

Insulin action and ovarian function

Stephen Franks
 Institute of Reproductive & Developmental Biology,
 Imperial College London, UK

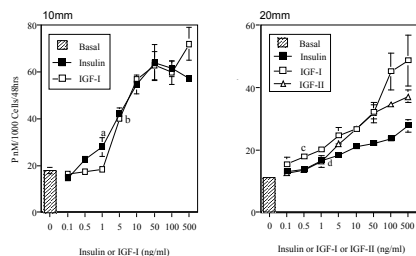
Imperial College
 London

BSc Endocrinology

"Harvesting" follicles from the human ovary



Insulin and IGFs stimulate steroidogenesis by human granulosa cells



Willis et al, 1998

Insulin resistance in PCOS

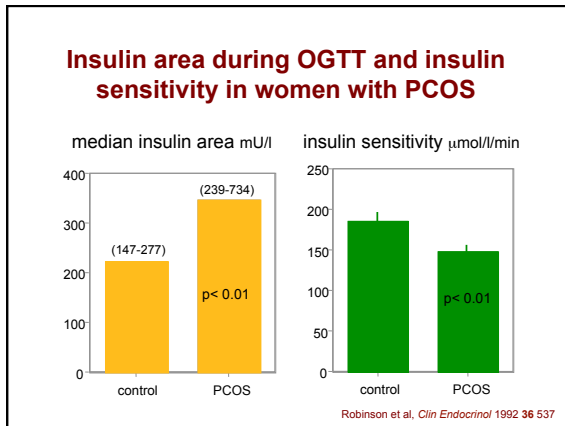
- Insulin resistance, polycystic ovaries and anovulation
- Insulin resistance, metabolic syndrome and diabetes in PCOS

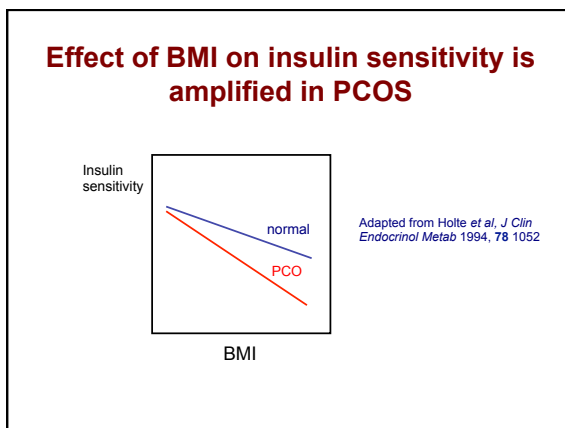
Polycystic ovary syndrome

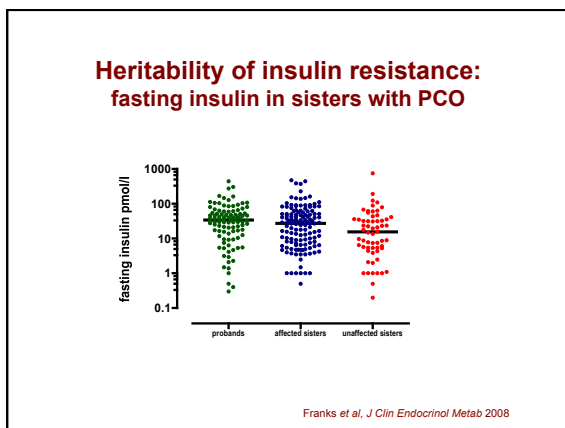
- Commonest cause of anovulatory infertility (>80% of cases) and of hirsutism
- Characterised by clinical (hirsutism/acne) and/or biochemical evidence of androgen excess
- Classic biochemical features are raised serum concentrations of LH and androgens
- Also associated with a characteristic metabolic disturbance and increased risk of type 2 diabetes (& GDM)
- Aetiology involves genetic and environmental factors

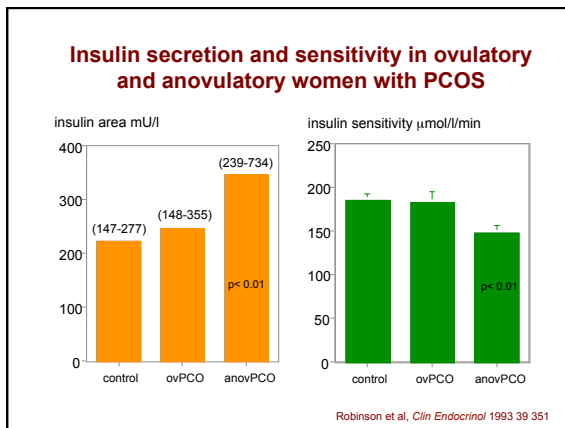
Insulin resistance in PCOS

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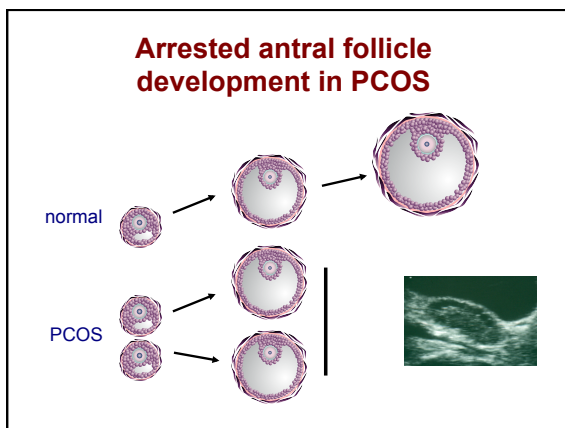


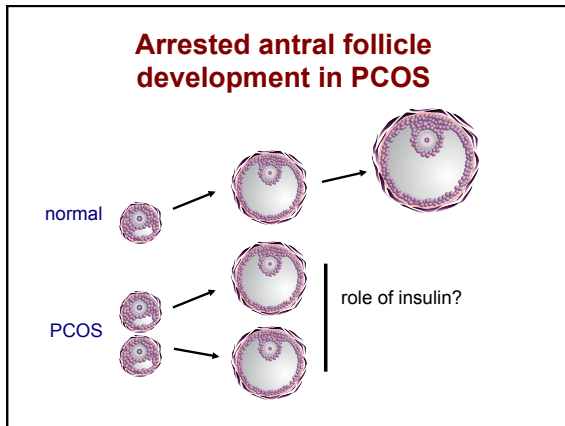


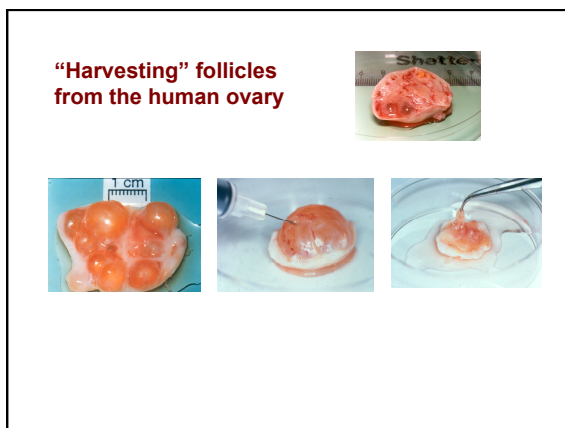


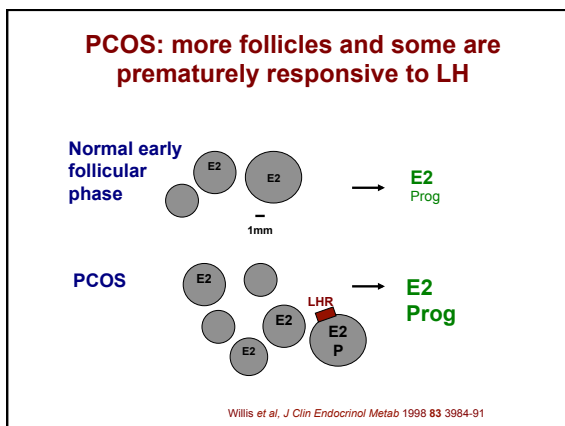
Hyperinsulinaemia in PCOS is associated with anovulation

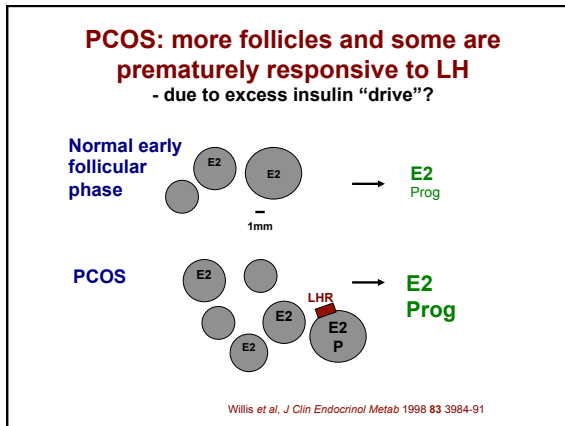
	normal	ov-PCO	anov-PCO
ovulation	✓	✓	X
testosterone ↑	X	✓	✓
LH ↑	X	✓	✓
insulin ↑	X	X	✓

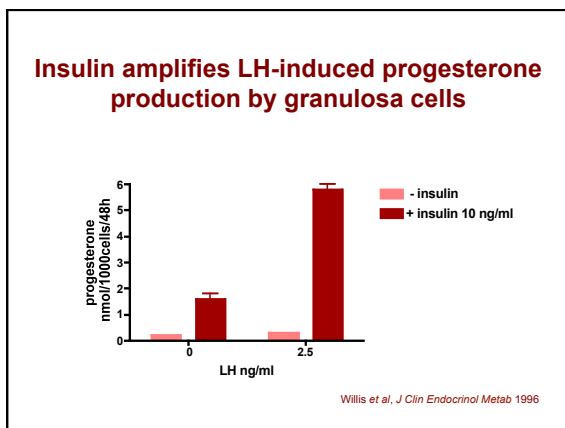


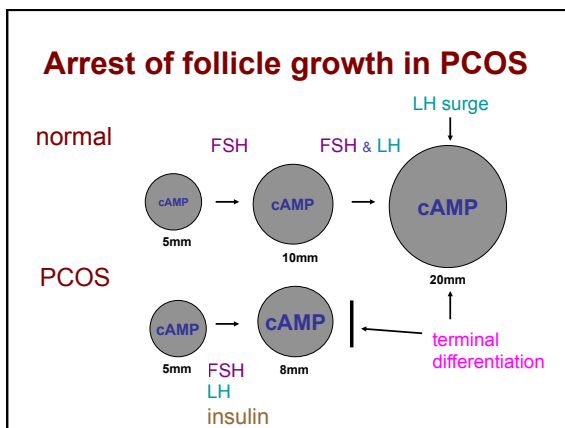












FSH concentrations are inappropriately low in anovPCOS

- Oestradiol and progesterone concentrations higher in anovPCOS than in normal early follicular phase
- Results in suppression of FSH and arrest of follicle maturation (Chavez-Ross *et al*, *J Maths Biol*, 1997; Franks, Stark & Hardy, *Hum Reprod Update*, 2008)

From Baird, 1983

Arrested antral follicle development in PCOS

normal

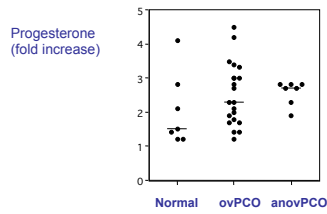
PCOS

- insulin and/or LH too high
- FSH too low

Insulin resistance in the ovary?

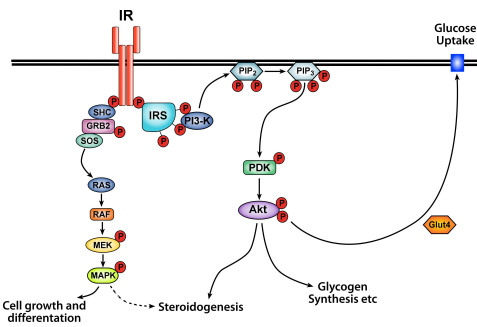
- Anovulatory, hyperandrogenaemic women with PCOS are insulin resistant
- Hyperinsulinaemia implicated in mechanism of anovulation
- Does the polycystic ovary "read" the high circulating insulin levels?

Progesterone response to insulin (10ng/ml) is not impaired in anovPCO

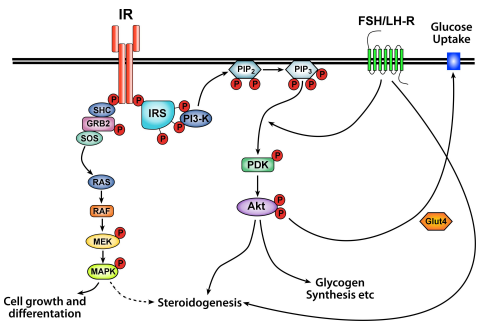


Willis et al, J Clin Endocrinol Metab 1996

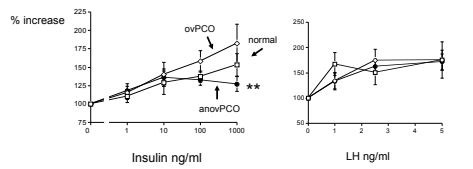
Insulin action in the granulosa cell



Insulin and FSH/LH action in the granulosa cell

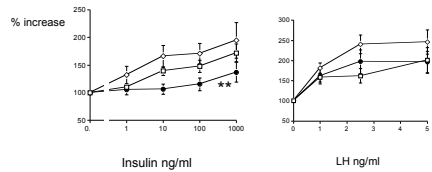


Impaired insulin-stimulated glucose uptake by GL cells from PCOS



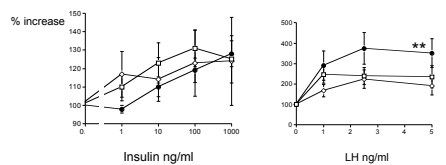
Rice et al, Hum Reprod 2005 20 373-81

Impaired insulin-stimulated lactate production by GL cells from PCOS



Rice et al, Hum Reprod 2005 20 373-81
(also: Lin, Fridstrom & Hillensjö, Hum Reprod 1997 12 2469-72)

Insulin-stimulated progesterone production by GL cells from PCOS not significantly impaired

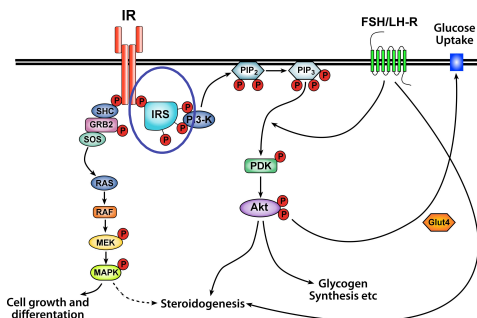


Rice et al, Hum Reprod 2005 20 373-81

Insulin/LH effects in GL cells from anovulatory PCO: summary

- Insulin-stimulated glucose metabolism impaired (but LH action not affected)
- Insulin-stimulated steroidogenesis not significantly impaired (but LH-stimulated steroidogenesis amplified)

Insulin and FSH/LH action in the granulosa cell



Insulin resistance in the polycystic ovary: summary

- Anovulation in PCOS is associated with insulin resistance and hyperinsulinaemia
- Hyperinsulinaemia contributes to the mechanism of follicle arrest and anovulation in PCOS
- Insulin resistance in the polycystic ovary differentially affects insulin-mediated glucose uptake and metabolism
- *What is the defect in the insulin signalling pathway?*

Insulin resistance in PCOS

- Insulin resistance, polycystic ovaries and anovulation
- Insulin resistance, metabolic syndrome and diabetes in PCOS

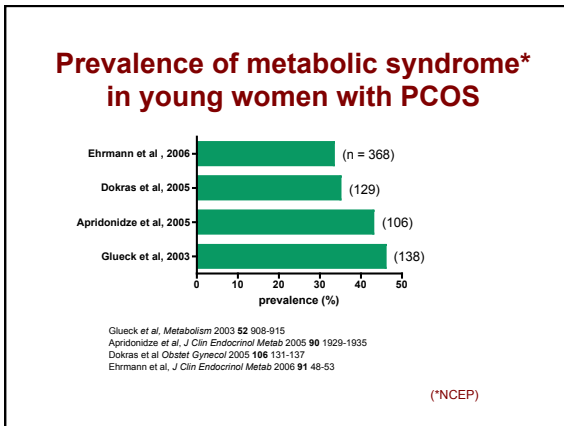
Gestational diabetes in women with PCOS

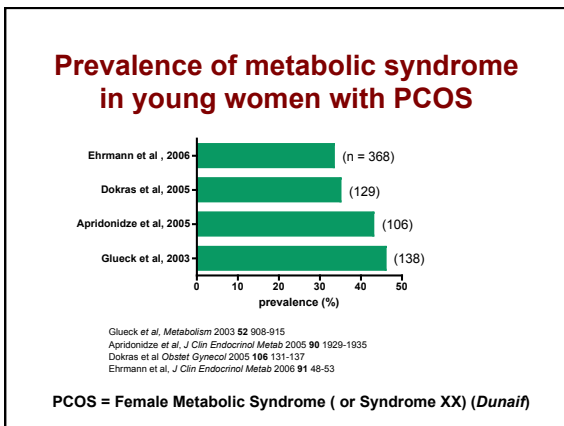
- High prevalence (52%) of polycystic ovaries in women with history of GDM
 - Kousta *et al*, *Clin Endocrinol* 2000 **53** 501-7
- Women with PCOS at increased risk of GDM (OR 2.94 (1.7 - 5.1))
 - Boomsma *et al*, *Hum Reprod Update* 2006 **12** 673-683 (meta-analysis)

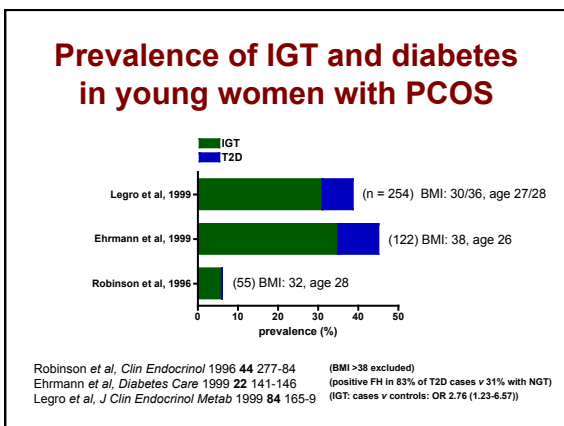
Metabolic syndrome: definitions

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

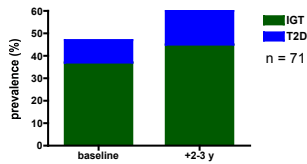
Skilton *et al*, *Atherosclerosis* 2007 **109** 416-22







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)

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)

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

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

Hum Reprod 2004 19 41-7

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

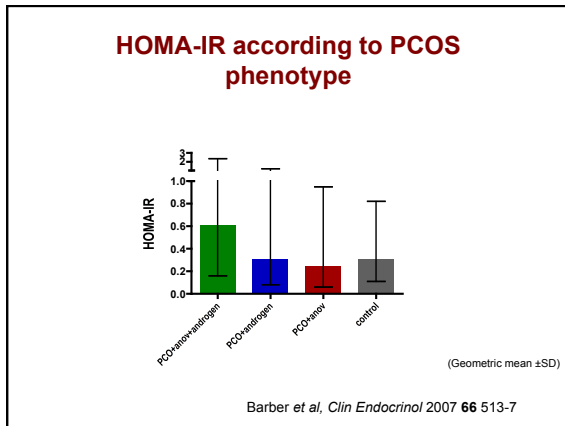
NIH 1990

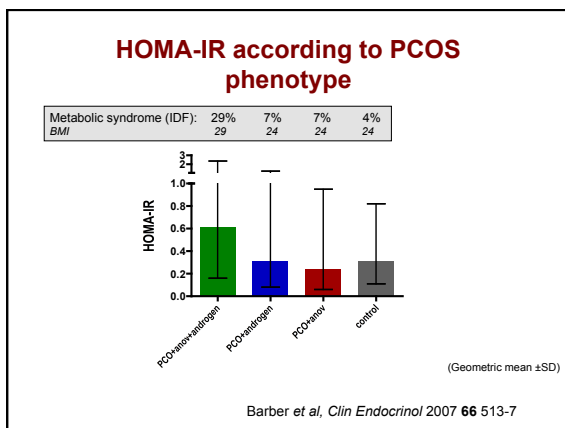
- Chronic anovulation
- Clinical and/or biochemical signs of hyperandrogenism (with exclusion of other aetiologies, eg CAH)
(both criteria needed)

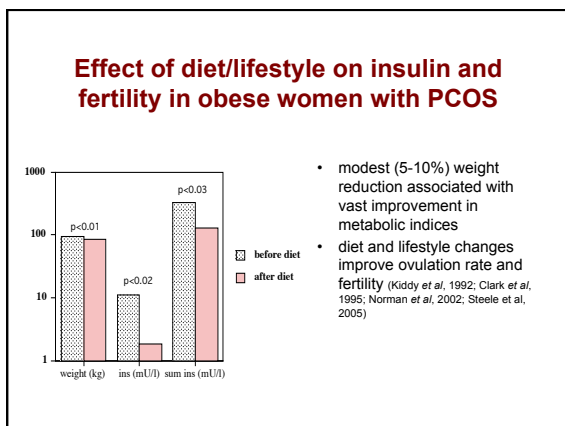
Rotterdam 2003

- 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)



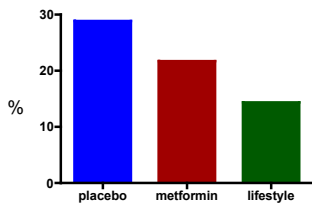




Metformin in treatment of PCOS

- *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 cyclicity
- 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
- Hyperinsulinaemia contributes to anovulation in PCOS
- Women with PCOS are at increased risk of developing metabolic syndrome and T2D
- Diet and lifestyle changes are most important ways of improving fertility and in prevention of diabetes in women with PCOS
