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

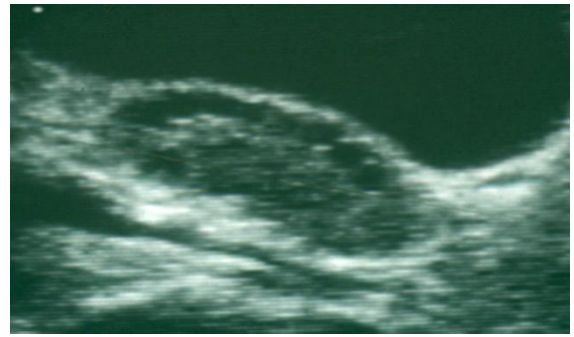
Adams Criteria for PCO

Increase in ovarian volume (>9 cm3)

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)
Ovarian Morphology		
Normal	**116 (73%)**	**76 (76%)**
Polycystic	**36 (23%)**	**20 (20%)**
Multifollicular	**5 (3%)**	**3 (3%)**
Uncertain	**1**	

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

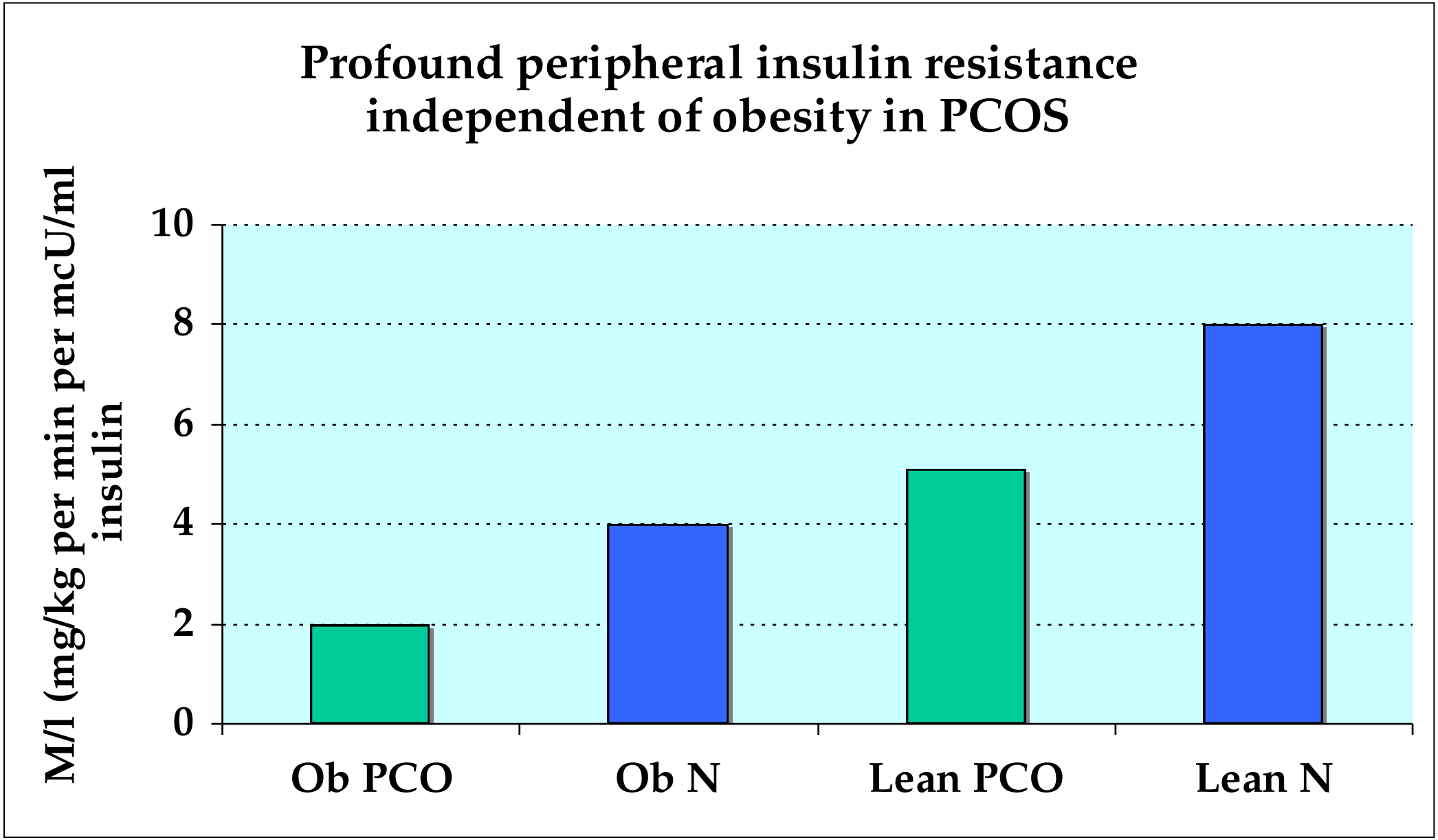
Oral GTT: increased glucose and insulin response

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
M/I (mg/kg per min per mcU/ml insulin
10
8
6
4
2
0
Ob PCO
Ob N
Lean PCO
Lean N

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

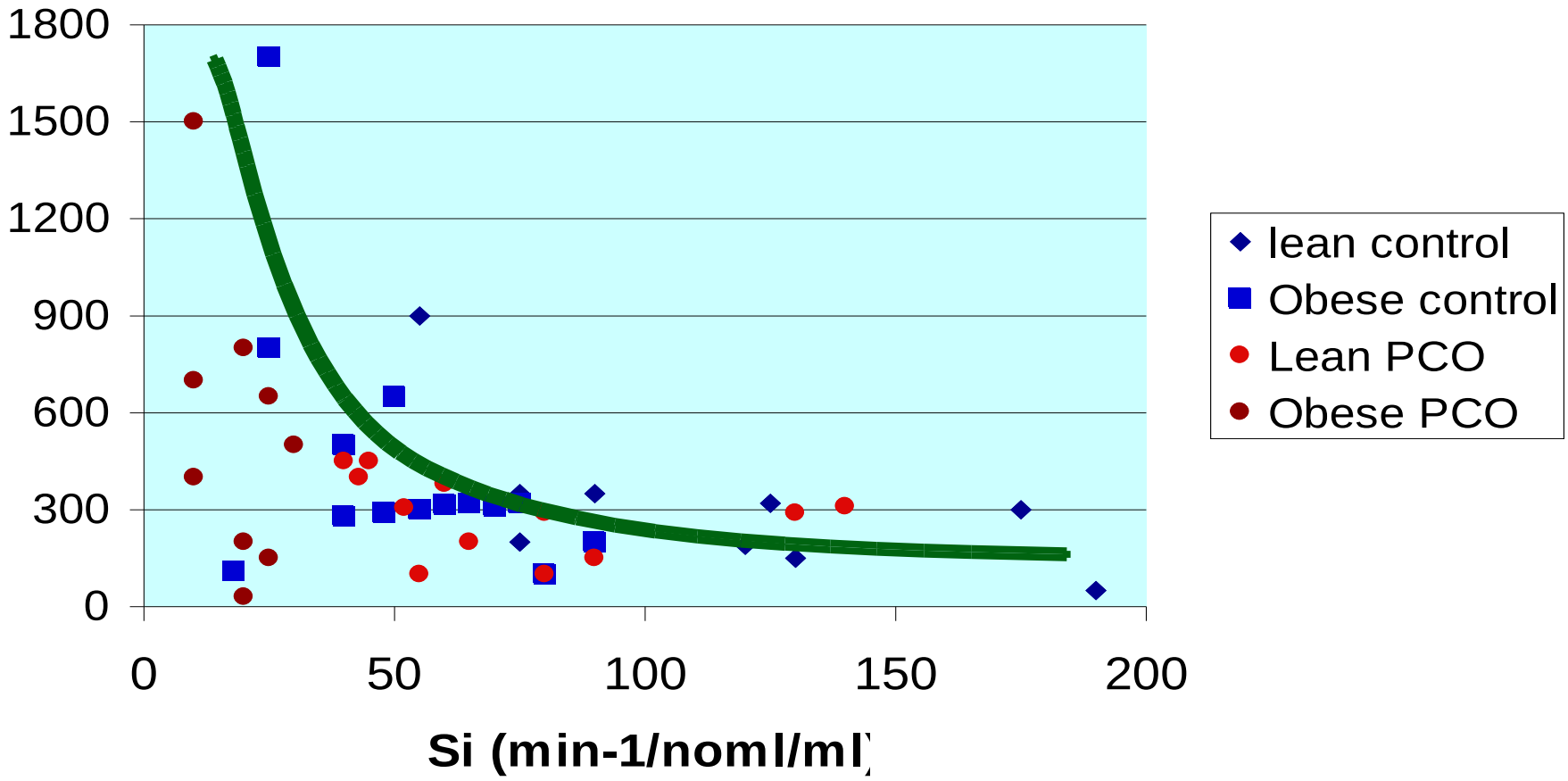
Frequently sampled IVGTT confirmed decreased insulin sensitivity in PCOS independent of obesity

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

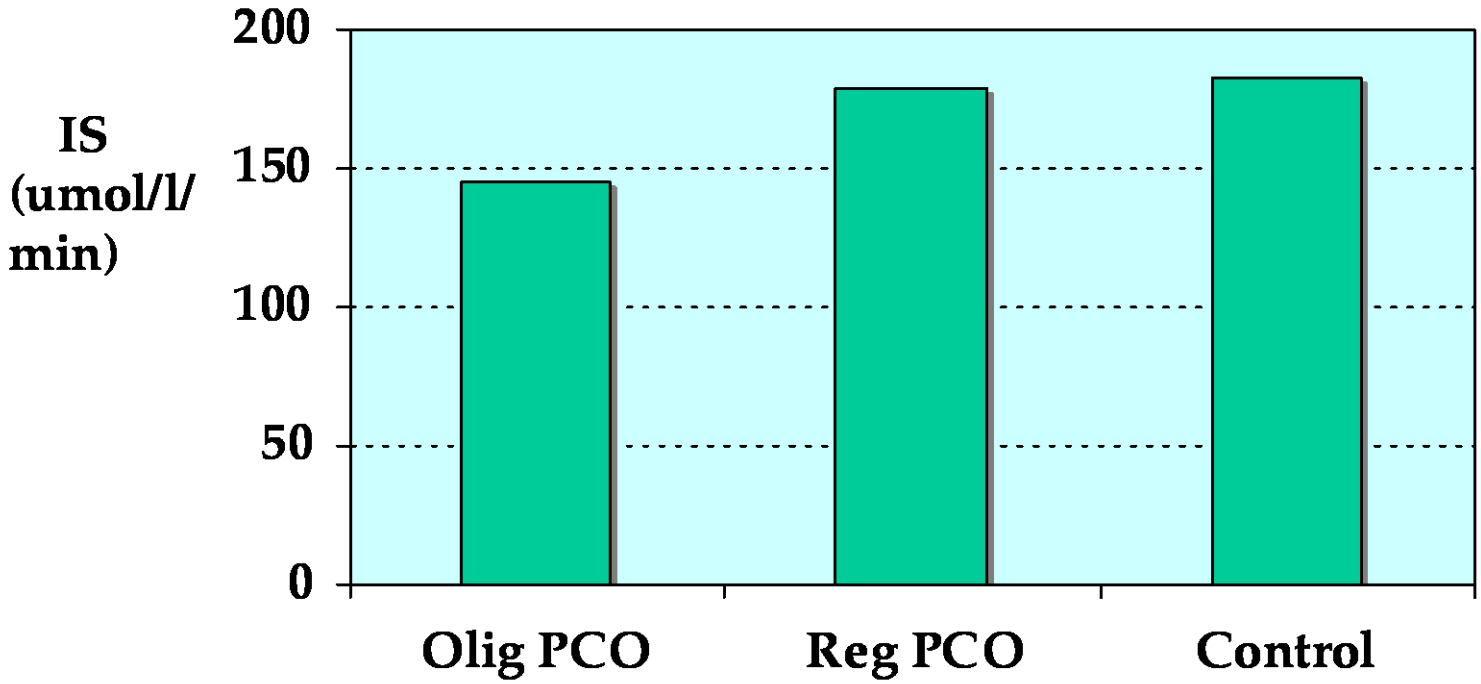
Ovulatory status in PCOS

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/m2) 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

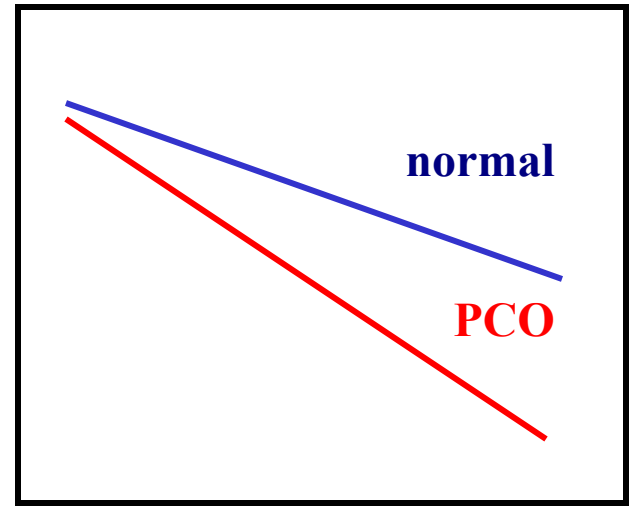
10 controls, PCO on ultrasound, regular cycles, ovulatory status confirmed during 2 month observation period with urinary pregnanediol glucuronide measurements

15 obese subjects completed the study

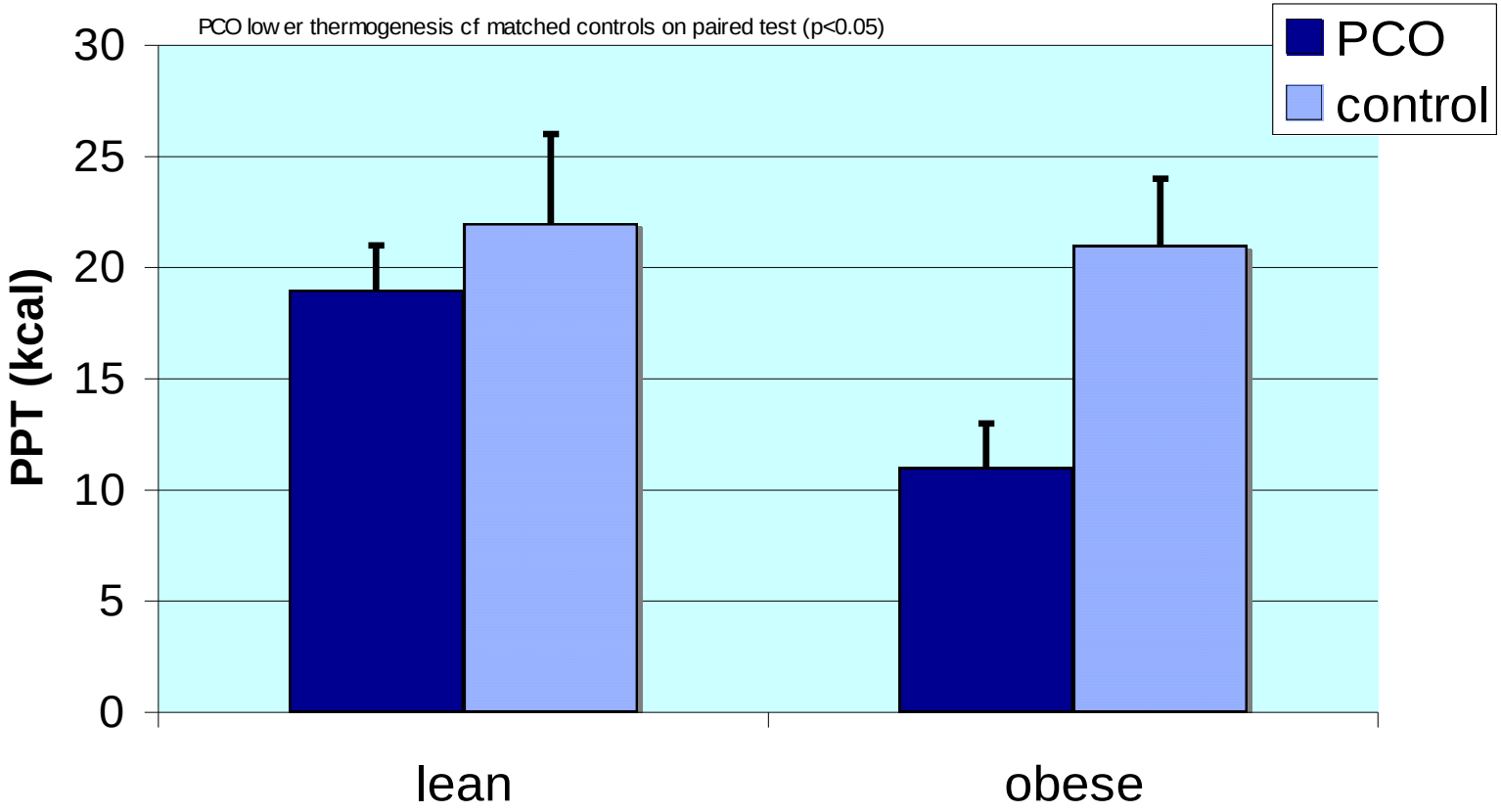
9 responded with mean weight loss between 2-5%

Significant improvement in insulin sensitivity

Significant fall in percentage central fat



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

spercific 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 incresed 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 cyclicity	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/m2 (metformin) vs 38.9 kg/m2 (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

Moll et al	*clomiphene + metformin (111)*	*clomiphene + placebo (114)*
Ovulation rate (%)	64	72
Conception rate (%)	40	46

Legro et al	*clomiphene + metformin (209)*	*clomiphene + placebo (209)*	*metformin + placebo (208)*
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