

PCOS, diabetes and cardiovascular disease

Stephen Franks

Institute of Reproductive & Developmental Biology
Imperial College London, Hammersmith Hospital,
London W12 0NN, UK

With special thanks to:

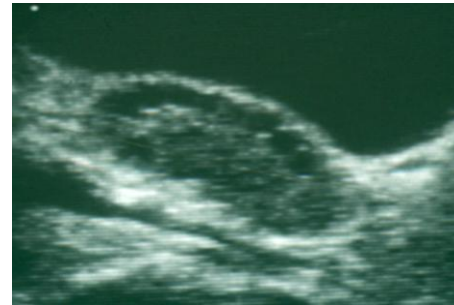
- Stephen Robinson & Desmond Johnston (Imperial College London)
- Tom Barber, John Wass & Mark McCarthy (University of Oxford)

PCOS, diabetes and cardiovascular disease

- Insulin resistance in PCOS
- Prevalence of metabolic syndrome, IGT and T2D in PCOS
- Investigation and management of metabolic dysfunction 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 anovulatory infertility (80%)
- Typical endocrine features are raised testosterone and LH
- Also associated with metabolic abnormalities and increased risk of type 2 diabetes

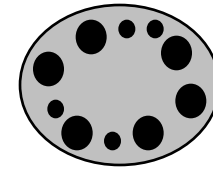
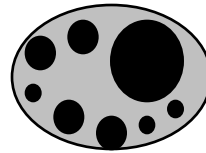
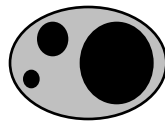


The spectrum of presentation of PCOS includes women with hyperandrogenism and regular, ovulatory cycles

normal

ov-PCO

anov-PCO



ovulation

✓

✓

X

testosterone



X

✓

✓

LH



X

✓

✓

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

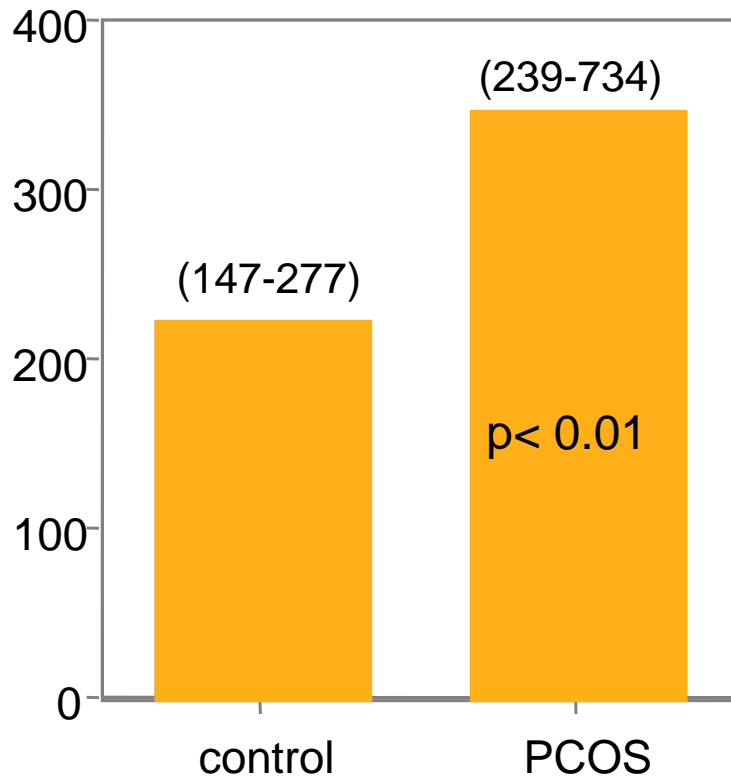
- Oligo- and/or anovulation
- Clinical and/or biochemical signs of hyperandrogenism
- Polycystic ovaries
(2 of 3 criteria needed)

PCOS, diabetes and cardiovascular disease

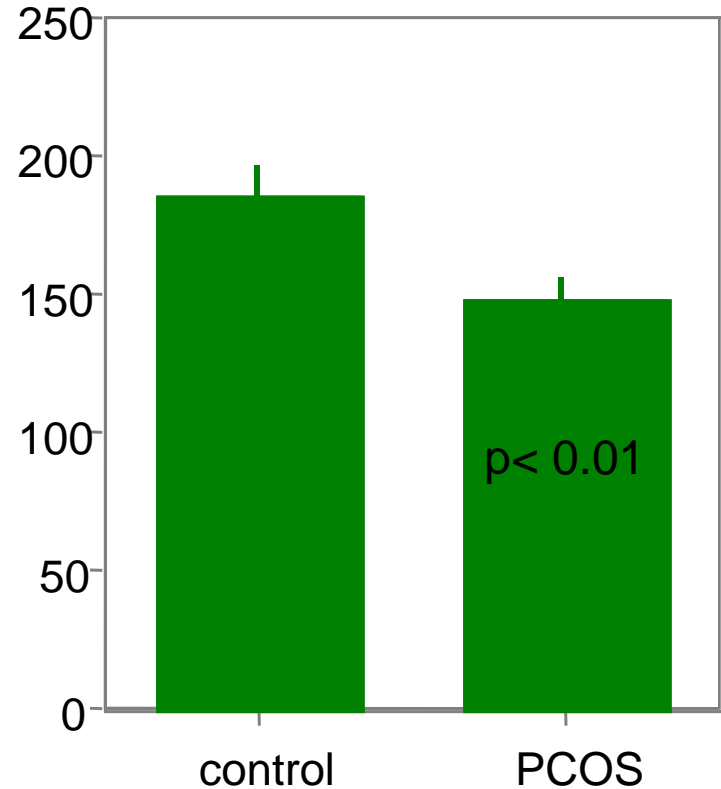
- Insulin resistance in PCOS
- Prevalence of metabolic syndrome, IGT and T2D in PCOS
- Investigation and management of metabolic dysfunction in PCOS

Insulin area during OGTT and insulin sensitivity in women with PCOS

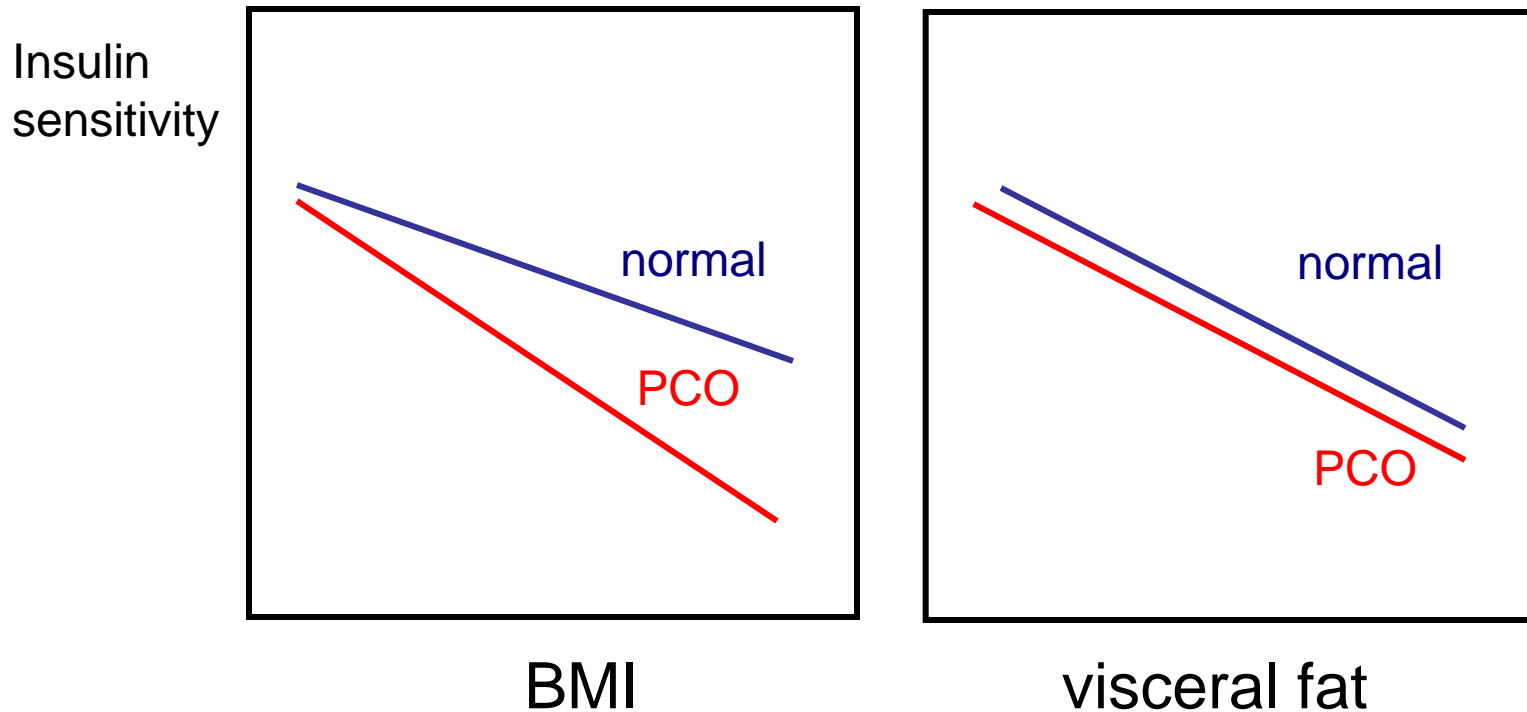
median insulin area mU/l



insulin sensitivity $\mu\text{mol/l/min}$



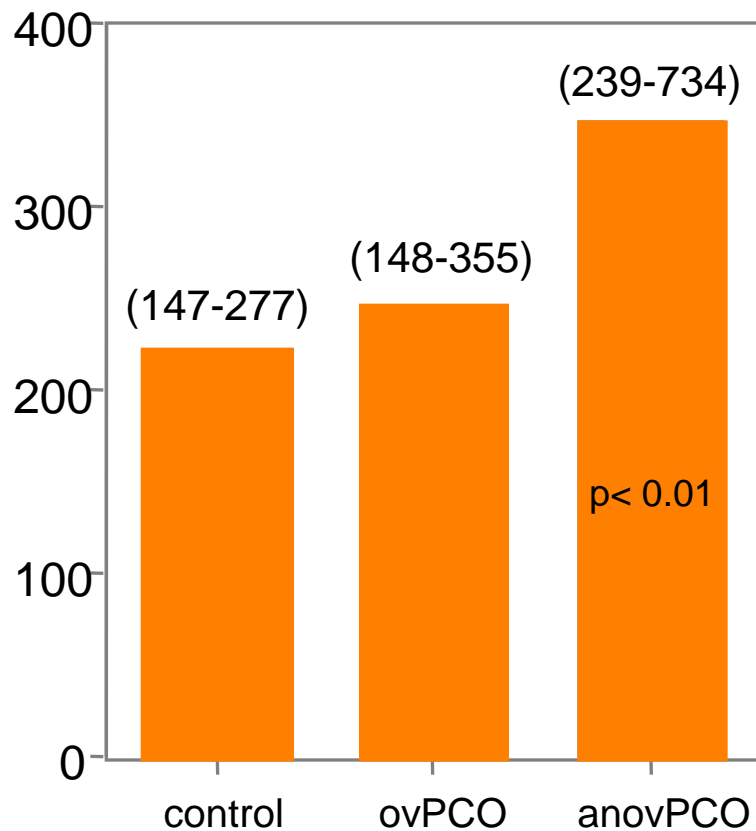
Reduced insulin sensitivity in women with PCOS



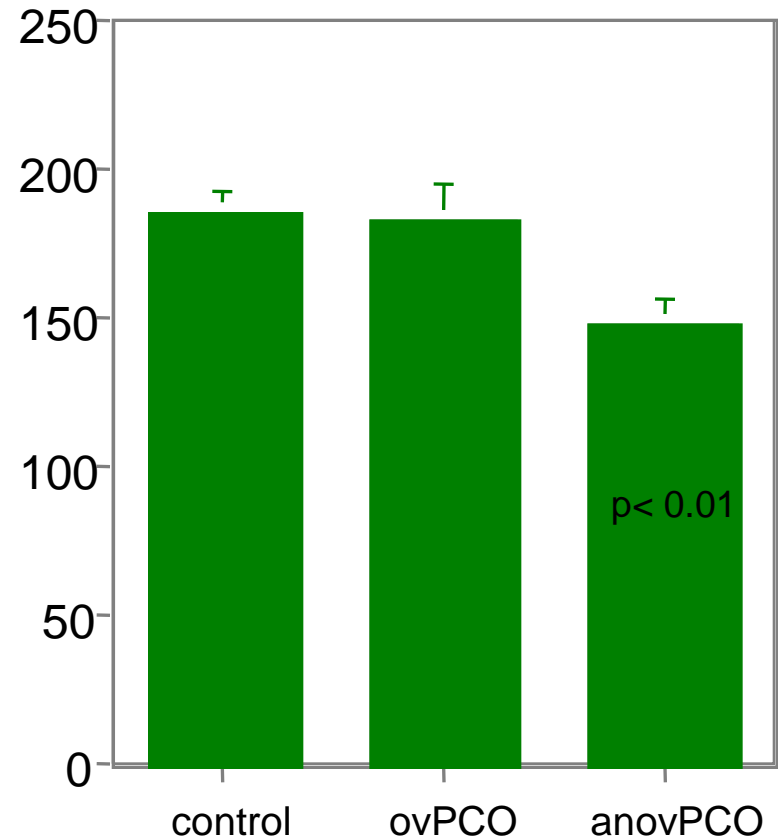
(Adapted from Holte *et al*, *J Clin Endocrinol Metab* 1994, **78** 1052)

Insulin secretion and sensitivity in ovulatory and anovulatory women with PCOS

insulin area mU/l



insulin sensitivity $\mu\text{mol/l/min}$

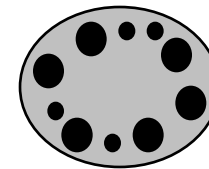
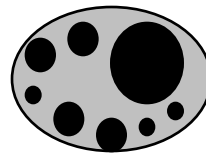
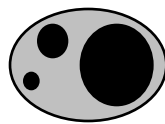


Hyperinsulinaemia in PCOS is associated with anovulation

normal

ov-PCO

anov-PCO



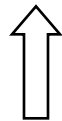
ovulation

✓

✓

X

testosterone

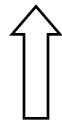


X

✓

✓

LH



X

✓

✓

insulin

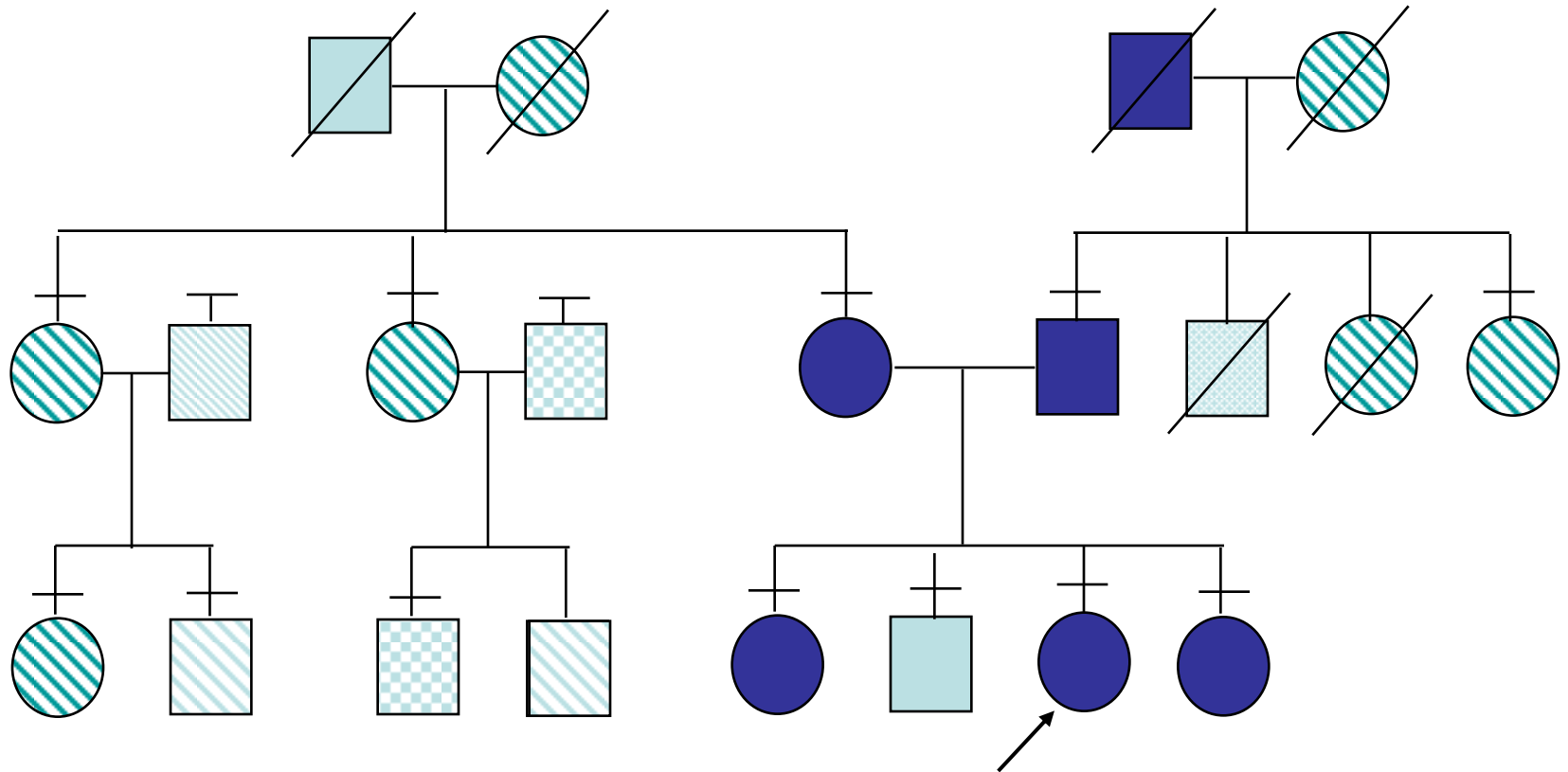


X

X

✓

Familial Polycystic Ovary Syndrome

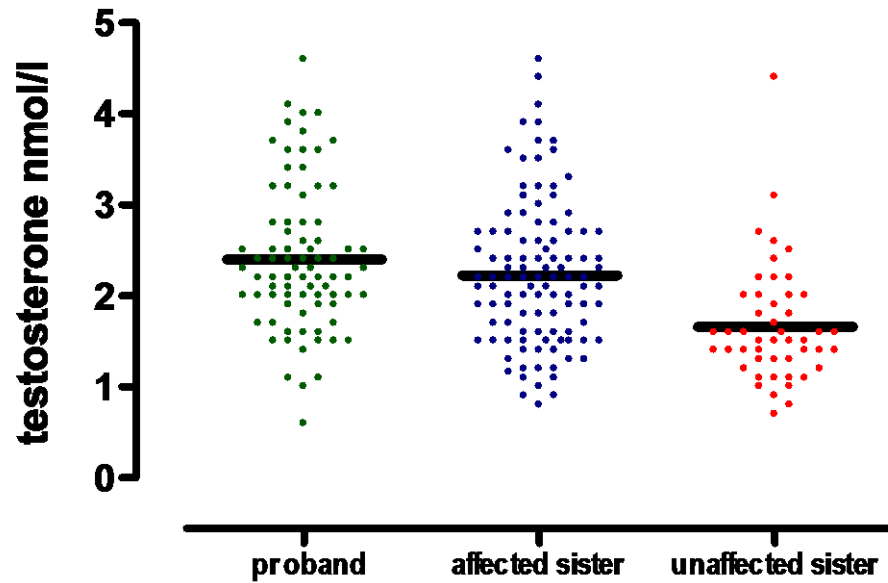


PCO

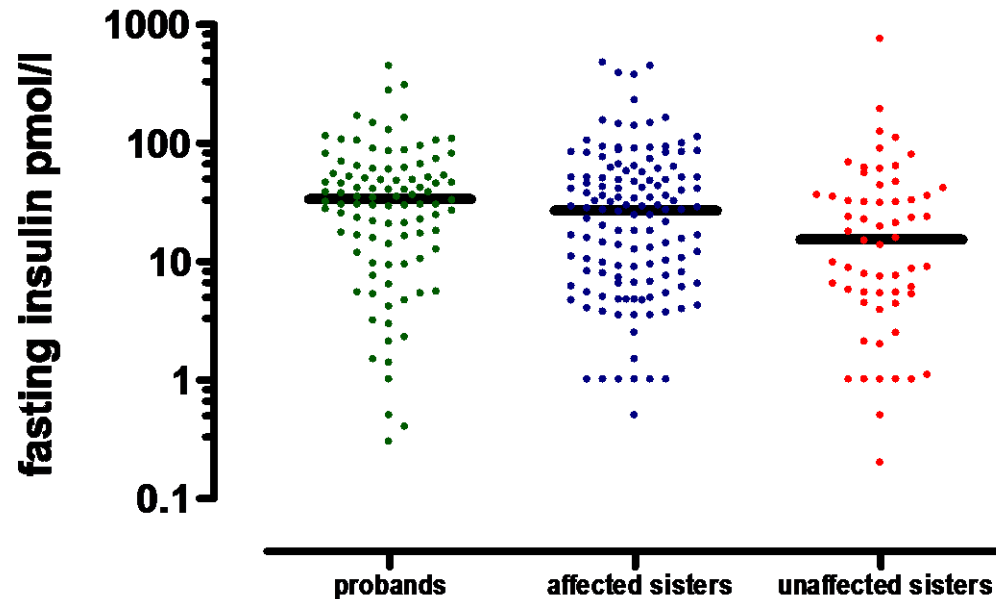


uncertain ovarian morphology

Serum testosterone in affected sister pairs with PCO



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

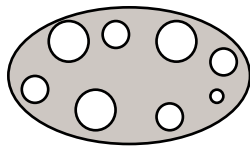


.....Despite differences in BMI

Developmental origin of PCOS

genetic predisposition to secrete excess androgen

activation prenatally, in infancy & at puberty



↑ **Testosterone**

↑ **LH**

anovulation

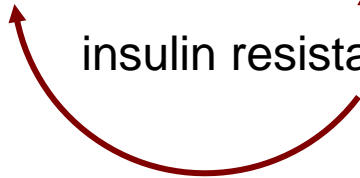
insulin resistance/hyperinsulinaemia

genes regulating

- folliculogenesis
- steroidogenesis

genes regulating

- insulin secretion
- insulin action



Candidate genes in PCOS

- Many genes identified as possible loci
- but**
- effect of any one gene is likely to be small
- and**
- populations are often heterogeneous
- therefore**
- conclusive case-control or TDT (parent-offspring trios) studies require
 - large numbers (cases *and* controls; 300+ per group)
 - homogeneous populations
 - replication in other populations

Candidate genes in PCOS

- >50 genes studied
 - (including “positive” T2D genes eg *KCNJ11* [β -cell K channel] and *TCF7L2*)
- Few have satisfied rigorous criteria of population selection and size, repeatability, and correction for multiple comparisons
- Locus on Chr19p13.2 (D19S884) appears to be the most promising candidate locus (Urbanek *et al* 1999, 2005; Tucci *et al*, 2001)
 - “Close” to (but not in LD with) IR gene
 - Candidate locus maps to intron of fibrillin 3 gene, FBN3 (TGF β binding protein) (Stewart *et al*, 2006)
- *FTO* ?

Recent reviews

Franks & McCarthy, *Rev Endocr Metab Disorders* 2004, 5 69-76

Escobar-Morreale *et al*, *Endocr Rev* 2005 26 251-82

Urbanek, *Nat Clin Practice* 2007, 3 103-11

The *FTO* gene

- Fat mass and obesity associated gene (Chr16)
- SNP rs9939609 associated with obesity (and T2D) in the general population (Frayling *et al*, 2007 *Science* 316:889-894; Freathy *et al*, 2008 *Diabetes* 57 1419-26)
- Does FTO variant contribute to genetic basis of PCOS?

***FTO* in PCOS - case control study**

- 324 cases of PCOS of British/Irish origin
- Reference population 771 B/I women
- rs9939609 variant associated with PCOS: OR 1.29 (1.14-1.49) (P=0.00053)
- Largely related to obesity (PCOS group have higher BMI) but still significant association after adjustment for BMI (P=0.005)

(Barber *et al*, 2008, *Diabetologia* 2008 51 1153-8)

PCOS, diabetes and cardiovascular disease

- Insulin resistance in PCOS
- Prevalence of metabolic syndrome, IGT and T2D in PCOS
- Investigation and management of metabolic dysfunction in PCOS

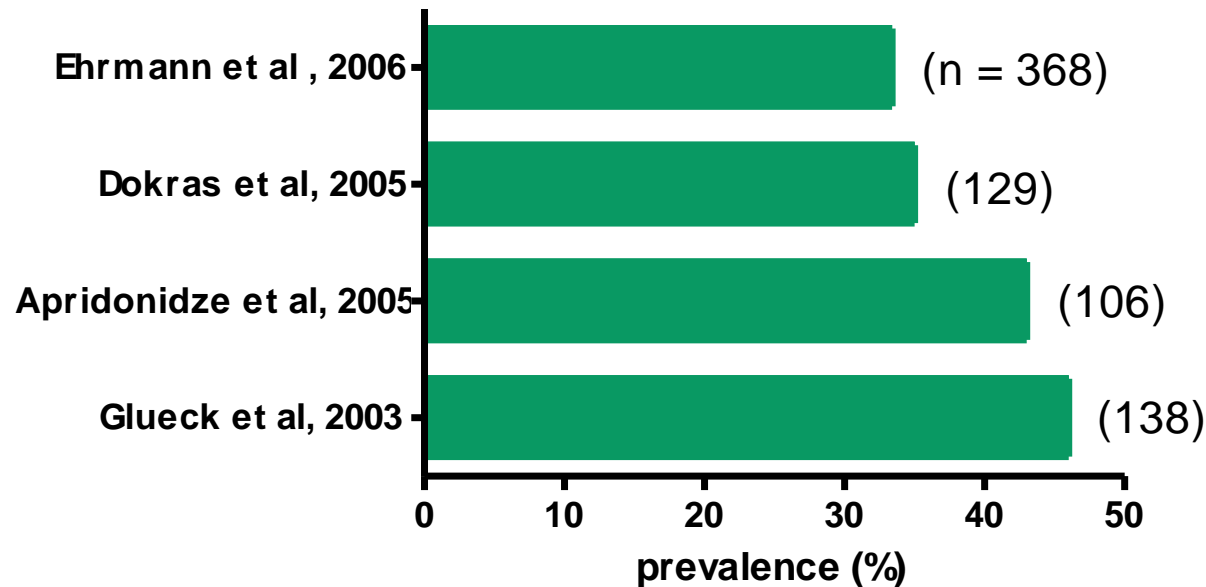
Gestational diabetes in women with PCOS

- 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)

Metabolic syndrome: definitions

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

Prevalence of metabolic syndrome* in young women with PCOS



Glueck *et al*, *Metabolism* 2003 **52** 908-915

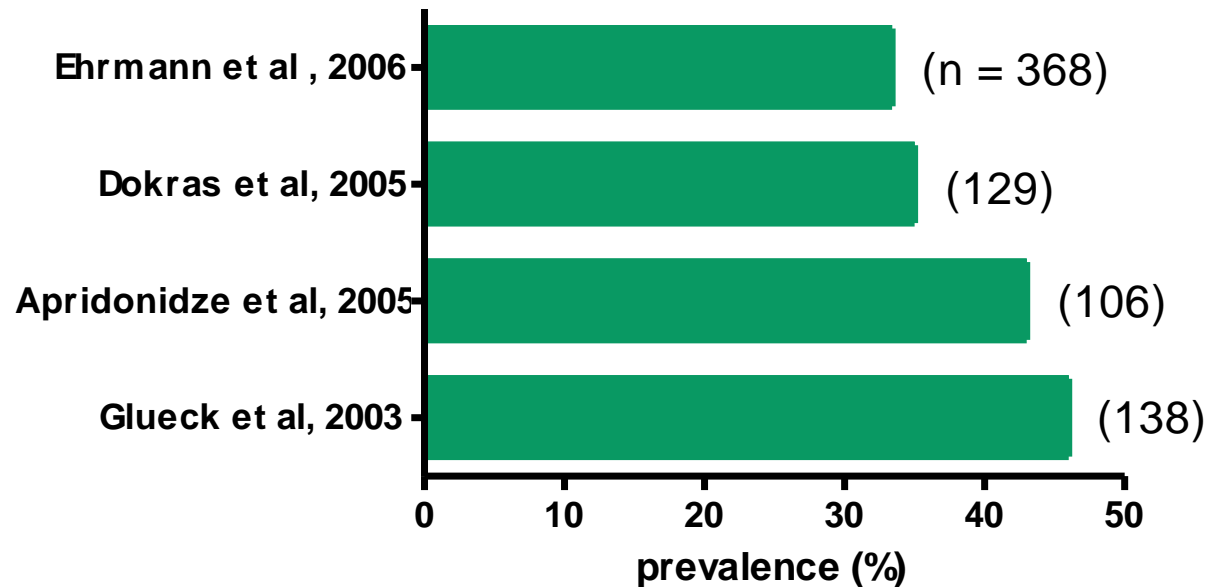
Apridonidze *et al*, *J Clin Endocrinol Metab* 2005 **90** 1929-1935

Dokras *et al* *Obstet Gynecol* 2005 **106** 131-137

Ehrmann *et al*, *J Clin Endocrinol Metab* 2006 **91** 48-53

(*NCEP)

Prevalence of metabolic syndrome in young women with PCOS



Glueck *et al*, *Metabolism* 2003 **52** 908-915

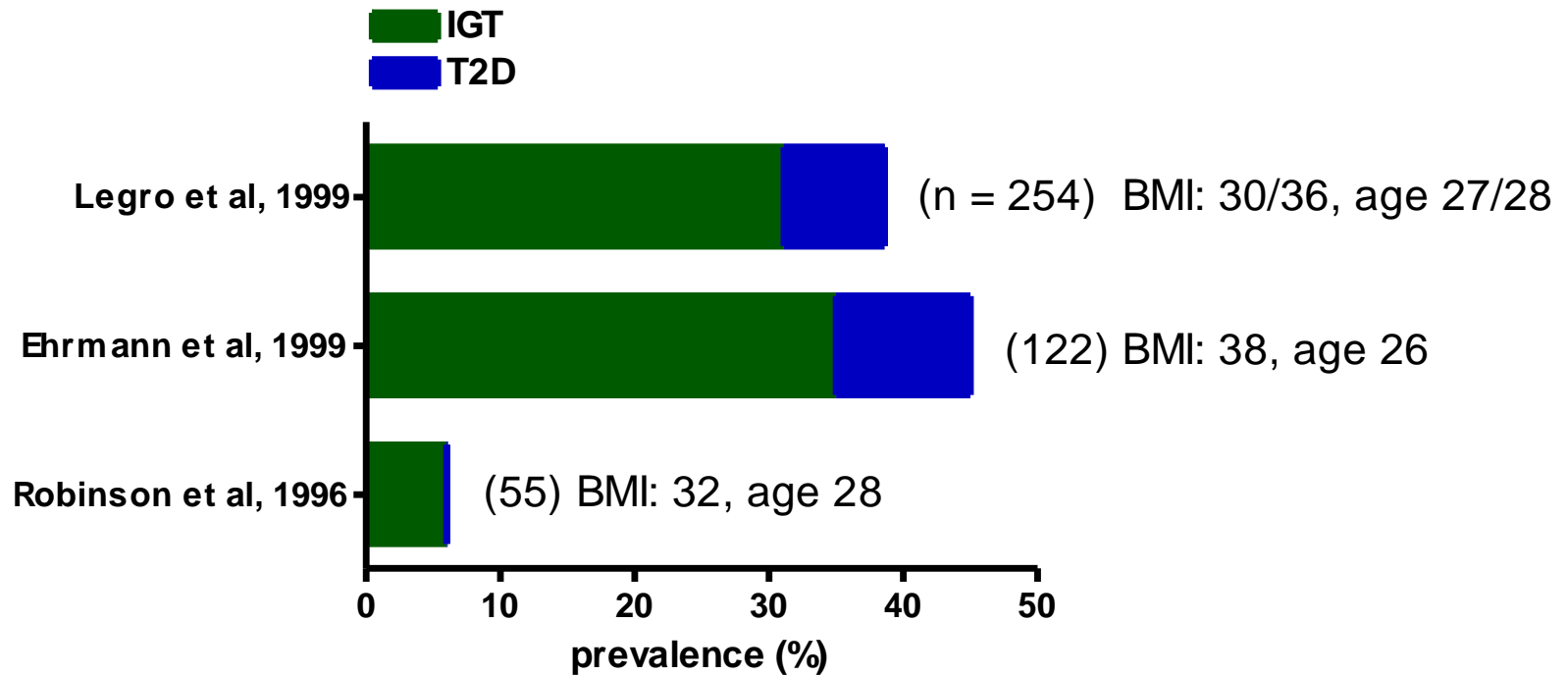
Apridonidze *et al*, *J Clin Endocrinol Metab* 2005 **90** 1929-1935

Dokras *et al* *Obstet Gynecol* 2005 **106** 131-137

Ehrmann *et al*, *J Clin Endocrinol Metab* 2006 **91** 48-53

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

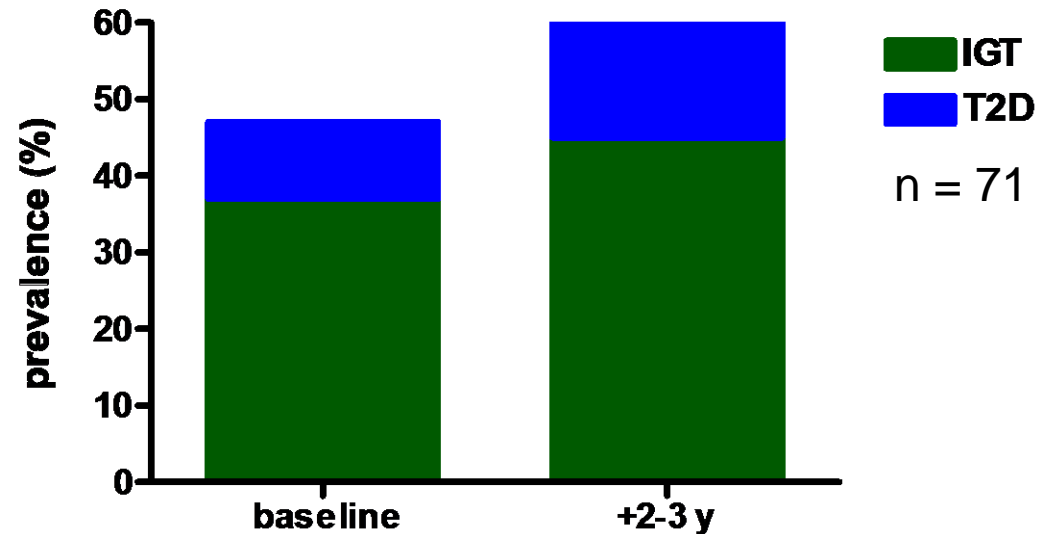
Legro *et al*, *J Clin Endocrinol Metab* 1999 **84** 165-9

(BMI >38 excluded)

(positive FH in 83% of T2D cases v 31% with NGT)

(IGT: cases v controls: OR 2.76 (1.23-6.57))

Longitudinal study of prevalence of IGT and diabetes in PCOS



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

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)
- *Increase in CHD risk factors but not of CHD: OR 1.5 (0.7-2.9)*

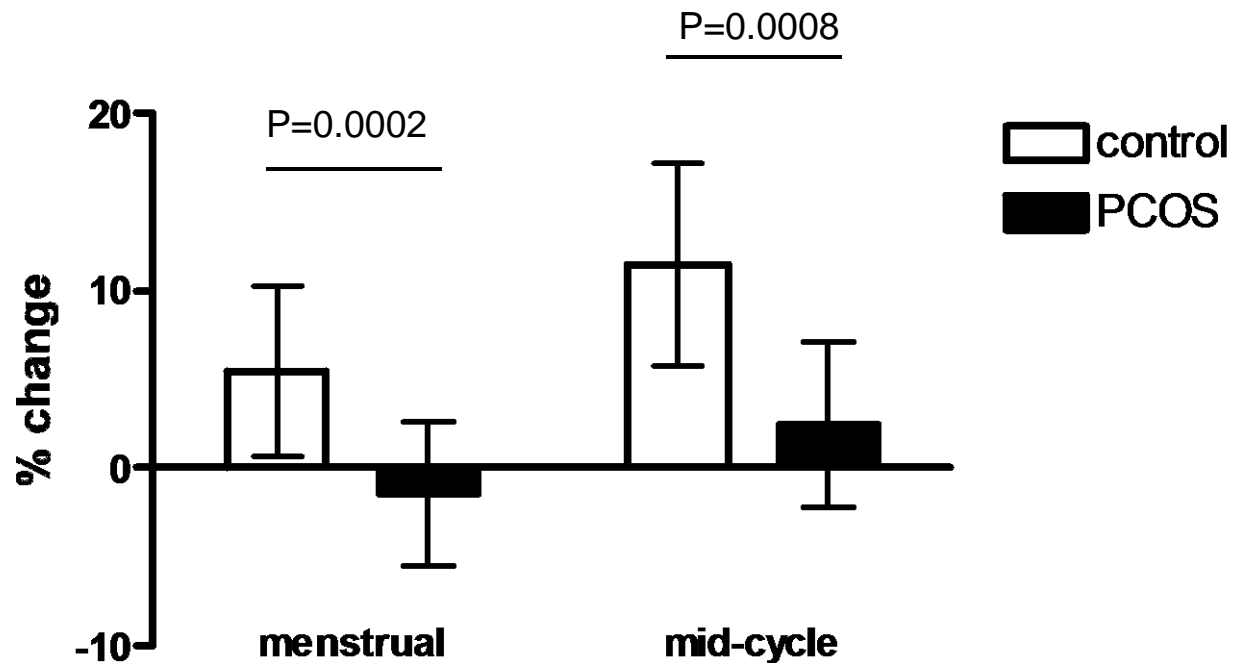
Wild S *et al*, *Clin Endocrinol* 2000 **52** 595-600

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)

Endothelial function (FMD) is significantly impaired in PCOS

...but is cardiovascular risk increased?



Fatal and non-fatal CHD in women with irregular cycles

	Regular	Usually irregular	Very irregular
RR (95% CI)	1.0	1.24 (1.04-1.44)	1.53 (1.24-1.90)

Nurses Health Study: 82,439 respondents re menstrual history at ages 20-35;
Follow up 14 years later (1417 incident cases of CHD)
Solomon C *et al*, *J Clin Endocrinol Metab* 2002 **87** 2013-7

Increased risk of T2D & CHD 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)
- *Increase in CHD risk factors but not of CHD: OR 1.5 (0.7-2.9)*

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

PCOS, diabetes and cardiovascular disease

- Insulin resistance in PCOS
- Prevalence of, metabolic syndrome, IGT and T2D in PCOS
- Investigation and management of metabolic dysfunction in PCOS

Screening for metabolic disorders in PCOS

Rotterdam consensus meeting

- 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

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

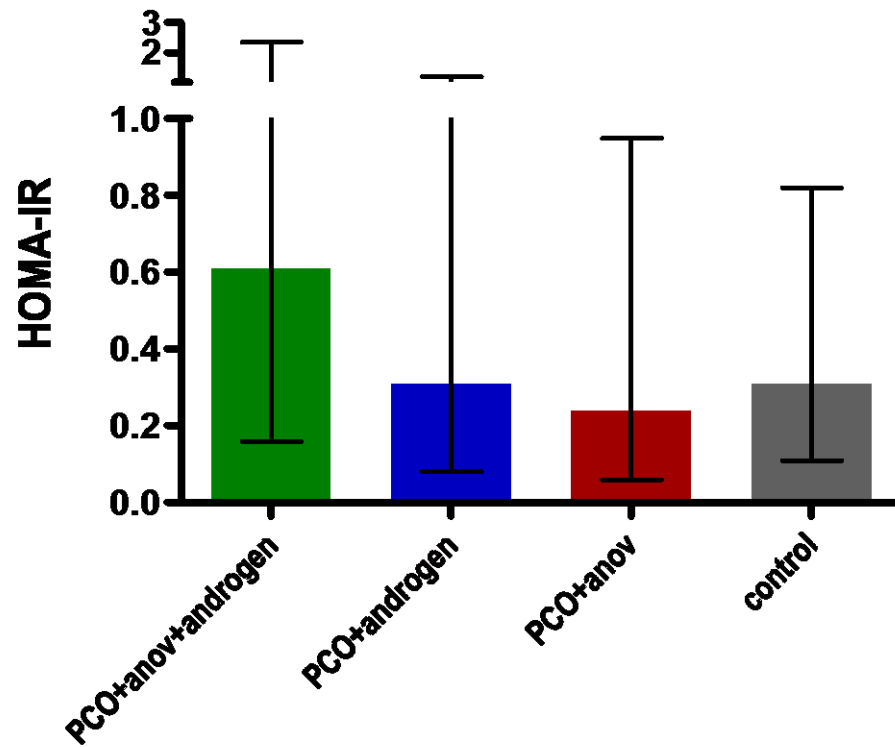
NIH 1990

- 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)

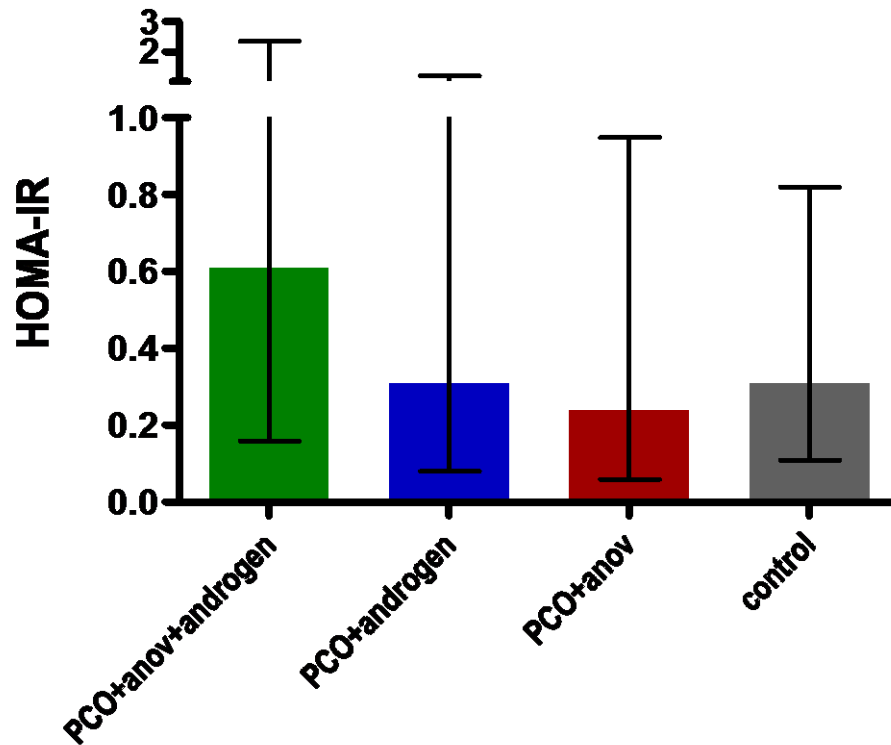
HOMA-IR according to PCOS phenotype



(Geometric mean \pm SD)

HOMA-IR according to PCOS phenotype

Metabolic syndrome (IDF):	29%	7%	7%	4%
<i>BMI</i>	29	24	24	24

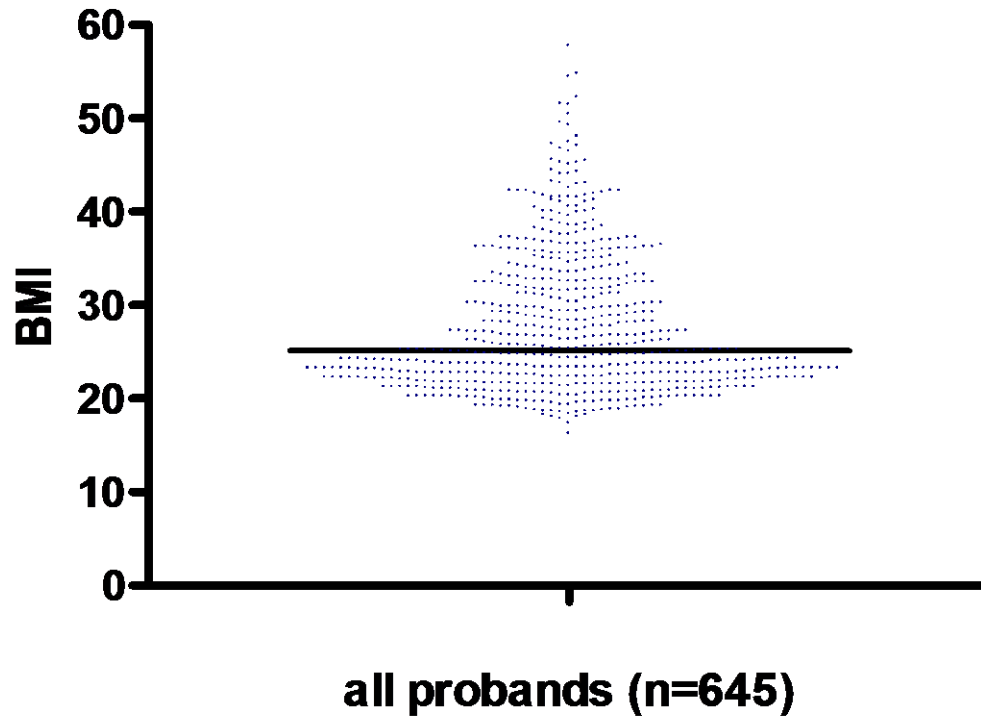


(Geometric mean \pm SD)

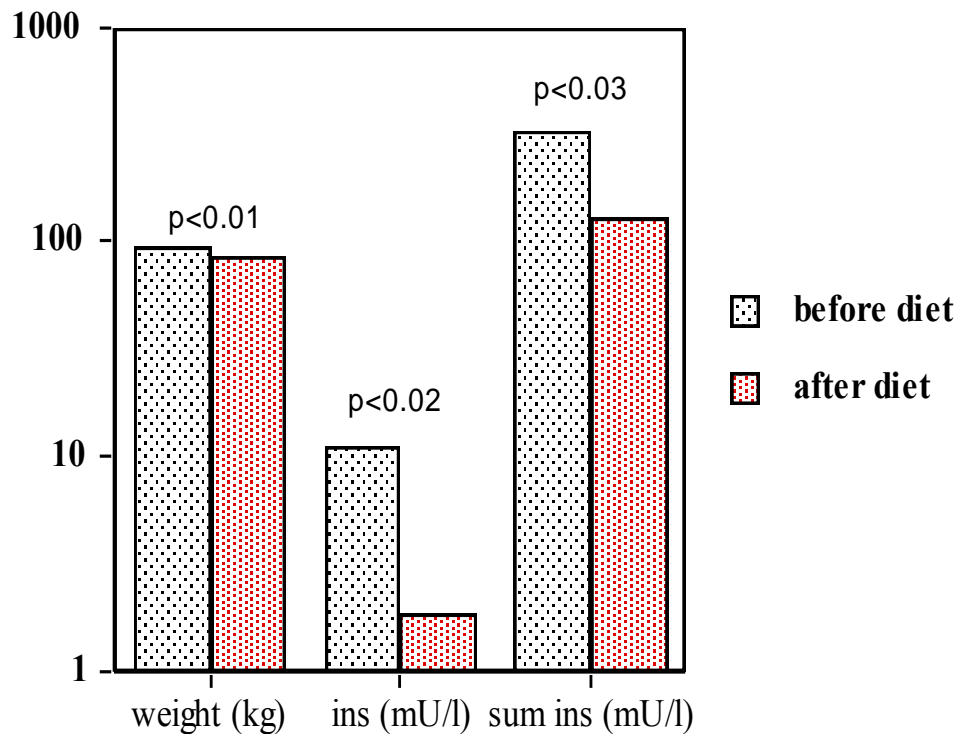
Prevention of diabetes in women with PCOS

- **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**

Not all PCOS patients are obese



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

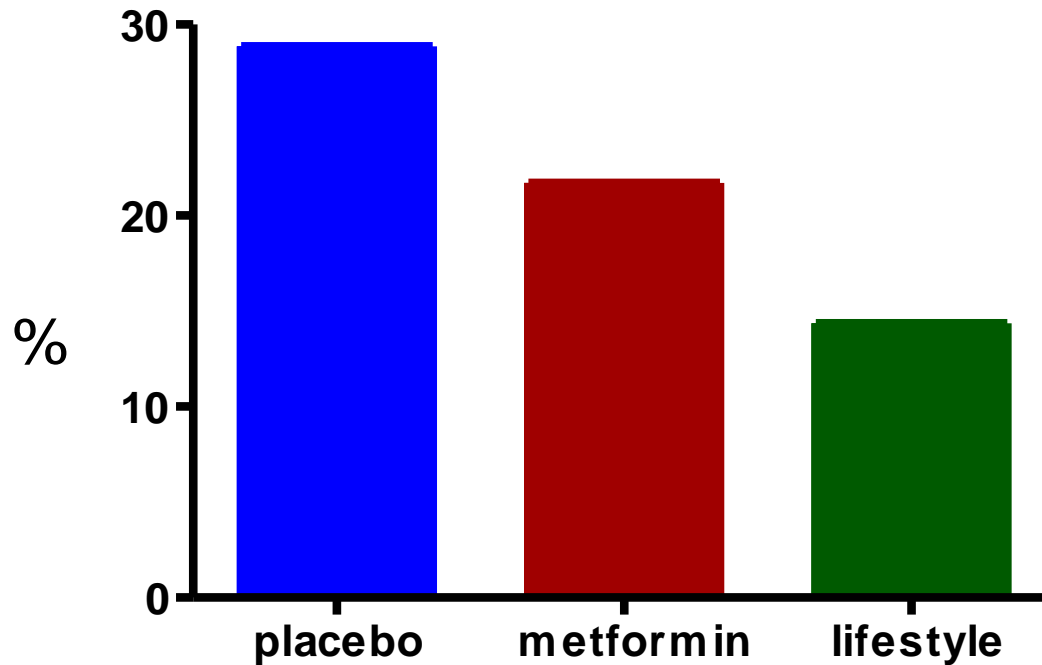


- modest (5-10%) weight reduction associated with vast improvement in metabolic indices
- diet and lifestyle changes improve ovulation rate and fertility (Kiddy *et al*, 1992; Clark *et al*, 1995; Norman *et al*, 2002; Steele *et al*, 2005)

Metformin in treatment of PCOS

- *Not* useful for treatment of infertility or menstrual disturbances
- *Not* very effective for treatment of hirsutism
- *May* 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 cyclicality
- Lipids not significantly altered and weight increased
- Concern about safety, particularly in women of reproductive age

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