POLYCYSTIC OVARY SYNDROME IN ADOLESCENTS

Ricardo Azziz, M.D., M.P.H., M.B.A.

Depts. Of Ob/Gyn and Medicine,
Medical College of Georgia
Georgia Regents University

PCOS in Teens and Adolescents

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

DIFFERENTIAL DIAGNOSIS AMONG 873 CONSECUTIVE UNTREATED PATIENTS EVALUATED FOR ANDROGEN EXCESS

Diagnosis	Total #	% Prevalence	% Unbiased Prevalence
Specific disorders			
ASNs	2	0.23	
CAH	6	0.69	
NCAH	18	2.06	1.60
HAIRAN	33	3.78	3.12
Disorders of exclusion			
PCOS	*716*	*82.02*	
IH	39	4.47	4.68
HA+Hirsutism	59	6.75	
Total	873	100.00%	

Azziz et al. J Clin Endocrinol Metab 89:453-62, 2004

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	√	√	√	

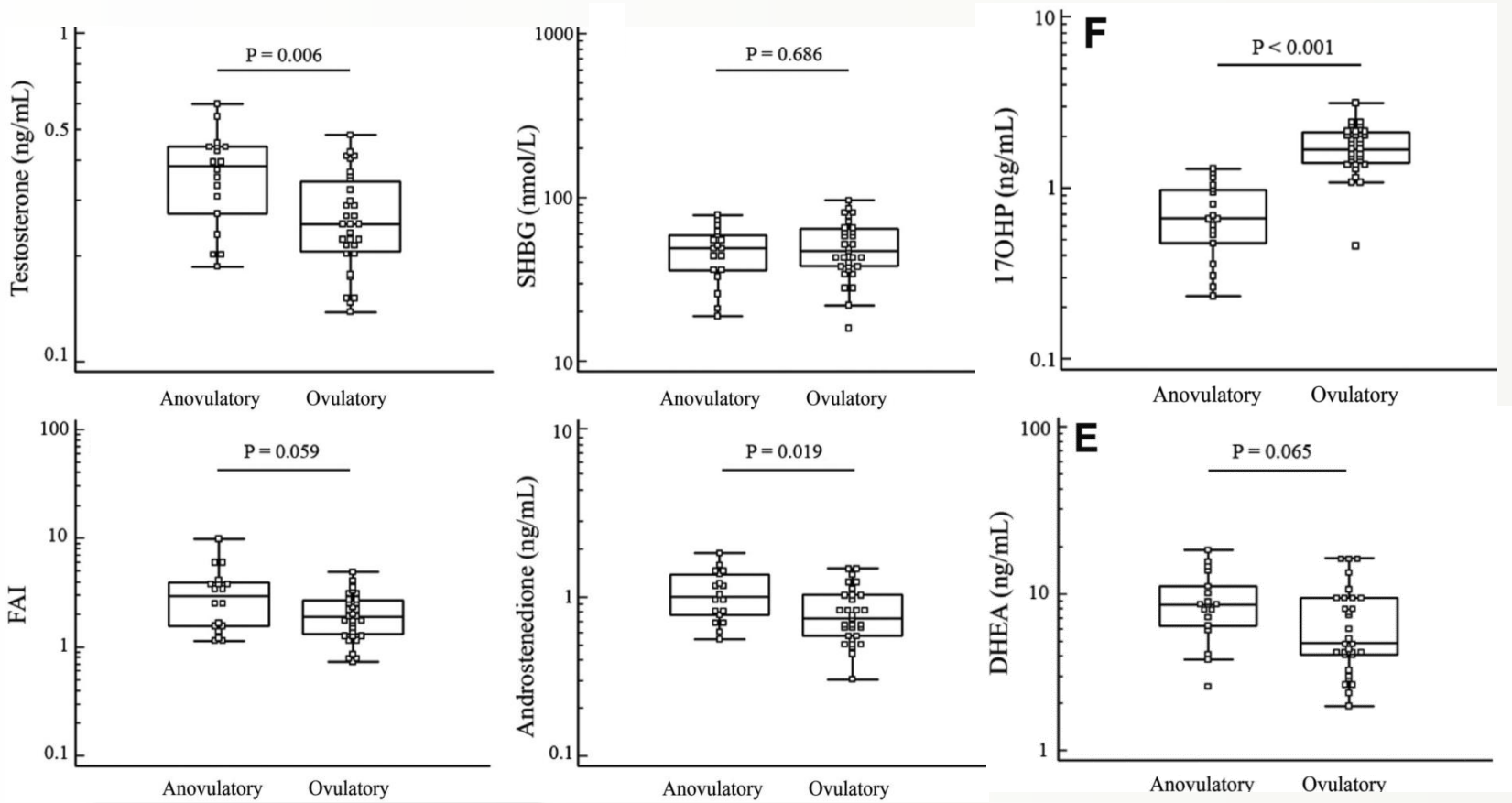
DIAGNOSING PCOS: DETECTING HYPERANDROGENEMIA

- Total and Free T, and DHEAS are most often used to detect HA in possible PCOS/AE
- A4 has occasional (e.g. NCAH), but limited value
- Free T has the highest predictive value and sensitivity for HA
- Most useful in girls/women without obvious clinical hyperandrogenism (e.g. hirsutism)
- Total T difficult to measure well.
  - Requires high quality assay (extraction & chromatography RIA, or mass spectrometry)
  - Requires well defined control (“normal”) levels

LIMITATIONS OF DEFINING PCOS BY ANDROGEN LEVELS

- Suppressed more rapidly by hormonal suppression than other clinical features, e.g. hirsutism
- Inaccurate and variable methods of measurement
- Normative values vary from lab to lab; and often are based on bias reference populations
- Little normative data in adolescent and older women
- May be altered by age (DHEAS) and BMI (SHBG & Free T)
- Wide variance in normal population, because....
- *No tight endogenous counter-regulatory mechanism for androgens in humans*

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



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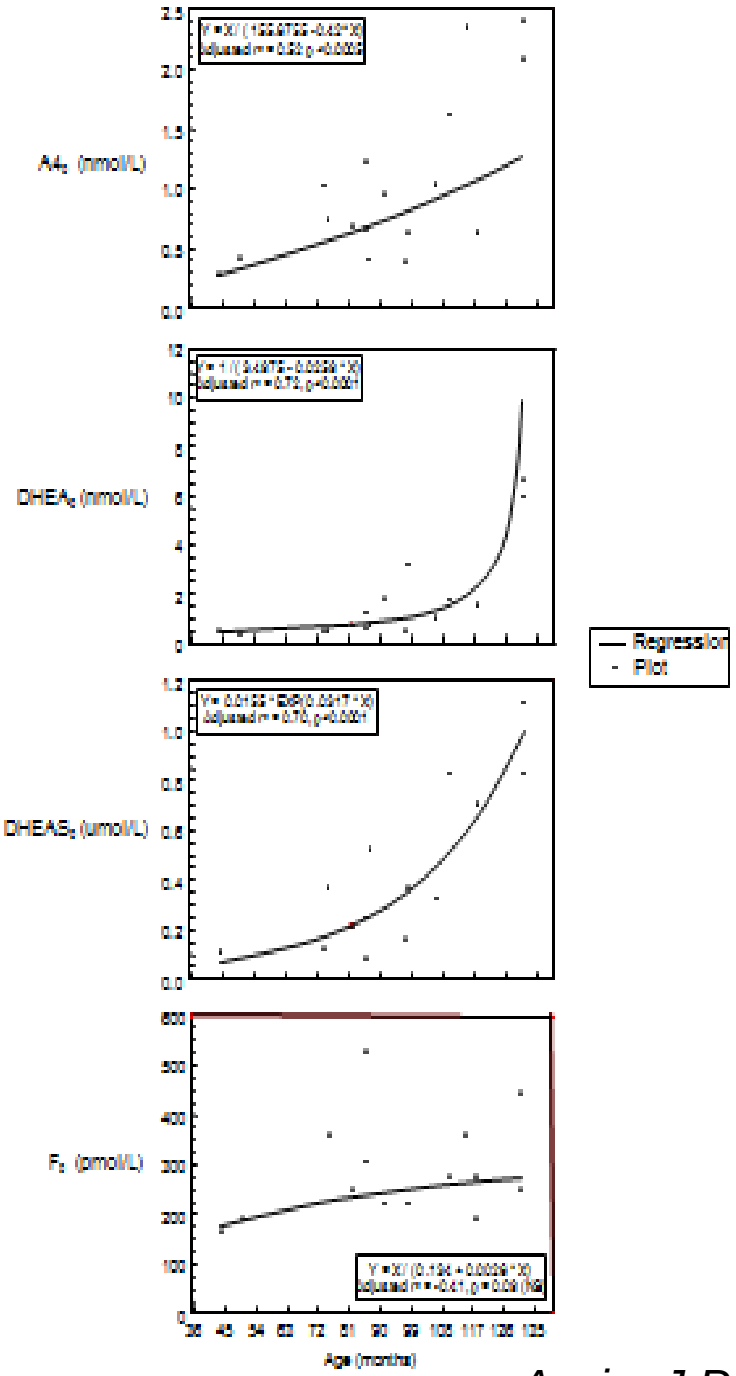
Fanelli et al. J Clin Endocrinol Metab. 2013;98:3058-67

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

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

EARLY ADRENARCHE IN NORMAL PREPUBERTAL GIRLS: A PROSPECTIVE LONGITUDINAL STUDY



- An increase in the circulating level of DHEAS appears to be the first event observed during adrenarche, prior to clinical evidence of the process

Azziz, J Ped Endocrinol Metab 17:1231-1237, 2004

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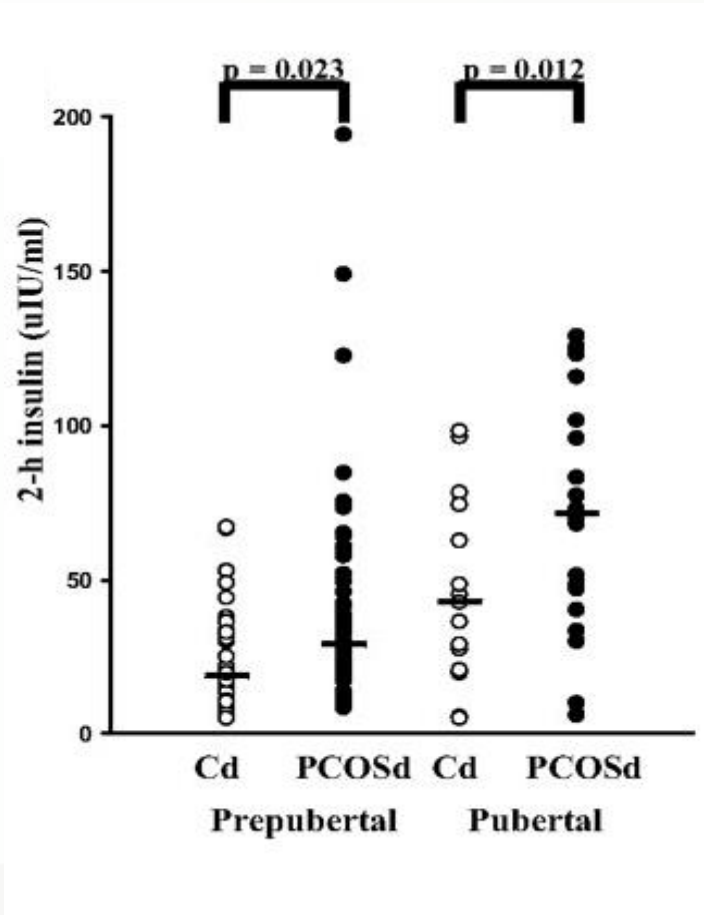
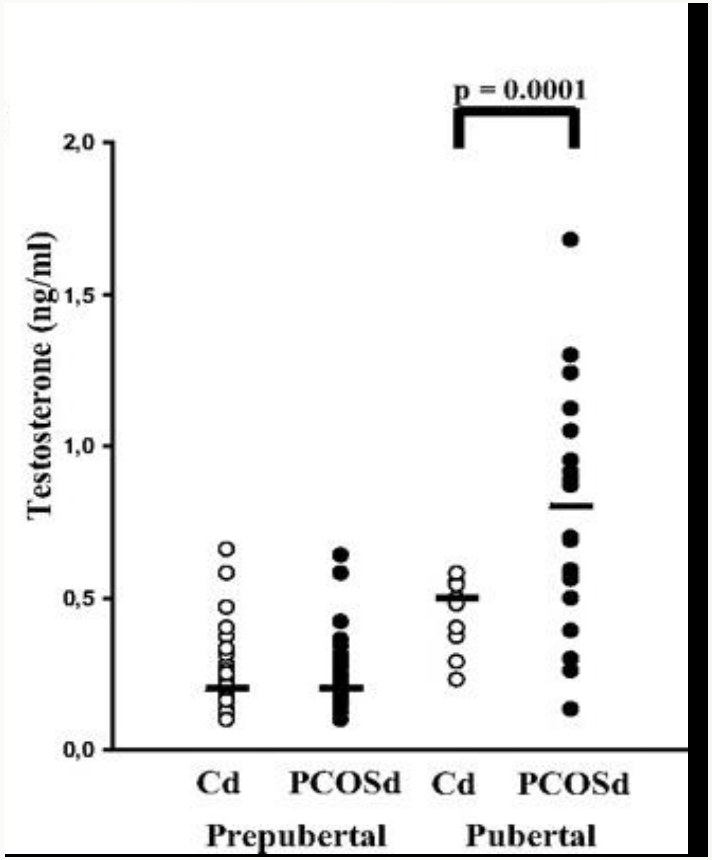
ADRENAL FUNCTION DURING CHILDHOOD & PUBERTY IN DAUGHTERS OF WOMEN WITH PCOS

- Included:
  - 98 PCOSd, 64 ages 4–8 yrs. and 34 ages 9–13 yrs.
  - 51 daughters of control women(Cd), 30 ages 4-8 yr. and 21 ages 9-13 yrs.
- Results:
  - PCOSd and Cd were similar in age and BMI
  - In the peripuberty (ages 9-13 yrs) basal and post- ACTH DHEAS were higher in PCOSd compared to Cd
  - Among PCOSd, 12.5% of girls in childhood and 32.4% in peripuberty had evidence of exaggerated adrenarche
  - Stimulated INS was higher in PCOSd compared to Cd during childhood and peripuberty
  - An advancement of 8 months between bone and chronological age was observed in peripubertal PCOSd compared to Cd
- Overall subtle differences in androgens , INS, and bone age can be observed during childhood and peripuberty in girls a risk for PCOS

Maliqueo et al. J Clin Endocrinol Metab 94: 3282–3288, 2009

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





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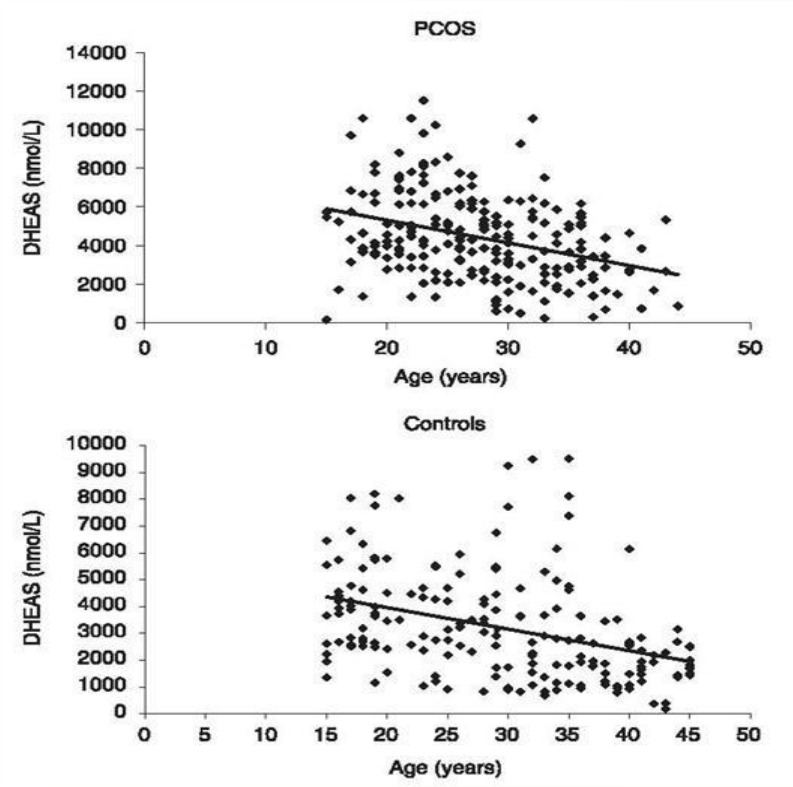
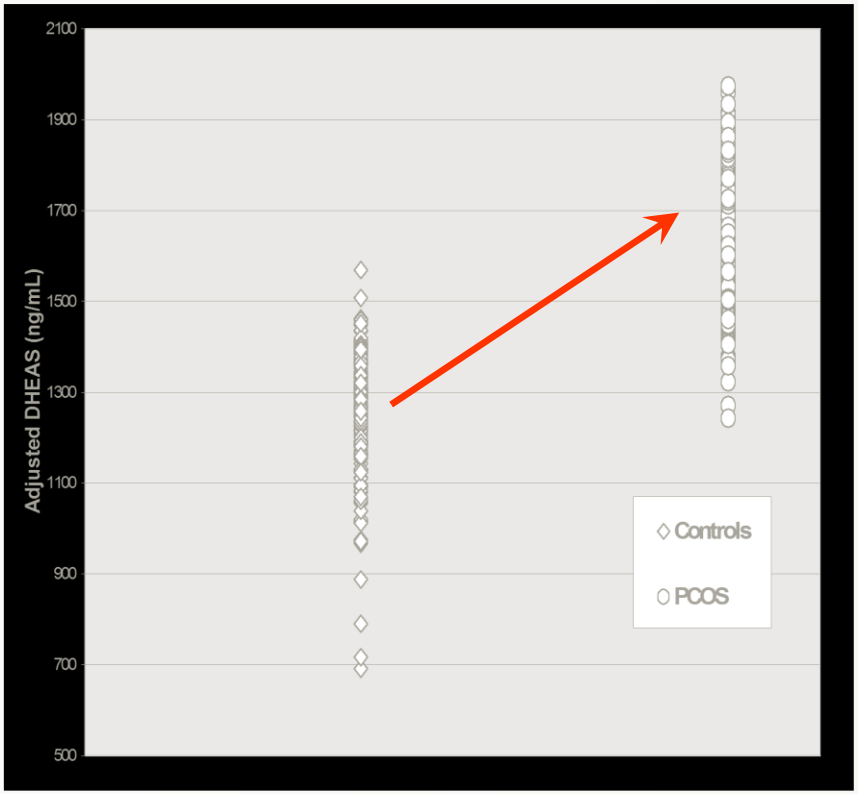
Sir-Petermann et al. J Clin Endocrinol Metab 2007;92:4637-4642

PREVALENCE OF AA EXCESS IN PCOS





- Absolute DHEAS excess is observed in 20-30% of PCOS women, using race, age and BMI 95th percentile normative values
- However, defining only those women with supranormal DHEAS as having AA excess belays the overall upward shift in DHEAS observed in PCOS

Adapted from 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 to 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
- Thus, we generally can use adult androgen levels for detecting HA and predicting PCOS in adolescents, recognizing that DHEAS will be higher normally

SPECIFICITY AND PREDICTIVE VALUE OF CIRCULATING TESTOSTERONE ASSESSED BY LC-MS/MS FOR THE DIAGNOSIS OF PCOS

Sensitivity, specificity, PPV, and NPV of FT cutoff values determined by the LC-MS/MS method

	FT cutoff≥ (pg/mL)											
	0.2	**1**	**1.5**	**1.8**	**2**	**2.5**	**3**	**3.3**	**3.5**	**4.0[a]**	**4.5**	**5.0[b]**
Sensitivity, %	100	96	95	91	87	80	75	73	71	**64[a]**	58	**52[b]**
Specificity, %	0	21	42	56	63	71	84	87	91	**97[a]**	98	**99[b]**
10% Prevalence												
PPV, %	10	12	15	19	21	23	34	38	47	70	76	**85[b]**
NPV, %	N/A	98	99	98	98	97	97	97	97	96	95	**95[b]**
70% Prevalence												
PPV, %	70	74	79	83	85	87	92	93	95	**98[a]**	99	99
NPV, %	N/A	69	78	73	68	60	59	58	57	**54[a]**	50	47

[a] The level(s) that have the highest combined PPV and NPV values useful for evaluation of patients in the clinical setting (prevalence of PCOS assumed to be ~70% of patients seen)

[b] The level(s) that have the highest combined PPV and NPV values useful for epidemiological studies (prevalence of PCOS assumed to be ~10% of population studied)

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Salameh et al, Fertil Steril. 2014;101:1135-1141

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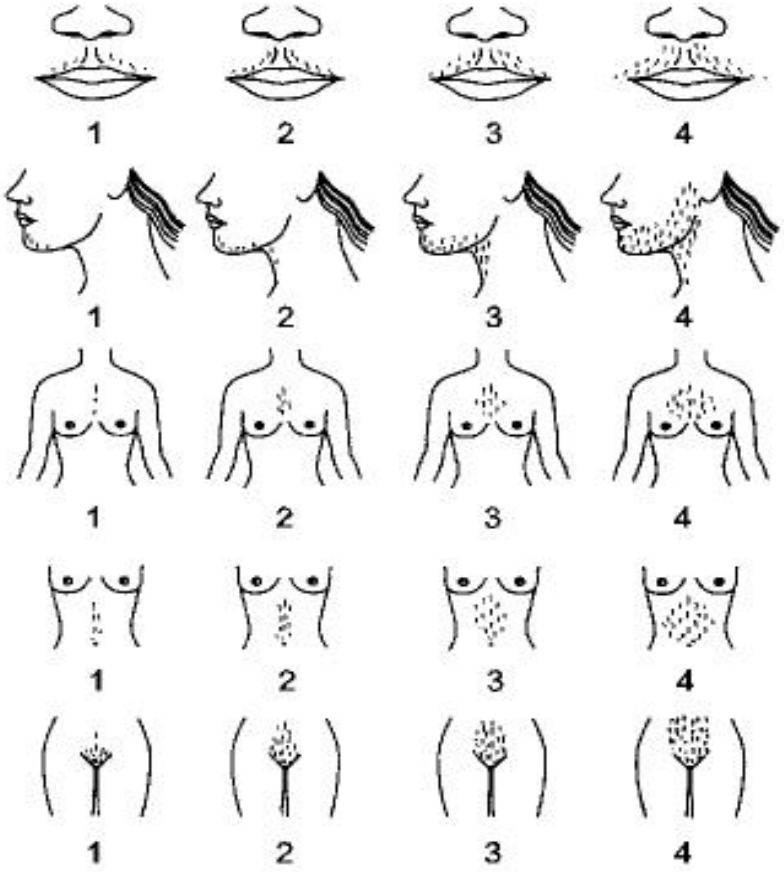
DIAGNOSING PCOS: DETECTING HIRSUTISM

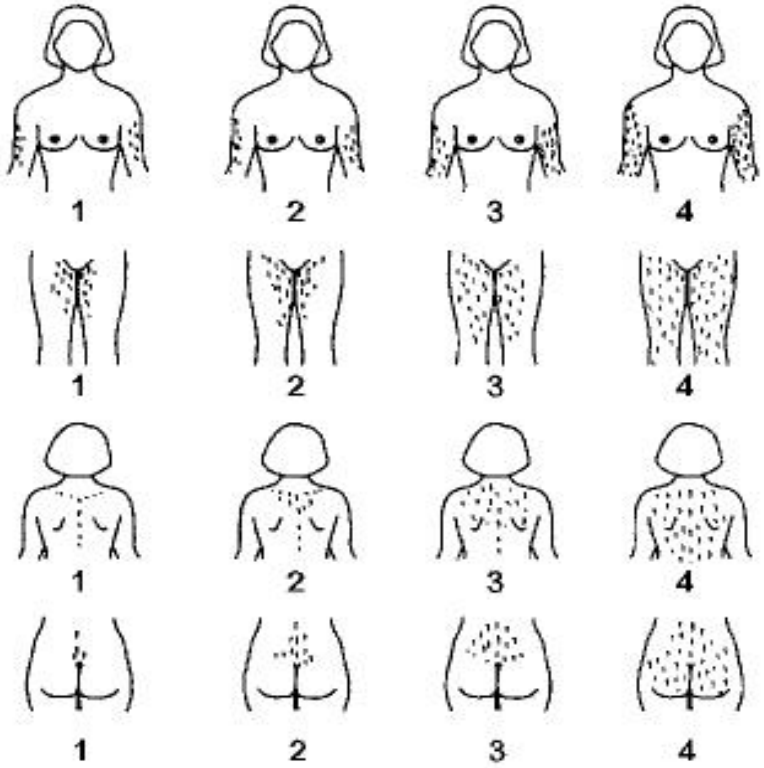
- Hirsutism is excess *terminal* hair growth in a *male-like* pattern
  - Distinguish from hypertrichosis (excess vellus hairs)
- Usually 9 body areas are assessed visually (modified Ferriman-Gallwey score)
- No correlation between mFG score and androgen levels (but positive with hyperinsulinemia / BMI)
- ~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

LIMITATIONS OF DEFINING PCOS BY HIRSUTISM

- Subjective scale
- A continuous psychosocially-influenced variable
- Often first symptom to be treated
- Less prominent in adolescents & older women
- Less prominent in Asian individuals

MODIFIED F-G SCORE





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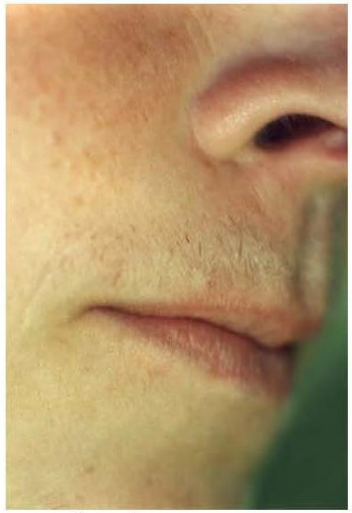
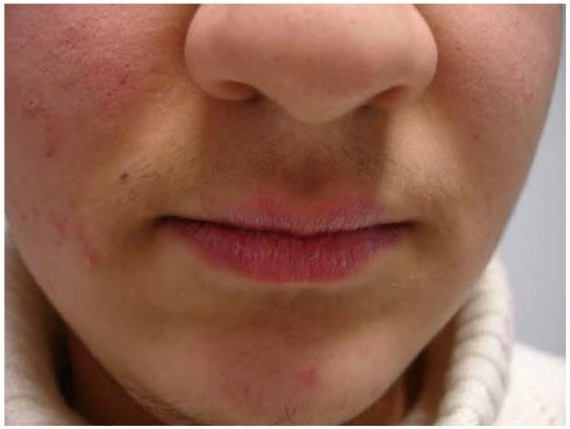
MODIFIED F-G SCORE

Lip



Score 1



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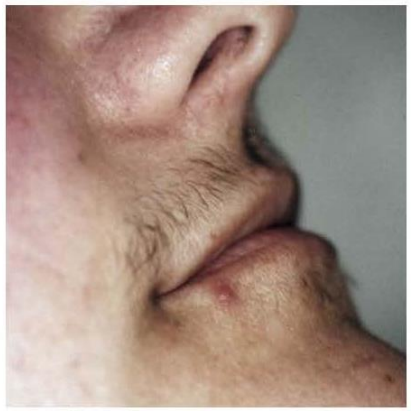

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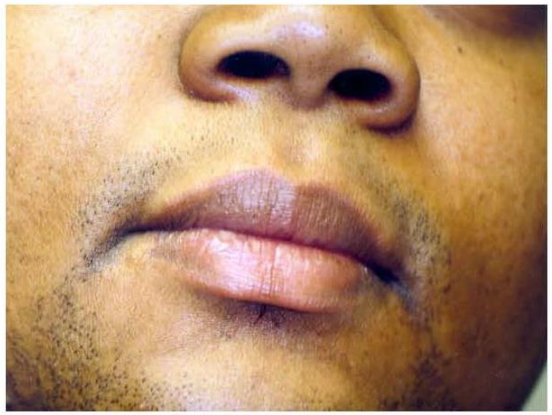
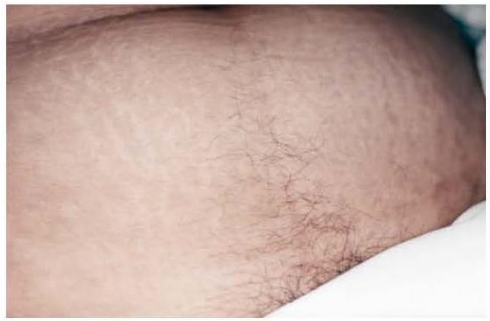


Score 4

Lower Abdomen



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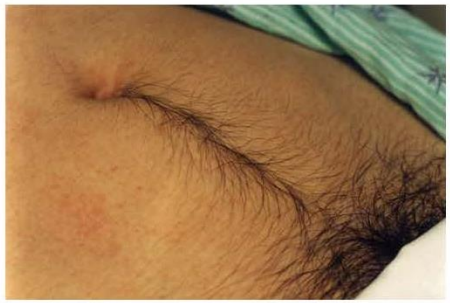

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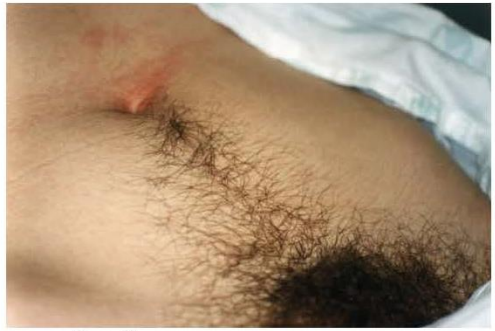

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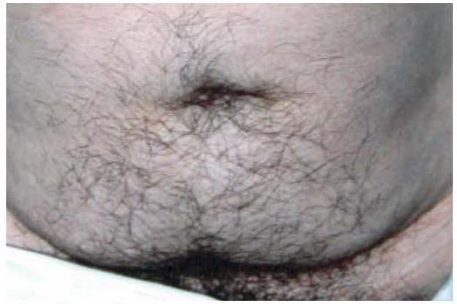

Score 4

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

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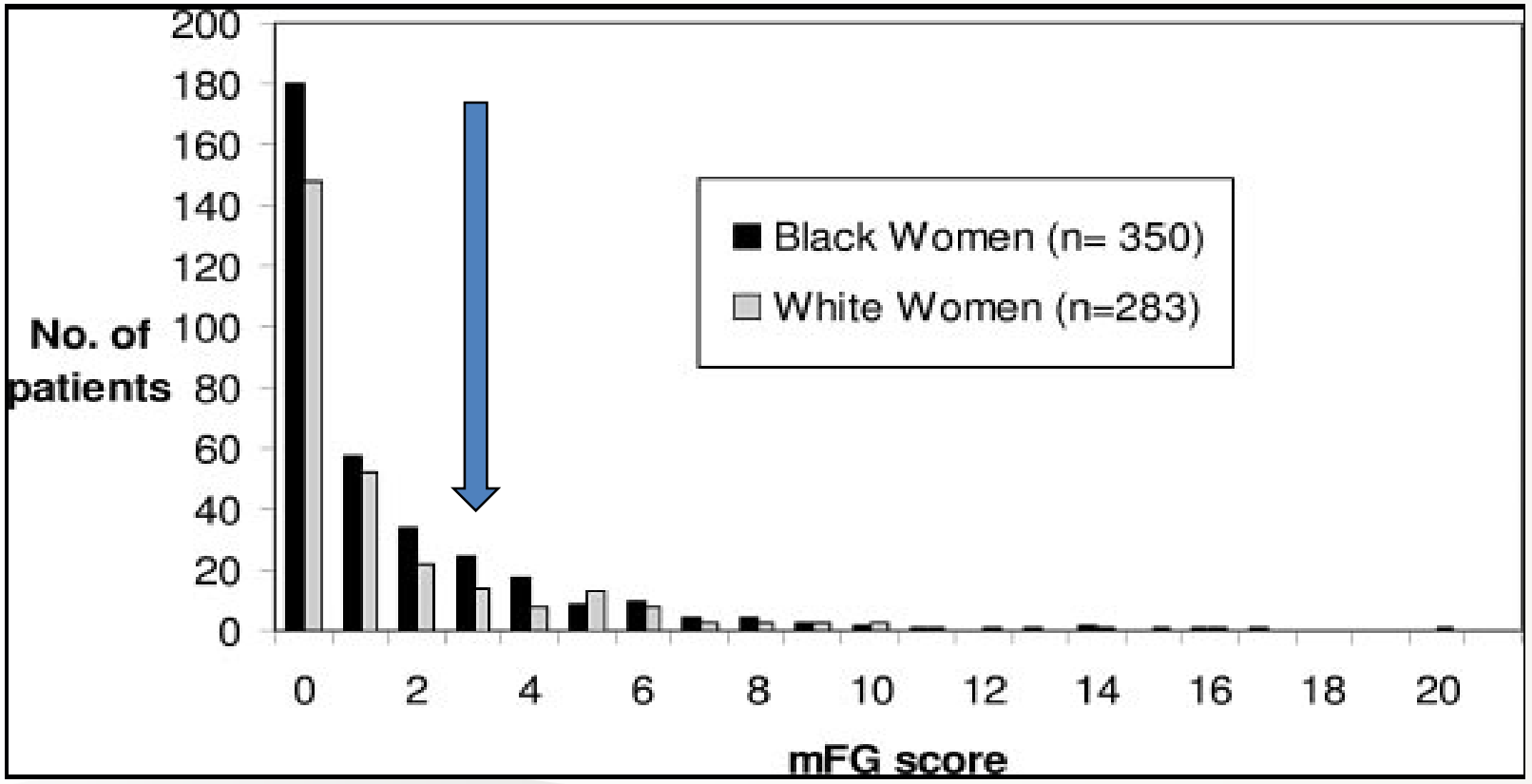
DISTRIBUTION OF mFG SCORES, ASSESSING TERMINAL BODY AND FACIAL HAIR GROWTH, IN 350 BLACK AND 283 WHITE UNSELECTED WOMEN



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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

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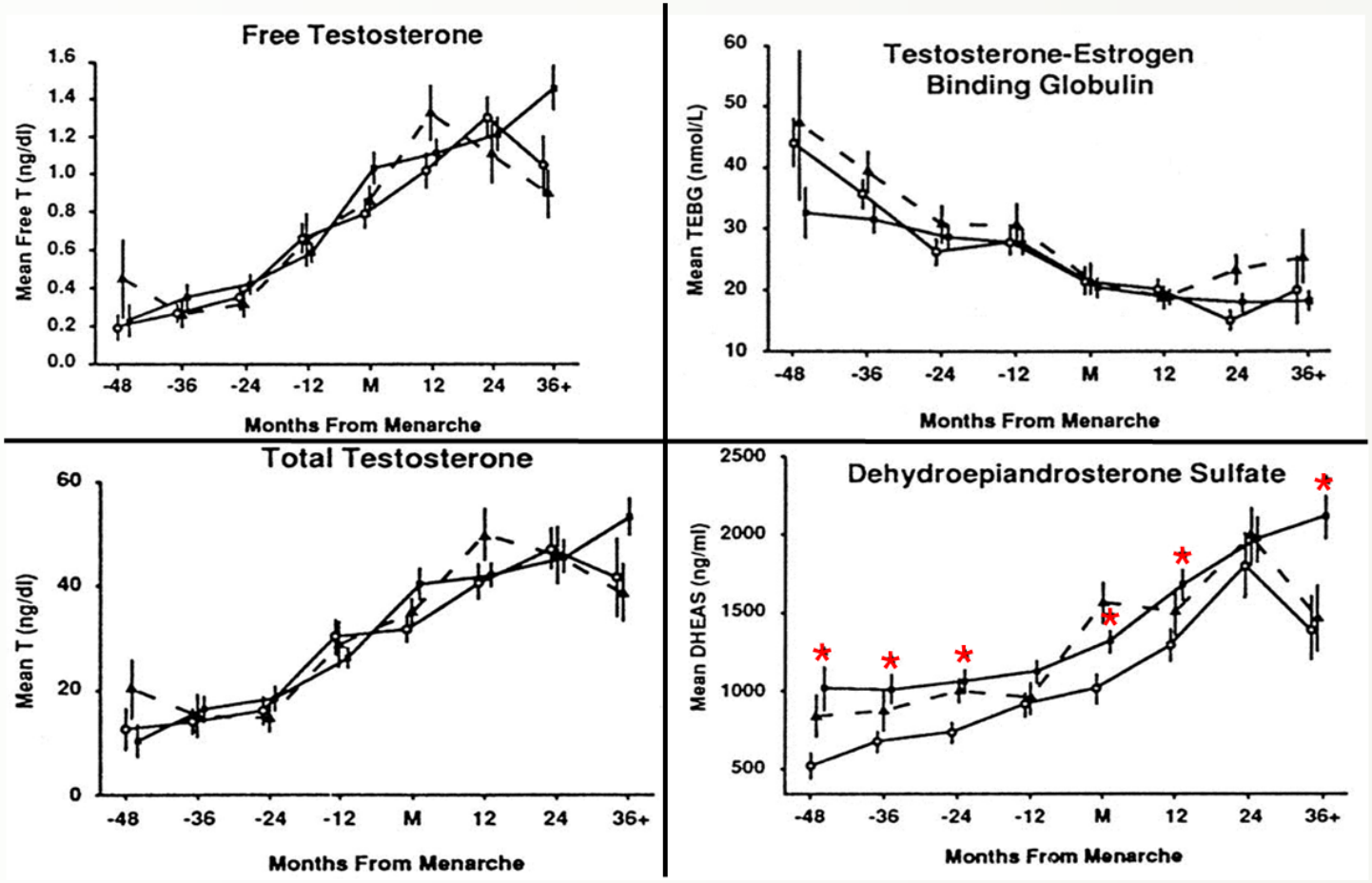
PREDICTORS OF SEVERITY OF ACNE VULGARIS IN YOUNG ADOLESCENT GIRLS: RESULTS OF A 5-YEAR LONGITUDINAL STUDY

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
- Acne may indicate HA, regardless of age & severity
- High quality assays for TT/FT may be a more useful marker of hyperandrogenism

DIAGNOSING PCOS: DETECTING OVULATORY DYSFUNCTION

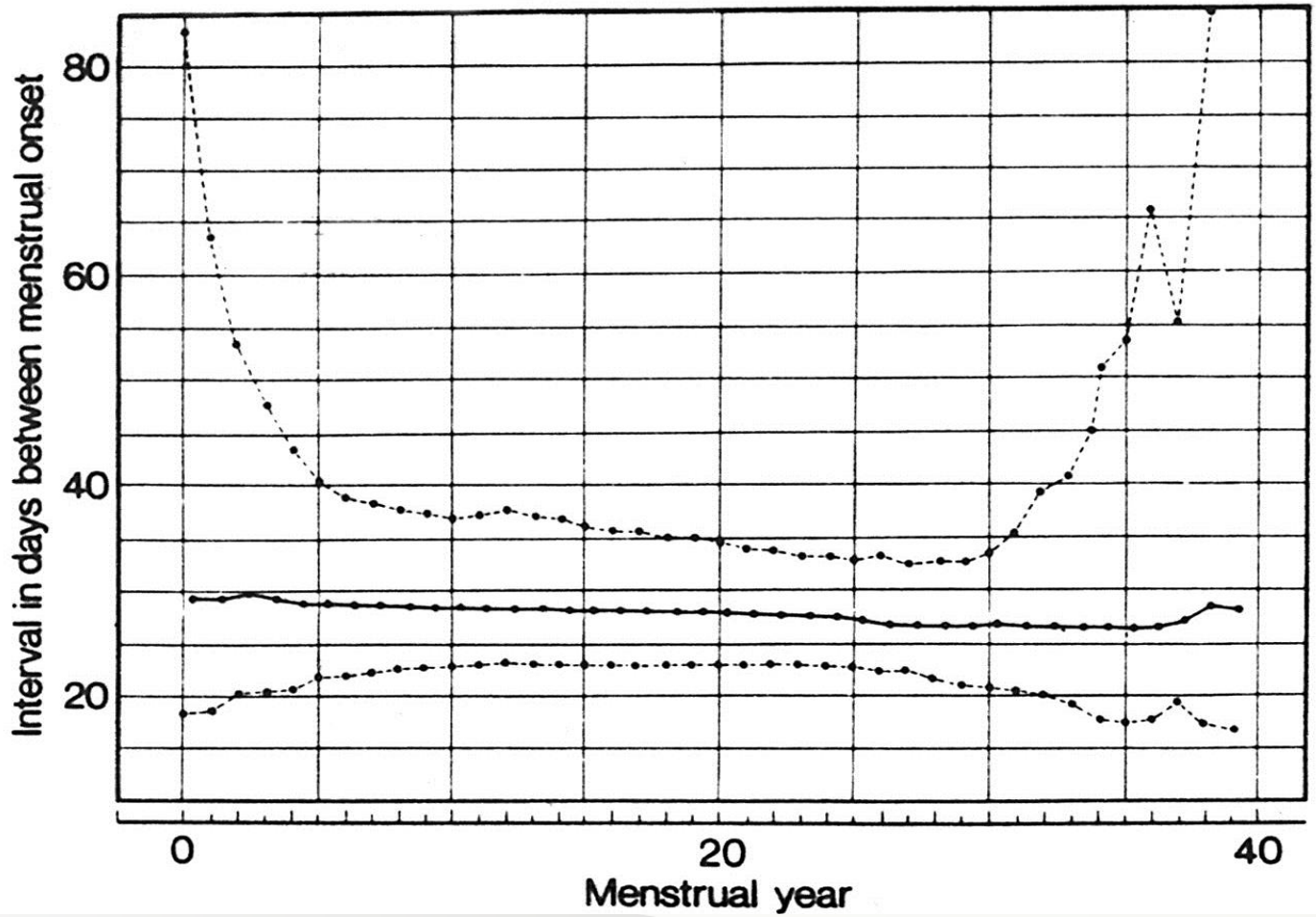
- Ovulatory dysfunction is usually reflected in clinically evident menstrual dysfunction
  - Oligo/amenorrhea (<10 cycles/yr, or cycles >34 d. intervals), or
  - Polymenorrhea (cycles <26 d. intervals)
- Severity of menstrual dysfunction predicts degree of IR, but not HA
- ~40% of adult women with hirsutism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

MENSTRUAL DYSFUNCTION AS A MARKER FOR OVULATORY DYSFUNCTION IN ANDROGEN EXCESS

- Regular vaginal bleeding does not necessarily predict regular ovulatory function, particularly in the presence of hirsutism
  - About 40% of eumenorrheic hirsute women are oligo-ovulatory
- Presence of premenstrual molima Sx (swelling, breast tenderness, mood changes) may be helpful, but specificity/sensitivity unclear.

Azziz et al. Fertil Steril 1998;70:274

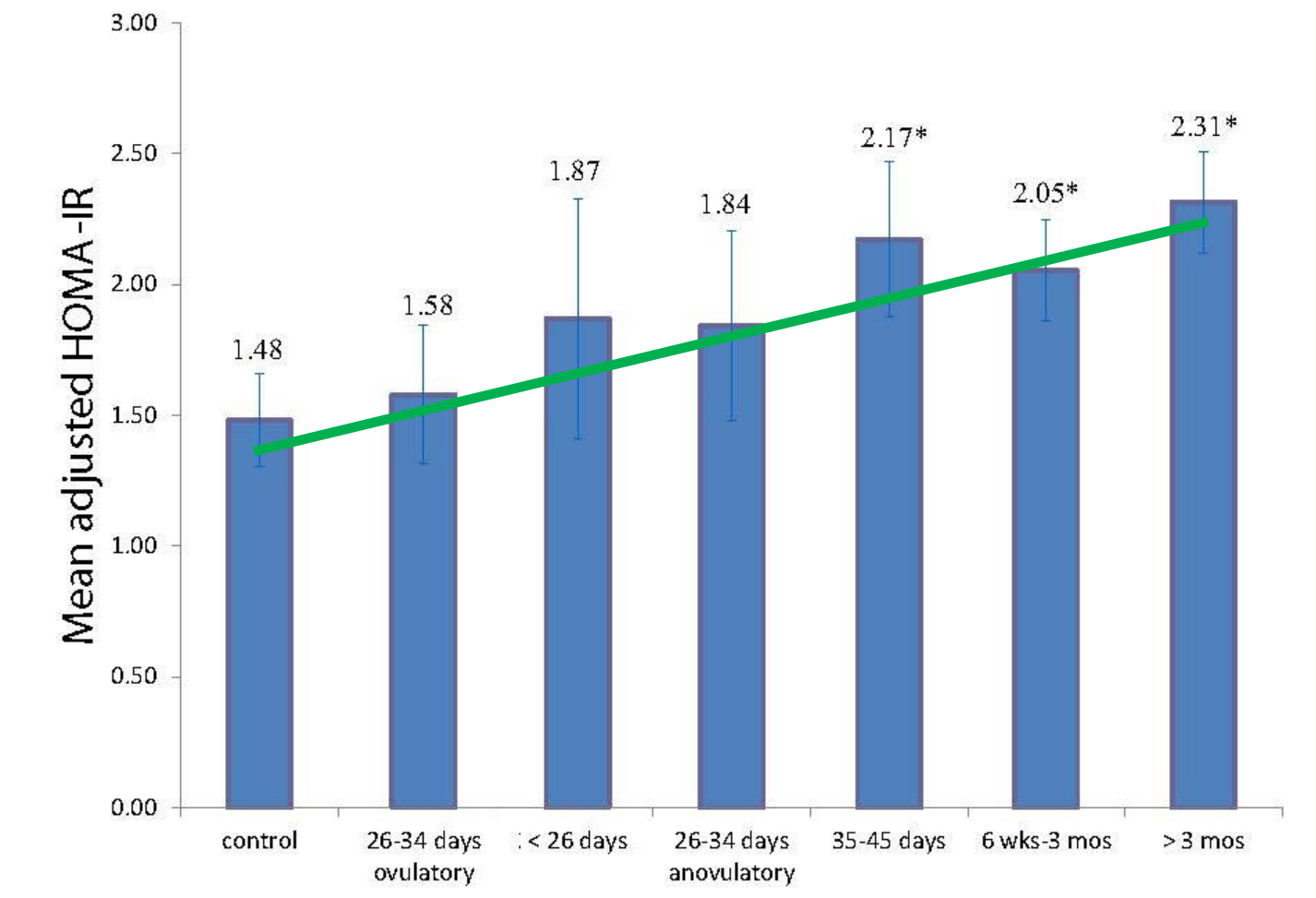
MEDIAN MENSTRUAL CYCLE LENGTHS THROUGHOUT THE REPRODUCTIVE LIFE OF WOMEN FROM MENARCHE (YEAR 0), TO MENOPAUSE (YEAR 40)



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

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

SEVERITY OF MENSTRUAL DYSFUNCTION PREDICTS DEGREE OF IR



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

- Followed a cohort of adolescents between ages 15 and 18 y.o.
- **Risk of developing Oligomenorrhea***
  - **1.6%** (2/128) for adolescents with regular menstrual cycles
  - **4%** (4/110) for girls with irregular menstrual cycles** and cycles between 22-34 d.
  - **34%** (13/38) for girls with irregular menstrual cycles** and cycle between 35 -41 days
- Overall, **51%** (34/67) of adolescents with Oligomenorrhea* at 15 y.o. remained so at 18 y.o.

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

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

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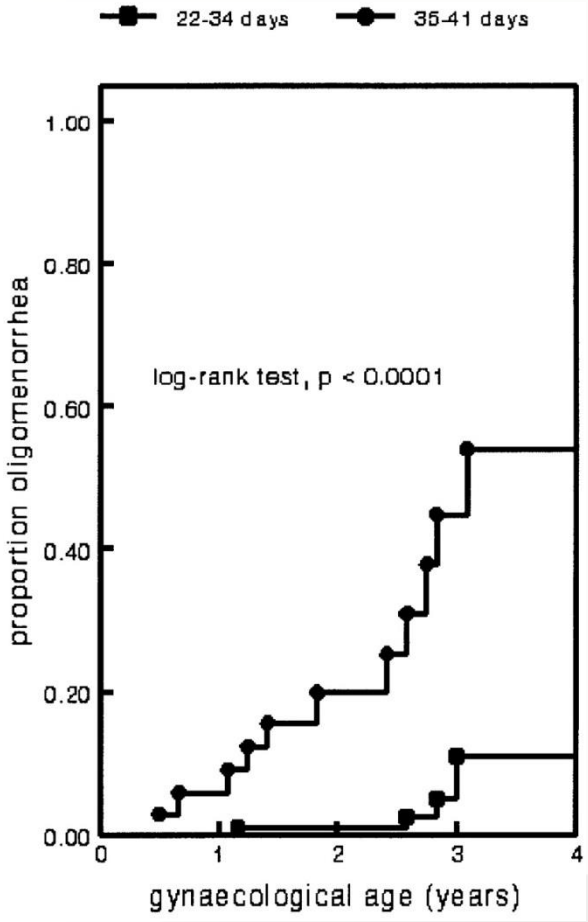
van Hooff M et al. Hum. Reprod. 2004;19:383-392

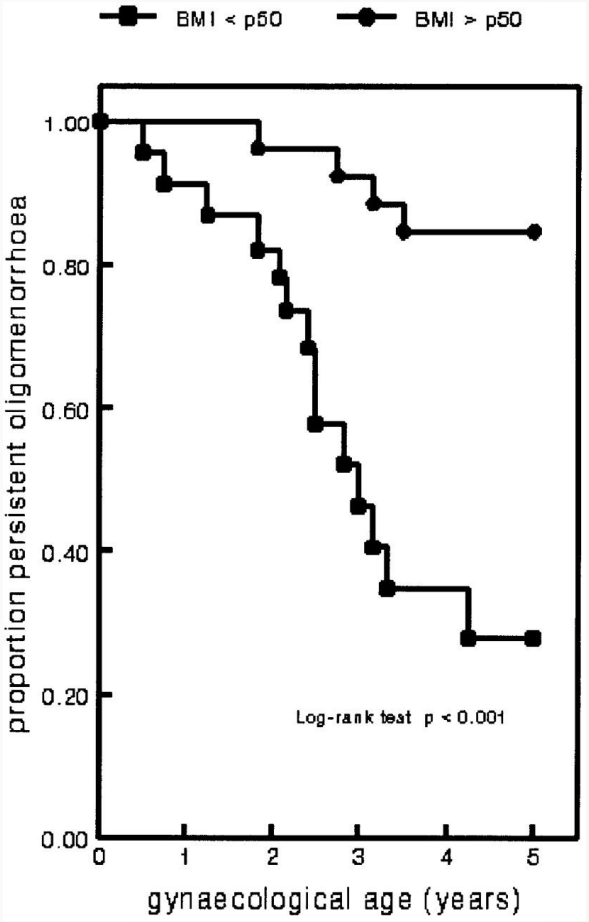
PREDICTORS AT AGE 15 YEARS FOR OLIGO-AMENORRHOEA AT AGE 18 YEARS



Risk of developing OLIGO in young women with irregular menstrual cycles, and:

a) **An average menstrual cycle length of 22-34 days; n = 110), or**

b) **An average menstrual cycle length of 35-41 days (n = 38)**



Risk for persistent OLIGO in young women with a BMI above or below the median BMI (p50 = 19.6 kg/m^2) of this subgroup

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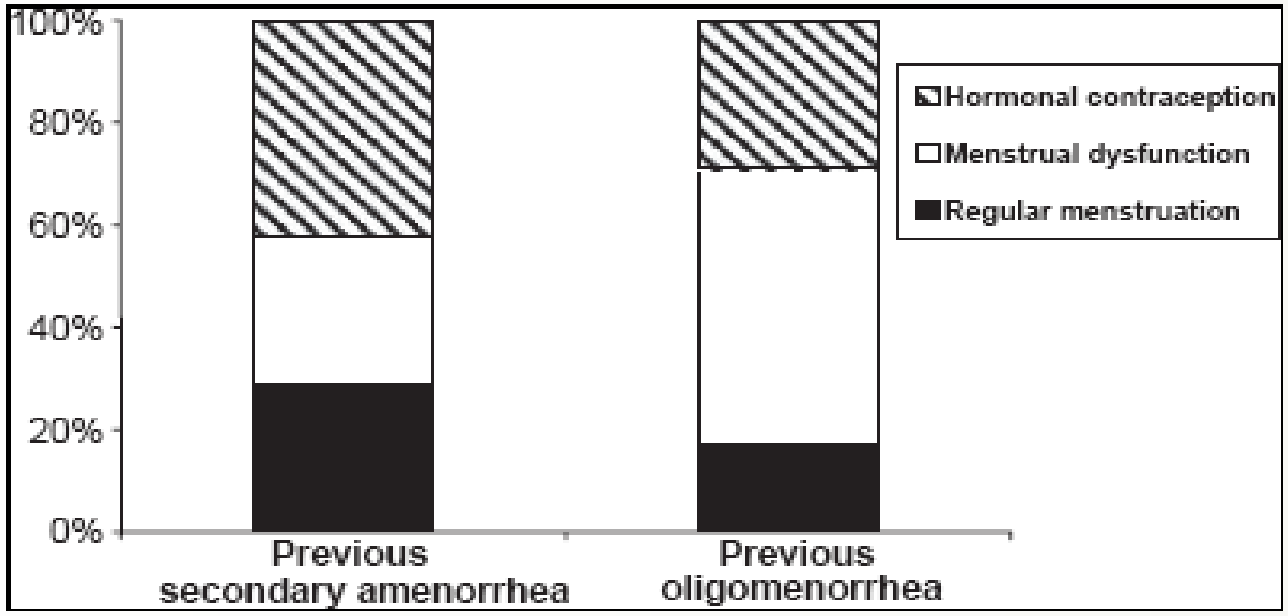
van Hooff M et al. Hum. Reprod. 2004;19:383-392

PROSPECTIVE FOLLOW-UP OF MENSTRUAL DISORDERS IN ADOLESCENCE AND PROGNOSTIC FACTORS



- Hypothalamic inhibition of the gonadal axis was by far the most common cause of secondary amenorrhea
- Hyperandrogenism and PCOS were more common in the girls with oligomenorrhea

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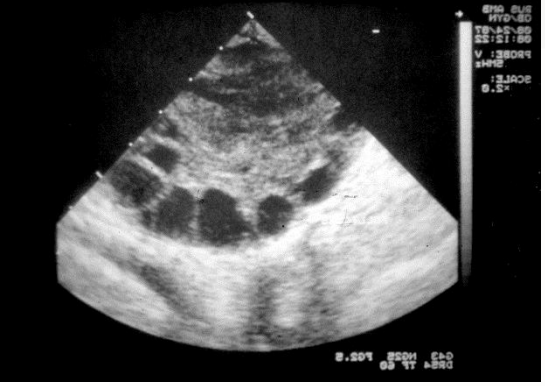
Wiksten-Almströmer et al, Acta Obstet Gynecol Scand 87: 1162-1168, 2010

CAVEATS FOR DIAGNOSING PCOS IN ADOLESCENTS: OVULATORY DYSFUNCTION

- A careful bleeding history 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 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

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?

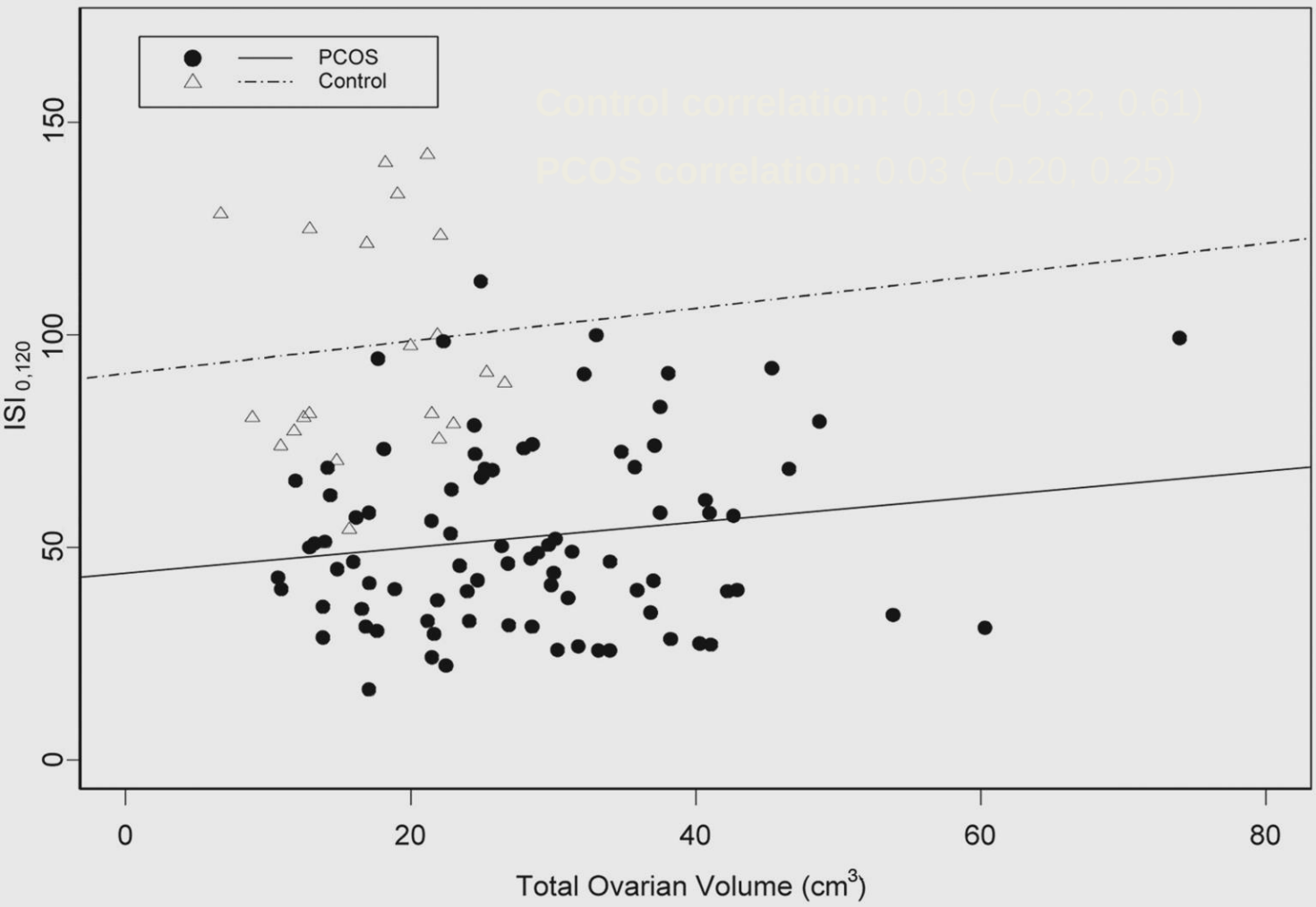
- 20-30% of patients with eating disorders have PCOM & irregular ovulation *(Jahanfar et al, 1995; Morgan et al, 2002)*
- 30-50% of patients with hyperprolactinemia, hypothalamic amenorrhea, or 21-OH deficient NCAH have PCOM *(Ardaens et al, 1991; Azziz et al, 1994)*
- NCAH & CAH patients have a similar 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
- LH and androgens were ↑, but INS and G:I ratio were similar, in girls w/ PCOM vs. w/o PCOM
- PCOM present in:
  - 9% of the girls with regular menstrual cycles
  - 28% of those with irregular menstrual cycles
  - 45% of oligomenorrheic girls
- 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

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

POLYCYSTIC OVARIES DO NOT PREDICT METABOLIC OR REPRODUCTIVE PHENOTYPE



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

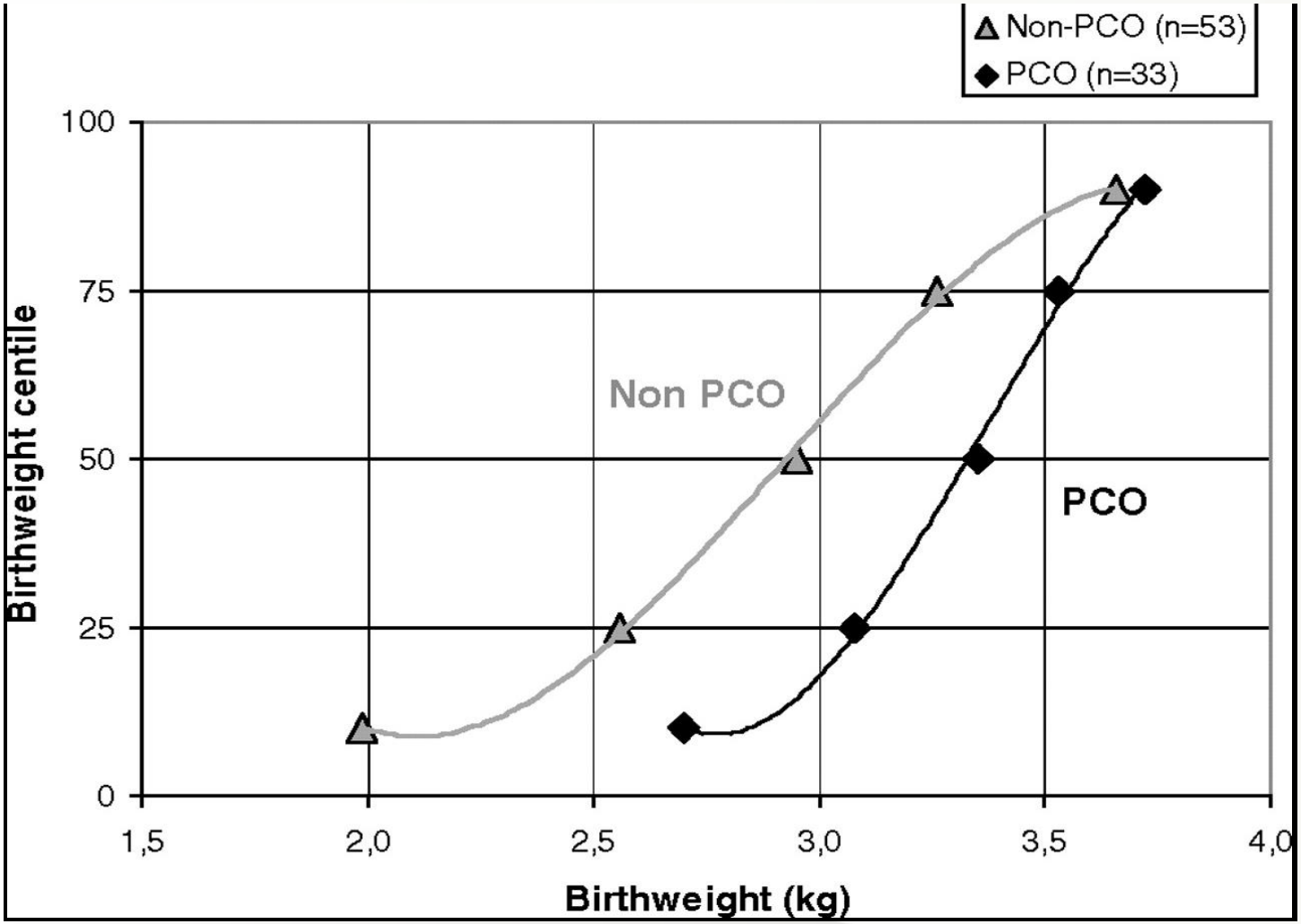
CAVEATS FOR DIAGNOSING PCOS IN ADOLESCENTS: POLYCYSTIC OVARIES

- 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 without PCO are lower (*P* <0.0005) than in patients with PCO

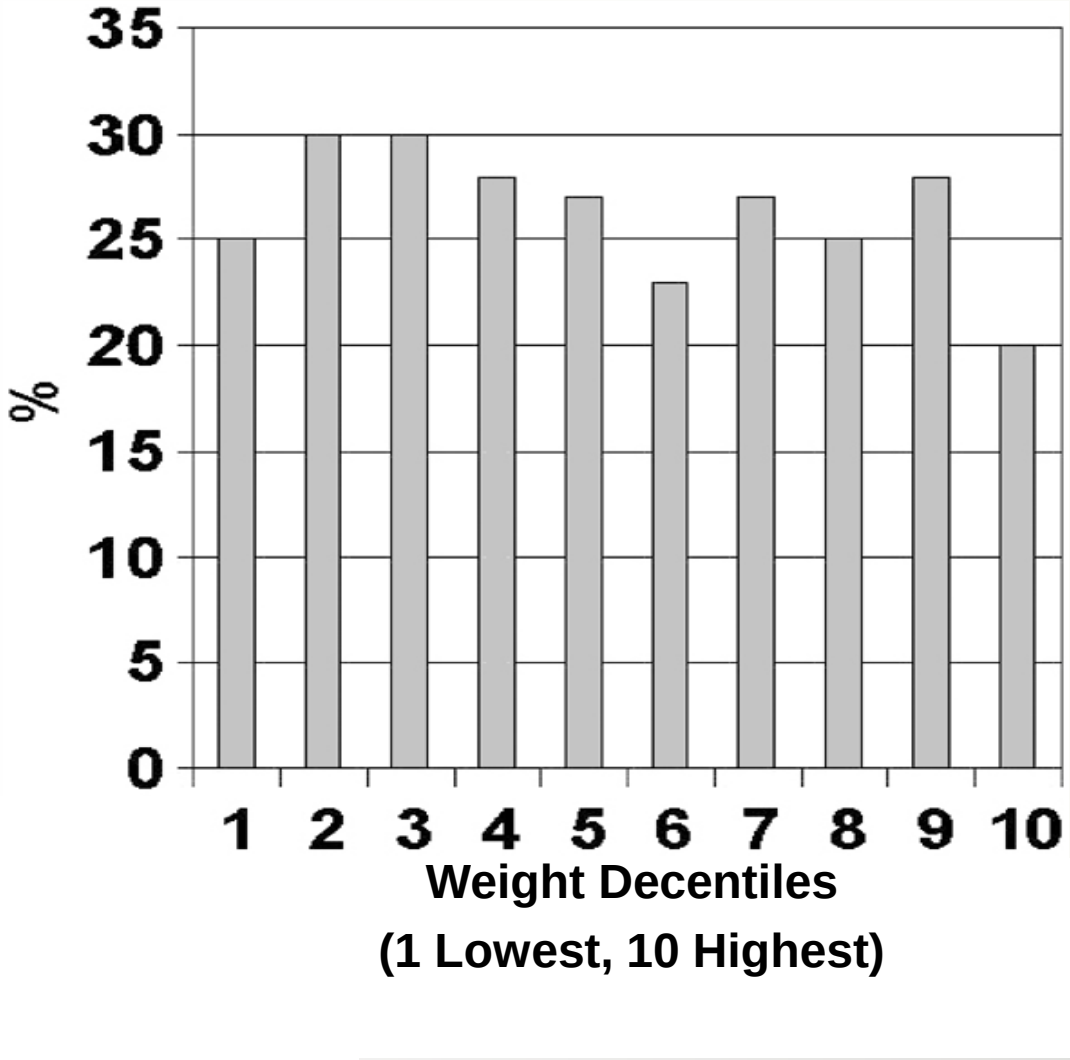
Ibanez et al. J Clin Endocrinol Metab 2008;93:196-199

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%

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**

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

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RISK OF PCOS BY BIRTHWEIGHT

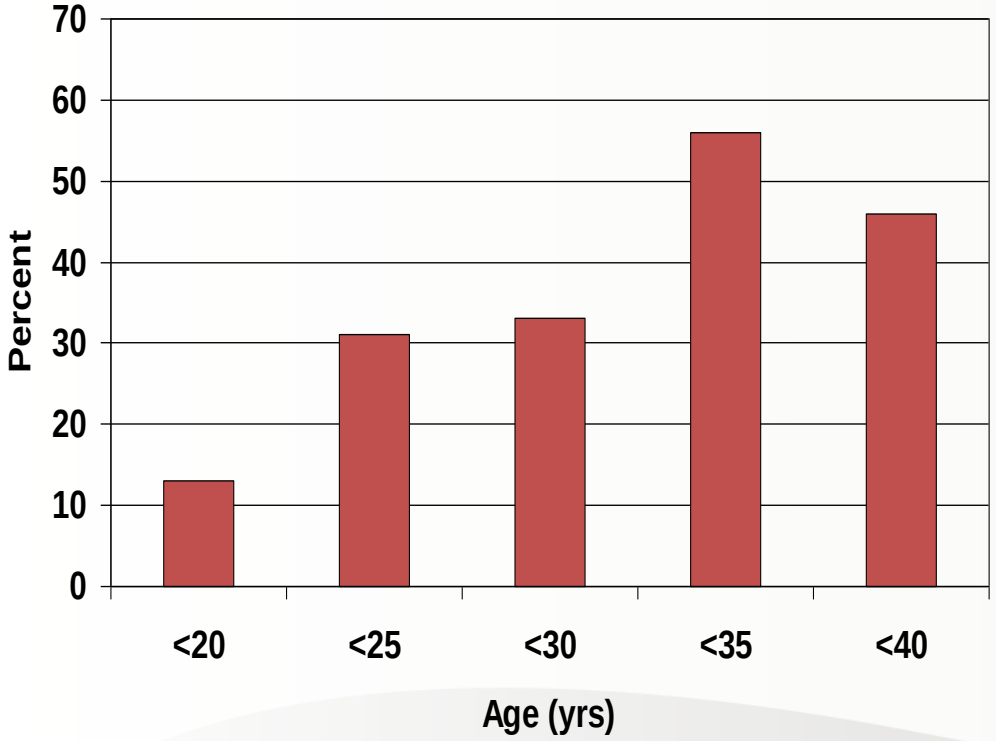
- Overall, although SGA (or LBW) predisposes to insulin resistance, it poses less risk for the development of PCOS in most populations studied to date

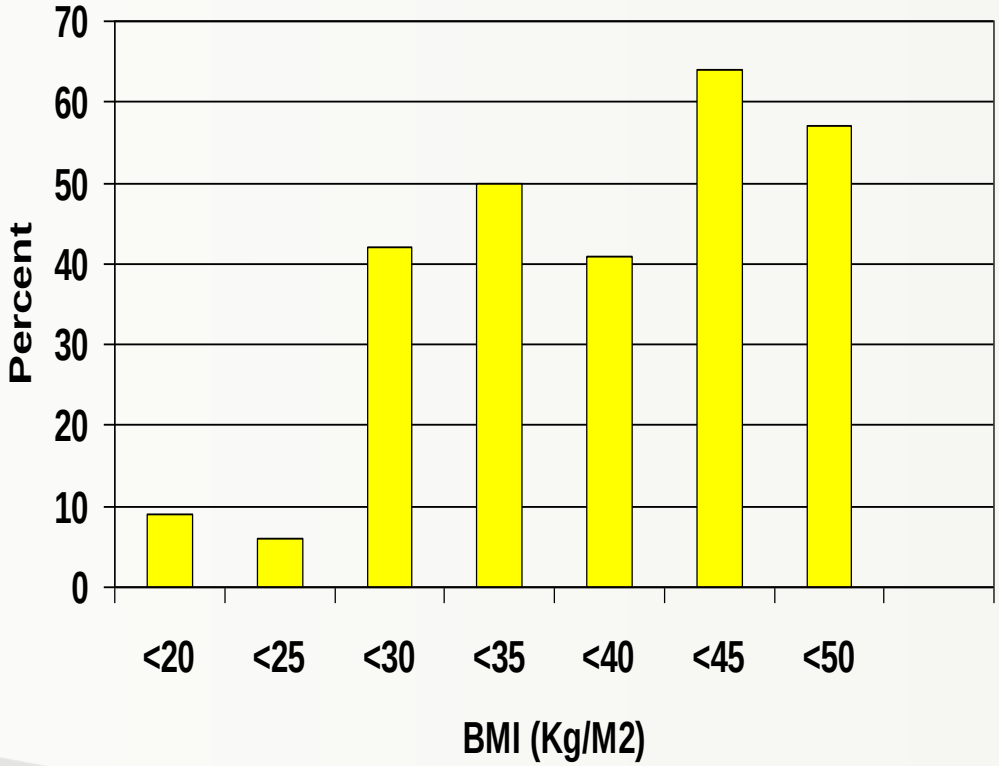
PREVALENCE AMONG MOTHERS AND SISTERS OF PCOS PATIENTS

	Mothers	*Sisters*
Total No.	78	50
PCOS	19 (24%)	16 (32%)
Hirsutism only	5 (6%)	1 (2%)
Oligomenorrhea	8 (10%)	6 (12%)

Kahsar-Miller & Azziz. Fertil Steril 2001;75:53-8

PREVALENCE OF GLUCOSE INTOLERANCE IN PCOS BY AGE AND BMI





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Legro et al. J Clin Endocrinol Metab 1999; 84:165

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:
  - 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 (> 12 cm^3?) over follicle number
  - Always exclude related/similar disorders (17-HP, TSH, Prl)

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

TREATMENT OF PCOS

- Goals include treatment & prevention of:
  - Infertility
  - Dermatologic disorders (hirsutism, acne, alopecia)
  - Ovulatory & menstrual dysfunction (DUB, endometrial hyperplasia or Ca)
  - Metabolic abnormalities, incl. dyslipidemia, glucose intolerance & obesity
- *Optimum treatment is generally combination therapy*

Androgen Excess Society

The Androgen Excess Society was founded in 2002 to promote knowledge, and original clinical and basic research, in every aspect of androgen excess disorders.

Membership includes basic and clinical scientists, and clinicians, whose major interest is the etiology, diagnosis, treatment and prevention of androgen excess disorders.

The Society is international in scope.

www.ae-society.org

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