Polycystic Ovarian Syndrome in Adolescents

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Polycystic Ovarian Syndrome (PCOS)

- First described by Irving Stein and Michael Leventhal in 1935:
  - Oligo-amenorrhea
  - Obesity
  - Hirsutism

- The most common endocrine disorder in reproductive-age women: 2-8%
Normal Ovary

- Volume < 8 cm³
- Spread out follicles

Polycystic Ovary

- Slightly enlarged
- Volume > 8 cm³
- Peripherally located follicles
- Increased stroma
PCOS

• PCOS is a syndrome, not a disease
• Anovulation starts with puberty
• Less than 6 menses per year
• Menstrual bleeding timing and amount cannot be predicted
• Excessive hairiness
• 70-80 % infertility
• DM, cardiac diseases?, endometrium Ca
• Sleep apnea, depression
Diagnosis

• Diagnosis of PCOS in adolescents is open to debate

• Metabolic syndrome and sleep disorders are more common
Definition

- PCOS diagnosis can be made when two out of three criteria mentioned below are met after excluding other etiologies:

(i) Oligomenorrhea - amenorrhea (oligo – anovulation)
(ii) Hyperandrogenemia and/or hyperandrogenism
(iii) Polycystic ovaries detected via USG: at least in one ovary 2-9 mm, at least 12 follicles; increased ovarian volume > 10 cm$^3$

*(Rotterdam ESHRE/ASRM 2003)*
• **Ultrasonography Criteria:**
  --- Increased ovarian volume
  --- Peripheral placement, 10-15 follicles < 10mm
  --- Increased echogenicity in ovarian stroma
NIH Criteria (1995-Zawadzki-Dunaif)

- Oligo - anovulation
- Biochemical or clinical hyperandrogenism

Androgen Excess Society (2009-Azziz)

- Primary clinical and/or biochemical excess androgen
- Chronic oligo - anovulation and polycystic ovaries
## Proposed diagnostic criteria for polycystic ovary syndrome

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<td>Clinical and/or biochemical signs of hyperandrogenism</td>
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<td>Ovarian dysfunction – oligo-anovulation and/or polycystic ovaries on ultrasound</td>
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<td>Exclusion of other disorders: NCCAH, androgen-secreting tumors</td>
<td>Polycystic ovaries (by ultrasound)</td>
<td>Exclusion of other androgen excess or ovulatory disorders</td>
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NIH: National Institutes of Health; AES: Androgen Excess Society; NCCAH: nonclassic congenital adrenal hyperplasia; PCOS: polycystic ovary syndrome.

* Rotterdam criteria based upon a 2003 consensus meeting held in Rotterdam (European Society of Human Reproduction and Embryology/American Society of Reproductive Medicine consensus workshop group).

### References:

PCOS Phenotypes:

[1] Type 1 classic PCOS
- Chronic anovulation
- Polycystic ovaries
- Hyperandrogenism

[2] Type II classic PCOS
- Chronic anovulation
- Normal ovaries
- Hyperandrogenism

[3] Ovulatory PCOS
- Ovulatory cycles
- Polycystic ovaries
- Hyperandrogenism

[4] Normoandrogenic PCOS
- Chronic anovulation
- Polycystic ovaries
- Normoandrogenism
Initiation

- Usually starts with maturation of H-H-O axis during puberty

- Exposure of female fetus to excess androgen due to environmental or genetic factors

- Excess LH secretion and insulin resistance are important
Irregular Cycles

• Anovulation – oligoovulation

• Obesity, insulin resistance, diabetes mellitus, metabolic syndrome and infertility
PCOS Diagnosis in Adolescents

- Irregular cycles are common after menarche
- 85% of cycles in the first year after menarche and 59% of cycles in three years are anovulatory
- Acne and mild hirsutism are common due to increased ovarian and adrenal androgen production
- However, *progressive hirsutism* is an important diagnostic factor
- Obesity can be seen in one out of five adolescents
Diagnosis

• If Rotterdam criteria are applied, many adolescents are diagnosed with PCOS

• Existence of 3 criteria:
  – hyperandrogenemia
  – oligomenorrhea that lasts more than 2 years after menarche
  – PCOS and increased ovarian volume $>10 \text{ cm}^3$

  – If only 2 criteria exist, then close follow-up and re-evaluation might be suitable
Differential Diagnosis

1. Hyperprolactinemia
   - Irregular menstrual cycles
   - Mild hyperandrogenism

2. Congenital Adrenal Hyperplasia
   - Early follicular phase morning serum 17-hydroxiprogesteron level > 200 ng/dL
   - High dosage (250 mcg) ACTH stimulation test: post-ACTH serum 17-hydroxiprogesteron value < 1000 ng/dL
3. Androgen secreting tumors
   – serum testosterone value > 150 ng/dL
   – adrenal tumors: serum DHEA-S > 800 mcg/dL
   – Low serum LH value

4. Cushing syndrome

5. Medication: Danazol
Insulin Resistance

• Several obese and non-obese women with PCOS have insulin resistance

• It is argued that insulin resistance plays an important role in the pathogenesis of PCOS
PCOS and Insulin Resistance
Egg-Chicken

• Do obesity and insulin resistance cause PCOS?
• Does PCOS cause insulin resistance and obesity?
• Or both?

Chicken or Egg?
PCOS and Insulin Resistance

- Insulin is a growth factor for ovaries
- 50% of obese adolescents with PCOS have insulin resistance
- 17% of non-obese adolescents with PCOS have insulin resistance
Hyperinsulinemia Causes Hyperandrogenism

Hyperinsulinemia

1) Increased P450c activity that converts P to 17-OH progesterone, androstenedione and testosterone,
2) Insulin decreases the synthesis of hepatic SHBG and IGF-BP1
Diagnosis of Insulin Resistance

• Fasting glucose/insulin < 4.5

• Fasting insulin > 24 μ IU/ml

• 75 gr OGTT –2 hours > 140 mg/dL

• Baillargeon and Carpentier, 2007.
Metabolic Syndrome Pathogenesis in PCOS

• Potential Theories:

(1) Insulin Resistance

(2) Obesity
Prevalance of Metabolic Syndrome

• MS Criteria:
  – Central obesity (waist > 88 cm)
  – Serum triglycerides > 150 mg/dL, HDL < 50 mg/dL
  – Systemic hypertension >130/85 mm Hg
  – Fasting plasma glucose >100 mg/dL

• % 22- 26

• Metabolic and cardiovascular risks have to be evaluated and prevented
Metabolic Markers

• In adolescents with PCOS, BMI and waist measurement, along with central obesity have to be evaluated

• **Risk Factors:**
  – Obesity, abdominal adiposity
  – Hypertension, dyslipidemia, subclinical vasculopathy
  – Abnormal glucose tolerance, family history of cardiovascular diseases

• Smoking
Metabolic Markers

• Activin A and B: Stimulates follicle growth and suppresses androgen production at theca cells

• **Follistatin**: Increases at PCOS
  • Neutralizes the effect of activin, suppresses FSH and folliculogenesis
  • Initiates inflammation and insulin resistance

• **Adiponectin, ghrelin, leptin**
Sleep Disorders

- Obstructive sleep apnea OSA
- Sleep disordered breathing
- Daytime extreme sleepiness
Evaluation

• Laboratory work-up:
  – hCG
  – FSH, LH, E2
  – TSH, PRL
  – Total and free testosterone
  – DHEAS
  – 17-OH progesterone

• TA or TV USG

• When PCOS diagnosis is made:
  – Fasting and 2-hour glucose tolerance test
  – Fasting insulin
  – Lipid panel
Differential Diagnosis In Case of Clinical Suspicion

• 24-hour urine free cortisol (Cushing)
• IGF-1 (acromegaly)
• DHEA-S (adrenal tumors)
• 17-OH Progesterone (congenital adrenal hyperplasia)
Treatment

• Lifestyle changes
  – Diet
  – Exercise

• Combined oral contraceptives

• Anti-androgen treatments, spironolakton

• Insulin sensitizing agents
Lifestyle Changes

• A weight loss of 5-10% can improve menstrual irregularities, hyperinsulinemia and hyperandrogenemia

• Women that lost weight in 1 year with changes in diet, physical activity and behavior experienced significant improvement in metabolic and reproductive parameters compared with women who did not lose weight
Weight Loss

• Improvement in blood pressure, insulin, testosterone, SHBG, TG, HDL levels
• Decrease in the thickness of carotid intima media
• Improvement in the menstrual cycles (61% of those who lose weight)
• Must be the first line of choice in adolescents with PCOS
• Not easy to maintain
PCOS  Exercise

• Peripheral muscle cells metabolize 80% of glucose

• Aerobic exercise:
  3-4 times per week, 30 minutes

• 40% improvement in insulin sensitivity in 48 hours

  • *J Appl Physiol* 71:2502, 1991
Long-Term

• Dysfunctional uterine bleeding and prevention of endometrium cancer

• Suppression of ovarian androgen production

• Identification and prevention of risk of diabetes
Insulin Sensitizing Agents

• Metformin

• Pioglitazone, rosiglitazone
Metformin

• Decrease in hepatic glucose production
• Improvement in insulin sensitivity
• Antilipolitic effect
• Increase in SHBG level
• Decrease in leptin production
• Endometrial effect of IGFBP-1 increases
• Effect of LH on theca cells decreases
Metformin and Adolescent PCOS

• In literature there is no significant data on the long-term use of metformin in adolescents

• In a small-scale randomized controlled trial, glucose, insulin, BMI and menstrual cycles improved

• Metformin’s effects disappear 3 months after discontinuing the drug

• Ibanez J et al JCEM 2001
Metformin in Non-Obese Hyperinsulinemic Adolescents with PCOS

• Low-dose metformin is effective

• Addition of antiandrogens provide better clinical outcome
Metformin in Early Ages (8-12)

- Metformin usage at 8-12 years old and 13-14 years old was compared in children with low-birth weight and precocious adrenarche.
- Hirsutism, hyperandrogenemia, oligomenorea, PCOS and abdominal adiposity were observed less.
- Early usage of metformin inhibited or delayed PCOS.
- Ibanez et al. J Clin Endocrinol Metabol 2011
Metformin - Questions

• To whom?
• Dosage?
• When?

• Obese patients when lifestyle changes are not successful
• High fasting glucose levels
• Family history of type 2 DM or cardiovascular diseases
Combined Oral Contraceptives

- Protection of endometrium
- Regular refractory bleeding
- Contraception
- Improvement in acne and hirsutism
OC

- Low-dose OC drugs:

- Cyproterone acetate, norgestimate, desogestrel, drospirenone: antiandrogenic progestins have a theoretical advantage
Therapeutic Effects of Desogestrel, Cyproterone Acetate and Drospirenon
Bhattacharya SM et al Fertil Steril 2012

- 171 PCOS, 58-56-57 desogestrel, CA, Drospirenone
- 6-12 months of treatment period
- No significant difference at the end of 6 months
- At the end of 12 months:
  - Ferriman-Gallwey: CA more effective than desogestrel and drospirenone
  - SHBG: CA more effective than desogestrel, drospirenon desogestrel
  - Free androgen index: CA more effective than desogestrel

- CA the most effective
If Not OC

- Cyclic progestins
- Androgen blocking treatments (spironolacton)
- Cosmetic treatments
- Laser
- Acne: OC
Conclusion

• To diagnose PCOS in adolescents AES criteria should be used or all 3 criteria of Rotterdam have to exist
• Early diagnosis of PCOS and metabolic disorders is important
• Lifestyle changes are more effective in adolescents
Thank you