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PCOS IN ADOLESCENTS

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PCOS IN TEENS AND ADOLESCENTS

- Diagnosing PCOS
- Caveats for diagnosing PCOS in adolescents:
  - Androgens
  - Hirsutism
  - Menstrual Cycles
  - PCOM ovaries
- Predictors of PCOS
- Recommendations

DIAGNOSING PCOS IN ADOLESCENCE

- There are no established criteria for the diagnosis of PCOS in adolescents
- The diagnosis of PCOS has life-long implications and the features of PCOS may be less well established in adolescents
- Thus, the diagnosis of PCOS in adolescents should be made with great caution
- If the diagnosis is unclear then the most prudent course may be:
  - Expectant management with regular, but not overzealous, follow-up
  - Reassurance and patient (and family) education
  - Lifestyle modification
  - Treatment of individual symptoms/complaints, if needed/desired

COMPARING THE PHENOTYPES OF PCOS BY NIH 1990, ROTTERDAM 2003, AND AE-PCOS 2006

	Phenotypes			
Characteristics	***A***	***B***	***C***	***D***
Hirsutism/HA	√	√	√	
Ovulatory Dysfunction	√	√		√
Polycystic ovaries	√		√	√
NIH 1990*	√	√		
Rotterdam 2003*	√	√	√	√
AE-PCOS 2006*	√	√	√	

*Always exclude related/similar/mimicking disorders (17-HP, TSH, Prl)

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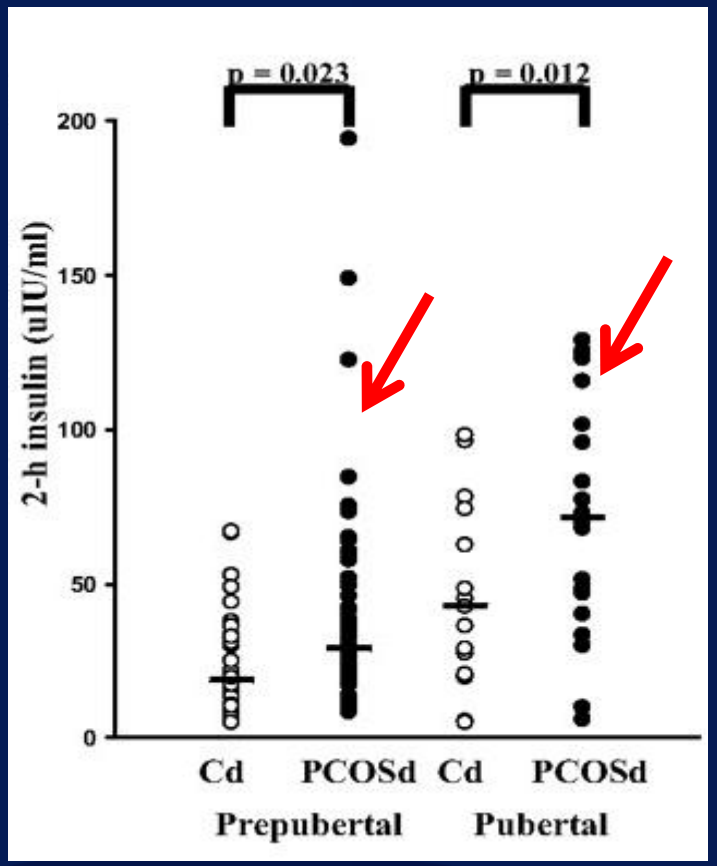
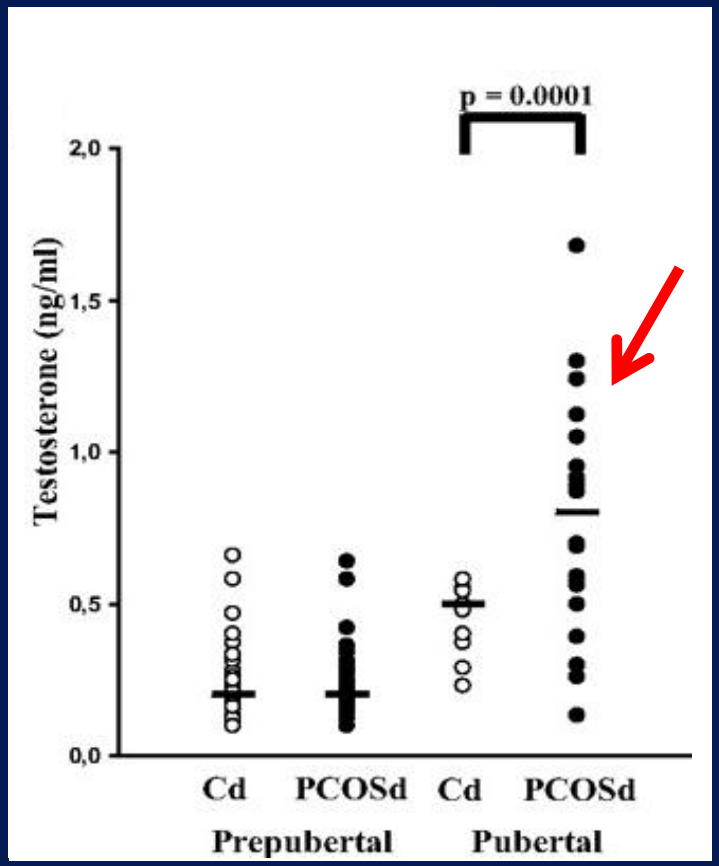
LABORATORY EVALUATION OF THE HIRSUTE OR POTENTIALLY HYPERANDROGENIC PATIENT

- **TSH & PRL**
  - In oligo-ovulatory patients, to R/O other causes of ovulatory dysfunction
- **17-HP**
  - To R/O 21-OH deficient NCAH
- **d. 22-24 P4 level**
  - In hirsute eumenorrheic women, 40% of which are anovulatory
- **Total & free T, and DHS**
  - Most importantly, in evaluating non-hirsute or minimally hirsute patients to R/O Androgen Excess
  - **MUST USE HIGH-QUALITY WELL-REFERENCED ASSAY**

2-H INSULIN AND TESTOSTERONE IN DAUGHTERS OF CONTROL (Cd) AND PCOS WOMEN (PCOSd) DURING THE PREPUBERTAL & PUBERTAL PERIODS





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Sir-Petermann et al. J Clin Endocrinol Metab 2007;92:4637-4642

FREE T IN ADOLESCENCE: SIMILAR TO ADULTHOOD

Reference ranges for free testosterone by equilibrium dialysis

Age (years)	Females (pg/mL)
5–9	0.2–5.0
10–13	0.1–7.4
14–17	0.5–3.9
18–29	0.2–6.3
30–39	0.2–6.3
40–49	0.2–6.2
50–59	0.2–6.6
60–69	0.2–6.5
70–79	0.1–3.9
80–89	0.4–3.5

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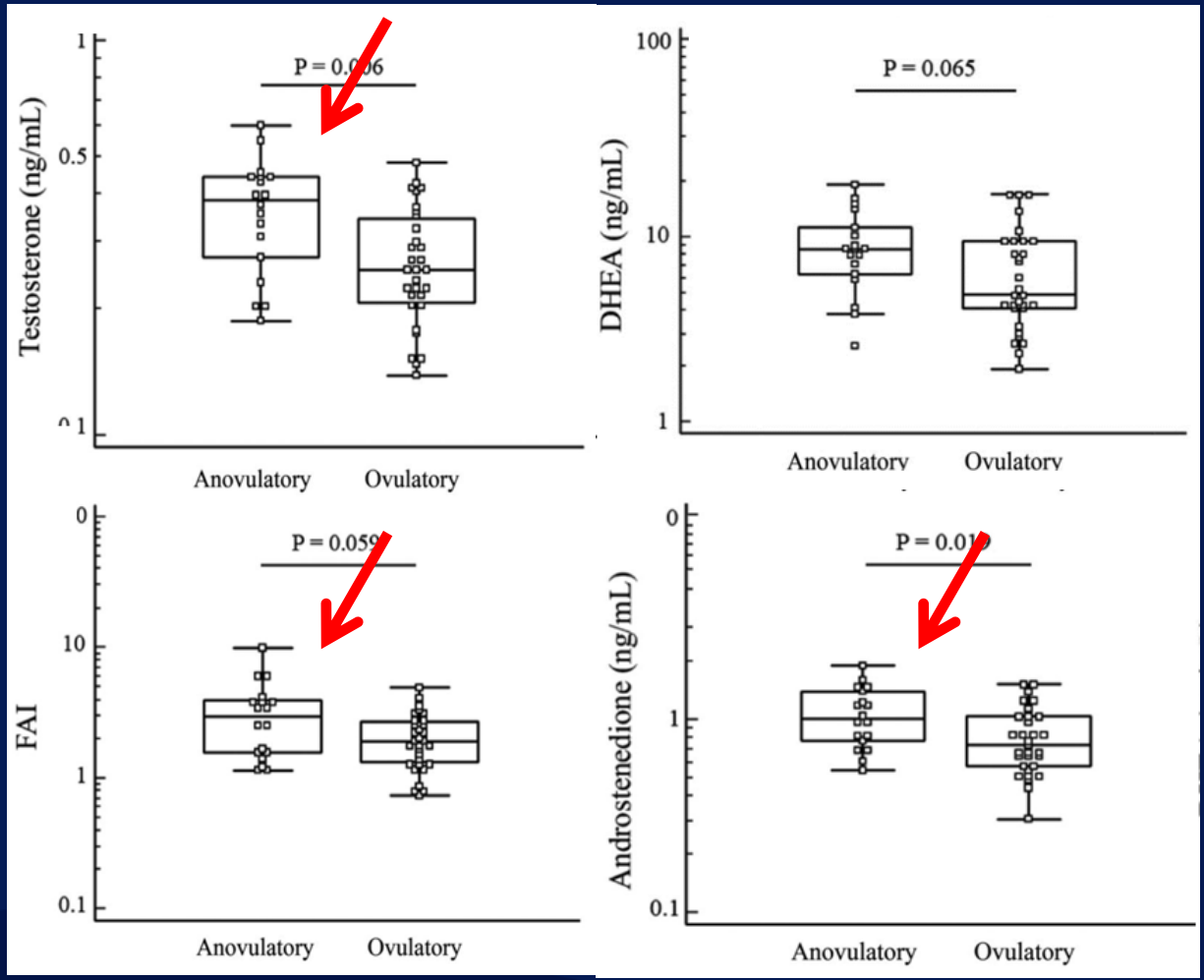
Salameh et al. Steroids 75:169-175, 2010

ASSOCIATION OF ANDROGEN LEVELS WITH ANOVULATION IN ADOLESCENT GIRLS AND YOUNG WOMEN



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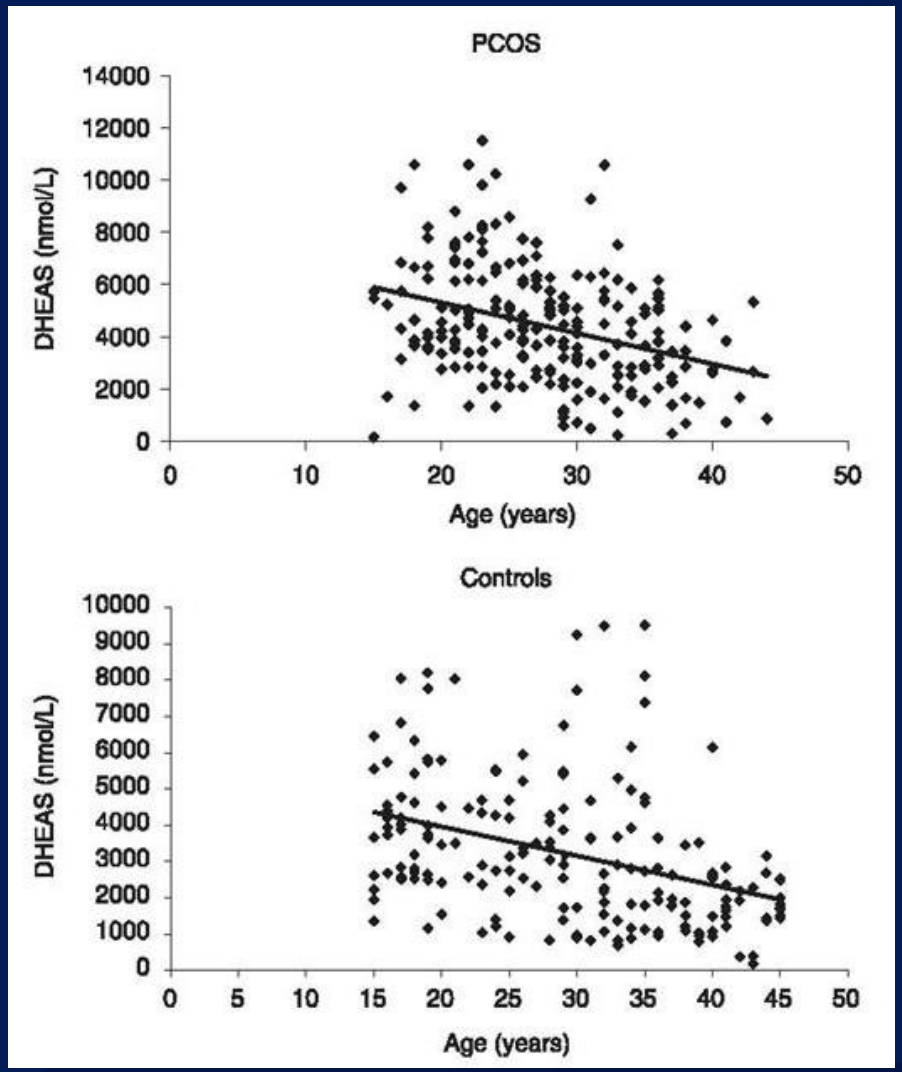
Fanelli et al. J Clin Endocrinol Metab. 2013;98:3058-67

DHEAS LEVELS IN PCOS AND CONTROLS BY AGE



- DHEAS levels are higher in adolescents, whether with or without PCOS
- Defining AA excess by DHEAS levels *without* taking into account age will lead to over-diagnosis of AA excess among adolescents

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Kumar et al. Clin Endocrinol 62:644, 2005

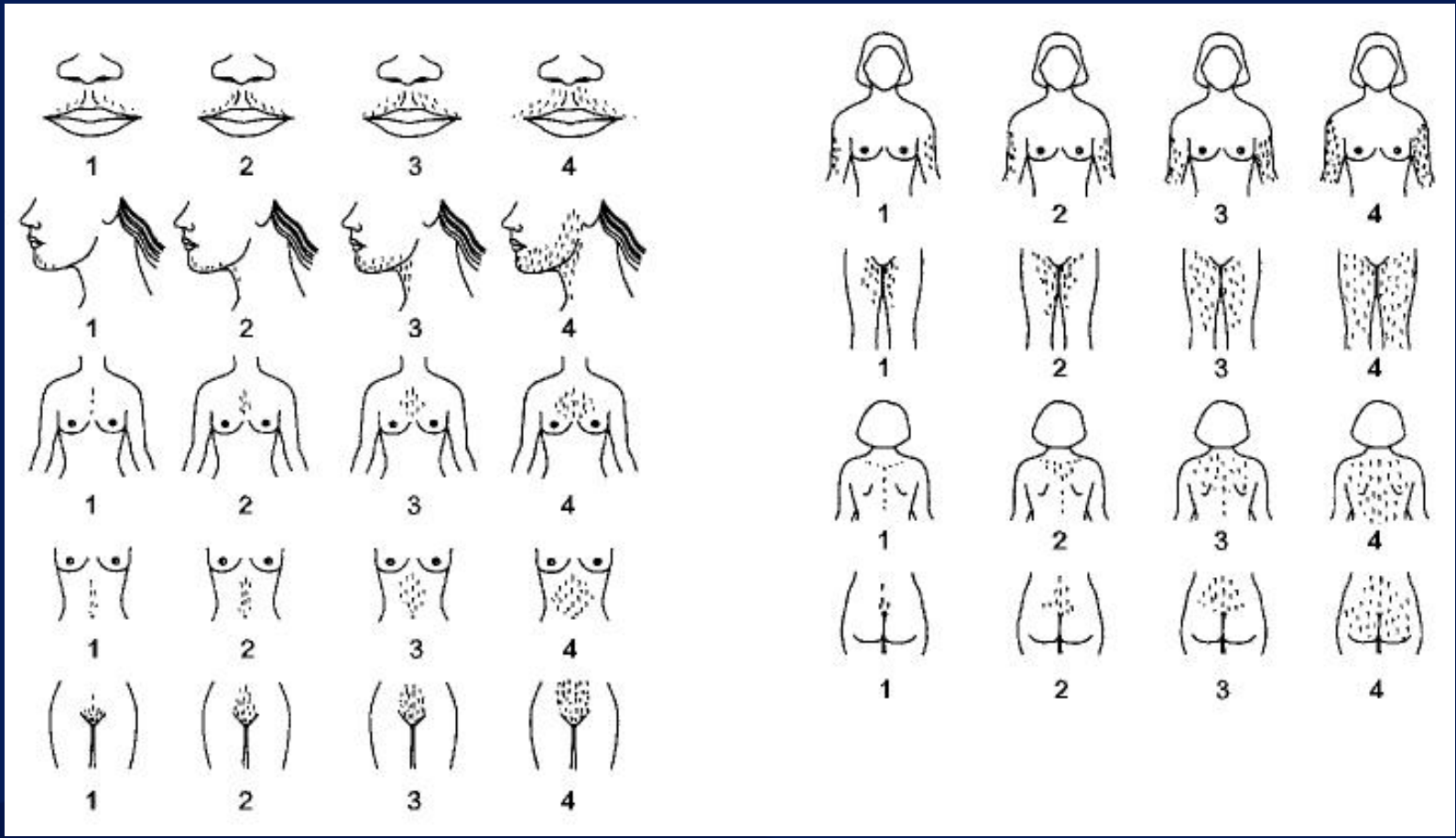
CAVEATS FOR DIAGNOSING PCOS IN ADOLESCENTS: ANDROGENS

- **Androgens levels are most useful to establish hyperandrogenism in patients who have minimal or no clinical evidence of AE (e.g. hirsutism)**
  - DHEAS will be higher in adolescence than in any other period
  - TT and FT peak early in adolescence, with adult levels by ~15 y.o. or earlier, and remain relatively stable through adulthood
  - In childhood/peripuberty, girls 'at risk' will have higher DHEAS and INS, but normal TT levels
- **We can use adult androgen levels for detecting HA and predicting PCOS in adolescents, recognizing that DHEAS will be normally higher**

DIAGNOSING PCOS: EVALUATING FOR CLINICAL HYPERANDROGENISM

- Hirsutism is excess *terminal* hair growth in a *male-like* pattern
  - Distinguish from hypertrichosis (excess vellus hairs)
- Usually 9 body areas are assessed visually (modified Ferriman-Gallwey score)
- No correlation between mFG score and androgen levels (but positive with hyperinsulinemia / BMI)
- ~50% of adult women with mFG scores of 3-5 seen in the clinical setting had PCOS/AE
- Acne may also predict AE, regardless of age

EVALUATING FOR CLINICAL HYPERANDROGENISM: THE MODIFIED F-G (mFG) SCORE



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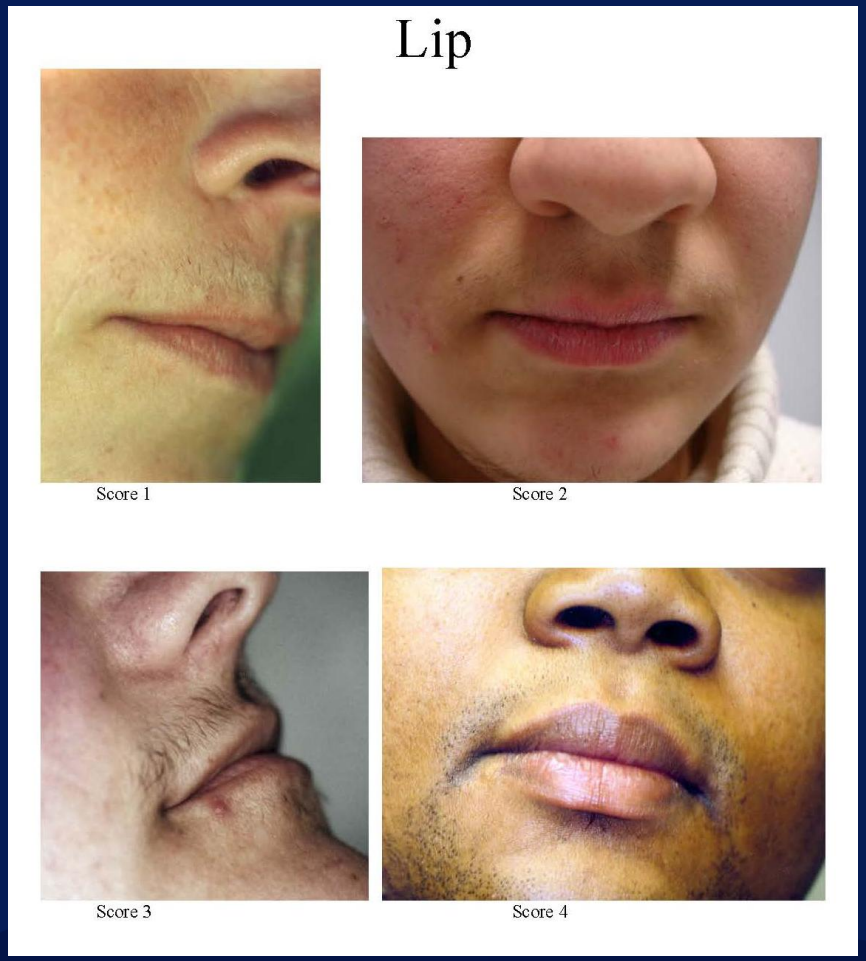
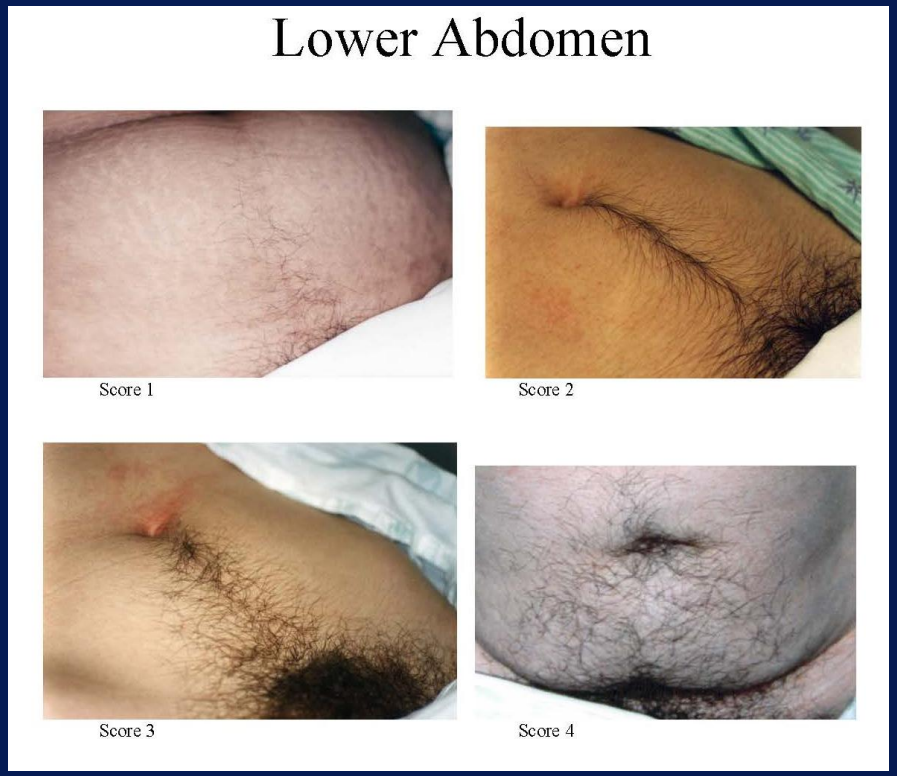
Yildiz et al, Hum Reprod Update 2010;16:51–64

EVALUATING FOR CLINICAL HYPERANDROGENISM: THE MODIFIED F-G (mFG) SCORE





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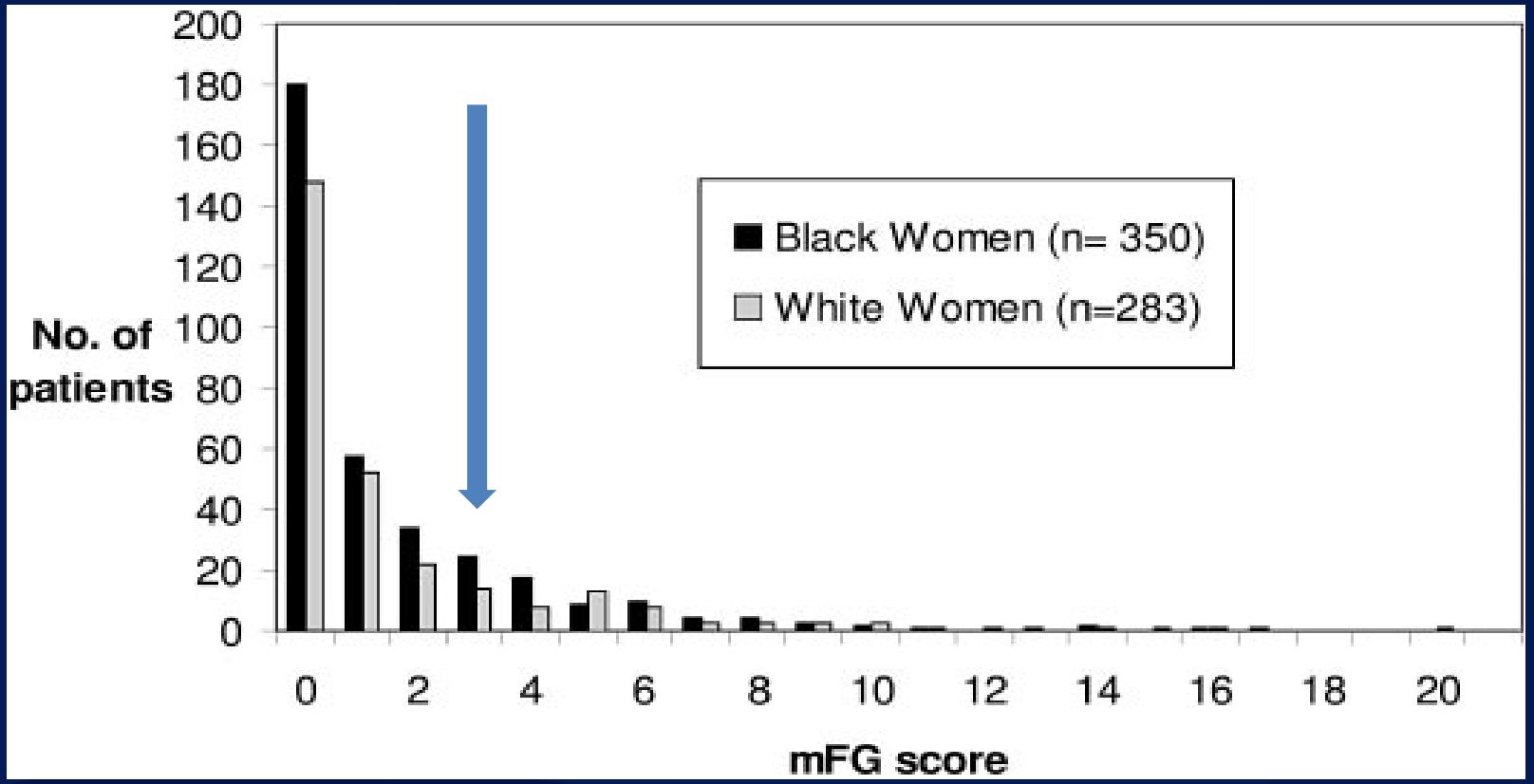
Yildiz et al, Hum Reprod Update 2010;16:51–64

DISTRIBUTION OF mFG SCORES, ASSESSING TERMINAL BODY AND FACIAL HAIR GROWTH, IN 350 BLACK AND 283 WHITE UNSELECTED WOMEN



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DeUgarte et al, J Clin Endocrinol Metab 91:1345–1350, 2006

PREDICTORS OF HIRSUTISM IN 749 ADULT PATIENTS WITH PCOS

TABLE 2

Univariate correlation coefficients for each independent variable with mFG score.

Variable	Mean	SD	n	Spearman correlation	Spearman *P* value
Total testosterone, ng/dL	91.2	61.2	748	−0.020	.5906
Free testosterone, ng/dL	0.9	0.6	746	−0.005	.8907
DHEAS, ng/mL	2331.5	1290.3	748	−0.039	.2849
Fasting insulin, mIU/mL	26.9	25.3	383	0.175	.0006
Fasting glucose, mg/dL	91.1	22.3	399	−0.039	.4372
HOMA-IR	114.7	143.8	380	0.152	.003
SHBG, nmol/L	180.3	69.7	746	−0.043	.246
17-Hydroxyprogesterone, ng/mL	1.4	1.1	736	0.093	.0118
Age, yrs	27.5	7.4	749	0.017	.6428
Body mass index, kg/m^2	33.6	9.3	749	0.121	.0009

Note: HOMA-IR = homeostatic model assessment for insulin resistance; mFG = modified Ferriman-Gallwey.

Landay. Determinants of hirsutism in PCOS. Fertil Steril 2009.

p<0.005 after Bonferroni adjustment for multiple comparisons

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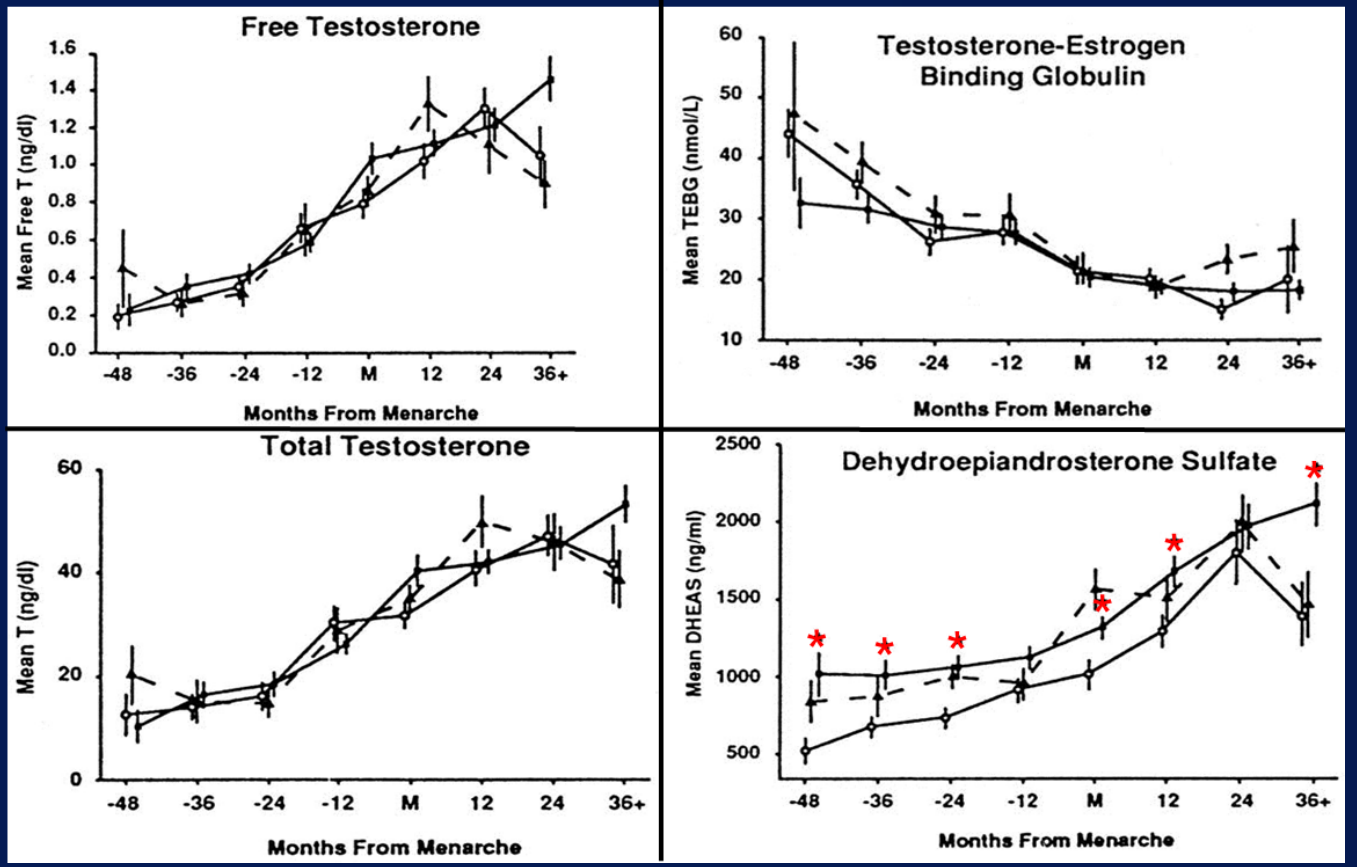
Landay et al, Fertil Steril 2009;92:643–7

PREDICTORS OF SEVERITY OF ACNE VULGARIS IN YOUNG ADOLESCENT GIRLS: RESULTS OF A 5-YEAR LONGITUDINAL STUDY

Mild acne
Moderate acne
Severe acne



- *DHEAS levels were significantly higher in girls who subsequently had severe acne, p<0.03-0.0009
- No other differences in hormones studied

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Lucky et al. J Pediatr. 1997; 130:30-9

CAVEATS FOR DIAGNOSING PCOS IN ADOLESCENTS: HIRSUTISM

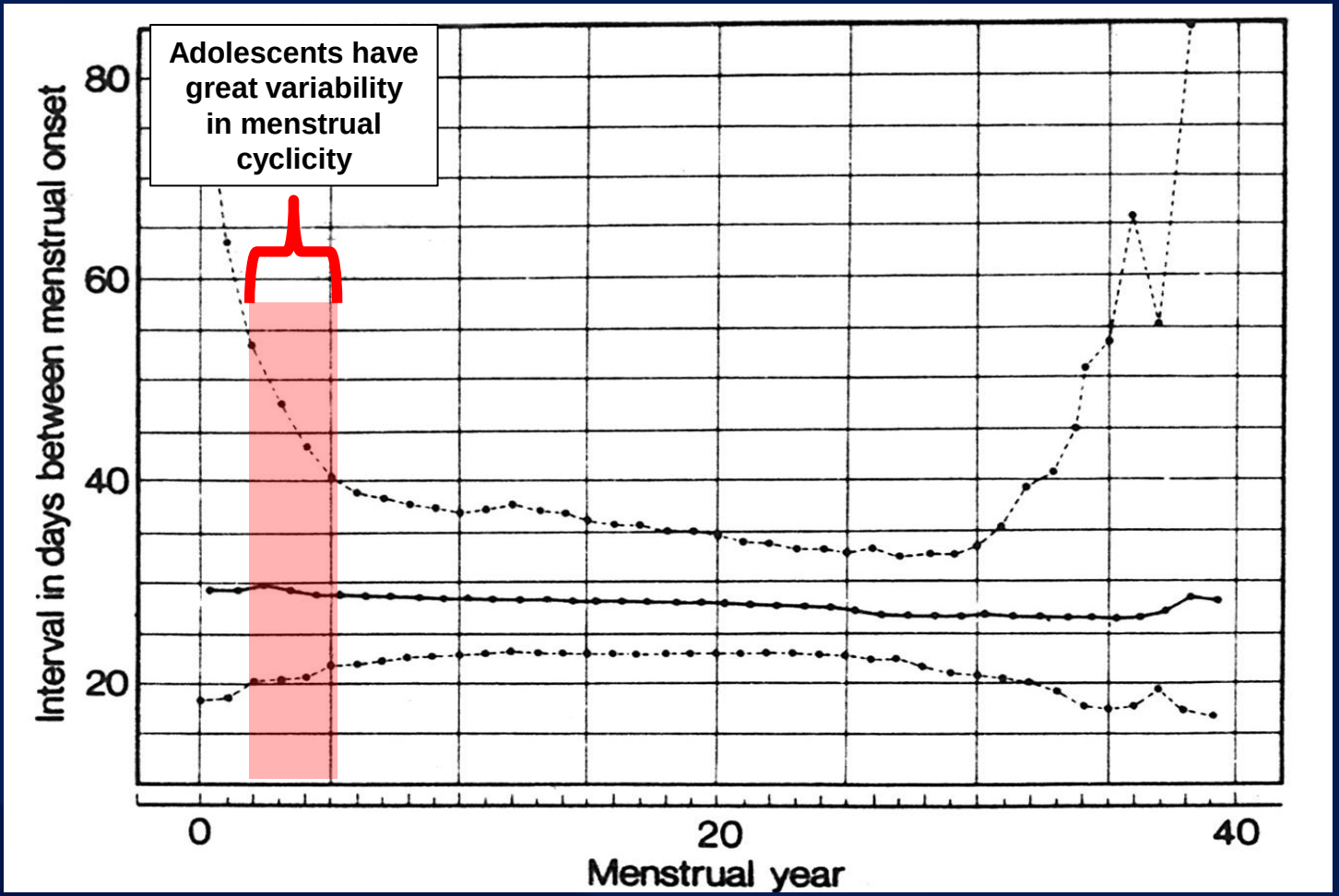
- Androgen-related terminal hair growth a male-like pattern in AE is progressive… so…
- Adolescents with significant HA may not (yet) have significant signs of hirsutism
- Patient's self-assessment is important
- However….
  - Need to distinguish hypertrichosis from hirsutism
  - Need to avoid creating unnecessary anxiety
- In adolescents high quality assays for TT/FT may be a more useful marker of hyperandrogenism
- Acne may indicate HA, regardless of age & severity

DIAGNOSING PCOS: DETECTING OVULATORY DYSFUNCTION

- Ovulatory dysfunction is usually reflected in clinically evident menstrual dysfunction
  - Oligo/amenorrhea (<10 cycles/yr, or cycles >34 d. intervals), or
  - Polymenorrhea (cycles <26 d. intervals)
- Severity of menstrual dysfunction predicts degree of IR, but not HA
- ~40% of adult women with hirsutism who claim to be 'eumenorrheic' have anovulation
  - Check d. 22-24 P4 level in 'hirsute women with 'normal cycles'

MEDIAN MENSTRUAL CYCLE LENGTHS THROUGHOUT THE REPRODUCTIVE LIFE OF WOMEN FROM MENARCHE (YEAR 0), TO MENOPAUSE (YEAR 40)

90% of all cycles fall within the upper and lower broken lines



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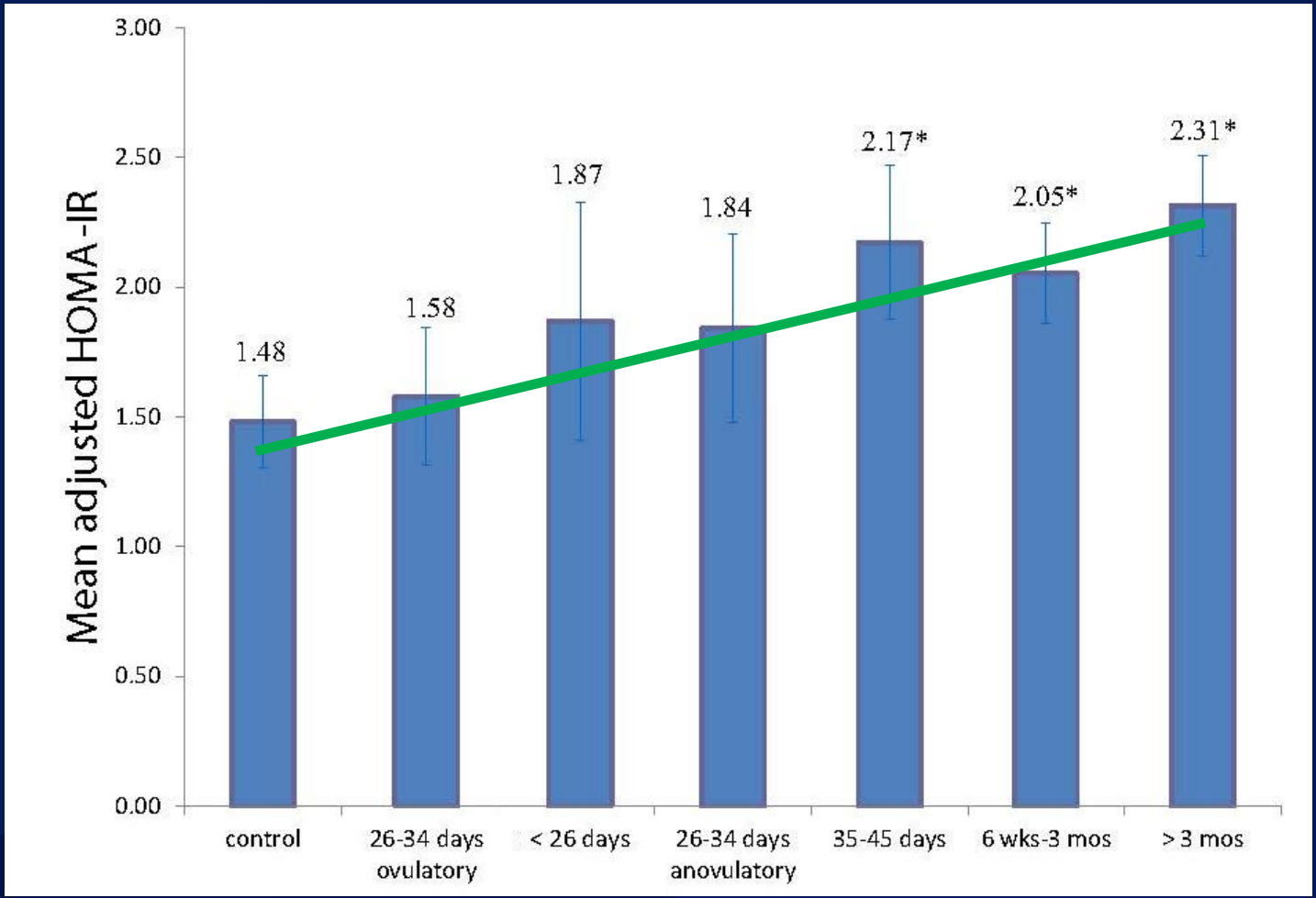
Treloar et al. Int J Fertil 12:77, 1967

SEVERITY OF MENSTRUAL DYSFUNCTION PREDICTS DEGREE OF IR



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Modified from Brower et al, J Clin Endocrinol Metab 98: E1967–E1971, 2013

PREDICTORS AT AGE 15 YEARS FOR OLIGO-AMENORRHEA AT AGE 18 YEARS

- **Adolescents were followed between ages 15 and 18 y.o.**
- **The risk of developing oligomenorrhea at 18 y.o. was:**
  - **2%** (2/128) for adolescents with regular menstrual cycles at 15 y.o.
  - **12%** (17/148) for girls with irregular menstrual cycles* at 15 y.o.
  - **51%** (34/67) for girls with oligomenorrhea* at 15 y.o.

Irregular menstrual cycle = *average cycle length 22-41 d., and 2 or more cycles <22 or >41 days in length during past year*

***Oligomenorrhea** = average length of the cycle of 42-180 d.

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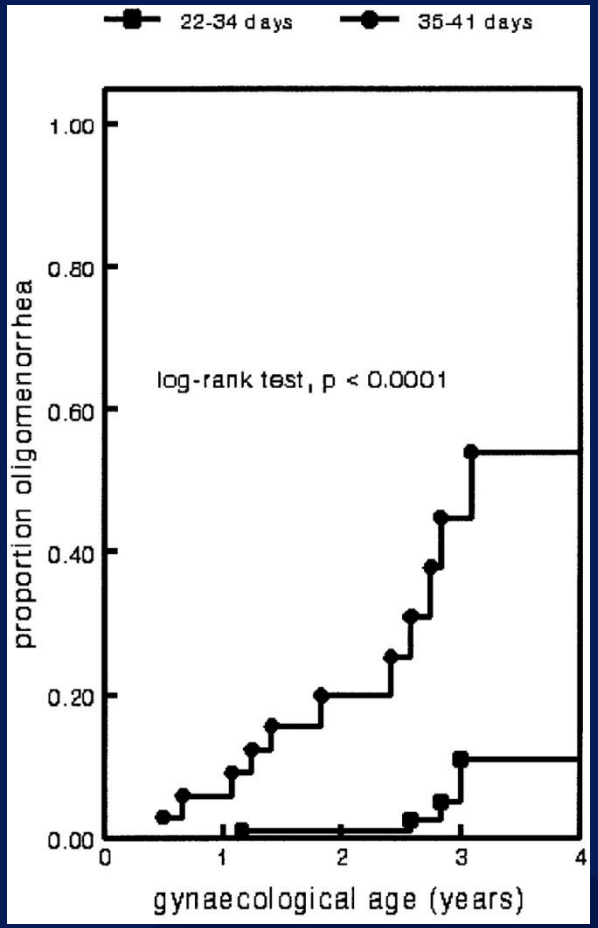
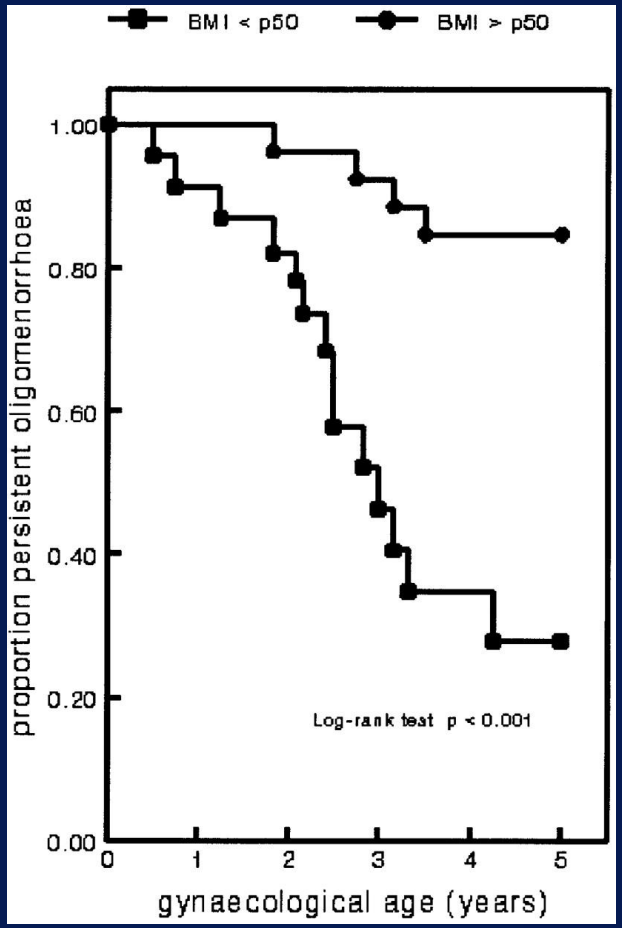
van Hooff M et al. Hum. Reprod. 2004;19:383-392

PREDICTORS AT AGE 15 YEARS FOR OLIGO-AMENORRHEA AT AGE 18 YEARS



The risk of developing persistent OLIGO in girls with irregular menstrual cycles is greater if their initial average menstrual cycle length is 35-41 days



The risk of persistent OLIGO in girls is greater if their initial BMI is above the median BMI (p50 = 19.6 kg/m² in this study)

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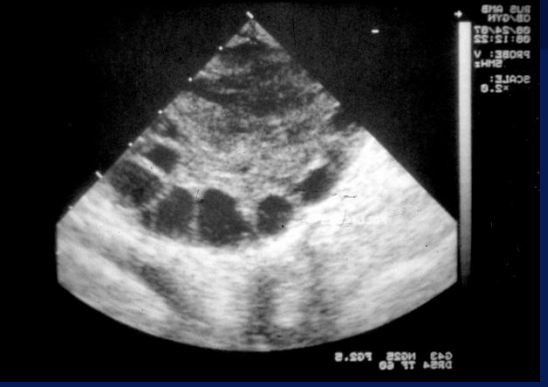
van Hooff M et al. Hum. Reprod. 2004;19:383-392

CAVEATS FOR DIAGNOSING PCOS IN ADOLESCENTS: OVULATORY DYSFUNCTION

- A careful history of vaginal bleeding must be taken
  - Age of adrenarche, telarche, and menarche
  - No. vaginal bleeds per year
  - Days between bleeds
  - Predictability of bleeds
  - Presence of Premenstrual Molimina Sx
- Normally cycles may be irregular for up to 2 years post-menarche, however…
- Oligomenorrhea (≥35 d. in length) is the best predictor of continued oligo-ovulation
- Adolescents with PCOS may present with 1^{ary} amenorrhea (never having had a cycle)



SONOGRAPHIC CRITERIA FOR PCOM

- Presence of 12 or more follicles (should this # be higher?) in each ovary measuring 2-9 mm in diameter, and/or
- Increased ovarian volume (> 10 ml)
- Only one ovary fitting this definition is sufficient to define PCOM
- Does not apply to women taking OCPs
- If evidence of a dominant follicle (> 10 mm) or a corpus luteum, scan should be repeated next cycle

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The Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Fertil Steril 81:19-25, 2004; & Hum Reprod 19:41-7, 2004

DO PATIENTS WITH POLYCYSTIC OVARIES AND IRREGULAR OVULATION HAVE PCOS?

- 20-30% of patients with eating disorders have PCOM & irregular ovulation *(Jahanfar et al, 1995; Morgan et al, 2002)*
- 30-50% of patients with hyperprolactinemia, hypothalamic amenorrhea, or 21-OH deficient NCAH have PCOM *(Ardaens et al, 1991; Azziz et al, 1994)*
- NCAH & CAH patients have a similar prevalence of PCOM as PCOS *(Dewailly et al, 1986; Azziz et al, 1994; Hague et al, 1990; Pignatelli et al, 2004)*
- Adolescents develop transient PCOM *(Giorlandino et al, 1989; Rosenfield et al, 2000)*

RELATIONSHIP OF PCOM WITH MENSTRUAL CYCLE PATTERNS IN ADOLESCENTS

- 58 adolescents with regular menstrual cycles, 50 with irregular menstrual cycles, and 29 with oligomenorrhea
- PCOM was present in:
  - 9% of the girls with regular menstrual cycles
  - 28% of those with irregular menstrual cycles
  - 45% of oligomenorrheic girls
- LH and androgens were ↑, but INS and G:I ratio were similar, in girls w/ PCOM vs. w/o PCOM
- OLIGO girls with PCOM had:
  - The highest androgen and LH levels
  - Similar INS and G:I as girls with regular menstrual cycles and normal ovaries

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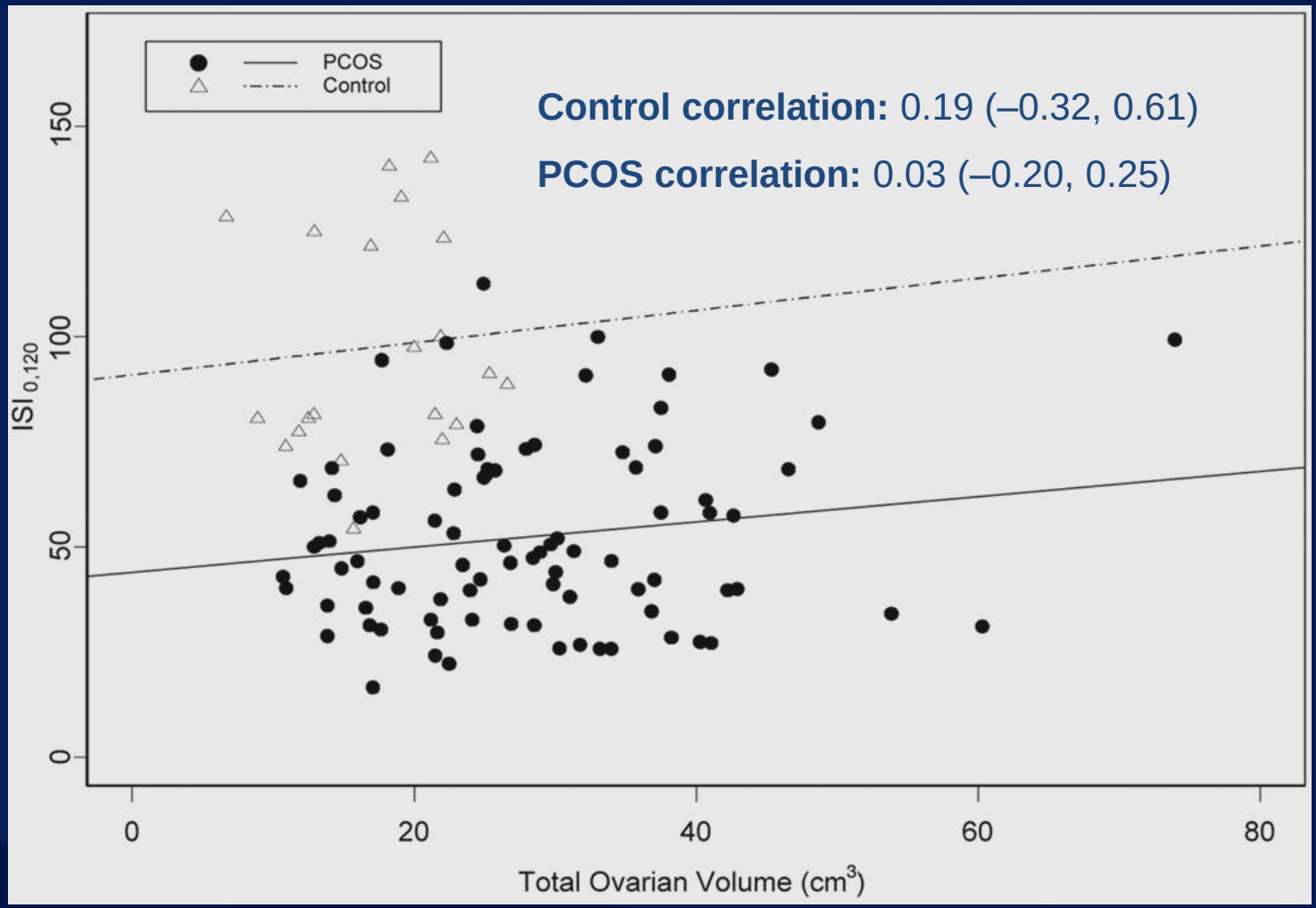
Van Hooff et al, Fertil Steril. 2000;74:49-58

POLYCYSTIC OVARIES DO NOT PREDICT METABOLIC OR REPRODUCTIVE PHENOTYPE



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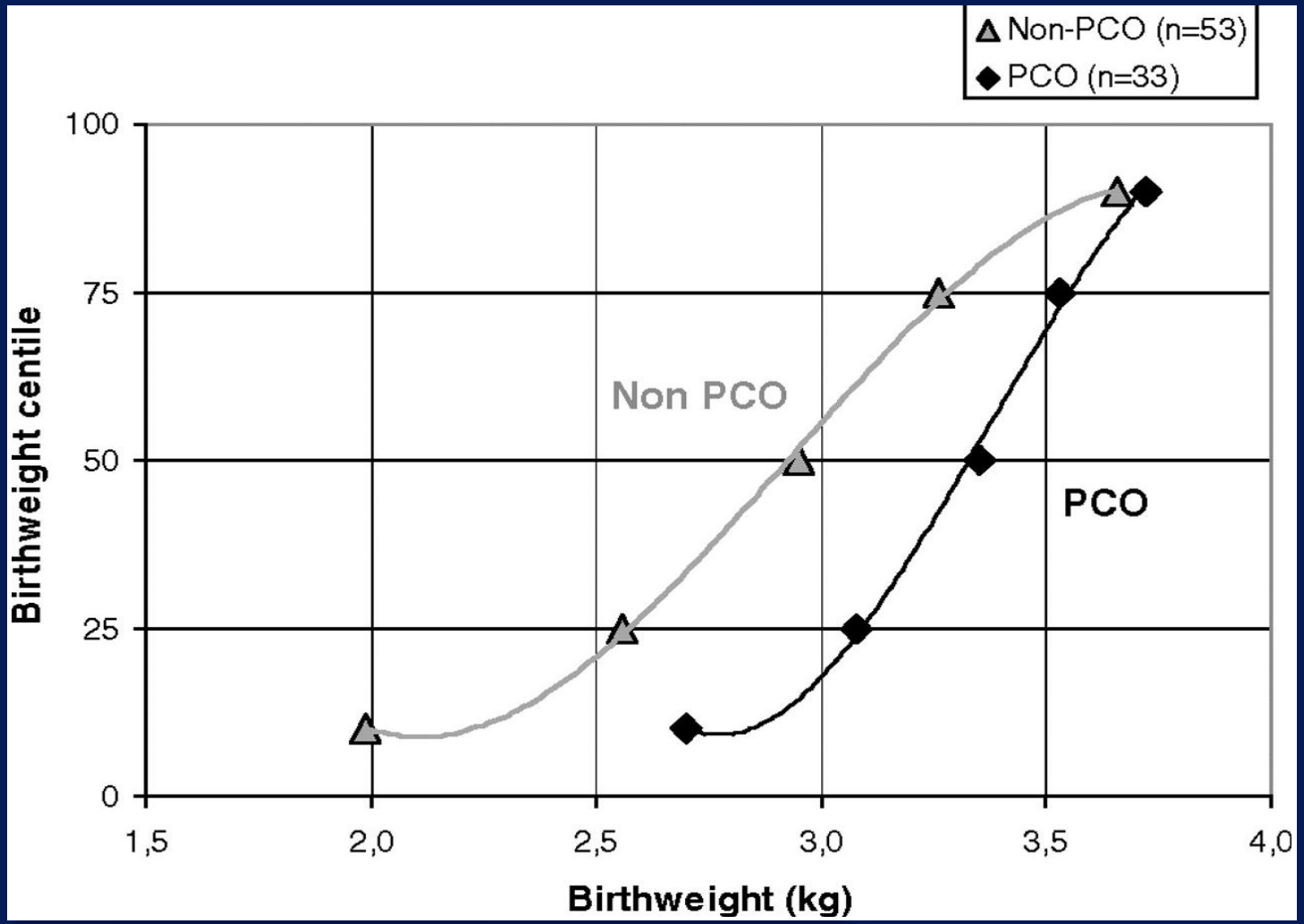
Legro et al. J Clin Endocrinol Metab 2005;90:2571-9

CAVEATS FOR DIAGNOSING PCOS IN ADOLESCENTS: POLYCYSTIC OVARIES

- Multifollicular ovaries can be a normal finding in adolescence and hence make it difficult to distinguish from polycystic ovaries
- Because the TV-US approach is not appropriate for use in virginal adolescents, it is more difficult to image ovaries in this age group, particularly in obese girls, than in adult women

Khan. J Pediatr Adolesc Gynecol (2007) 20:101-104

DISTRIBUTION OF BIRTH WEIGHTS IN NONOBESE ADOLESCENTS AND YOUNG WOMEN WITH OVARIAN ANDROGEN EXCESS



Birth weights in patients with PCO were higher than in patients without PCO (*P* <0.0005)

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Ibanez et al. J Clin Endocrinol Metab 2008;93:196-199

BIRTH-WEIGHT, LENGTH OF GESTATION, AND PCOM IN ADULT LIFE

	No. of women	% with PCOM
Birthweight (lb)		
≤5·5	13	15%
5·6–6·5	53	21%
6·6–7·5	89	18%
7·6–8·5	60	22%
>8·5	20	35%
Weeks of gestation		
≤38	32	16%
39	55	15%
40	76	21%
41	40	25%
≥42	32	31%
All women	235	21%

- The fraction of women who had PCOM tended to increase with birthweight, though the trend was not significant (p=0·25)
- The fraction of women with PCOM increased with length of gestation (p=0·05)
- The increase in th frequency of PCOM with length of gestation was, however, apparent only in thinner women

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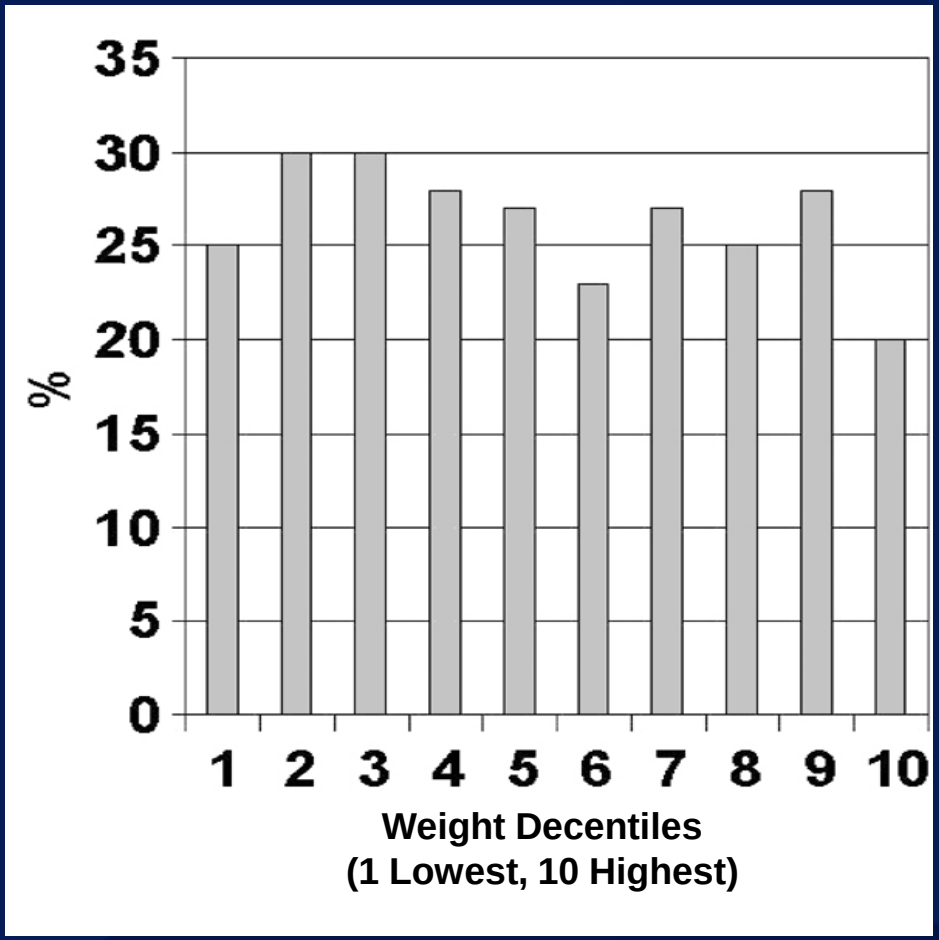
Cresswell et al. Lancet 1997;350:1131–1135

PROPORTION OF WOMEN WITH SELF-REPORTED PCOS SYMPTOMS BY BIRTH WEIGHT IN A FINNISH POPULATION



- Longitudinal, population-based study of a cohort of women born in 1966 in northern Finland
- Study population included 2007 women who were not pregnant and did not use hormonal contraception
- 528 (26%) had self-reported symptoms of PCOS
- **Overall, birth weight, gestational age, being small for gestational age, or growth retardation at birth were not associated with PCOS symptoms at 31 y.o.**

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Laitinen et al. Int J Obes Relat Metab Disord 2003 27:710–715

DIAGNOSING PCOS IN ADOLESCENCE

- Presenting signs and symptoms of PCOS are variable
- PCOS should be considered in any adolescent girl with:
  - Unwanted hair growth or frank hirsutism
  - Precocious or premature adrenarche
  - Persistent acne
  - Menstrual irregularity >2 years
  - Acanthosis nigricans
  - Obesity
  - Family history of PCOS, menstrual irregularity or hirsutism

DIAGNOSING PCOS IN ADOLESCENCE

- There are no established criteria for the diagnosis of PCOS in adolescents
- And:
  - **Lack of normative values for androgens**, and changing androgen levels over a few years time
    - Interpret high DHEAS with caution
    - Use adult normative ranges for TT and FT post-menarche
  - **Hirsutism may be incipient or still mild**
    - Examine fully and listen to the patient
  - **Irregular cycles are not uncommon in first 2-3 years post-menarche**
    - The more severe the oligomenorrhea, the higher the risk that it will persist
  - **Difficult to obtain good ovarian imagery**
    - Use ovarian volume (>10 cm^3) over follicle number

DIAGNOSING PCOS IN ADOLESCENCE

- The diagnosis of PCOS has life-long implications and the features of PCOS may be less well established in adolescents
- Thus, the diagnosis of PCOS in adolescents should be made with great caution
- If the diagnosis is unclear then the most prudent course may be:
  - Expectant management with regular, but not overzealous, follow-up
  - Reassurance and patient (and family) education
  - Lifestyle modification
  - Treatment of individual symptoms/complaints, if needed/desired

THANK YOU

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