

**Polycystic Ovary Syndrome  
and  
Insulin Resistance**

# **Definitions of polycystic ovaries (PCO) and polycystic ovary syndrome (PCOS)**

## **▣Hyperinsulinaemia in PCOS**

### **Insulin Resistance in PCOS**

### **Factors which influence insulin resistance in PCOS**

### **Ovulation in PCOS**

### **Use of insulin sensitising agents in PCOS**

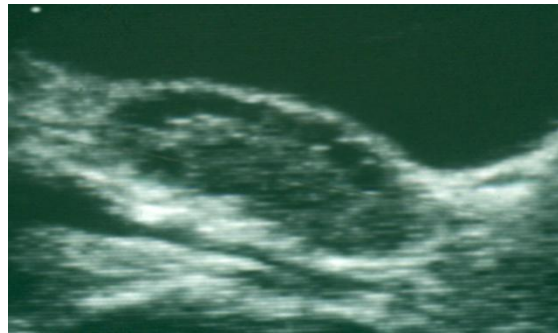
# Adams Criteria for PCO

Increase in ovarian volume (>9 cm<sup>3</sup>)

Increase in ovarian stroma

10 or more cysts <10mm in average diameter  
(usually peripherally arranged)

Adams et al. 1985, Lancet ii: 1375-1380



# Prevalence of PCO

257 unselected healthy volunteers

	Non-Pill Group (n=158)	Pill Group (n=99)
<b>Ovarian Morphology</b>		
<b>Normal</b>	<b>116 (73%)</b>	<b>76 (76%)</b>
<b>Polycystic</b>	<b>36 (23%)</b>	<b>20 (20%)</b>
<b>Multifollicular</b>	<b>5 (3%)</b>	<b>3 (3%)</b>
<b>Uncertain</b>	<b>1</b>	

Polson et al. 1988, Lancet: i 370-72

# Polycystic Ovary Syndrome

## PCO and Clinical Symptoms

**Androgen excess:**

**hirsutism**

**frontal hair loss**

**acne**

**Menstrual cycle disturbance:**

**oligomenorrhoea**

**amenorrhoea**

# Signs and Symptoms Associated with PCOS

Symptoms	No. Cases	Incidence (%)	
		Mean	Range
Obesity	600	41	16-49
Hirsutism	819	69	17-83
Virilisation	431	21	0-28
Cyclic menses	395	12	7-28
Amenorrhoea	640	51	15-77
Infertility	596	74	35-94
Corpus Luteum	391	22	0-71

Adapted from Goldzieher & Axelrod (1963) Fertil&Steril 14, 631-53

# Biochemical Markers of PCOS

## Hyperandrogenaemia

Increase in serum testosterone and free androgen index

## LH Hypersecretion

Increase in luteinising (LH) hormone with normal follicle stimulating hormone (FSH)

Increase in LH/FSH ratio (>2.0-3.0)

# Prevalence of Biochemical Markers in PCOS

	Inc Testosterone	LH Hypersecretion
Eden (1988)	Not Stated	70% (LH>10)
Franks (1989)	49% (T>2.6)	51% (LH>11.1)
Conway (1989)	61% (T>2.5)	44% (LH>10)
Obhrai (1990)	29% (T>3.66)	66% (LH>9.4)
Fox (1991)	74% (T>2.5)	60% (LH>10)
Robinson (1992)	75% (T>2.5)	35% (LH>8.2)



# Diagnostic Accuracy of Biochemical Tests in PCOS

	Diagnostic accuracy (%)		
	+ve test	-ve test	Overall
+ve progesterone Challenge	94	78	89
LH (>10 iU/l)	97	47	69
Testosterone (>3nmol/l)	100	49	71

Fox et al. (1991) Clin Endocrinol, 34: 127-131

# 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)

(with exclusion of other aetiologies)

Zawadzki & Dunaif 1990, 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 1-7)

# **PCOS and Hyperinsulinaemia**

**1980 first report of hyperinsulinaemia associated with PCOS**

**Burghen et al 1980 J Clin Endo & Metabolism: 50 (1), 113-116**

**8 obese women with PCOS**

**Hirsute with oligo/amenorrhoea**

**Elevated androgens and LH/FSH ratio**

**Fasting hyperinsulinaemia**

**Oral GTT: increased glucose and insulin response**

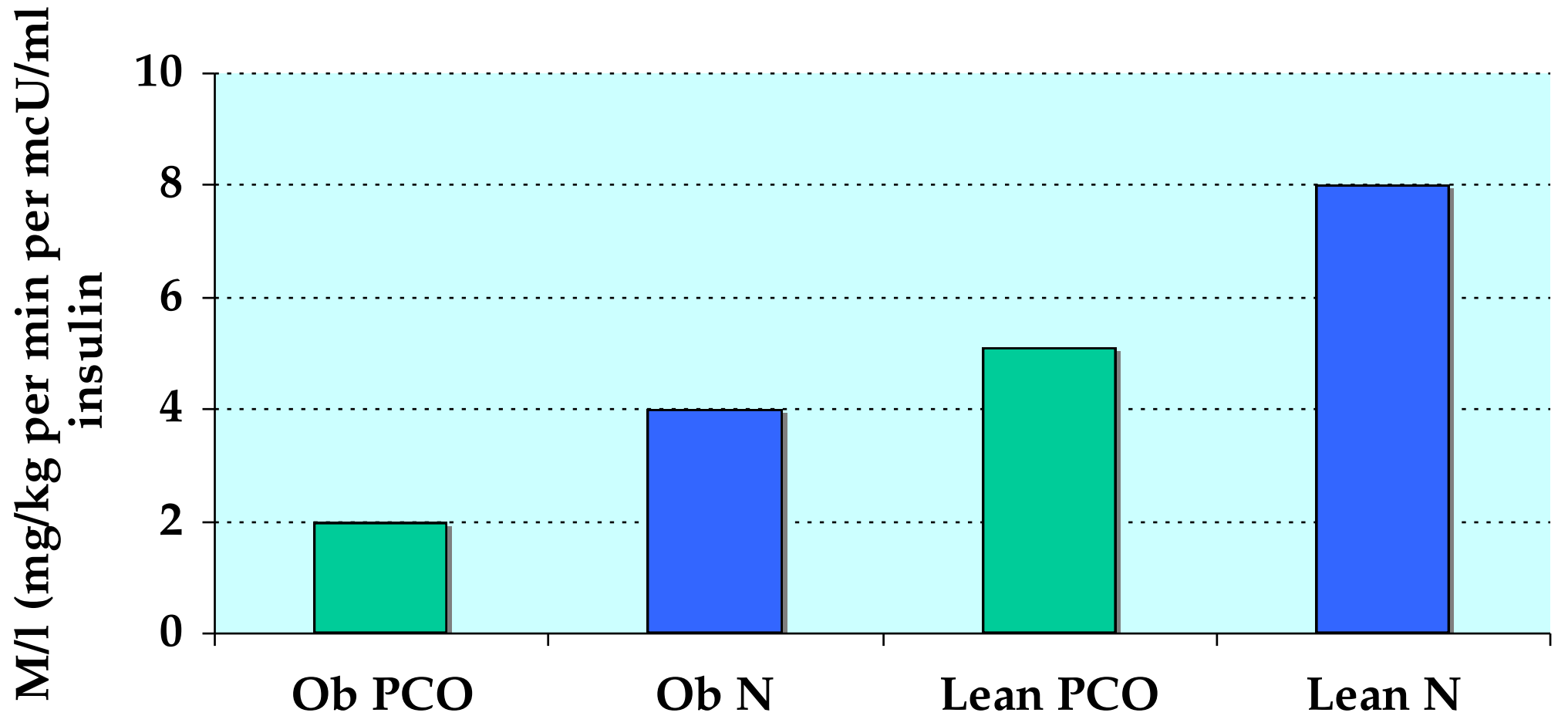
**Positive correlation insulin response and androgen levels**

## **Dunaif et al, Diabetes 1989: 36, 1165**

**29 women with PCOS, amenorrhoea, hyperandrogenaemia  
19 obese BMI 35.6 [1.3] and 10 non obese BMI 22.3 [0.5]  
Appropriate control population of 11 obese women and 8  
non-obese women with regular cycles, non hirsute and  
normal androgen levels and normal glucose tolerance  
Matched on the basis of age, BMI and body composition  
assessing fat free mass**

**PCOS women had significantly decreased insulin  
stimulated glucose disposal  
independent of obesity or alterations in fat free mass**

## Profound peripheral insulin resistance independent of obesity in PCOS



**Dunaif et al 1996 J Clin Endo & Metabolism 81 (3) 942-947**

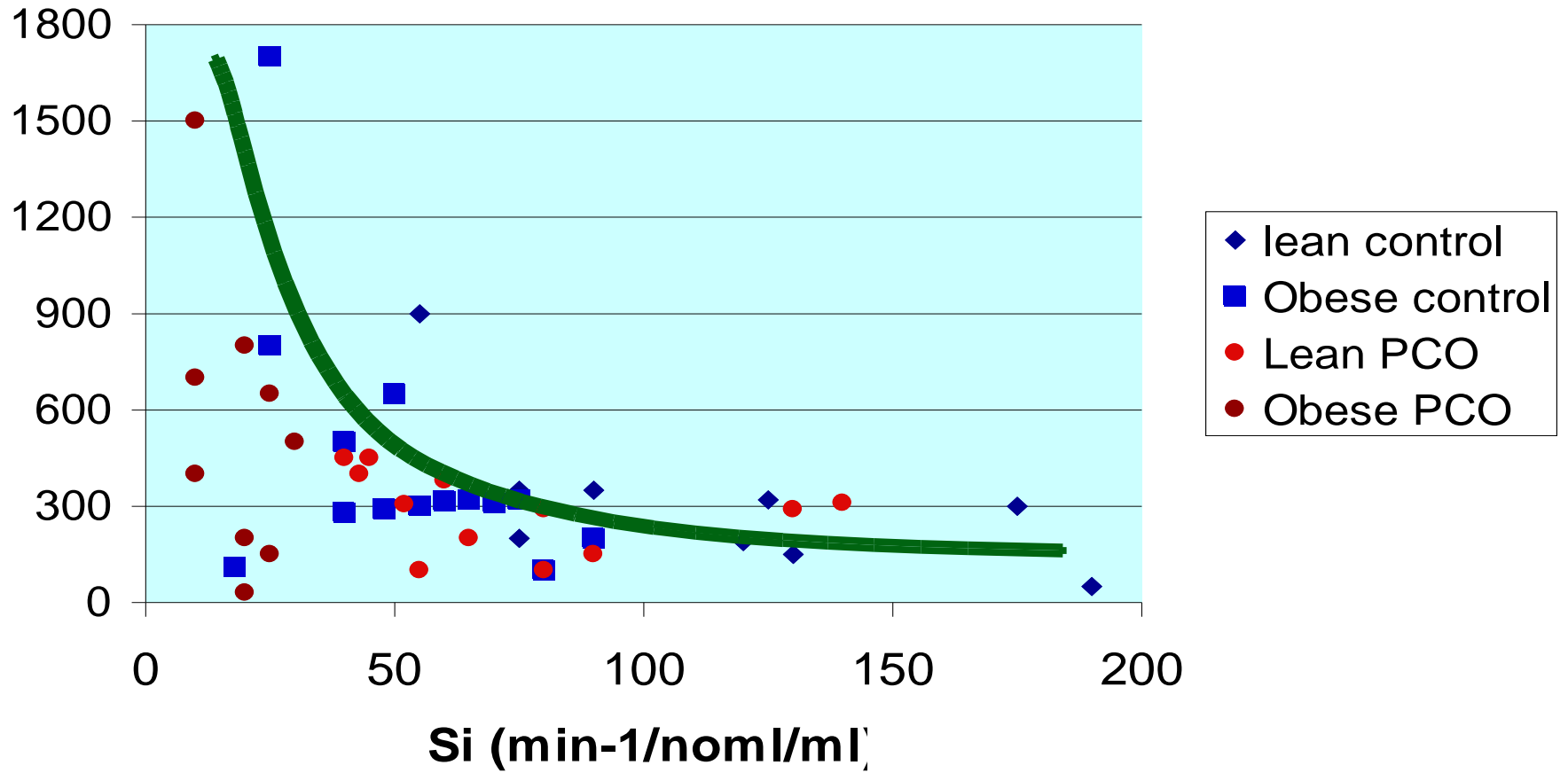
**Frequently sampled IVGTT confirmed decreased insulin sensitivity in PCOS independent of obesity**

**First phase insulin secretion in response to a glucose load AIRg similar in PCOS women and controls**

**The AIRg was significantly increased in obese PCOS and obese controls**

**The deposition index (insulin sensitivity x AIRg) was significantly decreased by both PCOS and obesity**

## B-cell dysfunction independent of obesity and glucose intolerance in PCOS



# Hyperinsulinaemia in PCOS

Increase in peripheral insulin resistance

Decrease in insulin sensitivity with an abnormal deposition index suggesting beta-cell dysfunction

Independent of obesity

Independent of androgen levels



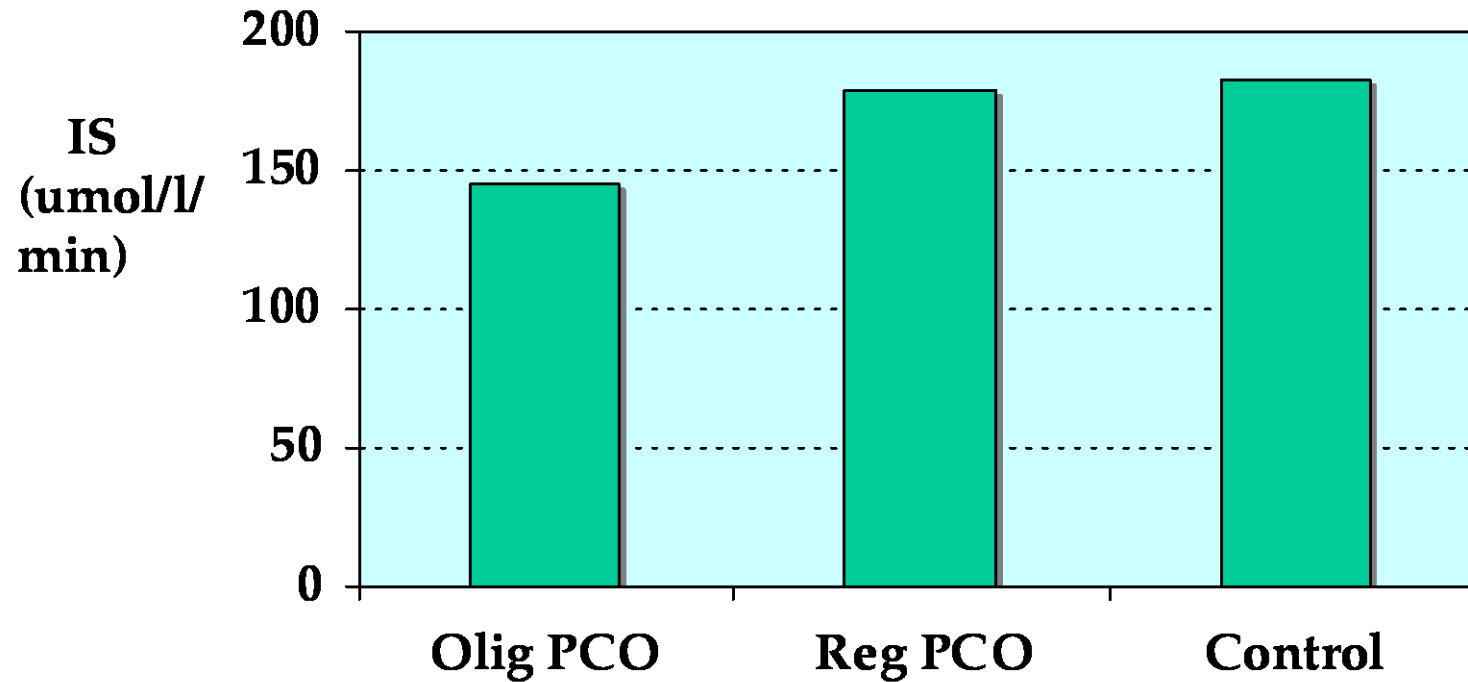
# **Ovulatory status in PCOS**

**70% of women who present with anovulation have PCOS**

**However not all women with PCOS have cycle disturbance**

**Robinson et al studied 72 women with PCO on ultrasound scan, all with clinical or biochemical evidence of hyperandrogenaemia compared 19 women with regular cycles to 52 women with oligo/amenorrhoea**

## The relationship of Insulin sensitivity to menstrual pattern in women with hyperandrogenism and PCO



# Methods of decreasing insulin resistance

1. Weight loss
2. Diazoxide
3. Thiazolidinediones eg. troglitazone
4. Biguanides eg. metformin

# Weight Reduction

Bates et al, 1982 Fertil & Steril 38, 407

18 obese (>20% above IBW) women PCOS, all  
anovulatory

13 lost weight, mean loss 15% of body weight

10/13 (77%) conceived spontaneously

an additional patient resumed regular cycles

significant decrease in total testosterone levels

## **Kiddy et al 1992, Clin Endocrinol 36; 105**

**24 obese women (BMI mean 34.1, SD 4.9 kg/m<sup>2</sup>) with PCOS on long term dietary restriction (1000 kcal for 6 months)**

**13 patients lost >5% of initial weight**

**5 conceived**

**8 improvement in menstrual function**

**Significant increase in SHBG**

**Significant decrease in free testosterone, fasting and glucose-stimulated insulin**

**Huber-Buchholz e al. 1999, J Clin Endo & Metabol 84 (4) 1470**

**18 obese anovulatory women with PCOS**

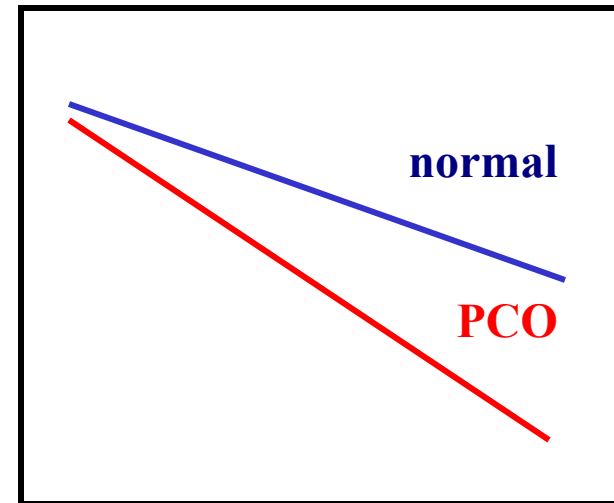
**10 controls, PCO on ultrasound, regular cycles, ovulatory status confirmed during 2 month observation period with urinary pregnanediol glucuronide measurements**

**15 obese subjects completed the study**

**9 responded with mean weight loss between 2-5%**

**Significant improvement in insulin sensitivity**

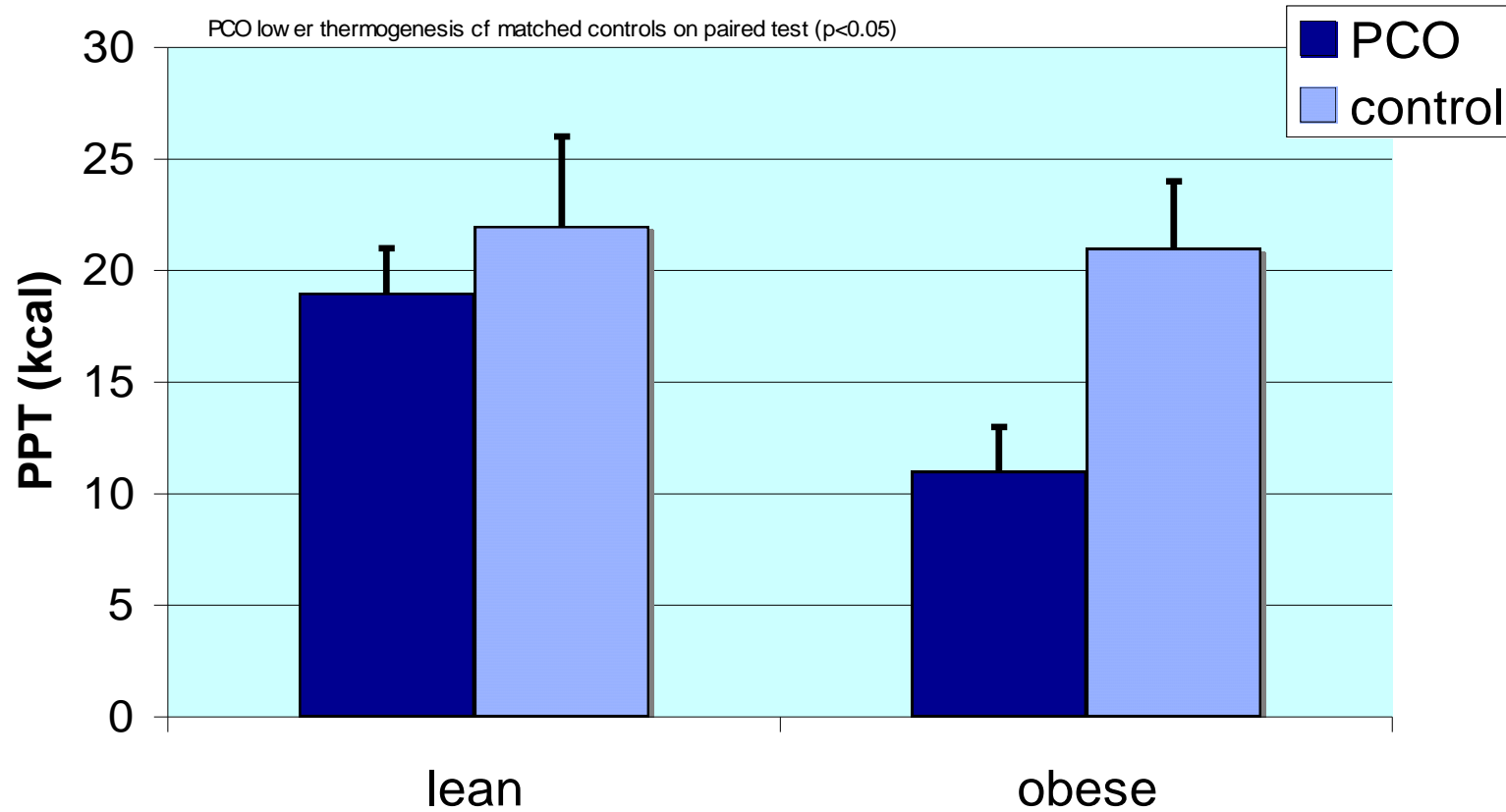
**Significant fall in percentage central fat**



**BMI**

**Insulin sensitivity**

## Post prandial thermogenesis in lean and obese women with PCO



# Patient perspective on PCOS and Insulin Resistance

**“a high protein, low CHO, zero sugar diet is very good for PCO. I am convinced that every PCO patient should try insulin control medication for 2-6 months to see if it works for them”**

**“doctors are allowed to prescribe an approved insulin sensitising drug for any purpose they wish, but some (especially those who aren't up to date on the new research) may not be willing to do this”**



# **Use of insulin sensitising agents in PCOS**

**Insulin sensitising agents currently available**

**In vitro data on effect of insulin sensitising agents on ovarian function**

**Clinical studies on women with PCOS**

# Diazoxide

Nestler et al 1989, J Clin Endo & Metab; 68 1027

5 obese women with PCOS

10 days of diazoxide (300mg/day)

Decreased insulin release and worsened glucose tolerance

Significant reduction in total testosterone (basal 2.5[0.4] vs post diazoxide 2.1[0.3]) and free testosterone without changing SHBG levels

# Troglitazone

**primary effect on glucose disposal rates improving insulin sensitivity in the periphery, particularly in skeletal muscle**

**modest effect on glucose hepatic output**

**improves fasting and post prandial hyperglycaemia in NIDDM**

# Troglitazone

**In vitro data**

**1 study using porcine granulosa cells**

**Gasic et al, 1998 Endocrinol; 139, 4962**

**inhibited progesterone production in a time and dose dependant manner**

**specific inhibition of 3beta-hydroxysteroid dehydrogenase**

## Clinical studies with troglitazone

Dunaif et al. established in the 1st published clinical study that 400mg/ day of troglitazone is required

	Year	No. subjects	Mean BMI	Weeks of treatment
Dunaif et al	1996	23	42.0	12
Ehrmann et al	1997	13	39.9	12
Hasegawa et al	1999	13	28.7	12

Fall in insulin, LH and androgen levels with no change in BMI

2/3 improved insulin sensitivity

1/3 reduction in ovarian androgen response to GnRH agonist

# Use of troglitazone and clomiphene citrate with outcome assessed by ovulation rates

Hasegawa et al, 1999

1 cycle of troglitazone alone the clomiphene added in subsequent cycle if patient requested

13 patients treated

	Ovulatory cycles/Number of cycles	
clomiphene citrate alone	15/43	(35%)
troglitazone alone	11/26	(42%)
co-administration	8/11	(73%)

# Metformin

**primary site of action reduction in hepatic glucose output**

**reduces fasting glucose concentrations, improves glucose tolerance usually with a modest reduction in plasma insulin levels in NIDDM**

# Summary of the effect of metformin in human cell culture

## Granulosa cells

Metformin inhibited FSH stimulated oestradiol and progesterone production

In the presence of insulin metformin inhibited steroid production

## Theca cells

Metformin inhibited basal and insulin stimulated androstenedione production

Metformin had no effect on basal progesterone production but increased insulin stimulated progesterone production



# Clinical studies with Metformin

**20 published studies**

**Dose of metformin used 1500-2550mg/day**

**Number of subjects in each trial 13-39 except 1 study with 61 patients**

**Length of treatment 4 weeks-6 months**

**Potential outcomes**

**Number of studies  
reporting positive outcome**

**Fall in basal insulin levels 14**

**Improved insulin sensitivity 2**

**Fall in androgen levels 17**

**Fall in BMI 4**

**Improved menstrual cyclicality 9**

**Improved ovulation rate either  
spontaneous or with additional  
treatment 4**

# Uncontrolled studies

10 studies

Selection criteria:

PCOS, anovulatory, increased basal insulin and  
glucose stimulated AUC

usually obese with hyperandrogenaemia

Additional assessment in some studies of plasminogen  
inactivator inhibitor

steroid response to ACTH, hCG

7 spontaneous pregnancies reported

**IR Pirwany et al 1999 Human Reproduct 14, 2963**

**15 women completed treatment with metformin  
850mg bd for 8 weeks**

**No change in BMI**

**Subgroup of 9 patients with testosterone >3.0 nmol/l  
significant improvement in ovulation rates (4 luteal  
weeks in 27 observation weeks before treatment vs  
28 luteal weeks in 72 observation weeks during  
treatment {p=0.005})**

# Effect of metformin on insulin resistance in PCOS

	Number	BMI	weeks of treatment	Assessment	Effect of metformin
Acbay et al	16	30.2 [1.8] stable	8	IVGTT OGTT	No change
Ehrmann et al	14	39.0 [7.7] stable	12	IVGTT OGTT graded iv glucose infusion	No change
Diamenti- Kandarakis et al	13	33.6 [6.0]	26	Euglycaemic clamp OGTT	Inc glucose utilisation
Moghetti et al	16	19-38.7	26	Euglycaemic clamp OGTT	Improved insulin sensitivity

# Placebo controlled studies with metformin

	Number	BMI	weeks of treatment	with diet	Outcome	Improvement with metformin
Crave et al	24	35.2 [1.2]	16	yes	both groups lost weight	no
Nestler et al	24	34.1 [1.5]	4-8	no	fall in I freeT rise in SHBG	yes
Nestler et al	31	None	4-8	no	fall in I freeT rise in SHBG	yes
Moghetti et al	23	Placebo group heavier	26	no	improved insulin sensitivity	yes
Pasquali et al	20 PCOS 20 controls	BMI >28	26	yes	metformin additional effect	yes

# Metformin and clomiphene citrate for ovulation induction

Nestler et al, 1998: NEJM 338, 1876

61 women with PCOS randomised to metformin or placebo

All obese (BMI>25), hyperandrogenaemic (raised free testosterone)

	Metformin	Placebo
number	35	26
spontaneous ovulation	12 (34%)	1 (4%)
number	21	25
ovulation with clomiphene	19(90%)	2(8%)

# **Metformin vs placebo or no treatment**

**7 randomised controlled trials, meta analysis**

**Improvement in ovulation rates reported with metformin**

**5 trials reporting clinical pregnancy rates  
no evidence of benefit**

**Lord et al BMJ 25th Oct 2003, 951**



## **Use of Metformin with additional clomiphene**

**4 reported trials where metformin combined with clomiphene improves ovulation rate when compared to clomiphene alone.**

**2 studies report no additional effect of metformin**

# **RCT Lifestyle Modification and Metformin vs Placebo**

Tang et al, Hum Reprod 2006 Jan, 21(1):80-9

143 subjects, 69 randomised to metformin, 74 received placebo  
Morbidly obese BMI 37.6 kg/m<sup>2</sup> (metformin) vs 38.9 kg/m<sup>2</sup> (placebo)

**Primary outcome measures**

**No change in menstrual frequency**

**Both groups similar reductions in weight and BMI**

**Significant reduction in waist circumference in metformin group**

**Endocrine parameters**

**No change in insulin nor glucose levels**

## **Secondary Outcome Measures**

**Pregnancy rates**

**No difference between the 2 groups**

**2 pregnancies in each arm of the study within 2 months of commencing treatment**

**A further 4 pregnancies in the metformin group in the 5th and 6th**

**months of the study**

**Metformin pregnancy rate 8.7% vs 2.7 % in placebo group  
( $p=0.233$ )**

# Metformin and clomiphene in treatment of PCOS: RCTs

<i>Moll et al</i>	<i>clomiphene + metformin (111)</i>	<i>clomiphene + placebo (114)</i>
Ovulation rate (%)	64	72
Conception rate (%)	40	46

<i>Legro et al</i>	<i>clomiphene + metformin (209)</i>	<i>clomiphene + placebo (209)</i>	<i>metformin + placebo (208)</i>
Conception rate (%)	38.3	29.7	12.0
Live birth rate (%)	26.8	22.5	7.2

Moll *et al*, *BMJ* 2006, **332** 1485-8

Legro *et al*, *New Engl J Med* 2007 **356** 551-66

# Conclusions

1. Insulin resistance is present in anovulatory women with PCOS
2. The insulin resistance is more severe in obese women with PCOS compared to lean women with PCOS
3. Weight reduction improves insulin sensitivity

**4. The published data to assess changes in insulin sensitivity with metformin are conflicting**

**5. The place of insulin sensitising agents in clinical practise remains uncertain**

**Larger RCT's show no significant improvement in ovulation or pregnancy rates, independent of weight loss, using metformin with or without the addition of clomiphene**