PCOS and type 2 diabetes mellitus

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PCOS and type 2 diabetes mellitus:
topics covered

- Insulin resistance and PCOS
- Prevalence of impaired glucose tolerance and diabetes
- Diabetes genes and PCOS
- Risk groups for IGT and T2D
- Prevention of T2D in PCOS

Polycystic ovary syndrome

- Characterised by anovulation with clinical (hirsutism/acne) and/or biochemical evidence of androgen excess
- Typically presents during adolescence
- Affects >5% women of reproductive age
- Commonest cause of menstrual dysfunction (>80% cases of anovulatory infertility) and hirsutism
- Typical endocrine features are raised testosterone and LH
- Also associated with metabolic abnormalities and increased risk of type 2 diabetes

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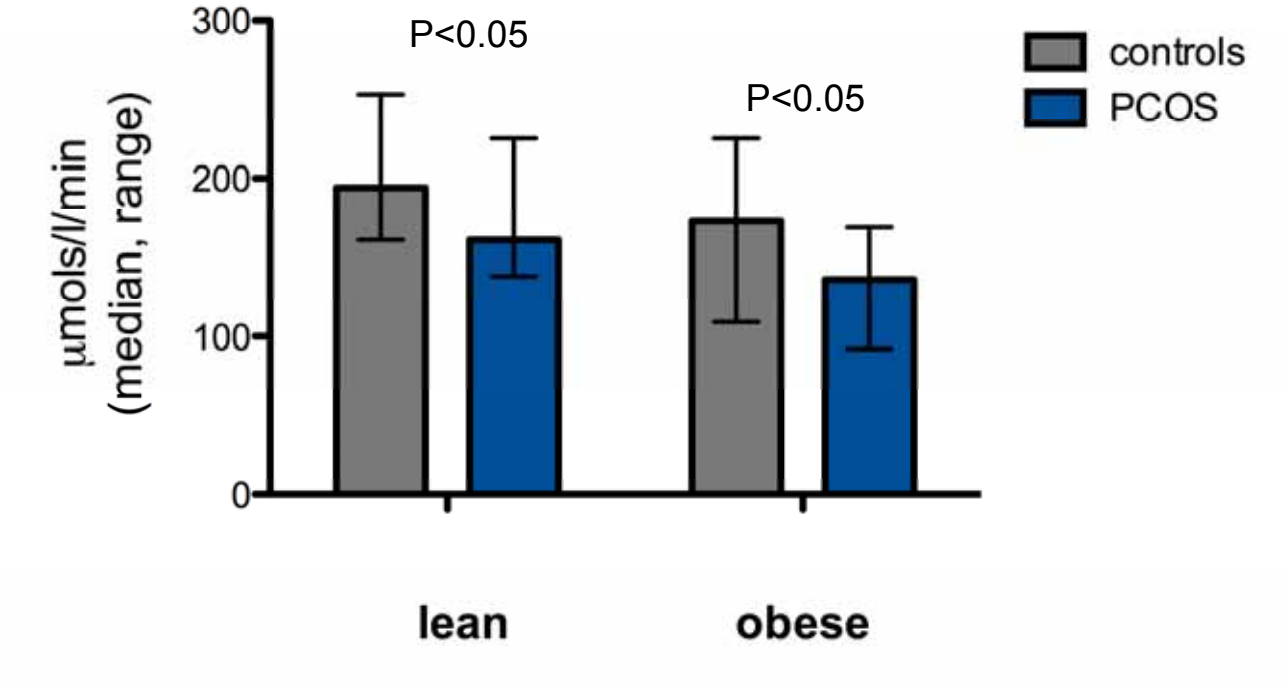
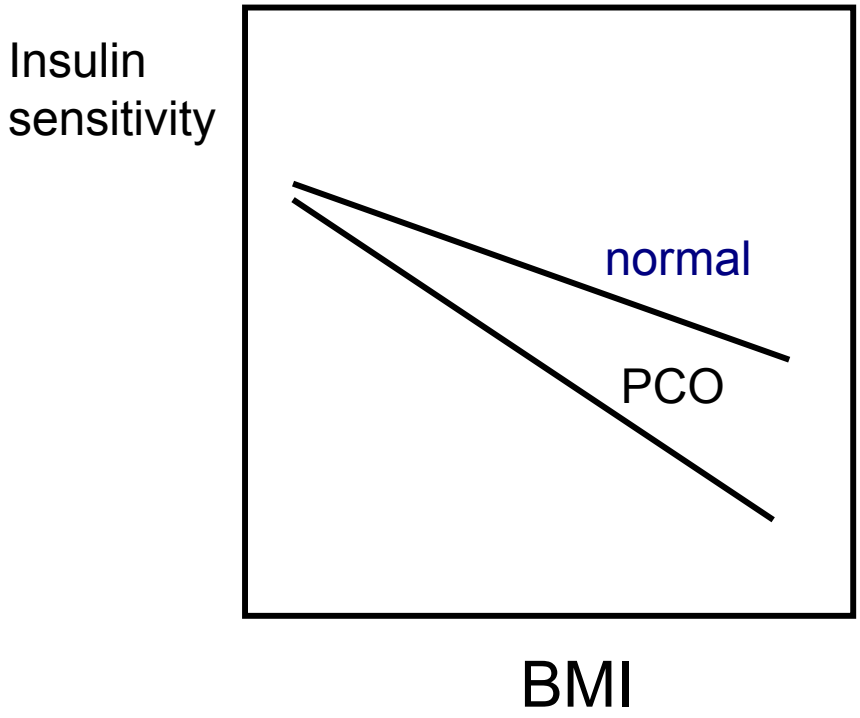
Insulin sensitivity is reduced in lean and obese women with PCOS



Robinson et al, *Clin Endocrinol* 1992 **36** 537

Obesity amplifies insulin resistance in women with PCOS



(Adapted from Holte *et al, J Clin Endocrinol Metab* 1994, **78** 1052)

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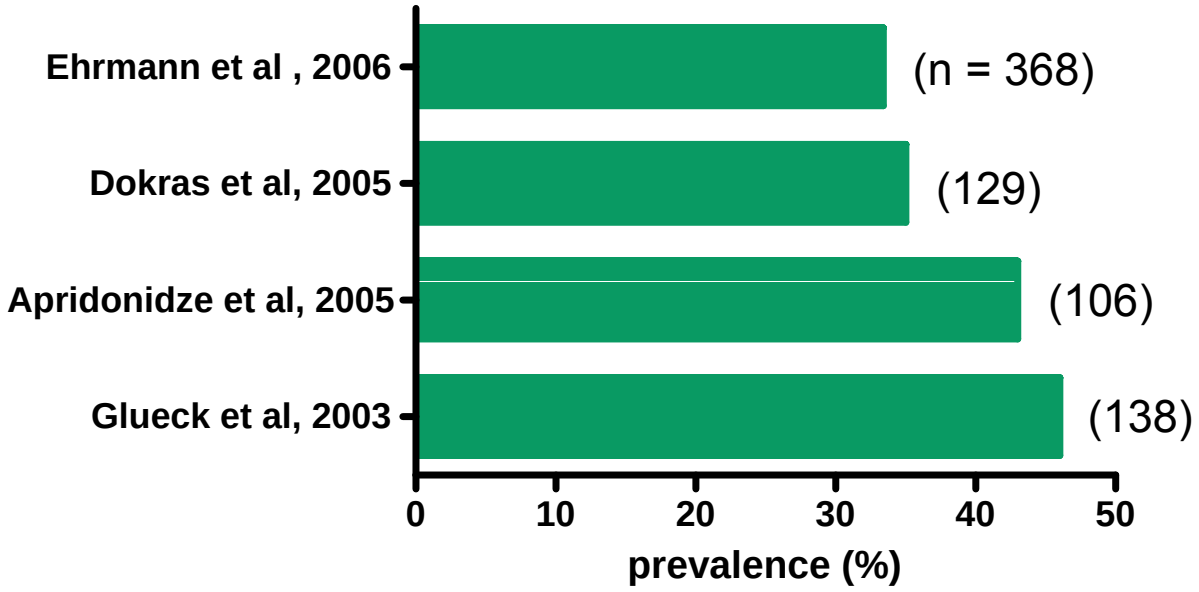
Metabolic syndrome: definitions

- National Cholesterol Education Program - 3rd Adult Treatment Panel (NECP-ATPIII)
  - 3 from 5
    - Central obesity (waist circumference >88cm)
    - Triglycerides ≥150mg/dL (1.69mmol/l)
    - BP ≥130/85
    - Fasting glucose ≥110mg/dL (6.11mmol/l)
    - HDL<50mg/dL (1.29mmol/l)
- International Diabetes Federation (IDF)
  - Central obesity (waist circumference >80cm)
  - + 2 from 4
    - Triglycerides ≥150mg/dL
    - BP ≥130/85
    - Fasting glucose ≥110mg/dL
    - HDL<50mg/dL

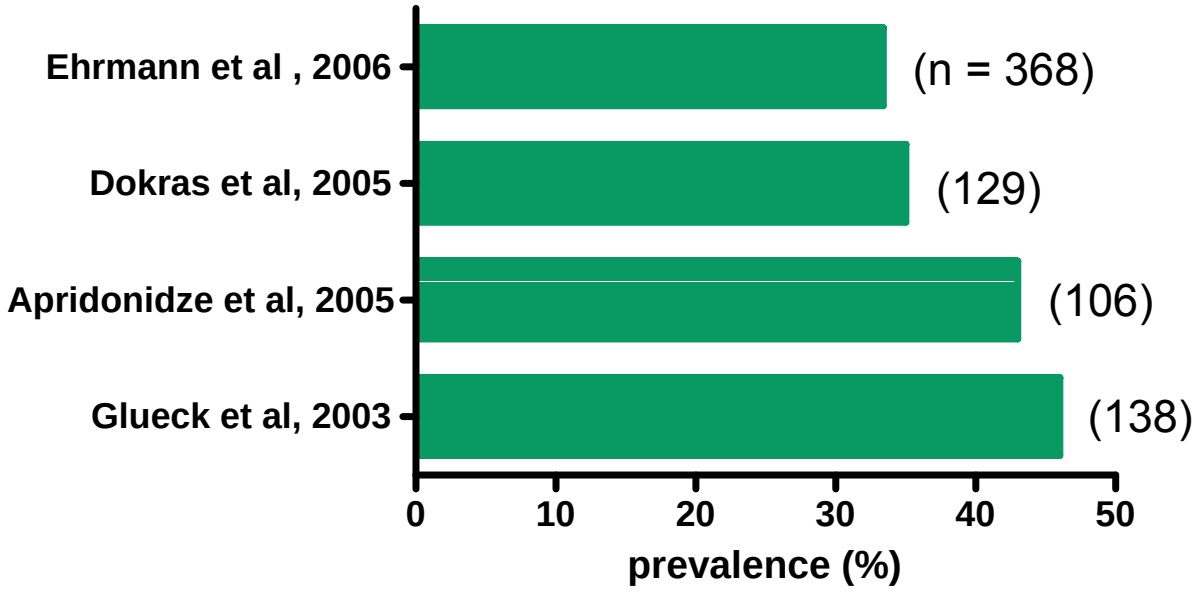
Skilton *et al, Atherosclerosis* 2007 109 416-22

Prevalence of metabolic syndrome in young women with PCOS



Glueck *et al, Metabolism* 2003 **52** 908-915
Apridonidze *et al*, *J Clin Endocrinol Metab* 2005 **90** 1929-1935
Dokras et al *Obstet Gynecol* 2005 **106** 131-137
Ehrmann et al, *J Clin Endocrinol Metab* 2006 **91** 48-53

Prevalence of metabolic syndrome in young women with PCOS



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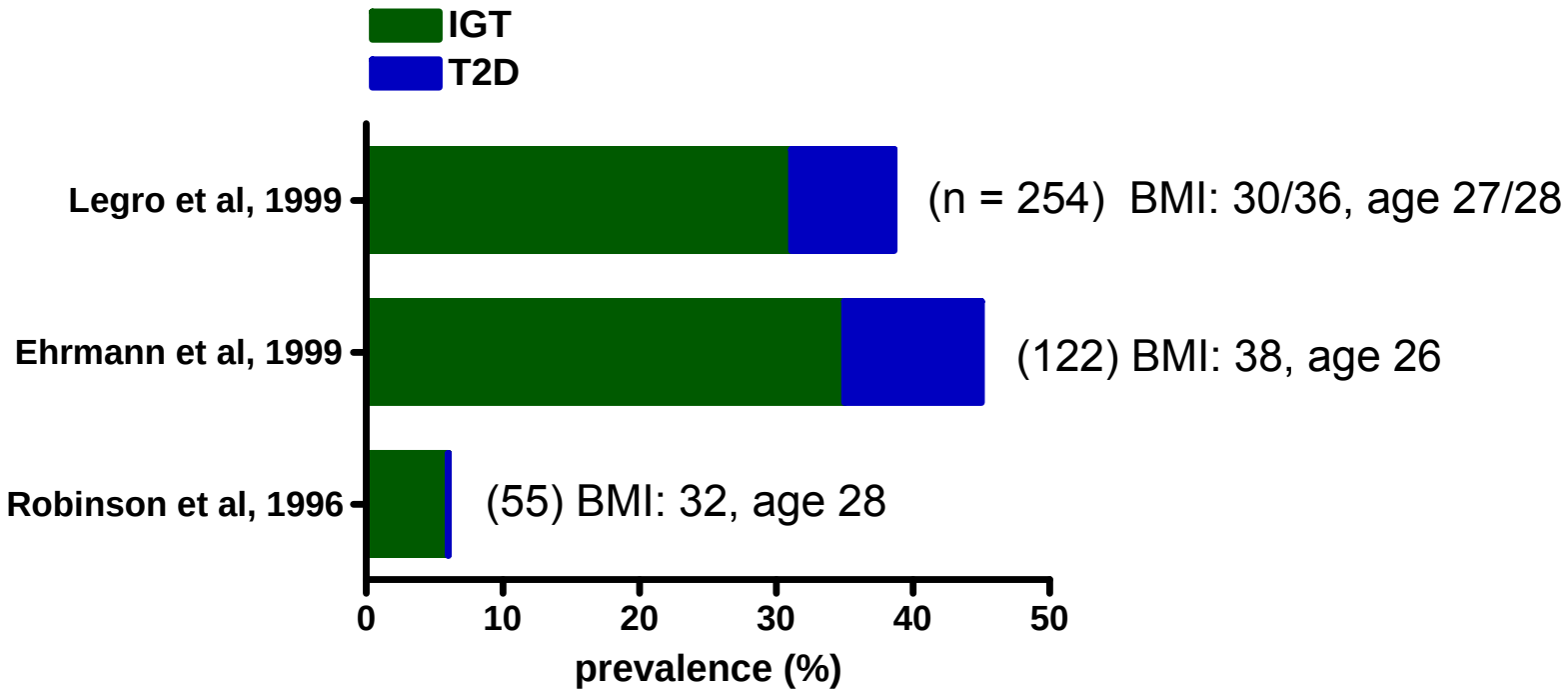
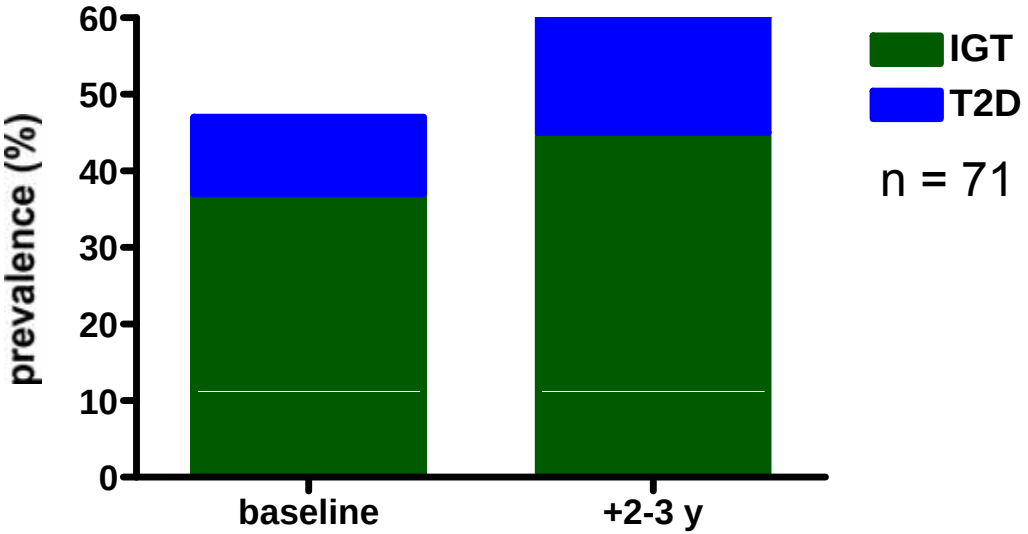
PCOS = Female Metabolic Syndrome (or Syndrome XX) (*Dunaif*)

Prevalence of IGT and diabetes in young women with PCOS



Robinson *et al, Clin Endocrinol* 1996 44 277-84
Ehrmann *et al, Diabetes Care* 1999 22 141-146
Legro *et al, J Clin Endocrinol Metab* 1999 84 165-9

Longitudinal study of prevalence of IGT and diabetes in PCOS



Legro *et al, J Clin Endocrinol Metab* 2005 90 3236-42

Gestational diabetes in women with PCOS

- High prevalence (52%) of polycystic ovaries in women with history of GDM
  - Kousta *et al, Clin Endocrinol* 2000 **53** 501-7
- Women with PCOS at increased risk of GDM (OR 2.94 (1.7 - 5.1))
  - Boomsma *et al, Hum Reprod Update* 2006 **12** 673-683 (meta-analysis)
- High prevalence of GDM in women with PCOS (42% of 50 women)
  - Veltman-Verhulst *et al, Hum Reprod* 2010 (Epub, October)

Increased risk of T2D in older women with proven PCOS

- 319 cases of PCOS age 56.7 (38 - 98) with reference group of 1060 subjects
- Increased risk of diabetes after adjustment for BMI: OR 2.2 (0.9 - 5.2)
- Higher risk if obese subjects included: OR 2.8 (1.5 - 5.5)

Wild *et al, Clin Endocrinol* 2000 **52** 595-600

Increased risk of T2D in women with symptoms of “PCOS”

- Relative risk of T2D in women with history oligomenorrhoea/irregular cycle: 2.08 (1.62 - 2.66)
- Independent of obesity but RR increased further in obese subjects: 3.86 (2.33 - 6.38)

  (studied at age 34)

Nurses Health II: Solomon *et al, JAMA* 2001 **286** 2421-6

Meta-analysis of studies reporting risk of T2D in women with PCOS

- IGT: OR 2.54 [1.44 - 4.47]
- T2D: OR 4.00 [1.97 - 8.10]

  in BMI-matched groups

  35 studies analysed

  Moran *et al Hum Reprod Update* 2010 **16** 347-63

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- **Diabetes genes and PCOS**
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Evidence for genetic basis of polycystic ovary syndrome

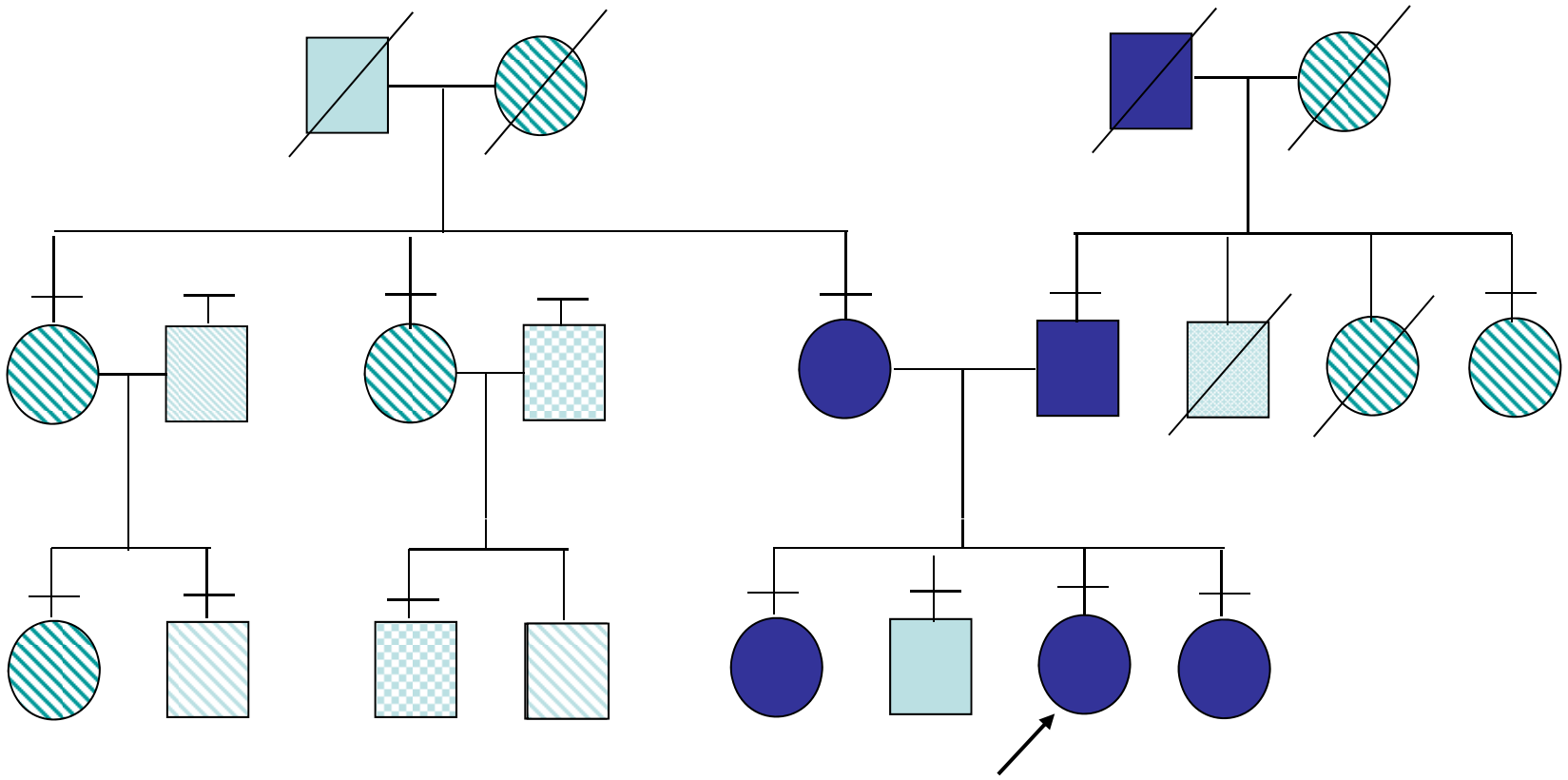
- Familial clustering of cases
- Concordance greater in identical than in non-identical twin pairs (tetrachoric correlation 0.71 vs 0.38; estimated genetic influence 79%, environment 21%; Vink *et al*, 2006)
- Heritability of endocrine and metabolic features (Legro *et al*, 1998, 2002; Franks *et al*, 2008)

Mode of inheritance uncertain. Complex endocrine disorder (like type 2 diabetes) likely to be oligogenic or polygenic (Franks *et al*, 1997; Urbanek *et al*, 2007)

Candidate genes in PCOS

- Steroid hormone production and metabolism
  - *CYP11a* (P450scc)
  - *CYP17* (P450c17)
  - *CYP19* ($P450_{arom}$)
- Metabolic: insulin secretion and action; obesity
  - Beta cell function: *INS VNTR*, *TCF7L2, KCNJ11*
  - Insulin resistance: *IR, PPAR*γ
  - Obesity: *FTO*
- Androgen action
  - Androgen receptor
- Ovarian follicle development
  - Follistatin; *FBN3*

Familial Polycystic Ovary Syndrome



PCO

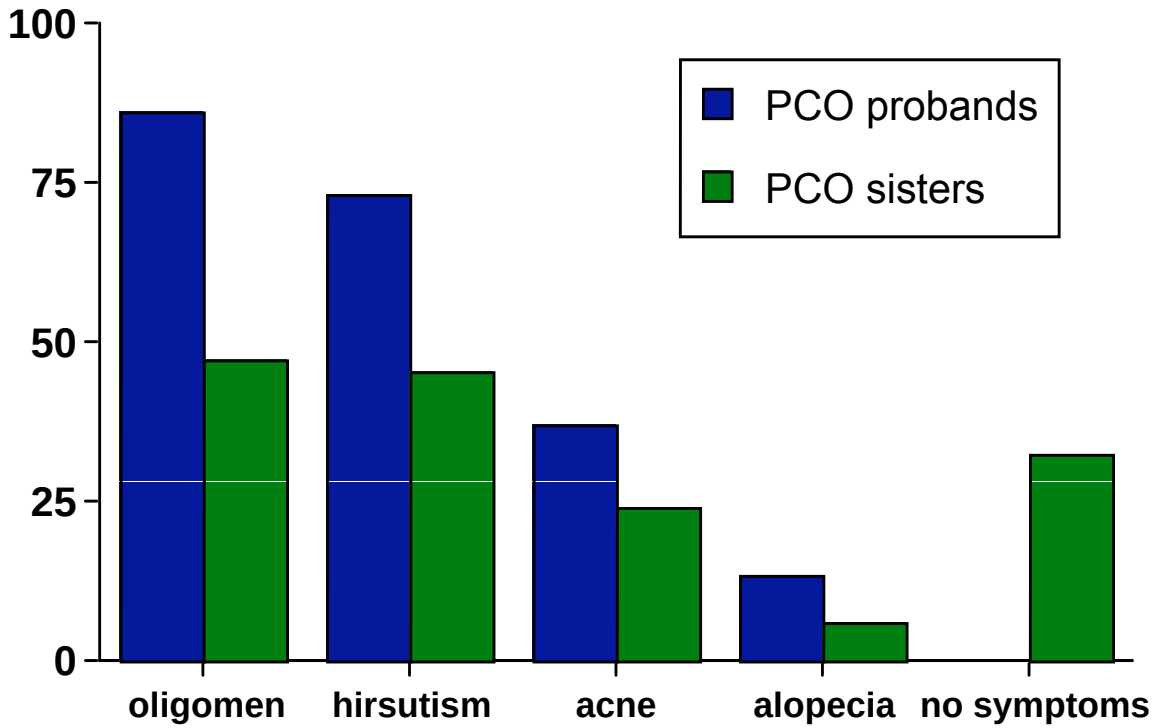
uncertain ovarian morphology

Problems with genetic studies in PCOS

- Presents only in women of reproductive age
- No obvious male phenotype
- Large affected families uncommon
- Heterogeneity of phenotype and disagreement about diagnostic criteria

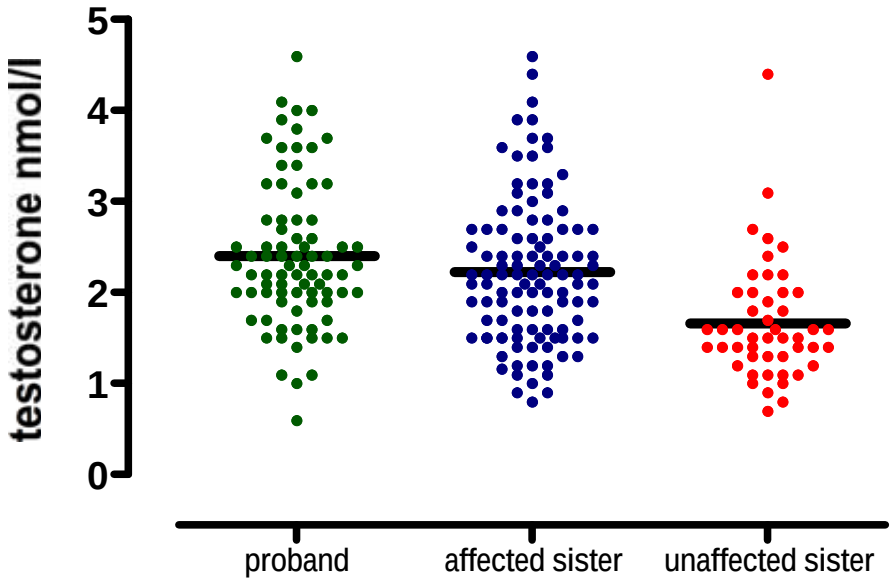
Affected sister pairs with PCO

(affected = PCO on ultrasound)



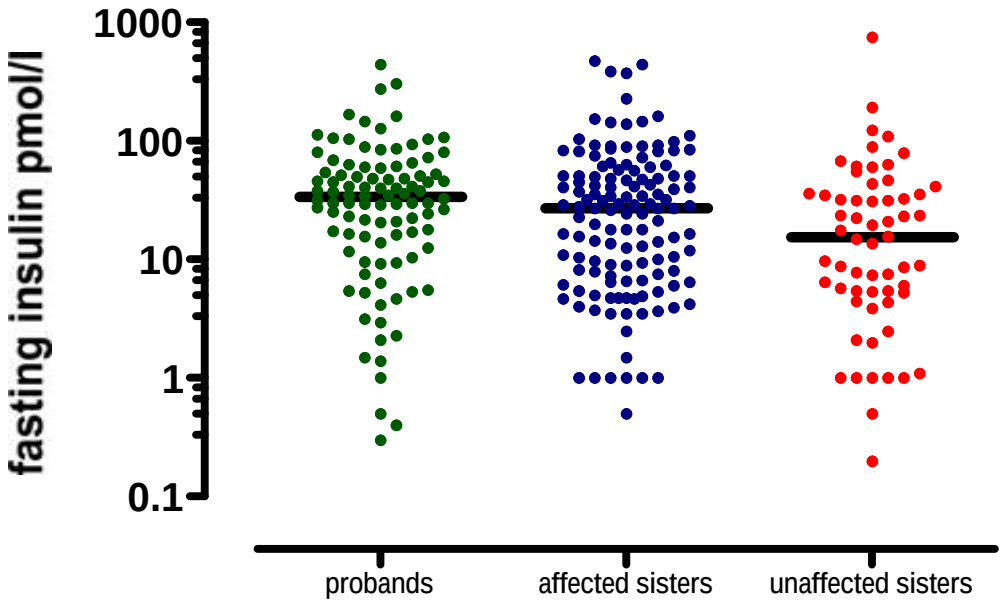
Franks *et al, J Clin Endocrinol Metab* 2008 93 3396-3402

Serum testosterone in affected sister pairs with PCO



Franks *et al, J Clin Endocrinol Metab* 2008 **93** 3396-3402

Fasting insulin levels are similar in affected sister-pairs with PCO



Diabetes genes and PCOS

- Insulin gene *VNTR*
  - No clear evidence
- *TCF7L2*
  - No association with PCOS at TCF7L2 T2D locus but association of other polymorphisms with PCOS (rs11196236, rs11196229 rs7903146) (Barber et al, 2007; Christopoulous et al, 2008; Biyasheva et al, 2009)
- *KCNJ11*(E23K)
  - No association with PCOS (Barber et al, 2007; Christopoulous, 2008)
- *Calpain 10* (CAPN10)
  - No clear evidence
- *PPARγ* (Pro12Ala)
  - No clear evidence
- *FTO*
  - Association with obesity in PCOS (Barber et al, 2008; Tan et al, 2010)

The *FTO* gene

- Fat mass and obesity associated gene (Chr16)
- SNP rs9939609 associated with obesity in the general population (Frayling *et al*, 2007 *Science* 316:889-894)
- Does FTO variant contribute to genetic basis of PCOS?

Case-control association analyses for variants at *FTO* rs9939609 and PCOS in UK samples

(Barber *et al*, 2008, *Diabetologia* **51** 1153-58)

Alleles	TT	AT	AA	P-value (Cases vs combined controls)
UK cases (n=463)	133 (28.7%)	231 (49.9%)	99 (21.4%)	5.3×10^{-4}
Combined female controls (n=1778)	642 (36.1%)	849 (47.8%)	287 (16.1%)	
Delta	-7.4%	+2.1%	+5.3%	

Data shown are genotype counts (and percentages); P values represent Cochran-Armitage test results

Following adjustment for BMI in the comparison between UK cases and combined control group, the association with PCOS was attenuated but not eradicated (P-value=2.9 x 10-3).

FTO in PCOS - case control study

- The rs9939609 variant associated with PCOS: OR 1.29 (1.14-1.49)
- Largely related to obesity (PCOS group have higher BMI) but still significant association after adjustment for BMI

Independent replication studies: association of FTO with PCOS (predominantly with obesity & metabolic parameters)

(Attaoua *et al*, *Biochem Biophys Res Commun* 2008 **373** 230-234; also Wehr *et al, Metabolism* 2010 **59** 575-80; Tan *et a*l, *BMC Med Genet* 2010 **11** 12)

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Screening for metabolic disorders in PCOS

- No test of insulin resistance is needed to make diagnosis of PCOS or to select treatment
- Obese women with PCOS (and/or those with abdominal obesity) should have an OGTT (or fasting glucose) and lipid profile
- Utility of these tests in non-obese women with PCOS is not yet known
  - Rotterdam consensus meeting (*Hum Reprod* 2004 19 41-7)

- *SHBG as a screening test for metabolic abnormalities?*

Who is at risk of T2D?

PCOS (2-fold)

PCOS + obesity (3-fold)

PCOS + obesity + FH of diabetes

PCOS + obesity + GDM

PCOS + obesity + IGT

Diagnostic criteria for PCOS

NIH 1990

- Chronic anovulation
- Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other aetiologies, eg CAH)

(both criteria needed)

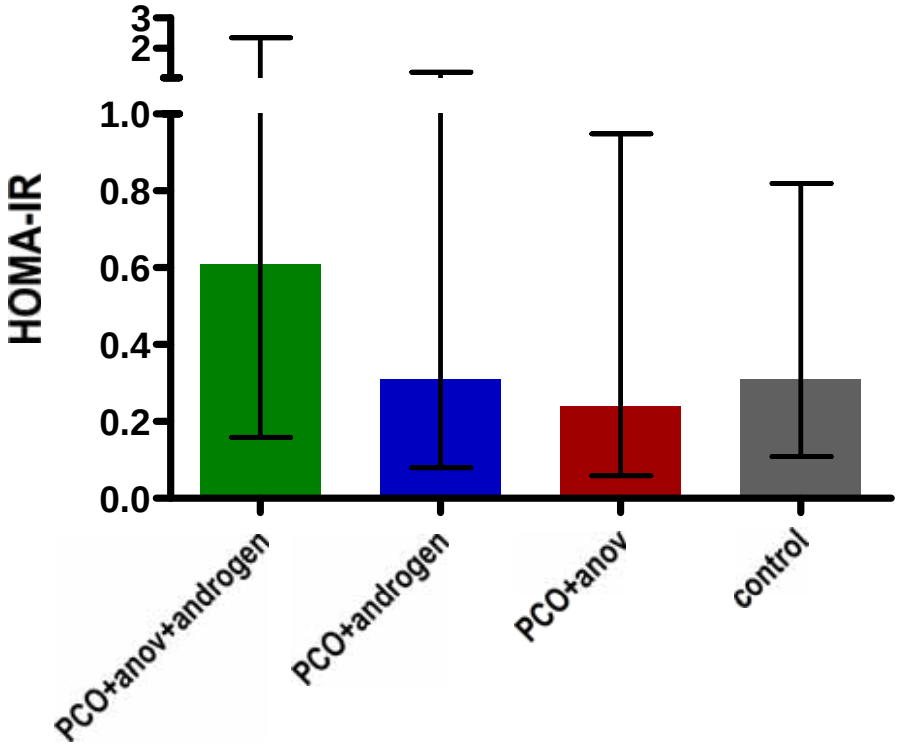
Rotterdam 2003

- Oligo- and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries

(2 of 3 criteria needed)

Zawadzki & Dunaif 1992, in *Polycystic Ovary Syndrome*, Dunaif et al (eds), Boston: Blackwell Scientific pp 377-84
Rotterdam ESHRE/ASRM sponsored PCOS Consensus Workshop Group (*Hum Reprod* 2004 19 41-7)

HOMA-IR according to PCOS phenotype

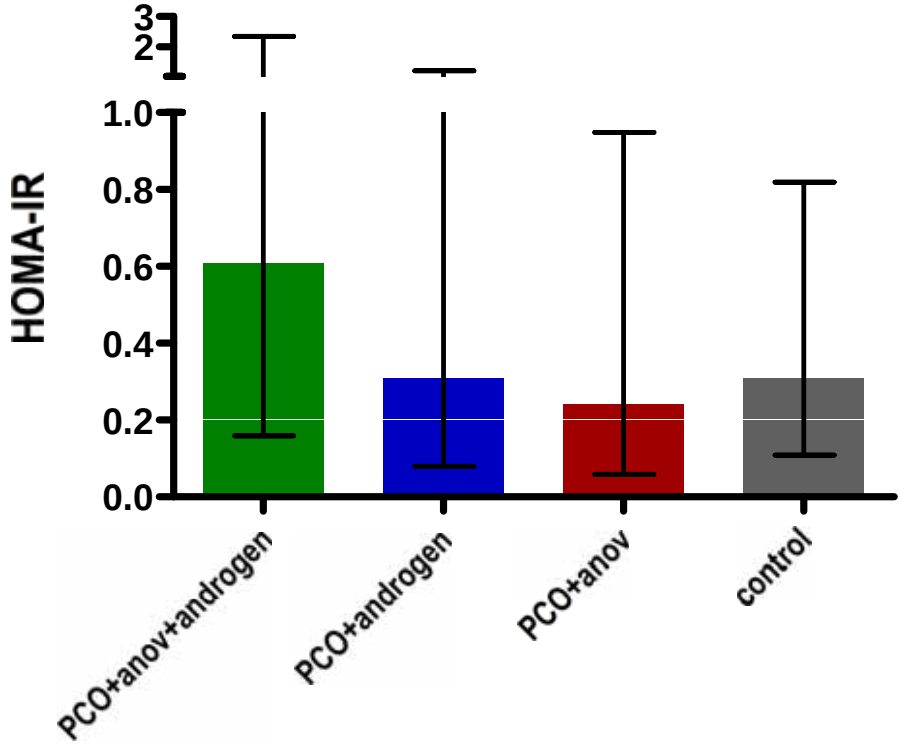


(Geometric mean ±SD)

Barber *et al, Clin Endocrinol* 2007 66 513-7

HOMA-IR according to PCOS phenotype

Metabolic syndrome (IDF):	29%	7%	7%	4%
BMI	*29*	*24*	*24*	*24*



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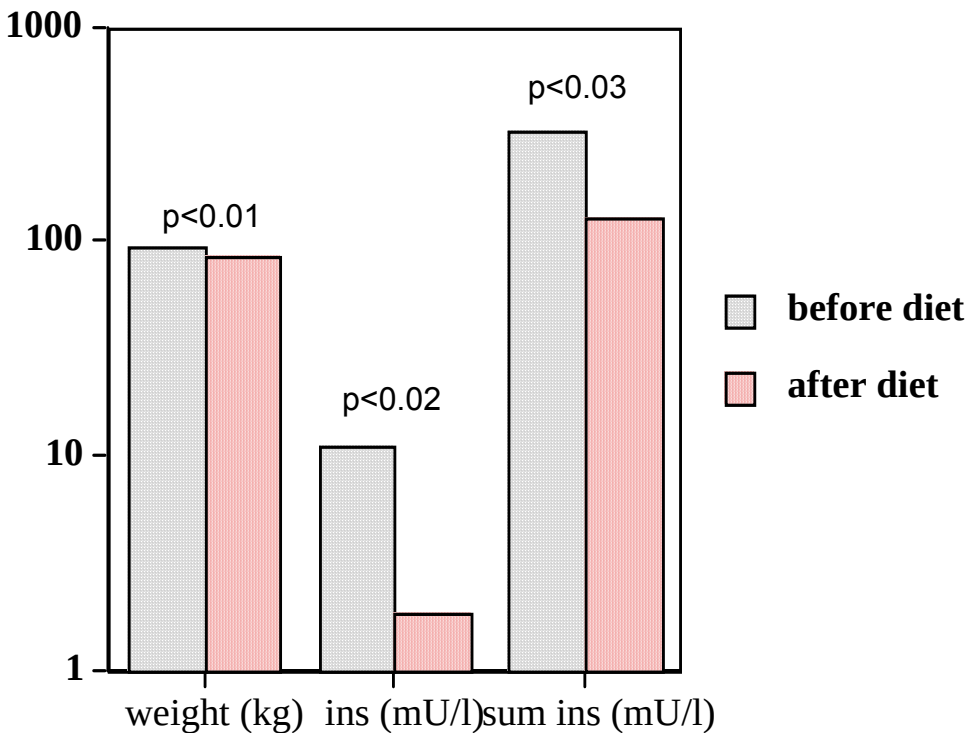
Prevention of diabetes in women with PCOS

- **Make an *early* diagnosis**
- **Lean women with PCOS should not get fat**
- Obese women with PCOS should be advised re diet and lifestyle
- Those at high risk may need need medication as well as lifestyle changes

Effect of diet/lifestyle on insulin and fertility in obese women with PCOS



- modest (5-10%) weight reduction associated with vast improvement in metabolic indices
- diet and lifestyle changes improve ovulation rate and fertility (Kiddy *et al*, 1992; Clark *et al*, 1995; Norman *et al*, 2002; Steele et al, 2005)

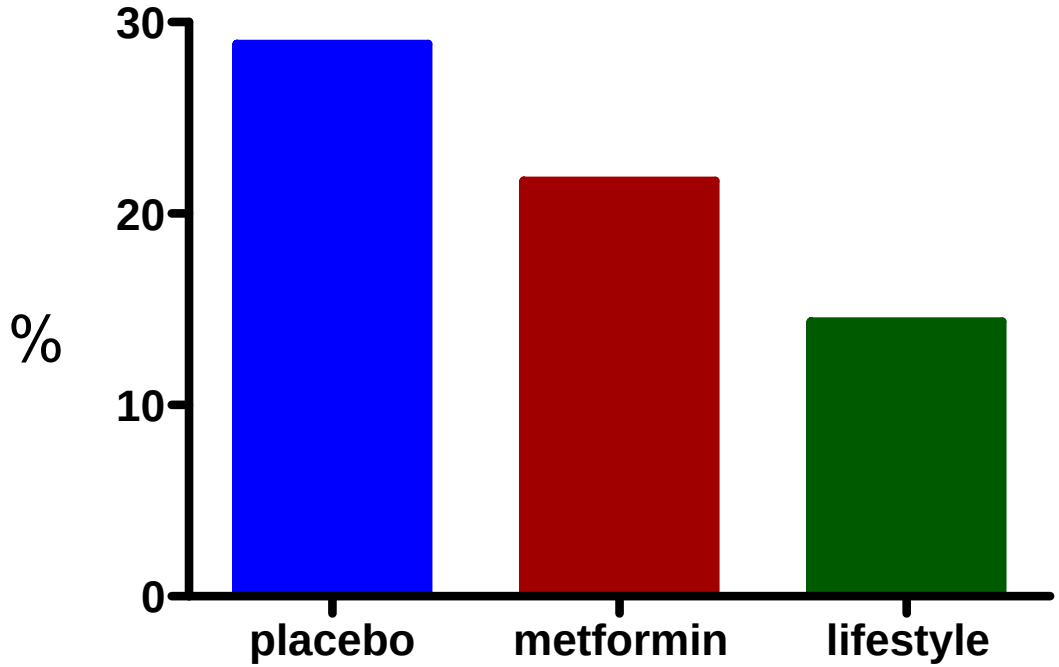
Metformin in treatment of PCOS

- Small number of properly-conducted clinical trials
  - Significant but very modest increase in ovulation rate
  - Questionable effect on unwanted body hair (no data on acne)
  - *No* effect independent of weight loss on ovulation rate (Tang *et al, Hum Reprod* 2006 21 80–89)
- Efficacy and indications for treatment unclear
- Recent large clinical trials (and review of evidence) suggest that the usefulness of metformin has been overestimated (Tang *et al, Cochrane Database Syst Rev* 2010 Issue 1. Art. No.: CD003053. DOI:10.1002/14651858)

Metformin in treatment of PCOS

- *Not* useful for treatment of infertility or menstrual disturbances
- *Not* very effective for treatment of hirsutism
- *Does* have a place in management of women at high risk of developing diabetes

Cumulative incidence of T2D at 3 years



3234 subjects with IGT

Knowler WC *et al* Diabetes Prevention Program Research Group
N Engl J Med 2002 346 393-403

Role of thiazolidinediones (glitazones) in PCOS

- Improvement in insulin sensitivity, androgens and cyclicity
- Lipids not significantly altered and weight increased
- Concern about safety, particularly in women of reproductive age
  - Similar concerns about glucagon-like peptides (GLP-1) agonists

Summary

- Insulin resistance and abnormal β-cell function are features of PCOS
- Women with PCOS are at increased risk of developing metabolic syndrome and T2D
- **PCOS is a prediabetic state that presents in young women - usually in adolescence**
- Diet and lifestyle changes are most important ways of improving fertility and in prevention of diabetes in women with PCOS