Polycystic Ovary Syndrome (PCOS) in Adolescents

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Disclosures

- I have nothing to disclose.

Learning Objectives

1. Discuss the epidemiology, pathophysiology and clinical manifestations of PCOS in adolescents.

2. Describe adolescent specific practice guidelines for the diagnosis and management of polycystic ovary syndrome (PCOS).

3. Explain the evidence supporting adolescent specific practice guidelines for the diagnosis and management of polycystic ovary syndrome (PCOS).

4. Select the appropriate diagnostic testing for adolescents who present with signs/symptoms of PCOS.

5. Outline an appropriate treatment plan for the management of PCOS in an adolescent patient.

PCOS: definition and history

- Polycystic Ovary Syndrome (PCOS) is a complex hormonal condition characterized by ovulatory dysfunction and hyperandrogenism

- 1935, Stein & Leventhal Syndrome, group of 7 women with common features of menstruation disturbances, hirsutism, and enlarge ovaries with many small follicles

- 1958, investigators describe imbalance in hormone levels (increased levels of luteinizing hormone (LH) and testosterone levels)

Background/Significance

- The most common endocrine disorder in females of reproductive age
- Long term complications of metabolic, reproductive and psychologic health
- Adverse physical characteristics associated with PCOS: hirsutism, acne, excess body weight
- Significant negative impact on QOL and association with depression and anxiety
- Patients report frustration with their experience in diagnosis and management of PCOS
- Commonly presents in adolescents, but often undiagnosed until adulthood
- Early diagnosis important to mitigate long term complications and to promote health seeking behavior at early age

Background/Significance

- Misunderstanding of diagnostic criteria
  - Three different sets of diagnostic criteria; limited application to adolescent population: 1990 NIH criteria, 2003 Rotterdam Criteria, 2006 Androgen Excess Society Criteria
  - Characteristics of normal puberty often overlap with signs and symptoms of PCOS
- Research demonstrates significant knowledge gaps among specialty providers (gynecology and reproductive endocrinology)
- Limited dissemination of updated international guidelines
  - 2015 international consensus statement on diagnostic criteria specific to adolescents; updated in 2017
  - 2018 International Evidence-Based guidelines for the assessment and management of PCOS throughout the life span

A full copy of the 2018 international guidelines can be downloaded from:
https://www.monash.edu/__data/assets/pdf_file/0004/1412644/PCOS_Evidence-Based-Guidelines_20181009.pdf

PCOS: Epidemiology

- Common endocrine disorder in females of reproductive age
  - Estimate to account for 71% of women presenting with hirsutism
- Prevalence : 8-13% in adult women, and 6% in adolescent females
- Prevalence: 20-40% prevalence in families with PCOS (inherited autosomal dominant trait with variable penetrance)
- Limited epidemiological data

PCOS: pathophysiology

- Several pathophysiologic components that may be involved*
  - Ovarian dysfunction
  - Insulin resistance
  - Alteration in signaling from neuroendocrine hormones
  - Genetics
  - Epigenetics
  - Alterations in sympathetic nerve activity

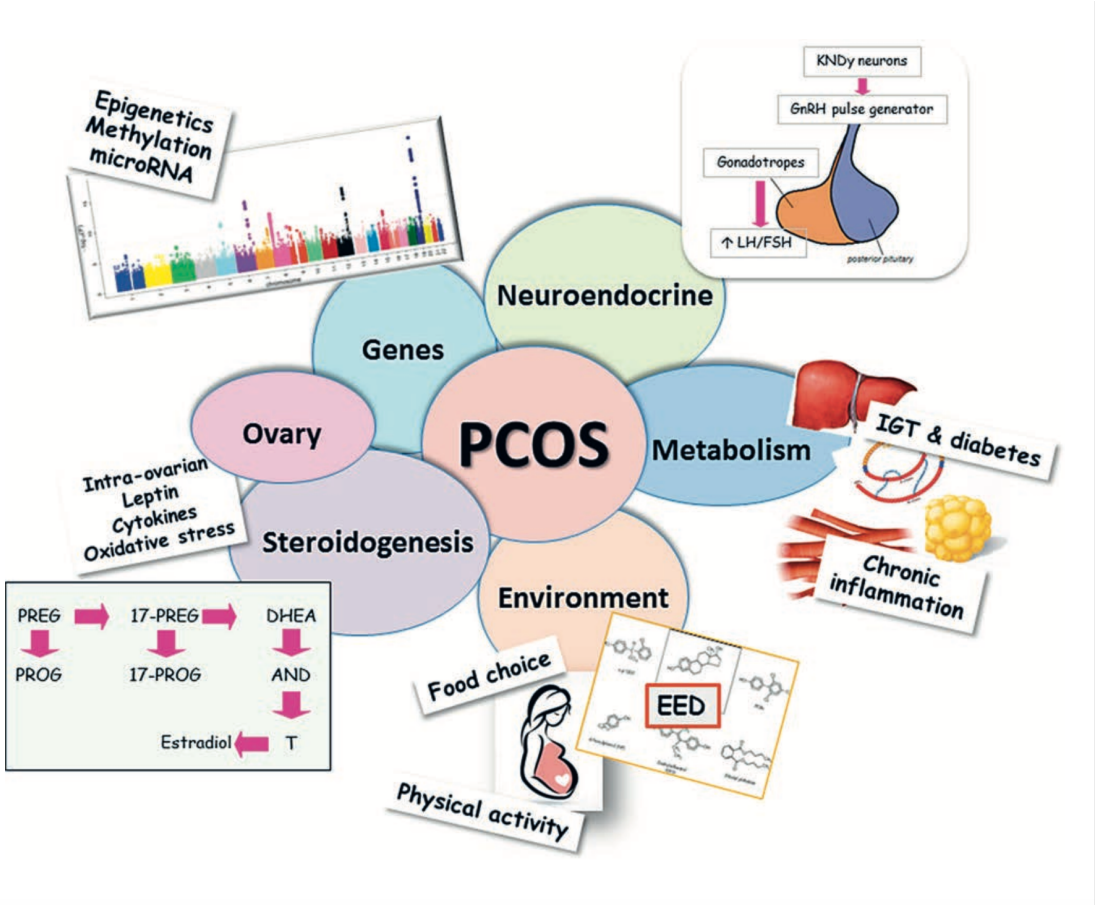


Figure from: Ibanez, et al., 2017

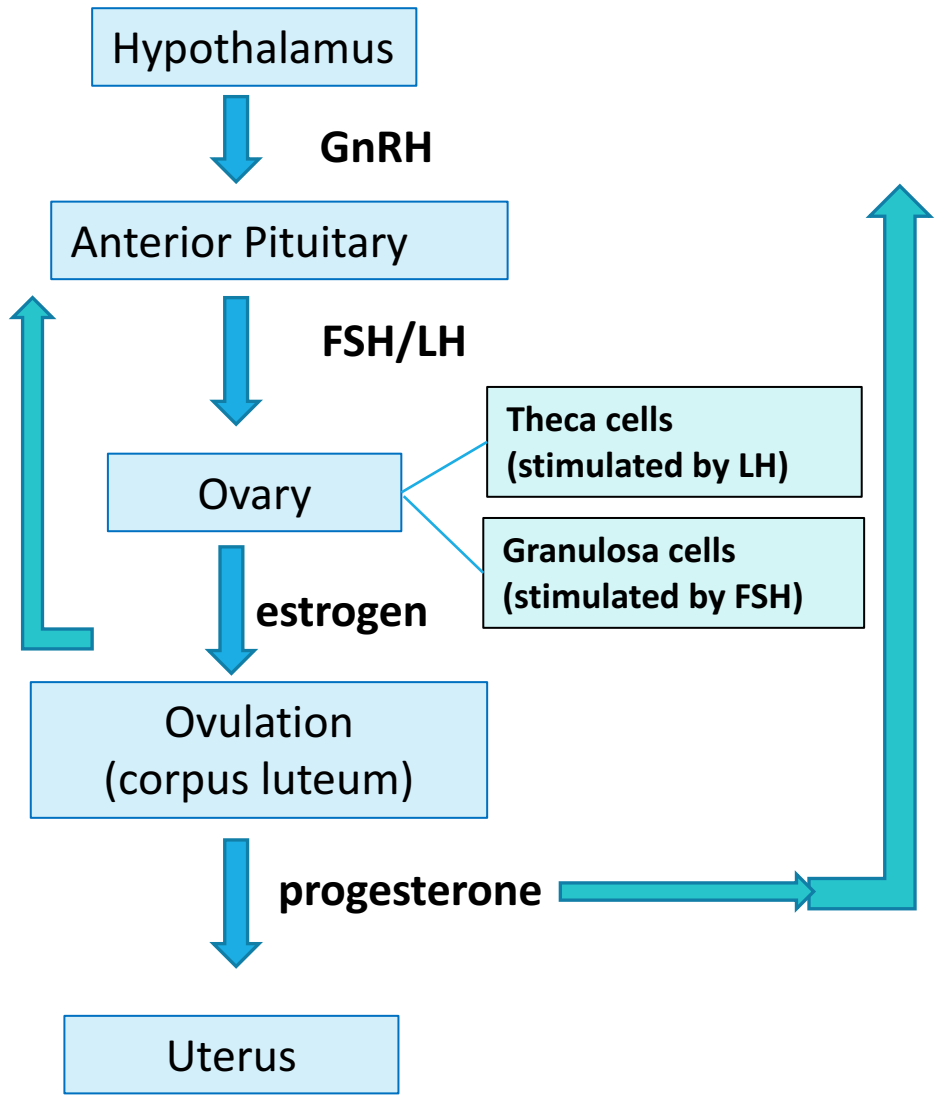
***Not all factors play a role in each individual.**

PCOS: pathophysiology

- Imbalance of FSH and LH (LH:FSH 2:1 in 60% of patients)
- High LH causes over-activation of theca cells, producing **excessive androgens**
- Low FSH levels do not adequately stimulate granulosa cells, resulting inadequate estradiol production from ovary (ovarian dysfunction)
- Results in continuous feedback to HPO-Pituitary axis so that LH levels remain high relative to FSH and follicle are not properly stimulated due to low FSH level

Hypothalamus-Pituitary-Ovarian Axis

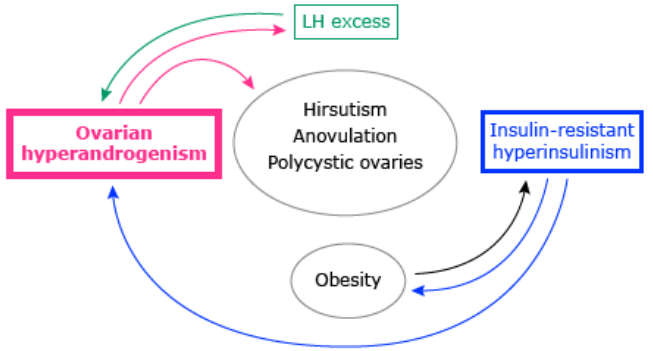
Normal function: balance of FSH and LH regulate hormone production in ovaries to develop follicles, leads to ovulation. Estrogen and progesterone levels have +/- feedback to hypothalamus and pituitary to regulate cycle.



PCOS: pathophysiology

- **Insulin resistance (IR)** and **hyperinsulinemia** are common findings in PCOS
- IR does not seem to be dependent upon increases in adipose tissue as it is also found in lean women with PCOS
- IR drives the pancreas to produce more insulin
- Increased insulin contributes to hyperandrogenism through multiple mechanisms
  - high insulin levels may play a role in increasing production of adrenal androgens
  - high levels of insulin have been found to decrease production of sex-hormone binding globulin (SHBG) in the liver, thus decreasing the circulation of SHBG to bind free testosterone

Minimal model for the pathogenesis of polycystic ovary syndrome (PCOS)



A minimal model for the pathogenesis of PCOS. Ovarian hyperandrogenism is nearly universal and causes the cardinal clinical features of the syndrome. About half of patients have insulin-resistant hyperinsulinism, which aggravates ovarian hyperandrogenism and contributes to adiposity. Androgen excess may also cause LH excess, which aggravates ovarian hyperandrogenism in the presence of hyperinsulinism. Obesity increases insulin resistance, and the resultant increased hyperinsulinism further aggravates hyperandrogenism.

The cause of the ovarian hyperandrogenism and insulin resistance is usually intrinsic, and may have common genetic or environmental determinants. This model does not exclude the possibility that the unknown intrinsic ovarian defects that underpin the ovarian steroidogenic dysfunction also involve granulosa cell folliculogenesis as well, and it does not depict other associated defects, such as the adrenal hyperandrogenism that parallels the ovarian hyperandrogenism.

Excess adipose tissue can produce excess androgen as well as estrogen. However, in the absence of an intrinsic ovarian defect, the hyperandrogenemia of simple obesity is mild and polycystic ovaries unusual. In contrast to PCOS, the anovulation of simple obesity is the consequence of suppression, rather than augmentation, of LH pulsatility.

PCOS: polycystic ovary syndrome; LH: luteinizing hormone.

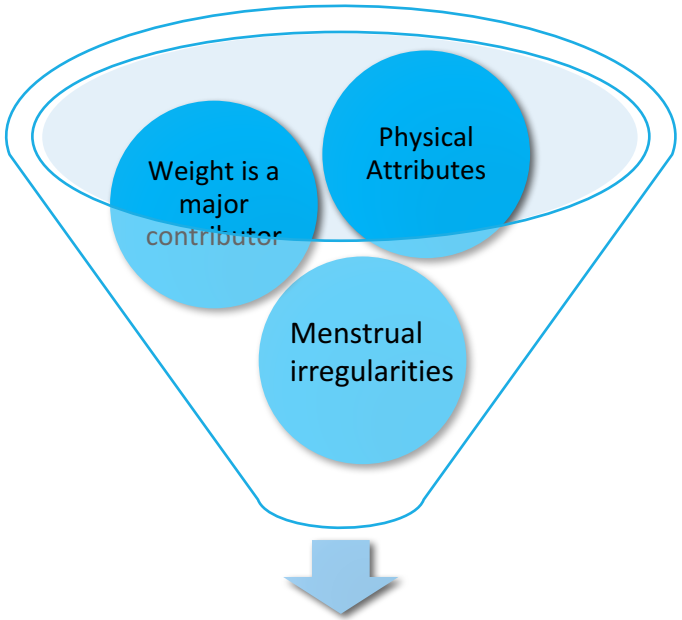
Courtesy of Dr. Robert Rosenfield.

PCOS: clinical manifestations

- **Irregular menses**- oligomenorrhea, secondary amenorrhea, or dysfunctional uterine bleeding

- Excess androgenic hormones
  - **Hirsutism** – excessive, coarse male pattern hair growth
  - **Acne**- moderate to severe inflammatory acne unresponsive to topical treatment

PCOS: clinical presentation in adolescents



- Complaints of irregular menses and/or infertility is the most common clinical presentation of adults with PCOS
- Complaints of acne and/or hirsutism is the most common clinical presentation in adolescents
  - Irregular menses can be a normal finding in adolescents
  - Approx. 2/3 of patient with PCOS have excess body weight or obesity
    - Common finding, but not a hallmark feature of PCOS
  - All physical attributes of PCOS can impact quality of life

Diagnostic Criteria for PCOS in Adolescents

Criteria for PCOS in Adolescent according to 2015 international consensus statement

Otherwise unexplained (**must exclude other causes**) combination of:

1. Abnormal bleeding pattern **(persist 2 years after menarche)** (level B)
2. Evidence of hyperandrogenism
   a. Persistent testosterone elevation (Level A)

   b. Moderate-severe hirsutism is evidence of hyperandrogenism (level B)

   c. Moderate-severe acne is indication **to test** for hyperandrogenism

PCOS: evaluation in adolescents

- **Ovulatory dysfunction**
  - Primary amenorrhea: No menses by age 15 years or > 3 years post thelarche
  - Irregular menstrual cycles defined as:
    - Normal in first year post menarche
    - From 1-3 years post menarche: <21 or > 45 days
    - **From 3 years post menarche: < 21 days or > 35 days or < 8 cycles per year**
    - Any menstrual cycle > 90 days for any one cycle > 1 year post menarche

PCOS: evaluation in adolescents

- **Hyperandrogenism**
  - **Clinical**
    - Hirsutism (modified Ferriman-Gallwey (mFG) score > 4-6 according to ethnicity as a guide to suspect significant hirsutism; mFG score cut offs based on adult not adolescent females)
    - Acne- moderate to severe and unresponsive to evidence-based treatments; no validated assessment to score acne severity
    - Alopecia (Ludwig visual scoring system)
  - **Biochemical**
    - Use high-quality assays for total or free testosterone (liquid chromatography-mass spectroscopy or extraction/chromatography immunoassays)
    - Androstenedione and dehydroepiandrosterone sulfate (DHEA-S) can be considered if testosterone levels within normal range, otherwise mostly beneficial to rule out other causes of hyperandrogenism
    - Cannot accurately assess when patient is using hormonal contraception
    - Interpret based on normal ranges of the testing laboratory

Diagnostic Criteria for PCOS in Adolescents

- **Ultrasound evidence of polycystic ovary morphology is not indicated (level A)**
  - Ovarian volume increased in puberty
  - Follicle size changes with age and greatest # of small follicles is during adolescence
  - Transvaginal routes invasive; transabdominal route not reliable
  - Presence of polycystic ovarian morphology in an adolescent who does not have hyperandrogenism/irregular menses does not indicate a diagnosis of PCOS (level A)

Diagnostic Criteria for PCOS in Adolescents

Insulin resistance in Context of PCOS

- Insulin resistance and compensatory hyperinsulinemia have been documented in women with PCOS since the 1980s.
- Insulin resistance is not only associated with obesity, but is documented in lean women with PCOS
- Prevalence of glucose intolerance in obesity PCOS adolescents is 40%; compared with obese adolescents without PCOS at 15-20%
- **NOT considered to be diagnostic criteria (level A)**

PCOS: evaluation in adolescents

- **PCOS is a diagnosis of exclusion**- other conditions to rule out:
  - Pregnancy
  - Hypothyroidism
  - Non-classic congenital adrenal hyperplasia- 21 hydroxylase deficiency
  - Hyperprolactinemia
  - Cushing's disease- glucocorticoid excess
  - Androgen-secreting ovarian or adrenal tumor

PCOS: evaluation in adolescents

- History
  - Menstrual history
  - Sexual history
  - Family medical history
  - Past medical history
- Physical Exam
  - Hirsutism (Ferriman–Gallwey scoring system for hirsutism)
  - Acne
  - Alopecia
  - Tanner staging (to rule out other conditions)

PCOS: evaluation

Laboratory Test	Indication
Beta-HCG quantitative	Rule out pregnancy
TSH	Rule out thyroid dysfunction.
Prolactin	Rule out hyperprolactinemia in patient with amenorrhea
17-OH progesterone	Part of testing to rule out non-classic congenital adrenal hyperplasia
Dehydroepiandrosterone sulfate (DHEAS)	Part of testing to rule out non-classic congenital adrenal hyperplasia, may helps to document hyperandrogenism in PCOS when other disorders have been ruled out.
Total testosterone	To document hyperandrogenism, elevated in PCOS.
FSH, LH, estradiol	Reserve for patients with amenorrhea to rule out premature ovarian failure and hypoestrogenism due to hypothalamus pituitary insufficiency

Diagnostic Criteria for PCOS in Adolescents

Biomarkers for PCOS

- Antimullerian hormone (AMH) – glycoprotein secreted by granulosa cells of small, growing follicles
  - Elevated in adults with PCOS, not reliable in adolescents (level C)

PCOS: long-term complications

- Insulin resistance/impaired glucose tolerance (30-35% of young girls with PCOS; 50-70% of all cases of PCOS)
- Excess weight or obesity (50-80% of young girls with PCOS)
- Increase lifelong risk of:
  - metabolic syndrome
  - Type 2 DM
  - Hypertension
  - Hyperlipidemia
  - CV disease
  - Fatty liver disease (5X higher than women without PCOS)
- Increase lifelong risk of:
  - Endometrial hyperplasia
  - Endometrial cancer (2-3X higher than women without PCOS)
  - Mood disorders – negative impact on quality of life
    - Depression
    - Anxiety
- Infertility – most common cause of female infertility in the U.S.

PCOS: management in adolescents

- Lifestyle modifications is mainstay of management
- Combined hormonal oral contraception have greatest benefit to help with both menstrual irregularity and hyperandrogenism
- Spironolactone has anti-androgenic activity
- Metformin benefits insulin resistance/glucose intolerance
  - Unclear evidence to support benefit of metformin in absence of insulin resistance

***Begin with the patient's main concern in mind!**

PCOS: management in adolescents

- Early diagnosis important to mitigate long term complications and to promote health seeking behavior at early age

- Complex condition requiring a multidisciplinary approach and management throughout the lifespan

PCOS: Management

Clinical manifestation of PCOS	Recommended treatment	Impact/outcome of treatment
All patients	Life style modifications: combine weight loss and physical exercise (first line intervention) ± Metformin	Decrease androgen levels Normalize menstrual cycles Improve markers of cardio metabolic health
Patients with insulin resistance/ hyperinsulinemia	Metformin	Decrease androgen level Normalizes menstrual cycles
Localized hirsutism	Photoepilation	Removal of unwanted hair growth
Features of hyperandrogenism	Anti-androgen agents	Reduce excess androgen features
Menstrual irregularities	Combined hormonal oral contraceptive pills	Normalizes menstrual cycles Suppress ovarian androgen production Increase hepatic production of SHBG

PCOS: Management

Consideration with contraception therapy

- Combined hormonal oral contraception have greatest benefit to help with both menstrual irregularity and hyperandrogenism
- Norgestimate, desogestrel, and drospirenone have strongest anti-androgenic properties, although desogestrel and drospirenone may have increased risk for VTE
  - **Note: risk of VTE in overall population is 1 in 10,000; risk for all OCP 4-6 in 10,000; risk in normal pregnancy 8-10 in 10,000**
- Obese adolescents may require higher estrogen content, 35 mcg
- Progestin only pills offer endometrial protection, but do not effect androgen levels or SHBG
- Limited data in use of IUDs and implants in adolescent with PCOS, but will offer endometrial protection

PCOS: Management

Should metformin be reserve only for those patients with demonstrated glucose intolerance?

- Systematic review and meta-analysis of RCT to evaluate metformin vs OCP for treatment of PCOS in patients age 11-19 years of age
- 4 RCT met inclusion/exclusion criteria
- 170 patients total
- Measures: changes in menstrual irregularities, Hirsutism, Acne, BMI, Testosterone level, Lipids
  - OCP – modest reduction in acne; improved menstrual irregularities
  - Metformin- significant BMI reduction; improved measures of dysglycemia; lower LDL
  - OCP and metformin have similar impact on hirsutism, triglycerides and HDL
- Overall conclusion that trials were very low to low quality evidence (small study size)

PCOS: management in adolescents

- Life-long screening for co-morbid conditions
  - Insulin resistance
  - Obesity
  - T2DM
  - CV disease
  - Fatty liver disease
  - Mental health conditions (depression and anxiety screening)
- Address risk for endometrial hyperplasia if anovulatory bleeding pattern persists
- Address family planning!

PCOS in adolescents: key points

- Adverse physical characteristics associated with PCOS: hirsutism, acne, excess body weight
- Several long term complications: infertility, type 2 DM, sleep disorders, cardiovascular disease, endometrial cancer, depression and anxiety
- Commonly presents in adolescents, but often undiagnosed until adulthood
- Early diagnosis important to mitigate long term complications and to promote health seeking behavior at early age
- International consensus statement provides adolescent-specific guidance for the diagnosis and management of PCOS

Review

REVIEW

PCOS is associated with increased risk for which of the following?

A. Infertility

B. Endometrial cancer

C. Diabetes

D. A and C

E. All of the above

REVIEW

Which of the following is necessary to diagnosis an adolescent with PCOS according to the 2015 international consensus statement and 2018 International Guidelines for the assessment and management of PCOS throughout the lifespan?

A. Menstrual irregularities persistent 2 years after menarche

B. Ultrasound evidence of polycystic ovaries

C. Decreased levels of total or free testosterone

D. Obesity

E. Elevated levels of luteinizing hormone (LH)

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Thank you!

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