



Park Nicollet

Polycystic Ovary Syndrome (PCOS) and Insulin Resistance in Children and Adolescents

Betsy Schwartz, MD
Pediatric Endocrinology
Park Nicollet Clinic

Disclosures

- ◆ I have no relevant financial interests or conflicts of interest to disclose.
- ◆ Off-label use:
 - ◆ Metformin for PCOS and insulin resistance

Objectives

- ◆ Identify when to suspect PCOS and insulin resistance
- ◆ Screening and evaluation for PCOS and insulin resistance
- ◆ Treatment of PCOS and insulin resistance in the primary care office
- ◆ When to refer to a specialist

PCOS: Epidemiology

- ◆ Most common endocrine disorder of reproductive age women
- ◆ Affects 7-10% of women
- ◆ More limited data in adolescents
 - ◆ 3-10% of adolescent girls
- ◆ Incidence of diagnosis in adolescents is increasing
 - ◆ Likely related to obesity epidemic

PCOS: Diagnostic Criteria

- ◆ **Rotterdam criteria 2003** (need 2 of 3)
 - ◆ Chronic anovulation
 - ◆ Clinical or biochemical hyperandrogenism – acne, hirsutism
 - ◆ Ultrasound finding of polycystic ovaries (in 20% normal women)
- ◆ **Androgen Excess Society 2006**
 - ◆ Must have clinical or biochemical hyperandrogenism
 - ◆ Either chronic anovulation or ultrasound findings of polycystic ovaries
- ◆ **Androgen Excess and PCOS Society 2009**
 - ◆ Hyperandrogenism (clinical or biochemical) and
 - ◆ Either chronic anovulation or ultrasound findings of polycystic ovaries
 - ◆ Exclusion of other androgen excess or related disorders

PCOS: Diagnostic Criteria

- ◆ Proposed criteria for adolescents
- ◆ Need 4 out of 5
 - ◆ Oligo- or amenorrhea persistent 2 years after menarche
 - Considers physiologic adolescent anovulation
 - ◆ Clinical hyperandrogenism
 - ◆ Biochemical hyperandrogenism
 - ◆ Insulin resistance or hyperinsulinemia
 - ◆ Polycystic Ovaries on Ultrasound

Brewer, et al. Minerva Pediatr 2010;62:459-73

PCOS: Clinical Features

- ◆ **Presents during adolescence**
- ◆ **Irregular menstrual cycles**
 - ◆ Usually less than 6 menses per year
 - ◆ May present with primary amenorrhea (8%)
- ◆ **Hyperandrogenism**
 - ◆ Acne (50%)
 - ◆ Hirsutism (50-76%)
 - ◆ Androgenic Alopecia
- ◆ **Acanthosis nigricans**
- ◆ **Overweight or Obesity**
 - ◆ 60% patients with PCOS are overweight or obese
 - ◆ Even normal weight females found to have relatively increased visceral adiposity

PCOS: Clinical Presentation



© Jere Mammino, DO

PCOS: Additional Features

◆ Insulin resistance

- ◆ Decreased ability of insulin to stimulate uptake of glucose by muscle and adipose tissues
- ◆ Leads to compensatory hyperinsulinism
- ◆ Primary factor driving increased androgen production
- ◆ Insulin resistance is common in PCOS and occurs independent of obesity or BMI
- ◆ 31% of women with PCOS have impaired glucose tolerance
- ◆ Type 2 diabetes is undiagnosed in up to 10% of women with PCOS
- ◆ 37% of adolescents with PCOS have the **Metabolic Syndrome**

Definition of Metabolic Syndrome

- ◆ No standard criteria in children
- ◆ Some studies use elements of adult NCEP or WHO definitions
- ◆ 3 or more of the following:

Cook et al, Arch Ped Adol Med

Obesity	Waist circumf $\geq 90^{\text{th}}\%$ <u>or</u> BMI $\geq 95^{\text{th}}\%$
High triglycerides	>110 mg/dl <u>Or</u> $>95^{\text{th}}\%$
Low HDL	≤ 40 mg/dl <u>Or</u> $<5^{\text{th}}\%$
High BP	$\geq 95^{\text{th}}\%$ for age, ht, sex
High fasting Blood glucose	>100 mg/dl <u>Or</u> 2hr 140-200 mg/dl (OGTT)

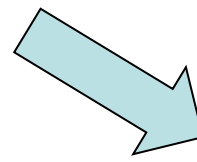
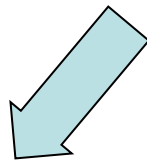
PCOS: Long Term Health Risks

- ◆ 10-fold increased risk for **type 2 diabetes** in adulthood
- ◆ 2-fold increased risk for **metabolic syndrome**
- ◆ Fertility difficulties
 - ◆ Due to menstrual irregularities and anovulation
- ◆ Increased risk for endometrial cancer

PCOS: Pathogenesis

◆ Pathogenesis still uncertain

Insulin resistance → **Hyperinsulinemia**



Disordered pituitary function

Hyperandrogenism

PCOS: Pathogenesis

◆ Hyperandrogenism

- ◆ Principal androgen source is the ovary
- ◆ Testosterone is the principal circulating androgen in females
- ◆ May have elevated adrenal androgens – DHEAS, androstenedione
- ◆ May have normal testosterone levels but typically have **elevated free testosterone**
 - Due to low sex-hormone binding globulin (SHBG) – key circulating protein that binds to testosterone

PCOS: Pathogenesis

◆ Disordered Pituitary Function

- ◆ High LH secretion in relation to FSH
- ◆ Leads to increased ovarian thecal production of androgens
- ◆ Androgen excess interferes with negative feedback of progesterone and estradiol on LH secretion
- ◆ Further elevation of LH and androgens

PCOS: Pathogenesis

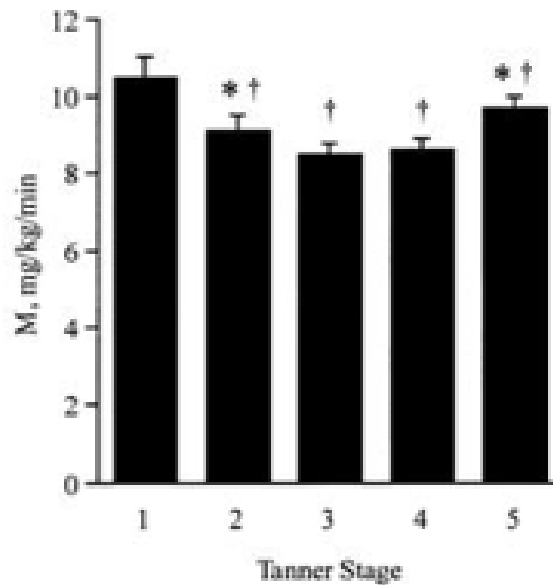
- ◆ Insulin resistance and hyperinsulinemia
 - ◆ Insulin acts synergistically with LH on thecal cells
 - Stimulating androgen production from ovaries
 - ◆ Insulin increases the sensitivity of the pituitary gland to GnRH
 - Stimulating LH secretion
 - ◆ Insulin inhibits hepatic production of SHBG
 - Increasing free testosterone levels

Additional Risk Factors

- ◆ Small for gestational age
 - ◆ With rapid weight gain in first few years of life
- ◆ Large for gestational age
- ◆ Increased intrauterine exposure to androgens
 - ◆ CAH, congenital adrenal virilizing tumors
 - Despite normalization of androgen levels after birth
- ◆ Premature adrenarche (15-20% increased risk)
- ◆ Family history of PCOS
 - ◆ Syndrome found to aggregate in families
 - Large number of genetic studies, no single gene found

Additional Risk Factors

◆ Physiologic insulin resistance of puberty



Moran, Diabetes 1999

PCOS: Laboratory Evaluation

- ◆ No consensus guidelines exist for evaluation
- ◆ Laboratory studies
 - ◆ Free and total testosterone
 - Free testosterone elevation most sensitive
 - ◆ DHEAS and androstenedione
 - May also be elevated
 - ◆ Elevated LH:FSH (>2:1) and decreased SHBG
 - not required for diagnosis
 - ◆ Fasting glucose, insulin, 2 hour oral glucose tolerance test
 - ◆ Rule out other etiologies: 8 am 17-OHP, TSH, prolactin, FSH and estradiol, pregnancy test

PCOS Evaluation: Imaging

◆ Pelvic ultrasound

- ◆ PCO = at least 12 follicles in at least one ovary with diameter of 2-9 mm and/or increased ovarian vol >10 ml
- ◆ Difficult to visualize via transabdominal U/S in obese females
- ◆ Not needed for the diagnosis of PCOS in adolescents

◆ If concerned about adrenal tumor

- ◆ CT or MRI of the adrenal glands

PCOS: Treatment

◆ Goals

- ◆ Control symptoms of androgen excess
- ◆ Regulate menses
- ◆ Reduce long term metabolic complications (type 2 DM)
- ◆ Address psychological aspects of this condition
 - poor self-esteem, depression

◆ Lifestyle Modification

- ◆ Adult studies
 - 5-10% weight loss through diet and exercise
 - ◆ Reduction in androgen levels
 - ◆ Improved menstrual function

Treatment: Lifestyle Intervention

- ◆ Lass et al. study from Germany *Endocrine Research*, November 2011
 - ◆ 127 obese girls with PCOS (ages 12-17) recruited
 - ◆ 59 completed the program
 - ◆ 1 year lifestyle intervention
 - Pediatricians, dieticians, psychologists, exercise physiologists
 - 6 nutrition sessions, 6 parent sessions in 1st 3 months
 - Weekly exercise throughout the year
 - ◆ 26 lost weight
 - Significant improvements in BP, triglycerides, HDL, carotid intimal medial thickness, lower testosterone levels, higher SHBG levels
 - 61% normalization of menstrual periods
 - ◆ Only girls with weight reduction showed improvement of the components of PCOS

Treatment: Lifestyle Intervention



Healthy NH



Fruits and vegetables... more is better! Eat at least 5 servings a day. Limit 100% fruit juice.



Cut screen time to 2 hours or less a day.



Participate in at least one hour of physical activity every day.



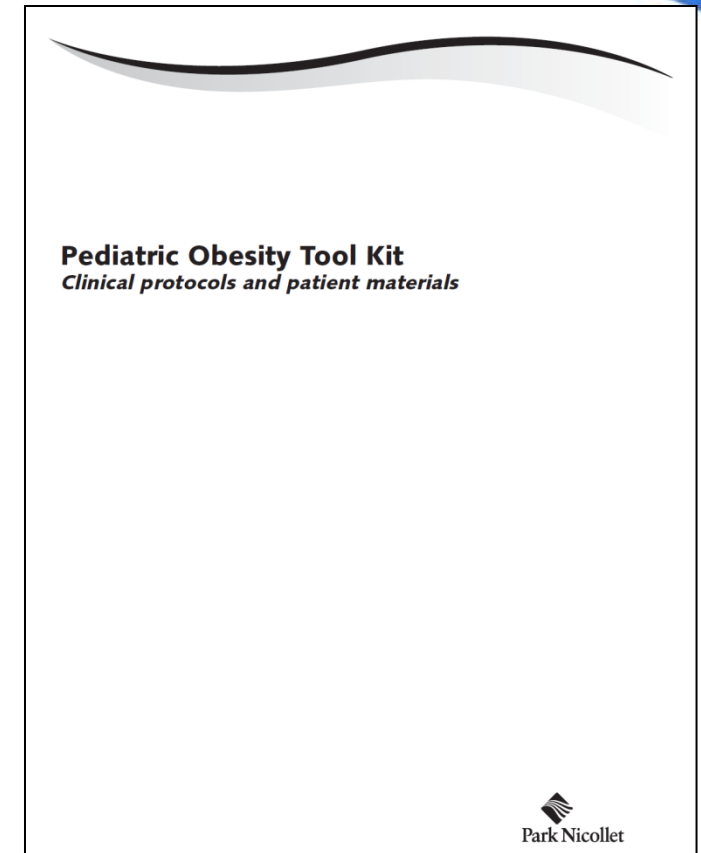
Restrict soda and sugar-sweetened sports and fruit drinks. Instead, drink water and 3-4 servings a day of skim or 1% milk.



Tools and clinical resources

The American Academy of Pediatrics **Minnesota Chapter** has an obesity taskforce and shares tools and resources for:

- ◆ Assessment
- ◆ Treatment
- ◆ Prevention
- ◆ tool kit



www.mnaap.org/obesityclinicalresources.html

Treatment of PCOS

- ◆ What if the teen with PCOS is not obese or if lifestyle intervention is not effective in the obese patient?
- ◆ Further management tailored to individual risks and needs
- ◆ Medication
 - ◆ Oral contraceptives
 - ◆ Antiandrogens
 - ◆ Insulin sensitizing agents
- ◆ Dermatological interventions

Treatment of PCOS: Oral Contraceptives

- ◆ Combined with both estrogen and progestin
- ◆ Produce regular menstrual cycles
- ◆ Improve acne and hirsutism
- ◆ Estrogens increase SHBG production, suppress LH
 - ◆ Decrease circulating free androgens
- ◆ Progestins protect endometrium from unopposed estrogen
- ◆ Yasmin - progestin drospirenone anti-androgenic
 - ◆ Equivalent to about 25 mg spironolactone
- ◆ Do not improve insulin resistance (may worsen)

Treatment of PCOS: Antiandrogens

◆ Spironolactone

- ◆ May improve hirsutism and acne in large doses
 - 100-200 mg daily
- ◆ Improvements not seen until 6-12 months of therapy
 - due to long growth cycles of terminal hair
- ◆ Blocks dihydrotestosterone at the androgen receptor
 - Prescribe with an OCP - teratogenic
- ◆ Also a potassium sparing diuretic
 - Polyuria, postural hypotension, theoretically hyperkalemia

◆ Other agents not commonly used

- ◆ Flutamide has potential for hepatotoxicity

Treatment of PCOS: Metformin

- ◆ Inhibits hepatic glucose production and increases peripheral tissue insulin sensitivity
- ◆ Reduces androgens, improves hirsutism, decreases insulin levels, normalizes menstrual cycles in adolescents, may improve BMI and lipid profile
- ◆ Do not regulate menses or decrease hyperandrogenism as quickly as oral contraceptives
- ◆ Loss of benefits after cessation of medication
- ◆ Take with multivitamin, consider contraception (ovulatory function improved)
- ◆ GI side effects – better tolerated if dose increased gradually
- ◆ Monitor liver enzymes, vitamin B12
- ◆ Insufficient long term data – still considered “off label”

Treatment of PCOS: Hair removal

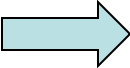
◆ Hair removal techniques

- ◆ Waxing, shaving, depilation, plucking
- ◆ Permanent: laser and electrolysis
- ◆ Pharmacologic agents often needed to prevent new hair growth
- ◆ Vaniqa – ornithine decarboxylase inhibitor
 - Hair growth resumes after discontinuation of therapy
 - Expensive, often not covered by insurance

◆ Combination therapy

- ◆ Most commonly – OCP and Metformin

Insulin Resistance: Mechanism

- ◆ Obesity  insulin resistance
 - ◆ Elevated free fatty acids
 - Decrease insulin stimulated glucose uptake
 - Impair insulin secretion
 - Increase hepatic glucose production
 - ◆ Cytokines released by adipocytes
 - Leptin, CRP, TNF-alpha, visfatin, IL-6
 - Adiponectin inversely associated with insulin resistance/obesity
- ◆ Poor glucose uptake by muscle and fat
- ◆ Compensatory increase in insulin secretion to maintain normal glucose levels

Insulin Resistance: Risk Factors

- ◆ Obesity
- ◆ Puberty
- ◆ Family history of type 2 diabetes
 - ◆ 74-100% youth w/ type 2 DM have 1st or 2nd degree relative w/type 2
 - ◆ High risk susceptibility genes have been found
- ◆ Race/Ethnicity
 - ◆ Native American, African-American, Hispanic, Asian or Pacific Islander youth
- ◆ Conditions associated with insulin resistance
 - ◆ Acanthosis nigricans, PCOS, hypertension, dyslipidemia
- ◆ Intrauterine and early life factors
 - ◆ High or low birth weight, off-spring of mothers with diabetes during pregnancy
 - ◆ Breastfeeding protective

Insulin Resistance: Evaluation

◆ Screening Recommendations (Expert Committee 2007)

◆ Fasting Glucose level

- BMI >85th percentile plus risk factor
 - ◆ Family History of type 2 diabetes in 1st or 2nd degree relative
 - ◆ High-risk race/ethnicity
 - ◆ Signs/symptoms of insulin resistance (acanthosis nigricans, PCOS, HTN, dyslipidemia)
- BMI >95th percentile

◆ Additional Measures

◆ Fasting Insulin level

◆ 2 hour Oral Glucose Tolerance Test

- Recommended if fasting glucose is >100
- Recommended in adults with PCOS

◆ Hemoglobin A1C

- 5.7-6.4% is considered “pre-diabetes”

Insulin Resistance: What is Pre-diabetes?

- ◆ Impaired fasting glucose/glucose tolerance
 - ◆ Decline in first-phase insulin secretion
 - Early marker of beta cell failure
 - ◆ 21% of obese adolescents (Sinha et al, NEJM 2008)
- ◆ Impaired fasting glucose
 - ◆ Fasting BG ≥ 100 -125 mg/dl
- ◆ Impaired glucose tolerance
 - ◆ OGTT 2hr BG ≥ 140 -199 mg/dl
 - ◆ Casual BG ≥ 140 -199 mg/dl

Blood Glucose and A1C Levels

Fasting

OGTT

A1C

Diabetes
>126 mg/dL

Diabetes
>200 mg/dL

Diabetes
>6.5%

Impaired fasting
glucose
100-125 mg/dL

Impaired glucose
tolerance
140-199 mg/dL

High risk for
diabetes
5.7-6.4%

←Prediabetes

←“Increased
Risk for
Diabetes”

Normal
70-99
mg/dL

Normal
<140
mg/dL

Normal
<5.7%



Why worry about pre-diabetes?

- ◆ Rapid deterioration to type 2 diabetes
- ◆ Longitudinal study 117 obese youth
 - ◆ 24% with impaired glucose tolerance developed type 2 diabetes in 2 yrs
 - ◆ Compared to adult progression, suggests β -cell failure more rapid in youth

Weiss et al, Diabetes Care 2005

Type 2 Diabetes

- ◆ Prior to the 1990's type 2 diabetes rarely reported among children
- ◆ Dramatic rise over the past two decades
- ◆ Now accounts for 8-45% of diabetes diagnosed in U.S. pediatric centers
- ◆ Risk Factors: Obesity, race/ethnicity, puberty, family history, metabolic syndrome

Type 2 Diabetes

- ◆ Proportion of type 2 diabetes among cases of diabetes
 - SEARCH for Diabetes in Youth Study

	0-9 yrs	10-19 yrs
White	0.4%	5.8%
African American	0.1%	32.7%
Hispanic	1.3%	21.9%
Asian/Pacific Islanders	6.7%	40.1%
Native American	13.3%	76.4%

Insulin Resistance: Treatment

- ◆ Lifestyle Change – 1st line intervention
- ◆ Metformin
 - ◆ Approved for type 2 DM in children 10 years and older
 - ◆ Use for insulin resistance still controversial, not established
- ◆ Arguments against Metformin
 - ◆ Doesn't help develop skills of self-efficacy and improve self-esteem
 - ◆ Diabetes Prevention Program (DPP) Trial
 - Lifestyle intervention more effective in reducing incidence of diabetes than metformin
 - 2 wks after metformin discontinuation – OGTT results same as placebo

Insulin Resistance: Metformin

- ◆ Studies in youth give mixed results on reduction in weight and insulin resistance
- ◆ Largest trial placebo controlled trial
 - ◆ 85 adolescents with insulin resistance
 - ◆ No affect on weight overall
 - ◆ Modest wt loss (BMI reduction of 5%) only in those (27%) who both adhered to medication and made lifestyle change – particularly decrease portion size
 - ◆ Insulin resistance more likely to improve if there was weight loss

Insulin Resistance: Metformin

◆ Adverse effects

- ◆ GI distress (10-15%)
- ◆ Vitamin B malabsorption
- ◆ Lactic acidosis (not described in children)

◆ Candidates

- ◆ Impaired fasting BG or glucose tolerance
- ◆ Severe insulin resistance, metabolic syndrome, Hgb A1C >6%
- ◆ PCOS
- ◆ Particularly if strong fm hx type 2 DM, early CVD
- ◆ Reserved for obese, not “overweight”, adolescents
- ◆ Consider if obesity/co-morbidities persist despite lifestyle change
- ◆ Lifestyle counseling must precede and accompany drug therapy

Dr. Michael Freemark



Park Nicollet

When to Refer to a Pediatric Endocrinologist?

- ◆ Multidisciplinary team approach
 - ◆ Physician
 - ◆ Dietician
 - ◆ Health psychologist/family therapist
- ◆ Expertise in evaluation and treatment of PCOS insulin resistance, pre-diabetes, type 2 diabetes and components of the metabolic syndrome

When to Refer to a Pediatric Endocrinologist?

◆ Insulin resistant patient

- ◆ Impaired fasting glucose or impaired glucose tolerance
- ◆ Type 2 diabetes
- ◆ Patient with insulin resistance refractory to lifestyle change

◆ Patient with PCOS

- ◆ PCOS associated with insulin resistance or metabolic syndrome
- ◆ Significant hyperandrogenism
- ◆ Multiple medication therapy

References

- ◆ Barlow S. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 120 (2007) S164-192
- ◆ Bremer A. Polycystic Ovary Syndrome in the Pediatric Population. *Metabolic Syndrome and Related Disorders* 8 (2010) 375-394.
- ◆ Brewer et al. A review of polycystic ovary syndrome in adolescents. *Minerva Pediatr* 62 (2010) 459-473.
- ◆ Criego A, Schwartz B. Diabetes in Children and Adolescents. Chapter in *Educational Review Manual in Endocrinology, Diabetes, and Metabolism*, 3rd Ed. 2009. Published by CCGMP.
- ◆ Lass, et al. Effect of Lifestyle Intervention on Features of Polycystic Ovarian Syndrome, Metabolic Syndrome, and Intima-Media Thickness in Obese Adolescent Girls. *J Clin Endocrinol Metab* 96(2011) 3533-3540.
- ◆ Love-Osborne, et al. Addition of Metformin to a Lifestyle Modification Program in Adolescents with Insulin Resistance. *J Pediatr* 152(2008) 817-822.
- ◆ Ojaniemi et al. Management of Polycystic Ovary Syndrome in Children and Adolescents. *Horm Res Paediatr* 74(2010) 372-375.