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Difficulties in diagnosing polycystic ovarian syndrome in adolescents: a narrative review

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We review the diagnostic criteria of polycystic ovarian syndrome (PCOS) in adolescents. It is important to recognise PCOS early for timely management. Clinicians should be aware of the difficulties in diagnosing PCOS in adolescents. A multi-disciplinary approach for diagnosis and treatment is suggested. For high-risk cases, re-evaluation may avoid under-diagnosing or over-diagnosing PCOS.

Keywords: Adolescent; Polycystic ovarian syndrome

Introduction

Polycystic ovarian syndrome (PCOS) is the most common endocrine disorder affecting reproductive women[1], with an estimated prevalence of 6% to 10%[2] to 18%[3]. It has complex genetic and environmental aetiologies[4]. Diagnosing PCOS is difficult because it has a broad spectrum of presentation, which is further complicated in adolescents, as the symptoms may mimic normal pubertal events[5]. PCOS is associated with subfertility, increased risk of endometrial pathology and metabolic diseases, emotional disturbances, and hirsute features resulting from excessive androgen.[1] Early diagnosis is crucial to optimise care and health outcomes.

Adolescents are individuals aged 10 to 19 years who undergo a transitional phase from childhood to adulthood with rapid physical and psychological development[6]. Functional variations in the hypothalamic-pituitary-ovarian axis result in overlapping features of PCOS with physiological changes of puberty[5]. Thus, the diagnostic criteria of PCOS for adults may result in mis- or over-diagnosis in adolescents.

Diagnostic criteria for PCOS in adolescents

To diagnose PCOS, clinicians commonly use the National Institute of Health Criteria[7], the Rotterdam Criteria[8], and the Androgen-Excess and PCOS Society Criteria[9] (Table). The three major clinical features are ovulatory dysfunction, hyperandrogenism, and polycystic ovary morphology. However, these criteria are not appropriate for adolescents[10]. In 2018, the international evidence-based guideline for assessment and management of PCOS suggest including only hyperandrogenism and irregular cycles for diagnosing PCOS in adolescents.[12] Ultrasonographic features are not indicative owing to PCOS features overlapping with normal reproductive physiology during adolescence period[12].

Ovarian dysfunction reflected by irregular menstrual cycles is the key diagnostic feature of PCOS. In the Rotterdam criteria, there is no specific definition of oligo-/anovulation in terms of pubertal status. This poses a challenge to defining adolescents as having irregular menstrual cycles because maturation of the hypothalamic-pituitary-ovarian axis may take years to complete[13], with anovulatory cycles lasting up to 5 years after menarche. Therefore, the latest guideline defines irregular menstrual cycles with respect to menarche and age[12]. Irregular menstrual cycles are normal within the first year of menarche. Within 1 to 3 years of menarche, irregular menstrual cycles are defined as cycles <21 days or >45 days or >90 days for any one cycle, whereas from >3 years of menarche to perimenopausal, irregular menstrual cycles are defined as cycles <21 days or >45 days or >90 days for any one cycle or <8 cycles per year. Primary amenorrhea is defined as amenorrhea by the age of 15 years or after >3 years of thelarche. Clinicians should undertake further assessment for possible PCOS in adolescents with irregular menstrual cycles.

Hyperandrogenism refers to both clinical and biochemical hyperandrogenism. It includes acne, alopecia, and hirsutism in adults, as well as severe acne

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Table. Diagnostic criteria for polycystic ovarian syndrome (PCOS) according to the National Institute of Health Criteria, the Rotterdam Criteria, and the Androgen-Excess and PCOS Society Criteria

Feature	National Institute of Health criteria	Rotterdam criteria	Androgen-Excess and PCOS Society criteria
Hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism
Ovulation	Chronic anovulation	Oligo/anovulation	Oligo/anovulation
Ovarian morphology	Not specified	Polycystic ovarian morphology	Polycystic ovarian morphology
Exclusion of other pathologies needed?	Yes	Yes	Yes
Number of criteria needed	Both hyperandrogenism and ovulation as well as exclusion of other endocrinopathies	Two of the three features as well as exclusion of other endocrinopathies	Hyperandrogenism and either ovulation or ovarian morphology as well as exclusion of other endocrinopathies

and hirsutism in adolescents[12]. Alopecia refers to the loss of terminal hair, usually on the scalp[14]. Alopecia is a poor marker for hyperandrogenaemia[15] and is rarely seen in adolescents[16] and should not be used for assessment in adolescents. Acne is common in adolescents even without hyperandrogenism. Its severity is categorised based on the number of facial lesions and lesion types[11]. However, medications for treatment of acne may render assessment difficult[18]. Hirsutism refers to the male-like pattern of terminal hair distribution. Over 70% of women with hirsutism show elevated androgens, whereas <5% of women with hirsutism do not demonstrate other PCOS features[17]. Hirsutism is the most recognisable sign of hyperandrogenism. It can be assessed visually using the modified Ferriman-Gallwey score with photographic atlas[19]; the cut off scores were ≥4 to 6. However, hirsutism has ethnic variation. Visual assessment is subjective and thus inter- and intra-observer variability are high[20]. Self-treatment for excessive terminal hair may further complicate visual assessment[21].

Identifying biochemical hyperandrogenism in adolescents remain challenging, as testosterone levels rise since puberty[23]. Calculated free testosterone or free androgen index has higher sensitivity than direct free testosterone assays[12]. It is uncertain whether mild hyperandrogenaemia represents a physiological peri-menarcheal situation and whether genuine adolescent hyperandrogenaemia persists into adulthood[23].

Polycystic ovaries are defined based on the ovarian volume and the number of follicles. According to the Rotterdam criteria, polycystic ovaries are defined as having one or both ovaries with ≥12 follicles measuring 2 to 9 mm in diameter or with >10 cm^3 of ovarian volume[24]. However, polycystic ovarian morphology is highly prevalent (30% to 40%) in adolescent girls[25], owing to the physiological changes during puberty (Figure). Using these ultrasonographic criteria may result in over-diagnosis in adolescents. Transvaginal ultrasonography is not appropriate for sexually inactive adolescents. Transabdominal ultrasonography is technically difficult for inexperienced operators and may not detect up to 30% of polycystic ovaries that are otherwise identified on transvaginal ultrasonographic study[24]. Ovaries maybe obscured in patients with an inadequately distended urinary bladder, and an over-distended urinary bladder may compress the ovaries and result in inadequate application of the ellipsoid model in calculation of ovarian volume[24]. Therefore, ultrasonography is not recommended for diagnosing PCOS in patients <8 years after menarche. Magnetic resonance imaging of the pelvis is an alternative because it enables assessment of the number of follicles and ovarian volume. However, it is expensive and is not warranted solely for the assessment for possible polycystic ovarian morphology.

The diagnosis of PCOS requires exclusion of other pathologies. In adolescents, the most frequent differential diagnosis of PCOS is congenital adrenal hyperplasia, which has similar phenotypic features[26], followed by thyroid disease, hyperprolactinaemia, and adrenocortical diseases[27]. Exclusion of other pathologies should be based on combined clinical, radiological, and biochemical assessments.

Difficulties in diagnosing PCOS in adolescents

After excluding ultrasonography as a diagnostic tool for polycystic ovarian morphology in adolescents,

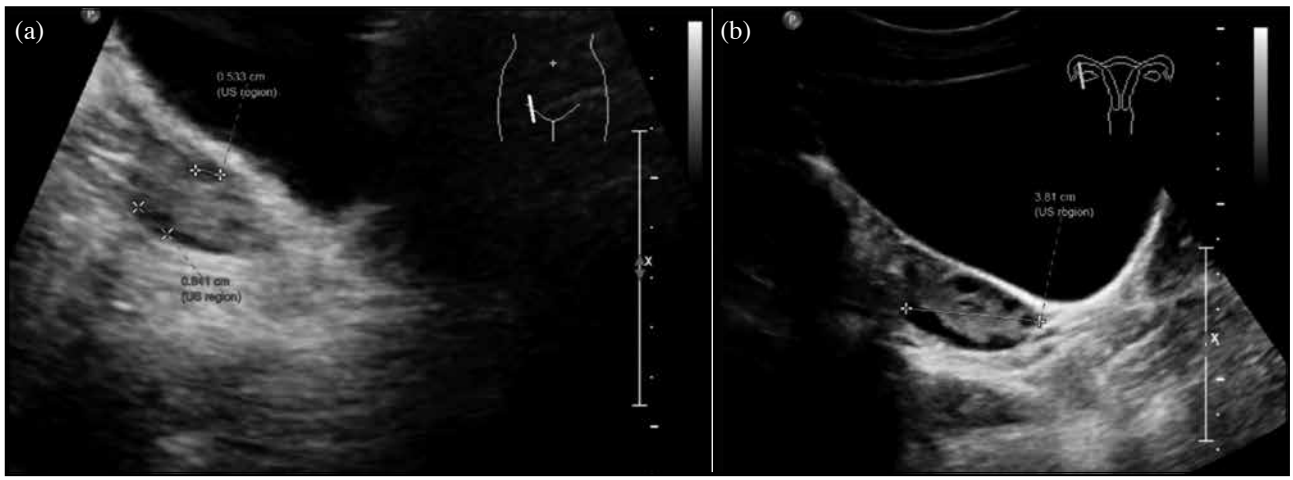

Figure. A 14-year-old girl presented with irregular long cycles with prolonged bleeding. Her menarche was at 12 years old. (a) Transabdominal ultrasonography showing no polycystic ovarian morphology. She continued to have irregular long cycles and secondary amenorrhea. (b) Follow-up transabdominal ultrasonography at 17 years old showing polycystic ovaries. This case illustrates the need of regular follow-up for at-risk teenagers.

the diagnosis of PCOS necessitates presentation of both hyper-androgenism and irregular menstrual cycles. Ultrasonographic assessment is not necessary even for adults if the other two criteria are fulfilled. For adolescents who have features of PCOS but do not fulfil the diagnosis should be considered at risk and be followed up until full reproductive maturity[12]. At-risk adolescents include those with PCOS features before use of combined oral contraceptive pills, those with significant weight gain, and those with persisting clinical features.

Patients may first present to non-gynaecologists for reasons other than irregular menstrual cycles such as acne, hirsutism, and obesity. The presentation may further be complicated by psychosocial morbidity and low self-esteem from discrimination or strained peer relationships[28], and by self-treatment such as using over-the-counter medication for acne, shaving or waxing hair, and dieting. For young adolescents who present with irregular menstrual cycle, clinicians may wrongly attribute it to normal pubertal development and therefore under-diagnosing ovarian dysfunction.

Over-diagnosis or incorrect diagnosis of PCOS may lead to unjustified investigations, interventions, and anxiety. A prompt diagnosis of PCOS enables therapeutic interventions[29], but over-diagnosis or incorrect diagnosis affects the patient's quality of life and creates unnecessary anxiety. Clinicians are reluctant to make a diagnosis of PCOS in young adolescents. Hence, identifying at-risk adolescents with possible PCOS and follow-up for re-evaluation can avoid under- or over-diagnosis and their implications[12].

Conclusion

It is important to recognise PCOS early for timely management. Clinicians should be aware of the difficulties in diagnosing PCOS in adolescents. A multi-disciplinary approach for diagnosis and treatment is suggested. For high-risk cases, re-evaluation may avoid under-diagnosing or over-diagnosing of PCOS.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

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