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Obesity, Oligomenorrhoea and PCOS in Adolescence

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Abstract
Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy affecting female reproductive health. The diagnosis of PCOS in adolescence is challenging due to the high prevalence of menstrual dysfunction and acne in the normal adolescent population. Hirsutism should prompt further investigation and alert the clinician to the possibility of PCOS. Early identification of adolescents at risk of PCOS with timeous intervention may impact on long term metabolic and cardiovascular health.

Introduction

Obesity is defined as a body mass index (BMI) in excess of 30kg/m^2 in adults and a BMI per age above the 95th centile for children.[1] In the past two decades obesity has become a world-wide epidemic, mostly due to a sedentary lifestyle and consumption of fast foods and refined carbohydrate diets.

In the United States 17% of girls between the ages of 6 and 19 years are obese.[1] According to the Heart and Stroke foundation of South Africa, 14.2% of primary school children are overweight, whilst in urban areas 30% of girls have a BMI above 25.[2]

BMI is reflective of overall adiposity, whereas waist circumference is reflective of central obesity. Central obesity is more closely related to increased cardiovascular risk, as abdominal adipose tissue has greater metabolic activity. In a study on adolescents aged 12 to 19 years in the United states, a waist circumference above 81cm were linked to abnormal blood pressure, lipogram and fasting glucose values.[3]

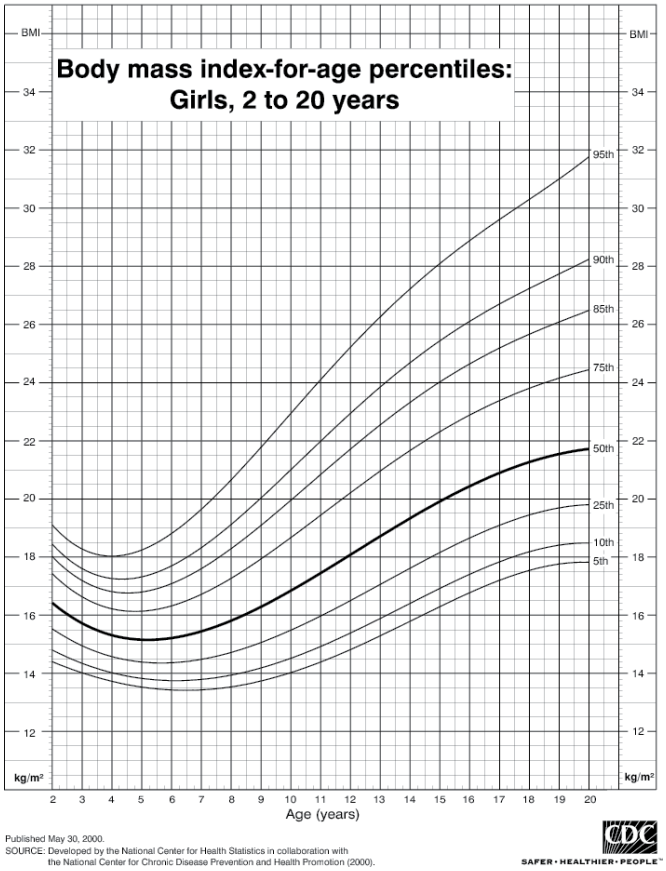
In adolescence obesity is linked to premature puberty, as BMI and leptin levels are crucial for the activation of the Hypothalamic Pituitary Ovarian Axis.

The incidence of obesity and PCOS is proportionate. Amongst lean adults the incidence of PCOS is 5.5% compared to 28% for those with a BMI above 25kg/m^2.[1] The incidence of obesity amongst patients with PCOS is 3 to 4 fold higher than that of unaffected patients.[1] In a recent Turkish study 54.9% of adolescents with PCOS were overweight and 25.7% had metabolic syndrome.[4]

Obesity exacerbates the metabolic manifestations of PCOS. It promotes insulin resistance, which results in arrest of follicular maturation and promotes ovarian androgen production.[1,5] Obesity is associated with lower SHBG levels, which also results in higher free androgen levels. Thus with a rise in BMI, there is a proportional increase in free serum testosterone.[5]

Patients who are obese have higher endogenous estrogen levels - as aromatase in adipose tissue converts androgens to estrogen. In the anovulatory PCOS patient, the unopposed estrogen places them at higher risk to have hormone sensitive malignancies such as breast or endometrial carcinoma later in life.

CDC Growth Charts: United States



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PCOS Aetiology

PCOS is thought to occur via an interplay between environmental and genetic factors. More than a hundred genes involved in steroidogenesis have been identified as potential role players in PCOS.[5] More recently, with the aid of genome wide association studies (GWAS), several SNPs (Single nucleotide polymorphisms) have been identified in patients with PCOS. For example a SNP on the FSH- β polypeptide is associated with high LH concentrations.[6] Environmentally, endocrine disrupting chemicals such as Bisphenol A and phthalates in food packaging can impact on hormone homeostasis. Antenatal exposure to high levels of maternal serum androgens has been associated with PCOS in offspring.[5] The link between intra-uterine growth restriction and precocious pubarche, hyperinsulinaemia and functional ovarian hyperandrogenism have already been established more than two decades ago.[7] The etiology of this association is thought to arise by epigenetic modification - programming low birth weight babies for metabolic syndrome later in life.

PCOS diagnosis

There are several sets of diagnostic criteria for the diagnosis of PCOS, of which the Rotterdam criteria[8] are most commonly used in adults. As many adolescents have irregular cycles, acne and a large amount of antral follicles on ultrasound, the classical Rotterdam criteria are not as useful. Great caution should be exercised with the precocious diagnosis of PCOS in adolescence.

PCOS Diagnostic Classification	
Traditional Classification	
Rotterdam 2003[8]	AE-PCOS Society[9]
1 OD 2 PCOM 3 HA [Need 2 criteria]	OD or PCOM And HA
PCOS Phenotypic Classification	
NIH 2012 Extension[10]	Lizneva 2016[11]
A: HA + OD + PCOM B: HA + OD C: HA + PCOM D: OD + PCOM	Classic PCOS Ovulatory PCOS Non hyperandrogenic PCOS
OD: Ovulatory dysfunction HA: Hyperandrogenism (Clinical or Biochemical) PCOM: Polycystic ovarian morphology	

In a recent Turkish study on adolescents, by Altintas et al,[4] there was a correlation between the PCOS phenotype and the incidence of metabolic syndrome. In NIH phenotype A/Classic PCOS 39.5% had metabolic syndrome, compared to 15% in NIH phenotype D. The incidence of insulin resistance however was similar amongst all 4 phenotypes. Those with metabolic syndrome had a higher BMI and testosterone levels. The most common lipid abnormality was a low HDL-C, which was seen in all 4 phenotypes.[4]

Currently an international evidence-based guideline for PCOS assessment and management is under development, with the draft publication available for public comment.[12]

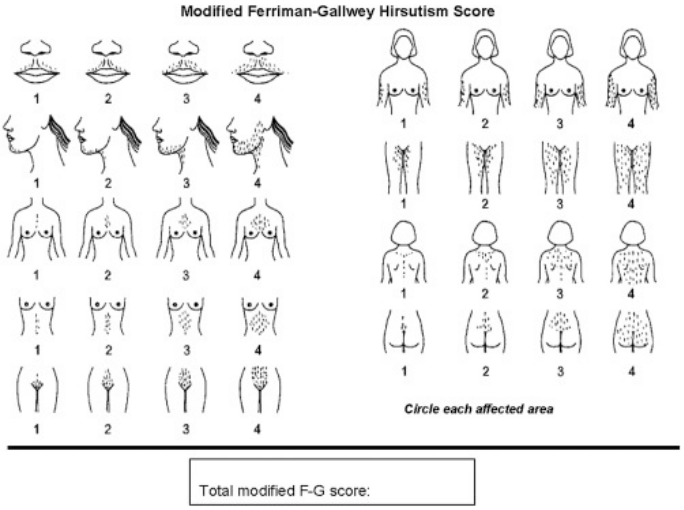
Irregular menses

Irregular cycles are common shortly after menarche as the hypothalamic-pituitary-ovarian axis matures and ovulatory cycles become more frequent. By the third post-menarchal year 95% of adolescents have regular cycles, which comprises of 10 or more cycles per year.[8] Evaluation is advised when irregular cycles (shorter than 21 days or longer than 35 days) persist 2 years after the onset of menarche, or in patients with primary amenorrhoea at the age of 15-16 years or two years after thelarche.[5,6,9,12]

With oligomenorrhoea in puberty it is vital to investigate as for other causes of anovulation, as PCOS is a diagnosis of exclusion. Recommended baseline investigations include: Prolactin, Thyroid function, LH, FSH and Estradiol levels. Patients with PCOS usually have LH, FSH and estradiol levels within normal ranges.

Hyperandrogenism

Hyperandrogenism is the cardinal symptom which should alert the clinician to the possibility of PCOS. Adolescents with PCOS have higher LH pulse amplitude and frequency compared to those without and commonly have an elevated LH:FSH ratio. The theca cells of the PCOS ovary have higher number of LH receptors which drive androgen synthesis.[5]



The complete Ferrimen Gallwey Scoring Sheet is available from https://pedclerk.bsd.uchicago.edu/page/hirsutism

With adrenarche, mild acne and hirsutism is considered normal. Moderate to severe acne (more than 11 inflammatory lesions) and moderate-severe hirsutism based on the Ferriman-Gallwey scoring ≥ 8 are indications to test for hyperandrogenaemia.[5] In an office setting the sum of scores from the lip, chin and pubic region may be sufficient to discriminate hirsute from non-hirsute women.[13] Biochemical testing includes serum total and free testosterone and SHBG. Adult female ranges can be used to interpret adolescent serum testosterone levels.[13] DHEAS and early morning follicular phase 17α-OHP should be performed to exclude adrenal tumours and non-classic congenital adrenal hyperplasia. Should there be other clinical signs of Cushing's syndrome eg central obesity, moon facies, buffalo hump, striae, and hypertension; then midnight salivary cortisol or 24 hour urinary cortisol excretion is advised.

Ultrasound

Classically PCOM was defined as 12 or more antral follicles (measuring 2-9mm) per ovary or an ovarian volume exceeding 10 ml. Adolescents commonly have poly-follicular ovaries, as more than half of normal adolescents meet the morphological criteria.[5]

In the hyperandrogenaemic patient, ovarian visualisation is important to exclude androgen producing ovarian tumours eg. Sertoli-Leydig cell tumours.

Clinicians are strongly discouraged from using ovarian morphology to diagnose PCOS in adolescents.[6,12]

AMH

Anti-Mullerian Hormone measurement is an expensive assay that is reflective of the follicular pool and ovarian reserve. Several studies have been conducted amongst adolescents with PCOS - Hart et al,[14] Wright et al.[15] They were found to have higher AMH levels than those without, but they were unable to establish a discriminatory level. Wiweko et al[16] recently published findings of a 3 year study based in Indonesia on 125 PCOS patients, diagnosed with the Rotterdam criteria. They found AMH to be strongly correlated with the PCOS phenotypes – with NIH A having the highest AMH, as well as the highest incidence of impaired glucose tolerance and metabolic syndrome. Currently AMH is not helpful in adolescents to diagnose PCOS and should not routinely be performed.[12]

Management

Treatment goals include:

- Regulation of menses
- Improvement of acne and hirsutism
- Identification and treatment of the metabolic syndrome and cardiovascular risk factors (hypertension, impaired glucose tolerance, dyslipidaemia)
- Improvement in self-esteem, psychosocial health and quality of life

Screening

An adolescent with irregular menses and hyperandrogenism should be screened for metabolic syndrome. Adult diagnostic criteria may be used from the age of twenty years – with adolescents the 90th centile for the population are better correlated with increased risk than absolute values.

The only exception is the fasting glucose cut off point of 5.6mmol/l which can be used for all ages.[17]

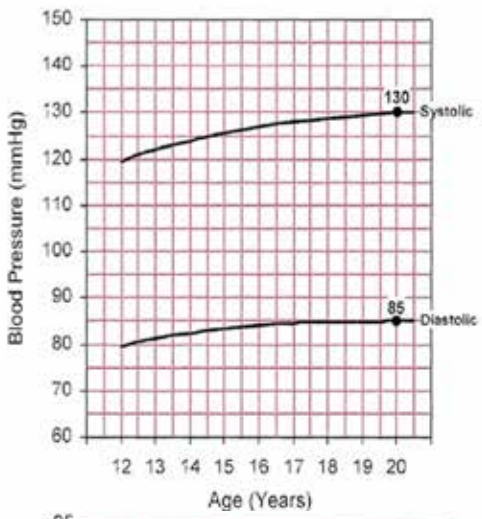
Diagnostic Criteria for the Metabolic Syndrome

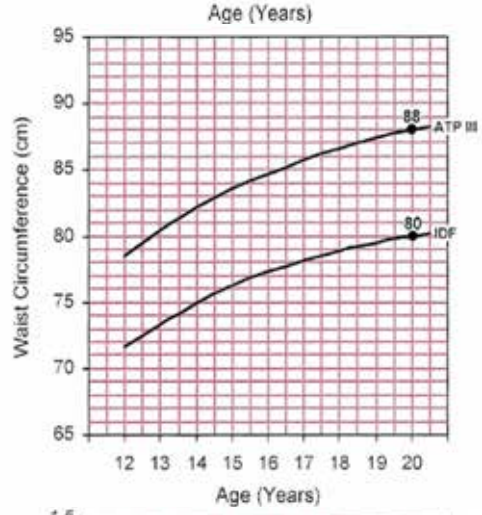
Waist Circumference	Fasting Glucose	BP	HDL	TG
>88cm	>5.6 mmol/l	>130/85 mm Hg	<1.29 mmol/l	>1.7 mmol/l

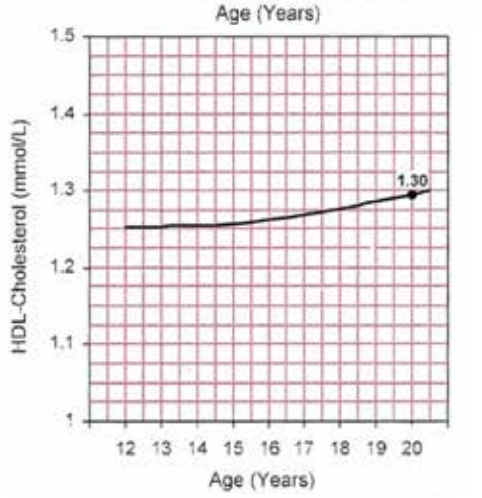
Criteria by Adults American Heart Association[18]

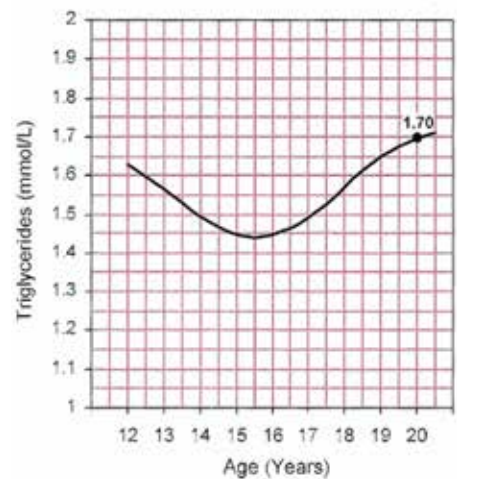
Ma et al [19] demonstrated that waist-height ratio strongly correlated with visceral adiposity and metabolic syndrome. A waist height ratio of 0.46 and above was reflective of increased cardiovascular risk.

In adolescents centile graphs should be used, as published by Joliffe et al[17] and depicted on the right.









Lifestyle

Maintenance of a normal BMI is of cardinal importance as obesity is linked to diabetes, hypertension, atherosclerotic cardiovascular disease and obstructive sleep apnoea. Weight loss should be considered first line therapy for PCOS in overweight individuals. Caloric restriction (energy

deficit of 30%) and exercise (60 minutes vigorous exercise 3 times per week) are advocated to achieve weight loss.[12] Exercise improves insulin sensitivity, lowers free androgen levels and lipids and increase SHBG levels. Compliance may be a challenge in the adolescent population and successfully addressed in a group setting.

Medical

Combined hormonal contraception (CHC) is considered first line therapy to address irregular menses and hyperandrogenism. The estradiol component increases SHBG levels, thereby decreasing the free androgen index. The progesterone, if anti-androgenic, can bind the androgen receptor in the skin and hair follicle to reduce acne and hirsutism. The progesterone also provides negative feedback to the pituitary gland to lower LH levels, which in turn reduces androgen production. CHC can be provided in the form of the pill, patch or ring. Compliance should be considered when prescribing a specific route.

CHC should not be used in patients with migraine with an aura, or a personal history of venous thrombo-embolism or gall bladder disease. The benefit of CHC includes menstrual regulation in terms of timing and volume, endometrial protection and contraception. It is preferable to commence a CHC with a lower dose of estradiol (20-30 ug).[12]

Anti-androgenic progesterones e.g Cyproterone should not be prescribed without reliable contraception, as it can cause male fetal undervirilisation.[12] It is especially useful in patients with androgenic alopecia.

Metformin is a biguanide that increases insulin sensitivity and decreases hepatic gluconeogenesis. It is indicated in adolescents with abnormal oral glucose tolerance testing – FBG >6.0 mmol/l and 2 hour value above 7.8 mmol/l. It improves menstrual regularity, but has no effect on androgen production. The recent international guidelines state that metformin can be considered in overweight adolescents, in combination with CHC, as well as in those with metabolic risk factors.[12] Metformin should be started at 500mg doses and increased slowly to allow adaptation to gastro-intestinal side effects.

Spironolactone, an aldosterone antagonist may also be used to treat hirsutism. It inhibits adrenal androgen synthesis and 5-alpha reductase activity within the hair follicle. A minimum of four months of therapy is advised to assess efficacy. Recommended starting dose in adolescents are 25mg per day and can be increased gradually to 100mg per day. It is contra-indicated in adolescents with renal impairment or hyperkalaemia. It should be given with effective contraception as it can cause fetal virilisation.[5]

Conclusion

PCOS is a diagnostic conundrum in the adolescent population and the diagnosis should be made with caution. It is advisable to rather label a patient to be 'at risk of PCOS' if they have irregular menses and hyperandrogenism. As there is a high incidence of metabolic syndrome under adolescents with PCOS, early recognition and lifestyle modification may prevent long term metabolic and cardiovascular morbidity. Studies on South African adolescents, amongst ethnically diverse groups, would assist use to construct nomograms for the South African population.

References:

1. *Anderson AD, Solorzano CMB, McCartney CR. Childhood obesity and its impact on the development of adolescent PCOS.SeminReprod Med. 2014; 32:202-213. DOI:10.1055/s-0034-1371092*
2. *Childhood Obesity in South Africa. Published Oct 2016. Available from: http://www.ngopulse.org/article/2016/10/1.*
3. *Taylor SH, Hergenroeder AC. Waist circumference predicts increased cardiometabolic risk in normal weight adolescent males. Pediatric Obesity. 2012. DOI: 10.3109/17477166.2011.575149.*
4. *Altintas KZ, Dilbaz B, Cirik DA, Ozelci R, Zengin T, Erginay ON, Dilbaz S. The incidence of metabolic syndrome in adolescents with different phenotypes of PCOS. GinkologicaPolska. 2017; 88(6):289-95. DOI:10.5603/GPa2017.0055*
5. *Rothenberg SS, Beverley R, Barnard E, Baradaran-Shoroka M, Sanfilippo JS. Polycystic ovary syndrome in adolescents. Best Practice & Research Clinical Obstetrics and Gynaecology. 2017. DOI: 10.1016/j.bpobgyn.2017.08.008*
6. *Witchel SF, Roumimper H, Oberfield S. Polycystic Ovary Syndrome in Adolescents. EndocrinolMetabClin N Am. 2016; 45:329-344. DOI:10.1016/j.ecl.2016.01.004*
7. *Ibanez L, Potau N, Francois I, De Zegher F. Precocious pubarche, hyperinsulinism and ovarian hyperandrogenism in girls: relation to reduced fetal growth. The Journal of Clinical Endocrinology and Metabolism. 1998; 83(10):3558-62.*
8. *Fauser BCJM. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. FertilSteril. 2004;91(2):456-88.*
9. *Roe AH, Prochaska E, Smith M, Sammel M, Dokras A. Using the Androgen Excess PCOS Society Criteria to Diagnose Polycystic Ovary Syndrome and the risk of Metabolic Syndrome in Adolescents. The Journal of Pediatrics. 2013; 162:937-41. DOI:10.1016/j.jpeds.2012.11.019*
10. *Timothy RB, Johnson MD, Lorrie Kline Kaplan. National institutes of health, evidence-based methodology workshop on polycystic ovary syndrome. Centres for Medicare & Exec Summ 2012. Available from: https://prevention.nih.gov/docs/programs/pcos/FinalReport.pdf.*
11. *Lizneva D, Suturina l, Walker W. Criteria, prevalence and phenotypes of polycystic ovary syndrome. FertilSteril. 2016;106:6-15.*
12. *International Evidence-based guidelines for the assessment and management of polycystic ovary syndrome. Copyright Monash University, Melbourne. 2018. Available from: http://pcos-cre.edu.au.*
13. *Strauss JF, Barbieri RL. Yen & Jaffe's Reproductive Endocrinology. 8th ed. Philadelphia: Elsevier; 2019.*
14. *Hart R, Doherty DA, Nroman RJ, Franks S, Dickinson JE, Sloboda DM. Serum antimullerian hormone (AMH) levels are elevated in adolescent girls with polycystic ovaries and the polycystic ovarian syndrome (PCOS). FertilSteril. 2010; 94(3):1118-1121.*
15. *Wright S, Gourgari E, Stratakis C, Gomez-Lobo V. J PediatrAdolesc Gynecol. 2015; 28:e41-78.*
16. *Wiweko B, Indra I, Susanto C, Natadisastra M, Hestiantoro A. The correlation between serum AMH and HOMA-IR among PCOS phenotypes. BMC Research notes. 2018; 11:114. DOI:10.1186/s13104-018-3207-y*
17. *Jolliffe CJ, Janssen I. Development of age specific adolescent metabolic syndrome criteria that are linked to the adult treatment panel III and International Diabetes Federation Criteria. Journal of the American College of Cardiology. 2007; 49(8):891-98. DOI: 10.1016/j.jacc.2006.08.065*
18. *Grundy SC, Cleeman JI, Daniels SR, Donato KR, Eckel RH, Franklin BA, Gordon DJ et al. Diagnosis and Management of the Metabolic Syndrome. AHA/NHLBI Scientific Statement. Circulation. 2005; 112:2735-52. DOI: 10.1161/CIRUCLATIONAHA.105.169404.*
19. *Ma CM, Yin FZ, Wang R, Lou DH, Lu Q. How to simplify the diagnostic criteria of metabolic syndrome in adolescents. Pediatrics and Neonatology. 2016; 58:178-184. DOI:10.1016/j.pedneo.2016.03.008.*