

Polycystic Ovarian Syndrome in Adolescents

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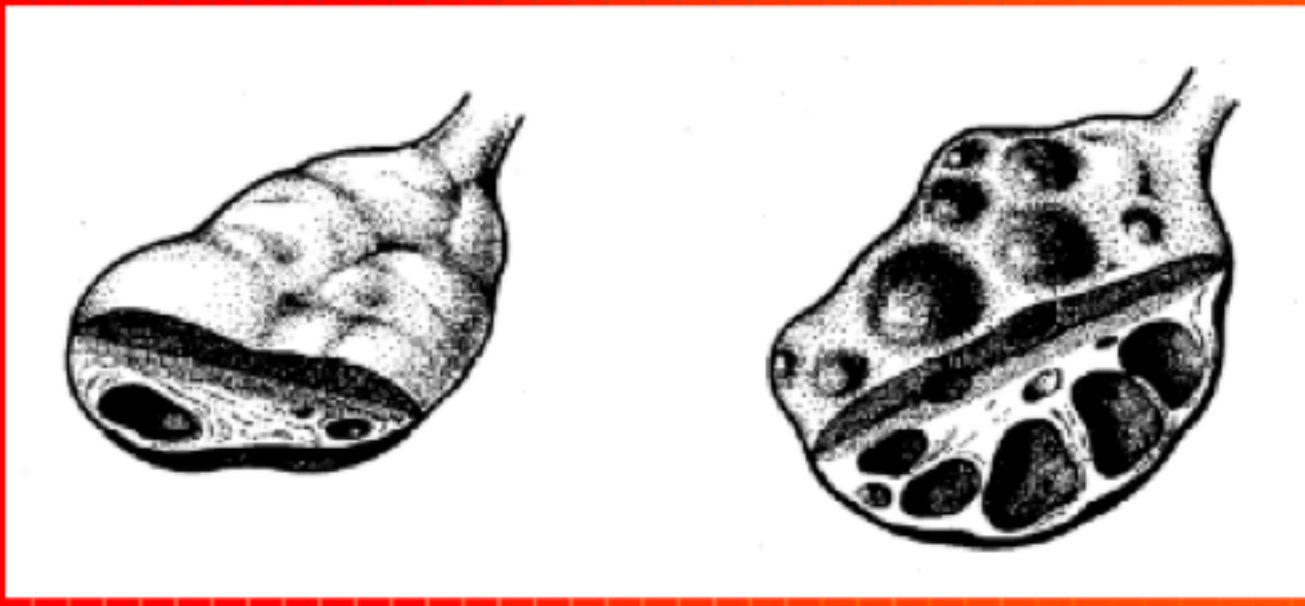
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Polycystic Ovarian Syndrome (PCOS)

- 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 $< 8 \text{ cm}^3$
- Spread out follicles

Polycystic Ovary

- Slightly enlarged
- Volume $> 8 \text{ cm}^3$
- 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

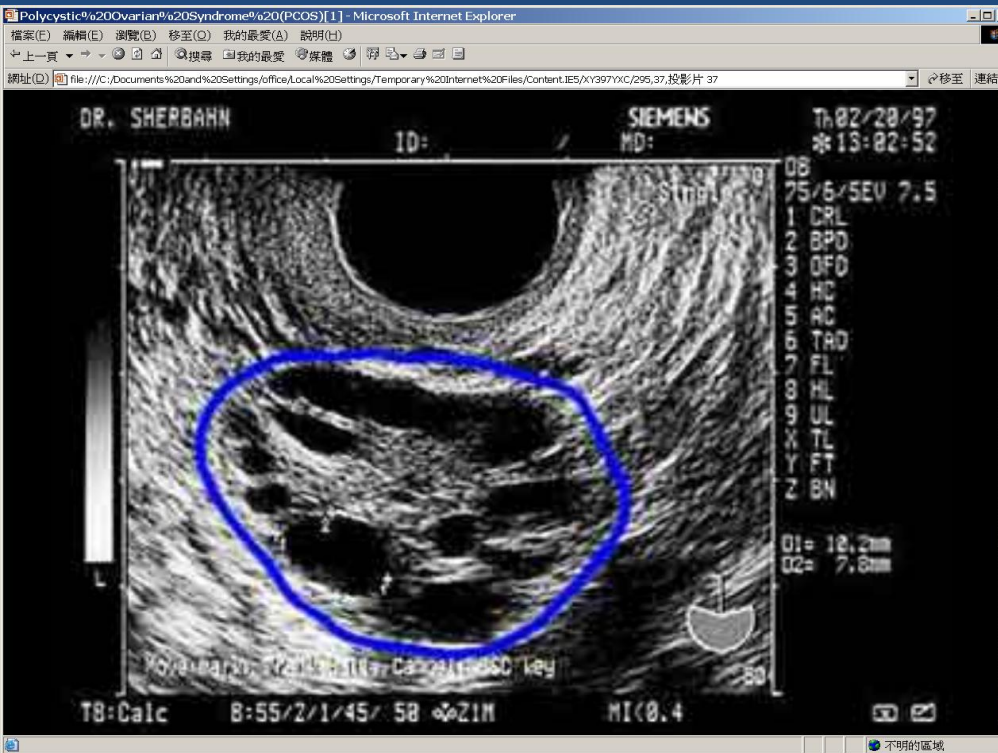
Diagnosis

- 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 $> 10 \text{ cm}^3$

(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

NIH consensus criteria 1990 [1] (all required)	Rotterdam criteria 2003* [2] (two out of three required)	AES definition 2008 [3] (all required)
Menstrual irregularity due to oligo- or anovulation	Oligo- or anovulation	Clinical and/or biochemical signs of hyperandrogenism
Clinical and/or biochemical signs of hyperandrogenism	Clinical and/or biochemical signs of hyperandrogenism	Ovarian dysfunction – oligo-anovulation and/or polycystic ovaries on ultrasound
Exclusion of other disorders: NCCAH, androgen-secreting tumors	Polycystic ovaries (by ultrasound)	Exclusion of other androgen excess or ovulatory disorders

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:

1. Zawadski JK, Dunaif A. *Diagnostic criteria for polycystic ovary syndrome: Towards a rational approach. In: Polycystic Ovary Syndrome (Current Issues in Endocrinology and Metabolism), Dunaif A, Givens JR, Haseltine FP, Merriam GE (Eds), Blackwell Scientific Inc., Boston 1992. p.377.*
2. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. *Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004; 19:41.*
3. Azziz R, Carmina E, Dewailly D, et al. *The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009; 91:456.*

PCOS Phenotypes:



Hyperandrogenism
[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



Normoandrogenism
[4] Normoandrogenic PCOS Chronic anovulation
Polycystic ovaries

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-hidroksiprogesteron level > 200 ng/dL
- High dosage (250 mcg) ACTH stimulation test: post-ACTH serum 17-hidroksiprogesteron 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?



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 $> 24 \mu$ 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, subclinic 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
- Antilipolytic 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 drospirenon
 - 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

