

# Teach the Teacher

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## Polycystic Ovary Syndrome in Adolescents

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### I. Background

1. **Definition:** Polycystic Ovary Syndrome (PCOS) is the leading cause of anovulation, hirsutism, and infertility in women of all ages. It is associated with ovulatory dysfunction beginning in the perimenarchal period, hyperandrogenism, hyperinsulinemia, and insulin resistance. For adult women the prevalence of PCOS ranges from 3% to 23%.

#### 2. Diagnostic Criteria

A. In 1935, Stein and Leventhal first described PCOS in adult women as a syndrome consisting of amenorrhea, hirsutism, and polycystic ovaries.

B. NIH criteria: In 1990, the National Institutes of Health (NIH) Conference defined PCOS as a syndrome with:

- chronic oligomenorrhea/anovulation
- clinical and/or biochemical signs of hyperandrogenism
- *and* exclusion of other etiologies: congenital adrenal hyperplasia, androgen-secreting tumors, Cushing's syndrome

C. Rotterdam criteria: In 2003, the European Society for Human Reproduction and Embryology (ESHRE) and the American Society of Reproductive Medicine (ASRM) consensus workshop redefined PCOS as a syndrome with two of three prerequisites:

- Oligo/anovulation *and/or*
- Clinical and/or biochemical signs of hyperandrogenism

- Polycystic ovaries by ultrasound
- *and* exclusion of other etiologies

The Rotterdam consensus acknowledges the fact that PCOS is a functional disorder: polycystic ovaries need not be present to make a diagnosis, and conversely, their presence alone does not establish the diagnosis.

3. **PCOS in Adolescents:** There are no established diagnostic criteria for the diagnosis of PCOS in adolescents. Both the NIH and the Rotterdam criteria are used in practice, with the following caveats:

- A. It is difficult to differentiate physiologic anovulation from that of PCOS in the early perimenarchal period because anovulation frequently occurs in the first two years after menarche.
- B. Multifollicular ovaries can be a normal finding in adolescence and hence make it difficult to distinguish from polycystic ovaries.
- C. Because the transvaginal ultrasound approach is not appropriate for use in virginal adolescents, it is more difficult to image ovaries in this age group, particularly in obese girls, than in adult women.
- D. It is difficult to define androgen excess in adolescents by the measurement of circulating androgen levels because there is little normative data for the adolescent population.

### II. Etiology

No single factor accounts for the spectrum of abnormalities noted in PCOS. Several lines of evidence suggest the role of heredity in PCOS. It is thought to be a complex multigenic disorder.

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1. **Neuroendocrine Pathology:** Primary hypothalamic defect
  - A. Pituitary hypersensitivity to gonadotropin-releasing hormone (GnRH).
  - B. Disordered diurnal secretory patterns of luteinizing hormone (LH) with exaggerated pulsatile release of LH and increased pulse frequency and amplitude.
  - C. Normal to low levels of follicle stimulation hormone (FSH).
2. **Ovarian Pathology**
  - A. Increased ovarian production of androstenedione and 17-OH progesterone
  - B. Diffuse ovarian hyperresponsiveness vs. specific enzyme defect resulting in hyperandrogenism
3. **Adrenal Gland Pathology**
  - A. Generalized adrenal hyperresponsiveness vs. single adrenal enzyme defect.
  - B. Insulin increases adrenal responsiveness to adrenocorticotrophic hormone (ACTH).
4. **Insulin Resistance**
  - A. Insulin and the insulin-like growth factor (IGF) system play a direct and indirect role in the hyperandrogenism noted in PCOS
  - B. Insulin potentiates the action of GnRH on LH and increases the efficacy of the LH produced
  - C. Insulin inhibits hepatic synthesis of sex hormone binding globulin (SHBG) that binds testosterone and thus increases the proportion of free, unbound testosterone in the circulation
5. **Role of Obesity**
  - A. Increased adiposity is associated with decreased hepatic sex hormone binding globulin synthesis and increased androgen bioavailability
  - B. Adipose cell aromatase converts androgens to estrogens, and chronically high levels of estrogen promote adipocyte replication

### III. Evaluation

- Presenting signs and symptoms of PCOS are variable.
  - PCOS should be considered in any adolescent girl with hirsutism, or precocious puberty, persistent acne, menstrual irregularity, acanthosis nigricans, or obesity.
- It is important to remember that some adolescents with PCOS may appear clinically normal with no signs of hyperandrogenism or hyperinsulinism.
1. **History**
    - A. **Menstrual irregularities:** Normal menstrual cyclicity does not always signify ovulatory cycles. In addition it may be difficult initially to distinguish between PCOS and physiologic anovulation. In general, in girls with persistent irregular cycles two years after menarche, the chance of hyperandrogenemia is high. Approximately two thirds of patients have anovulatory symptoms, which could present as:
      - Amenorrhea (either primary or secondary)
      - Oligomenorrhea (defined as irregular infrequent menses)
      - Dysfunctional uterine bleeding secondary to endometrial hyperplasia in anovulatory cycles
    - B. Patients may present to their primary physicians or dermatologists for severe, resistant **acne**.
    - C. **Hirsutism** can be a presenting symptom with increase in the number of terminal hairs on the face, chest, arms and legs, although virilization is uncommon.
    - D. A small number of patients may present with precocious puberty or premature adrenarche because of increased androgens.
    - E. **Infertility**
  2. **Physical:** Look for clinical manifestations of hyperandrogenism. Also look for signs of hyperinsulinism as these patients are at high risk of developing diabetes.
    - A. Note blood pressure and BMI.
    - B. Acne, especially if severe.
    - C. Hirsutism: defined as an increase in male pattern terminal hair. Ask patients if they use any measures to remove hair. Patient can show on a pictorial representation of the Ferriman-Gallway (FGS) scoring system how much hair they have before removal. An FGS of  $\geq 8$  is considered hirsute.
    - D. Virilization: clitoromegaly, male pattern baldness.
    - E. Thyroid exam for enlargement or nodules.
    - F. Signs of hyperinsulinism, i.e. acanthosis nigricans, in the neck, axillae, chest, back, perineal area, hands and feet.
  3. **Laboratory Investigations:** There is no consensus regarding which laboratory tests are most helpful for the assessment of PCOS. Again, the goals are to document hyperandrogenism, rule out other endocrinopathies, and to look for metabolic abnormalities commonly seen in patients with PCOS. The following tests are commonly ordered:

- A. Total and/or Free Testosterone which may be elevated
  - B. Serum sex hormone binding globulin (SHBG) may be decreased
  - C. An increased ratio of LH to FSH of  $> 2$  is found in 60% to 70% of women with PCOS and is more commonly seen in non-obese women
  - D. Lipid panel to rule out dyslipidemias
  - E. 2-hour OGTT to rule out diabetes or impaired glucose tolerance
  - F. Prolactin should be checked to rule out prolactinomas
  - G. Thyroid function tests, because both hyper and hypothyroidism are associated with menstrual irregularities
  - H. Dehydroepiandrosterone sulfate (DHEA-S) to assess adrenal androgens
  - I. Fasting 17 OH-Progesterone to assess 21-Hydroxylase function in the adrenal gland
4. **Ultrasound:** Ultrasound, especially transvaginal ultrasound, is a sensitive and specific tool for detecting polycystic ovaries (PCO).
- A. PCO in adult women is defined as the “presence of 12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume ( $> 10\text{mL}$ ).”
  - B. Limitations: Transvaginal ultrasound is not widely used in the adolescent population because many girls are virginal. Transabdominal ultrasound is limited by the inability to visualize at least one ovary in 16% of women.

#### IV. Management

##### 1. Oligomenorrhea/Anovulation

- A. **Weight Loss:** Weight reduction is an effective therapeutic modality for PCOS in overweight women, but it is not possible to predict which obese women will experience improved menstrual function with weight reduction
- B. Combination oral contraceptives have been the mainstay of management. They treat both the anovulation and the amenorrhea by suppressing LH secretion, increasing SHBG and hence decreasing the levels of free testosterone. By decreasing endogenous androgen production by the ovary OCPs also help to treat both hirsutism and acne. OCPs also decrease the risk of endometrial cancer by causing regular shedding of the endometrium via withdrawal bleeds. Yasmin, which consists of 30  $\mu\text{g}$  of ethinyl estradiol and 3 mg of drospirenone, a spironolactone-derived progestin, has the added benefits of

mild antiandrogenic and antiminerocorticoid properties

- C. Use of depot medroxyprogesterone acetate and oral progestins decrease circulating androgens, by suppressing the pituitary gonadotropins. Medroxyprogesterone decreases SHBG. However, both methods have higher incidence of breakthrough bleeding and may have independent androgenic effects, thus worsening acne and hirsutism
- ##### 2. Metabolic Abnormalities
- A. Insulin sensitizing agents such as Metformin and thiazolidinediones decrease circulating insulin levels, which in turn decreases circulating androgen levels, improves ovulation and improves glucose tolerance. None of the drugs are FDA approved for treatment of PCOS but the off-label use is quite common in the adolescent population. Metformin can prevent the development of diabetes in high-risk population, especially those with impaired glucose tolerance. The effects of these drugs on preventing endometrial hyperplasia are unknown. Attention should be given to pregnancy prevention in adolescents treated with Metformin as these teens are not accustomed to ovulating regularly and may not understand their increased pregnancy risk.
  - B. Oral Contraceptive Pills (OCP) have shown to elevate HDL levels and TG levels at 12 months of use. However, there is no evidence that women with PCOS have more cardiovascular events than the general population when they use OCPs.
  - C. Weight loss helps in decreasing the metabolic complications associated with PCOS. Losing 5–10% of body weight in overweight individuals can make a significant improvement in menstrual regularity and decrease the risk of developing diabetes later in life.
- ##### 3. Hirsutism
- A. Antiandrogens (spironolactone, flutamide) antagonize the binding of androgens to the receptor. All have shown similar efficacy in improving hirsutism. All antiandrogens are teratogenic; hence they should be used in combination with OCPs.
  - B. Spironolactone also decreases ovarian and adrenal steroidogenesis, and competes for androgen receptors in hair follicles, and directly inhibits 5- $\alpha$ -reductase activity. Usually given as 25–100 mg BID. May take up to 6 months to see the full clinical effect. Should be used cautiously in women with renal impairment because of risk of hyperkalemia.

- C. Eflornithine is an inhibitor of ornithine decarboxylase and is used topically for hirsutism. May have notable benefit after 6 months of use. Additional benefits for women with PCOS are unknown.
- D. Mechanical hair removal (shaving, plucking, waxing, depilatory creams, electrolysis, and laser vaporization) is often the front line treatment for women.
- E. OCPs, especially the anti-androgenic properties of Yasmin, do show additive benefit when combined with other modalities.

## V. Counseling

1. **Follow-up:** Regular follow-ups with physician, to monitor menses and lessen the chance of developing diabetes and other problems.
2. **Screening:** Annual screening for diabetes, because the chances of developing diabetes is higher in girls with PCOS. This risk increases if patient is overweight or has a family history of diabetes. Patients also need to be screened for hyperlipidemias.
3. **Weight loss:** results in significant improvement in menstrual irregularity and decreases risk of developing diabetes later in life.
4. **Fertility:** Girls with PCOS have a normal uterus and healthy ova. Some girls with PCOS have trouble getting pregnant. Good nutrition, weight control, and reducing insulin and glucose levels may induce normal ovulation.
5. While there is no cure for PCOS, it can be treated.

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## Suggested reading

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