

Polycystic Ovary Syndrome Current Definitions and Management

BICOG 2010

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If it looks like PCOS,

and it responds like PCOS,

.....its probably PCOS..

PCOS

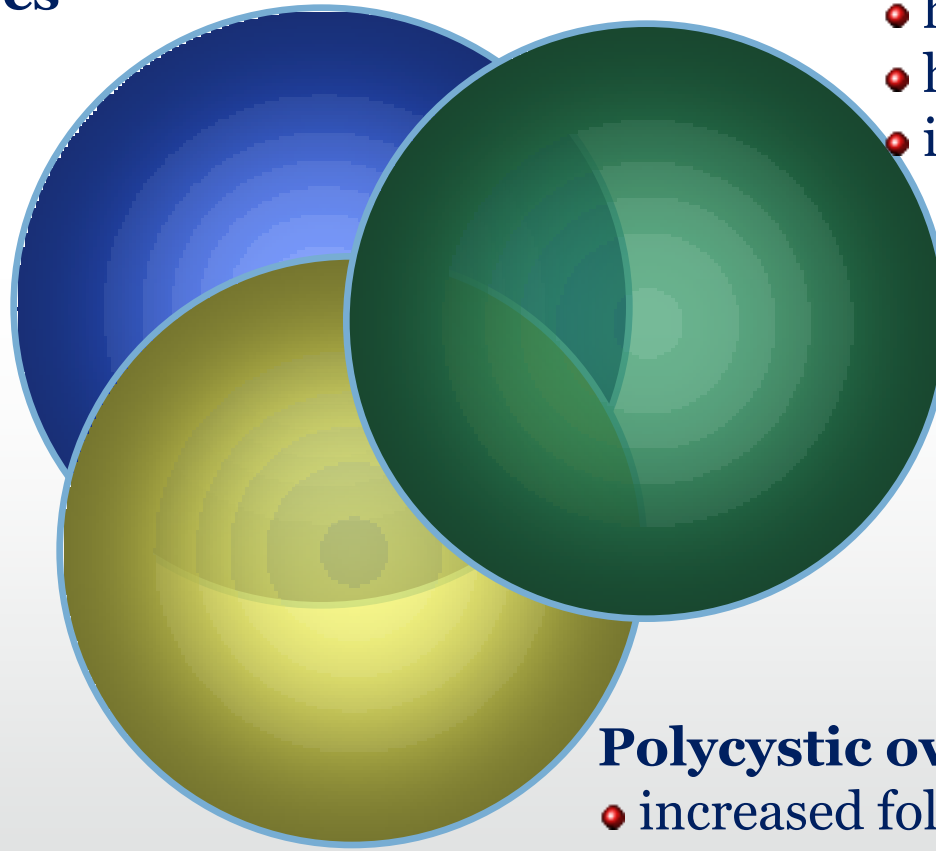
- diagnostic dilemmas -

Clinical features

- hirsutism
- obesity
- anovulation

Endocrine features

- high androgens
- high LH
- insulin resistance

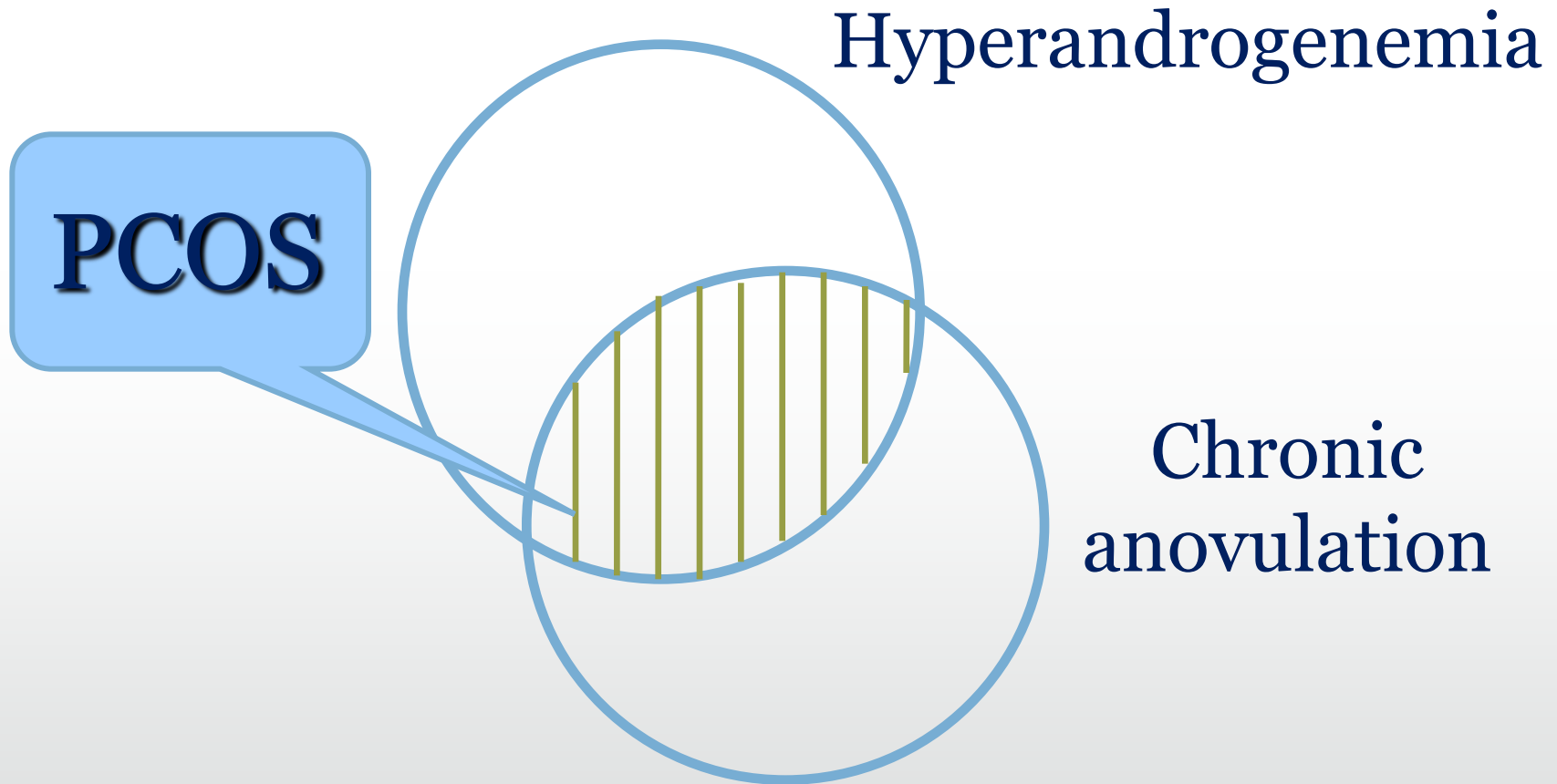


Polycystic ovaries

- increased follicle #
- increased stroma
- increased ovarian volume

PCOS diagnosis

- *1990 NIH criteria* -



Epidemiology of PCOS

<i>Population/ethnicity</i>	<i>sample size</i>	<i>PCOS</i>	<i>Reference</i>
Greek Island, Lesbos 17-45 yrs	192	NIH 6.8%	Diamanti, JCEM 99
Caucasian, reproductive age Blood donors, Spain	154	NIH 6.5%	Asuncion, JCEM 00
Preemployment physical, US 18-45 yrs (223 black, 166 white)	400	NIH 6.6%	Azziz, JCEM 04 Knochenhauer, JCEM 98

Why Revisit the NIH Criteria?

- First step to standardizing diagnosis
- Based on Questionnaire
- PCOS -broader spectrum of ovarian dysfunction
 - regular cycles and hyperandrogenism and/or PCO
 - PCO without hyperandrogenism
- May not be suitable for trials of clinical outcomes

ESHRE / ASRM endorsed PCOS Consensus Meeting Rotterdam, The Netherlands

UNIVERSITY OF
Southampton
School of Medicine



Rotterdam, May 2003

1999 NIH Criteria (both 1 and 2)

1. Chronic anovulation
2. Clinical and/or biochemical signs of hyperandrogenism

Exclusion of other aetiologies

Revised 2003 Rotterdam Criteria (2 out of 3)

1. Oligo- and/or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries

Exclusion of other aetiologies

PCOS diagnostic criteria

- Exclusion of other causes of androgen excess
 - ◆ Cushing, 21 hydroxylase deficiency
 - ◆ androgen producing tumours
- Exclusion of other causes of anovulation
 - ◆ Hypogonadotropic hypogonadism
 - ◆ Premature ovarian failure
 - ◆ Hyperprolactinaemia
- Often obesity (but not required)
- Often elevated LH (but not required)
- Often hyperinsulinemia (but not required)

PCOS

- polycystic ovaries -

- Presence of 12 or more follicles (2-9mm) per ovary. Location not important.
- Ovarian volume >10mls
 - $0.5 \times \text{length} \times \text{width} \times \text{thickness}$
- Ovarian stroma objective?
- One ovary sufficient for diagnosis
- Scan early follicular phase



*Balen et al,
HRU 2003*

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS)

CONSENSUS STATEMENT

The Rotterdam ESHRE/ASRM-sponsored PCOS Consensus Workshop Group

Correspondence to: Bart C.J.M.Fauser, Center of Reproductive Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands. E-mail: b.fauser@erasmusmc.nl

Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome

*The Rotterdam ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group
Rotterdam, The Netherlands*

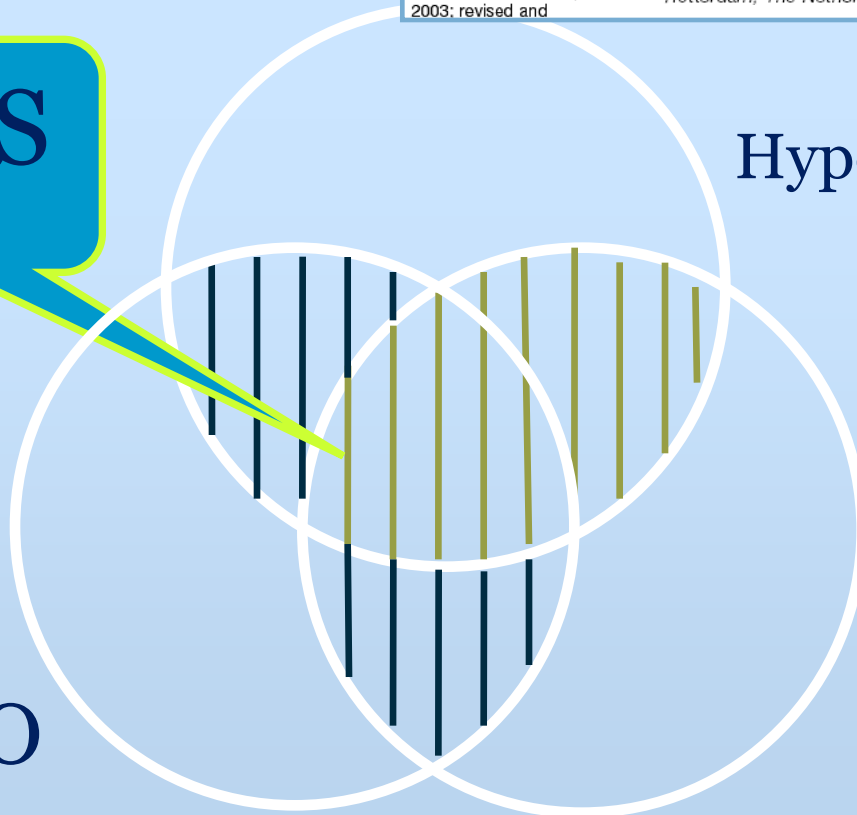
Received October 22, 2003; revised and accepted November 10, 2003

PCOS

Hyperandrogenemia

PCO

Oligo/anovulation
(WHO 2 type)



PCOS phenotypes

	NIH		Rotterdam additions	
	<hr/>	<hr/>	<hr/>	<hr/>
Oligo/anovulation	+	+	+	
Hyperandrogenemia	+	+		+
PCO		+	+	+

The Androgen Excess Society Guideline

- PCOS is above all a disorder of androgen excess.
- The diagnosis requires evidence of clinical or biochemical hyperandrogenism: hirsutism or raised free T levels.

REVIEW ARTICLE

The diagnosis of polycystic ovary syndrome: the criteria are insufficiently robust for clinical research

Julian H. Barth*, Ephra Yasmint† and Adam H. Balent

*Departments of Clinical Biochemistry & †Reproductive Medicine and Surgery, Leeds General Infirmary, Leeds, UK

Table 2. Factors that are known to alter serum testosterone concentrations

Physiological factors

Pulsatile release during the day⁴⁴

Diurnal rhythm: am > pm^{42,45,46}

Menstrual cycle: luteal > follicular^{31,47}

Season (no variation in total testosterone free testosterone shows 30% difference): summer > winter^{43,48}

Age (years) in women with and without polycystic ovary syndrome (PCOS): 20s > 40s^{49,50}

Analytical factors

Cross reactivity with other endogenous steroids³⁰

Interference by endogenous antibodies⁵¹

Poor performance in the female range: < 8 nmol/l^{1,29}

PCOS

- hyperandrogenemia -

Clinical:

- Acne
- Hirsutism



• Biochemical:

- Testosterone total or free (unbound)
- Free androgen index (T x 100 / SHBG)
- Androstenedione?
- DHEAS?
- combination

Normative data lacking

Subjective

May be less prevalent in East Asian Women

Variable laboratory methods

Wide variability in normal population

Normative ranges not well established in well characterized control populations

The Androgen Excess Society Guideline

- PCOS is above all a disorder of androgen excess.
- The diagnosis requires evidence of clinical or biochemical hyperandrogenism: hirsutism or raised free T levels.
- Recognize problems in reliably diagnosing hyperandrogenism
- Support for these criteria is based on associated risk of metabolic morbidity, and not on hyperandrogenism per se.
- Neither anovulation nor Polycystic ovaries required

Table 1. Criteria for the diagnosis of polycystic ovary syndrome (PCOS)

NIH (1990)

To include all of the following:

1: Hyperandrogenism and/or hyperandrogenaemia

2: Oligo-ovulation

3: Exclusion of related disorders

ESHRE/ARMS

(Rotterdam 2003)

To include two of the following, including the exclusion of related disorders:

1: Oligo- or anovulation

2: Clinical and/or biochemical signs of hyperandrogenism

3: Polycystic ovaries

Androgen Excess

Society (2006)

To include all of the following:

1: Hirsutism and/or hyperandrogenaemia

2: Oligo-anovulation and/or polycystic ovaries

3: Exclusion of androgen excess or related disorders

PCOS: a syndrome of 9 phenotypes?

TABLE 5. All possible phenotypes based on the presence or absence of oligoanovulation, hyperandrogenemia, hirsutism, and PCOS

Features	Potential phenotypes															
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
Hyperandrogenemia	+	+	+	+	-	-	+	-	+	-	+	-	-	-	+	-
Hirsutism	+	+	-	-	+	+	+	+	-	-	+	-	-	+	-	-
Oligoanovulation	+	+	+	+	+	+	-	-	-	+	-	-	+	-	-	-
Polycystic ovaries	+	-	+	-	+	-	+	+	+	+	-	+	-	-	-	-
NIH 1990 criteria	✓	✓	✓	✓	✓	✓										
Rotterdam 2003 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
AES 2006 criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓							

+ , Presence; - , absence.

- Phenotype can change
- Treat accordingly

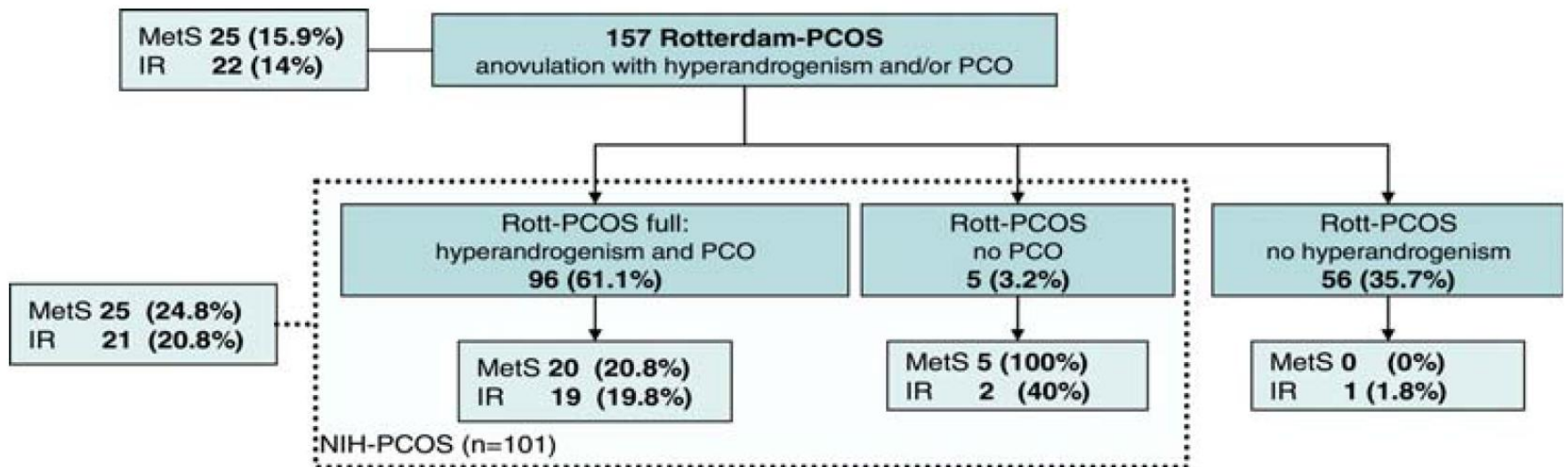
Indicators for metabolic disturbances in anovulatory women with polycystic ovary syndrome diagnosed according to the Rotterdam consensus criteria

A.J. Goverde^{1,3}, A.J.B. van Koert¹, M.J. Eijkemans¹, E.A.H. Knauff¹, H.E. Westerveld², B.C.J.M. Fauser¹, and F.J. Broekmans¹

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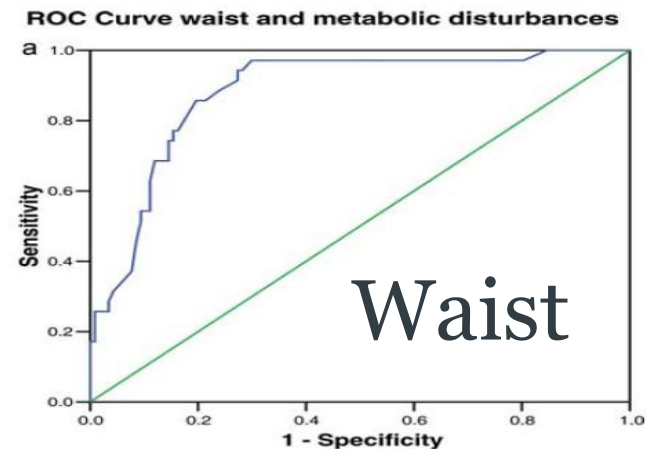
PCOS Beyond Fertility



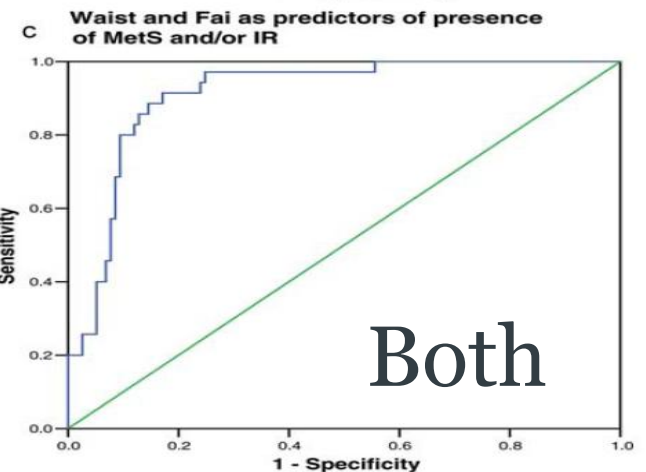
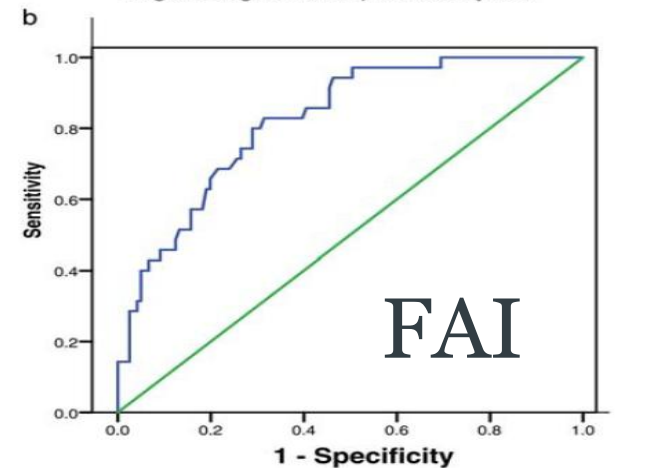
Predicting Metabolic Syndrome

Table II Logistic regression analysis showing the predictive association of several clinical variables and the presence of metabolic derailment (MetS and/or IR)

		P-value	Odds ratio	ROC-AUC ratio
Univariate analysis	PCO (y/n)	<0.0001	0	0.571
	Hyperandrogenism (y/n)	<0.0001	27.91	0.712
	FAI (>4.5 y/n)	<0.0001	1.317	0.826
	Age (years)	0.562	1.024	0.531
	Race	0.050		0.609
	Caucasean (n = 130)		1	
	Mediterranean (n = 11)		5.3	
	Asiatic (n = 10)		1.893	
	Hindustanic (n = 2)		0	
	Negroid (n = 3)		2.208	
	Arabic (n = 1)		na	
	Waist (cm)	<0.0001	1.111	0.881
	WHR (cm/cm)	<0.0001	5.078	0.864
Multivariate analysis	Waist (cm)	<0.0001		
	FAI (>4.5 y/n)	<0.0001		
	WHR (cm/cm)	0.026		0.927



Diagonal segments are produced by ties.



AUC, area under the curve; ROC, receiver operating characteristic; n, no; y, yes; FAI, free androgen index; na, not assumable; WHR, waist/hip-ratio; MetS, metabolic syndrome.

If it looks like PCOS,

But isn't strictly PCOS,

.....probably treat it as PCOS..

TREATMENT OF PCOS

Human Reproduction Vol.23, No.3 pp. 462–477, 2008

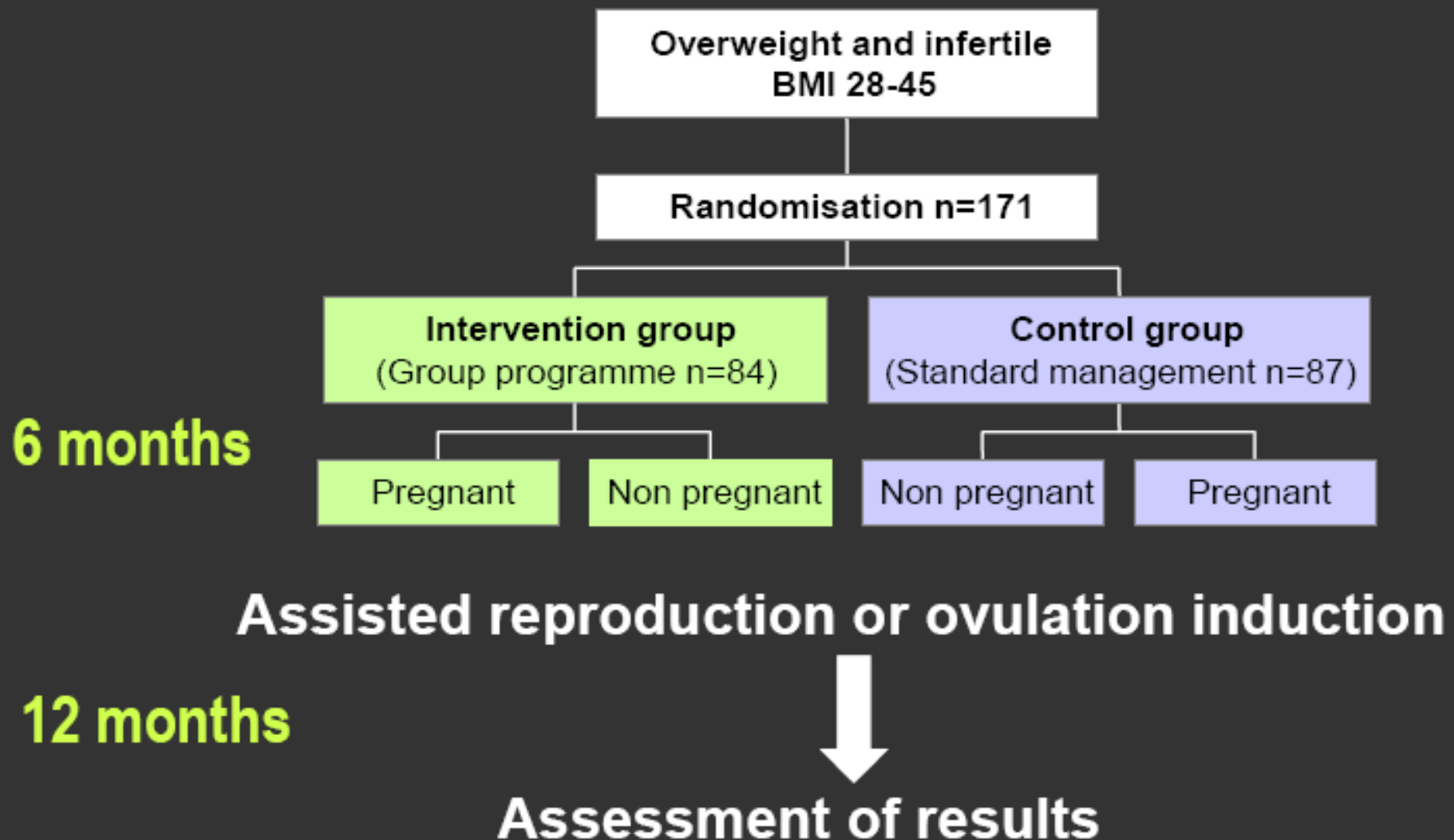
doi:10.1093/humrep/dem426

Consensus on infertility treatment related to polycystic ovary syndrome

The Thessaloniki ESHRE/ASRM-Sponsored PCOS Consensus Workshop Group March 2–3, 2007, Thessaloniki, Greece*

‘Before any intervention is initiated, preconceptional counselling should be provided emphasizing the importance of life style, especially weight reduction and exercise in overweight women, smoking and alcohol consumption’.

Intervention in overweight infertile women



Results of RCT

	Control (n=84)	Intervention (n=87)
Weight loss (kg)	1.3 (0.2)	4.7 (0.3) *
Pregnancies at 18months	18 (21.4%)	53 (61%) *
Miscarriage	3 (16.6%)	6 (11.3%)
ART pregnancies	8	32 *
Spontaneous pregnancies	10	21 *

* p<0.001

Dietary Composition in Restoring Reproductive and Metabolic Physiology in Overweight Women with Polycystic Ovary Syndrome

L. J. MORAN, M. NOAKES, P. M. CLIFTON, L. TOMLINSON, AND R. J. NORMAN

Reproductive Medicine Unit, Department of Obstetrics and Gynecology, University of Adelaide, Queen Elizabeth Hospital (L.J.M., L.T., R.J.N.), Woodville, South Australia 5011, Australia; and CSIRO Health Sciences and Nutrition (L.J.M., M.N., P.M.C.), Adelaide, South Australia 5000, Australia

- 12 week energy restriction diet
- Randomised to high or low protein diet

RESULTS

- : Both interventions improved cyclicity, lipid profile and IR
- : Mean weightloss 7.5%
- : LP diet
 - HDLs decreased 10%
 - FAI increased 44%

CONCLUSIONS:

- Both diets work
- High protein diet may have slight advantages

The Effect of a Hypocaloric Diet with and without Exercise Training on Body Composition, Cardiometabolic Risk Profile, and Reproductive Function in Overweight and Obese Women with Polycystic Ovary Syndrome

Rebecca L. Thomson, Jonathan D. Buckley, Manny Noakes, Peter M. Clifton, Robert J. Norman,

Patients and Intervention: Ninety-four overweight and obese women with PCOS (age 29.3 ± 0.7 yr; body mass index 36.1 ± 0.5 kg/m²) were randomized to diet only (DO; n = 30), diet and aerobic exercise (DA; n = 31), or diet and combined aerobic-resistance exercise (DC; n = 33).

Conclusion: In overweight and obese women with PCOS, the addition of aerobic or combined aerobic-resistance exercise to an energy-restricted diet improved body composition but had no additional effect on improvements in cardiometabolic, hormonal, and reproductive outcomes relative to diet alone. (*J Clin Endocrinol Metab* 93: 3373–3380, 2008)

Moment of caution...



Effect of a very-low-calorie diet on in vitro fertilization outcomes

A low-calorie diet in a group of overweight or obese patients for a short period before and during IVF results in variable tolerance to the dietary regime and an unsatisfactory IVF outcome. (Fertil Steril® 2006;86:227–9. ©2006 by American Society for Reproductive Medicine.)

10 women, 18-40 years, BMI >28, indication for IVF

Diet from day 14 or day 21 of previous cycle to day of OPU

- 4 patients withdrew
- Mean duration of diet: 27-41 days
- Weight loss: 5.3-8.2 kg (mean 6.3% of body weight)
- 3 patients : Total Fertilization Failure

Ovulation Induction

Type of ovarian stimulation aimed at

restoring normal fertility

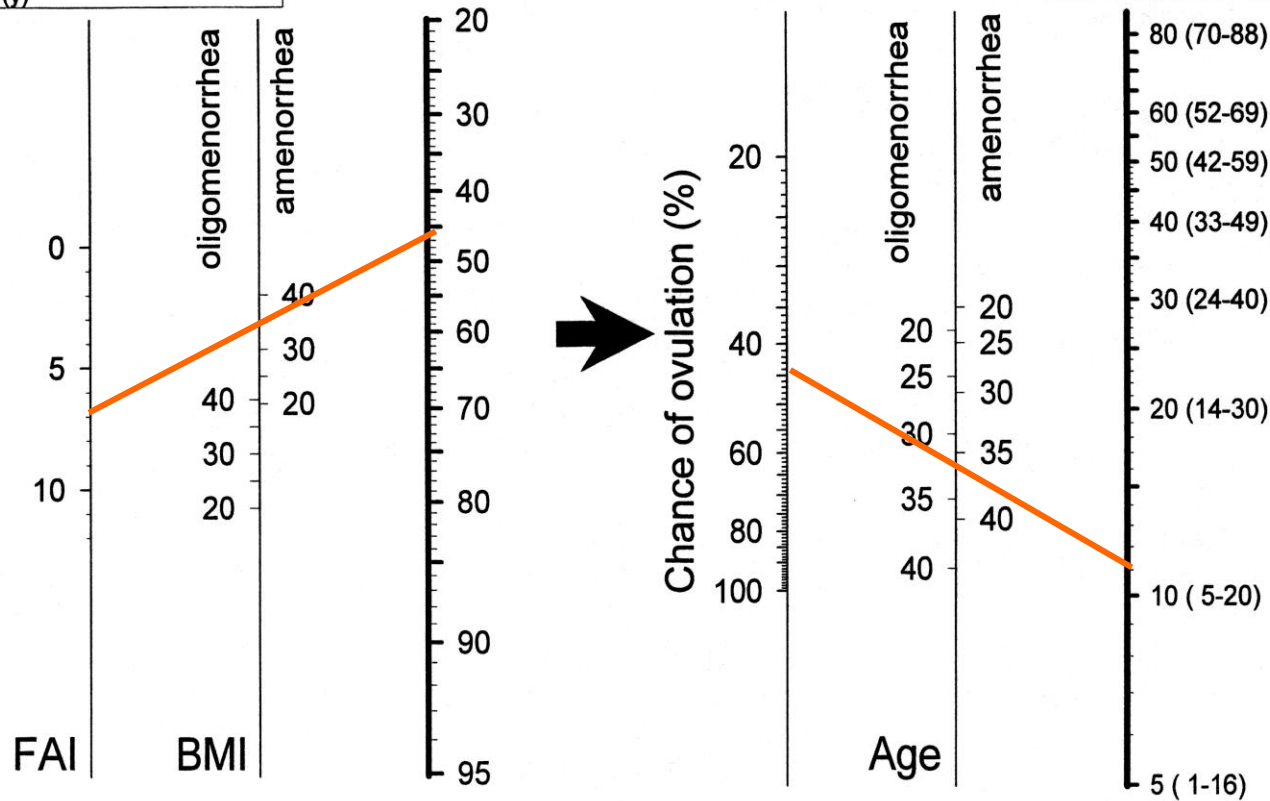
by inducing single dominant follicle selection,
ovulation and hence normo-ovulatory cycles.

Who should move immediately to other therapies?

Required screening information
 - Amenorrhea or oligomenorrhea
 - BMI (kg/m^2)
 - FAI ($\text{T} \times 100/\text{SHBG}$)
 - Age (y)

Chance of ovulation (%)

Chance of a live birth (%)
(95% CI)



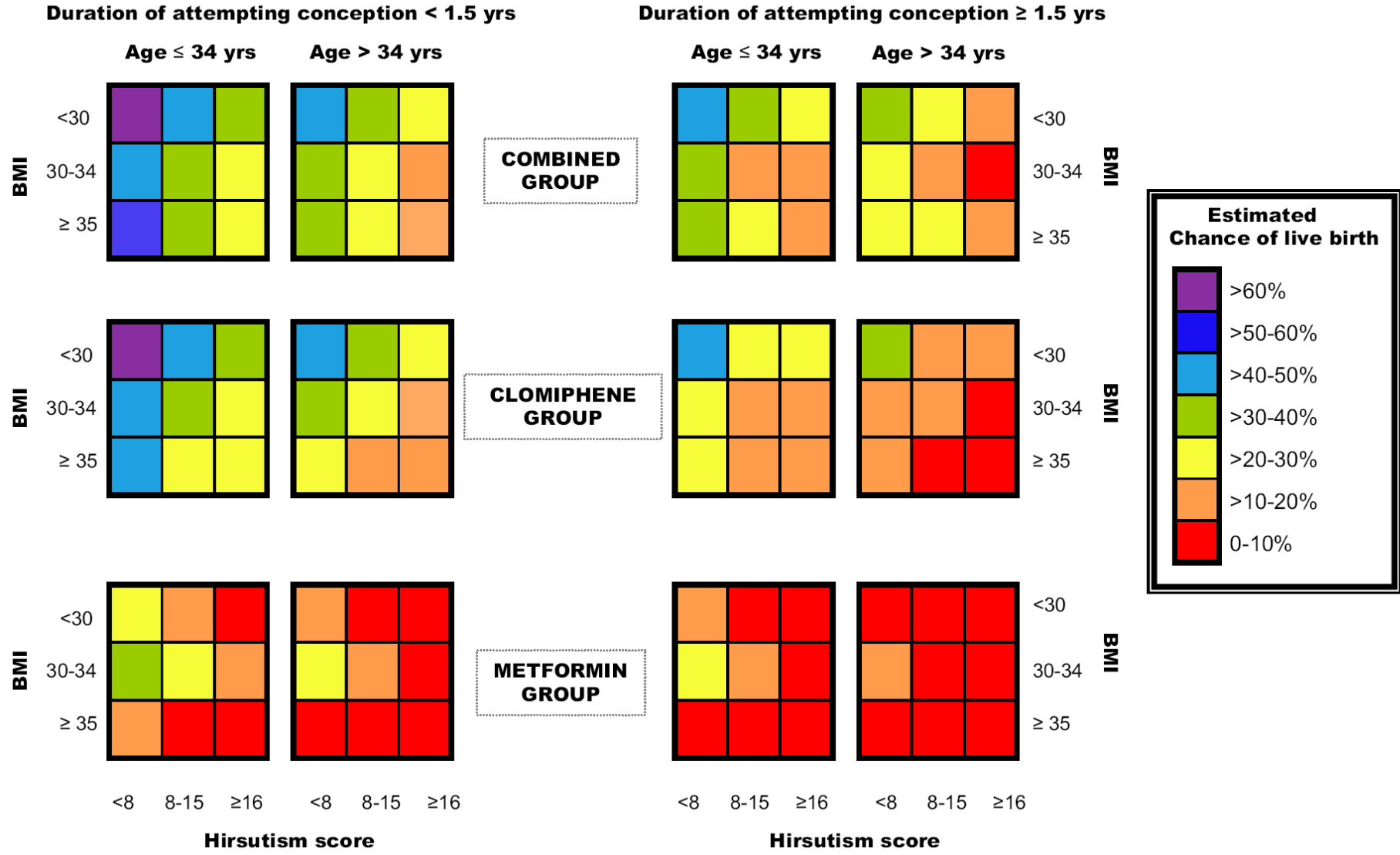
CASE:

36years
 BMI 35
 Amenorrhea
 FAI 7

Predictors of Pregnancy in Women with Polycystic Ovary Syndrome

Mary E. Rausch, Richard S. Legro, Huiman X. Barnhart, William D. Schlaff, Bruce R. Carr, Michael P. Diamond, Sandra A. Carson, Michael P. Steinkampf.

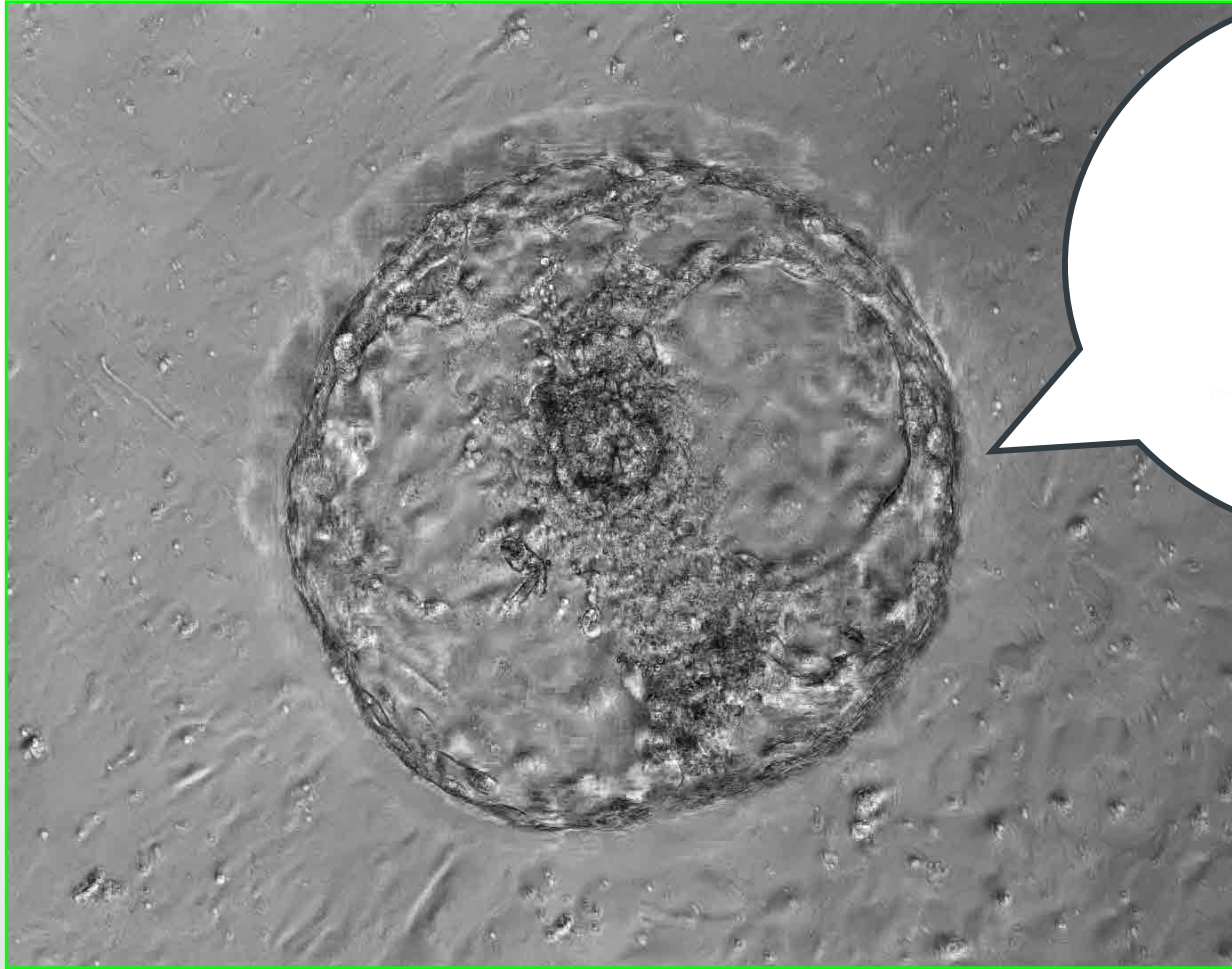
JCEM 2009



PCOS and IVF outcome: a meta-analysis

- Increased cancellation rate (13% vs 4%)
- Longer ovarian stimulation required (1.2 days)
- More oocytes obtained
- Fertilization rates similar
- No difference in clinical pregnancy rate
- (Increased risk of OHSS)

Your other PCOS patient



PCOS
SUCKS

A meta-analysis of pregnancy outcomes in women with polycystic ovary syndrome

C.M.Boomsma^{1,7}, M.J.C.Eijkemans², E.G.Hughes³, G.H.A.Visser⁴, B.C.J.M.Fauser⁵
and N.S.Macklon⁶

Meta-analysis: 720 women with PCOS vs 4505 controls

	OR	95% CI
Gestational Diabetes:	2.94	1.70-5.08
Pregnancy induced hypertension:	3.67	1.98-6.81
pre-eclampsia	3.47	1.95-6.17
Pre-term birth	1.75	1.16-2.62
Peri-natal mortality	3.07	1.03-9.21

Preparing the PCOS patient

- Glucose tolerance test
- Fasting cholesterol, triglycerides, SHBG
- Risk of fatty liver?
- Baseline blood pressure

- Ultrasound: Exclude endometrial hyperplasia
Ensure visibility of ovaries

- Address obesity
- Role of exercise, diet, metformin

- Manage as an at risk pregnancy



Conclusions

- PCOS is a heterogeneous condition, but is clinically readily recognized.
- The Rotterdam Criteria have been widely accepted but not universally.
- Clear criteria important for research purposes
- Lifestyle interventions merit attention
- Ovulation induction works
- Pregnancy should be considered 'High Risk'
- PCOS affects more than just fertility
- Long term follow up for selected groups is indicated