It's More than Reproduction: The Cardiometabolic Manifestations of Polycystic Ovary Syndrome

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Disclosures

- **Dr. Hammond:**
  - **Speakers' Bureau for AbbVie Pharmaceuticals**
- **Dr. Cataldo:**
  - **Nothing to disclose**

Objectives

At the end of this presentation, the participant will be able to:

- Define polycystic ovary syndrome (PCOS)
- Describe and assess cardiometabolic risk in PCOS
- List treatment approaches to reduce this risk

What is Polycystic Ovary Syndrome?

- A syndrome, NOT a unique disease
  - A collection of symptoms and presentations
- Not everyone agrees on the definition of PCOS
  - What criteria should be included in the definition
    - Irregular/absent menses, androgen excess, polycystic ovary morphology
    - No other specific disorder that can explain the above
  - What is not part of the definition, even though seen frequently
    - Insulin resistance, obesity, elevations of LH or AMH

Prevalence of PCOS

- Most common endocrine disorder in women ages 18-44
- Impacts 2-20% of this age group, depending on definition
  - Different in clinic-based *versus* general-population samples
- Most common cause of ovulatory dysfunction in
  - Women presenting with infertility
  - Women of reproductive age with irregular menses

Definitions of PCOS Have Evolved

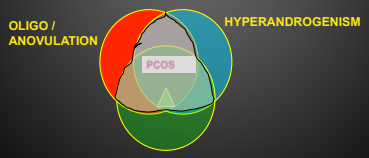
NIH/NICHD	Rotterdam	AE Society
Must meet both criteria	Must meet 2 of 3 criteria	Must meet both criteria

• Hyperandrogenism
  • Clinical +/- biochemical
• Menstrual dysfunction
	• Hyperandrogenism
	  • Clinical +/- biochemical
	• Oligo– or anovulation
	• Polycystic ovaries
	  • >12 follicles 2-9 mm
		• Hyperandrogenism
		  • Clinical +/- biochemical
		PLUS
		• Ovulatory dysfunction
		OR polycystic ovaries

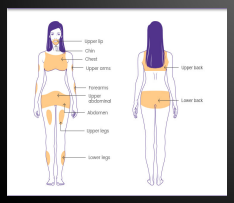
This definition for adolescents

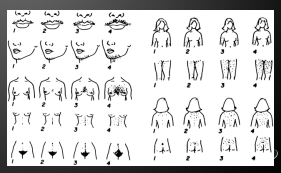
AE, Androgen Excess

Definitions of PCOS Overlap



Clinical Hyperandrogenism





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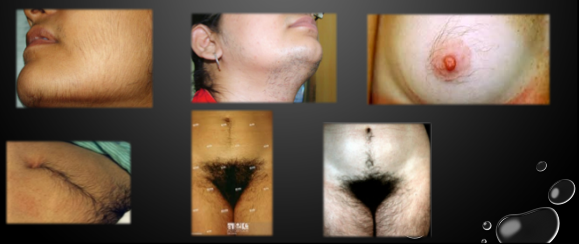

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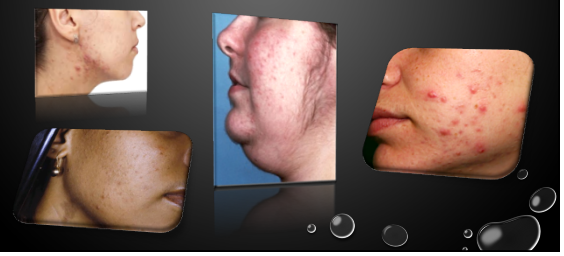

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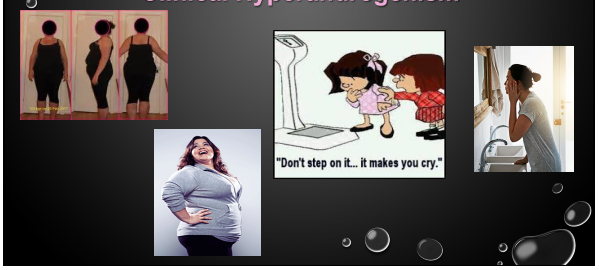


Biochemical Hyperandrogenism

- Ovarian androgens
  - Testosterone (total and free); calculated free T better than direct assays
  - Free testosterone increased by low SHBG resulting from insulin excess
- Adrenal androgens
  - DHEA sulfate is a weak androgen but a pro-hormone
  - 17-OH-progesterone is high in congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Androstenedione: mixed ovarian/adrenal sources, not useful
- In general, only measures of total and free T are useful in PCOS
  - Assays vary in technique and quality; mass-spec–based assays more available now
  - May be clinically useful when race/ethnicity limits expression of hirsutism
  - Beware of listed "normal" ranges

Menstrual/Ovulatory Dysfunction

- Small antral follicles ("cysts") are arrested in development, don't ovulate
- Reason this happens is not known with certainty
  - In normal cycle, lead follicle inhibits growth of trailing ones
    - This is what results in one or at most two follilces ovulating per cycle
  - In PCOS, useful to think of the crowd of small antral follicles as like a "logjam"
    - Too many other ones the same size for any one to break into the lead and mature to preovulatory stage
    - Treatments that induce ovulation in PCOS include stimulatory drugs and partial ovarian destruction
- Androgen excess within ovary may over-recruit resting follicles into development
- Insulin excess and elevated anti-Müllerian hormone (AMH)
  - May be causal or merely marker(s) of this abnormality

Polycystic Ovaries

- Excessive number of 2-9mm follicles by ultrasound
  - Ability to see follicles depends on route and transducer frequency
  - Old guidelines → 12/ovary, newer guidelines suggest 19 or even 26

Reproductive Issues

- Absent or inconsistent ovulation
  - Some women with PCOS do ovulate occasionally (~2-3x a year)
  - Without ovulation, endometrium grows under estrogen influence
    - Progesterone remains low, endometrium not primed to shed efficiently
    - Can promote pre-cancerous and cancerous changes
- Infrequent or no menses +/- irregular vaginal bleeding
  - In epidemiologic studies, irregular menses can be surrogate for PCOS

What is insulin resistance?

Insulin resistance is defined as

- The relative inability of insulin to achieve the uptake of glucose from the bloodstream into its major target tissues, muscle, adipose tissue, and liver.

Why is insulin resistance bad for the ovary?

- Circulating insulin usually rises to insure euglycemia
  - "Compensatory" hyperinsulinemia
  - T2DM results when pancreas no longer able to secrete enough insulin
- Not all sites of insulin action show this resistance (*e.g.,* ovary)
- Hyperinsulinemia results in pathophysiology
  - Drives excess androgen production/secretion by ovaries
  - In so doing, increases likelihood of PCOS phenotype
  - PCOS thus serves as a "marker" of insulin resistance / hyperinsulinemia

Metabolic Syndrome (Insulin resistance syndrome, Syndrome X)

- Three of 5 signs associated with insulin resistance:
  - Abdominal obesity (>88 cm in women)
  - Triglycerides (>=150 mg/dL)
  - HDL-cholesterol (<50 mg/dL)
  - Blood pressure (systolic >=130, diastolic >=85 mmHg)
  - Fasting glucose (>110 mg/dL)

National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (2002)

Metabolic syndrome increases risk for

- Type 2 diabetes
- Independently, atherosclerotic cardiovascular diseases
  - Coronary disease
  - Stroke
- Non-alcoholic fatty liver disease (NAFLD)
- Obstructive sleep apnea
- Polycystic ovary syndrome

PCOS, insulin resistance (IR) and reproduction: a teleological perspective

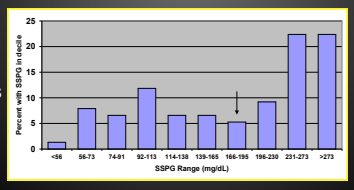
- Why should PCOS, which leads to infertility, be so common?
  - Especially troubling given an apparent genetic component to PCOS
- In developed societies, diet/lifestyle lead to overnutrition
- With food scarcity, weight loss can stop ovulation
  - "Thrifty genes" associated with IR are adaptive in this situation
  - Allow these women to reproduce in food-scarce situations
    - "Preserves and continues tribe" even though many women stop ovulating
    - Fewer babies to feed
- When food plentiful, 5-10% of women becoming infertile is not selected against
  - Women with "thrifty" genotype (may) develop PCOS when nutrition plentiful
  - May account for increased prevalence of IR and PCOS in some ethnic minorities in USA
  - Particularly if recent ancestors lived in less food-abundant societies

Are all women with PCOS insulin-resistant?

- Insulin sensitivity/resistance exists across a wide range
  - Both in women without and with PCOS
- There is no clear cutoff between normal and insulin-resistant
- Both lean and overweight/obese women with PCOS can have IR
  - But IR is more extreme with higher BMI
  - And some women with PCOS are not IR, regardless of BMI
- Over all, about 2/3 of women with PCOS are "significantly" IR
  - May be lower when Rotterdam definition used
- IR is associated with central, especially visceral adiposity (high WHR)

Are all women with PCOS insulin-resistant?

Percent of Women with NICHD PCOS



Deciles of steady-state plasma glucose (SSPG) on insulin suppression test

Do women with PCOS have greater level of risk for cardiometabolic diseases?

- In general, YES
- Many of these diseases become more apparent after menopause
  - But how to diagnose postmenopausal women with PCOS unclear
- Women with hyperandrogenic PCOS more likely to have significant insulin resistance than other subtypes

Do women with PCOS have greater level of risk for cardiometabolic diseases?

- Primary prevention includes screening for their risk factors
  - Modifiable risks include obesity, HTN, abnormal lipids, dysglycemia
  - Much effort into defining best diet composition, exercise prescription
    - Exercise increases muscle insulin sensitivity independent of weight loss
  - These risk factors are easy to screen for in office visit
    - Debate continues whether to advise oral GTT for all women with PCOS
    - Insulin levels not generally recommended because of lack of standardization

Does a PCOS diagnosis indicate greater level of cardiometabolic disease risk?

- What elements of the PCOS definition associate with risk?
  - Recall that insulin resistance is not part of any definition of PCOS
- Hyperandrogenism most associated with risk
  - Generally a stable phenotype through reproductive years
  - Post-menopausally, hyperandrogenism may persist
- Dysovulation may improve as women approach menopause

Women with PCOS and Hypertension

- Young women with PCOS have greater prevalence of HTN
  - Difference not found when adjusted for BMI and diabetes
- Peri- and postmenopausal aged women show similar findings

Women with PCOS and Dyslipidemia

- LDL-C and triglycerides are elevated, HDL-C is lower
- LDL abnormality persists after adjustment for BMI
  - Associated with hyperandrogenic phenotype
- Triglycerides, HDL-C more abnormal in PCOS than control
  - Difference between PCOS and non-PCOS mainly with high BMI
  - These are components of insulin resistance syndrome
- Dyslipidemia in PCOS persists after menopause
  - Especially if hyperandrogenic

Women with PCOS and Dysglycemia

- In NICHD PCOS, IGT reported in ~30%, DM in ~5%
- Increased odds of both IGT and T2DM in reproductive age
  - OR~4-fold for each, ~2-fold when adjusted for BMI
- Similar finding for IGT in perimenopausal PCOS (SWAN)
- Risk of incident T2DM continues to increase after menopause
  - PCOS = recalled abnormal menses, current or past androgen excess
- Insufficient insulin secretory response to glucose causes T2DM

Women with PCOS and Novel CVD risks

- Intravascular inflammation, oxidative stress, fibrinolysis
- Can assess through
  - Cytokine, hsCRP, homocysteine assays
  - Brachial flow-mediated dilatation
- Generally worse in women meeting NIH criteria
  - Parallels degree of insulin resistance

Women with PCOS and subclinical atherosclerosis

- Carotid intima-media thickness
- Carotid plaque
- Coronary artery calcium
- Endothelial dysfunction as marker
  - Brachial artery flow-mediated dilation

Women with PCOS and clinical atherosclerotic events

- Myocardial infarction
- Stroke
- Cardiovascular death

How can IR-associated risk be managed?

- Lifestyle and diet
  - Aerobic exercise, Calorie reduction
  - Multidisciplinary PCOS-centered programs work best, support groups
  - May also improve menstrual cyclicity
- Weight loss notoriously hard to achieve
  - 5-10% may be sufficient
  - Bariatric surgery for BMI >40
    - May ameliorate or abolish signs of PCOS
- Treatment of specific abnormalities
  - Antihypertensives, statins – must tailor to possibility of pregnancy
- Insulin sensitizer medications

Insulin sensitizer medications

- Drugs approved for T2DM, off-label for non-diabetic PCOS
- Two categories
  - Thiazolidinediones (“glitazones”)
    - Troglitazone – liver toxicity, withdrawn from market ~1999
    - Rosiglitzone – fluid retention and CHF in T2DM, rarely used now
    - Pioglitazone – limited studies in PCOS, unknown early pregnancy risk
    - Glitazones enhance ovulation and reduce testosterone
- Metformin

Metformin in PCOS

- FDA approval, first reported use in PCOS in 1994
- Improves menstrual pattern, enhances ovulation potential
- Reduces free testosterone, possibly only by raising SHBG
- Slight weight loss may be due to GI symptoms after fried food
- Synergism with clomiphene for ovulation induction
- Large NICHD study showed no improvement in livebirth rate
- Well tolerated, extended release available

Metformin and metabolic risk in PCOS

- Diabetes Prevention Project trial: alternative to lifestyle mod in preventing progression of impaired glucose tolerance to T2DM
  - Metformin not specifically tested in longitudinal trial in PCOS
  - 16% of women with PCOS + IGT develop T2DM per year
- Metformin appropriate for adolescents with PCOS
- Metformin may be more effective for diabetes-prone ethnicities

Monitoring metabolic risk in PCOS

- Risk factors often worsen over time
- Weight, waist circumference and BP every 6-12 months
- Inquire about physical activity, smoking
- Repeat lipid profile if abnormal or CVD risk elevated
- Repeat OGTT at intervals of 2-5 years (find IGT, T2DM)
- Screen for obstructive sleep apnea based only on symptoms

Combined oral contraceptives in PCOS

- First-line treatment for menstrual disorder
- Suppress LH/FSH–driven follicle development
  - Reduce ovarian androgen secretion
- High-estrogen milieu drives SHBG production
  - Reduces free fraction of testosterone
- Useful in management of hirsutism and acne
  - Spironolactone or metformin added if COC alone not successful
- Also provides benefit of regularizing/reducing uterine bleeding
- Best evidence suggests COC do not worsen insulin resistance

Summary

- Most but not all women with a PCOS diagnosis have insulin resistance that may drive or reinforce features of PCOS
- Insulin resistance underpins cardiovascular risk in PCOS
- Because PCOS is a phenotype of reproductive age, ascertainment of PCOS among postmenopausal women is problematic
  - History of irregular menses, current hyperandrogenemia helpful

Summary

- Few longitudinal studies to guide care recommendations
  - Makes for many gaps in evidence to base practice
- Many have studied women who present for PCOS care
  - These women have more extreme phenotype and are more obese
  - May lead to biased over-estimate of true CVD risk levels in PCOS
- Studies needed that are population–, not clinic-based
  - Nurses' Health Study: menstrual irregularity can mark T2DM risk
- Studies needed with sufficient numbers of actual CVD events

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