Insulin action and ovarian function

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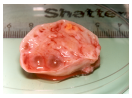
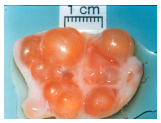
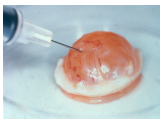
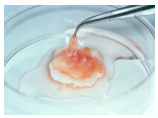
"Harvesting" follicles from the human ovary

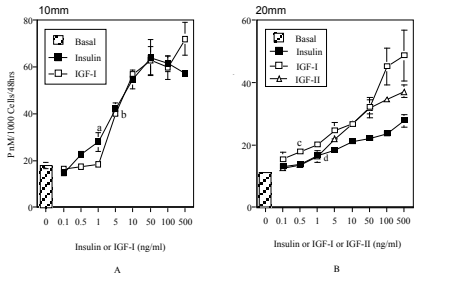








Insulin and IGFs stimulate steroidogenesis by human granulosa cells



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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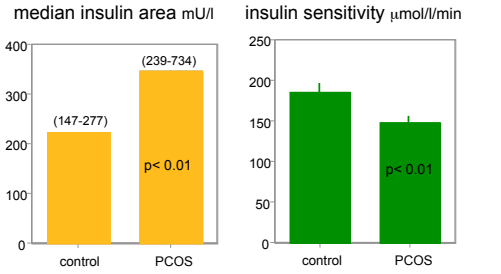
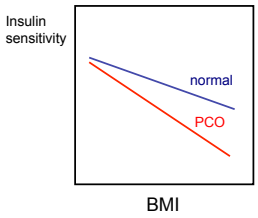
- Insulin resistance, metabolic syndrome and diabetes in PCOS

Insulin area during OGTT and insulin sensitivity in women with PCOS



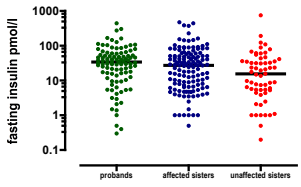
Robinson et al, *Clin Endocrinol* 1992 **36** 537

Effect of BMI on insulin sensitivity is amplified in PCOS



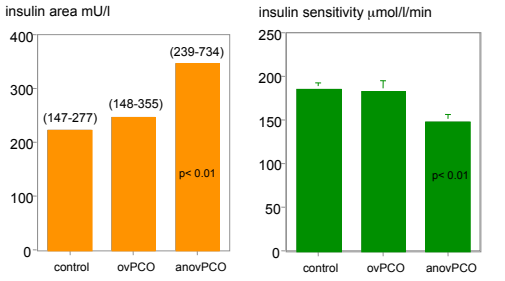
Adapted from Holte *et al, J Clin Endocrinol Metab* 1994, **78** 1052

Heritability of insulin resistance: fasting insulin in sisters with PCO



Franks *et al, J Clin Endocrinol Metab* 2008

Insulin secretion and sensitivity in ovulatory and anovulatory women with PCOS

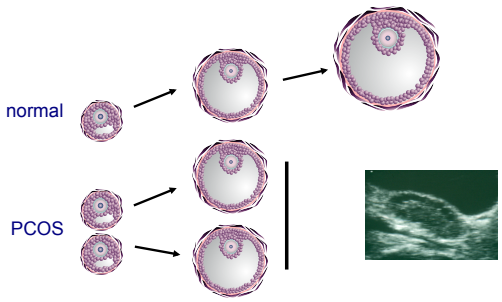


Robinson et al, *Clin Endocrinol* 1993 39 351

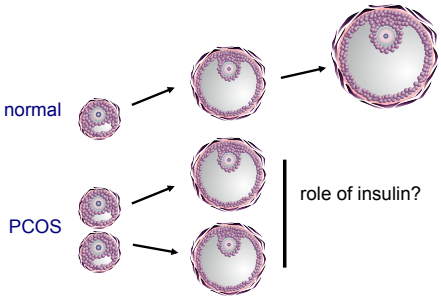
Hyperinsulinaemia in PCOS is associated with anovulation

	normal	ov-PCO	anov-PCO
ovulation	√	√	X
testosterone ⇧	X	√	√
LH ⇧	X	√	√
insulin ⇧	X	X	√

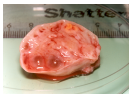
Arrested antral follicle development in PCOS

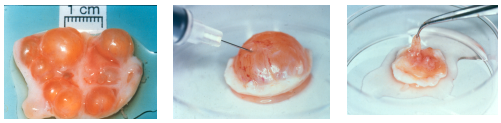


Arrested antral follicle development in PCOS

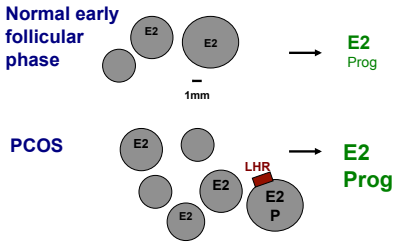


"Harvesting" follicles from the human ovary





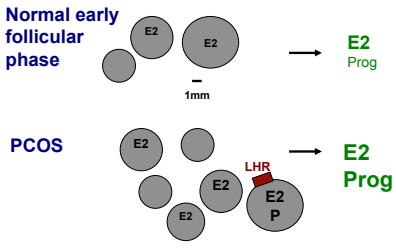
PCOS: more follicles and some are prematurely responsive to LH



Willis *et al, J Clin Endocrinol Metab* 1998 **83** 3984-91

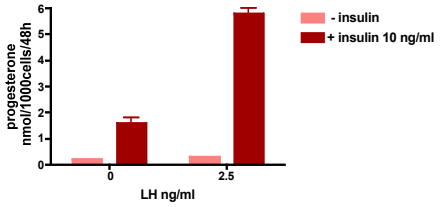
PCOS: more follicles and some are prematurely responsive to LH

- due to excess insulin "drive"?



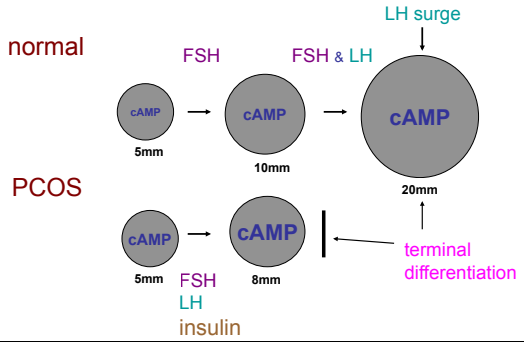
Willis *et al, J Clin Endocrinol Metab* 1998 **83** 3984-91

Insulin amplifies LH-induced progesterone production by granulosa cells



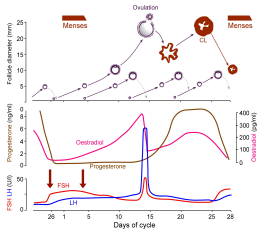
Willis *et al, J Clin Endocrinol Metab* 1996

Arrest of follicle growth in PCOS



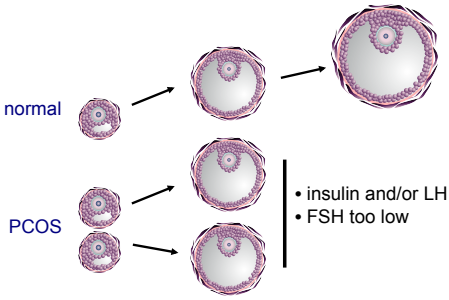
FSH concentrations are inappropriately low in anovPCOS

- 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

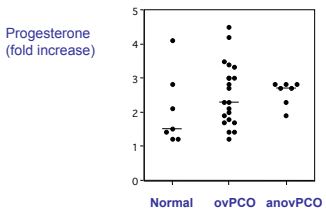


- insulin and/or LH too high
- FSH too low

Insulin resistance in the ovary?

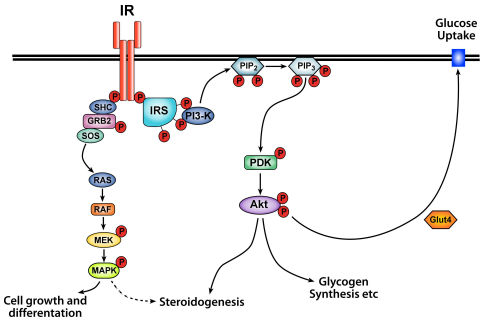
- Anovulatory, hyperandrogenaemic women with PCOS are insulin resistant
- Hyperinsulinaemia implicated in mechanism of anovulation
- *Does the polycystic ovary "read" the high circulating insulin levels?*

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

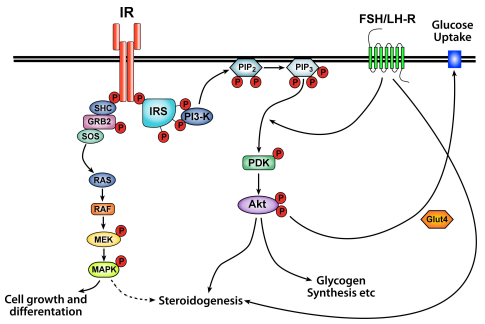


Willis *et al*, *J Clin Endocrinol Metab* 1996

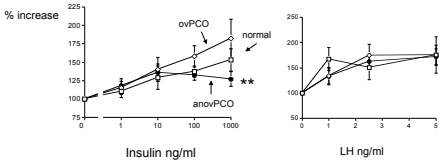
Insulin action in the granulosa cell



Insulin and FSH/LH action in the granulosa cell

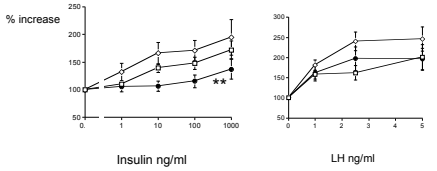


Impaired insulin-stimulated glucose uptake by GL cells from PCOS



Rice *et al, Hum Reprod* 2005 **20** 373-81

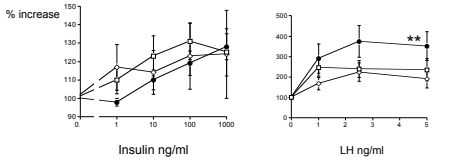
Impaired insulin-stimulated lactate production by GL cells from PCOS



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

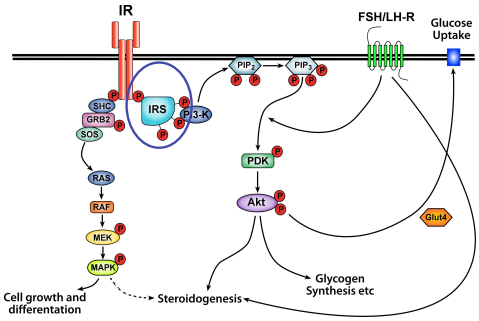


Rice *et al, Hum Reprod* 2005 **20** 373-81

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

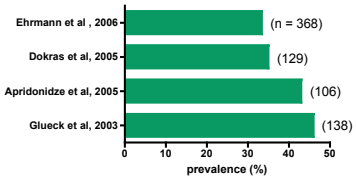
- High prevalence (52%) of polycystic ovaries in women with history of GDM
  - Kousta *et al, Clin Endocrinol* 2000 **53** 501-7
- Women with PCOS at 2-3 fold increased risk of GDM
  - Boomsma *et al, Hum Reprod Update* 2006 **12** 673-683 (meta-analysis)
  - Roos *et al, BMJ* 2011 Oct 13;343:d6309.

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

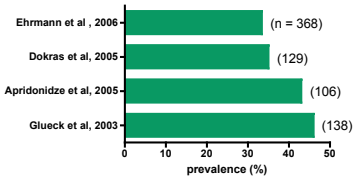
Prevalence of metabolic syndrome* in young women with PCOS



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

(*NCEP)

Prevalence of metabolic syndrome in young women with PCOS



Glueck *et al, Metabolism* 2003 **52** 908-915
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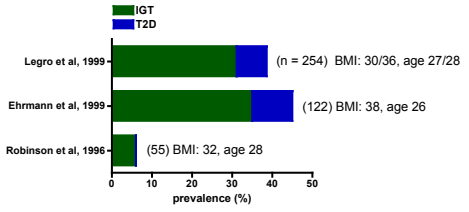
Ehrmann et al, *J Clin Endocrinol Metab* 2006 **91** 48-53

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

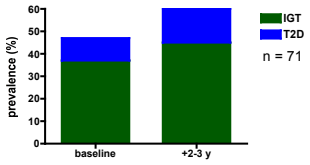
Prevalence of IGT and diabetes in young women with PCOS



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)

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)

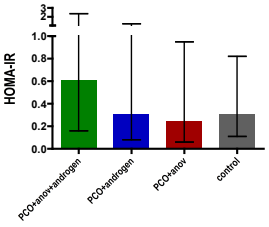
Rotterdam 2003

- 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)

HOMA-IR according to PCOS phenotype

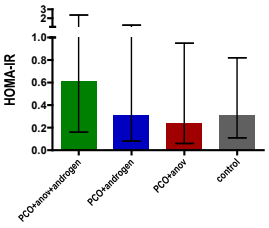


(Geometric mean ±SD)

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

HOMA-IR according to PCOS phenotype

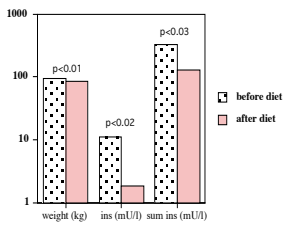
Metabolic syndrome (IDF):	29%	7%	7%	4%
BMI	*29*	*24*	*24*	*24*



(Geometric mean ±SD)

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

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

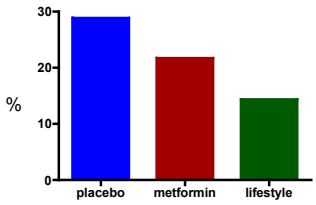


- modest (5-10%) weight reduction associated with vast improvement in metabolic indices
- diet and lifestyle changes improve ovulation rate and fertility (Kiddy *et al*, 1992; Clark *et al*, 1995; Norman *et al*, 2002; Steele et al, 2005)

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 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