THE DIAGNOSIS OF PCOS IN ADOLESCENCE

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DISCLOSURE

• Dr. Bonny has no significant disclosures.

• Dr. Gomez-Lobo has no significant disclosures.
LEARNING OBJECTIVES

• Describe the process of the recent consensus publication regarding the diagnosis of PCOS during adolescence.

• Explain the background and recommendations of each key diagnostic question.

• Outline the summary recommendations.

The Diagnosis of Polycystic Ovary Syndrome during Adolescence

Selma E. Witchel, Sharon Oberfield, Robert L. Rosenfield, Ethel Codner, Andrea Benney, Lourdes Ibáñez, Aldea Pena, Reiko Honkawa, Veronica Gomez-Lobo, Dipakshama Joel, Hala Hafiz, Shiva Arslanian, Preeth Deodhao, Cecilia Garcia Fudacz, Peter A. Lee

Background/Aims: The diagnostic criteria for polycystic ovary syndrome (PCOS) in adolescence are controversial, primarily because the diagnostic pathological features used in adult women may be normal pubertal physiological variants. Hence, international pediatric and adolescent specialty societies have defined criteria that have sufficient evidence to be used for the diagnosis of PCOS in adolescents.

Methods: The
PROCESS

- **Pediatric Endocrine Society (PES) invited representatives from:**
  - Androgen Excess-PCOS Society (AE-PCOS): Selma F. Witchel, Sharon Oberfield
  - Australasian Pediatric Endocrine Group (APEG): Alexia Pena
  - Asia Pacific Pediatric Endocrine Society (APPES): Preeti Dabdghao, Cecilia Garcia Rudaz
  - African Society for Pediatric and Adolescent Endocrinology (ASPAE): Joel Dipesalema
  - European Society for Pediatric Endocrinology (ESPE): Lourdes Ibáñez
  - Japanese Society for Pediatric Endocrinology (JSPE): Reiko Horikawa
  - Japanese Society of Obstetrics and Gynecology (JSOG): Reiko Horikawa
  - Pediatric Endocrine Society (PES): Selma F. Witchel, Sharon Oberfield, Robert L. Rosenfield, Silva Arslanian, Peter A. Lee
  - Latin American Society for Pediatric Endocrinology (SLEP): Ethel Codner

PROCESS

- Questions developed; small groups drafted background and recommendations for each section; sections then shared with the entire group for edits and approval.
- Evidence graded according to the AGREE criteria
  - Level A requires at least one randomized controlled trial (RCT) as part of a body of literature of overall good quality and consistency that addresses the specific recommendation.
  - Level B requires the availability of well-controlled clinical studies, but no RCTs are available on the topics of recommendation.
  - Level C requires evidence obtained from expert committee reports of opinions and/or clinical experiences of respected authorities, which indicates an absence of directly applicable clinical studies of good quality.
WHAT ARE THE CRITERIA FOR EVIDENCE OF CLINICAL HYPERANDROGENISM IN THE ADOLESCENT GIRL?

QUESTION 1

CLINICAL HYPERANDROGENISM BACKGROUND

- Hirsutism:
  - Severity of hirsutism does not correlate well with circulating androgen concentrations
  - Due to ethnic/genetic differences, hirsutism may be a less prominent feature of hyperandrogenism in some populations.
  - FG scale: sparse normative data in adolescents
    - Upper lip scores of 3–4 present in <3% of Black & White US adolescents
    - Upper lip score of 1–2
      - 7.3% at <2 years after menarche
      - 28.2% at >2 years after menarche

- Acne
  - Common in adolescent girls
  - But moderate or severe comedonal acne (i.e., 10 or more facial lesions) in early puberty or moderate inflammatory acne through the peri-menarcheal years is uncommon (<5%)
CLINICAL HYPERANDROGENISM RECOMMENDATIONS

1) Isolated mild hirsutism should not be considered clinical evidence of hyperandrogenism in the early post-menarcheal years when it may be in a developmental phase (Level C).

2) Moderate to severe hirsutism constitutes clinical evidence of hyperandrogenism (Level B).

3) Girls with acne that is persistent and poorly responsive to topical dermatologic therapy should be evaluated for the presence of hyperandrogenemia before initiation of any medical therapies (Level C).

WHAT ARE THE CRITERIA FOR EVIDENCE OF BIOCHEMICAL HYPERANDROGENISM IN THE ADOLESCENT GIRL?

QUESTION 2
BIOCHEMICAL HYPERANDROGENISM BACKGROUND

- Total and/or free testosterone have been the most recommended hormone determinations to document hyperandrogenemia
- Diurnal rhythm, stage of puberty, phase of menstrual cycle, and sex hormone-binding globulin (SHBG) concentrations influence testosterone concentrations
- Assay problems:
  - inadequate assay sensitivity to measure low testosterone concentrations in children and women
  - assay interference due to simultaneous presence of other steroid molecules with similar structure
  - lack of well-defined normative values
  - binding of testosterone to SHBG and other proteins in the peripheral circulation
  - technical aspects of testosterone assays
- Testosterone levels have long been known to rise during puberty to reach a level approximating those in adults within a few years after menarche
- How often adolescent hyperandrogenemia persists and predicts adult hyperandrogenemia is unclear

BIOCHEMICAL HYPERANDROGENISM BACKGROUND

- No clear cutoff testosterone concentrations
  - Variability in the results of testosterone assays
  - Limited data on the normal developmental fluctuations in testosterone levels during puberty
- Testosterone concentrations should be considered elevated:
  - When persistently greater than adult female normative values
  - When utilizing assays performed by specialty laboratories with well defined reference intervals
  - Total testosterone concentrations >55 ng/dl consistent with hyperandrogenism when quantified by an assay using an extraction step
BIOCHEMICAL HYPERANDROGENISM RECOMMENDATIONS

1) Hyperandrogenemia needs to be defined based on the detailed characteristics of the testosterone assay used (Level A).

2) Biochemical evidence of hyperandrogenism, as indicated by persistent elevation of serum total and/or free testosterone levels and determined in a reliable reference laboratory, provides the clearest support for the presence of hyperandrogenism in an adolescent girl with symptoms of PCOS (Level B).

3) A single androgen level >2 SD above the mean for the specific assay should not be considered to be evidence of hyperandrogenism in an otherwise asymptomatic adolescent girl (Level C).

WHAT ARE THE CRITERIA FOR EVIDENCE OF OLIGO-ANOVULATION IN ADOLESCENTS?

QUESTION 3
EVIDENCE OF OLIGO-ANOVULATION

BACKGROUND

• Menstrual irregularity is common in adolescents
• The challenge for the clinician is differentiation of “physiological anovulation” from true ovulatory dysfunction
• 98% of females will have had menarche by 15 years
• Most normal cycles range from 20 – 90 days even if the 1st gynecologic year.
  • Statistically uncommon for adolescent to remain amenorrheic >90 days regardless of gynecologic age
  • With increasing gynecologic age few females experience cycles exceeding 45 days

EVIDENCE OF OLIGO-ANOVULATION

RECOMMENDATIONS

1) The majority of adolescents establish a menstrual interval of 20-45 days within the first 2 years after menarche. Menstrual intervals persistently shorter than 20 days or greater than 45 days in individuals 2 or more years after menarche are evidence of oligo-anovulation (Level B).

2) A menstrual interval greater than 90 days is unusual even in the first year after menarche. As such, consecutive menstrual intervals greater than 90 days are rare and require further investigation regardless of years after menarche (Level B).

3) Lack of onset of menses by age 15 years or by more than 2-3 years after thelarche regardless of chronologic age is statistically uncommon and warrants evaluation and consideration of diagnoses such as PCOS (Level B).
WHAT ARE THE CRITERIA FOR PCOM IN AN ADOLESCENT GIRL?

QUESTION 4

CRITERIA FOR PCOM BACKGROUND

- Ovary enlarges at the time of puberty
- Increase in follicles and multi-follicular ovaries
- Difficulty in performing transvaginal ultrasound
- PCOM, variously defined, has been reported with a prevalence of 30-40% (range 26 - 54%) in adolescent girls
- Similar levels of androgens, insulin, and indexes of insulin sensitivity in girls with and without PCOM
CRITERIA FOR PCOM RECOMMENDATIONS

1) No compelling criteria to define PCOM have been established for adolescents. Until further research establishes definitive criteria, an ovarian volume >12.0 cm³ (by formula for a prolate ellipsoid) can be considered enlarged. Follicle counts should not be utilized to define PCOM in adolescents (Level B).

2) A multifollicular pattern, defined by the presence of large follicles distributed throughout the ovary, does not have a relationship with hyperandrogenism, is more common in adolescents, and should not be considered a pathological finding (Level C).

3) In healthy girls without hyperandrogenism and with regular menstrual cycles, PCOM does not indicate a diagnosis of PCOS (Level B).

4) Abdominal ultrasound in adolescents, particularly obese girls, may yield inadequate information (Level C).

5) AMH should not be used to characterize PCOM (Level B).

6) Until better quality-consistent data are available, ovarian imaging can be deferred during the diagnostic evaluation for PCOS (Level C).

WHAT DIAGNOSTIC PROCEDURES ARE APPROPRIATE IN ADOLESCENTS TO EXCLUDE OTHER CAUSES OF HYPERANDROGENISM & AMENORRHEA?

QUESTION 5
EXCLUSION OF OTHER CAUSES
BACKGROUND

• All diagnostic criteria for PCOS include the proviso that other causes of androgen excess and amenorrhea have been excluded
• Differential diagnosis
  • Most frequent is nonclassic congenital adrenal hyperplasia
  • Other include: Cushing’s syndrome, primary pigmented nodular adrenocortical disease, McCune-Albright syndrome, glucocorticoid resistance, ovarian androgen secreting tumors, thyroid dysfunction, hyperprolactinemia, and adrenal tumors
• If androgen secreting tumor suspected, abdominal and pelvic U/S should be 1st line screen

EXCLUSION OF OTHER CAUSES
BACKGROUND

• Diagnostic approach begins with thorough medical history and physical exam
• Typical blood work: 17-OHP, total & free testosterone, SHBG, androstenedione, and DHEAS
• Clinical findings guide need for other blood work i.e. TFT’s, prolactin, and ACTH stimulation test
• ACTH stimulation test on all adolescents with suspected NCAH is not feasible. Use of follicular phase morning 17-OHP is advocated.
EXCLUSION OF OTHER CAUSES
RECOMMENDATIONS

1) A thorough medical history, physical examination, and appropriate laboratory assessment are essential to provide the information necessary to exclude other disorders associated with androgen excess (Level A).

WHAT IS THE ROLE OF INSULIN RESISTANCE/HYPERINSULINEMIA IN THE DIAGNOSIS OF PCOS IN ADOLESCENTS?

QUESTION 6
ROLE OF INSULIN RESISTANCE

BACKGROUND

- High prevalence of insulin resistance (IR) and hyperinsulinemia (HI) in adolescents with PCOS, lean or obese
  - Inherent to the syndrome and over and above that conferred by obesity
  - Increasing evidence for a link between IR/HI and androgen excess in adolescents with PCOS
- With the exception of one, none of the current published PCOS definitions include IR/HI as a diagnostic criteria
- IR/HI should be viewed as warnings to investigate and treat PCOS comorbidities such as pre-diabetes and type 2 diabetes

ROLE OF INSULIN RESISTANCE

RECOMMENDATIONS

1) Although prevalent among adolescents at risk for PCOS, insulin resistance and hyperinsulinemia should not be utilized as diagnostic criteria (Level B).
2) Insulin resistance and hyperinsulinemia can be considered as indications to investigate and treat potential comorbidities (Level B).
DOES A DIAGNOSIS OF PCOS IN ADOLESCENCE PROVIDE AN OPPORTUNITY FOR MEANINGFUL INTERVENTION? RISKS OF OVERDIAGNOSIS?

QUESTION 7

RISKS OF OVER-DIAGNOSIS
BACKGROUND

- Benefits of a timely diagnosis:
  - Awareness of a lifelong condition associated with hormonal and metabolic complications
  - An opportunity for meaningful intervention
    - Healthy lifestyle counseling
    - Testing for comorbidities
    - Medications
  - Intervention trials in adolescents with PCOS show benefit with respect to:
    - Decreased androgen levels, hirsutism, ovulation, QoL, sleep, lipid profile, adipocytokine levels and IR
    - Trials, however, limited by short duration (<6 mos).
    - Adequately powered, placebo controlled trials are lacking
RISKS OF OVER-DIAGNOSIS

BACKGROUND

- Risk of over diagnosing PCOS:
  - Unnecessary labeling
  - Unwarranted interventions and medications
  - Impact on patient's QoL and/or anxiety

- It is crucial to re-evaluate all adolescents with features suggestive of PCOS.

RISKS OF OVER-DIAGNOSIS

RECOMMENDATIONS

1) A timely diagnosis of PCOS in symptomatic adolescent girls is important for the initiation of appropriate screening and treatment (Level A).
2) Validated diagnostic criteria supported by robust clinical and hormonal findings are needed to avoid over diagnosis and unnecessary treatment in otherwise healthy normal girls without hyperandrogenism (Level C).
3) Research evaluating long-term interventions using high-quality RCTs and lifelong follow-up of girls with PCOS diagnosed during adolescence would be ideal (Level C).
CONCLUSIONS

- The overlap between normal pubertal development and characteristics of PCOS may confound an accurate diagnosis of PCOS in adolescent girls (Level A).
- Other disorders associated with irregular menses or hyperandrogenism need to be excluded from diagnostic consideration (Level A).

CONCLUSIONS

- Great caution should be taken before diagnosing PCOS in adolescent girls with clinical features of androgen excess such as hirsutism and biochemical hyperandrogenism if oligomenorrhea has not persisted for more than 2 years. These girls can be considered “at risk” for PCOS. To avoid misdiagnosing physiological pubertal changes as PCOS, deferred diagnostic labeling accompanied by frequent longitudinal re-evaluation of these girls deemed “at risk” is beneficial and prudent during adolescence (Level C).
CONCLUSIONS

- Even in the absence of a definitive diagnosis and the lack of an approved therapy for PCOS in adolescents, treatment options that both alleviate the current symptoms and decrease the risk for subsequent associated comorbidities are recommended (Level B).
- Although obesity, insulin resistance, and hyperinsulinemia are common findings in adolescents with hyperandrogenism, these features should not be used to diagnose PCOS in adolescent girls (Level A).

CONCLUSIONS

- Prospective longitudinal research studies will be helpful to understand the natural history for girls considered to be “at risk” for PCOS. Research evaluating long-term interventions using high-quality RCTs and follow-up of girls with PCOS diagnosed during adolescence would be ideal. Through such research studies, it is hoped that validated diagnostic criteria supported by robust clinical and hormonal findings can be established to facilitate timely diagnosis while preventing over-diagnosis and unnecessary treatment in otherwise healthy normal pubertal girls (Level C).