PCOS in Adolescence

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- **Defining PCOS and polycystic ovaries**
- **Menstrual regularity in a normal young population**
- **PCOS in childhood and adolescence**
- **Managing PCOS in adolescence**

The Rotterdam ESHRE/ASRM Consensus Group Revised 2003 Diagnostic Criteria for PCOS

2 out of 3 criteria required

- Oligomenorrhoea and/or amenorrhoea
- Hyperandrogenism (clinical and/or biochemical)
- Polycystic ovaries

Exclusion of other causes of menstrual disturbance or androgen excess

Human Reproduction 2004; 19: 41-47. Fertility & Sterility, 2004; 81: 19-25.

PCOS in Adults

Oligomenorrhoea: > 90% PCOS

Amenorrhoea: ~ 30 – 50% PCOS

Anovulatory infertility: > 90% PCOS

Acne in women: > 95% PCOS

Hirsutism: > 95% PCOS

Polycystic ovaries:

Female caucasian population: 20 – 33% PCO
15 – 25% PCOS

U.K. Asian population: 50% PCOS

Normal Adolescents

Oligomenorrhoea

Amenorrhoea

Acne

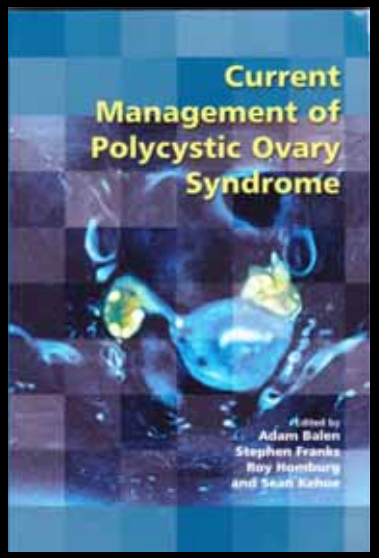
“Multicystic” ovaries

PCOS in Adolescence

- Whilst PCOS is a real entity in the adolescent population, there is no clear consensus on diagnostic criteria

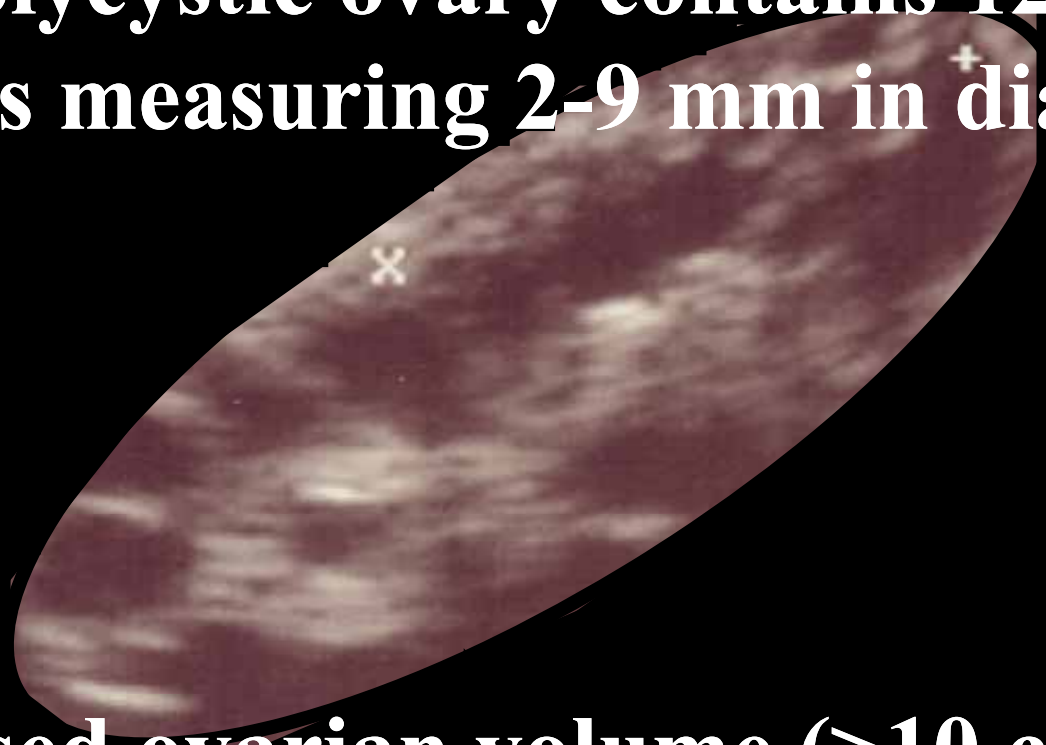
- The characteristics of the menstrual cycle in healthy girls in the years immediately following menarche, together with the variability of certain investigations, result in particular problems in adolescence

RCOG Scientific Study Group, 2010



Ultrasound Assessment of the Polycystic Ovary: International Consensus Definitions

The polycystic ovary contains 12 or more follicles measuring 2-9 mm in diameter



and/or

increased ovarian volume (>10 cm^3)

Balen, Laven, Tan & Dewailly; Hum Reprod Update 2003; 9: 505
ESHRE/ASRM Consensus 2003

Further debates:

Volume should be adjusted to 7 cm^3

Jonard et al, Human Reprod 2005; 20:2893

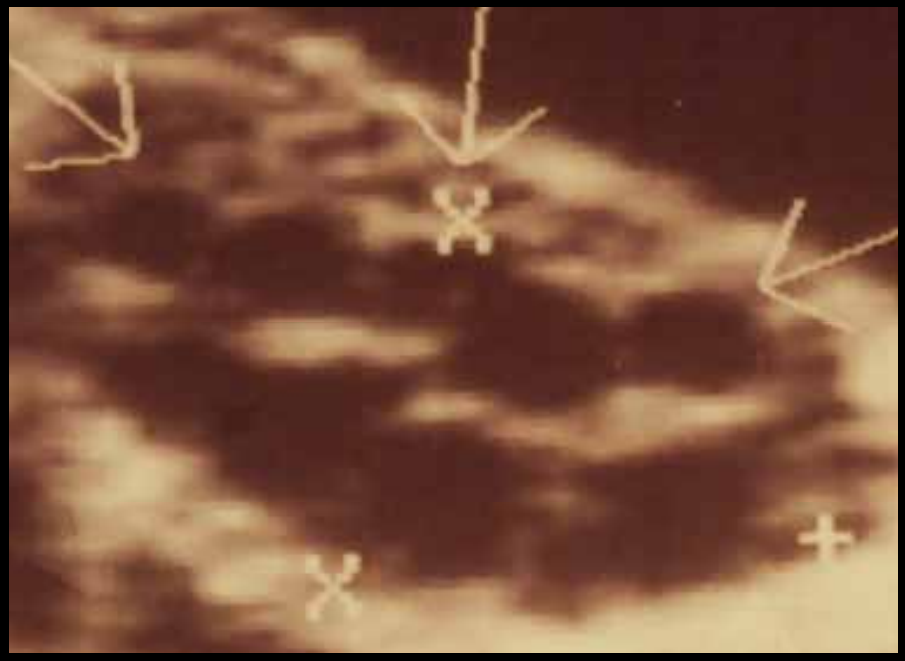
Follicle size most representative 2-5mm

PCOS (n = 457)

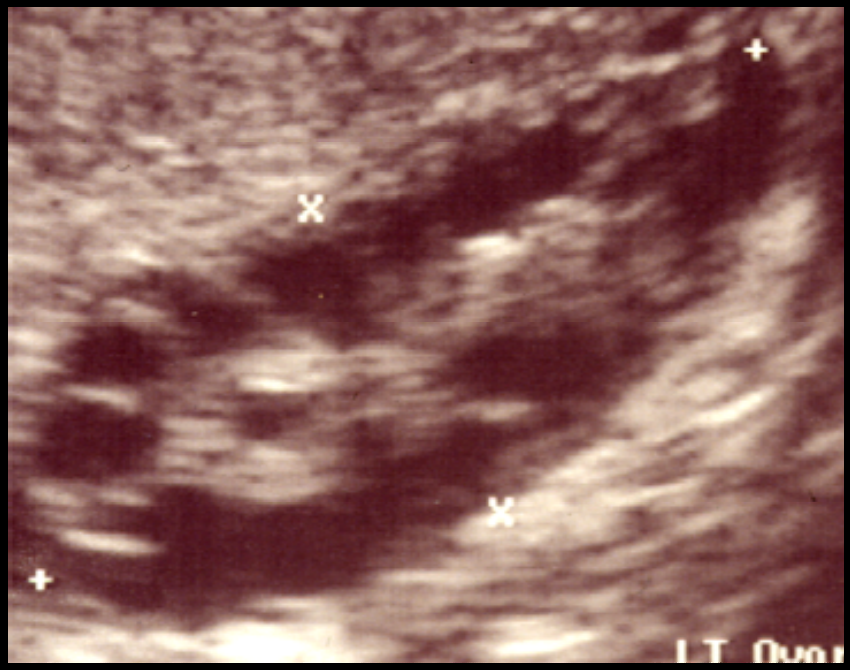
	Amenorrhoea	Oligomen.	Reg cycles	Controls (n=188)
2-5mm	18 (17-40)	14 (4-28)	12 (4-25)	5 (2-10)
6-9mm	2 (0-10)	4 (0-12)	4 (0-12)	2 (0-6)

Dewailly et al, Human Reprod 2007; 22:1562

Multicystic ovary



Polycystic ovary



Detection of polycystic ovaries in 428 girls aged 3 – 18 years

6y : 6%

10y : 18%

15y : 26%

All : 24%

Bridges et al F & S 1993; 60: 456-60

Polycystic ovaries in prepubertal girls

7.6 ± 0.6 years

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

vs 0% in control daughters

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

- ↑ ovarian volume (>10 cm^3) in 43% 10–18 y with PCOS

Shah et al. J Pediatr Adolesc Gynecol 2010;23:146–52

- ↑ ovarian volume in daughters of women with PCOS in comparison with daughters of women without PCOS

- Only when Tanner stage 5, is ovarian volume abnormal by adult standards:

  13.9 cm^3 [SD 4.4 cm^3] vs 6.9 cm^3 [SD 3.9 cm^3] in controls

- ∴ earlier in puberty a lower cut-off ovarian volume for pco may be appropriate

Sir-Petermann et al. J CEM 2009;94:1923–30

Polycystic ovarian morphology (PCOM) in adolescents

20 healthy adolescents followed 2–4 years after menarche

PCOM in 40%, 35% & 33.3% at 2, 3 & 4 years after menarche

PCOM not associated with abnormalities in ovulatory rate, menstrual cycle duration, androgens or insulin resistance

Lower FSH in girls with PCOM

PCOM may correspond to a physiologic condition during early adolescence

Codner, et al, Chile F&S 2010

Robust normative data in the adolescent population is required,
recording the number and size of ovarian follicles and ovarian volume in conjunction with features of the menstrual cycle

Other endocrine tests for PCOS:

AMH :

- correlates well with AFC
- proposed as most accurate biochemical marker for PCOS
- correlates best with 2-5 mm follicles

Pigny et al JCEM 2003; 88:5957

Laven et al JCEM 2004; 89:318

AMH in Puberty

- Elevated AMH in girls born to mothers with PCOS,
- Both in infancy and pre-pubertally (4–7 years),
- Suggests that follicular development altered in infancy

- Adequate longitudinal reference data throughout childhood and puberty in healthy girls not born to mothers with PCOS are required

Sir-Petermann et al. J Clin Endocrinol Metab 2006;91:3105–9

AMH in Adolescent Girls

- 213 girls 15.1y (range 14.5 - 17.6y)
- 53% irregular menses
- 28% biochemical HA
- 35% PCOM
- 30% PCOS (Rotterdam criteria)

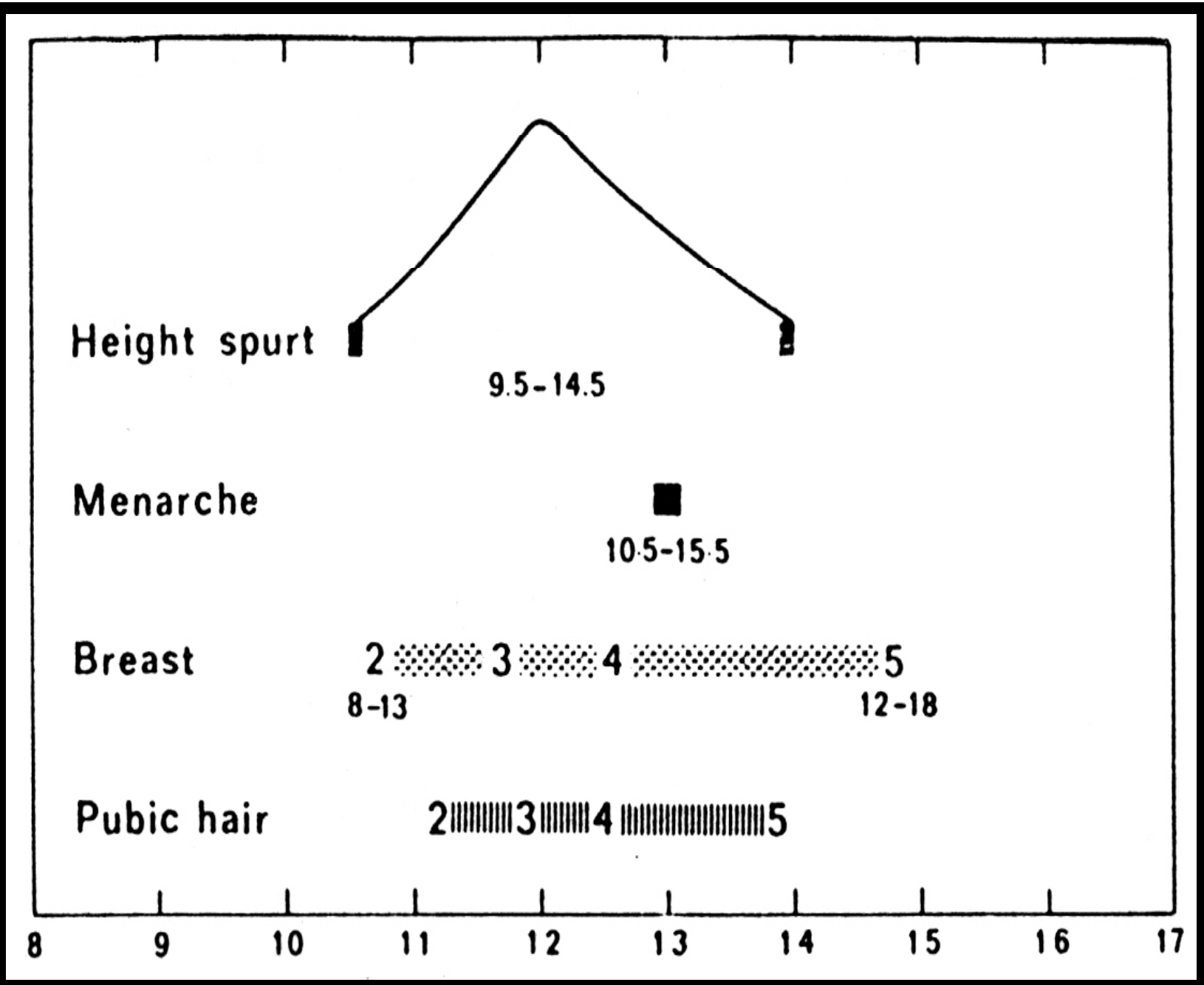
- Median AMH 22 pmol/l in controls vs 32 PCO $p < 0.001$
  vs 31 in PCOS $p = 0.002$

- But large ranges and so poor ability to predict PCO or PCOS, using 30 as cut-off

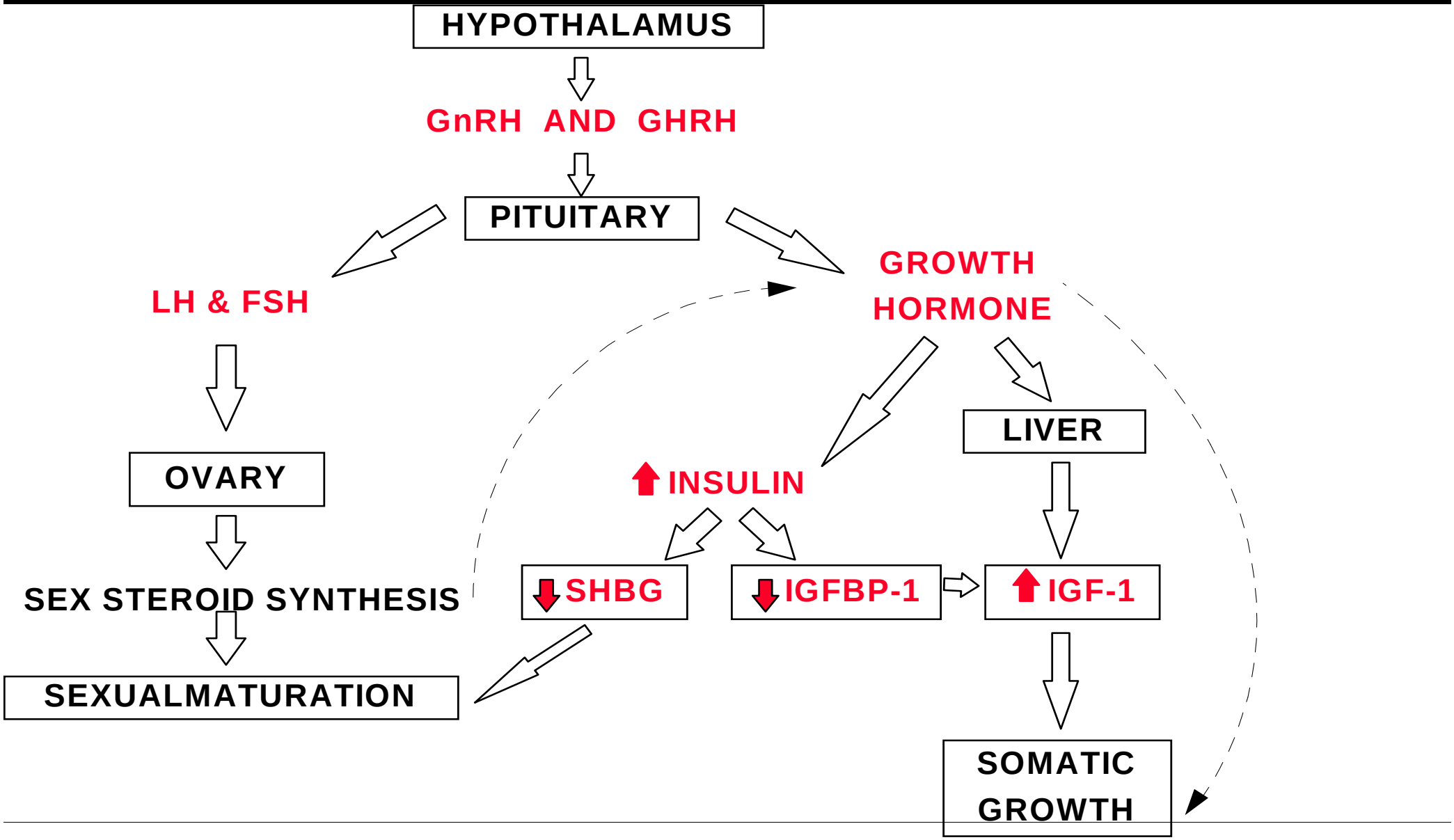
Hart et al. F&S 2010; 94: 1118-1121

Puberty

- Growth associated with profound metabolic changes
- Basal metabolic rate slows at end of linear growth and predisposes to weight gain



Sequence of normal puberty in girls, after Tanner 1989


HYPOTHALAMUS
GnRH AND GHRH
PITUITARY
LH & FSH
GROWTH HORMONE
OVARY
INSULIN
LIVER
SEX STEROID SYNTHESIS
SHBG
IGFBP-1
IGF-1
SEXUALMATURATION
SOMATIC GROWTH

Two phases of increased ovarian growth

- Adrenarche – in response to ↑ androgens
- Rising gonadotropins, GH, insulin and IGF-1

Sampoalo et al 1994
Nobels & Dewailly 1992

Biochemistry of Normal Puberty

- Steady rise in androgen concentrations coupled with a fall in sex hormone-binding globulin (SHBG) with progression through puberty
- Physiological increase in insulin resistance
- An apparent elevation in fasting insulin concentration may reflect a physiological rather than pathological insulin resistance

Caprio et al. J Pediatr 1989;114:963–7

Rosenfield et al. J Pediatr Endocrinol Metab 2000;13 Suppl 5:1285–9

Biochemical hyperandrogenism

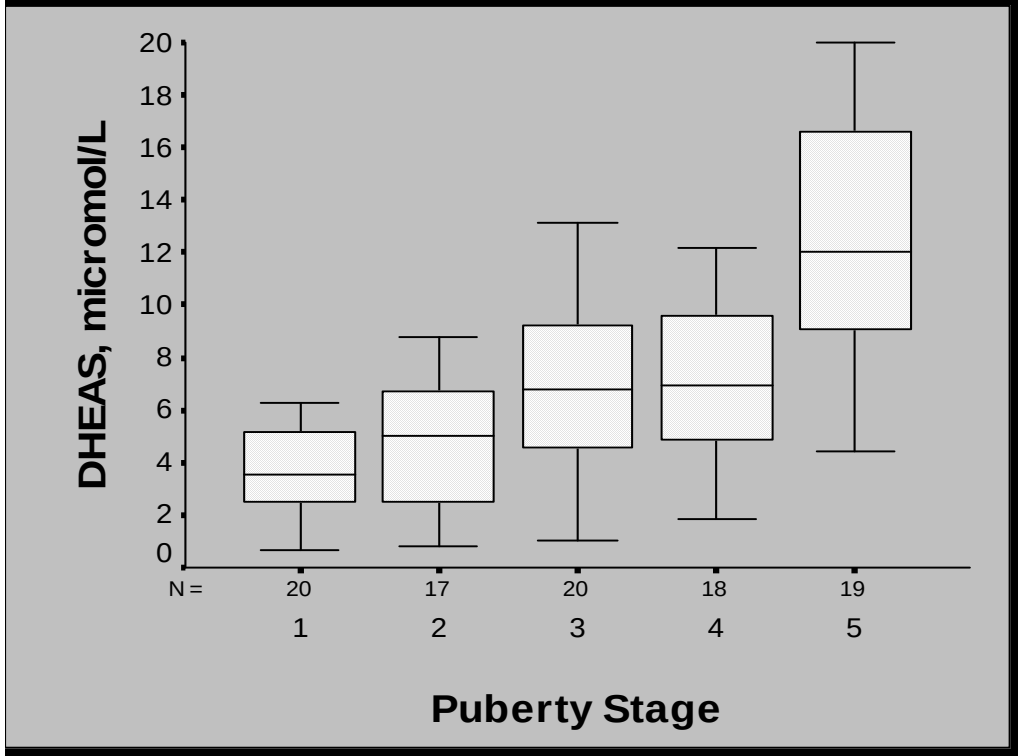
- which androgen should be measured ?
- how often should it/they be measured ?
- what are normal values ?
  - they should they be constructed by weight and age
  - for each analytical method
- which analytical technique should be used ?

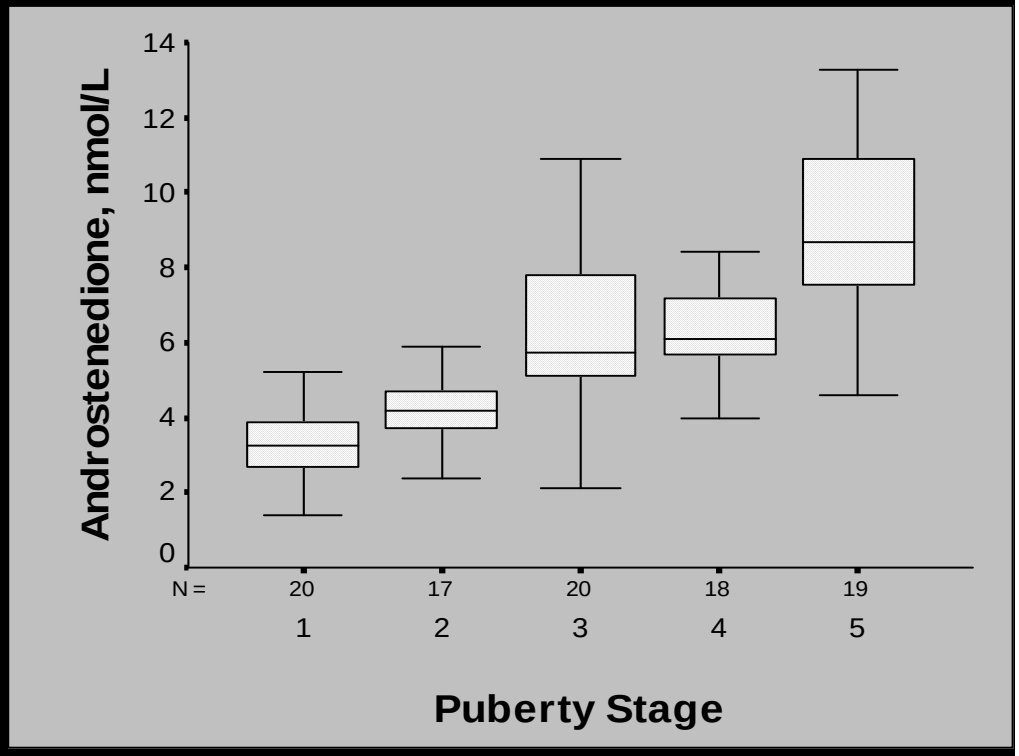
Changes in Androgens in Normal Puberty

Tanner stage	Age (years)	Testosterone (nmol/litre)	SHBG (nmol/litre)	DHEAS (micromol/litre)	A4 (nmol/litre)
1	10.2 (9.6–10.7)	0.3 (0.3–0.5)	66 (56–94)	3.5 (2.4–5.2)	3.3 (2.7–4.0)
2	11.4 (10.5–11.9)	0.3 (0.3–0.8)	57 (48–69)	5.1 (2.4–7.5)	4.2 (3.4–4.8)
3	12.2 (11.6–12.8)	0.8 (0.5–1.1)	57 (40–71)	6.8 (4.5–9.6)	5.8 (5.1–7.9)
4	13.2 (12.6–13.8)	1.1 (0.8–1.5)	45 (34–66)	7.0 (4.6–10.0)	6.1 (5.7–7.5)
5	14.9 (14.2–15.2)	1.4 (1.1–1.6)	43 (33–61)	12.1 (9.0–17.7)	8.7 (7.4–11.3)

Ahmed ML. Endocrine changes during puberty.
Pubertal Growth in Diabetic Children. PhD thesis, The Open University; 2008.

Normal girls: Adrenal Androgens, longitudinal changes





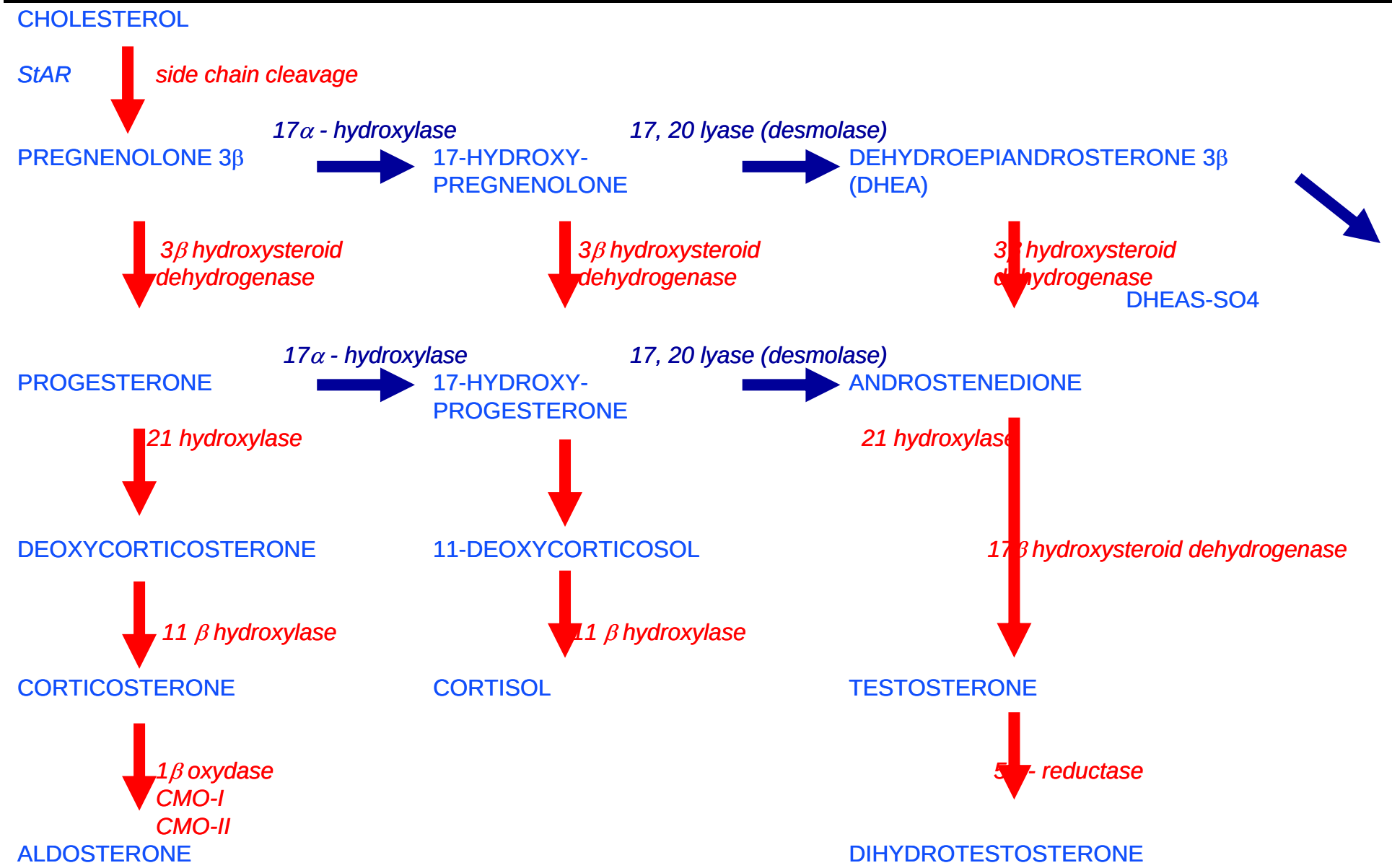
PCOS after precocious pubarche

- SGA infants show postnatal catch up growth
- Increased risk of precocious pubarche (<8y)
- Associated with ovarian HA / PCOS, dyslipidaemia, increased central fat insulin resistance
- Management with metformin, flutamide and COCP (containing drosperinone)

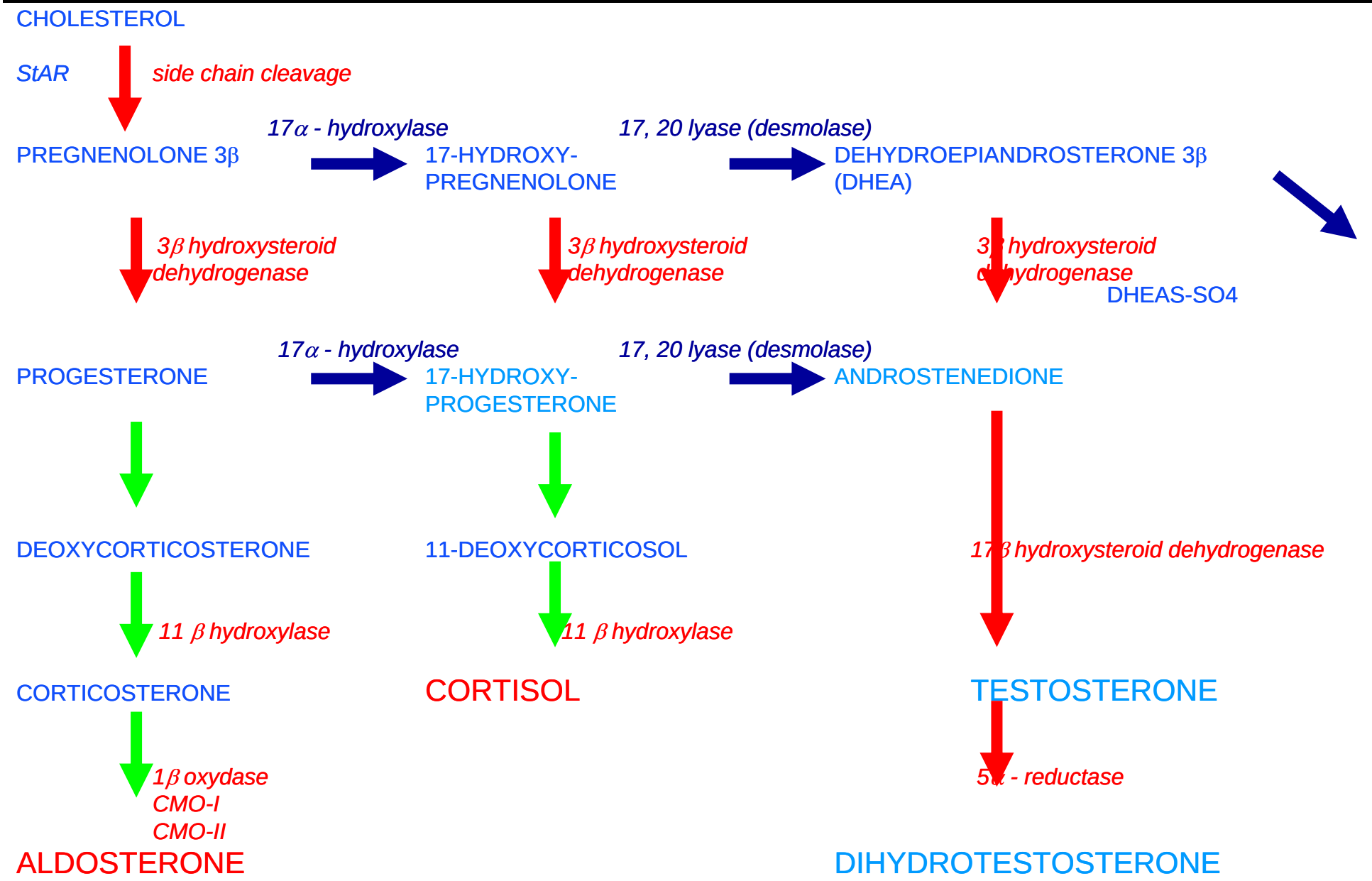
Ibanez et al 1998-2005

Other causes of androgen excess

- Late onset congenital adrenal hyperplasia
- Androgen secreting tumours
- Cushing's syndrome



(StAR = steroidogenic acute regulatory protein, delivers cholesterol to mitochondria)


CHOLESTEROL
StAR
side chain cleavage
PREGNENOLONE 3β
17α - hydroxylase
17-HYDROXY-
PREGNENOLONE
17, 20 lyase (desmolase)
DEHYDROEPIANDROSTERONE 3β
(DHEA)
3β hydroxysteroid
dehydrogenase
3β hydroxysteroid
dehydrogenase
3β hydroxysteroid
dehydrogenase
DHEAS-SO4
PROGESTERONE
17α - hydroxylase
17-HYDROXY-
PROGESTERONE
17, 20 lyase (desmolase)
ANDROSTENEDIONE
DEOXYCORTICOSTERONE
11-DEOXYCORTICOSOL
17β hydroxysteroid dehydrogenase
11 β hydroxylase
11 β hydroxylase
CORTICOSTERONE
CORTISOL
TESTOSTERONE
1β oxydase
CMO-I
CMO-II
5α - reductase
ALDOSTERONE
DIHYDROTESTOSTERONE

Congenital Adrenal Hyperplasia

21 hydroxylase deficiency (95% of CAH)

1:5,000 – 1:20,000 births
carrier status in 1:80
racial differences

classical salt wasting ~ 60%
non-salt wasting ~ 20%
late onset (non-classical / NCAH) ~ 20%

NCAH

21 hydroxylase deficiency

- > 100 mutations of *CYP21*
- Most CAH and NCAH are compound heterozygotes
- 1-10% of adolescents with HA
- Anglo-Saxons < Latin/Mediterranean < Ashkenazi Jews / Middle-East

Non-Classical CAH

21 hydroxylase deficiency

- Not virilised
- ↑ 17-OHP, Androstendione
- Measure 17-OHP, early morning, early follicular phase

  < 6 nmol/l (2ng/mL) excludes NCAH

  > 12 nmol/l (4ng/mL) diagnostic

- ACTH-stimulation (250mcg) test if basal > 6 nmol/l

  Post-stimulation > 30-36 nmol/l (10-12ng/mL) diagnostic

  > 50-60 nmol/l diagnostic classical CAH

NCAH

21 hydroxylase deficiency

- Pre-conception counselling
- Risk of child with CAH 2.6% (95% CI 0.7-6.4%)
- Risk of child with NCAH 15.4% (95% CI 9.4-21.3%)

Body fat and age at menarche

- **26-28% body fat required for regular ovulatory cycles**

  Frisch, Baillere's Clin Obstet Gynaecol 1990; 4:419-439

- **Obesity associated with early menarche and PCOS**

  Stoll, Cancer Res Treat 1998; 49: 187-193

  van Hoff et al, JCEM 2000; 85: 1394-1400

- Defining PCOS and polycystic ovaries
- Menstrual regularity in a normal young population
- PCOS in childhood and adolescence
- Managing PCOS in adolescence

Features of the menstrual cycle in healthy girls in the first 2 years post menarche

	Diaz et al. (1996)	Hickey and Balen (2003)
Age at menarche	12.4 years	12–13 years
Menstrual cycle interval	21–45 days	21–45 days
95th centile for cycle interval	90 days	90 days
Menstrual flow length	< 7 days	2–7 days
Blood flow	3–6 pads or tampons per day	3–6 pads per day

Features of the menstrual cycle in healthy girls

- First 2 ys anovulation and irregular cycles common
- 3 years post menarche, 59% of cycles anovulatory, but the majority 21-34d
- Regular cycles established more quickly by 3 years, in girls who experience an earlier menarche

Diaz et al. (1996)
Hickey and Balen (2003)

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PCOS in Singaporean Adolescents

150 girls aged 12-22 y, “majority” 15-18y
All presented with menstrual disturbance

Mean age menarche in Singapore 12.6 ± 1.3 y

In PCOS: 53% had menarche 9 - 12 y
33% > 12y
14% primary amenorrhoea
21% secondary amenorrhoea

Dramusic et al J Ped Adol Gyn 1997; 10: 125-132

PCOS in Singaporean Adolescents

Of those with primary amenorrhoea or secondary amenorrhoa of more than 1 year duration,
43% were obese

Dramusic et al J Ped Adol Gyn 1997; 10: 125-132

Age at menarche and ovarian function

	Controls	PCOS	POF
	n = 957	265	98
Age at menarche			
< 11y	12%	16%	21%*
12-14y	74%	59%	58%
➢15y	14%	26%*	21%

* Significant compared with controls

Sadrzadeh et al Hum Reprod 2003; 10: 2225

PCOS in adolescence

Adolescents, mean age 16.7 ± 0.9 years

Regular cycle (58)	Irreg. (50)	Oligomen. (29)
PCO 9%	PCO 28%	PCO 45%

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

PCOS in adolescence

Oligomenorrhoeic adolescents (mean age 15.7 ± 0.6y) higher LH and androgens than those with regular cycles

Proportion with irregular cycles (22- 41d) declines with age

Oligomenorrhoea in adolescents is an early sign of PCOS and not a stage in maturation of H-P-O axis

van Hoff et al Hum Rep 1999; 14:2223

PCOS in adolescence

Increasing LH and androgens in those with PCO, compared with controls

No differences in insulin sensitivity overall, unless oligomenorrhoeic (and with ↑ BMI)

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

Adolescents with oligomenorrhoea 2 y post menarche more likely to regulate cycle over next 40 months if LH normal

Venturoli et al JCEM 1992; 74: 836

Menstrual irregularity aged 15y better predictor for later oligomenorrhoea than LH or androgens

Increased body weight helps predict persistent oligomenorrhoea but also normal weight oligomen adolescents have high risk of staying so

van Hoff et al Hum Rep 2004; 19:383

60% adolescents with oligomenorrhoea 2y after menarche keep this pattern for at least 8 years

Southam & Richart Am J Obstet Gynecol 1966; 94: 637

70 adolescents with PCOS, Wisconsin, USA

Mean age 16.2 years (range 13–22 years),

14% were overweight
70% were obese

Oligomenorrhoea 43%
Secondary amenorrhoea 21%
Regular menses 21%

Acne 70%
Hirsutism 60%

IGT 6%
Type 2 diabetes 3%

Bekx et al. J Pediatr Adolesc Gynecol 2010;23:7–10

Oligomenorrhoea 2 years post menarche may be regarded as possible early clinical sign of PCOS

Homburg & Lambalk Human Reprod 2004; 19: 1039-1042

- Defining PCOS and polycystic ovaries
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Management of adolescent girls with PCOS

- Psychological support
- Lifestyle advice
- COCP …. *which, when?*
- Endometrial protection

Eating disorders

- **Common during adolescence**

- **Amplify endocrine disturbances**

224 women 17-24 years:

30% episodes over-eating,

4% extreme methods weight control

Michelmore KF, Balen AH, Dunger DB
Human Reproduction, 2001; 16: 765-769

The PCOS Health-Related Quality of Life Questionnaire (PCOSQ)

Women and adolescents with PCOS

Worst health concerns:

- **weight**
- **infertility**
- **emotional limitations and poor energy**
- **hirsutism / acne**

Jones et al Human Reprod 2004; 19:371

Hall et al ESHRE 2007

Obesity and quality of life in adolescent girls with PCOS

186 healthy girls (BMI 23.5)
vs 96 with PCOS (BMI 31.7)

Body weight primary factor affecting quality of life

Trent et al, Ambul Pediatr 2005; 5: 107-11

PCOS and eating disorders

- Menstrual irregularity and acne common in PCOS and bulimia nervosa
- Women with PCOS more likely to have abnormal eating patterns (21% vs 2.5%)
- Bulimia affects insulin secretion which might promote PCOS
- PCOS affects body image which might promote Bulimia

McCluskey 1991; Jahanfar 1991; Raphael 1995

Treatment of PCOS during adolescence

Lifestyle intervention

Oral Contraceptive Pill

- Low dose oestrogen
- Drospirenone
- Cyproterone acetate

PCOS after precocious pubarche

- SGA infants show postnatal catch up growth
- Increased risk of precocious pubarche (<8y)
- Associated with ovarian HA / PCOS,
- dyslipidaemia, increased central fat
  insulin resistance
- Management with metformin, flutamide and COCP (containing drosperinone)

Ibanez et al 1998-2005

Metformin

- 22 adolescent girls (13–18 y) with PCOS
- RCT metformin (750 mg bd) vs placebo
- Reduction of androgen concentrations
- Restoration of regular menses
- HDL cholesterol ↑
- Insulin sensitivity→

Bridger et al. Arch Pediatr Adolesc Med 2006;160:241–6

- Catalan girls presenting with PP who later progress to PCOS
- Metformin leads to improvement in insulin sensitivity, dyslipidaemia
- Improvement of hirsutism
- Regular menses

Ibáñez et al. J Clin Endocrinol Metab 2000;85:3526–30

- Obese girls with PCOS with IGT
- Metformin (850 mg twice daily for 3 months)
- Improved glucose tolerance and insulin sensitivity
- Reduced androgens

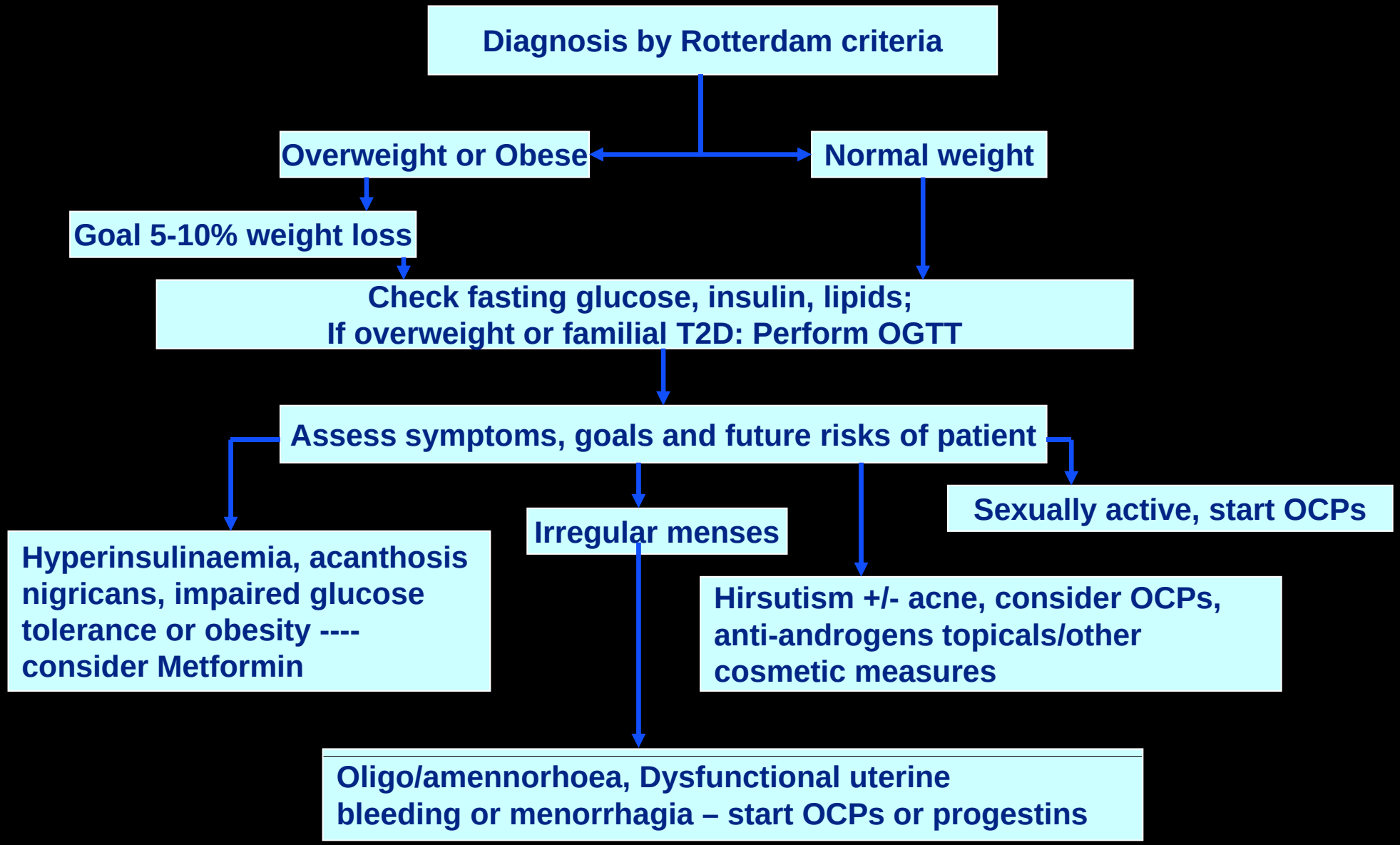
Arslanian SA, et al. J Clin Endocrinol Metab 2002;87:1555–9

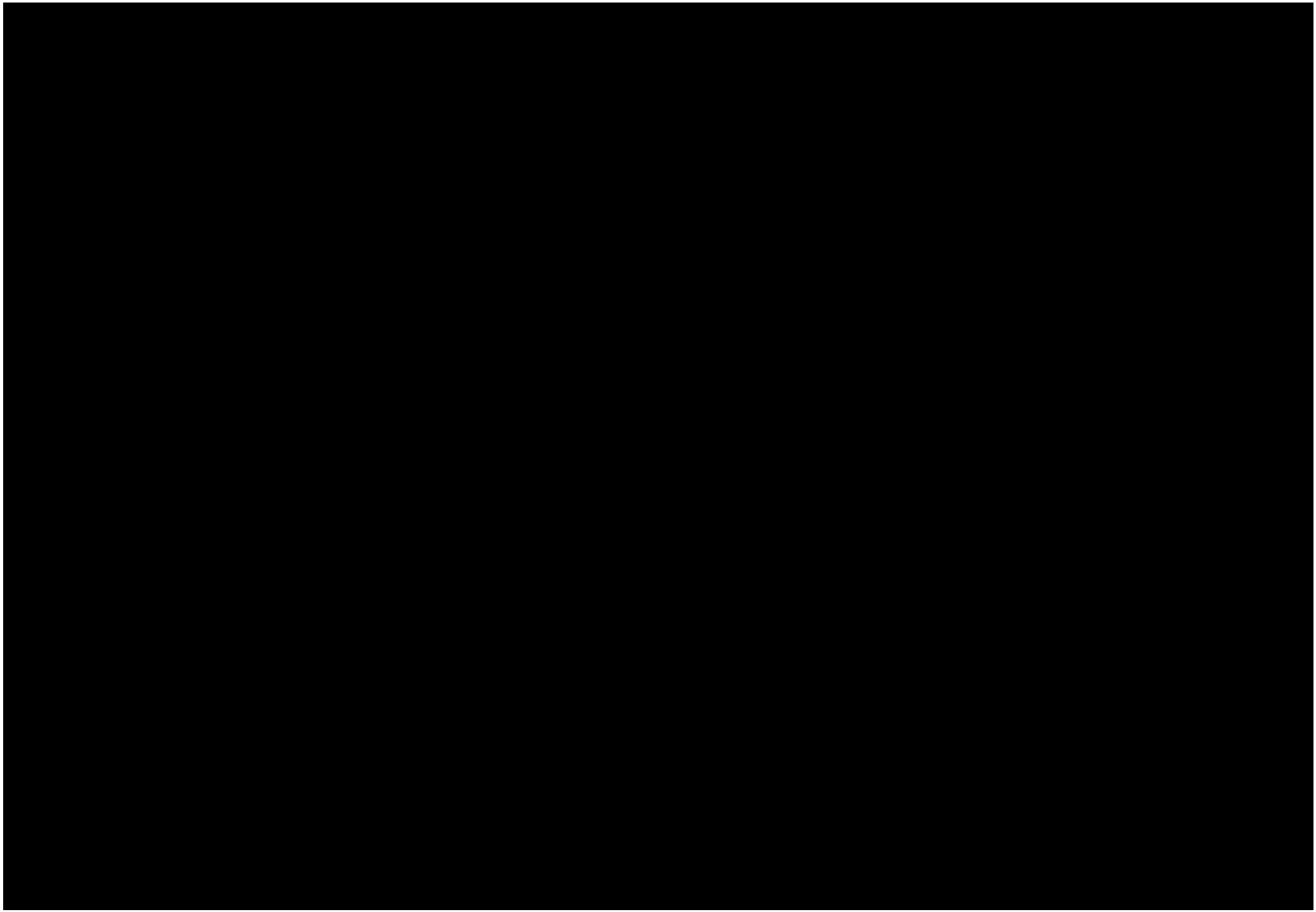
- In another study, metformin with lifestyle modifications and dietary advice led to modest weight loss, with improvements in insulin resistance and lipid variables leading to resumption of regular menses

Glueck CJ, et al. Metabolism 2006;55:508–14

Proposed Management Algorithm for Adolescent PCOS

Hassan A and Gordon CM, 2007 Curr Opin Peds





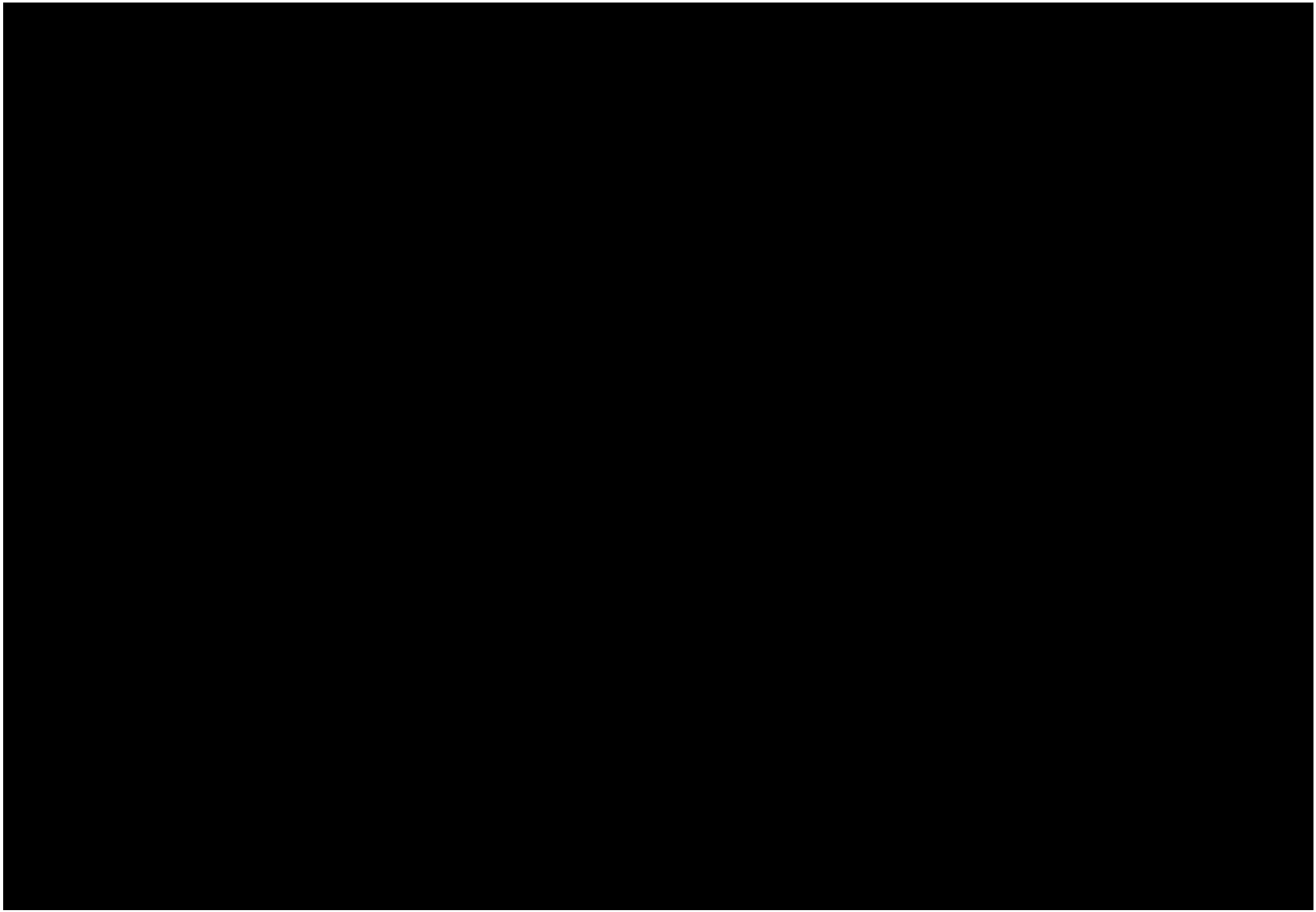
PCOS adolescence

- PCOS may present with early menarche and oligomenorrhoea / irregular bleeding,

  or in some with late menarche / primary amenorrhoea

- Obesity associated with increased ovarian and uterine volume and PCO in adolescence

- Oligomenorrhoea 2 years post menarche may be regarded as possible early clinical sign of PCOS



Volunteer Study of Women's Health

Kathy Michelmore, Adam Balen, David Dunger, Martin Vessey

- **224 female volunteers, 17-25y**
- **33% polycystic ovaries**
- **80% with polycystic ovaries had a least one feature of PCOS**

Michelmore et al, Clin Endocrinol 1999; 51: 779

224 women 17-25y, 33% polycystic ovaries

	PCO	Normal ovaries	P
Irreg cycles	65%	45%	n.s., 0.07
Acne	58%	50%	n.s.
Hirsutism	12%	10%	n.s.
BMI > 25	26%	22%	n.s.

224 women 17-25y, 33% polycystic ovaries

	PCO	Normal ovaries	P
BMI kg/m^2	23.3	23.1	n.s.
% body fat	30.4	29.4	0.048
Birthweight kg	3.49	3.28	0.004
Testo. nmol/l	2.67	2.47	0.03

PCOS in South Asians and Caucasians living in the U.K.

Case control study of anovulatory PCOS:

47 South Asian PCOS and 11 controls

40 Caucasian PCOS and 22 controls

Wijeyaratne et al, Clin Endocrinol 2002; 57: 243

S. Asians had:

similar age menarche 12.9 vs 12.8 y

similar degree of menstrual irregularity

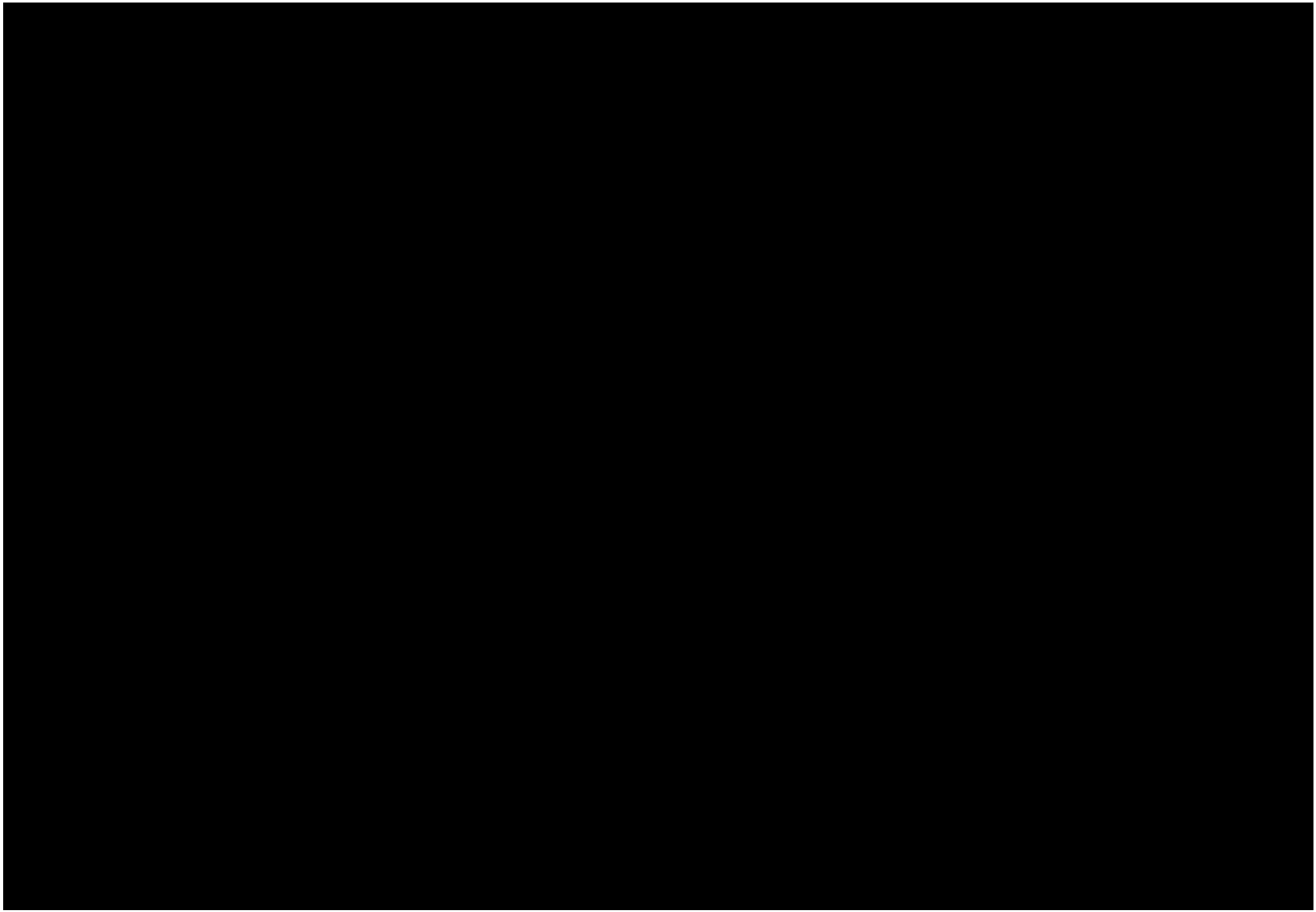
↓ age onset hirsutism	**p < 0.01**
↑ hirsutism, acne & acanthosis nigricans	**p < 0.001**

similar BMI & W:H

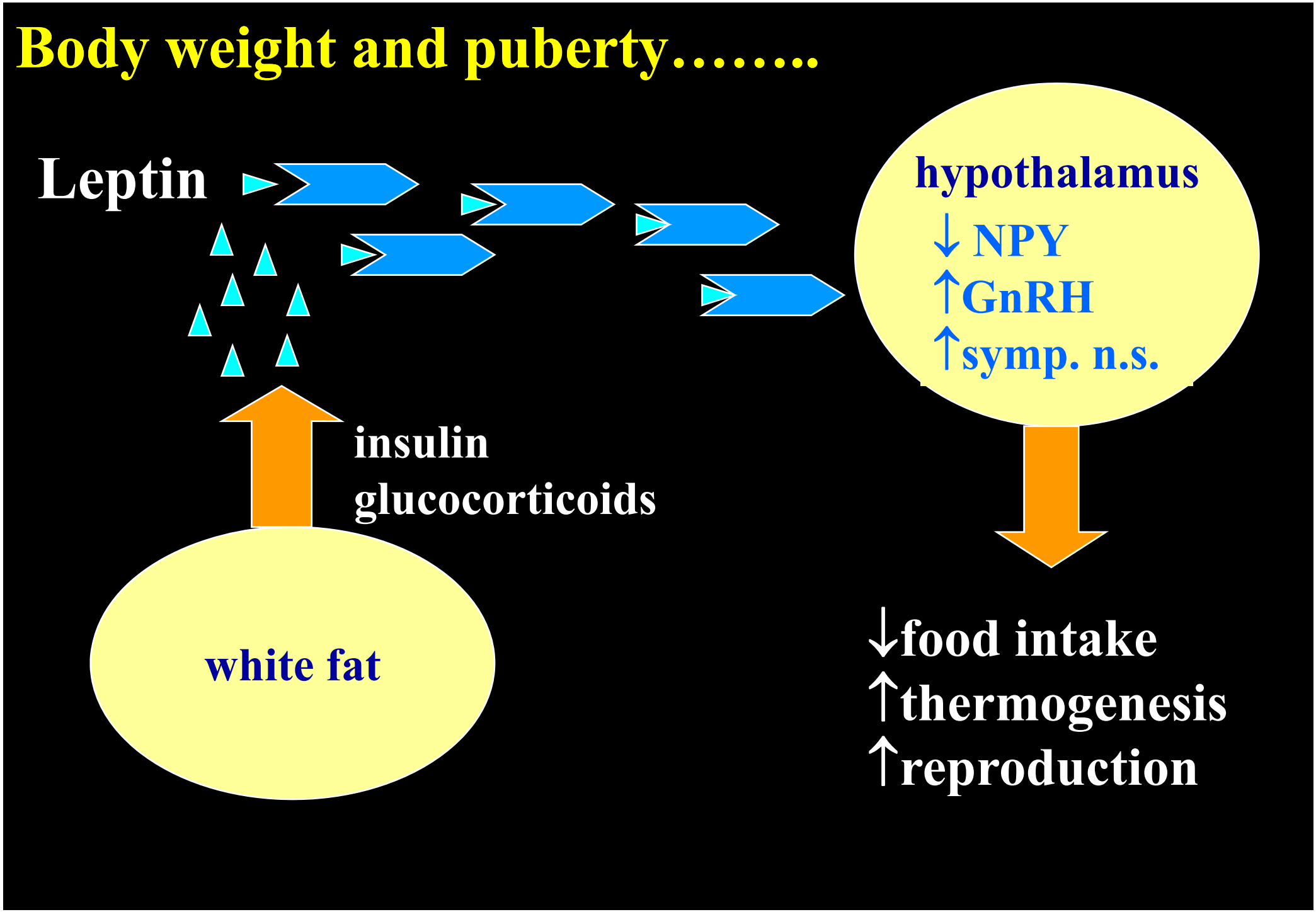
similar total Testosterone

↑ insulin and ↓ SHBG	**p < 0.001**

Wijeyaratne et al, Clin Endocrinol 2002; 57: 243



Body weight and puberty……..



- **Weight gain due to increased fat mass is common in girls post menarche and it has been suggested that this may accentuate the normal insulin resistance of puberty, leading to functional hyperandrogenism.**

- **Indeed, PCOS is more often reported in obese rather than lean adolescents and there has been a concern that the increasing rates of adolescent obesity may precipitate PCOS in those with a genetic or developmental predisposition.**

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
Rosefeld. et al. Journal of Pediatric Endocrinology and Metabolism 2000

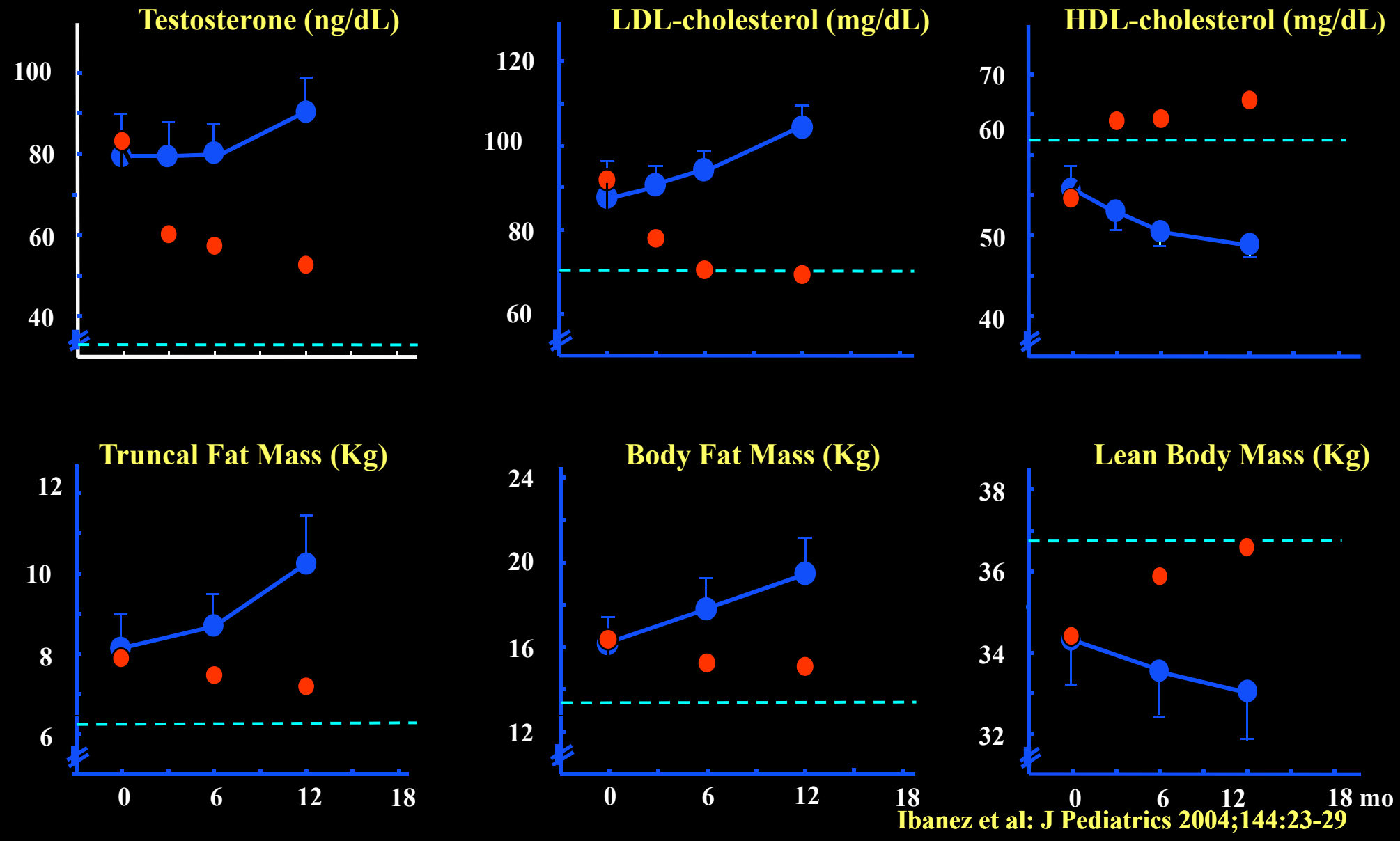
Precocious Adrenarche / Pubarche

- Onset of pubic hair < 8yrs (girls)
- Bone Age advance
- Raised DHEA and DHEAS
- Final height not compromised

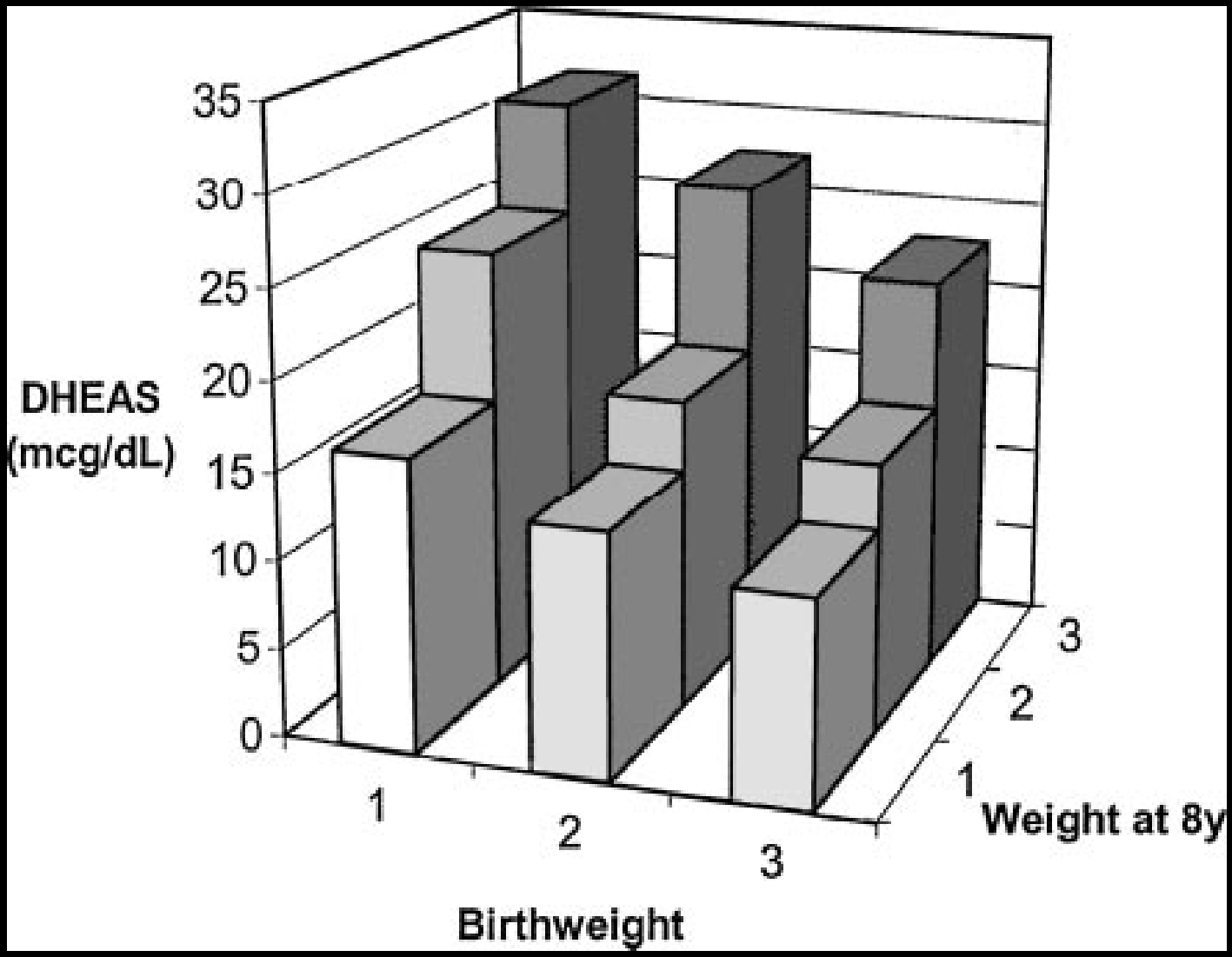
<u>Increased risks in low birth weight populations for:</u>

- Functional ovarian hyperandrogenism
- PCOS
- Syndrome X

Metformin (850 mg/d) Reverses Progression from PP to PCOS in SGA girls

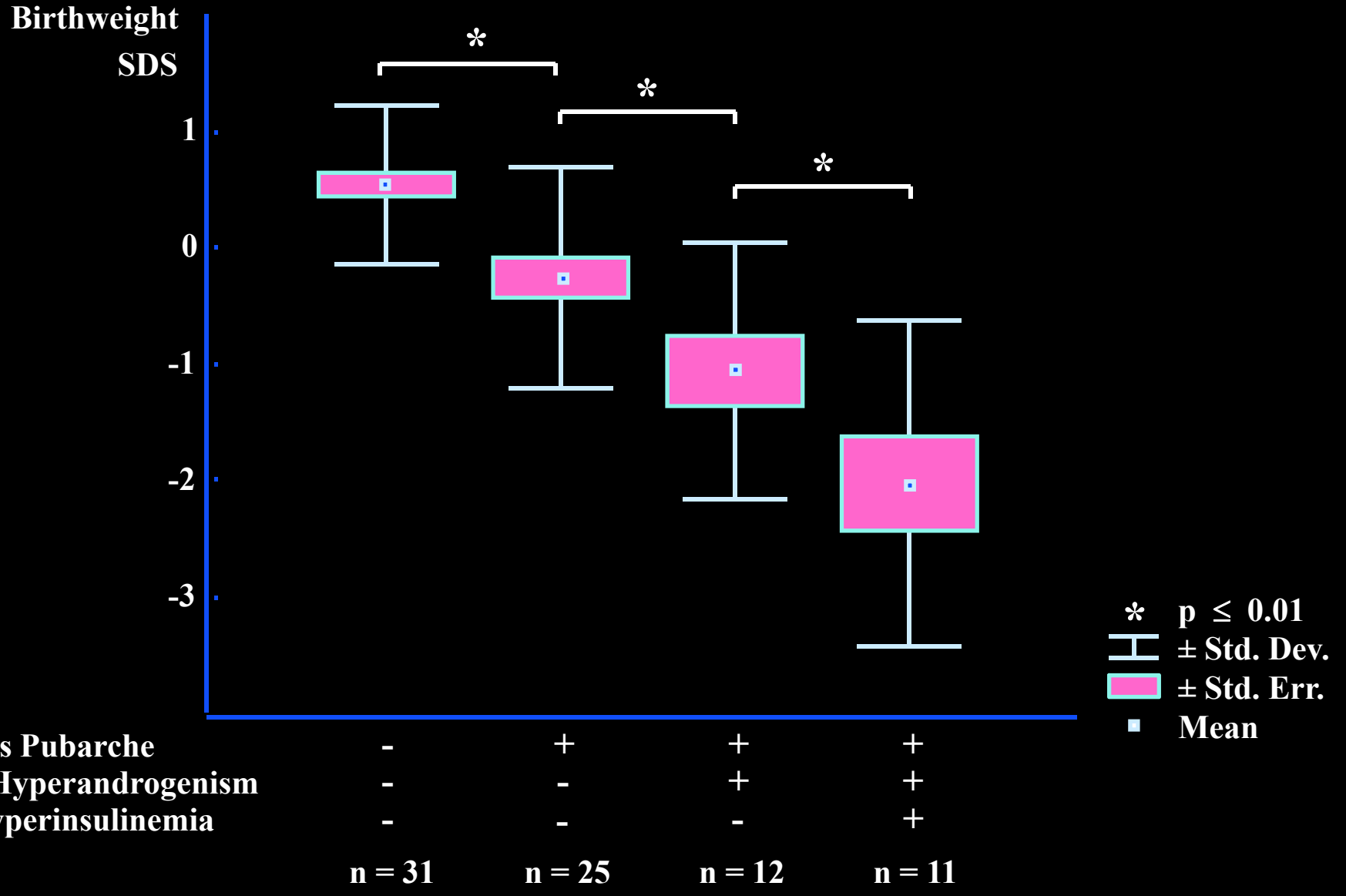


Ibanez et al: J Pediatrics 2004;144:23-29



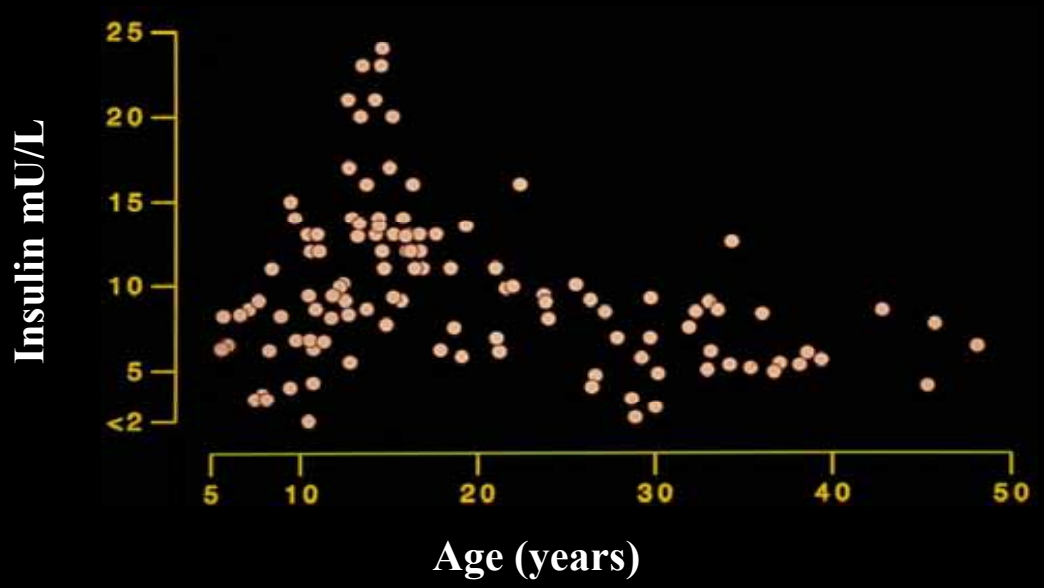
Ong et al. J Clin Endocrinol Metab 2004;89:2647--2651

PCOS after Precocious Pubarche: Relation to Reduced Foetal Growth

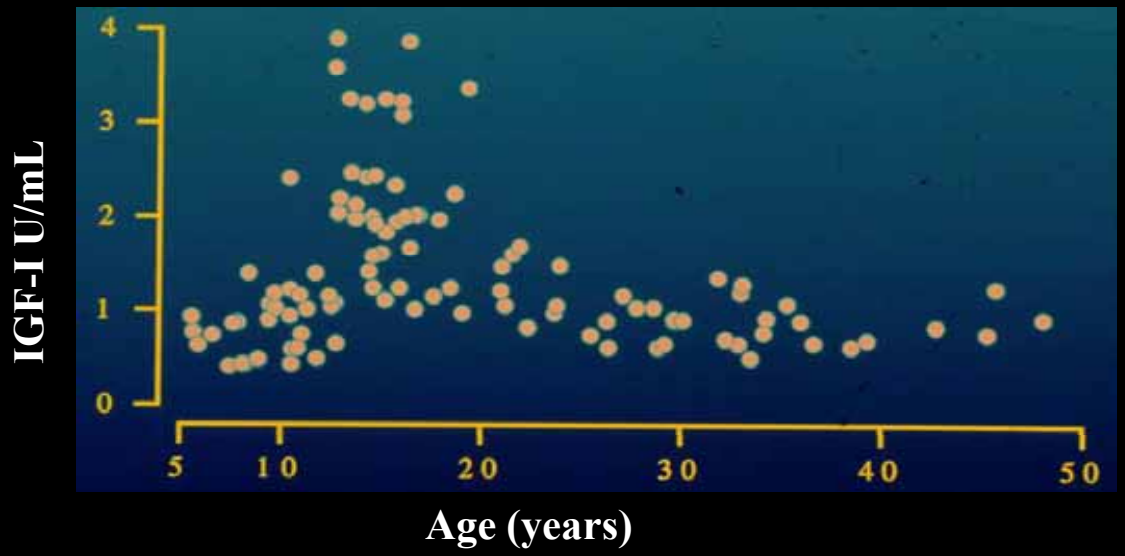


J Clin Endocrinol Metab, 1998

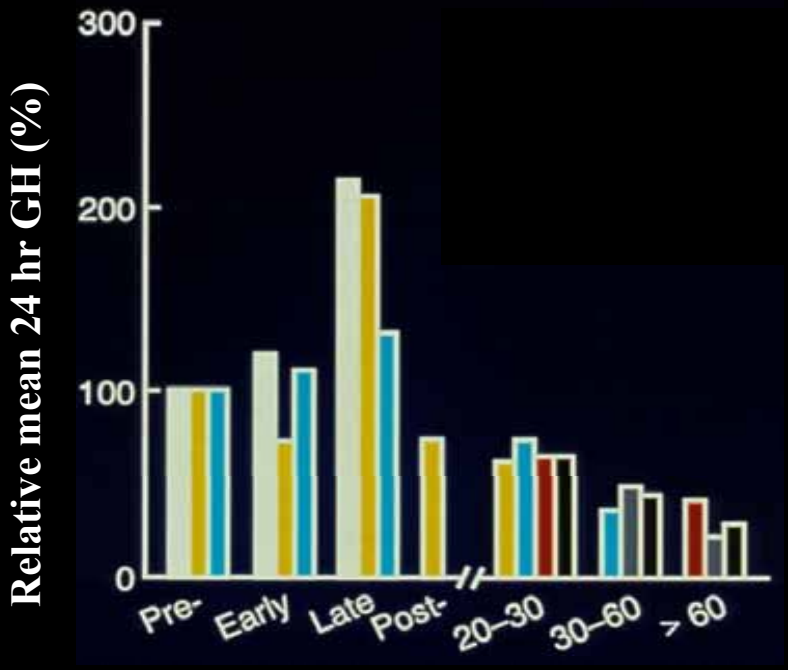
Fasting Insulin



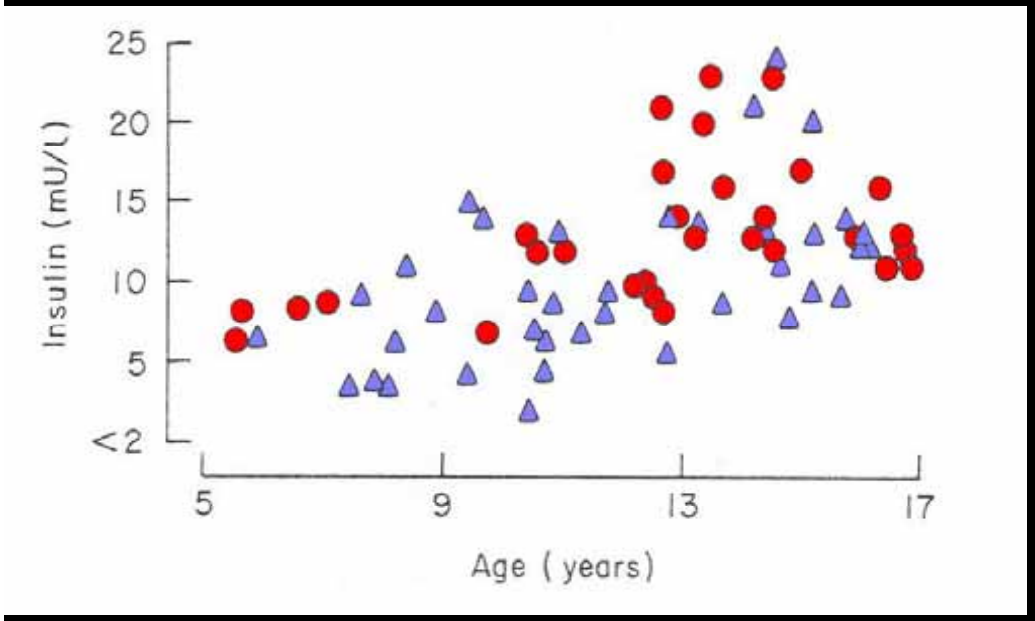
IGF-I

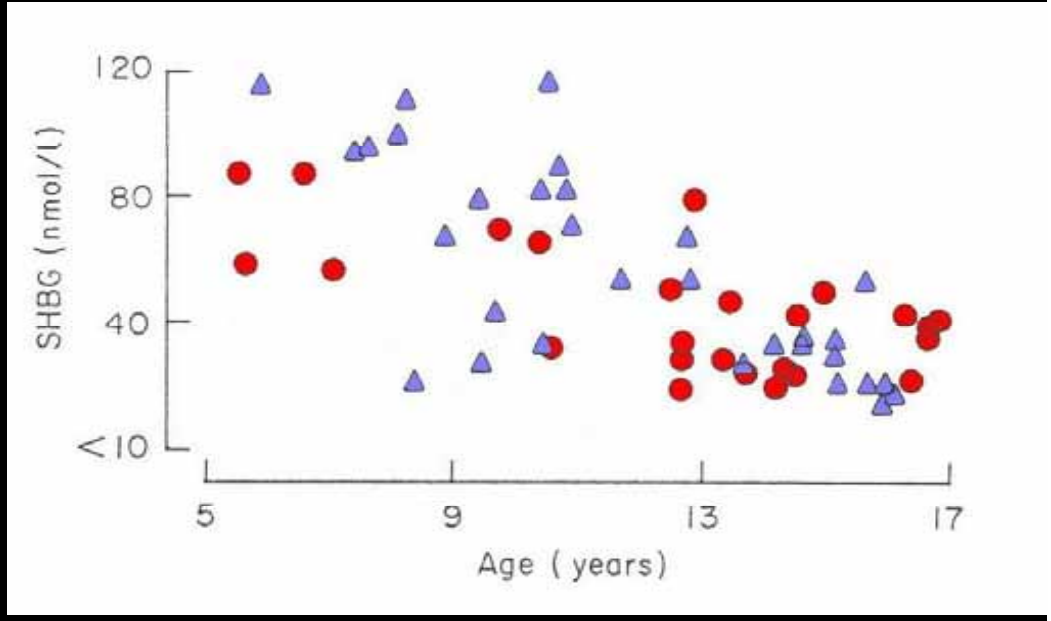


Growth Hormone



Insulin levels and SHBG

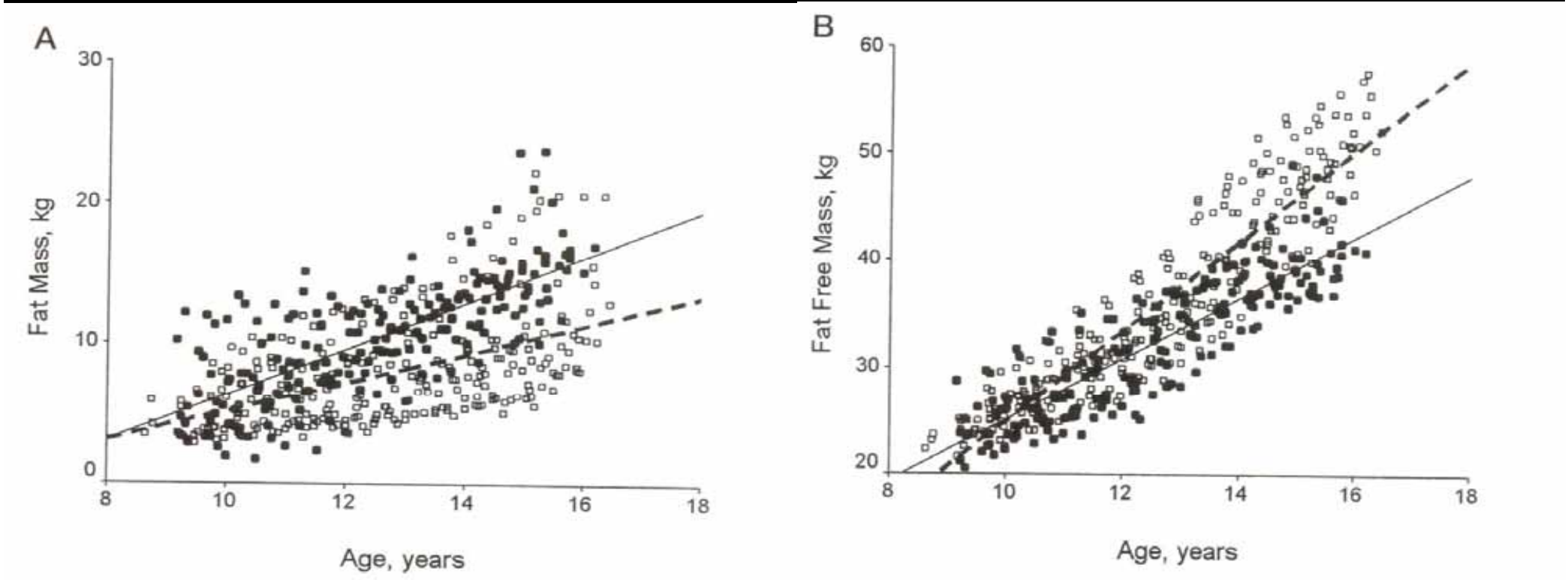




- Females
- Males

Holly et al. Clin Endocrinol 1989;31:277-284

Fat mass and fat free mass in boys and girls



Boys □ and ---
Girls ● and —

Boys □ and ---
Girls ● and —

Ahmed et al. JCEM 1999;84:899-905

- **↑ ovarian volume (>10 cm^3) in 43% of girls (10–18 y) with a diagnosis of PCOS**

Shah et al. Endometrial thickness, uterine, and ovarian ultrasonographic features in adolescents with polycystic ovarian syndrome. J Pediatr Adolesc Gynecol 2010;23:146–52.

- **↑ ovarian volume in daughters of women with PCOS in comparison with daughters of women without PCOS Only when the girls reach Tanner stage 5 is their ovarian volume is abnormal by adult standards (mean volume 13.9 cm^3 [SD 4.4 cm^3] versus 6.9 cm^3 [SD 3.9 cm^3] in controls, suggesting that earlier in puberty a cut-off ovarian volume of lower than this may be appropriate.**

Sir-Petermann et al. Metabolic and reproductive features before and during puberty in daughters of women with polycystic ovary syndrome. J CEM 2009;94:1923–30.

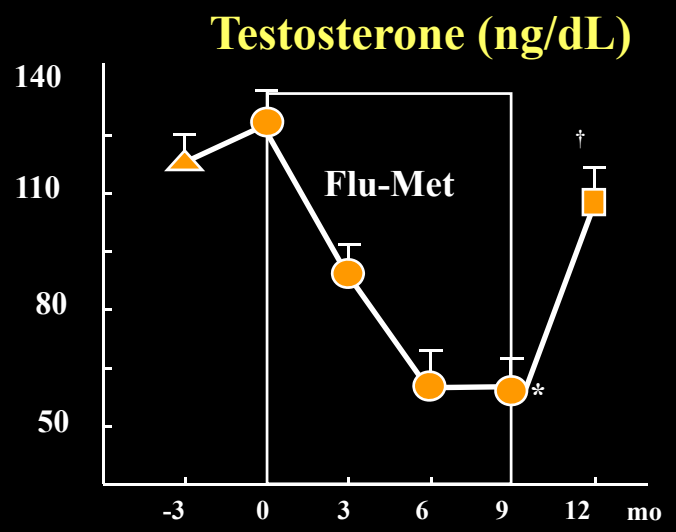
Precocious pubarche (PP) sequence

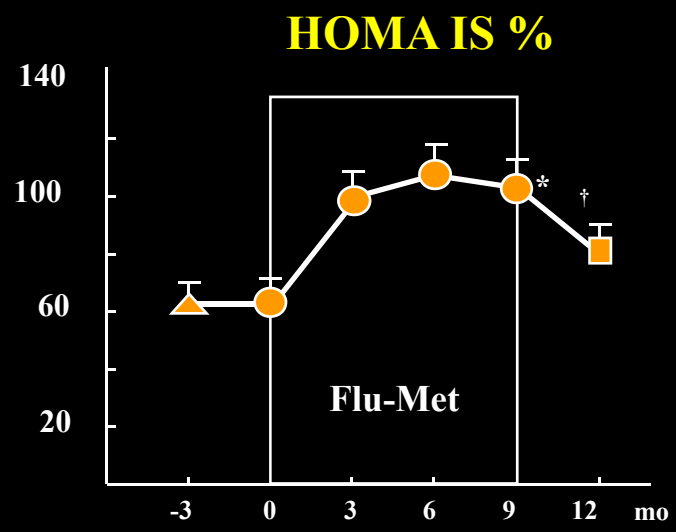
- PP is defined by the onset of pubic hair under the age of 8 years
- Associated with bone age advance and raised DHEA and DHEAS
- Low birth weight and rapid postnatal weight gain increases the risk for progression to functional ovarian hyperandrogenism and PCOS

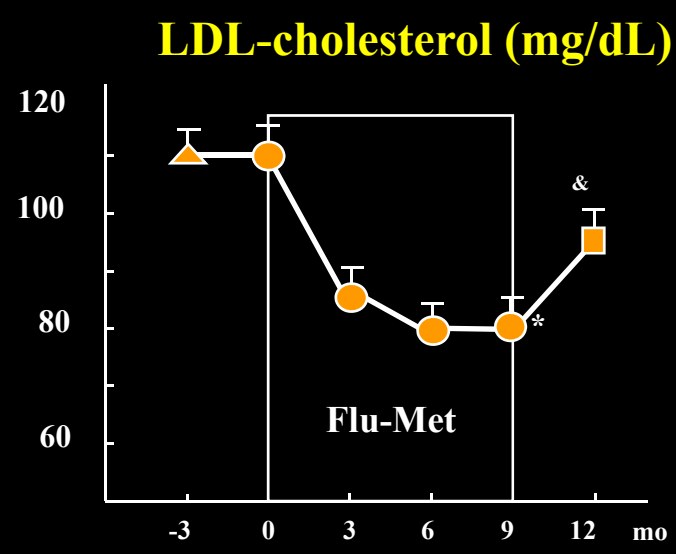
Ibañez L, et al. JCEM 1993;76:1599–603.

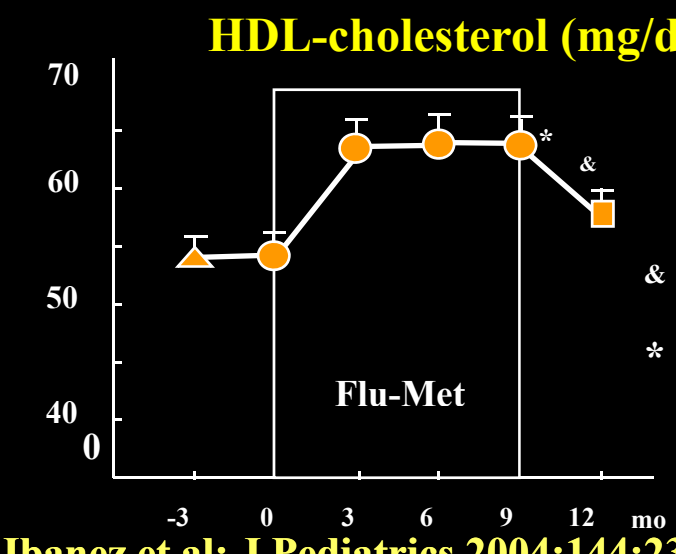
Ong KK, et al; Avon Longitudinal Study of Parents and Children Study Team. Opposing influences of prenatal and postnatal weight gain on adrenarche in normal boys and girls. JCEM 2004;89:2647–51.

Free Androgen Index, Insulin Sensitivity and Serum Lipids in Girls with Precocious Pubarche: Effect of Metformin and Flutamide









Ibanez et al: J Pediatrics 2004;144:23-29

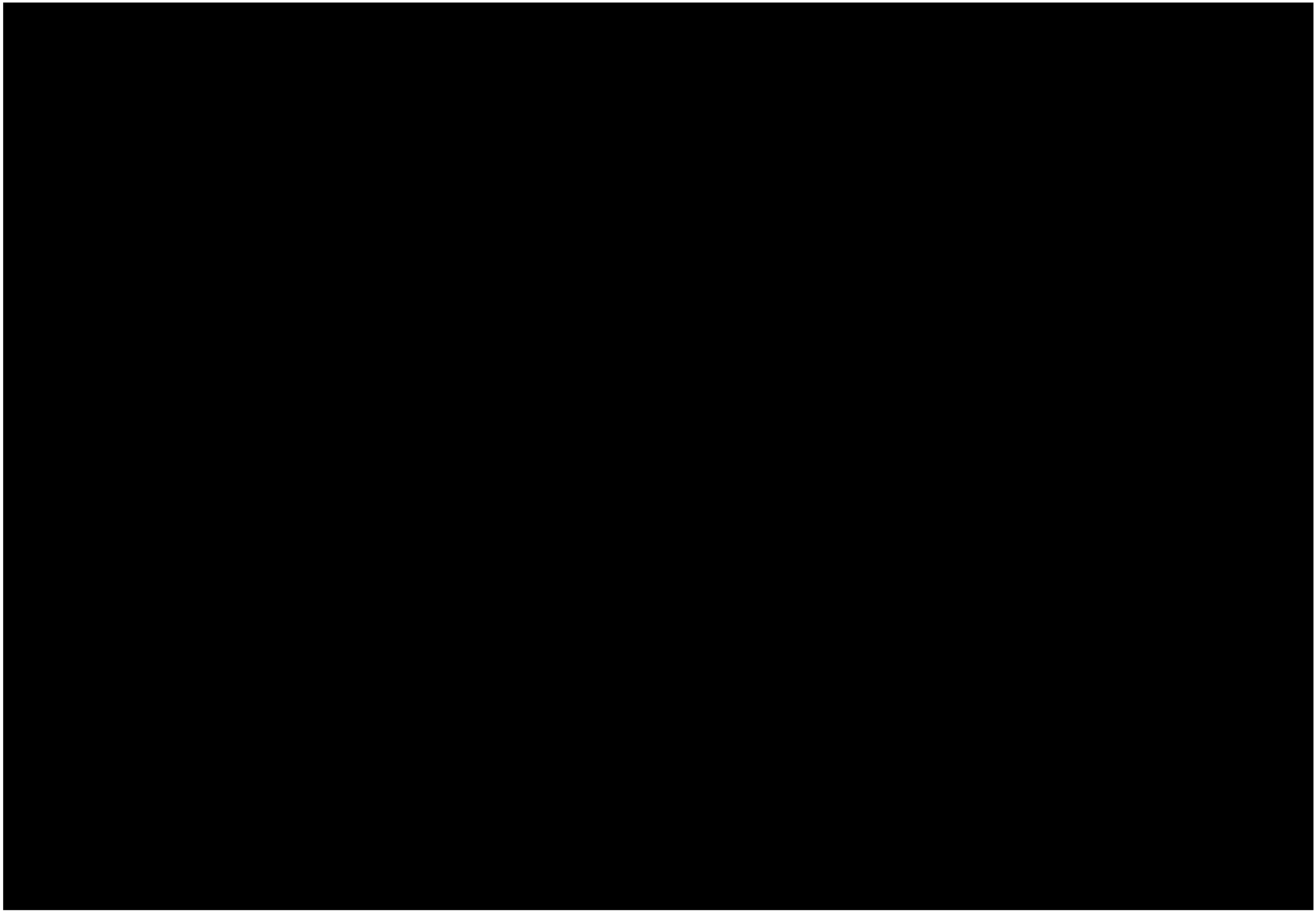
Factors known to alter serum testosterone concentrations

Physiological factors

- Pulsatile release during the day
- Diurnal rhythm: am > pm
- Menstrual cycle: follicular < mid cycle > luteal
- Season: no variation in total testosterone
- Free testosterone shows 30% difference: summer > winter
- Age in women with and without PCOS

Analytical factors

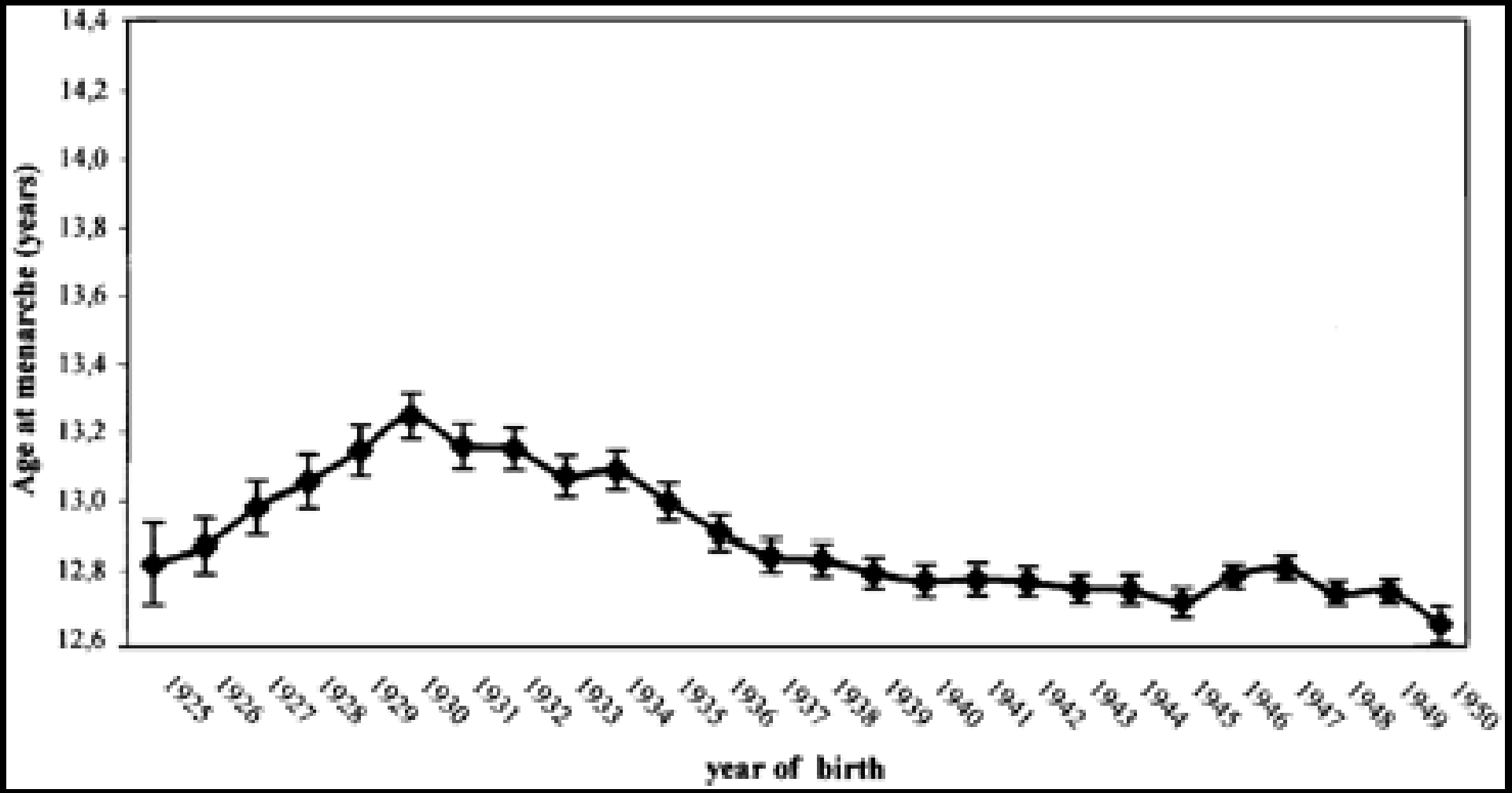
- Cross reactivity with other endogenous steroids
- Interference by endogenous antibodies
- Poor performance in the female range ie < 8 nmol/L



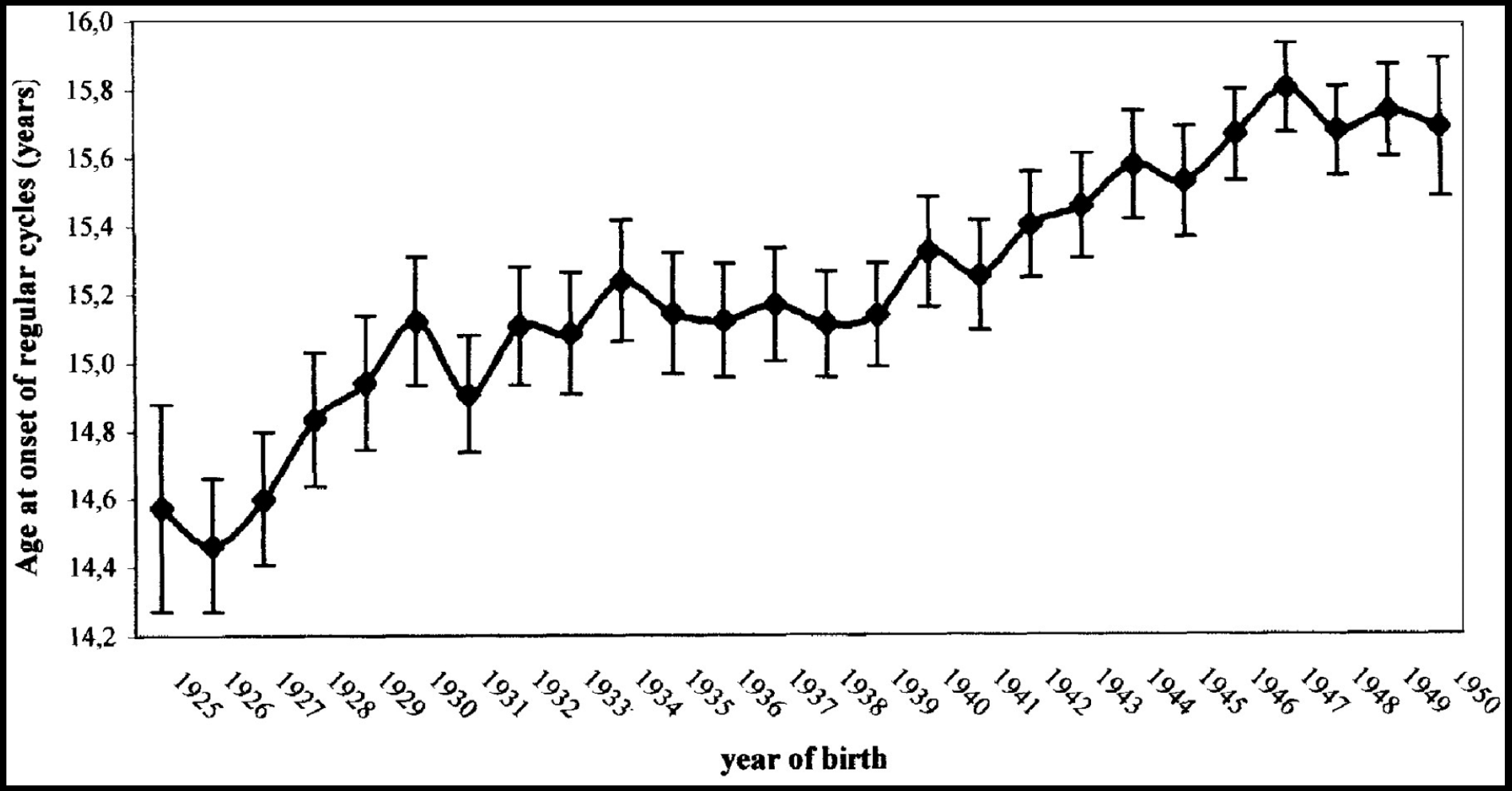
Age at menarche and at onset regular cycling:

- 85,683 questionnaires from women aged 40-65y
  reliable data on ~ 60,000
- Age menarche 7 - 20 y
- 53,272 reported age of regular menstruation from 7- 25 y
- 7,707 reported never having had regular menses

Clavel-Chapelon & E3N-European Prospective Investigation into Cancer, Human Reprod 2002; 17: 228-232



Evolution of age at menarche by birth cohort in theE3N-EPIC population (*n* = 85 683).



Evolution of age at onset of regular cycles by birth cohort in the E3N-EPIC population (*n* = 53 272).

Age at Menarche

	≤ 11y	≥ 15 y
1926-30	15.6%	16.4%
1946-50	17.9%	9.4%

Age at regular cycling

	≤ 12y	≥ 19 y
1926-30	17.4%	8.4%
1946-50	17.6%	18.1%

Age of regular cycling has become older

In those who developed regular cycles:

Menarche together with regular cycles:	26%
Regular cycles within 1 year of menarche:	32%
Regular cycles 1-5 years of menarche:	26%
Regular cycles > 5 years of menarche:	16%

With younger generations decrease in rapidity of achieving regularity from 64% to 53%

Those waiting > 5 years rose from 9% to 21% from 1925 to 1945

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