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

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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, hirsuitism
  - 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

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%)
  ◆ Hirsuitism (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
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:
  - Obesity
    - Waist circumf ≥90\textsuperscript{th}% or BMI ≥ 95\textsuperscript{th}%
  - High triglycerides
    - >110 mg/dl or >95\textsuperscript{th}%
  - Low HDL
    - ≤40 mg/dl or <5\textsuperscript{th}%
  - High BP
    - ≥95\textsuperscript{th}% for age, ht, sex
  - High fasting Blood glucose
    - >100 mg/dl or 2hr 140-200 mg/dl (OGTT)

Cook et al, Arch Ped Adol Med
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
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

5
Healthy NH

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

2
Cut screen time to 2 hours or less a day.

1
Participate in at least one hour of physical activity every day.

0
Restrict soda and sugar-sweetened sports and fruit drinks. Instead, drink water and 3-4 servings a day of skim or 1% milk.

Everyone caring, every day

Park Nicollet
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 hirsuitism
- 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 hirsuitism 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 hirsuitism, 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
  - OGGT 2hr BG ≥140-199 mg/dl
  - Casual BG ≥140-199 mg/dl
Blood Glucose and A1C Levels

**Fasting**
- **Diabetes** >126 mg/dL
- Impaired fasting glucose 100-125 mg/dL
- Normal 70-99 mg/dL

**OGTT**
- **Diabetes** >200 mg/dL
- Impaired glucose tolerance 140-199 mg/dL
- Normal <140 mg/dL

**A1C**
- **Diabetes** >6.5%
- High risk for diabetes 5.7-6.4%
- Normal <5.7%

*ADA Clinical Practice Recommendations 2011; Suppl.1; ADA, EASD, IDF International Expert Committee Report on A1C for Diagnosis of Diabetes.*
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

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Insulin Resistance: Treatment

- **Lifestyle Change** – 1\textsuperscript{st} 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
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