Irregular Periods/PCOS

Pediatric Endocrinology Update
January 31, 2020
Jaime Haidet, MD
Objectives

• Define irregular menses
• Know the diagnostic criteria for PCOS
• Know the labs to obtain when evaluating for PCOS
Normal Menstrual Cycles in Adolescents

• Results from complex feedback system involving the hypothalamus, pituitary, ovary, and uterus

• Cycle lasts 21-45 days with 2-7 days of menstrual bleeding
  – Menstrual cycles vary considerably within the first few years after menarche
  – By the 3rd postmenarcheal year, 95% of cycles fall within this range
Definition of Irregular menses in Adolescent Girls

• **Normal during the first year postmenarche**

• **From 1 to 3 y postmenarche:**
  – <21 d or >45 d

• **From 3 y postmenarche to perimenopause:**
  – <21 d or >35 d or fewer than 8 cycles/year

• **From 1 y postmenarche:**
  – >90 d for any one cycle

• **Primary amenorrhea by age 15 y or >3 y after thelarche**
PCOS

- Most common endocrine disorder affecting reproductive age women
- Prevalence is 8-13% in women and 6% in adolescent girls
- Signs and symptoms of androgen excess, irregular menses, chronic anovulation, and infertility characterize the clinical phenotype
- Increased risk to develop diabetes, obesity, dyslipidemia, hypertension, anxiety, and depression
Diagnostic criteria

- 1935 Drs. Stein and Leventhal reported a series of women with amenorrhea and polycystic ovaries
- 1990 National Institutes of Health (NIH) criteria
- 2003 Rotterdam criteria
- 2008 Androgen Excess Society criteria

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Menstrual irregularity due to oligo- or anovulation</td>
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<td>Clinical and/or biochemical signs of hyperandrogenism</td>
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<td>Ovarian dysfunction - oligo/anovulation and/or polycystic ovaries on ultrasound</td>
</tr>
<tr>
<td>Exclusion of other disorders: NCCAH, androgen-secreting tumors</td>
<td>Polycystic ovaries (by ultrasound)</td>
<td>Exclusion of other androgen excess or ovulatory disorders</td>
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[^1]: [1]
[^2]: [2]
[^3]: [3]
Diagnostic criteria

• The diagnostic definitions overlap with the normal physiology of pubertal development and reproductive system maturation, presenting unique challenges to diagnosing and managing the adolescent girl with menstrual irregularity and signs of hyperandrogenism.
  - For at least 2 years after menarche, $\frac{1}{2}$ of menses are anovulatory, which contributes to the typical variability of menses length experienced during this time
  - Polycystic ovaries are a physiologic variant in normal girls
  - Cutaneous manifestations of hyperandrogenism may be a normal physiological occurrence in early to mid-adolescence, so they may not indicate pathology
  - No established normal ranges for total and free testosterone levels in adolescent girls
Diagnostic Criteria

Clinical Practice

An International Consortium Update: Pathophysiology, Diagnosis, and Treatment of Polycystic Ovarian Syndrome in Adolescence

Lourdes Ibáñez, Sharon E. Oberfield, Selma F. Witchel, Richard J. Auchus, R. Jeffrey Chang, Ethel Codner, Preeti Dabadghao, Feyza Darendeliler, Nancy Samir Elbarbary, Alessandra Gambineri, Cecilia Garcia Rudaz, Kathleen M. Hoeger, Abel López-Bermejo, Ken Ong, Alexia S. Peña, Thomas Reinehr, Nicola Santoro, Manuel Tena-Sempere, Rachel Tao, Bulent O. Yildiz, Haya Alkhayyat, Asma Deeb, Dipesalema Joel, Reiko Horikawa, Francis de Zegher, Peter A. Lee

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Akron Children's Hospital
Recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome

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Diagnostic Criteria

Table 1. Diagnostic criteria for polycystic ovary syndrome

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- Ovulatory dysfunction can still occur with regular cycles. Anovulation can be confirmed by measuring appropriately timed progesterone concentrations

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Diagnostic Criteria

Table 1. Diagnostic criteria for polycystic ovary syndrome

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Abnormal Menstrual/Ovulatory Function

- **Primary amenorrhea:**
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Clinical Hyperandrogenism

• A comprehensive history and physical exam should be completed for symptoms and signs including severe acne and hirsutism in adolescents

• Hirsutism is excessive terminal hair that appears in a male pattern in women.
  – Standardized visual scales are preferred when assessing hirsutism
FERRIMAN-GALLWEY HIRSUTISM SCORING SYSTEM

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- A comprehensive history and physical exam should be completed for symptoms and signs including severe acne and hirsutism in adolescents
- Hirsutism is excessive terminal hair that appears in a male pattern in women.
  - Standardized visual scales are preferred when assessing hirsutism
  - A level of ≥4-6 using the modified Ferriman Gallwey score indicates hirsutism, depending on ethnicity
    - Acknowledge self treatment is common and can limit clinical assessment
    - Ethnic variation in vellus hair density is notable, only consider terminal hairs
      - Clinically growing >5mm in length if left untreated
      - Varying in shape and texture
      - Generally being pigmented
- There are no universally accepted visual assessments for evaluating acne
Biochemical Hyperandrogenism

- In the absence of normative data for testosterone levels in adolescent girls, use of the reference labs’ adult women norms is recommended

- Calculated free testosterone, free androgen index, or calculated bioavailable testosterone should be used

- High-quality assays such as liquid chromatography-mass spectrometry (LCMS) and extraction/chromatography immunoassays should be used for the most accurate assessment of total or free testosterone
  - Radiometric or enzyme-linked assays should not be used

- Androstenedione and dehydroepiandrosterone sulfate (DHEAS) could be considered if total or free testosterone are not elevated
Biochemical Hyperandrogenism

- Assessment of biochemical hyperandrogenism is not possible with hormonal contraception/hormonal replacement therapy due to effects on sex hormone-binding globulin and altered gonadotropin-dependent androgen production
  - Drug withdrawal is recommended for 3 months or longer before measurement (and use of non-hormonal alternative contraception if applicable)
- Biochemical assessment is most useful where clinical signs of hyperandrogenism (in particular hirsutism) are unclear or absent
Ultrasound and PCOM

• US should NOT be used for the diagnosis of PCOS in those with gynecological age of <8 years (<8 years after menarche)
  – Due to the high incidence of multi-follicular ovaries in this life stage
Ultrasound and PCOM

• US for diagnosis of PCOS in those with gynecological age ≥8 years
  – In patients with irregular menses and hyperandrogenism, an ovarian US is not necessary for PCOS diagnosis
  – Transabdominal US
    • An ovarian volume ≥10 mL on either ovary
    • Follicle number criteria not included given the difficulty of reliably assessing follicle number with this approach
  – Transvaginal US
    • Preferred (if sexually active and if acceptable to the individual)
    • Transducer bandwidth frequency that includes 8 MHz
    • A follicle number per ovary ≥20
      and/or
      An ovarian volume ≥10 mL on either ovary
      (ensuring no corpora lutea, cysts or dominant follicles are present)
Diagnostic Criteria

- Exclusion of other diagnoses that may cause hyperandrogenism with menstrual irregularity

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Suggestive Symptoms and Signs</th>
<th>Screening Tests</th>
<th>Confirmatory Diagnostic Tests</th>
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<tbody>
<tr>
<td>Nonclassical congenital adrenal hyperplasia</td>
<td>History of premature adrenarche and/or advanced bone age in childhood</td>
<td>Morning (8 am) 17-OHP (&gt;200 ng/dL)</td>
<td>Cosyntropin stimulation test (250 mcg) should stimulate 17-OHP &gt;1,000 ng/dL Genetic testing</td>
</tr>
<tr>
<td>Androgen-secreting tumor</td>
<td>Rapid and severe virilization</td>
<td>Serum testosterone, androstenedione, and DHEA-S levels (markedly elevated for age)</td>
<td>Ovarian ultrasound Abdomen/pelvis MRI</td>
</tr>
<tr>
<td>Cushing syndrome</td>
<td>Purple striae, plethora, buffalo hump, hypertension, truncal obesity, myopathy, easy bruising</td>
<td>Late-night salivary cortisol (elevated) Overnight dexamethasone suppression test (no suppression) 24-hour urine-free cortisol level (elevated)</td>
<td>Dexamethasone-CRH test Imaging as needed</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Amenorrhea as opposed to oligomenorrhea, breast tenderness/fullness, uterine cramps</td>
<td>Serum or urine HCG (elevated)</td>
<td>Refer to obstetrics/gynecology</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>Goiter, temperature intolerance, abnormal bowel movements, weight changes, skin/hair changes, fatigue</td>
<td>TSH level (elevated with hypothyroidism/suppressed with hyperthyroidism)</td>
<td>Thyroid hormone level along with thyroid antibodies</td>
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<tr>
<td>Hyperprolactinemia</td>
<td>Galactorrhea</td>
<td>Prolactin level (elevated)</td>
<td>Pituitary MRI to evaluate for adenomas</td>
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Abbreviations: 17-OHP, 17-hydroxyprogesterone; CRH, corticotropin-releasing hormone; DHEA-S, dehydroepiandrosterone sulfate; HCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.
Biochemical Evaluation

- 17-hydroxyprogesterone
- Total testosterone, free testosterone, SHBG
- Androstenedione and DHEAS
- LH, FSH
- TSH, free T4
- Prolactin

- CMP
- Insulin

- Late night salivary cortisol or 24-hour urine for free cortisol (and creatinine)
- Serum or urine HCG
- Insulin or OGTT
Benefits of Diagnosis

• Leads to awareness of this lifelong condition
• Provides an opportunity for meaningful intervention
  – Lifestyle
  – Monitoring for comorbidities
    • Diabetes
    • Hypertension
    • Dyslipidemia
    • Depression and anxiety
    • Sleep apnea
  – Medication
Treatment

• No pharmacological treatment has been approved thus far by the FDA for adolescents with PCOS
Treatment

• Lifestyle Intervention
• Cosmetic Therapy
  – Cosmetic hair removal: Bleaching, Chemical epilation, Plucking, Waxing, Shaving, Electrolysis, Laser hair removal
• Additive Pharmaceuticals
  – Metformin
  – Oral contraceptive pills
  – Anti-androgens
“It takes the village....”

- Pediatric Endocrinologist
- Reproductive Endocrinologist
- Pediatrician
- Adult Endocrinologist
- Internist
- Adolescent medicine
- Registered Dietician
- Ob/Gyn
- Dermatologist
- Psychologist/Behavioral Science

Multi-disciplinary Team

Family

Adolescent
Conclusion

• Recent guidelines provide some clarification in diagnosis of PCOS in adolescents
• Treatment must be individualized to meet the specific goals of the patient
• Regular reassessment of goals and treatment progress are needed to guide therapy