Understanding the young PCOS
A multifaceted task

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Adolescent PCOS

- Incidence of PCOS and see if PCOS start before puberty?
- Are the adult criteria for PCOS applicable in adolescent patients and what are the problems in diagnosis?
- What are the clinical and metabolic features of normal puberty and is an adolescent PCOS different?
- Is hyperandrogenemia and insulin resistance an early feature in girls with PCOS?
- Managing PCOS in adolescence – is it different?
PCOS, starts in adolescence or teenage years

But

Unfortunately, not always diagnosed at that age

As Clinical Expression varied
Incidence

Rate of detection of PCOS

6 years - 6%

10 years - 18%  
*Bridges et al  
F & S 1993*

15 years - 26%

Easy to detect in older girls as ovarian size increases

30% detection rate by *TAS*  
100% detection rate by *TVS*  
*Fox et al*
Polycystic ovaries in pre-pubertal girls

7.6 ± 0.6 years

93% (14/15) had PCO if their mothers had PCOS

Vs

0% in control daughters

Battaglia et al Human Reprod 2002; 17: 771-776

Low birth weight and rapid postnatal weight gain

✓ precocious Adrenarche / Pubarche

✓ increases the risk for progression to functional ovarian hyperandrogenism and PCOS

J Clin Endocrinol Metab, 1998
Etiology

Multifactorial disease with full clinical expression being the result of synergistic pathological interaction of genetic, epigenetic and environmental factors.
Polycystic ovarian syndrome (PCOS) is characterized by genetic and environmental factors leading to hyperandrogenemia and hyperinsulinaemia, which contribute to anovulatory infertility, menstrual irregularities, hirsutism, acne, alopecia, and metabolic syndrome. Hyperinsulinaemia is associated with hypertension, CVD, and DM-2.
<table>
<thead>
<tr>
<th>Criteria for Diagnosis of PCOS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCOS definition</strong> <strong>NIH 1990</strong></td>
</tr>
<tr>
<td>Patient demonstrates both:</td>
</tr>
<tr>
<td>1. Clinical and/or biochemical signs of hyperandrogenism</td>
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<tr>
<td>2. Oligo- or chronic anovulation</td>
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<tr>
<td><strong>Rotterdam criteria 2003 (ESHRE/ASRM)</strong></td>
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<tr>
<td>Two of the following three manifestations:</td>
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<tr>
<td>1. Irregular or absent ovulation</td>
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<td>2. Hyperandrogenism (clinical or biochemical)</td>
</tr>
<tr>
<td>3. PCO on USG</td>
</tr>
<tr>
<td><strong>AES Criteria 2006</strong></td>
</tr>
<tr>
<td>Patient demonstrates both:</td>
</tr>
<tr>
<td>1. Hirsutism and/or hyperandrogenemia</td>
</tr>
<tr>
<td>2. Oligo-anovulation and/or polycystic ovaries</td>
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</table>

Exclude other etiologies of androgen excess - Late onset congenital adrenal hyperplasia, Androgen secreting tumours, Cushing’s syndrome
Can we use these criteria to diagnose PCOS in Adolescence?

No

Normal Adolescents

Oligomenorrhea
Amenorrhea
Acne

“Multicystic” ovaries
Problems in Diagnosis of PCOS in Adolescence

Using a broader definition may be problematic

Prematurely assigning a diagnostic label of PCOS to an adolescent

- Several features may be in evolution, or only be transitory during the transition to adulthood
- All Rotterdam criteria may be transient during adolescence
- AES PCOS criteria more adaptable but need to be modified to be specific

- May be incorrect
- May result in not needed treatments
- May worsen psychological distress as PCOS is associated with disorders and therapies involving body image
Anovulation:
*85 percent of cycles anovulatory in first year of menstruation.
*59 percent of cycles anovulatory in the third year
*25 percent of the cycles still anovulatory in the sixth year

Metabolic features
Insulin resistance
↑ insulin due high GH
hyperpulsatile GnRH secretion
decreased levels ↑SHBG

PCOM at USG in 40%, 35% & 33.3% at 2, 3 & 4 years after menarche
Corresponds to a physiologic condition during early adolescence
Not associated with abnormalities in ovulation menstrual cycle duration androgens or IR

However all return to normal at the end of normal puberty but remain elevated in PCOS

RCOG Scientific Study Group, 2010
Hallmark of adult PCOS that seems to be most reliable in young PCOS is elevated androgen levels

Christine M. Schroeder, Ph.D.  
www.inciid.org/pcos/PCOS-paediatrics
### Age at Menarche and Ovarian Function

<table>
<thead>
<tr>
<th>Age at Menarche</th>
<th>Controls</th>
<th>PCOS</th>
<th>POF</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 11y</td>
<td>12%</td>
<td>16%</td>
<td>21%*</td>
</tr>
<tr>
<td>12-14y</td>
<td>74%</td>
<td>59%</td>
<td>58%</td>
</tr>
<tr>
<td>&gt; 15y</td>
<td>14%</td>
<td>26%*</td>
<td>21%</td>
</tr>
</tbody>
</table>

- * Significant compared with controls

- Obesity associated with early menarche and PCOS

*Sadrzadeh et al, Hum Reprod 2003; 10: 2225*

PCOS in adolescence

Adolescents, mean age 16.7 ± 0.9 years

<table>
<thead>
<tr>
<th>Regular cycle (58)</th>
<th>Irregular (50)</th>
<th>Oligomenorrhea (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCO 9%</td>
<td>PCO 28%</td>
<td>PCO 45%</td>
</tr>
</tbody>
</table>

van Hoff et al F&S 2000;74:49

The later the onset of menarche, the longer until start of regular menses

< 11 y: 14% took > 5 y

> 17 y: 33% took > 5 y
During adolescence, menstrual irregularities are not a proof of adult chronic anovulation.

Persistent Oligomenorrhoea for 2 years post menarche with elevated LH and androgens is diagnostic of PCOS.

Follow-up of Adolescent Menstrual disorders in 87 Swedish Girls

Hyperandrogenemia in Adolescent PCOS

PUBERTY
LH pulses > 25 pulses / 24 h

INSULIN resistance

Ratio of LH/FSH: 2-3/1

ANDROGEN INCREASE

Hirsutism - Absolute increase in androgen levels, alteration in ratio of hormone levels, exaggerated response of the skin to relative normal androgen levels

Acne - transitory phenomenon in normal adolescents

Alopecia - Minimal data available

Acanthosis Nigricans

ANOVULATION
Hyperinsulinaemia & Hyperandrogenaemia

Insulin Receptor Dysfunction

Pancreas

Hyperinsulinaemia

Liver

Liver

Reduced SHBG

↑ Free androgens

Elevated DHEAS

Elevated Androgens

Hypothalamus

LHRH

Pituitary

LH

FSH

Adrenal

Stroma

Follicle
Hyperinsulinaemia and Insulin Resistance in Adolescent PCOS

- Impaired GTT
- Early development of type 2 diabetes
- Dyslipidemia
- Central obesity
- Acanthosis Nigricans

Obesity → Insulin Resistance

Hyperinsulinaemia → NEFA → Hyperglycemia → Muscle

Visceral Adipose Tissue → Lipoprotein lipase activity → ↑ 17,20 lyase activity → ↑ Androgens

Liver → Dyslipidemia (↑TG, ↓HDL)

HTN → Visceral Adipose Tissue

Ovaries → Androgens

PCOS
Clinical features of PCOS in Adolescence
Mainly due to Hyperinsulinaemia & Hyperandrogenaemia

1. **Hirsutism** - good marker of hyperandrogenism

Hirsutism represents Diagnosis of PCOS only in presence of
- Progressive hirsutism
- Biochemical hyperandrogenemia and not biological

2. **Alopecia** - Frontal balding and anterior hairline recession seen only in more severe cases of androgen excess
3. Acne and seborrhea

Due to androgen stimulation of pilosebaceous unit

- Skin problems that wax and wane with the menstrual cycle

4. Acanthosis nigricans - 5 - 10%

Result of insulin resistance

- Diffuse velvety-thickening and hyperpigmentation of the skin

- Most often seen on the back of the neck, axillae and beneath the breasts and exposed areas (elbows, knuckles)
Typical obesity of PCOS is described as "centripetal," or "apple" type of fat distribution - center of the body, as opposed to the thighs and hips.

Waist Circumference > 88 cm
marker of Central / Visceral Obesity

Body weight primary factor affecting quality of life

In Adolescence
abnormalities in insulin metabolism evolve following weight gain

Obesity

↑ Insulin

↓ SHBG

↑ IGF-1

alfa reductase activity is stimulated

↑ Free testosterone

IGF*** insulin like growth factor
Body weight and Puberty
Leptin Resistance

Abnormalities of leptin secretion predispose to weight gain in PCOS

Leptin resistance seen in insulin resistant states & overweight women
## Characters of main PCOS Phenotype

<table>
<thead>
<tr>
<th></th>
<th>Androgen levels</th>
<th>LH/FSH</th>
<th>Insulin resistance</th>
<th>CV risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Classic PCOS</strong></td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Classic PCOS</strong></td>
<td>Increased</td>
<td>Mild increase</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td><strong>Ovulatory PCOS</strong></td>
<td>Increased</td>
<td>Normal</td>
<td>Mild increase</td>
<td>Mild increase</td>
</tr>
<tr>
<td><strong>Normoandrogenic PCOS</strong></td>
<td>Normal</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal?</td>
</tr>
</tbody>
</table>
**PCOS Phenotype during Adolescence**

- During adolescence, only most severe phenotype **Type 1 Classic PCOS** is diagnosed.
- Other PCOS phenotypes cannot be diagnosed.
- Patients who present *incomplete symptoms* have to be included in a **strict follow up** and the final diagnosis should be determined only after 18 years.
Proposed diagnostic criteria for PCOS during Adolescence

Sultan and coll. (Fertil Steril 2006; 86(Suppl 1) 56) have suggested diagnosis on following criteria:

- Clinical Hyperandrogenism
- Biological Hyperandrogenism
- Hyperinsulinism
- Oligo/amenorrhea
- Polycystic ovaries

Diagnosis of PCOS requires the presence of 4 out of 5 criteria.
Proposed diagnostic criteria for PCOS during Adolescence

*Carmina, Oberfield and Lobo. AJOG 2010*

Hyperandrogenism biochemically confirmed

+ Menstrual irregularities
  Present for at least 2 years post menarche

+ Polycystic Ovaries
  include both increased size and increased number of follicles
PCOS presentation during adolescence

- 30% Menstrual irregularities
- 60% Androgen excess
- 84% Overweight
- 9% IGT or T2D
- Infertility rarely an issue

Bekx. et al. Pediatric and Adolescent Gynecology 2009
Management of adolescent girls with PCOS

- Psychological support
- Lifestyle advice - Weight loss and exercise
  - Healthy approach to eating
- Symptom oriented Rx
- Antiandrogens and Insulin-sensitizing agents
- Oral Contraceptive Pill - Low dose oestrogen, Drospirenone, Cyproterone acetate
- Endometrial protection
Integrated, Individualized, Comprehensive, Scientifically designed, Multi-faceted approach to address all aspects of Adolescent PCOS

- Cognitive Behavioral therapy
- Exercise plan
- Nutrition Plan And diet
- Addiction awareness Plan
- Nutraceutical Complementary & Pharmaceutical agents
- Bariatric surgery
- Weekly support & reinforce
<table>
<thead>
<tr>
<th><strong>Assessment - History</strong></th>
<th><strong>Cognitive Behavioural Assessment</strong></th>
<th><strong>Dietary counselling</strong></th>
<th><strong>Exercise</strong></th>
<th><strong>Pharmacotherapy &amp; Surgery</strong></th>
<th><strong>Regular Review</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &amp; WHR to determine degree &amp; distribution of fat</td>
<td>Screen for depression, mood &amp; eating disorders</td>
<td>Low GI &amp; Calorie restricted food</td>
<td>Daily moderate exercise for 30 mins &amp; to high intensity for 60 mins</td>
<td>Antiandrogens</td>
<td>Reinforce goals for weight loss</td>
</tr>
<tr>
<td>Hormone - LH &amp; Androgens, Glucose &amp; Lipid profile</td>
<td>Assess mental barriers &amp; readiness to change</td>
<td>Aim is to Achieve weight loss of 5-10% of body weight over 6 months</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Maintenance of discipline</td>
</tr>
<tr>
<td>USG</td>
<td>Devise lifestyle modification strategies with patient &amp; family</td>
<td>Tackling addictions</td>
<td>Bariatric surgery</td>
<td>Orlistat</td>
<td>Prevent weight regain</td>
</tr>
<tr>
<td>If obese assess &amp; Rx obesity &amp; related co-morbidities</td>
<td>Tackling addictions</td>
<td>Smoking, Alcohol, Caffeine, Food</td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

**the low GI diet**
### Reduce androgen excess

#### Androgen suppression
- Oral contraceptive pills
- GnRH agonists
- Ketoconazole
- Glucocorticoids/Dexa

#### Anti-androgens
- Cyproterone acetate 100mg/day
- Spironolactone 100-200 mg/day
- Flutamide - 250 mg TDS for 3 mts, gradually to 200 mg, then 150 mg

#### 5 alpha Reductase inhibitors
- Finasteride

#### Insulin-lowering agents
- Treatment - controversial
  - Metformin 500 – 850 mg twice or thrice daily
  - Thiazolidinediones
  - D-Chiro-inositol
Treatment of symptoms related to androgen Excess

Hirsutism -
- Rule out idiopathic from functional
- **Cosmetic measures**
  - Waxing, shaving, laser
- **Oral contraceptive**
- **Metformin**
- **Anti-androgens**
- **5-alpha-reductase inhibitors**

Acne - Antibiotic and topical therapies
- **Tetracycline, erythromycin & minocycline**
- Used in conjunction with antiandrogen Tx
- Topical non-steroidal antiandrogen, onconterone acetate, benzoyl peroxide, 13-cis-retinoic acid (tretinoin)

Alopecia - 2% minoxidil BD with antiandrogen Tx
Prevent side effects of unopposed estrogen action

Progesterone in 2nd half of cycle - Synthetic progesterone or Dydrogesterone
Weight loss of only 5% of total body weight is associated with:

✓ Decreased insulin and LH levels
✓ Increased SHBG and Decreased Free E2
✓ Improved menstrual function
✓ Reduced hirsutism and acne
✓ Lower testosterone levels

*Kiddy DS, Hamilton FD, Bush A.* - *Clin endocrinol 1992*

Lifestyle Intervention - Diet and Exercise Important
Psychological intervention

Psychological counseling
both individually and in group

☑ behavioral problem

☑ abnormal eating patterns (21% vs 2.5%)

☑ damaged self confidence due to acne, hirsutism
   and obesity

☑ increased levels of anxiety & depression
**Diagnosis of PCOS**

- **Overweight or Obese**
  - Goal 5-10% weight loss
  - Check fasting glucose, insulin, lipids;
    If overweight or familial T2D: Perform OGTT

- **Normal weight**

**Assess symptoms, goals and future risks of patient**

- **Irregular menses**
  - Hirsutism +/- acne, consider OCPs, anti-androgens topicals/other cosmetic measures

- **Hyperinsulinaemia, acanthosis nigricans, impaired glucose tolerance or obesity** ---- consider Metformin

- **Sexually active, start OCPs**

- **Oligo/amenorrhoea, Dysfunctional uterine bleeding or menorrhagia** – start OCPs or progestins
Conclusion

- Adolescent PCOS may present with early menarche and oligomenorrhoea / irregular bleeding, or in some with late menarche / primary amenorrhoea.

- Obesity in adolescent PCOS associated with increased:
  - insulin resistance leading to functional hyperandrogenism
  - ovarian and uterine volume and PCO
  - clinical manifestation in those with a genetic or developmental predisposition.
Thank You

She is a Woman...