Polycystic ovary syndrome: The pros and cons of various diagnostic criteria and biomarkers

Ashutosh Halder
MD, DNB, DM, MRCOG I, Common. Sch. (Fetal Med), FAMS
Professor & Head
Department of Reproductive Biology
AIIMS, New Delhi
PCOS: Original Description

Stein IF and Leventhal ML.
Amenorrhea associated with bilateral polycystic ovaries.

Oral presentation at a meeting of the Central Association of Obstetricians and Gynecologists, Nov. 1-3, 1934
7 cases (5 amenorrheic & 2 irregular cycles); 5 conceived after wedge resection

1. Secondary amenorrhea/ irregular periods and sterility
2. Bilateral and symmetrically enlarged ovaries
3. Normal amounts of 17-KS and FSH in urine (exclude CAH & POF)

About 50 percent of patients, there was a varying degree of hirsutism. The breasts were smaller than normal in 50%, and uterine hypoplasia in 75%
PCOS: Diagnostic Criteria

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chronic anovulation</td>
<td>• Oligo- and/or anovulation</td>
<td>• Clinical and/or biochemical signs of hyperandrogenism</td>
</tr>
<tr>
<td>• Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies, e.g., congenital adrenal hyperplasia)</td>
<td>• Clinical and/or biochemical signs of hyperandrogenism</td>
<td>• Ovarian dysfunction (Oligo-anovulation and/or polycystic ovarian morphology)</td>
</tr>
<tr>
<td>(Both criteria needed)</td>
<td>• Polycystic ovaries (Two of three criteria needed)</td>
<td>(Both criteria needed)</td>
</tr>
</tbody>
</table>

Revised in 2016; AMH may be used in place of USG

1990 NIH consensus

2003 Rotterdam consensus

NIH: Prevalence~10%  AES: Prevalence~12%  Rot: Prevalence~15%
Definitions related to PCOS

Oligomenorrhoea or amenorrhoea
Oligomenorrhoea: menstrual cycle length >35/45 to 182 days
Amenorrhoea: no menstruation for >182 days with normal FSH & E2

Hyperandrogenism (HA): Clinical &/or Biochemical
Clinical HA:
for hirsutism assessment Ferriman-Gallwey score ≥ 9
Biochemical HA:
FAI>4.5/high T (>0.6 ng/ml)

Poly Cystic Ovaries (PCO) &/or Enlarged Ovaries (EO)
Ovaries >10 ml (one or both)
Follicles size 2-9 mm and count ≥ 12 (one or both ovaries)

FAI: total testosterone (nmol/l; 1ng/dl = 0.0347 nmol/l) divided by the SHBG (nmol/l), and then multiplying 100
Ferriman-Gallwey score (≥9)
Our study (n=153) after exclusion of secondary causes

- Total no. of cases referred as PCOS (suspected) 258
- No. of cases fulfils Rotterdam criteria 153
- No. of cases fulfils AES/AES+ criteria 124/128
- No. of cases fulfils NIH criteria 114
- No. of cases fulfils all 3 criteria 068
- No. of cases fulfils SLS criteria 097

Work-up: BMI, FGS, total testosterone, LH, FSH, AMH, Inhibin B, DHEAS, 17-OH P, cortisol, insulin (F), BS (F), prolactin, TSH, E2, P4, etc (FAI in few, chromosome in specific cases, etc)
PCOS: NIH criteria do not consider PCO/EO

• Polycystic ovarian morphology or enlarged ovary: not necessary to diagnose the syndrome (PCO/EO term coined by Stein and Leventhal)

• Need to assign a new name if continued to follow this diagnostic criteria

What is appropriate name?

oligomenorrhoea/amenorrhoea due to hyperandrogenism (HA)

Clinical HA/Hirsutism: good marker but Biochemical HA is a bad marker in our study

Missing large number of cases compared Rotterdam criteria \( n=39 \)
Cases without HA are many \( n=29 \)
AES criteria (revised in 2016)

- **Clinical Hyperandrogenism** (Ferriman-Gallwey score ≥9) or **Biochemical Hyperandrogenism** (FAI >4.5/high Testosterone >0.6 ng/ml)

- **Oligomeno/amenorrhea** (chronic anovulation) or **Polycystic Ovary** (>24 follicles on USG/8MHz probe) or **Enlarged Ovary** (each ovarian volume >12 ml/10 ml in case low resolution probe)

  or

- **AMH** (>10 ng/ml definite or >7 ng/ml likely or >5 ng/ml may be)

Missing large number of cases compared to Amsterdam criteria (n=29)
Cases without HA (n=29) going to be missed
### Summary

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Oligo/Amenn</th>
<th>FGS &gt;8</th>
<th>PCO/EO on USG</th>
<th>High Testo &gt;0.6 ng/ml</th>
<th>AMH &gt;7/5 ng/ml</th>
<th>LH/FSH &gt;2</th>
<th>High Inhibin B &gt;100 pg/ml</th>
<th>High DHEAS &gt;450 ug/dl</th>
<th>BMIMI high/low &gt;25/&lt;18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterd (n=153)</td>
<td>93.5%</td>
<td>78%</td>
<td>81.7%</td>
<td>26.5%</td>
<td>61/78%</td>
<td>24.7%</td>
<td>30.3%</td>
<td>3.6%</td>
<td>50.9% /3.9%</td>
</tr>
<tr>
<td>AES (n=124)</td>
<td>92%</td>
<td>94.3%</td>
<td>76.4%</td>
<td>32.5%</td>
<td>61/78%</td>
<td>25.4%</td>
<td>31%</td>
<td>3.5%</td>
<td>53% /4%</td>
</tr>
<tr>
<td>NIH (n=114)</td>
<td>100%</td>
<td>93.8%</td>
<td>73.9%</td>
<td>32.7%</td>
<td>60.9/79%</td>
<td>25.9%</td>
<td>31.9%</td>
<td>2.8%</td>
<td>54.4% /4.4%</td>
</tr>
<tr>
<td>SLS (n=97)</td>
<td>100%</td>
<td>65.6%</td>
<td>100%</td>
<td>24.7%</td>
<td>62.2/81%</td>
<td>29%</td>
<td>33.9%</td>
<td>3.4%</td>
<td>45.3% /4%</td>
</tr>
<tr>
<td>All 3 (n=67)</td>
<td>100%</td>
<td>94%</td>
<td>100%</td>
<td>35.4%</td>
<td>65.6/85%</td>
<td>32.8%</td>
<td>29.2%</td>
<td>3.2%</td>
<td>46.2% /4.4%</td>
</tr>
</tbody>
</table>

Similar specificity/sensitivity (after exclusion of CAH & other secondary causes)
### Summary (cont.)

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cortisol high &gt;20 ug/dl</th>
<th>Cortisol low &lt;3.5 ug/dl</th>
<th>17-OH P4 high &gt;3 ng/ml</th>
<th>Insulin high &gt;25 miu/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rotterd (n=153)</td>
<td>2.2%</td>
<td>2.2%</td>
<td>11.5%</td>
<td>7.2%</td>
</tr>
<tr>
<td>AES (n=124)</td>
<td>2.7%</td>
<td>2.7%</td>
<td>11.5%</td>
<td>7%</td>
</tr>
<tr>
<td>NIH (n=114)</td>
<td>2%</td>
<td>2%</td>
<td>11.2%</td>
<td>6.7%</td>
</tr>
<tr>
<td>SLS (n=97)</td>
<td>1.2%</td>
<td>2.3%</td>
<td>14.3%</td>
<td>5.7%</td>
</tr>
<tr>
<td>All 3 (n=67)</td>
<td>1.7%</td>
<td>3.4%</td>
<td>15.5%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

*Similar specificity/sensitivity (after exclusion of CAH & other secondary causes)*
## Secondary cause of PCOS (suspected)

<table>
<thead>
<tr>
<th>Am/olig</th>
<th>PCO/EO</th>
<th>FG S &gt;8</th>
<th>T</th>
<th>17-OHP</th>
<th>Corti</th>
<th>DHE-AS</th>
<th>AMH</th>
<th>FSH</th>
<th>LH</th>
<th>E2/P4</th>
<th>PCO criter</th>
<th>Prov Diag</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pri Am</td>
<td>Normal</td>
<td>21</td>
<td>2.8</td>
<td>&gt;20</td>
<td>5.5</td>
<td>1024</td>
<td>3.3</td>
<td>3.2</td>
<td>0.9</td>
<td>49/ 0.5</td>
<td>NIH, AES, RDC</td>
<td>CAH comp.</td>
</tr>
<tr>
<td>Pri Am</td>
<td>Not visible</td>
<td>30</td>
<td>2.3</td>
<td>0.4</td>
<td>15</td>
<td>164</td>
<td>0.3</td>
<td>35</td>
<td>13</td>
<td>18/xx</td>
<td>NIH, AES, RDC</td>
<td>XY DSD 5ARD</td>
</tr>
<tr>
<td>olig</td>
<td>yes</td>
<td>9</td>
<td>1.2</td>
<td>9.1</td>
<td>2.1</td>
<td>164</td>
<td>0.16</td>
<td>4.3</td>
<td>9.8</td>
<td>114/0.2</td>
<td>all</td>
<td>CAH non-c</td>
</tr>
<tr>
<td>olig</td>
<td>yes</td>
<td>8</td>
<td>0.4</td>
<td>0.2</td>
<td>5</td>
<td>123</td>
<td>11.2</td>
<td>5.5</td>
<td>5.6</td>
<td>0.2/66</td>
<td>RDC SLC</td>
<td>CAH ?17 OH D</td>
</tr>
<tr>
<td>olig</td>
<td>Normal</td>
<td>10</td>
<td>0.3</td>
<td>1.1</td>
<td>8</td>
<td>170</td>
<td>0.19</td>
<td>21</td>
<td>5.5</td>
<td>12/0.2</td>
<td>NIH, AES, RDC</td>
<td>Ov Ins</td>
</tr>
<tr>
<td>olig</td>
<td>yes</td>
<td>4</td>
<td>0.8</td>
<td>8.9</td>
<td>23</td>
<td>788</td>
<td>11.8</td>
<td>3.3</td>
<td>2.2</td>
<td>30/0.7</td>
<td>all</td>
<td>Adren hyper</td>
</tr>
</tbody>
</table>

None criteria seems differentiate primary to secondary PCOS, although SLC relatively better in excluding most
18 yrs; BMI 25.8 (n<25)
Primary amenorrhea
FG score 14 & T 1.48 (n<0.6)
USG msf & enlarged ovary
(17, 18 ml),
AMH >25 ng/ml
LH/FSH ratio 2.1 (n<2)
Cortisol 5.5 ug/dl (n>3.7)
17-OH P 2.4 ng/ml (n<3)
Insulin (F) 15 uiu/ml (n<20)
DHEAS 144 ug/dl (n<550)
E2 80 pg/ml (n>20 efp)
P 0.3 ng/ml
PRL 6.5 ng/ml (n<28)
FSH 2.06 miu/ml (n 1-8)

PCOS as per all criteria (NIH/AES/Rot/SLC)

PCOS
Age: 16+ yrs

**Pr Amenorrhea**

FGS 21; T 2.8 (<0.6 ng/ml)

**USG: normal**

AMH 3.28 ng/ml

DHEAS 1123 (<550 ug/dl)

17-OHP >200 ng/ml

Cortisol 5.58 (3.5-20) compensated

LH/FSH <1 (FSH 3.2)

PRL 30 ng/ml; E2 78.2 pg/dl

Insulin 7.4 uiu/ml

Ch. 46,XX; BP 140/90

PCOS as per NIH/AES/Rot, but **X SLS criteria**

**CAH (compensated)**
20 years; reared as girl
Primary amenorrhoea
FGS 30, T 2.3
USG-no ov/ut
Excess hair growth, change in voice, body habitus & behavi, clitororomegally, etc
AMH 0.3; LH-13, FSH-35
17-OHP-0.4, cortisol 15,
DHEAS-164,
Inhibin B-3.8, E2-18
Ch 46,XY; SRY +ve, AZF +ve
PCOS:NIH,AES,RDC; X SLC
46,XY DSD (?5ARD)
Observation

- Oligomenorrhoea/amenorrhea: observed in >90% (10-15% cases amenorrhoea; maximum with NIH & minimum with SLC)

- Clinical HA: Ferriman-Gallwey score of >8 observed in 65-90% cases (minimum in SLC & maximum in AES/NIH)

- Features like hair fall, acne, voice change, etc are frequent but less reliable (need guideline to include in work-up)

- Biochemical HA: FAI >4.5 in very few cases; high total testosterone in only 25% (SLC) - 35% (AES) cases

- Adrenal dysfunction (mild/atypical CAH or hypercorticism) is common (10-20% cases) but difficult to exclude; 17-hydroxylase deficiency exist

- AMH >7 in 60%/>5 in 80% (not conclusive, 40% <7/20% <5)

- DHEAS (<4%) or LH/FSH ratio (~25%) are poor markers

- Insulin resistance/hyperinsulinemia in only 5-7% cases

- BMI>25 in 50% (45% in SLC/55% in AES) & <18 in 4% cases
Conclusion

• We should follow Rotterdam criteria which at present detects most cases of PCOS (if facility to exclude secondary causes exist) as this is most sensitive and as specific as NIH/AES criteria in north Indian PCOS cases. Secondary causes are adrenal dysfunction (hypo/ hyper), ovarian insufficiency, gonadal dysgenesis/DSD, etc (USG, LH, FSH, AMH, T, 17-OH P, cortisol, DHEAS, prolactin, TSH, E2/P4, chromosome, etc).

• Otherwise we should follow SLC criteria as it has ability to exclude most secondary causes (↑specific but ↓sensitive).

• AMH value of 7 (>60%) or >5 (80%) is better biomarker than T, LH/FSH, DHEAS, 17-OH P & Inhibin B (4-25%).

About 9/6% suspected PCOS cases (not fitting any criteria) had >5/7 AMH
Thank you