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*PCOS in the Adolescent and Young  
Adult: Diagnosis, Treatment &  
Implications*

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Speaker Disclosures

- No conflicts of interest
- Discussion will include off-label uses for several medications in the adolescent population

## Outline & Objectives

- Define the phenotype of PCOS in teens
- Identify core laboratory features of PCOS
- Recognize genetic and environmental causes of PCOS
- Know the co-morbidities of PCOS
- Understand the rationale for medical treatment
- Be able to plan transition from adolescent to adult care

## Controversies in defining PCOS

### Problems using adult PCOS criteria for teens

- Adolescents have functional ovarian cysts as normal sonographic findings
  - Maximum ovarian volume occurs in adolescence
  - Transabdominal sonography inaccurate
- Anovulatory and/or irregular periods occur in ~40% of girls until about 2-3 years following menarche
- Clinical evidence of androgen excess (esp acne) is common during puberty and resolves over time
- High prevalence of obesity confounds diagnosis
  - BMI>24 is associated with oligomenorrhea

### Suggested adolescent criteria for PCOS

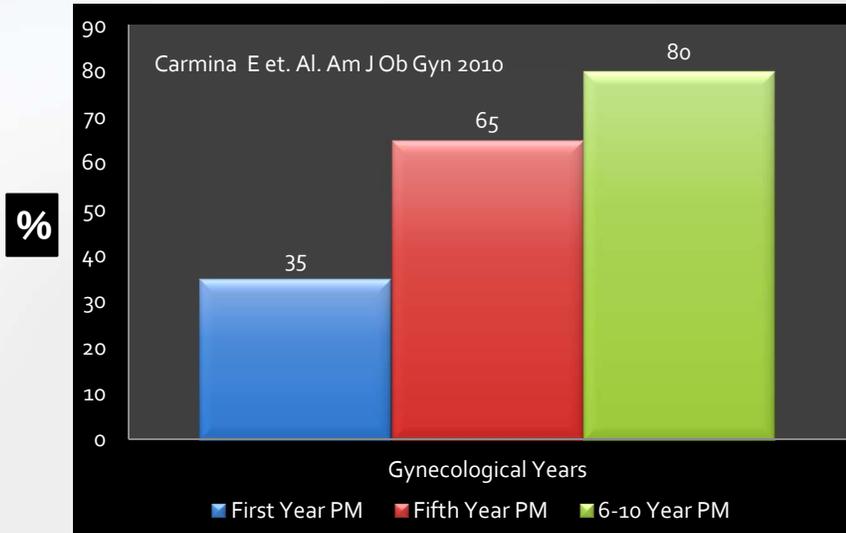
- Persistence of ovulatory dysfunction 2-3 years after menarche.
- Rapid progression & exacerbation of hyperandrogenism at menarche.

## Controversies in defining PCOS in adults

1990 NIH Criteria	2003 Rotterdam Criteria	2006 Androgen Excess Society
3 out of 3	2 out of 3	
<ol style="list-style-type: none"> <li>1. Oligo-ovulation</li> <li>2. Clinical and/or biochemical hyperandrogenism</li> <li>3. <i>Exclusion of related disorders</i></li> </ol>	<ol style="list-style-type: none"> <li>1. Oligo-ovulation or anovulation</li> <li>2. Clinical and/or biochemical hyperandrogenism</li> <li>3. <i>Polycystic ovaries</i></li> </ol>	<ol style="list-style-type: none"> <li>1. Hyperandrogenism - Hirsutism and/or hyperandrogenism</li> <li>2. Ovarian Dysfunction- Oligo-anovulation and/or polycystic ovaries</li> </ol>

## Menstrual cycles in adolescents

Ovulatory cycles achieved in 65% of girls by the 5<sup>th</sup> post-menarchal (PM) year



Menstrual cycle length at 15y predicts oligomenorrhea at 18y in Dutch teens

Length of cycles at 15y (days) <i>OCP users excluded</i>	Number of subjects	Odds ratio of oligomenorrhea at 18y
22-34	38	2.1
35-41	13	21
<b>&gt;42</b>	<b>28</b>	<b>31</b> <b>(51% remain oligomenorrheic)</b>

Van Hoof MH et al. Hum Repro 2004

## The history and physical examination

### HPI

- Menarche
  - Menstrual frequency, duration
- Excess facial or body hair
  - Onset
  - Static or worsening
  - Type of hair removal
  - Frequency of hair removal
- Acne
  - Severity
  - Treatments
- Hair loss
  - Location & severity
- Voice changes

## Clinical features of androgen excess in PCOS

- Hirsutism 75%
  - Ferriman Gallwey score >9
- Oligomenorrhea ~70-80%
  - <8 menses/year; >2y post-menarche
- Acne 10-34%
  - 90% gen pop of teens have acne, but only 15% seek dermatology consultation
- Androgenic alopecia ?%
- Rare: Voice changes, clitoral enlargement, hyperlipidemia, polycythemia

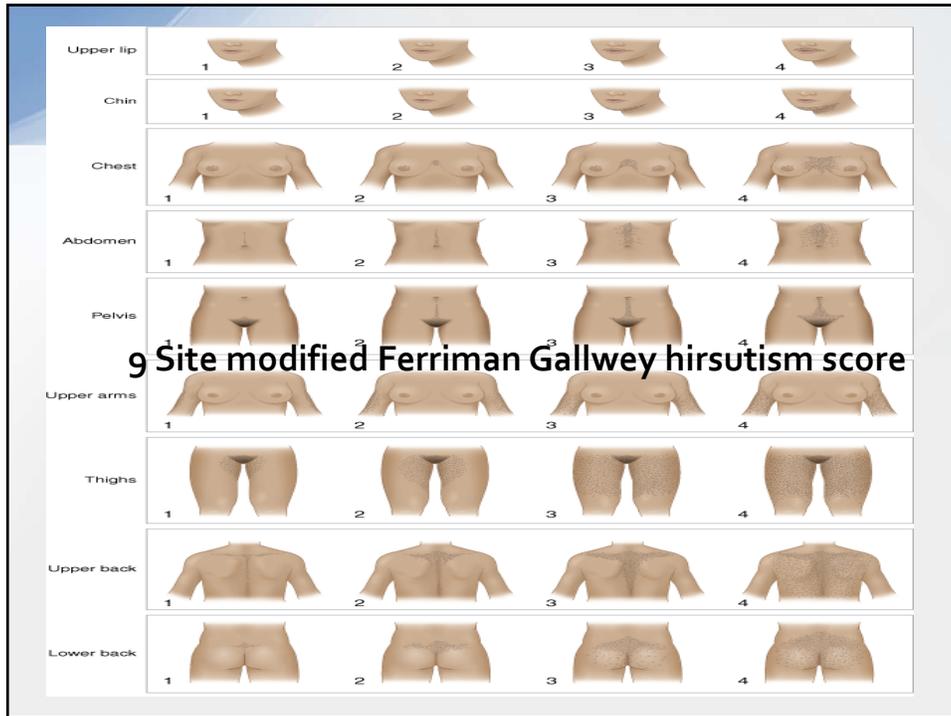
## Physical findings in PCOS



Grade 4 facial hirsutism



Severe pustular/cystic acne vulgaris with comedones on lower 3<sup>rd</sup> of face



## Hormonal tests & imaging

## Suggested lab tests in teens suspected of PCOS

- TSH
- Prolactin
- Total testosterone (LC/MS/MS;  $>2$  SD above ref range)
- SHBG
- DHEA-S
- 17-OH progesterone (LC/MS/MS,  $< 0800$ )
- FSH, LH
- Estradiol (in amenorrheic adolescents)
- If PCOS seems likely, consider:
  - Fasting and 2-hour GTT
  - Lipid panel
  - Fasting insulin

## Pelvic ultrasound is not a sine qua for PCOS



~75% of PCOS women: 12 follicles of 2-9 mm or increased volume of 10 mL.

~40% of oligomenorrheic teens have multiple cysts within 2y PM



Codner E et al. Fertil Steril 2011

## Genetic and epigenetic risks for PCOS

### Pathogenesis of PCOS is multi-factorial: Genetic-environmental interactions

- Common feature: Excess androgen secretion by ovarian theca cells.
- Animal models: PCOS phenotype simulated by:
  - Over-expressing LH
  - Exposure to BPA, an endocrine disrupting chemical (EDC)
  - Altered DNA methylation
    - Related to prenatal androgen/EDC exposure
- Hormonal phenotype in animals & women:
  - Insulin resistance &/or obesity
  - Up-regulation of AMH & AMH-R
    - Possibly related to excess LH & androgens

## Genetic analysis of PCOS

- Over-expression of genes in theca cells:
  - LH-R
  - DENND1A (promotes exchange of GDP to GTP)
  - CYP17A1
  - P450SCC
  - IRS1/2
- Under-expression of genes in granulosa cells:
  - P450Aromatase

## PCOS and human genotype

- Candidate gene approach has not yielded any conclusive findings due to small sample sizes in women with PCOS studies.
- Polymorphisms identified in PCOS F in genes for:
  - **DENND1A**
  - THADA
  - **CYP17A1**
  - **LH-R**
  - FTO
  - **IRS1**
  - AR (CAG repeat length)
  - YAP1
  - RAB5/SUOX

Bolded genes have also been implicated in vitro studies of gene expression

Welt CK. Semin Reprod Med 2014

## PCOS families

- Daughters of PCOS women begin to show hyperinsulinism and increased ovarian volume at Tanner stage 1.
- Androgen excess and metabolic syndrome develop in PCOS daughters at Tanner stage 4.

Sir-Peterman, et al. JCEM 2009

## Epigenetic risk factors for PCOS

### Prenatal

Congenital virilization  
IUGR  
LGA

### Infancy

IUGR w/  
rapid catch-up  
growth

### Childhood

Premature adrenarche  
Atypical puberty  
Metabolic syndrome

### Adolescence

Hyperandrogenism  
Anovulation  
Polycystic ovaries  
Metabolic syndrome

Obesity

## Co-morbidities of PCOS in adolescents

### Key factors exacerbating PCOS

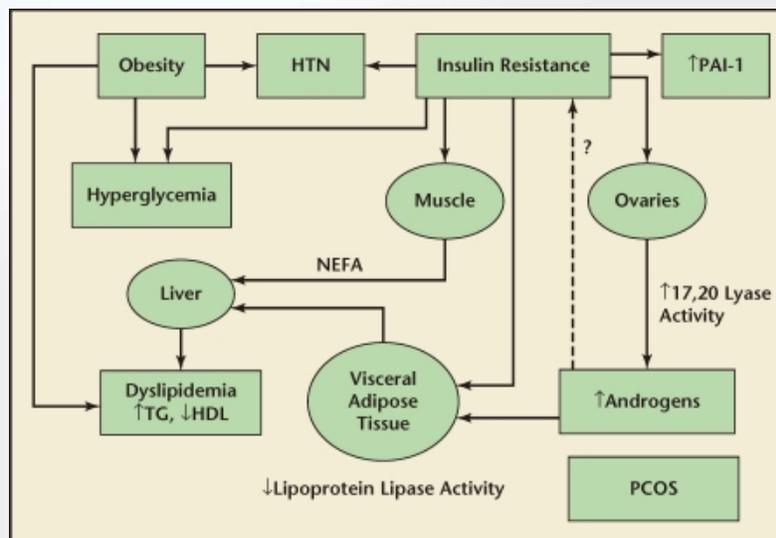
- Obesity
- Insulin resistance
- Metabolic syndrome

## Metabolic syndrome in adolescents

- Present in 5-10% of non-obese teen population\*, but **12-40% of obese teens, and ~30% of PCOS teens.**
- Diagnostic criteria for MetS\* vary:

Author	Cook 2008	De Ferranti 2004	Weiss 2004
Weight	WC $\geq 90\%$	WC $\geq 75\%$	BMI z score $\geq 2$
Glucose	FBG $\geq 100$ mg/dl	FBG $\geq 110$	2hr PP BG $\geq 140$
Lipids	TG $\geq 150$ mg/dl or HDL $< 40$	TG $\geq 100$ or HDL $< 50$	TG $> 95\%$ or HDL $< 5\%$ Sex & ethnic specific
BP	$\geq 90\%$	$\geq 90\%$	$\geq 95\%$

## Pathogenesis of metabolic syndrome in PCOS



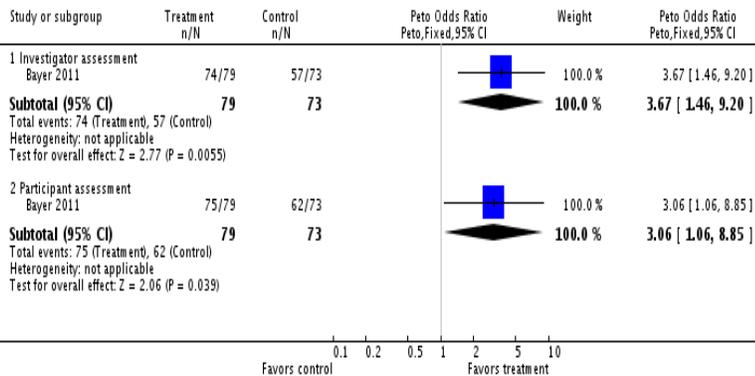
## Treatment of PCOS

### Hierarchy of medical treatments

- Combined contraceptives
  - Most effective in restoring eumenorrhea
  - Suppress androgen excess
  - Ameliorates hyperandrogenic symptoms
- Metformin
  - Supports weight loss
  - Reduces insulin resistance
  - Alleviates metabolic syndrome, inflammatory markers & related risks
- [Cyproterone acetate, CPA- EU]
  - After 1y of treatment, CPA is more effective than drospirenone in reducing hyperandrogenic symptoms (FG score; Fertil Steril 2012)

## 3<sup>rd</sup> generation OCP = effective acne treatment

Review: Combined oral contraceptive pills for treatment of acne  
 Comparison: 5 DRSP 3 mg / EE 20 µg versus placebo  
 Outcome: 3 Participants classified as 'improved' at cycle 6



Cochrane Database of Systematic Reviews 2012

## Adjunctive treatments

- Hair removal
- Weight loss: Diet + Exercise
  - Weight reduction decreases androgens
  - Improves insulin sensitivity
  - Both low carb & low fat diets equally effective
- Inositol
- Other

## Transition from adolescent to adult care

### Adolescent

- Irregular *menses*
- *Hirsutism*
- Acne
- *Weight management*
  - Dyslipidemia
  - Metabolic syndrome

### Adult

- Anovulatory *menses*
- *Hirsutism*
- Infertility
- *Weight management*
  - Dyslipidemia
  - Metabolic syndrome
  - Type 2 diabetes
  - Hypertension
- Endometrial hyperplasia

## Irregular menses predict PCOS & infertility

- Finnish study of >2000 women who completed questionnaires at age 16 and again at age 26.
- Only 10.5% of subjects with irregular menses at 16 had irregular menses at age 26.
- 68% of women in both the irregular menses group and controls conceived, NS.
- 26% vs 28% had delivered a child at age 26, NS.

	Adjusted Risk	P value
Irregular menses	1.4	0.05
PCOS	2.9	<0.001
Infertility	2.1	0.01

West S, et al. Hum Reprod 2014; 29:2339

## Educating the patient about transition

- Basis for the diagnosis of PCOS should be addressed in adolescence with patient & family
  - Often uncertain criteria in teen years
  - Overlap of obesity and PCOS symptoms/signs
- Need for ongoing evaluation emphasized
  - Importance of lifestyle, weight loss
  - Screen yearly for metabolic & cardiovascular problems
- Discuss idea of modifying therapy to suit individual needs over time
  - Input from reproductive endocrinology & OB/GYN
  - Change therapy from OCP to clomiphene (or metformin) when pregnancy is desired

## Transition planning

- Educate the adolescent as to how to manage her medical care independently
- Review the adolescent's concerns about her physical, reproductive, sexual and mental health
  - Explain that sexually active individuals should use birth control, since PCOS patients ovulate randomly and they can become pregnant.
- Provide the adolescent with a medical summary and list of medications and doses.
- Discuss referral to adult providers, preferably in the context of joint clinical encounters.

## Management of reproductive concerns

- Collaborative, inter-disciplinary care
  - Endocrinology
  - Reproductive Endocrinology
  - OB/GYN
  - Nutrition

Questions?