Polycystic ovarian syndrome in adolescent girls

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Abstract

Polycystic ovary syndrome is a spectrum of disorders consisting of chronic oligo-anovulation, androgen excess, obesity, insulin resistance and polycystic ovaries. The diagnosis carries life-long implications with increased risk for infertility, endometrial hyperplasia/carcinoma, metabolic syndrome, type 2 diabetes and cardiovascular disease. Lack of well-defined diagnostic criteria makes identification of this common condition challenging. Because of the varying clinical presentation and manifestation of PCOS, adolescent and young adult woman can present to a variety of healthcare professionals including general practitioners, general paediatricians, adult physicians, gynaecologists, dermatologists or endocrinologists (paediatric and adult). Treatment of adolescent girls with PCOS includes weight reduction if associated with obesity, exercise and various pharmacological interventions. As many women with PCOS have the onset of symptoms during adolescence, it is important for paediatricians to be familiar with the disorder and be able to facilitate a management plan and consider treatments to ameliorate symptoms and reduce the risk of long-term sequelae. This review will focus on the diagnosis and current management of PCOS in adolescent girls.

Keywords hirsutism; hyperandrogenism; insulin resistance; menstrual irregularities; obesity; polycystic ovaries

Introduction

Polycystic ovarian syndrome (PCOS) is one of the most common endocrinopathies in reproductive age women with an estimated prevalence of 4–10%. It was originally described in 1935 by Stein and Levinthal in women with amenorrhea some of whom were hirsute and/or obese. The definition of PCOS in woman has changed and evolved since its original description with at least three major consensus statements having similar diagnostic criteria summarised in Table 1. In adolescent girls the Androgen Excess Society (AES) 2006 criteria are widely accepted but need consideration of the following caveats:

a) Anovulation frequently occurs in the first two years after menarche (physiologic anovulation).
b) Multifollicular ovaries can be a normal finding in adolescence.
c) It is more difficult to image ovaries in this group where transabdominal ultrasound scanning (USS) is unreliable, particularly in obese girls, and transvaginal USS is considered unacceptable.
d) Defining biochemical androgen excess in adolescent girls is difficult as normative ranges fluctuate during puberty and acne and mild hirsutism are common and obesity is becoming more prevalent. Furthermore, documented hyperandrogenemia amongst such girls has been associated with later normal ovulatory cycles.

Although diagnosing PCOS in adolescent girls is challenging, a clear understanding of the clinical features and appropriate use of investigative procedures should aid in identifying girls who meet the diagnostic criteria and allow appropriate counselling and therapeutic intervention.

Clinical features and diagnosis

Early diagnosis and treatment of PCOS in adolescent girls is important as it helps identify risk factors which are amenable to intervention to ensure good adulthood health and restore self-esteem. There are several recognised predisposing risk factors for developing PCOS summarised in Table 2. Many studies have now demonstrated an increased risk of obesity, premature adrenarche (appearance of pubic hair less than 8 years) and insulin resistance in babies born small for gestational age and these in turn are all associated with increased risk of developing PCOS. Other risk factors include antenatal exposure to androgens, certain medications (e.g. sodium valproate), diabetes and a family history of PCOS.

A diagnosis of PCOS is based on hyperandrogenism and/or chronic anovulation in the absence of specific pituitary or adrenal disease, supported by biochemical and radiological findings. Secondary causes of hyperandrogenism such as late-onset congenital adrenal hyperplasia (CAH), virilising tumours (adrenal/ovarian), Cushing's syndrome, exogenous ingestion of anabolic steroids, extreme forms of insulin resistance (such as insulin receptor mutations) and conditions such as hypothyroidism and hyperprolactinaemia which cause ammenorhoea can usually be excluded by careful history taking, physical examination and appropriate investigations where necessary.

Hyperandrogenism and chronic anovulation can present with a range of symptoms in adolescent girls with the most common complaints being menstrual irregularities, acne, hirsuitism, and obesity. The spectrum of irregular periods estimated to be present in about two-thirds of girls with PCOS includes:

- primary amenorrhea (absence of menarche by 16 years of age)
- oligomenorrhea (menstrual periods at intervals of >35 days)
- secondary amenorrhea (more than 90 days without a menstrual period) after initially menstruating normally
- dysfunctional uterine bleeding with oligomenorrhea.

Chronic anovulation is important to recognise as it is associated with an increased risk of developing endometrial hyperplasia/carcinoma due to unopposed circulating oestrogens and also increases the risk of infertility. Acne and hirsutism are very common findings in PCOS secondary to hyperandrogenaemia. The degree of hirsutism needs to be evaluated both clinically (see below) and from the extent to which it impacts on the individual's quality of life when making decisions about the

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Diagnostic criteria for PCOS

US NIH[a] (1990)	Rotterdam criteria (2003) (ESHRE/ASRM)[a]	Androgen Excess Society (AES) (2006)
Oligo-ovulation	Oligo- or anovulation	Clinical and/or biochemical hyperandrogenism
Clinical and/or biochemical hyperandrogenism	Clinical and/or biochemical hyperandrogenism	Ovarian dysfunction: oligoanovulation and/or
Both criteria must be present	Polycystic ovaries on pelvic ultrasound	polycystic ovaries on pelvic ultrasound
	Two of the three criteria must be present	Both criteria must be present

All three definitions assume exclusion of other diagnoses which may mimic the symptoms of PCOS (e.g. non classical Congenital Adrenal Hyperplasia, Androgen-secreting tumours, Cushing syndrome, Hyperprolactinemia, thyroid dysfunction etc).

[a] US NIH = United States National Institutes of Health; ESHRE/ASRM = European Society for Human Reproduction and Embryology/American Society of Reproductive Medicine.

Table adapted from Hernandez MI, Mericq V. *Polycystic Ovarian Syndrome*. In: Brook C, Clayton P, Brown R, eds. *Brook's clinical paediatric endocrinology*. Blackwell, 2009; 559–570.

Table 1

Predisposing factors of PCOS

1. Prenatal exposure to androgens
   - Poorly controlled maternal CAH
   - Offspring of mothers with PCOS
   - Androgen secreting tumours
2. Low birth weight/Small for gestational age
3. Premature adrenarche
4. Epilepsy & anti-epileptic drugs (eg: Valproate)
5. Onset of type 1 diabetes mellitus-before menarche
6. Obesity +/– insulin resistance
7. Family history of PCOS

Adapted from Hernandez MI, Mericq V. *Polycystic Ovarian Syndrome*. In: Brook C, Clayton P, Brown R, eds. *Brook's clinical paediatric endocrinology*. Blackwell, 2009; 559–570.

Table 2

appropriateness of therapy. Obesity is present in approximately half of patients with PCOS, often beginning in mid-childhood and is typically central in nature (android) with increased waist to hip ratio. Even normal-weight women with PCOS are reported to have a body composition constituting 50% more fat than normal.

Both obesity and PCOS either independently or in combination predispose to the development of insulin resistance which can manifest itself both clinically in the form of acanthosis nigricans and biochemically as the metabolic syndrome. Acanthosis nigricans is a velvety brown rash on neck, axilla or groin often associated with skin tags and is seen in 1–3% of patients with PCOS (Figure 1). The metabolic syndrome can be defined as a cluster of abdominal obesity, hypertension, raised serum triglycerides, low HDL cholesterol, and glucose intolerance leading to risks of cardiovascular disease and stroke. Adolescent girls with PCOS, both lean and obese, have increased risk of impaired glucose tolerance and type 2 diabetes which are attributed to a defect in insulin action and pancreatic ß-cell dysfunction.

History and physical examination are mandatory parts of assessment of girls suspected of having PCOS. History should include information about the patient's age at thelarche, adrenarche, menarche and characteristics of the menstrual cycle (frequency, duration etc). If obese, the time of onset, progression and comorbidities such as obstructive sleep apnoea symptoms, exercise intolerance, metabolic syndrome, depression, and orthopaedic problems should be explored. Lifestyle parameters such as diet, exercise and smoking need evaluation, as do the age of onset and progression of hirsutism and/or acne. Any medications used and their effects on acne and hirsutism should also be considered. Family History should explore infertility, menstrual disorders, age of puberty and hirsutism in female relatives, early baldness in male relatives, and features of metabolic syndrome.

Physical examination includes general body habitus (gynecoid versus android), obesity (central vs. generalised), body mass index (weight/height^2), blood pressure, presence of acne, male pattern of baldness and evidence of acanthosis nigricans. The severity and distribution of hirsutism should be graded clinically so that if therapeutic intervention is considered, response to therapy can be monitored. The most common grading system used is the Ferriman–Gallewey score (Figure 2). Girls with PCOS with marked hyperandrogenism such as clitoromegaly, deepening of the voice, or a masculine body habitus should alert one to the possibility of virilising adrenal/ovarian tumours or CAH.

Investigation

Making a diagnosis of PCOS should mainly be based on careful history taking and characterisation of symptoms described above. Biochemical and radiological investigations can be helpful in confirming the diagnosis but they should not be used in isolation. A clear understanding of the biochemical pathogenesis of PCOS aids interpretation of the investigations given below. There are several biochemical abnormalities of the hypothalamic pituitary ovarian axis which aid the diagnosis but abnormal findings at all levels of the axis are not necessarily found in all girls with PCOS.

In PCOS, accelerated hypothalamic gonadotropin releasing hormone (GnRH) pulse activity results in an exaggerated release of lutenising hormone (LH). Even a mild chronic elevation of LH can blunt the effect of the mid cycle LH surge leading to anovulation (Figure 3). LH secreted at a higher rate in relation to follicle stimulating hormone (FSH) results in increased thecal and intraovarian androgens, specifically androstenedione which is converted to testosterone known as functional ovarian hyperandrogenism (FOH).