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

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PCOS: Original Description

Stein IF and Leventhal ML. Amenorrhea associated with bilateral polycystic ovaries. Am J Obstet Gynecol 1935; 29:181-191.

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

Stein

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%

Leventhal

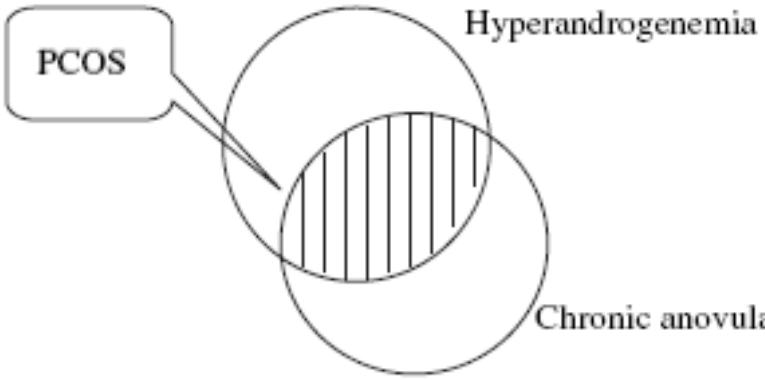
PCOS: Diagnostic Criteria

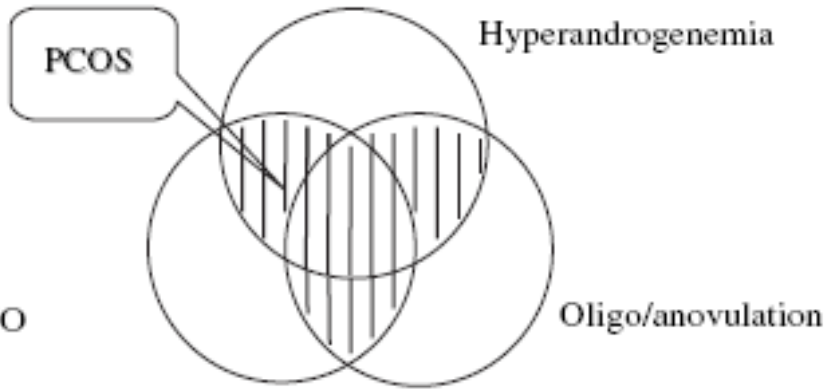
revised in 2016; AMH may be used in place of USG

NIH 1990	Rotterdam 2003	AE-PCOS Society 2006
• Chronic anovulation • Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other etiologies, e.g., congenital adrenal hyperplasia) *(Both criteria needed)*	• Oligo- and/or anovulation • Clinical and/or biochemical signs of hyperandrogenism • Polycystic ovaries *(Two of three criteria needed)*	• Clinical and/or biochemical signs of hyperandrogenism • Ovarian dysfunction (Oligo-anovulation and/or polycystic ovarian morphology) *(Both criteria needed)*

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:

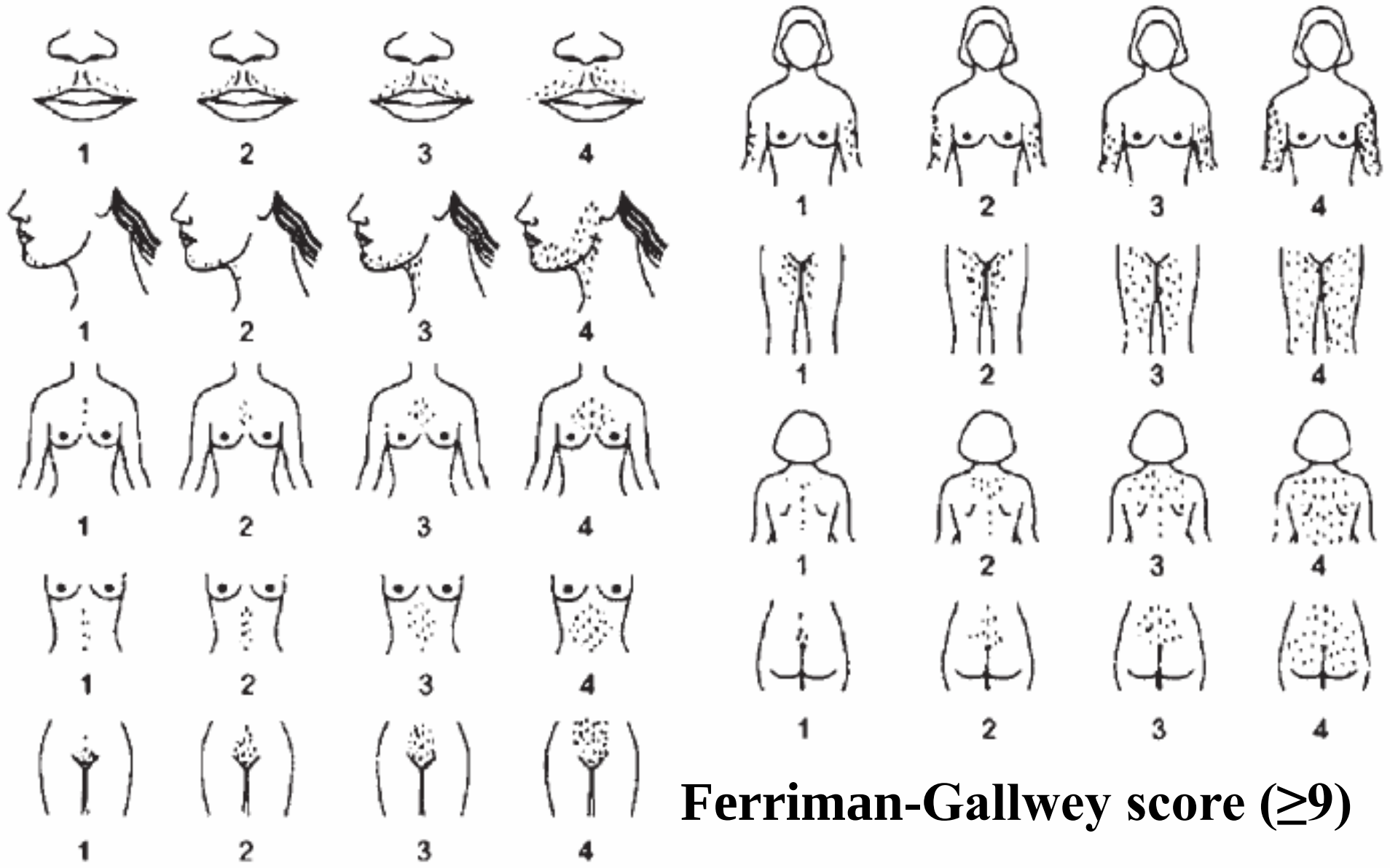
FAI>4.5/high T (>0.6 ng/ml)

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

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

Similar specificity/sensitivity (after exclusion of CAH & other secondary causes)

Summary (cont.)

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

Similar specificity/sensitivity (after exclusion of CAH & other secondary causes)

Secondary cause of PCOS (suspected)

Am/ olig	PCO/ EO	FG S >8	T	17-OHP	Corti	DHE-AS	AMH	FSH	LH	E2/P4	PCO criter	Prov Diag
Pri Am	Nor-mal	**21**	**2.8**	**>20**	5.5	**1024**	3.3	3.2	0.9	49/ 0.5	NIH, AES, RDC	**CAH comp.**
Pri Am	Not visible	**30**	**2.3**	0.4	15	164	**0.3**	**35**	13	**18**/xx	NIH, AES, RDC	**XY DSD 5ARD**
olig	**yes**	**9**	**1.2**	**9.1**	**2.1**	164	**0.16**	4.3	9.8	114/0.2	**all**	**CAH non-c**
olig	**yes**	8	0.4	**0.2**	**5**	**123**	11.2	5.5	5.6	**0.2/66**	RDC **SLC**	**CAH ?17 OH D**
olig	Nor-mal	**10**	0.3	1.1	8	170	**0.19**	**21**	5.5	**12**/0.2	NIH, AES, RDC	**Ov Ins**
olig	**yes**	4	**0.8**	**8.9**	**23**	**788**	11.8	3.3	2.2	30/0.7	**all**	**Adren hyper**

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**)

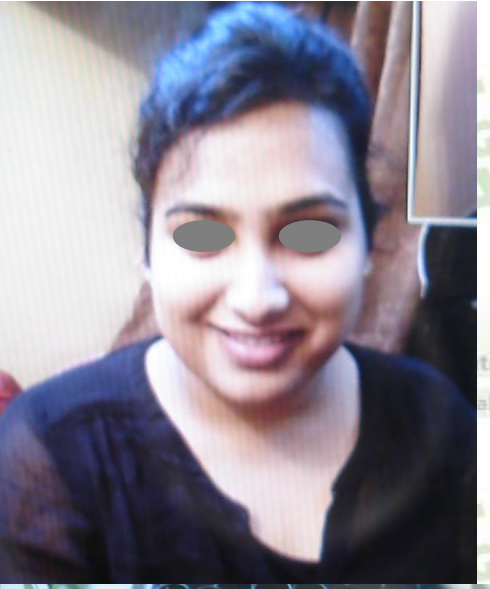
PRL **30** ng/ml; E2 **78.2** pg/dl

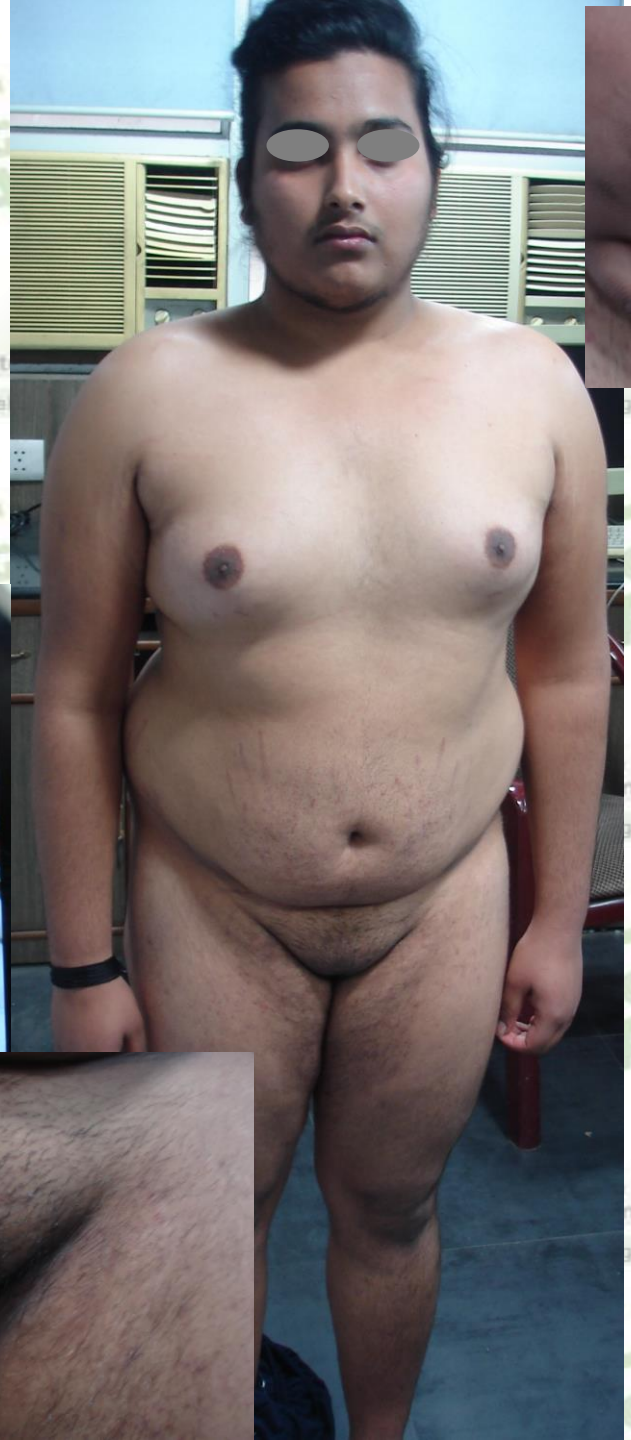
Insulin **7.4** uiu/ml

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, clitoromegally, 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 insuffiency, 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

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