism. The general practice is to include all subgroups within the spectrum of PCOS. Some investigators have found that the different subgroups arising from the Rotterdam criteria have varying significance with respect to developing metabolic disturbances and the long term consequences, such as type 2 diabetes mellitus, which occurs in women who have PCOS. The non hyperandrogenic phenotype may represent a form of PCOS associated with a milder metabolic profile. The other controversy is the suitability of the Rotterdam criteria in adolescence. Using menstrual irregularity to diagnosis PCOS in the adolescent population is difficult, because a history of menstrual irregularity is considered normal in the first few years after menarche secondary to anovulation. Persistent irregularity of cycles for longer than 2 years after menarche is a strong predictor of continued irregularity and PCOS, because most adolescent have regular cycles 2 years after menarche. Furthermore, adolescents with irregular cycles within the first 3 years of menarche and no evidence of clinical hyperandrogenism may, in fact, have biochemical evidence of hyperandrogenism similar to that found in PCOS. Hyperandrogenism can occasionally be found in the postmenarchal years without significant sequelae in adolescents with anovulatory regular cycles. Some researchers think that the Rotterdam criteria may overestimate the diagnosis (i.e. it is less specific) in the adolescent.
ultrasound is the only option available in these girls and it is technically more difficult to assess the ovaries with it, especially in obese girls.

Amsterdam consensus conference

In 2012 the 3rd ESHRE and ASRAM sponsored consensus workshop on PCOS was conducted at Amsterdam. This workshop explored the various categories and has laid down certain criteria to be followed in diagnosing and treating adolescent PCOS, taking into account the limitations of the Rotterdam criteria in adolescence. According to this consensus meeting, all the three elements of the Rotterdam consensus should be present to make the diagnosis of adolescent PCOS. It was also recommended that overdiagnosis be avoided in teenagers, but at the same time individual manifestations should not be denied treatment. The other conclusions of the Amsterdam consensus meeting are dealt with under clinical presentation.10

Pathogenesis

Insulin resistance and compensatory hyperinsulinaemia are seen in most cases of polycystic ovary syndrome.11 In the normoinsulinaemic group hypersecretion of luteinising hormone (LH) is the main pathology. The hyperandrogenism in PCOS is mainly ovarian and is due to both the LH hypersecretion and the hyperinsulinaemia. Hyperinsulinaemia is responsible for the hyperandrogenism, which in turn causes dyslipidaemia with an increase in triglycerides and LDL and a decrease in HDL. Insulin resistance is one of the major factors resulting in the transition of a symptomless girl with polycystic ovaries to full blown PCOS. The theca cells of the ovaries have a generalised overactive steroidogenesis in PCOS. There is excess of oestradiol also in addition to the excess androgens. In the ovary inhibin is increased and this causes low FSH concentrations compared with LH, in girls with PCOS. Since inhibin stimulates androgen production and androgens in turn stimulate inhibin secretion, this results in a vicious cycle in the ovary that will inhibit follicular development and ovulation. Thus as a consequence of dysregulation of androgen synthesis in the ovary, adolescents with PCOS have ovarian hyperresponsiveness to LH.

There is a genetic component in addition to an environmental factor. Most cases of PCOS show a familial clustering with sisters showing the same clinical picture and there may be a family history of diabetes. A defect in the insulin receptor gene has been
should PCOS be diagnosed in adolescence?

The purpose of detecting PCOS in the late adolescence or early adulthood would be to identify a target population at risk of infertility and the metabolic syndrome and institute preventive measures at an early age. Also if these girls with PCOS are identified early enough, there would be scope for implementing lifestyle changes in an attempt to prevent development or progression of the metabolic syndrome. This would have a lot of public health importance in preventing the metabolic and cardiovascular sequelae of PCOS. It would also be cost effective as we are preventing a lot of future disease burden. There are a lot of immediate and long term problems associated with PCOS and hence the diagnosis of the syndrome assumes a lot of public health importance.

Immediate problems in adolescence

The immediate problems are menstrual disorders, cosmetic problems, obesity and psychosocial problems. Menstrual problems include irregular or excessive bleeding and amenorrhoea. Cosmetic problems are hirsutism and acne which are very distressing to the adolescent. Obesity also contributes to the loss of self esteem resulting in psychological problems. But these are only the tip of the iceberg and there are a whole lot of long term sequelae.

Long term problems

The most widely known and studied is of course infertility. PCOS is responsible for about 30-40% of the overall burden of infertility. This causes a lot of psychosocial stress and economic burden as the treatment of infertility is quite expensive. Even if the woman becomes pregnant there is increased morbidity due to an increased chance of miscarriage, gestational diabetes, pre eclampsia and all the associated problems of obesity. Apart from all this, the main public health importance today is the recognition that PCOS is a fore runner of the metabolic syndrome. Indeed many adolescent girls with PCOS will already exhibit features of the metabolic syndrome. And many more will develop the syndrome in a short time. This attains even more relevance as the prevalence of the metabolic syndrome especially type 2 diabetes is much more in India compared to the west. Obesity has also increased very much in adolescents and young adults in India. Apart from type 2 diabetes, there is an increased risk of coronary artery disease and non alcoholic liver disease. Also PCOS predisposes to
endometrial cancer, due to unopposed oestrogenic stimulation of the endometrium.

The metabolic syndrome is a constellation of cardiovascular disease risk factors associated with insulin resistance; glucose intolerance, dyslipidemia, hypertension, and central obesity. There is a growing appreciation that adolescents are at increasing risk for type 2 diabetes mellitus and cardiovascular disease, as the prevalence of obesity increases in this population. Analogous to the situation in adults, prevalence of the metabolic syndrome increases with obesity, reaching prevalence rates as high as 50% among morbidly obese adolescents. There is intriguing evidence that this increased risk may be conferred not only by insulin resistance but also by hyperandrogenema. There is an increased risk of the metabolic syndrome in girls and women with PCOS associated with increased androgen levels and independent of obesity. Paediatricians are increasingly concerned about the long-term health effects of childhood and adolescent metabolic syndrome and they believe that it may be associated with early cardiovascular disease in adulthood. Progress in defining the nature of the long term cardiovascular risk is hampered by the lack of consensus on criteria for the diagnosis of the metabolic syndrome in adolescents as well as lack of longitudinal studies with cardiovascular endpoints as opposed to surrogate markers. Cardiovascular event endpoints are difficult to target because of the long latency period between the onset of atherosclerosis and the first cardiovascular event. However, there is evidence from autopsy studies that atherosclerosis starts in childhood.

Table 1. Clinical characteristics of PCOS

<table>
<thead>
<tr>
<th>Presenting problems</th>
<th>Pregnancy related problems</th>
<th>Longterm problems</th>
</tr>
</thead>
</table>

Health Sciences 2013;2(1):JS004B
Clinical presentation

PCOS usually presents for the first time at puberty along with weight gain. The most common presentation is as menstrual disorders along with hirsuitism. 50 -70% of PCOS are obese.

Menstrual disorders

The menstrual disorder may be anovulation or oligoovulation and ranges from amenorrhoea to oligomenorrhoea. The amenorrhoea is usually secondary but may rarely be primary. Irregular or infrequent menstrual cycles are common in the first few years following menarche but are usually self limiting once ovulation is established. If it persists or is associated with signs of hyperandrogenism like hirsutism, it is best to start evaluation. The Amsterdam consensus meeting concluded that the diagnosis of PCOS should be made when oligomenorrhoea /amenorrhoea persists until two years after menarche or there is primary amenorrhoea at 16 years.\(^\text{11}\)

Hyperandrogenism

Progressive hirsutism is a manifestation of hyperandrogenism and should be assessed by the Ferriman Galwey scale. Acne is common in adolescence and hence is better not used as a marker of hyperandrogenism in adolescence. In addition the Amsterdam consensus conference concluded that progressive hirsutism should be evaluated biochemically in adolescent PCOS.\(^\text{11}\) Overt signs of virilisation like male pattern baldness, increased muscle mass, clitoromegaly and deepening of voice are very rarely seen in PCOS and usually
indicate the presence of an androgen producing tumour.

**Obesity**

50-70% PCOS will be obese. Obesity is assessed by calculating the body mass index. A normal BMI is considered 20-24. 25-29.9 is considered overweight and above 30 is considered obese according to international standards. A waist circumference more than 88 cm is also significant and indicative of the metabolic syndrome. The South Asian guidelines consider a BMI of 23 or more as overweight and 25 or more as obese. A waist circumference more than 80 cm is considered significant in the South Asian context. Obesity is not essential for the diagnosis of PCOS, but should be considered as at risk for the syndrome.

**Acanthosis nigricans**

This is the presence of dark, velvety patches in the armpits, nape of neck and under the breasts. This is a definite sign of insulin resistance and was what prompted scientists to investigate the association between PCOS and insulin resistance.

**Differential diagnosis**

The differential diagnosis includes other causes of menstrual irregularity and hirsutism.

- Hypothyroidism and hyperprolactinaemia
- Androgen secreting tumours of ovary and adrenal
- Late onset congenital adrenal hyperplasia
- Cushing’s syndrome

**Investigations**

1. **Ultrasound scan**

An ultrasound scan is done to rule out ovarian tumours and confirm the presence of polycystic ovaries. The sonographic criteria of polycystic ovaries are an ovarian volume more than 10 mL and/or 12 or more follicles 2-8 mm in diameter. However, in adolescence ovarian volume should always be included to make the diagnosis according to the Amsterdam consensus meeting. This is because multifollicular ovaries are common in adolescence.

2. **Hormonal investigations**

- Thyroid function tests
• Prolactin

• Free testosterone is the best marker of ovarian androgen production

• DHEAS is usually increased if there is an adrenal component

• 17α OH progesterone if late onset congenital adrenal hyperplasia is suspected

• Increased LH/FSH ratio

3 Tests to detect metabolic problems

• Fasting blood glucose and a 75 gram GTT may show overt diabetes or impaired glucose tolerance

• Lipid profile may show increased total cholesterol, triglycerides and LDL and low levels of HDL

At present there is no reliable test to detect insulin resistance. Dynamic tests like the hyperinsulinaemic euglycaemic clamp are sensitive but impractical. Glucose insulin ratio is the ratio of fasting glucose to fasting insulin and can be considered a marker for insulin resistance. A ratio below 4.5 may be suggestive of insulin resistance. But routine testing of insulin levels is not mandatory for detecting insulin resistance. The best markers of insulin resistance are clinical and include BMI, waist circumference more than 80 cm and acanthosis nigricans.

Management

The management is twofold and includes management of presenting complaint and prevention of long term sequelae. The presenting complaint may be menstrual problems like menorrhagia, irregular periods or amenorrhoea and cosmetic problems like hirsuitism. Adolescents with symptoms should not be denied treatment. In all girls with PCOS, consideration must be given to preventing long term sequelae. This would include endometrial protection with progesterone to prevent adenocarcinoma uterus and prevention and early detection of the metabolic syndrome.

Prevention of the metabolic syndrome

Lifestyle modification

Lifestyle modification by diet and regular moderate intensity aerobic exercise for a minimum of 30 minutes five days a week remains the first line of treatment especially in obese PCOS. Weight loss can cause spontaneous resumption of menses and lower androgen levels. Even a 5% reduction in weight can result in these changes. Weight loss results in lowered insulin levels.
leading to an increased sex hormone binding globulin and thereby a decrease in the free testosterone levels. This approach is ideal in the adolescent group as this is the period when lifestyle modification is easiest to achieve.

**Insulin sensitisers**

Insulin sensitisers help the body to utilise insulin in a more efficient manner. Metformin is the drug, which has been most widely used in adolescents. Metformin acts by decreasing glucose production by the liver. It produces improvement in insulin resistance, reduction in androgens and in many cases spontaneous resumption of periods has been seen. The dosage is 1000 – 1500 mg daily in divided doses. Side effects are nausea, vomiting and dyspepsia. Lactic acidosis is a rare side effect. It should be avoided in girls and women with altered renal or hepatic function. Long acting preparations are also available with fewer side effects. The use of metformin is best restricted to those with definite evidence of insulin resistance such as obesity, acanthosis nigricans or impaired glucose tolerance. At the moment lifestyle modification remains the best option in preventing long term sequelae. Further research is awaited regarding long term use of metformin in preventing the metabolic syndrome.

**Menstrual problems and hyperandrogenism**

**Cyclical progesterone**

Medroxy progesterone acetate 10 mg twice daily for 5 days or 10 mg daily for 10 days in a month will regularise periods. This has only minimal effect on hirsutism. It is important to remember that the only young women to get endometrial cancer are those with PCOS or oestrogen secreting tumours. Hence it is imperative that girls or women with PCOS should get withdrawal bleeds at least once in 2-3 months.

**Combination pills**

The low dose oral contraceptive pill containing ethinyl oestradiol and the third generation progestin desogestrel (Novelon and Femilon) are given to regularise periods and will also combat mild hirsutism. Another recently introduced combined oral contraceptive is the combined pill containing ethinyl oestradiol and drospirenone which is also being increasingly used in PCOS. Drospirenone is a spironolactone derivative and hence is effective in hirsutism and acne as well. A combined pill containing 35 µgm ethinyl oestradiol and 2 mg of an antiandrogen, cyproterone acetate (Diane 35 or Ginnette) is also effective. The effect on acne and seborrhoea is evident shortly after starting
treatment but 6 - 12 cycles are needed for a demonstrable effect on hirsutism. The best effects are seen in young girls and it is suggested to have beneficial effects on future fertility as well, by normalising the hormonal milieu.17

Other anti androgens

Higher doses of cyproterone acetate in a reverse sequential regimen are better for severe hirsutism where cyproterone is given 25 – 100 mg daily on day 5 – 15 of the cycle and ethinyl oestradiol 20 – 30 microgram is given on day 5 – 26 of the cycle. Liver toxicity has been reported with high doses of cyproterone acetate. Hence, assessment of liver function is advisable before commencing treatment, at 3 months and thereafter every 6 months. Spironolactone in the dose of 50-100 mg daily twice daily is also very effective in combating hirsutism. Spironolactone is an aldosterone antagonist. The side effect is menstrual irregularity. Other antiandrogens in clinical use are flutamide, finasteride and ketoconazole. Antiandrogens are best used in combination with the combined pill.

Other therapies

Antibiotics such as tetracycline, erythromycin and minocycline are the mainstay of treatment for acne and can be used in conjunction with antiandrogen therapy. Retinoic acid is indicated in intractable acne with severe scarring but such drugs are best administered by a dermatologist. 2% minoxidil applied topically may be useful for those with hair loss.

Cosmetic procedures

Cosmetic procedures can be combined with anti androgens for tackling hirsutism to provide an immediate effect, while the impact of long-term hormonal treatment is awaited. Electrolysis and laser are acceptable if done in good centres and are especially useful in removing hair, which has been present for a long time.

References


13. Andrea D. Coviello, Richard S. Legro, and Andrea Dunaif. Adolescent girls with PCOS have an increased risk of the metabolic syndrome associated with...
increasing androgen levels independent of obesity and insulin resistance *JCEM* 2006; 91:492-497.


