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Polycystic Ovary Syndrome

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PCOS Australian Alliance

CRE PCOS
Centre for Research Excellence in Polycystic Ovary Syndrome

Disclosures

Novo education grants

No advisory boards

No industry funding

Contracted research: funds to institution

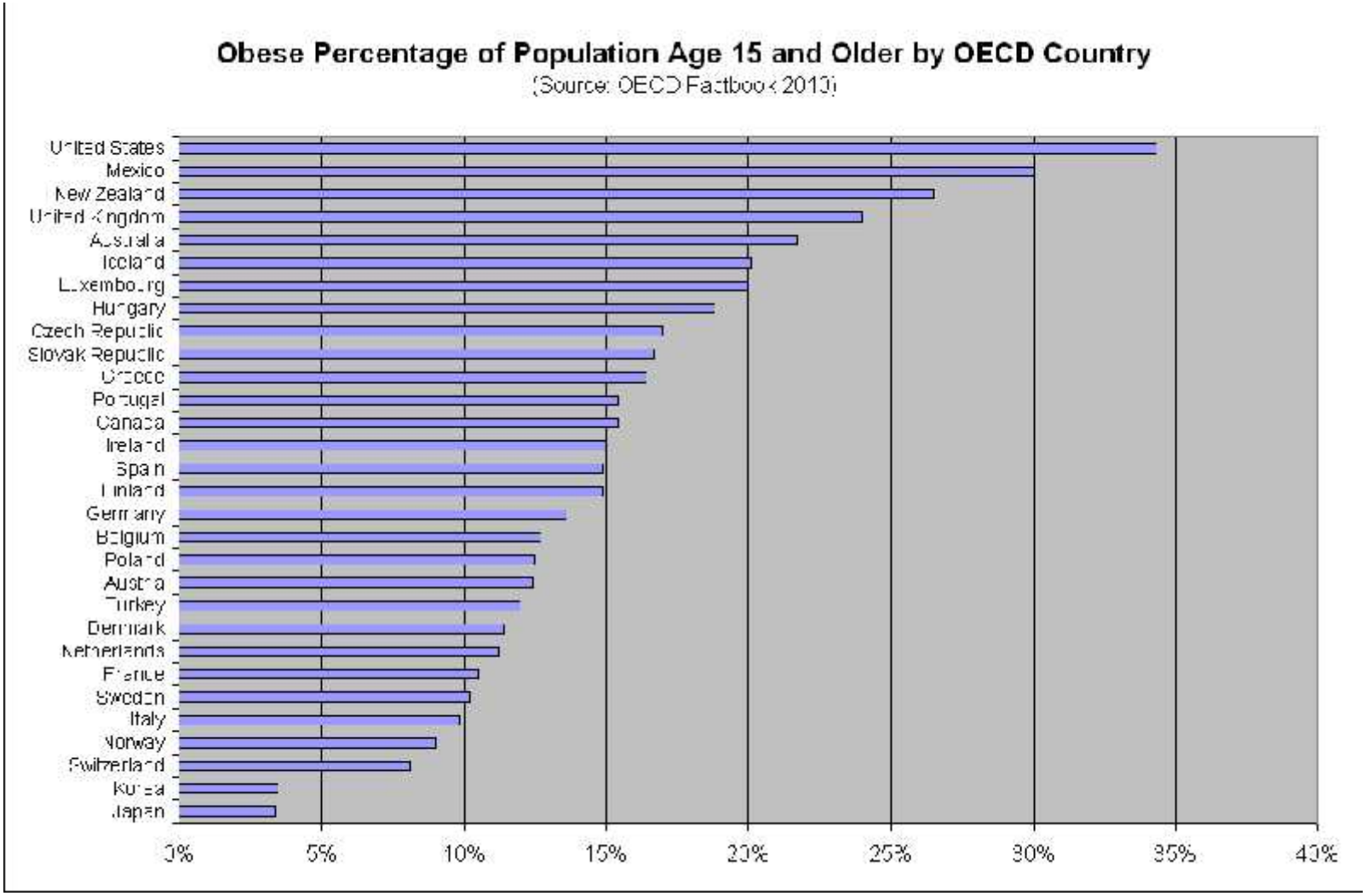
Outline

- PCOS overview
- Insulin resistance in PCOS
- Hyperandrogenism in PCOS
- AMH
- Management of PCOS

Obesity

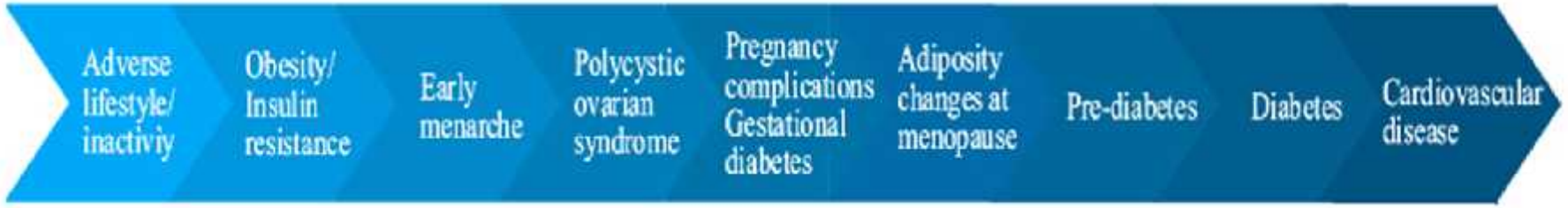
- Obesity is a major chronic disease
- Rising prevalence of obesity
- Growing health and economic burden
- Obesity, mediated via ↑ IR, is a/w ↑ risk of:
  - Impaired reproductive health
    - PCOS, infertility, GDM
  - Increases IR states such as T2DM
  - Hypertension
  - Dyslipidaemia
  - Cardiovascular disease (CVD)

Obesity in the modern world



Endocrine Society statement: “The Task Force agrees with the opinion of prominent medical societies that scientific evidence supports the view that obesity is a disease”

Continuum of adverse lifestyle related diseases in women



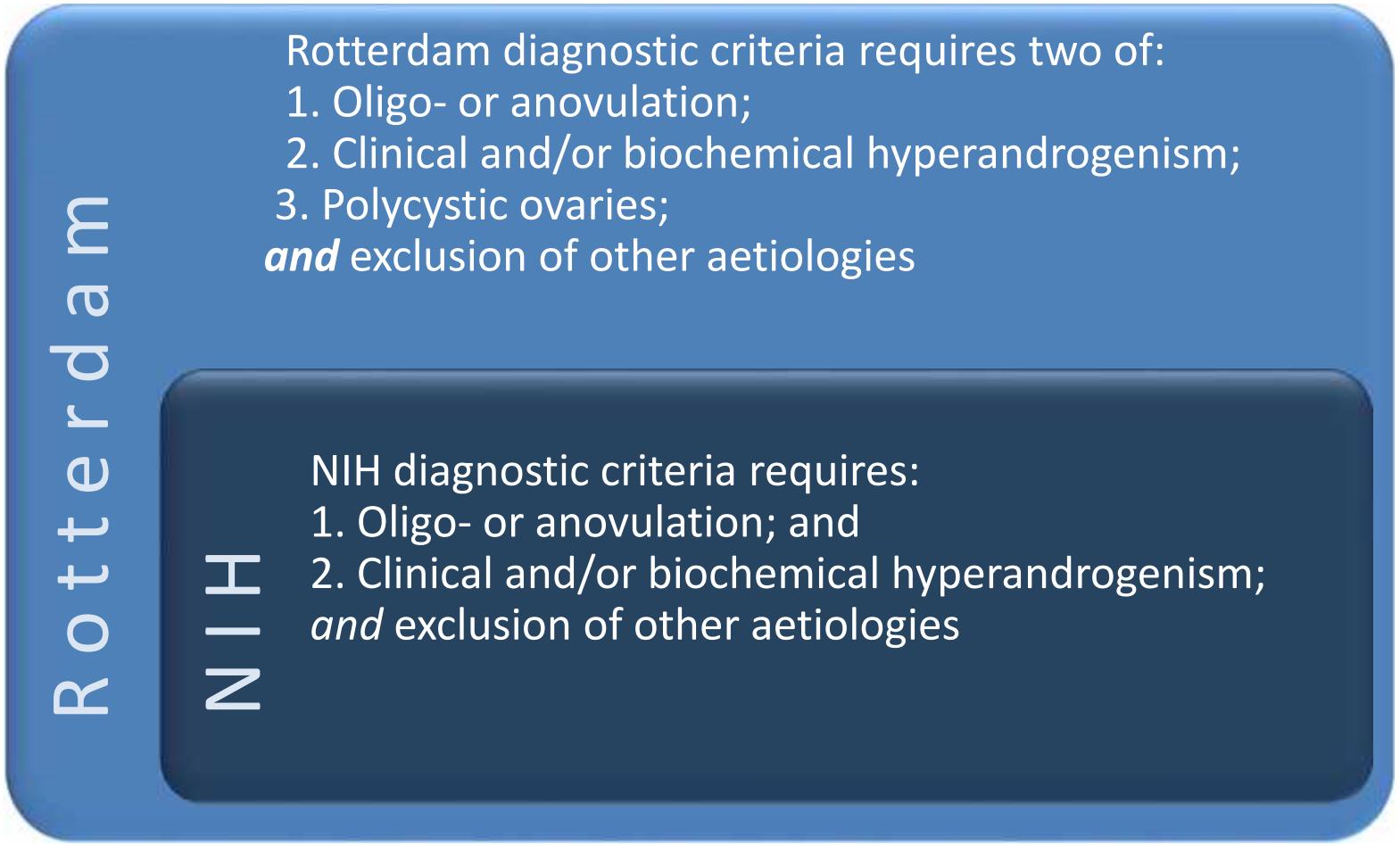
Teede TEM 2007

Polycystic Ovary Syndrome

- PCOS prevalence traditionally estimated at 4 - 8% - Greece, Spain, USA
  - Older diagnostic criteria (NIH)
- Australian (Rotterdam) prevalence 12-18%
- Indigenous populations ~21%
- Costs >$400 million/yr in Australia
- Major health and economic burden

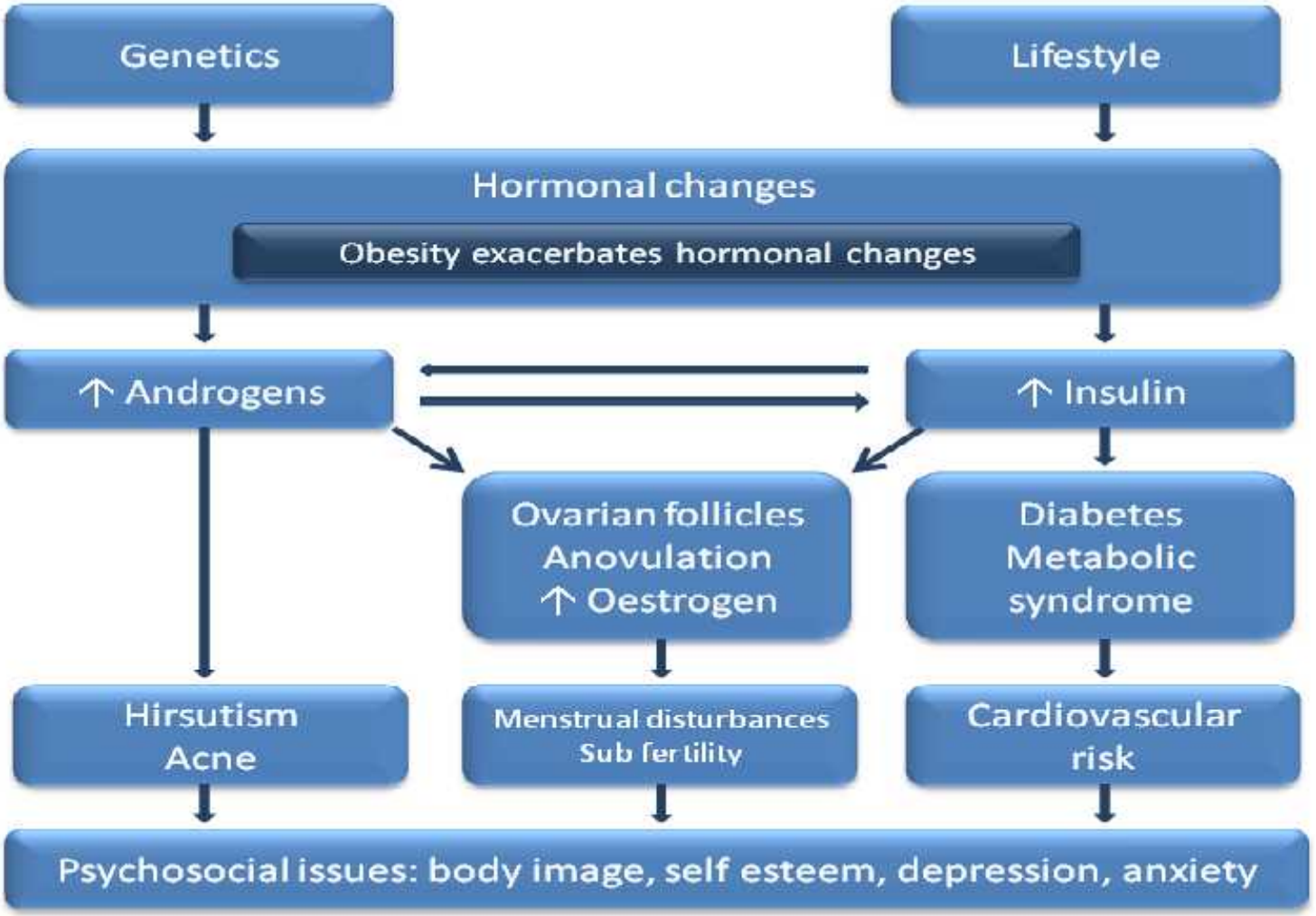
Diamanti-Kandarakis et al JCEM 1999; Knochenhauer et al JCEM 1998; Asuncion et al JCEM 2000; March et al Human Reprod 2010; Azziz et al JCEM 2005; Teede et al MJA 2007

PCOS diagnosis



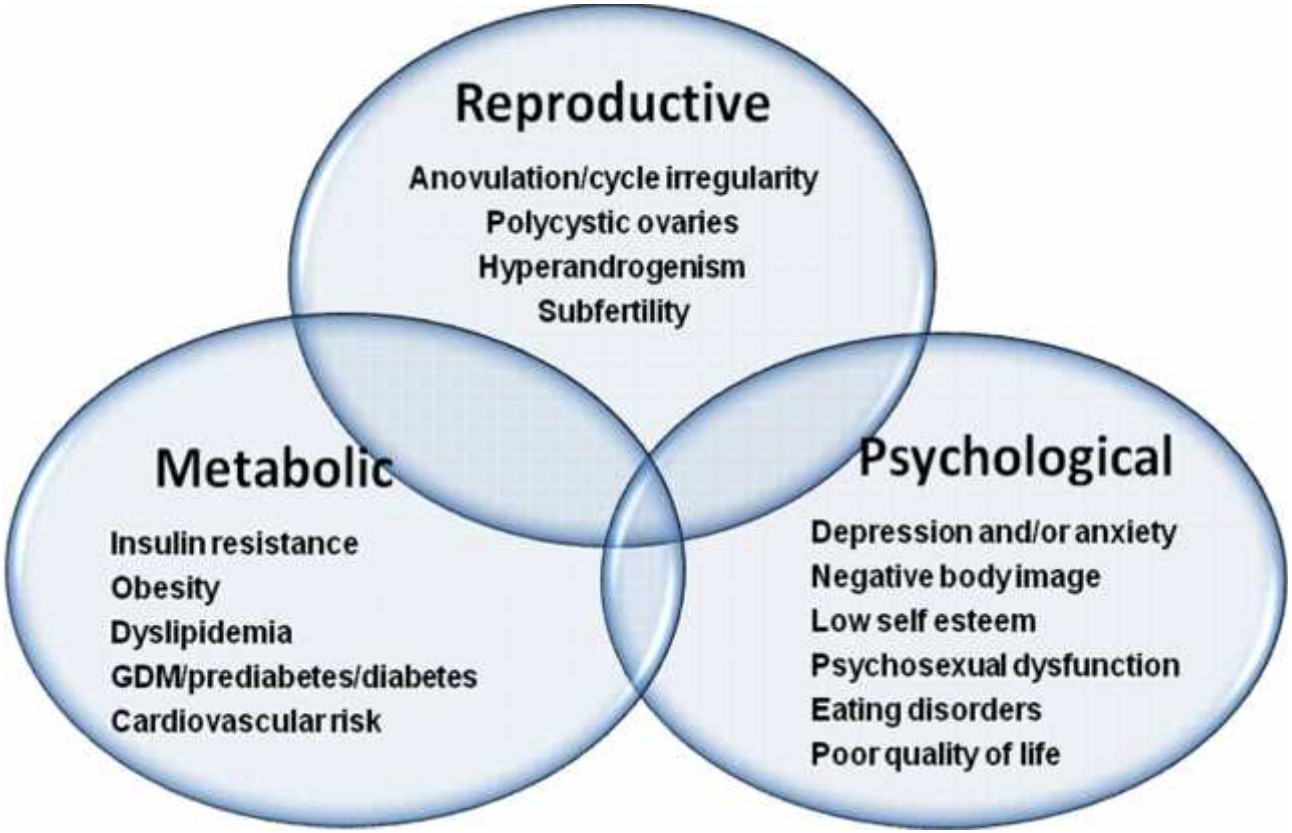
Teede et al MJA 2011

PCOS: complex clinical syndrome



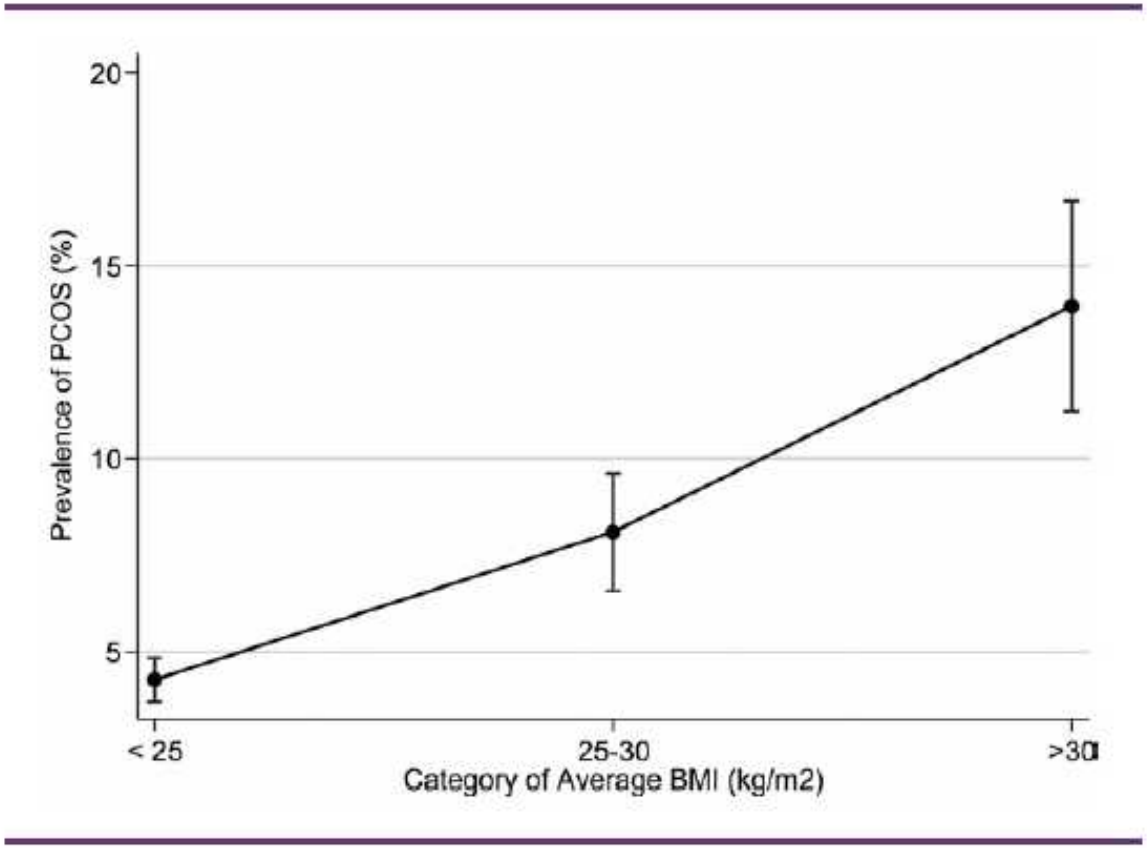
Teede et al BMC Medicine 2010, Norman et al Lancet 2007, Teede et al MJA 2011

PCOS clinical features



Norman et al Lancet 2007, Teede et al BMC Medicine 2010, Teede et al MJA 2011

Impact of excess weight



ALSWH: Longitudinal data 9% inc risk PCOS for 1 unit BMI

Teede et al Obesity 2013

Weight gain in PCOS

TABLE 1 Characteristics of women with PCOS and without PCOS at surveys 1 and 4[a]

	Survey 1		Survey 4	
	PCOS (n = 478)	Non-PCOS (n = 8,134)	PCOS (n = 478)	Non-PCOS (n = 8,134)
Age, y	20.71 ± 0.07	20.82 ± 0.02	30.51 ± 0.07	30.62 ± 0.02
Weight, kg[b]	67.4 ± 0.86	61.92 ± 0.14	76.16 ± 1.03	68.51 ± 0.19
BMI, kg/m^2[c]	24.49 ± 0.29	22.45 ± 0.05	27.83 ± 0.37	24.84 ± 0.07
Type 2 diabetes, %[d]	2.0	0.7	5.1	0.3
Hypertension, %[e]	7.1	4.2	5.5	2.0
Current smokers, %[f]	29.1	29.3	16.6	19.0
OCP use, %[g]	41.3	45.2	28.3	36.9

Teede et al, Obesity, 2013

Obesity in PCOS and phenotype

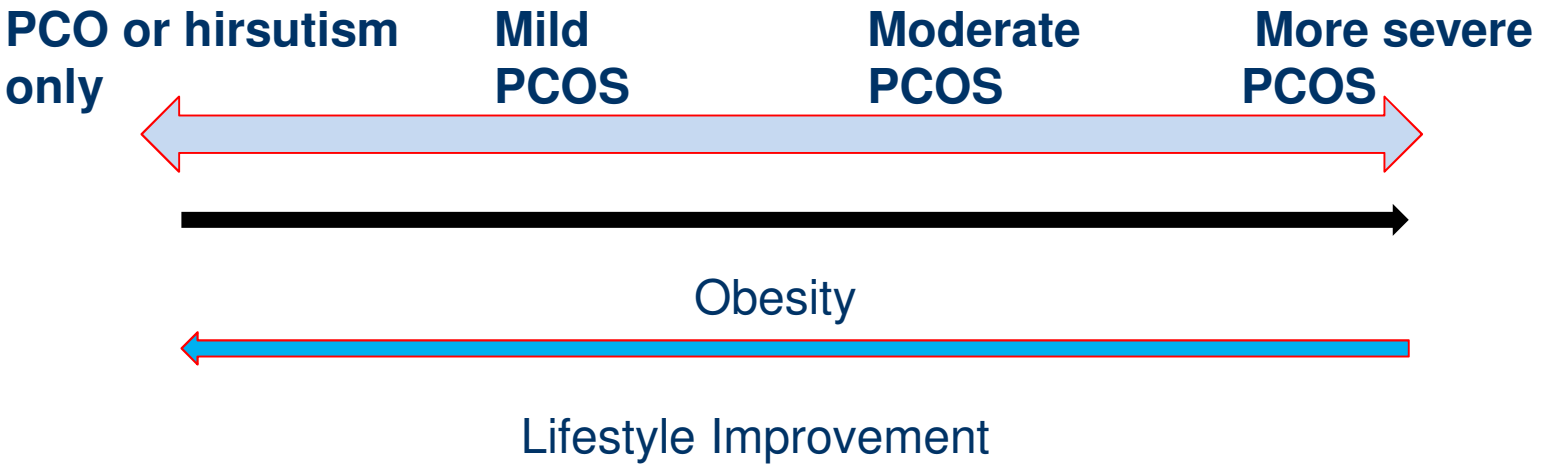
	All women	Original NIH	Rotterdam
Total	100%	6.1%	19.9%
Non-obese	90%	5.1%	19%
Obese	10.2%	15%	30%

Turkish government employees, prevalence of PCOS by BMI

Yildiz, Human Reprod 2012

Obesity and PCOS

- Obesity affects ~ 60% of women with PCOS
- Role in the pathophysiology of hyperandrogenism, chronic anovulation and metabolic abnormalities



Yildiz BO JCEM 2008, Kiddy DS Clin Endo 1990, Moran, L Fertil Steril 2009

Clinical assessment - examination

- Weight, height, BMI
- Waist circumference
- Blood pressure

- Assess:
  - Hirsutism
  - Acne
  - Alopecia
  - Acanthosis nigricans

- Screen clinically for:
  - Signs of virilisation if concerning hyperandrogenism (depending on rate of change of symptoms/signs, severity and if out of context)
    - Voice changes, cliteromegaly
  - Cushing's syndrome

Clinical assessment

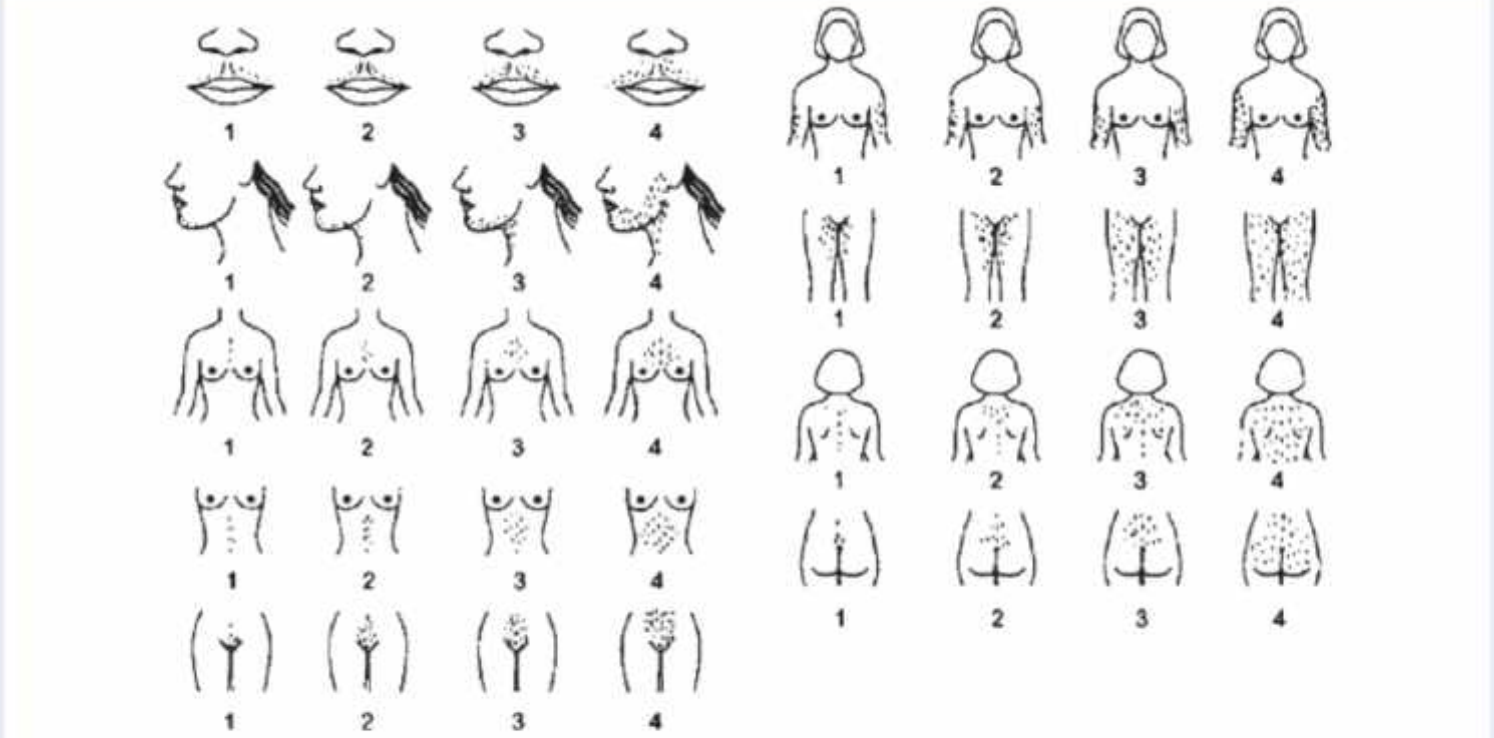


Figure 1 Schematic representation of the mFG score. Nine body areas (upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper back, lower back and thighs) are scored from 1 (minimal terminal hairs present) to 4 (equivalent to a hairy man). If no terminal hairs are observed in the body area being examined the score is zero (left blank). Clinically, terminal hairs can be distinguished from vellus hairs primarily by their length (i.e. >0.5 cm) and the fact that they are usually pigmented. Reproduced with permission from R. Azziz (Yildiz *et al.*, 2010). Copyright Oxford University Press, 2010.

Clinical assessment - hirsutism

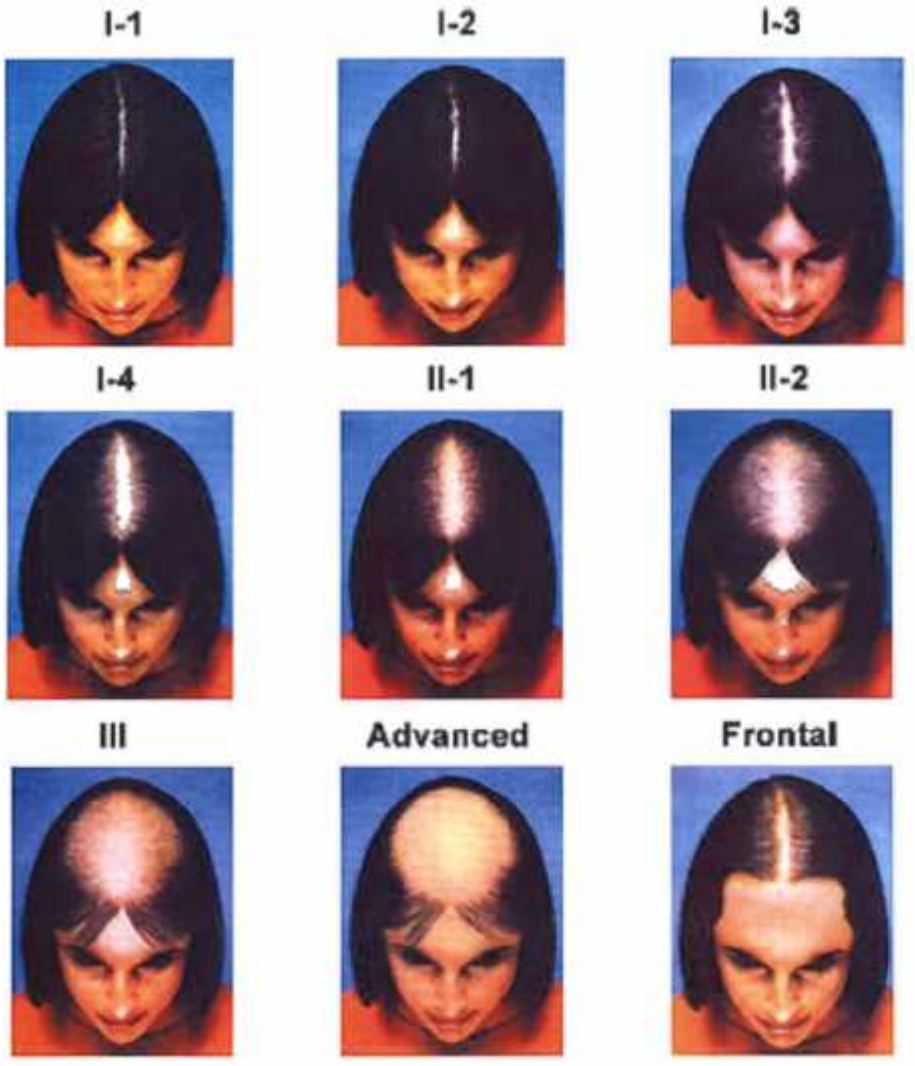
- Terminal hair growth
- Score ≥ 8 indicative of hirsutism
- But terminal hair growth has considerable ethnic variability
  - FG score ≥ 3 – hirsutism (South East Asian women)

Table I Suggested cut-offs for the mFG hirsutism score according to the 95 percentile in different unselected populations of premenopausal women.

Author, year	Year	Country	Race	Ethnicity	Sample size	Suggested mFG cut-off[a]
Tellez and Frenkel (1995)	1995	Chile	White	Hispanic	236	≥6
Asuncion *et al.* (2000)	2000	Spain	White	Mediterranean	154	≥8
Sagsoz *et al.* (2004)	2004	Turkey	White	Middle Eastern	204	≥9
Cheewadhanaraks *et al.* (2004)	2004	Thailand	Asian	Thai and Chinese	531	≥3
DeUgarte *et al.* (2006)	2006	USA	White	Caucasian and Hispanic	283	≥8
			Black	African-American	350	≥8
Zhao *et al.* (2007)	2007	China	Asian	Chinese Han	623	≥2
Api *et al.* (2009)	2009	Turkey	White	Middle Eastern	121	≥11
Moran *et al.* (2010)	2010	Mexico	White	Hispanic	150	≥10
Noorbala and Kefaie (2010)	2010	Iran	White	Middle Eastern	900	≥10
Kim *et al.* (2011)	2011	Korea	Asian	Chinese	1010	≥6
Gambineri (2011, personal communication)	2011	Italy	White	Mediterranean	200	≥9
Escobar-Morreale (2011, personal communication)	2011	Spain	White	Mediterranean	291	≥10

[a]As defined by the 95th percentile of an unselected population of premenopausal women.

Clinical assessment - alopecia



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Investigations

- Androgen profile
  - Total testosterone, SHBG, FAI
  - (DHEAS or androstenedione not routinely recommended)
- Exclude secondary causes
  - TFTs, prolactin
  - If clinical suspicion, consider
    - 17-hydroxyprogesterone
    - Cushings' screen
- AMH not recommended at this stage
- Metabolic screening
  - Fasting lipids
  - 75g OGTT
  - (No need to do insulin levels – assay variability & inaccuracy)

Investigations

- Pelvic ultrasound
  - Ovarian morphology
    - Presence of ≥ 12 follicles in the ovary measuring 2 to 9 mm in diameter and/or increased ovarian volume (>10 mL) – PCO if involving 1 or both ovaries
  - Endometrial thickness

Key points: overview of PCOS

- PCOS affects 12-21% of reproductive aged women
- Key hormonal abnormalities
  - Insulin resistance
  - Hyperandrogenism
- Metabolic, reproductive and psychological clinical features
- Obesity increases PCOS risk and severity

Outline

- PCOS overview
- Insulin resistance in PCOS
- Hyperandrogenism in PCOS
- AMH
- Management of PCOS

Insulin resistance

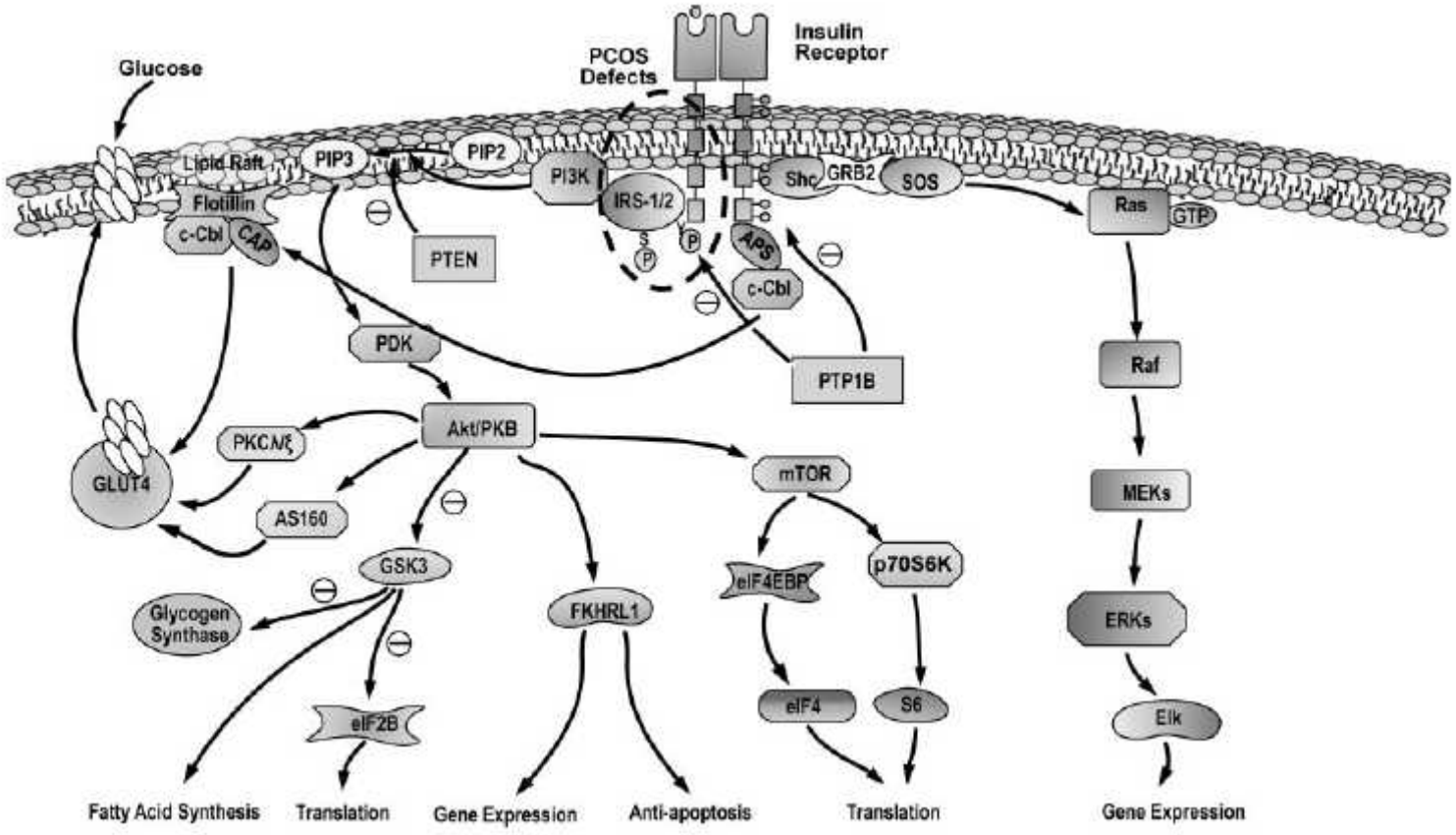
- Integral link between obesity, reproductive and metabolic features
- Gold standard measurement is hyperinsulinaemic euglycaemic clamps – direct measure
  - Difficult to perform in clinical setting

Insulin resistance in PCOS

- Intrinsic IR inherent to PCOS
- Obesity related extrinsic IR

- IR $\rightarrow \uparrow$ hyperinsulinaemia
- Pancreatic β-cell dysfunction $\rightarrow$ IGT and T2DM
- 4-8 fold increase in diabetes in PCOS

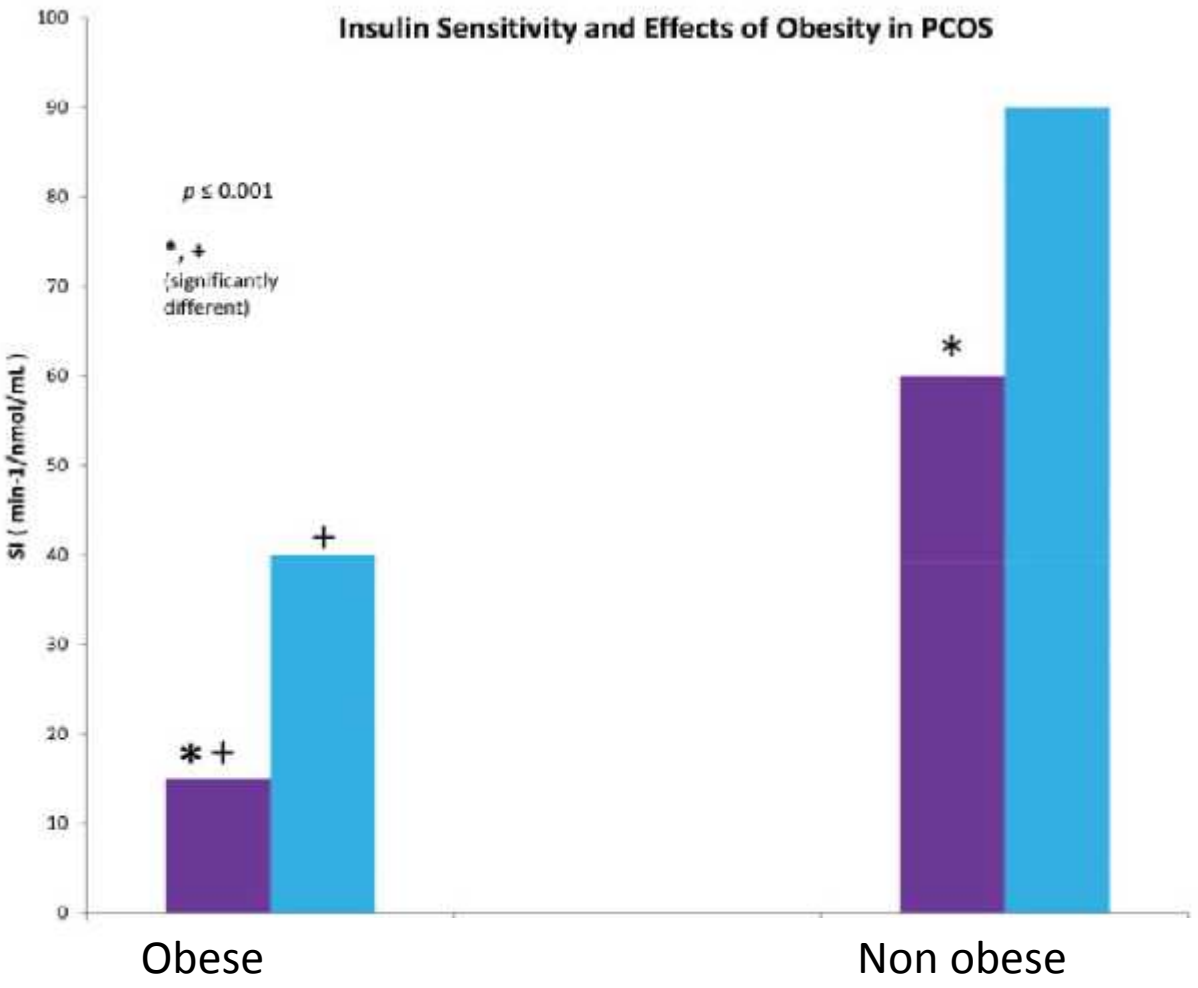
Mechanisms of IR in PCOS



Post receptor defect in early stages transduction

Diamanti-Kandarakis, Dunaif Endo Reviews 2012

Insulin resistance in PCOS

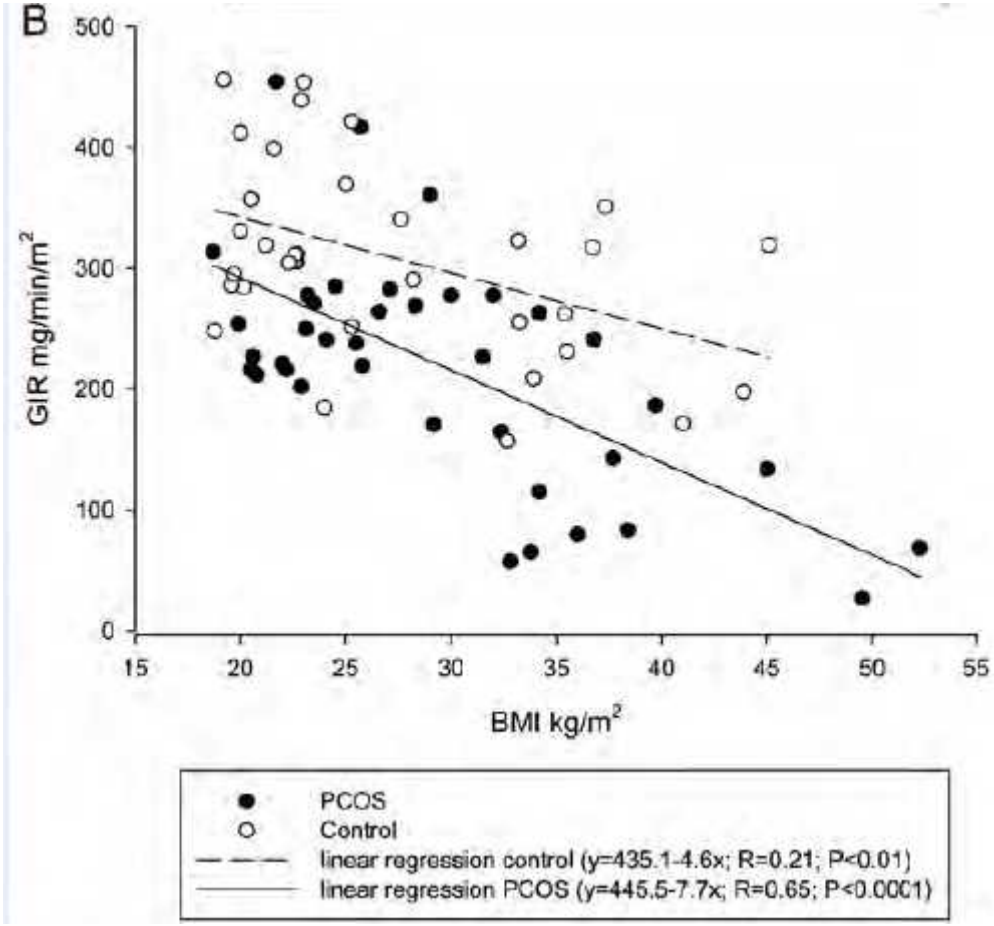


PCOS
Non PCOS

Freq sampled IVGTT

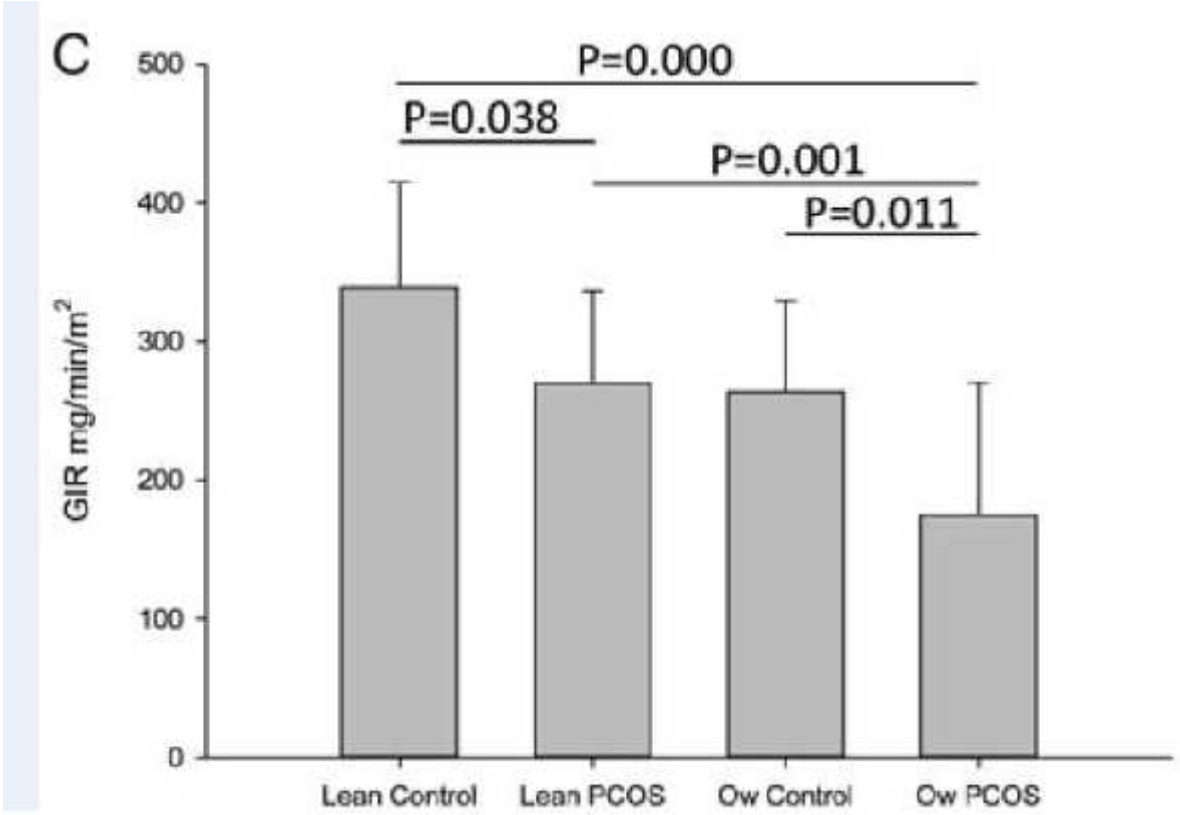
Legro adapted from Dunaif, Sem Reprod Med 2012

Obesity and IR: clamps



Hutchison et al, JCEM 2011

Insulin resistance, PCOS and obesity



WHO criteria for IR
<25th centile on clamp studies

IR was present in:
75% lean PCOS
62% obese controls
95% obese PCOS women

Overall 85% IR in PCOS

Stepto, Human Reprod 2013

Effect of obesity in PCOS

Table 3 Results of meta-analyses for studies comparing overweight and obese (BMI ≥ 25) to normal weight (BMI < 25) women with PCOS

Analysis	Studies	Participants	Mean difference (95% CI), statistical model, *P* value	χ^2 (*P* value)	I^2 (%)
SHBG (nmol L^{-1})	12	988	−22.57 (−25.39, −19.75), fixed, *P* < 0.001	11.80 (*P* = 0.37)	8
Testosterone (nmol L^{-1})	16	1,304	0.30 (0.05, 0.55), random, *P* = 0.02	140.60 (*P* < 0.001)	89
FAI	5	550	4.01 (2.28, 5.73), random, *P* < 0.001	11.97 (*P* = 0.02)	67
Hirsutism (FG score)	5	325	0.89 (0.22, 1.55), fixed, *P* = 0.009	5.70 (*P* = 0.13)	47
Fasting insulin (pmol L^{-1})	9	800	39.75 (29.95, 49.55), random, *P* < 0.001	20.40 (*P* = 0.09)	61
HOMA-IR	6	700	1.58 (1.00, 2.16), random, *P* < 0.001	46.10 (*P* < 0.001)	89
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2-h glucose (mmol L^{-1})	2	364	0.95 (0.31, 1.59), random, *P* = 0.004	4.80 (*P* = 0.03)	79
2-h insulin (pmol L^{-1})	1	184	443.30 (303.89, 582.71), fixed, *P* < 0.001	NA	NA
IFG/IGT, *n*	2	396	RR: 3.28 (0.21, 50.33), random, *P* = 0.39	11.06 (*P* < 0.001)	91
Diabetes, *n*	1	102	RR: 6.37 (0.38, 108.12), fixed, *P* = 0.20	NA	NA
Total-C (mmol L^{-1})	7	567	0.35 (0.07, 0.64), random, *P* = 0.01	19.08 (*P* = 0.004)	69
LDL-C (mmol L^{-1})	4	281	0.35 (0.23, 0.48), fixed, *P* < 0.001	5.53 (*P* = 0.14)	46
HDL-C (mmol L^{-1})	5	384	−0.23 (−0.38, −0.07), random, *P* = 0.005	16.29 (*P* = 0.003)	75
Triglyceride (mmol L^{-1})	7	567	0.37 (0.23, 0.50), random, *P* < 0.001	35.72 (*P* < 0.001)	83

Lim at al Obes Rev 2013

Measurement of IR and glycaemic abnormalities

- IR common in PCOS, but is not required for diagnosis
- Partly due to lack of accurate methods to measure IR in clinical setting
- Measurement of insulin levels not recommended in clinical setting due to assay variability and inaccuracy

Insulin assay

- American Diabetes Association task force - standardization of insulin assays in 1996
  - Wide variation in assay bias
  - Results for plasma and serum from the 17 assays studied varied by a factor of 2 (mostly RIAs)
  - Use of the same insulin reference preparation did not improve comparability, and the same assay method run in 2 laboratories yielded different results
- Confirmed by more recent studies
  - 2 fold variation

Robbins et al, Diabetes 2006; Manley et al, Clinical Chemistry 2007

Glycaemic abnormalities in PCOS

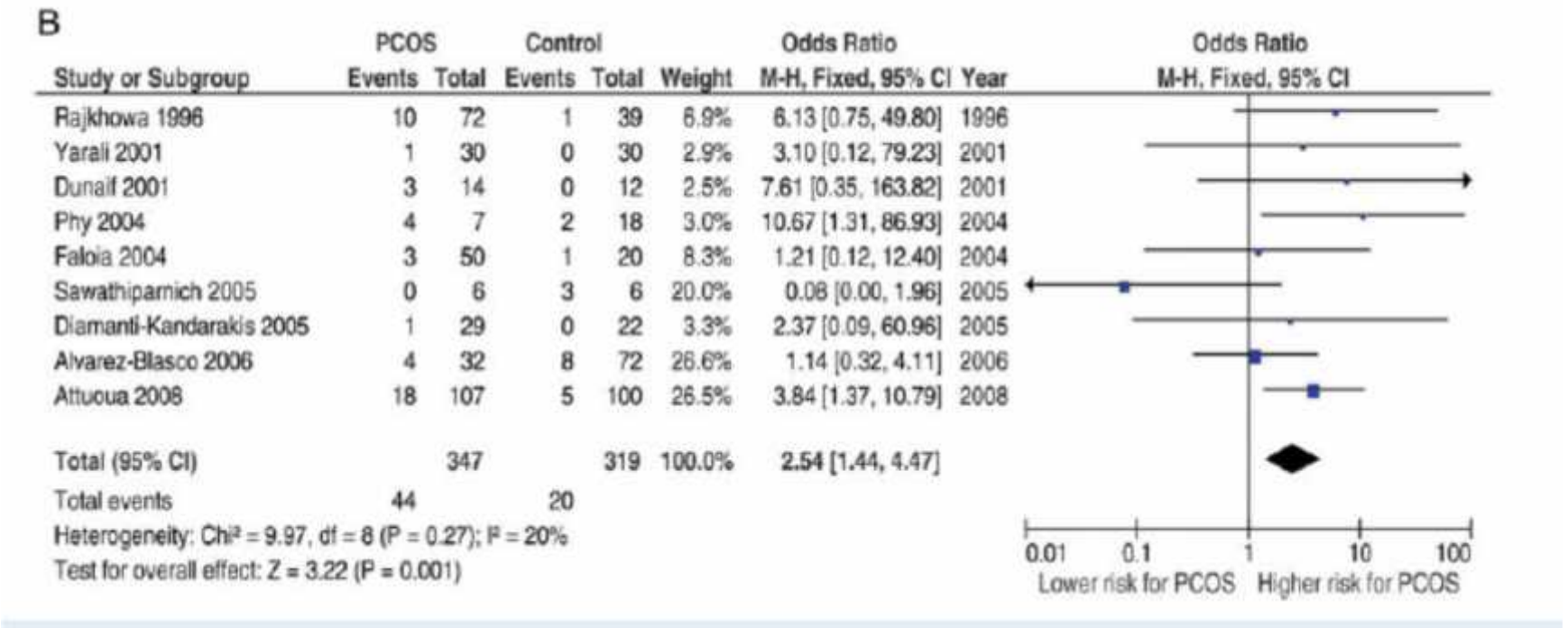
- Earlier onset of glycaemic abnormalities
- May convert more rapidly from IGT to T2DM
- Prevalence of IGT and T2DM in PCOS compared to age and weight-matched women without PCOS

	IGT	**T2DM**
PCOS	31.1%	7.5%
Non-PCOS	10.3%	1.5%

- 2.5 fold ↑ risk of IGT and a 4 fold ↑ risk of T2DM
- 2.94 fold ↑ risk of gestational diabetes (GDM)

Moran et al, Human Reproduction Update 2010
Boomsma et al, Human Reproduction Update 2006

Glycaemic abnormalities in PCOS



B

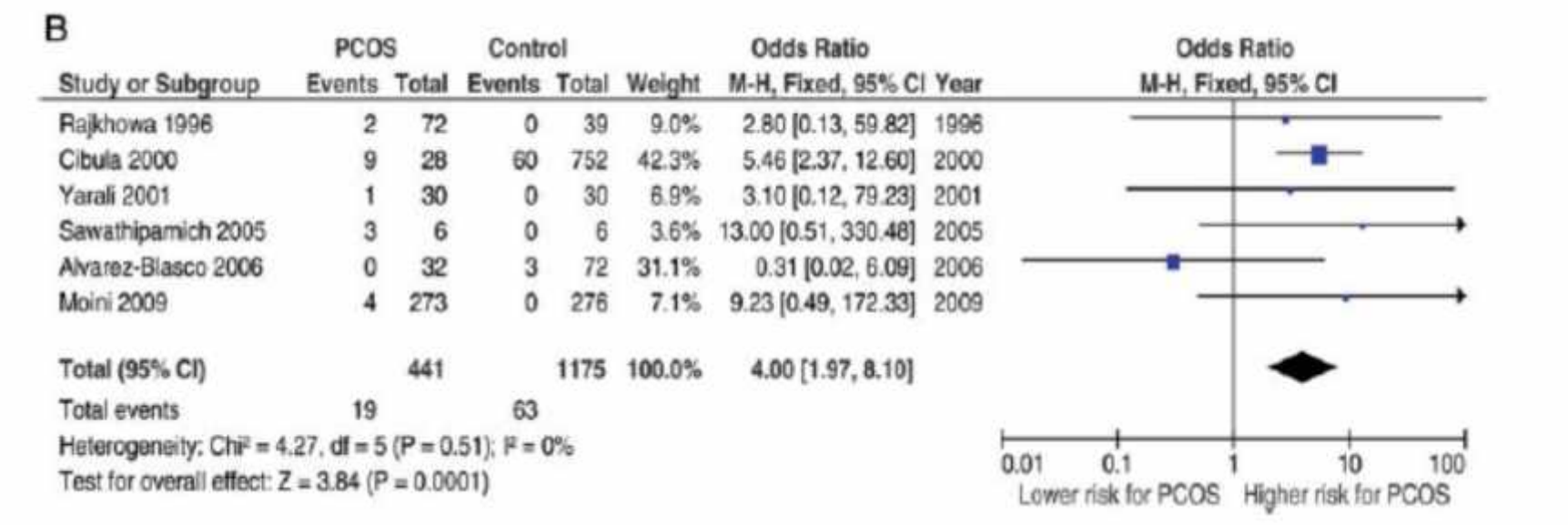
Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Rajkhowa 1996	10	72	1	39	6.9%	6.13 [0.75, 49.80]	1996
Yarali 2001	1	30	0	30	2.9%	3.10 [0.12, 79.23]	2001
Dunaif 2001	3	14	0	12	2.5%	7.61 [0.35, 163.82]	2001
Phy 2004	4	7	2	18	3.0%	10.67 [1.31, 86.93]	2004
Faloia 2004	3	50	1	20	8.3%	1.21 [0.12, 12.40]	2004
Sawathiparnich 2005	0	6	3	6	20.0%	0.08 [0.00, 1.96]	2005
Diamanti-Kandarakis 2005	1	29	0	22	3.3%	2.37 [0.09, 60.96]	2005
Alvarez-Blasco 2006	4	32	8	72	26.6%	1.14 [0.32, 4.11]	2006
Attuoua 2008	18	107	5	100	26.5%	3.84 [1.37, 10.79]	2008
Total (95% CI)		347		319	100.0%	**2.54** [1.44, 4.47]	
Total events	44		20				

Heterogeneity: Chi² = 9.97, df = 8 (P = 0.27); I² = 20%

Test for overall effect: Z = 3.22 (P = 0.001)

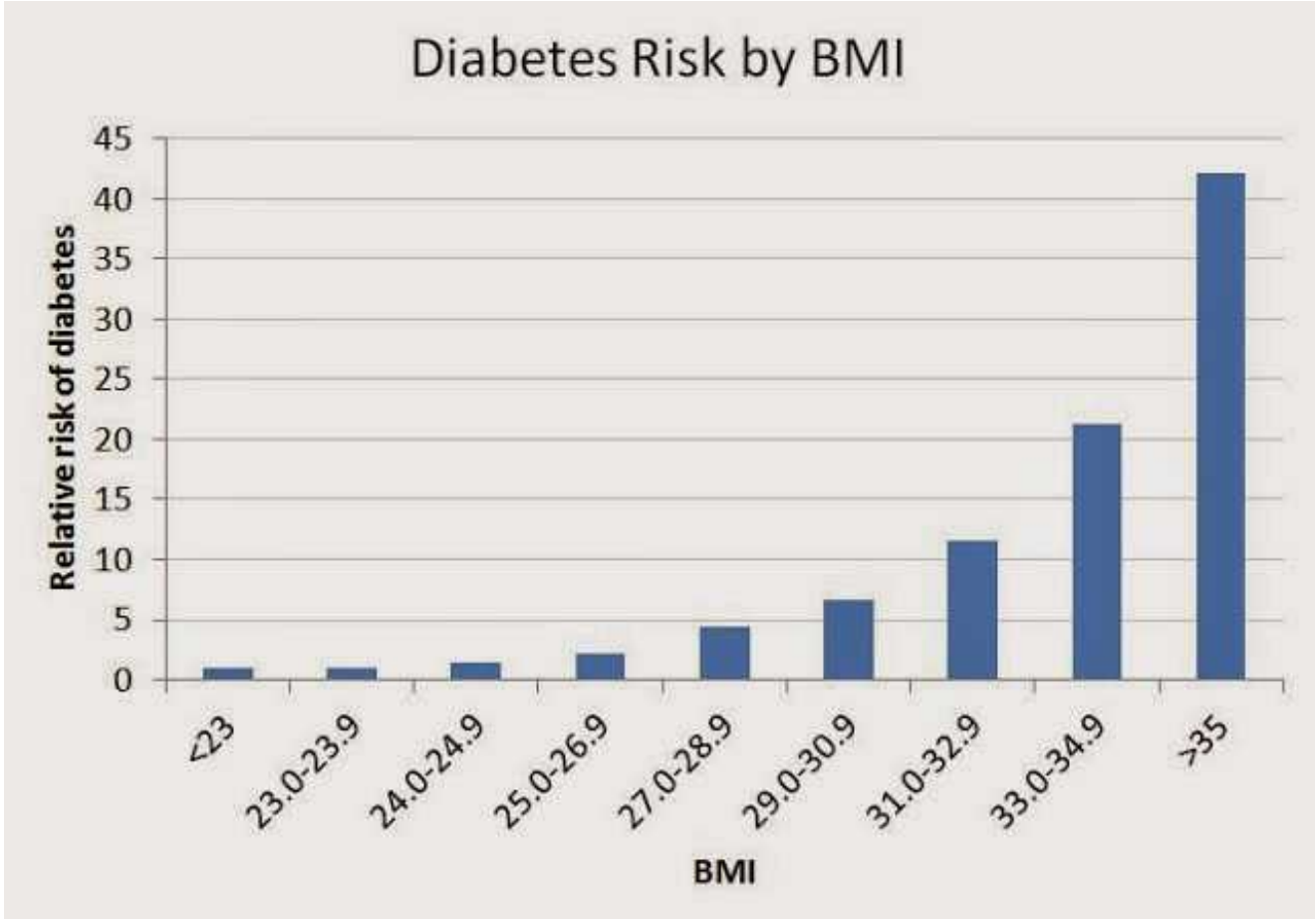
Moran et al, Human Reproduction Update, 2010

Glycaemic abnormalities in PCOS



Moran et al, Human Reproduction Update, 2010

Diabetes risk by BMI



Chan et al Diabetes Care

Role of OGTT in PCOS

- Impaired fasting glucose is a poor predictor of IGT in women in general and also particularly in PCOS
- Pre-diabetes presents vital prevention opportunity
- 90% with pre-diabetes missed on fasting glucose / HbA1c
- OGTT test of choice to detect pre-diabetes
    - reproductive aged women – pregnancy implications
    - opportunities for prevention of diabetes, guiding lifestyle

PCOS and diabetes screening

- Repeat OGTT every 2 years in women with PCOS
  - Consider repeat yearly in patients with additional risk factors
    - Age, gender, ethnicity, parental history of diabetes, history of high blood glucose, use of antihypertensive medications, smoking, physical inactivity, increased waist circumference
- Clinical practice point: If lean and young, frequency of testing could be reduced

Key points: PCOS, IR and obesity

- IR inherently increased in PCOS
- Exacerbated by obesity
- Impact of obesity on IR in PCOS more profound

- Clinical assessment
  - Insulin assay – variable and inaccurate
  - 75g OGTT for routine screening

Outline

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- Insulin resistance in PCOS
- Hyperandrogenism in PCOS
- AMH
- Management of PCOS

Hyperandrogenism in PCOS

- Prenatal exposure (Abbott, Walters, others)
  - Mechanistic models
  - Human relevance unclear
- Peripubertal exposure (Marshall, McCartney, others)
- Hyperandrogenism feature of PCOS - 80% affected
  - increased thecal secretion
  - increased responsiveness to androgens

Effect of obesity in PCOS

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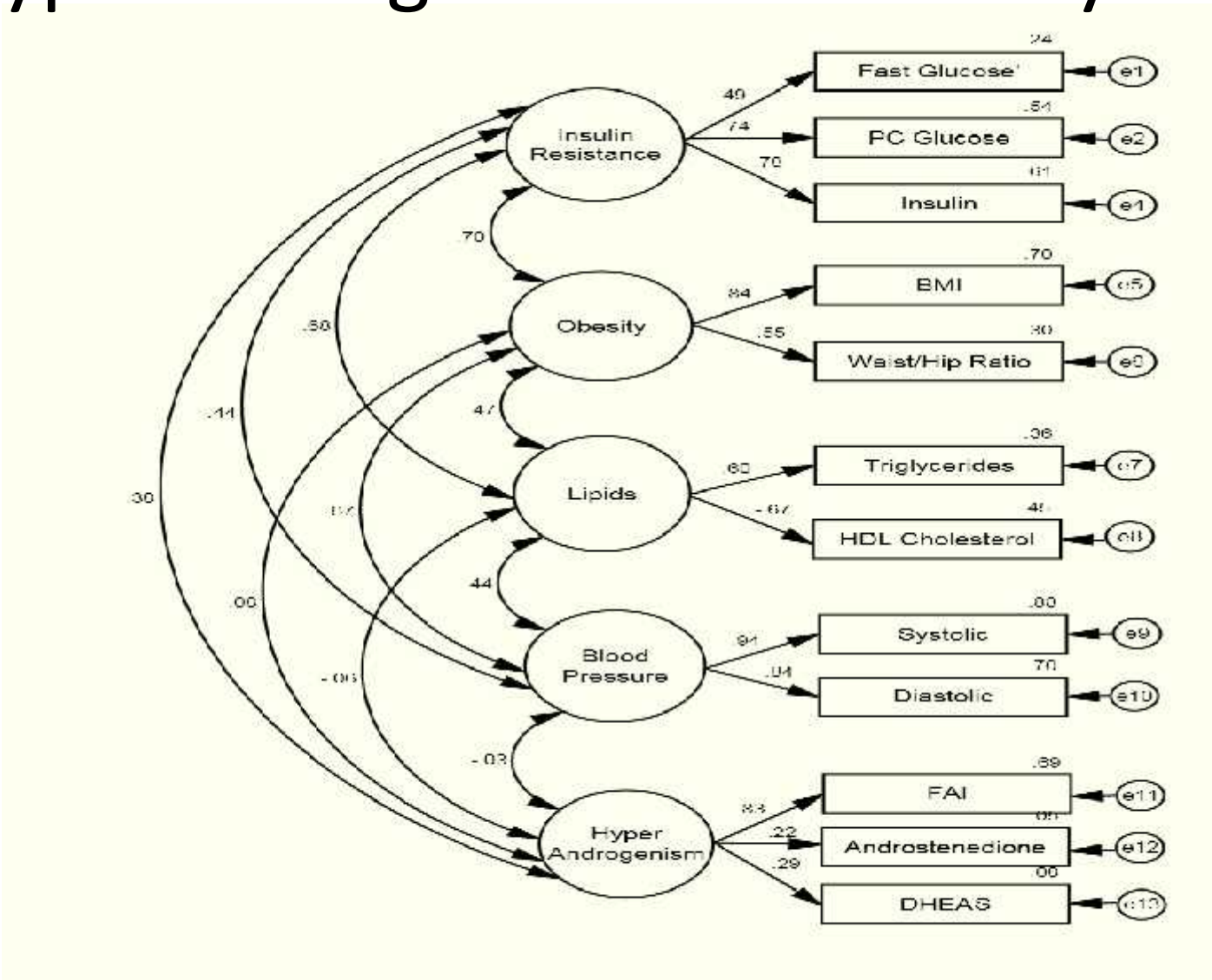
Lim at al Obes Rev 2013

Hyperandrogenism and obesity in PCOS



Ranasinha et al, Clinical Endocrinology, in press, 2015

Testosterone assays

- Testosterone assays originally developed to measure testosterone concentrations in the normal male range
- Reliable measurement of female testosterone concentrations is problematic
- Lack of precision and sensitivity of various commercially available testosterone assays

Testosterone assays

- RIA and chemiluminescence immunoassay
  - Most commonly used
  - Show good precision, but often show more bias, especially at lower range where they can be subject to increased interference and overestimation of steroid concentrations compared with other assays
- Extraction and chromatography methods preceding RIA
  - Advantage of removing interfering proteins and cross-reacting steroids.
  - Infrequently used in clinical practice because proper validation is lacking and extraction is labor intensive and time consuming
- Estimation of bioactive testosterone with calculation of FAI
  - FAI shown to correlate quite well with physical separation measures of female free testosterone
  - FAI is highly dependent on the quality of testosterone and SHBG assay measurements

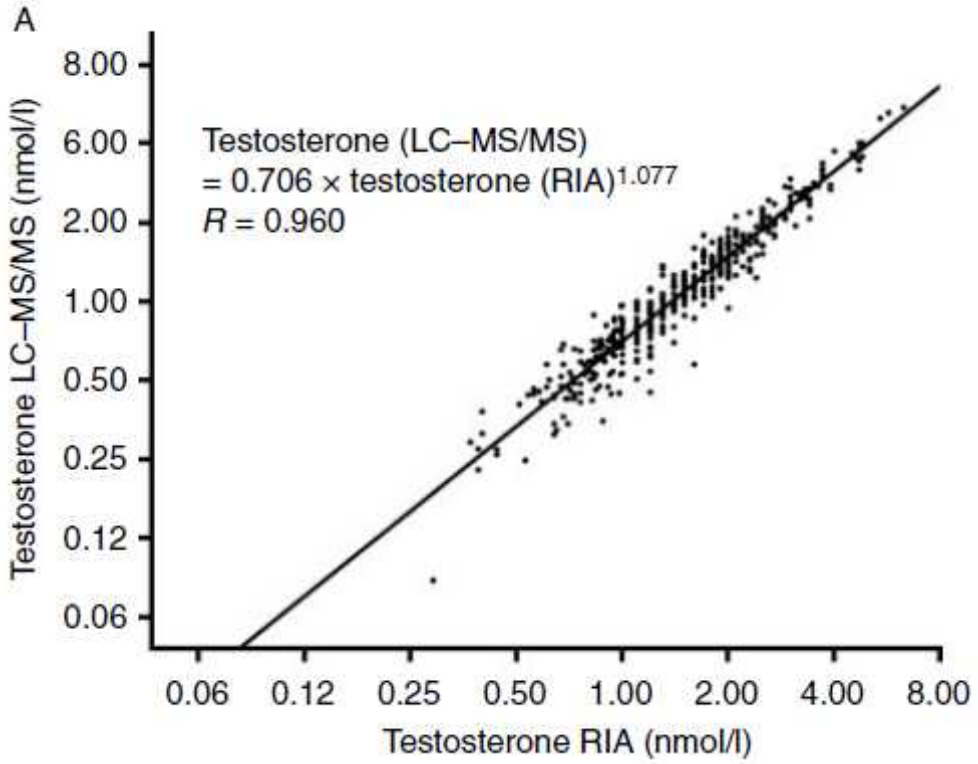
Vermeulen et al, JCEM 1999; Stanczyk Steroids 2003; Rosner et al, JCEM 2010

Tandem mass spectrometry

- Tandem mass spectrometry preceded by gas or liquid chromatography assays for steroid measurement is emerging
  - Equal or better precision compared to immunoassays
  - No interferences due to chromatographic separation and mass spectrometry analysis

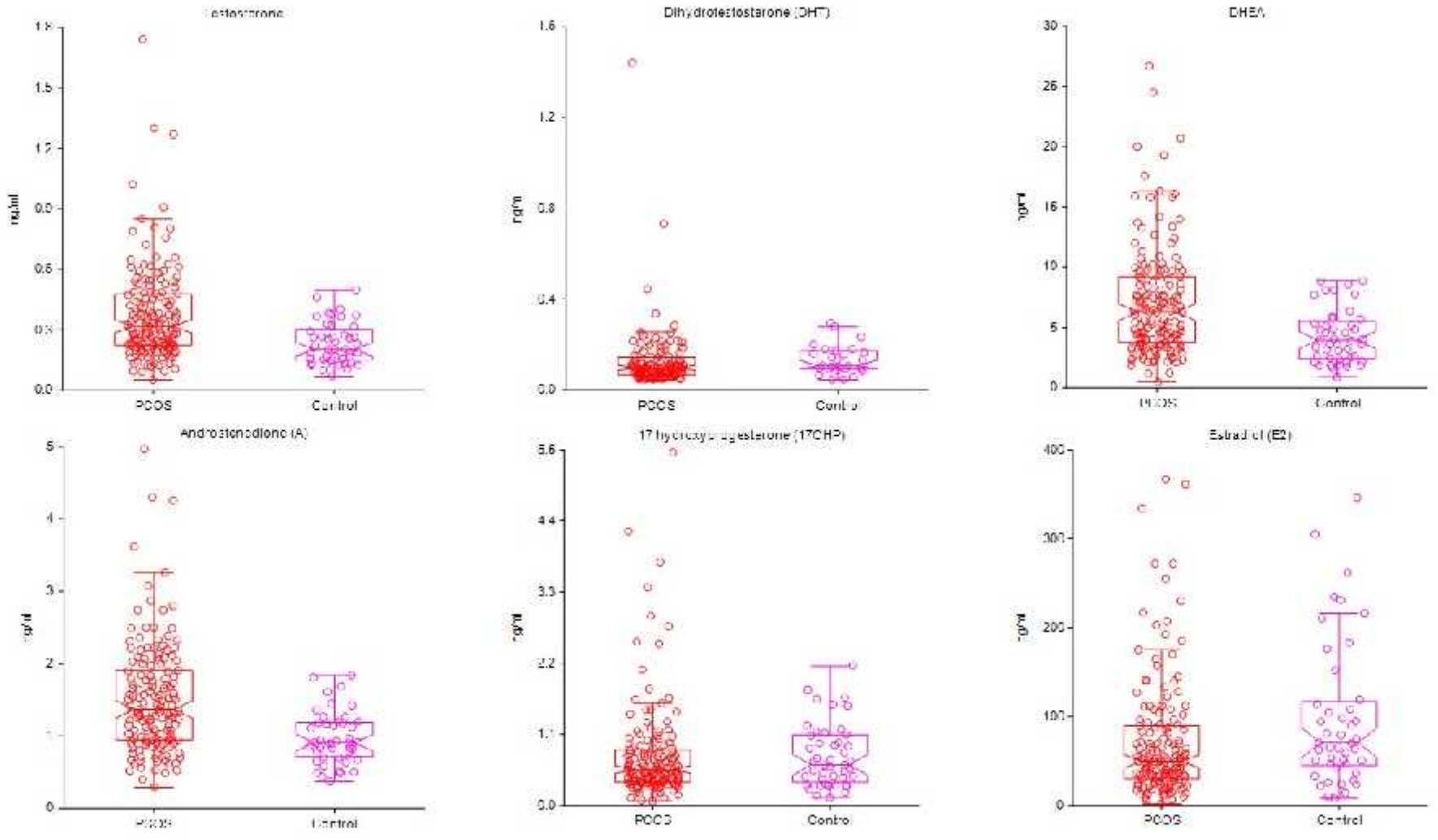
Janse et al, European Journal of Endocrinology, 2013

Tandem mass spectrometry



Janse et al, European Journal of Endocrinology, 2013

Hyperandrogenism in PCOS LC-MS



Does not differentiate between PCOS and non-PCOS

Handelsman, Teede, unpublished data 2015

Key points: hyperandrogenism in PCOS

- Hyperandrogenism key feature of PCOS - 80% affected

- Relationship with IR:
  - Driven by insulin, directly and via SHBG effects
- Exacerbated by obesity

- Testosterone assays – lack of precision and sensitivity
- LC-MS emerging

Outline

- PCOS overview
- Insulin resistance in PCOS
- Hyperandrogenism in PCOS
- AMH
- Management of PCOS

Anti-Mullerian hormone (AMH)

- AMH produced predominantly in ovarian granulosa cells of pre-antral and antral follicles
- Proposed as a marker of ovarian dysfunction
  - Disrupts folliculogenesis through diminishing follicular sensitivity to FSH
  - Inhibits follicle recruitment and growth
- A growing body of literature reports ↑ AMH concentrations in PCOS
  - May be related to increased number of pre-antral and antral follicles or ↑ production of AMH by these follicles
  - Mechanisms in PCOS are poorly understood
  - Have been attributed to obesity, IR, hyperandrogenism, gonadotrophins and their complex interactions

Pigny et al, JCEM 2003

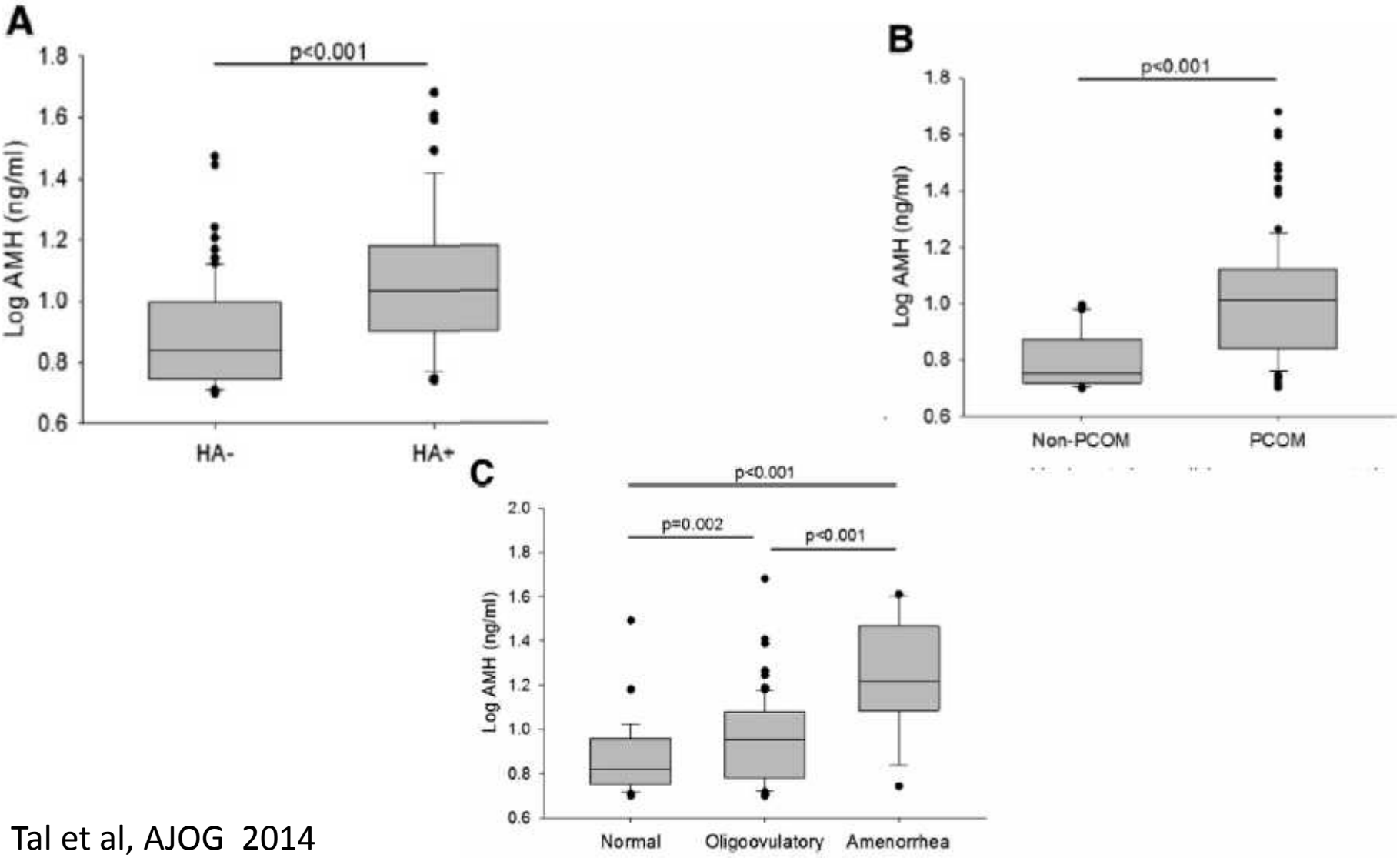
Patient clinical and biochemical data according to AMH group

Variable	Serum AMH, ng/mL			*P* value		
	5-10 (n = 84)	>10-14 (n = 30)	>14 (n = 20)	5-10 vs >10-14	5-10 vs >14	>10-14 vs >14
AMH, ng/mL	6.8 (1.5)	11.65 (1.1)	22.95 (10.1)			
BMI, kg/m^2	24.3 (5.0)	27.2 (5.7)	24.6 (4.5)	.01	NS	.04
Age, y	30.2 (5.2)	30.1 (3.9)	29.5 (4.6)	NS	NS	NS
FSH, IU/L	5.4 (2.2)	5.4 (1.5)	5.2 (1.6)	NS	NS	NS
LH, IU/L	5.3 (3.1)	8.6 (5.5)	11.9 (7.9)	.02	.002	NS
LH/FSH ratio	0.98 (0.6)	1.6 (1.0)	2.2 (1.1)	.01	.001	.04
Testosterone, ng/dL	42.8 (20.9)	56.2 (28.4)	75.9 (22.8)	.04	< .001	.02
DHEAS, μg/dL	201.3 (93.6)	188.1 (85)	249.2 (104)	NS	NS	.05
Hyperandrogenemia, %	38	47	80	NS	< .001	.03
Polycystic ovaries, %	54.2	97	100	< .001	< .001	NS
Menstrual regularity						
Regular periods, %	49.4	17	15	.002	.005	NS
Oligomenorrhea, %	49.4	77	55	.009	NS	NS
Amenorrhea, %	1.2	6.7	30	NS	< .0001	.03
PCOS diagnosis, %	51.8	97	100	< .001	< .001	NS
Infertility cause if present in addition to PCOS						
Male factor, %	40	36.7	33.3	NS	NS	NS
Tubal factor, %	10	10	5	NS	NS	NS
Endometriosis, %	1.2	3.3	0	NS	NS	NS

Data are given as mean (SD) or as percentages. Overall *P* values were determined by Kruskal-Wallis test. *P* value < .05 was considered statistically significant.

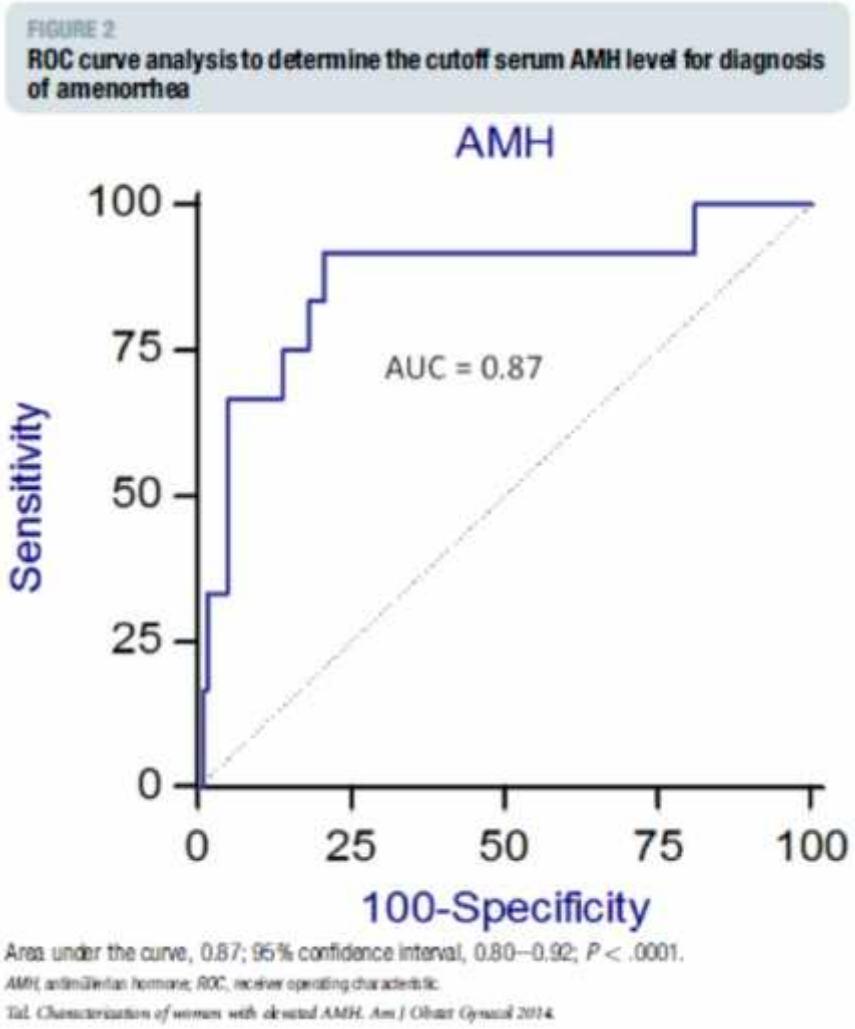
AMH, antimüllerian hormone; *BMI*, body mass index; *DHEAS*, dehydroepiandrosterone sulfate; *FSH*, follicle stimulating hormone; *LH*, luteinizing hormone; *NS*, nonsignature; *PCOS*, polycystic ovarian syndrome.

AMH



Tal et al, AJOG 2014

AMH



- AMH had strong diagnostic ability for amenorrhea in this study population
  - 91.7% specificity
  - 79.4% sensitivity

when the threshold AMH concentration was 11.4 ng/mL

AMH

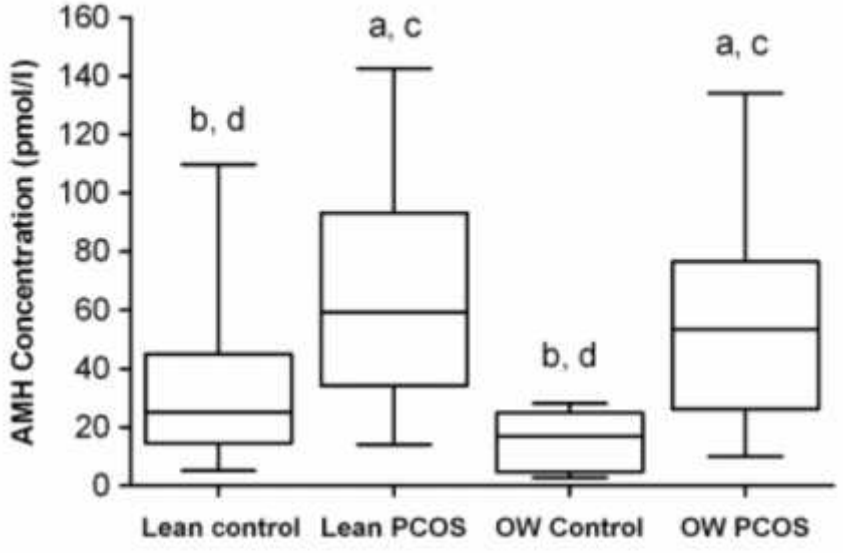


Fig. 1 Concentration of AMH is lean and overweight women with and without PCOS demonstrated by a box and whisker plot illustrating the median (central line), range (whiskers) and 25 and 75th percentiles (box). Abbreviations: OW, overweight. Significant difference $P < 0.05$ compared with the [a]lean control, [b]lean PCOS, [c]overweight control, [d]overweight PCOS group.

Cassar et al, Clinical Endocrinology, 2014

AMH

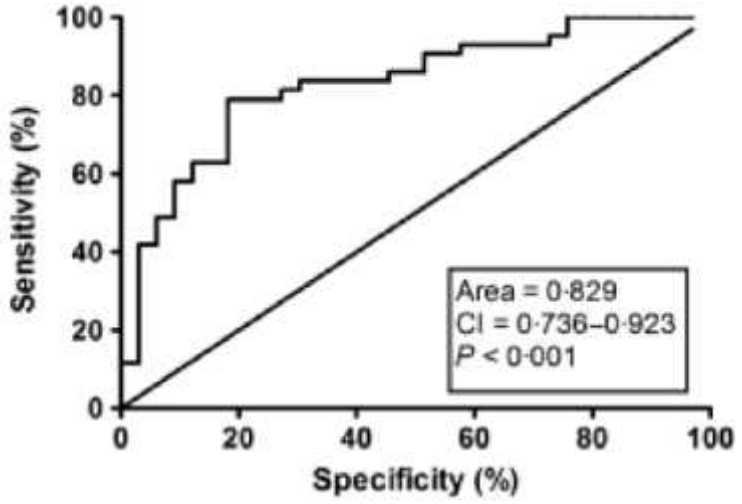


Fig. 2 ROC curve obtained from analysis of the AMH results. The sensitivity (true positive rate, *y*-axis) is plotted against the false positive rate or specificity (1-sensitivity, *x* = axis).

- ROC curve - ability of AMH to distinguish women with PCOS - threshold value of ≥ 30 pmol/l
- At this cutoff point, 79% specificity and 82% sensitivity

Cassar et al, Clinical Endocrinology, 2014

Key points: AMH

- AMH may be ↑ in women with PCOS
- AMH does not currently have a role in PCOS diagnosis

Outline

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- Insulin resistance in PCOS
- Hyperandrogenism in PCOS
- AMH
- Management of PCOS

PCOS management

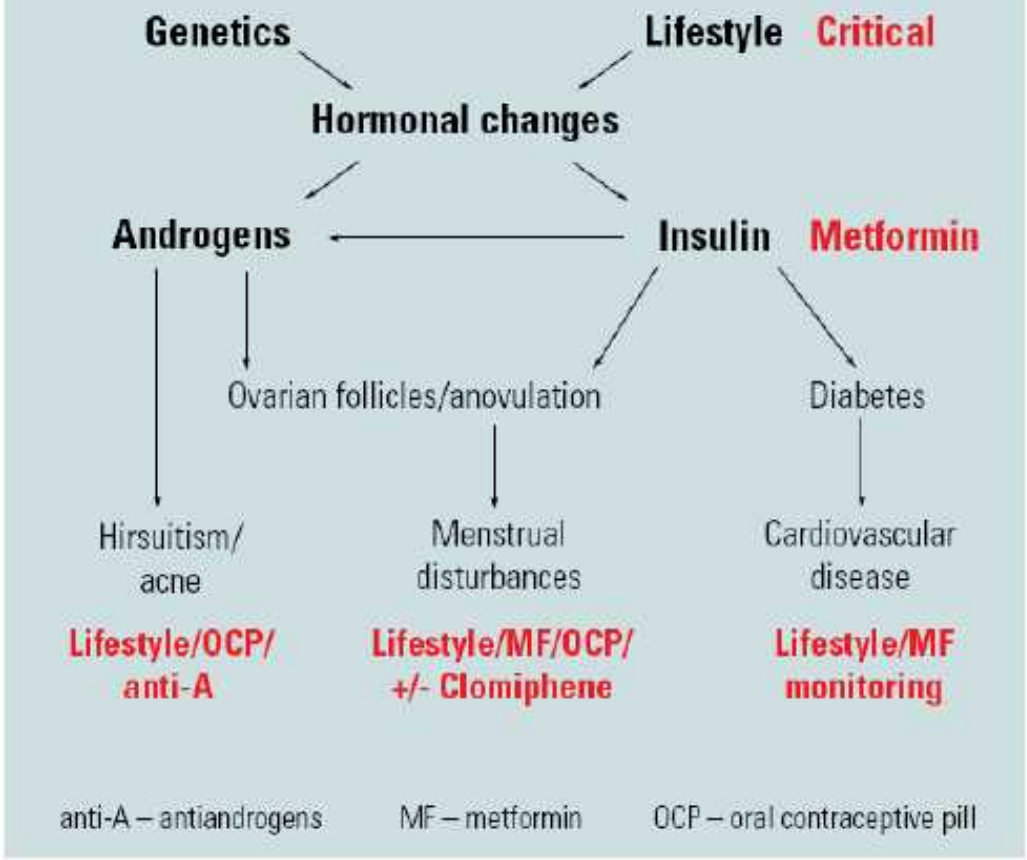

Figure 2 Summary of a targeted approach to therapy in polycystic ovary syndrome (PCOS). Reproduced with permission from [82].

Teede et al, BMC Medicine 2010

Cycle irregularity

- Lifestyle change (5-10% weight loss + exercise)
- Oral contraceptive pill (OCP)
- Cyclical progestins every 2-3 months
- Metformin (improves ovulation and cycles)

Teede et al BMC Medicine 2010

Infertility

- 60% get pregnant unaided
- Obesity independently exacerbates infertility and reduces effectiveness of interventions.
- Maternal and fetal pregnancy risks are greater
- Consider age related infertility
- Infertility therapies may include clomiphene, metformin, gonadotrophins and IVF

Teede et al BMC Medicine 2010

Hirsutism

- Cosmetic therapy first line
- Laser recommended
- Medical therapy
  - If concerned and cosmetic therapy ineffective, inaccessible or unaffordable
  - Primary therapy is the OCP
  - Anti-androgen (with contraception)
  - Trial therapies for $\geq$ 6 months before changing
  - Combination therapy – if ineffective
- Hair loss on scalp – often triple therapy

Teede et al BMC Medicine 2010

Metabolic syndrome, prediabetes, diabetes and cardiovascular disease risk

- Lifestyle / exercise is critical
- Prevention of weight gain vital
- Screening and prevention is critical
- Lifestyle change 5% weight loss reduces diabetes risk by ~50-60% and metformin by ~50% in high risk
- Metformin has role to relieve symptoms and reduce metabolic risk in high risk women with PCOS
- Metformin may limit weight gain

Teede et al BMC Medicine 2010

OCP or hormonal therapies

- OCP reduces androgenism/hair excess
- Contraception
- Endometrial protection

- Low dose OCP best

- OCP not approved in PCOS
- However recommended by international/national specialist societies and is evidence based

Metformin

- Improves ovulation/ cycles, limited fertility impact
- Reduces glucose, insulin and blood pressure
- Reduces progression to diabetes
- May prevent weight gain
- Side-effects
  - Gastrointestinal side effects
  - Rare but serious adverse effect - lactic acidosis (LA)

- Metformin not approved in PCOS
- However recommended by international/national specialist societies and is evidence based

Key points: management

- Complex condition, common
- Lifestyle critical for all
- Targeted therapy for reproductive dysfunction
- Metabolic- screen, prevent and manage risk
- Lifelong chronic illness; education

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