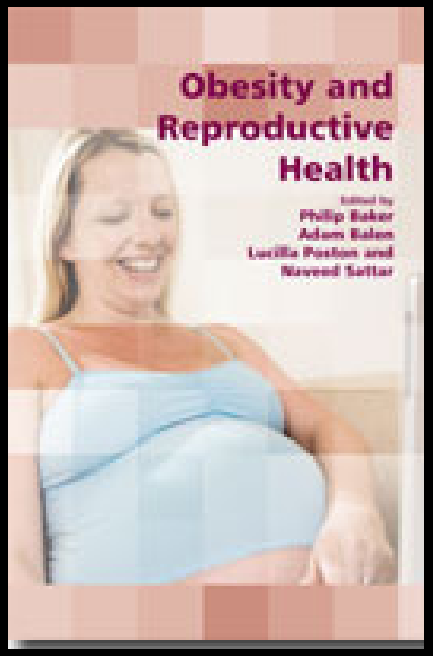
Obesity and Reproduction



Adam Balen
Department of Reproductive Medicine
Leeds Teaching Hospitals, UK

ESHRE Dubrovnic, 2010

Obesity and Reproduction

- **Obesity has a negative impact on:**
  - spontaneous conception,
  - miscarriage,
  - pregnancy,
  - long term health of children
  - (congenital anomalies and metabolic disease)
- **Obesity is associated with reduced response to fertility treatment and variable impact on ongoing pregnancy rates**
- **Obesity may affect safety of procedures:**
  - ability to see ovaries on scan,
  - provide safe anaesthesia for procedures etc…

Should there be a cut off weight / BMI before any treatment?

- Reduced chance conception
- Increased risk miscarriage
- Increased rate of congenital anomalies
- Obstetrical problems
  (Gest DM, PET, delivery ….)

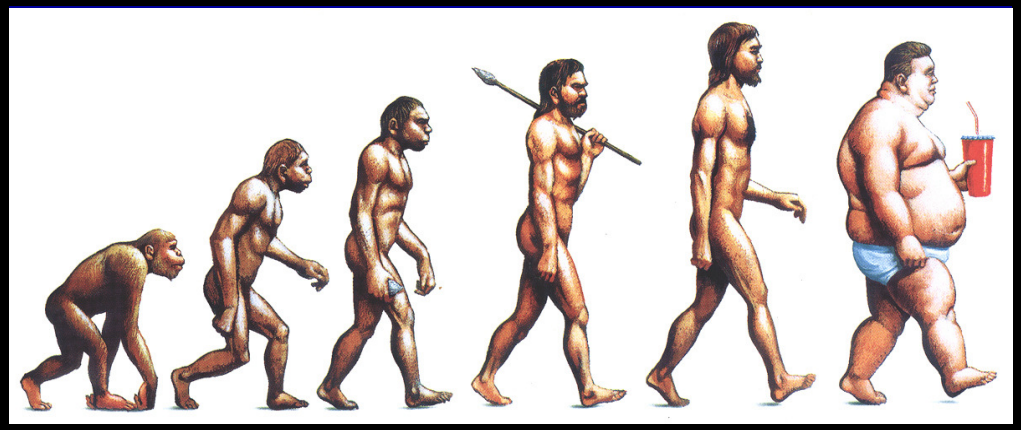
Balen, Dresner, Scott & Drife
BMJ 2006;332;434-435

1. Obesity – the modern epidemic

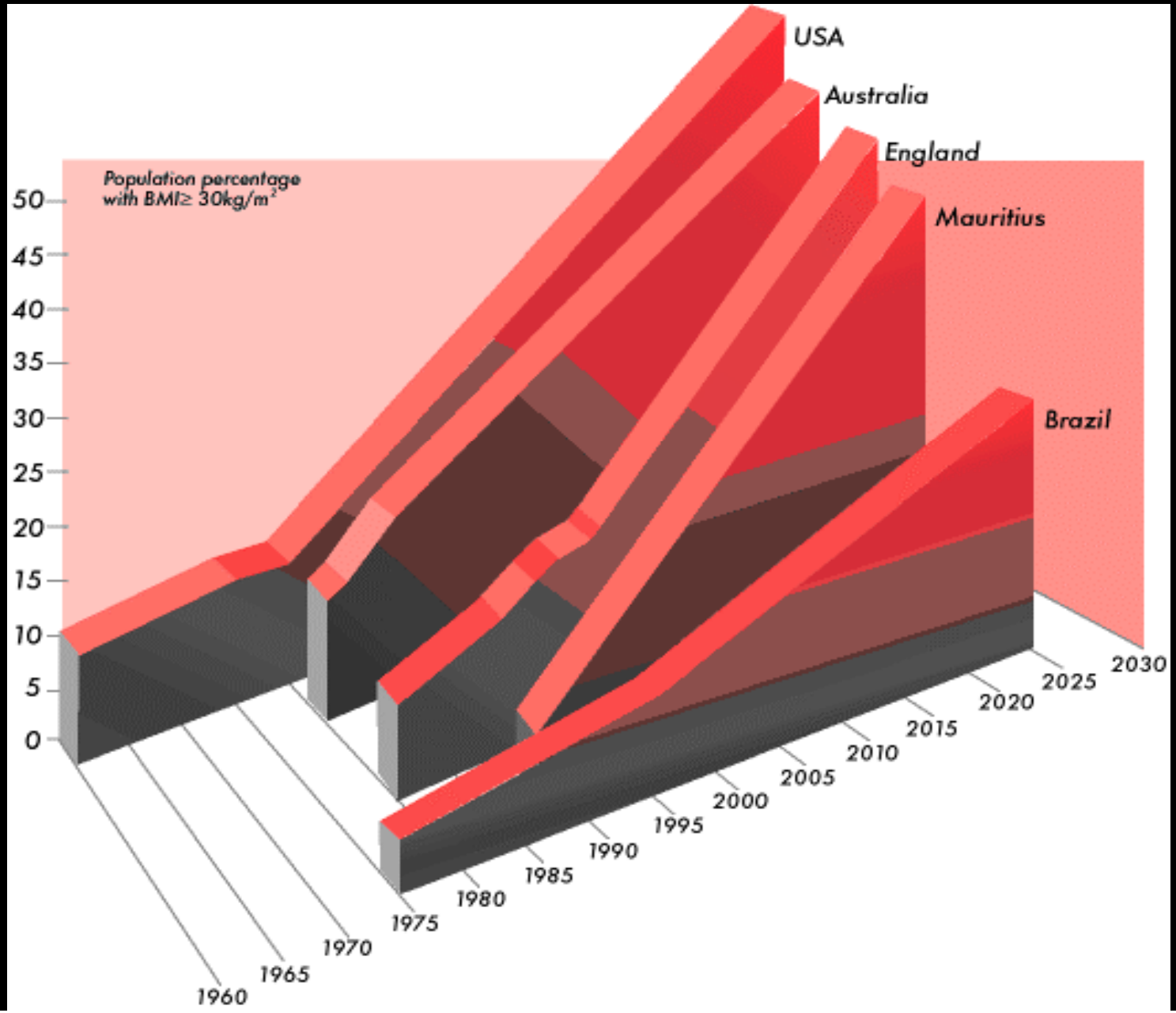
2. Obesity and reproduction
   - infertility / outcome of treatments
   - polycystic ovary syndrome
   - mechanisms
   - miscarriage

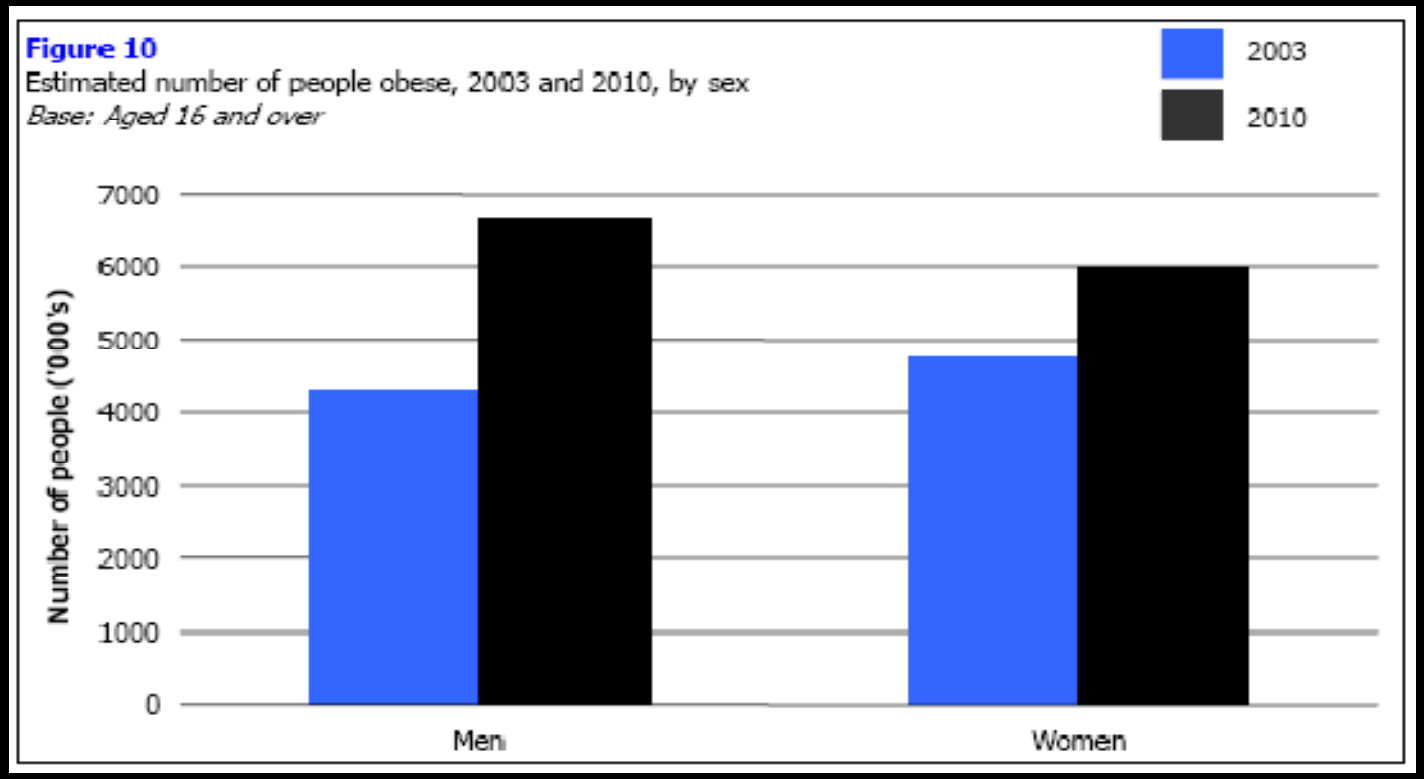
3. Weight loss

4. Limits for treatment



Percentage population with BMI > 30 kg/m^2



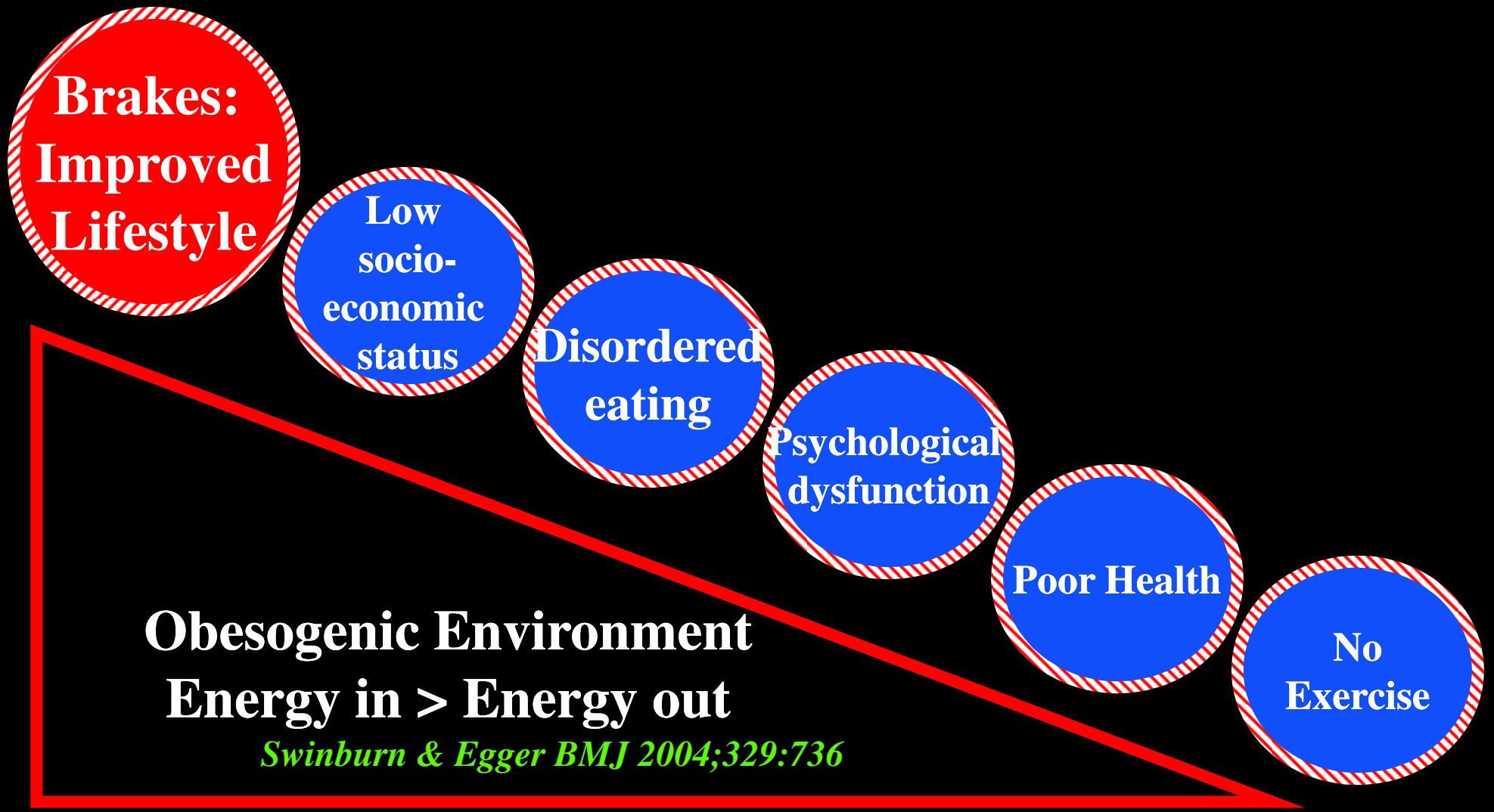


More than 12m adults (33% of men and 28% of women) and 1m children will be obese by 2010

19% of boys and 22% of girls (2-15y) will be obese

Having two obese parents → 5 x the risk of being obese

The runaway weight gain train: too many accelerators, not enough breaks



Medical Complications of Obesity

Stroke

Tiredness

Idiopathic intracranial hypertension
+ Loss of vision

Cataracts

Pulmonary disease
abnormal function
obstructive sleep apnea
hypoventilation syndrome

Coronary heart disease

Pancreatitis

Diabetes

Dyslipidemia

Hypertension

Nonalcoholic fatty liver disease
Steatosis/ steatohepatitis
cirrhosis

Gall bladder disease

Back pain

Gynaecologic abnormalities
abnormal menses / infertility
polycystic ovary syndrome
gestational diabetes
pre-eclampsia

Cancers
breast, uterus, cervix, prostate, kidney
colon, esophagus, pancreas, liver

Osteoarthritis

Oedema

Phlebitis
venous stasis
Venous thrombosis

Gout

Waist circumference - better than BMI

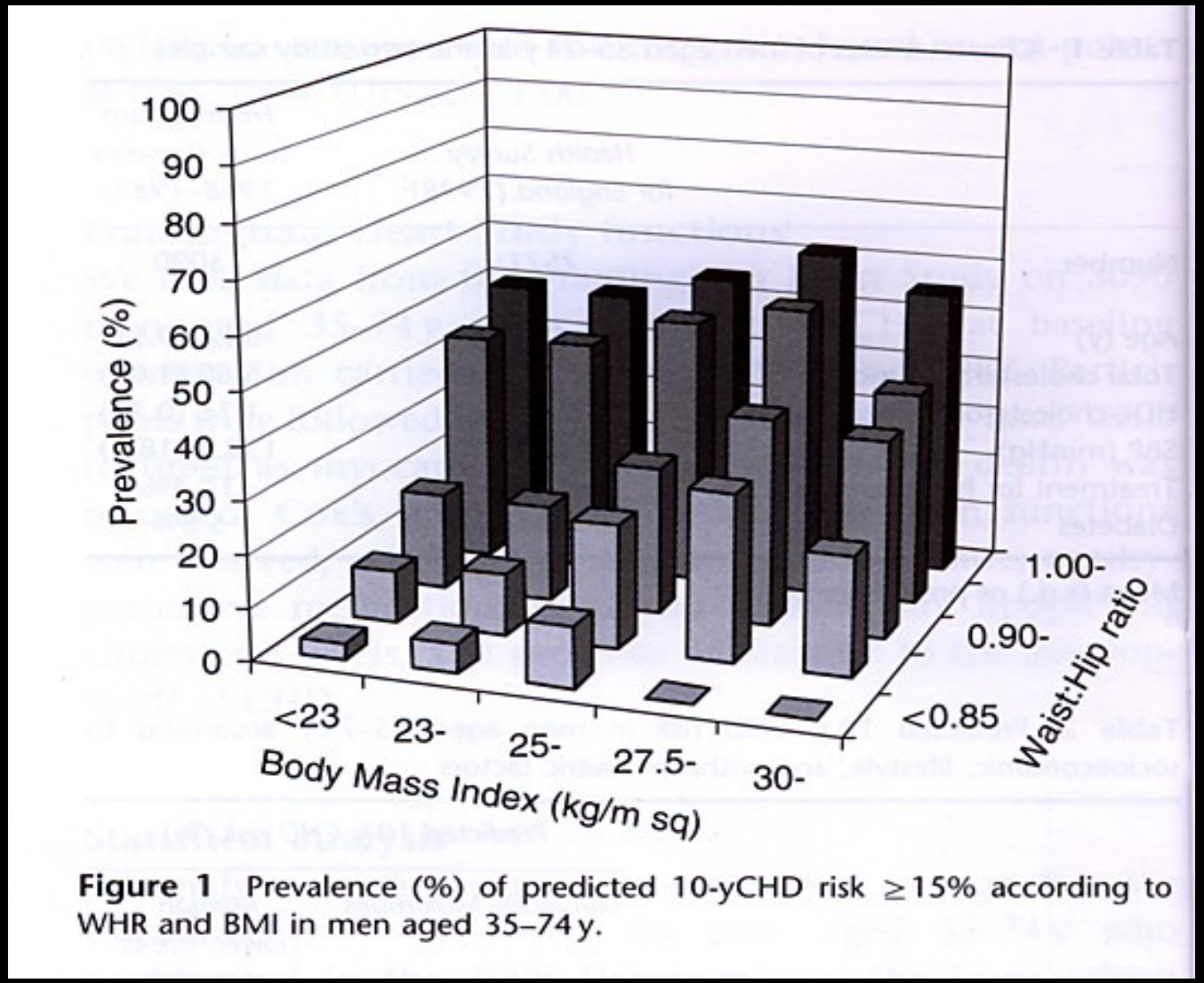


Figure 1 Prevalence (%) of predicted 10-yCHD risk ≥15% according to WHR and BMI in men aged 35–74 y.

Nanchahal K et al Int J Obes 2005 29; 317-323

1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - polycystic ovary syndrome
   - mechanisms
   - miscarriage

3. Weight loss

4. Limits for treatment

Body fat distribution and fertility

500 women receiving donor insemination

0.1 unit increase waist:hip → 30% ↓ conception

W:H ratio	% pregnant after 12 cycles
< 0.70	63%
0.7 – 0.75	51%
0.76 – 0.8	47%
0.81 – 0.85	41%
> 0.85	32%
BMI	
<20.0	40%
20.1-25	48%
25.1-30	48%
>30	18%

hazard ratio 0.705, 95% CI 0.562-0.887

Zaadstra et al BMJ 1993; 306:484

Anovulatory infertility (WHO Group II)

- **Infertility more likely with increasing BMI**

  Balen et al 1994

- **BMI > 27 kg/m^2 ass. with reduced chance ovulation**

  Grodstein et al 1994

- **Ovulation induction less effective if BMI > 28-30**

  Hamilton-Fairley et al 1992, Filicori et al 1994

- **Greater risks in pregnancy if obese (miscarriage, DM, delivery)** ***Gjoannaes et al 1984***

The effect of obesity in women with polycystic ovary syndrome

270 PCOS

receiving clomiphene citrate or gonadotrophins

Ovulation rate at 6 months :

BMI 18-24 kg/m^2	79%	
BMI 30-34 kg/m^2	15.3%	p <0.001
BMI ≥35 kg/m^2	12%	p <0.001

Al-Azemi et al. Arch Gynecol & Obst 2004; 270:205-10

The influence of body weight on response to ovulation induction with gonadotropins in 335 women with WHO Group II anovulatory infertility

Max BMI 35 kg/m^2 , mean BMI 25.3 kg/m^2

Increasing BMI significantly associated with:

- more antral follicles before stimulation
- more small & fewer intermediate sized follicles at ovulation
- more days of stimulation
- higher dose of gonadotrophins required
- no effect on ongoing pregnancy rates

Balen et al, BJOG 2006; 113: 1195

Predictors for outcome with gonadotropin ovulation induction in WHO Group II infertility: a meta-analysis

Degree of obesity positively correlated with amount of gonadotropin required:
weighted mean difference of 771 IU (95% CI 700-842)

Higher rate of cycle cancellation
(pooled OR 1.86, 95% CI: 1.13-3.06)

Reduction in ovulation rate
(OR 0.44, 95% CI: 0.31-0.61)

In those who ovulated:
no difference in pregnancy rates associated with obesity, but negative association with insulin resistance
(pooled OR 0.29, 95% CI: 0.10 - 0.80)

Mulders et al. Hum Reprod Update 2003; 9: 429-449

Obesity and IVF

Pregnancy rates after IVF 50% lower if BMI > 30 kg/m^2 compared with women with BMI < 25 kg/m^2

Loveland et al, J Assist Reprod Genet 2001;18:382;
Wittemer et al, J Assist Reprod Genet 2000;17:547;
Koloszar et al, Arch Androl 2002; 48: 323-7
Nichols et al, Fertil Steril 2003;79:645
Lintsen et al. Hum Reprod 2005; 20: 1867-75

Body mass and probability of pregnancy during assisted reproduction treatment

3586 women who had ART in Adelaide, 25% PCOS

logistic regression analysis confirmed independent effect of body weight, linear reduction in fecundity with obesity p<0.001

BMI	% achieving ≥1 pregnancy	OR (95% CI)
<20	45	0.81 (0.65-1.01)
20-24.9	48	1
25-29.9	42	0.81 (0.68-0.97)
30-34.9	40	0.73 (0.57-0.95)
>35	30	0.50 (0.32-0.77)

Wang et al BMJ 2000; 321:1320

Impact of overweight and underweight on pregnancy outcome in IVF/ICSI

5019 IVF/ICSI in 2660 couples
Cumulative live birth rate 3 cycles:

BMI 18.5-24.9 kg/m^2	50.3% [95% CI 47.0 - 53.7]
BMI 25-29.9 kg/m^2	44.9% [95% CI 38.4 - 51.3]
BMI ≥30 kg/m^2	41.4% [95% CI 32.1 - 50.7]

Compared with BMI <25, if BMI > 30

OR of live birth 0.75 [95% CI 0.57-0.98] p=0.05

OR of early pregnancy loss 1.69 [95% CI 1.13-2.51] p=0.003

Fedorcsak et al, Hum Reprod 2004; 2523-2528

Miscarriage after IVF?

- 1018 patients treated with IVF (37% PCOS)
- Miscarriage - PCOS 25%,
  - normal ovaries 18%
- Multivariate logistic regression showed higher risk of miscarriage in PCOS due to obesity

Wang et al, 2001

Obesity and IVF

Some authors report no effect:

- yet complex interaction between body mass and body fat distribution

- the intensity of the stimulation protocol may overcome some of the adverse effects of obesity

Lashan et al, Hum Reprod 1999; 14:712

Obesity & Miscarriage

- ↑ risk of miscarriage in moderately obese (BMI 25–27.9 kg/m^2)

Hamilton-Fairley et al Br J O G 1992;99:128

- ↑ miscarriage after IVF & ICSI (BMI 25.8 to 30.8 kg/m^2)

Fedorcsak et al Acta Obstet Gynecol Scand 2000;79:43

- BMI > 30 risk factor for miscarriage in oocyte recipients

Bellver J, et al Fertil Steril 2003;79:1136

Effect of overweight and obesity on assisted reproductive technology – systematic review

- Total of 1843 studies identified
- ART and obesity in 43 studies
- 14 fulfilled entry criteria
- All observational studies
- 3 Case control studies excluded

Maheshwari, Stofberg, Bhattycharya.
Human Reproduction Update, 2007; 13: 433-444

Findings

- Variable BMI cut off values
- Aggregated data on normal and low BMI
- Comparison groups: BMI of 25, 30, 35
- Inconsistent reporting of outcomes
- Live birth not reported in most studies
- No adjustment for confounders (e.g. age)

Parameter (BMI cut-off)	Number of papers	Number of patients	Findings
FSH dose (25 or 30)	2	5408	Highly sig increased dose in overweight
Cycle cancellation (25 or 30)	3	4039	Non-sig. trend to higher cancellation
Number of oocytes (25 or 30)	3	4039	Sig. fewer oocytes in overweight
OHSS (25 or 30)	2	1425	Non-sig. trend to increased OHSS in BMI>30
Pregnancy rate (25 or 30)	5	7571	Trend to increased PR in lighter weight
Pregnancy rate (20-25 vs. >25)	3	3694	Sig. lower PR in overweight
Pregnancy rate (35)	1	3146	Sig. lower PR in very overweight
Live birth (25 or 30)	2	3877	Non-sig. trend to increased LB in normal weight
Miscarriage (25)	8	6095	Non-sig. trend to increased losses in overweight
Miscarriage (30)	6	5652	Sig. increased losses in overweight
Miscarriage (35)	2	3376	Sig. increased losses in very overweight

Appraisal of existing evidence

- Limitations of existing evidence
- Values represent unadjusted odds
- Unable to rule out effect of age
- Inconsistency in cut-off values for BMI
- Few live birth data

Maheshwari *et al*, 2007

Effect of obesity on IVF

- Higher FSH requirement
- Lower oocyte yield
- Possibly lower pregnancy rates
- Higher miscarriage rates
- No evidence of effect on livebirth

Maheshwari *et al*, 2007

Conclusions of meta-analysis

- Negative effect of obesity on IVF
- Effect at several levels
- Results to be interpreted with caution
- Consensus to be reached on BMI limit
- Further work on obesity as predictor
- Meanwhile aim for optimum BMI in ART

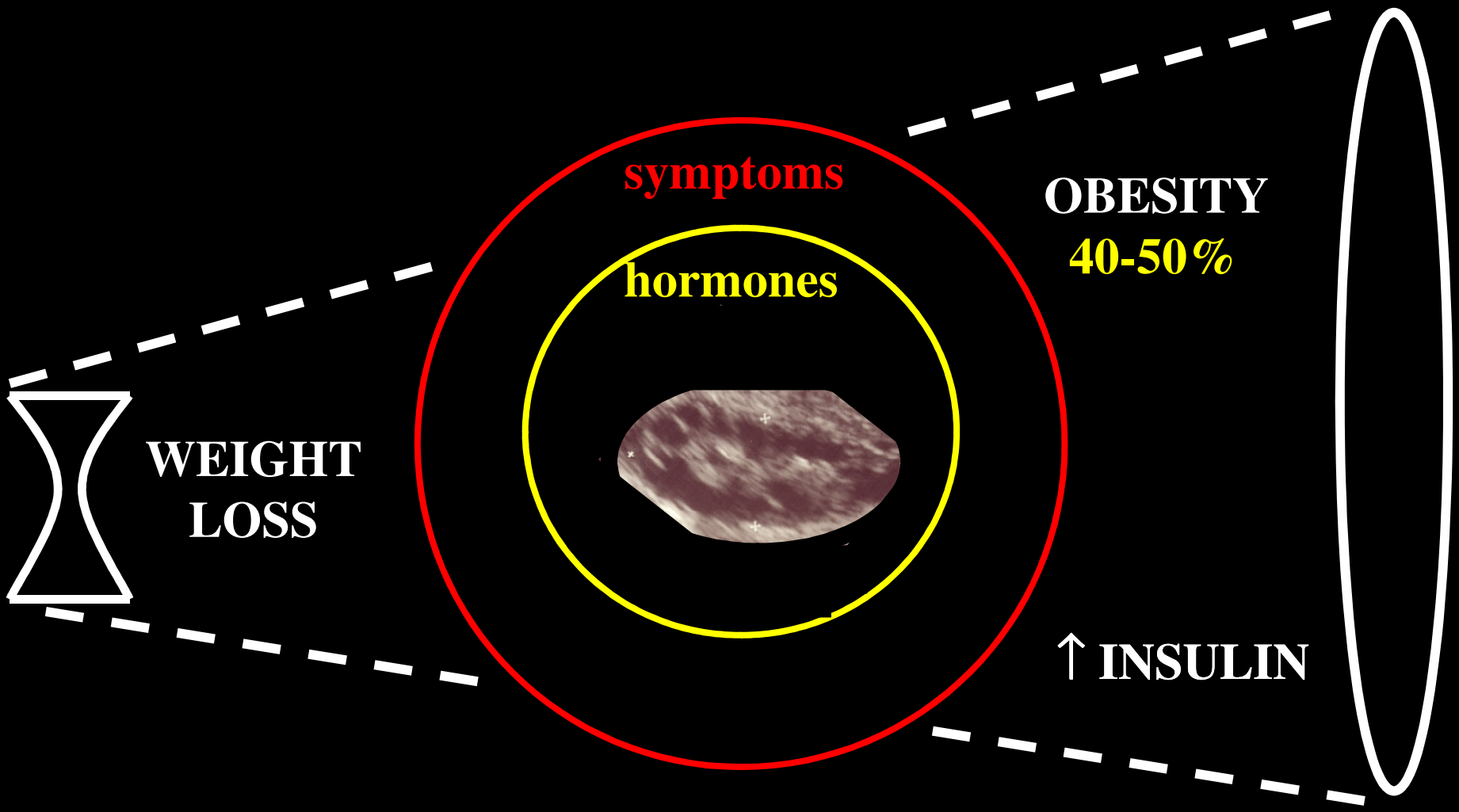
1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - polycystic ovary syndrome
   - miscarriage
   - mechanisms

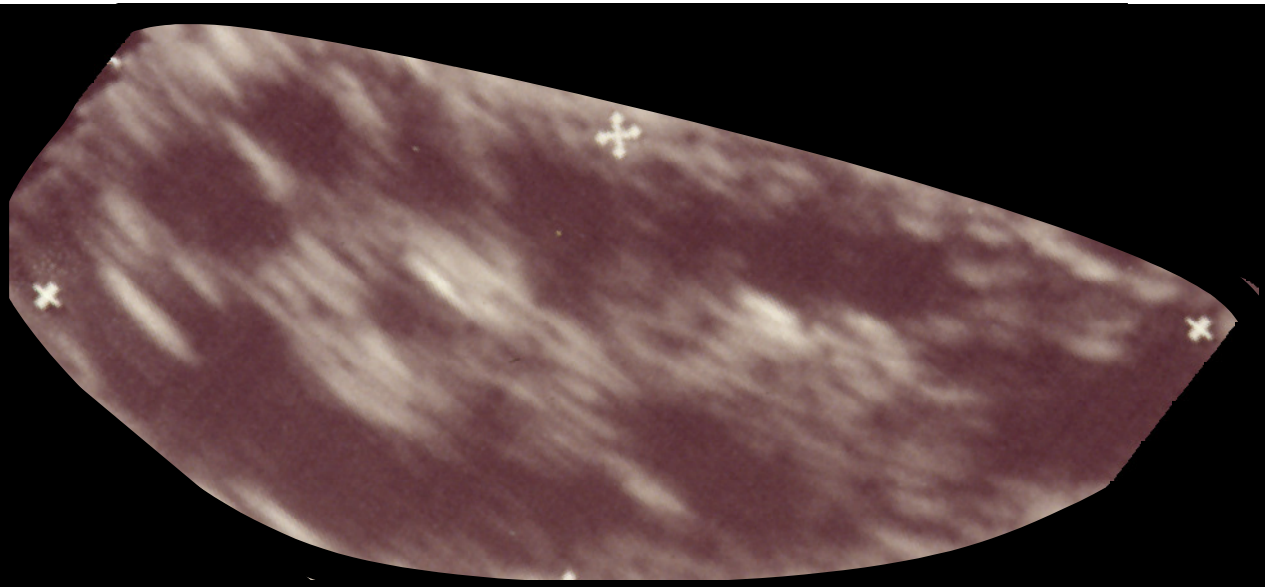
3. Weight loss

4. Limits for treatment

1741 Women with PCOS



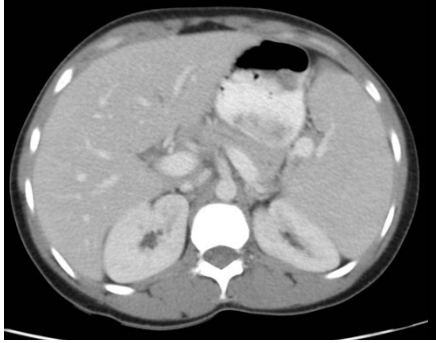
Balen et al Hum Reprod 1995; 10: 2107



Obesity:

BMI – WHO criteria (overweight 25-30, obese > 30 kg/m^2)

Waist Circumference > 80 cm



PCOS in South Asians and Caucasians living in the U.K.

S. Asians had significantly:

↓ age onset hirsutism	p < 0.01
↑ hirsutism, acne & acanthosis nigricans	p < 0.001
similar BMI & W:H	
similar total Testosterone	
↑ insulin and ↓ SHBG	p < 0.001

Wijeyaratne et al, Clin Endocrinol 2002; 57: 243
Wijeyeratne et al, Clin Endocrinol 2004; 60: 560
Palep-Singh et al. J Reprod Med 2008; 53:117

1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - polycystic ovary syndrome
   - mechanisms
   - miscarriage

3. Weight loss

4. Limits for treatment

Mechanisms?

Hyperinsulinaemia:

↑ androgens, ↓ SHBG, worsens PCOS
disrupts follicular maturation
GnRH pulsatility – LH secretion

Leptin & Ghrelin :

receptors on endometrium, follicle, oocyte, embryo
placenta, (testis)

Endorphins:

GnRH pulsatility

Cytokines, PAI-1, adiponectin, resistin, PYY3-36, glucocorticoids ….

Mechanisms?

Abnormal absorption & distribution of drugs ….

↓ Intrafollicular hCG, affects oocyte quality

Carrell et al 2001, RBM Online 3:109

Hyperinsulinaemia and miscarriage

- Hyperinsulinaemia is a risk factor for EPL
- Glycodelin: immunoregulatory peptide
  protects implantation
- ↓ glycodelin and IGFBP-1 in pregnancies that miscarry
- Metformin therapy may increase glycodelin and IGFBP-1

Nestler, 2003

Plasminogen activator inhibitor (PAI-1)

- Glycoprotein
- Potent inhibitor of fibrinolysis
- Elevated in PCOS, hyperinsulinemia

- High levels are risk factor for EPL in PCOS

Craig et al F&S 2002; 78:487
Glueck et al F&S 2000;74:394
Carrington, Rai, Regan 2005 (abs)

Hyperinsulinemia

Hyperinsulinemia associated with

- **Obesity**
- **High plasminogen activator inhibitor activity (PAI) = hypofibrinolysis**

Craig et al F&S 2002; 78:487
Glueck et al F&S 2000;74:394
Carrington, Rai, Regan 2005 (abs)

Hyperinsulinaemia and miscarriage

- Hyperinsulinaemia is a risk factor for EPL
- Associated impairement of fibrinolytic response during implantation
- Homozygosity for the 4G/4G polymorphism in the PAI1 gene promotor found more often in PCOS and rec misc

Craig et al F&S 2002; 78:487

Glueck et al F&S 2000;74:394

Carrington, Rai, Regan 2005 (abs)

Metformin therapy:

- **lower insulin**
- **E2**
- **T, FAI**
- **VEGF**

High androgens inversely related to [PP14]

Conclusions

- Women who have PCOS have higher rates of miscarriage than women with normal ovaries
- Obesity, hyperinsulinemia, high concentrations of LH, androgens and PAI-1 may all be involved
- Treatment to reduce weight, LH, insulin and androgen levels may improve the miscarriage rate

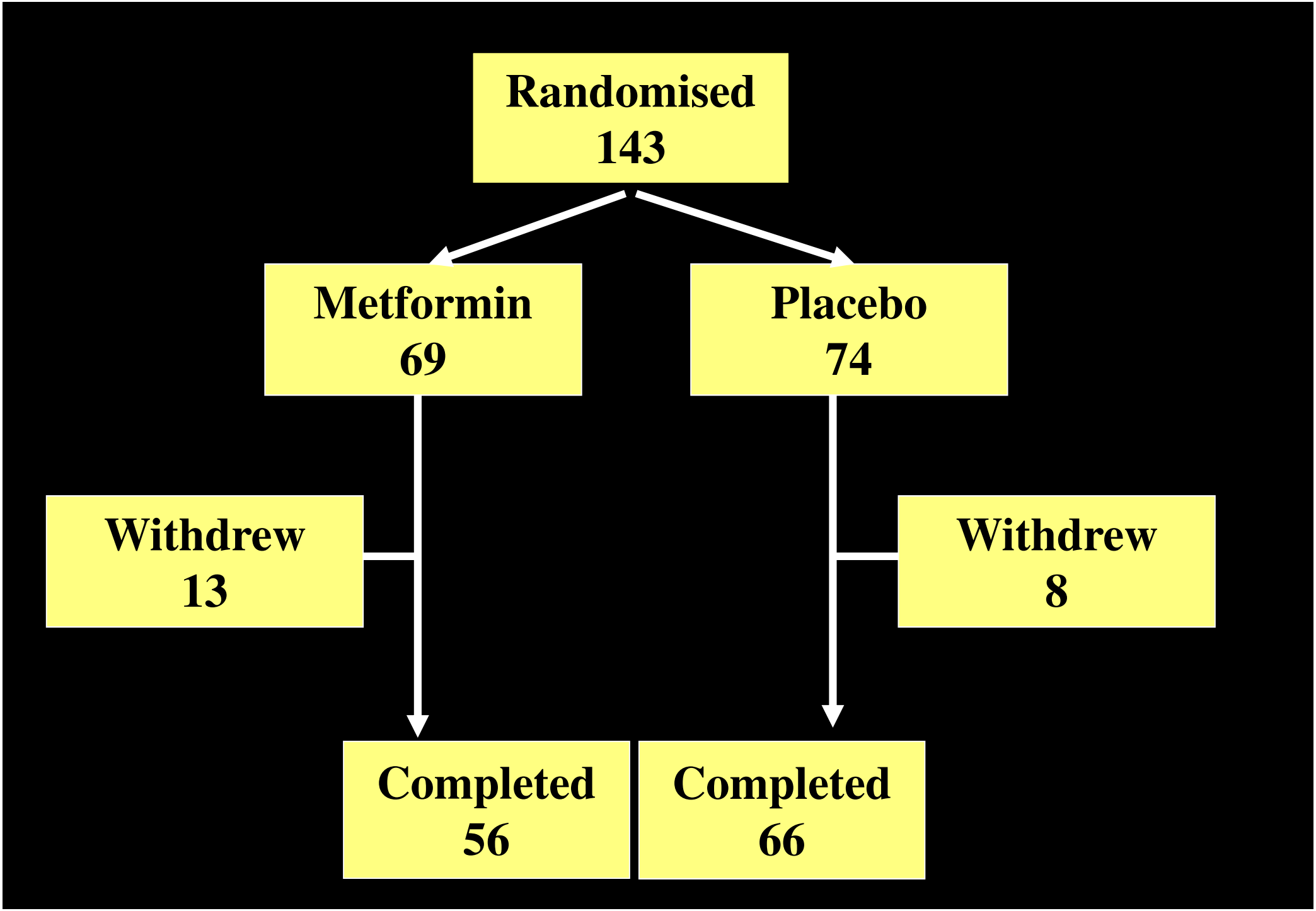
A multi-centre randomised, placebo-controlled , double-blind study, of combined life-style modification & metformin in obese patients with PCOS

- 8 centres U.K., co-ordinated by Leeds
- Placebo controlled, double blind RCT
- 6 months metformin 850mg b.d.
- 143 women randomised, with BMI > 30 kgm^{-2}

  mean BMI 38 kgm^{-2}

power 0.90 for significance 0.05, requires 55 per arm of study)

Tang et al, Human Reproduction 2006; 21: 80-89.


Randomised
143
Metformin
69
Placebo
74
Withdrew
13
Withdrew
8
Completed
56
Completed
66

Metformin vs Placebo

Significant increase in number of cycles,
and fall in BMI and waist circumference in both groups

No difference in ovulation rate between the groups

Improvements seen in those who lost weight in either group

Tang et al, Human Reproduction 2006; 21: 80-89.

A randomised double blind clinical trial comparing clomifene citrate plus metformin with clomifene citrate plus placebo in newly diagnosed PCOS

228 women with PCOS

Randomly allocated to receive either metformin 2000 mg/d or placebo for 1 month

Then clomifene citrate 50 up to 150 mg for 6 ovulations or until CC-resistance

BMI ~ 28 kg/m^2

Moll et al, BMJ; 332: 1485

Ovulation per dosage clomifene citrate

	CC + metformin	CC + placebo	P
CC 50mg	49/80 (61%)	50/92 (54%)	0.36
CC 100mg	27/44 (61%)	35/53 (66%)	0.63
CC 150mg	8/17 (47%)	13/23 (57%)	0.55

Moll et al BMJ 2006; 332: 1485

Ovulation, pregnancy and spontaneous abortion rates

	CC + metformin	CC + placebo	Relative Risk (95% CI)
	n=111	n=114	
Ovulation	71 (64%)	82 (72%)	0.89 (0.7 - 1.1)
Ongoing Pregnancy	44 (40%)	52 (46%)	0.87 (0.6 - 1.2)
Spontaneous Abortion	13 (12%)	12 (11%)	1.11 (0.5 - 2.3)

Moll et al BMJ 2006; 332: 1485

Discontinuation due to side effects:

16% versus 5% (95% CI 5 - 16%)

Moll et al BMJ 2006; 332: 1485

CC and/or metformin alone or in combination

626 anovulatory PCOS

Metformin vs Placebo 2000 mg / day

Clomiphene or Placebo 50 – 150 mg for 5d

6 cycles or 30 weeks

Mean BMI ~ 35 kg/m^2

Legro et al, NEJM 2007, 356:551

CC and/or metformin alone or in combination

	CC	M	CC + M
Conception /ovulation	**39.5%**	**8.4%**	**46.0%**
Miscarriage	**8.3%**	**20.8%**	**9.2%**
Live birth	**22.5%** (47/209)	**7.2%** (15/208)	**26.8%** (56/209)

CC superior to metformin and combination confers no advantage in achieving live birth

Legro et al, NEJM 2007, 356:551

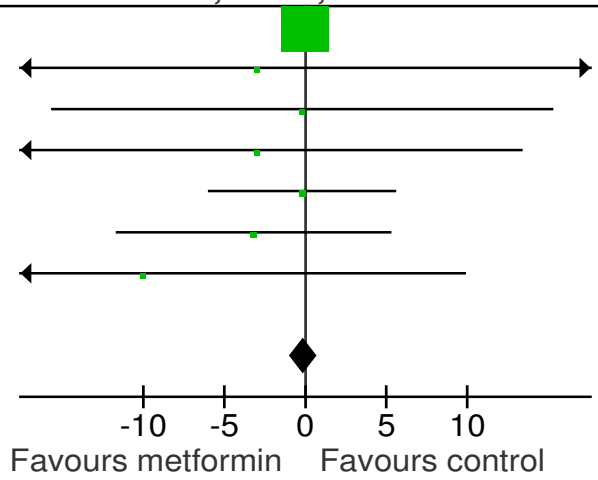
Revised Cochrane Meta-analysis

Metformin vs placebo or no treatment: Body weight

	Metformin			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Baillargeon 2004	61.4	1.6	28	61.4	1.6	30	96.3%	0.00 [-0.82, 0.82]
Kelly 2002	91	24	10	94	31	10	0.1%	-3.00 [-27.30, 21.30]
Lord 2006	94.7	27.1	16	94.9	15.5	15	0.3%	-0.20 [-15.62, 15.22]
Pasquali 2000	94	17	10	97	18	8	0.2%	-3.00 [-19.33, 13.33]
Tang 2006	99	15	56	99.2	17.3	66	2.0%	-0.20 [-5.93, 5.53]
Trolle2007	92.9	19	42	96.1	21.1	45	0.9%	-3.20 [-11.63, 5.23]
Vandermolen 2001	96.9	26.53	11	106.9	23.2	14	0.2%	-10.00 [-29.84, 9.84]
Total (95% CI)			**173**			**188**	**100.0%**	**-0.06 [-0.87, 0.75]**

Heterogeneity: Chi² = 1.70, df = 6 (P = 0.94); I² = 0%

Test for overall effect: Z = 0.15 (P = 0.88)



OR -0.06 95% CI -0.87, 0.75

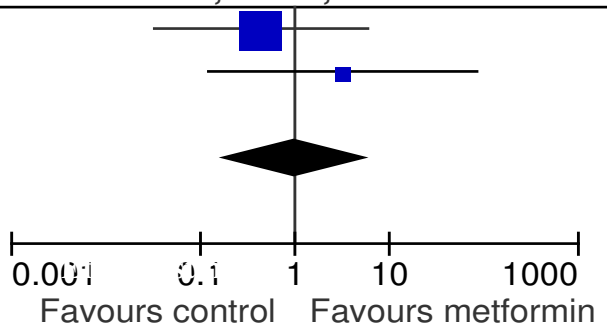
Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH.
sulin-sensitising drugs Cochrane Database of Systematic Reviews 2009 , Issue 3 .
Art. No.: CD003053. DOI:10.1002/14651858.CD003053.pub2 .

Metformin versus placebo or no treatment: Live birth rate

Study or Subgroup	Metformin Events	Metformin Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ng 2001	1	9	2	9	79.6%	0.44 [0.03, 5.93]
Yarali 2002	1	16	0	16	20.4%	3.19 [0.12, 84.43]
Total (95% CI)		**25**		**25**	**100.0%**	**1.00 [0.16, 6.39]**
Total events	2		2			

Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%

Test for overall effect: Z = 0.00 (P = 1.00)



Live birth rate: OR 1.00 95% CI 0.16, 6.39

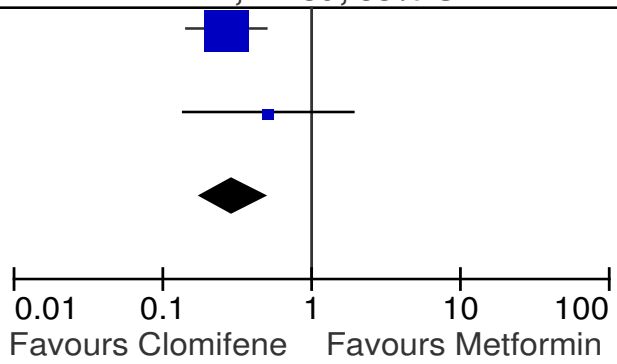
Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH.
sulin-sensitising drugs Cochrane Database of Systematic Reviews 2009 , Issue 3 .
Art. No.: CD003053. DOI:10.1002/14651858.CD003053.pub2 .

Metformin versus Clomiphene Citrate: Live birth Rate

Study or Subgroup	Metformin Events	Metformin Total	Clomifene Events	Clomifene Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Legro 2007	15	208	47	209	87.2%	0.27 [0.14, 0.50]
Palomba 2005	26	50	9	50	0.0%	4.94 [1.99, 12.26]
Zain 2008	4	42	7	41	12.8%	0.51 [0.14, 1.90]
Total (95% CI)		**300**		**300**	**100.0%**	**0.30 [0.17, 0.52]**
Total events	45		63			

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%

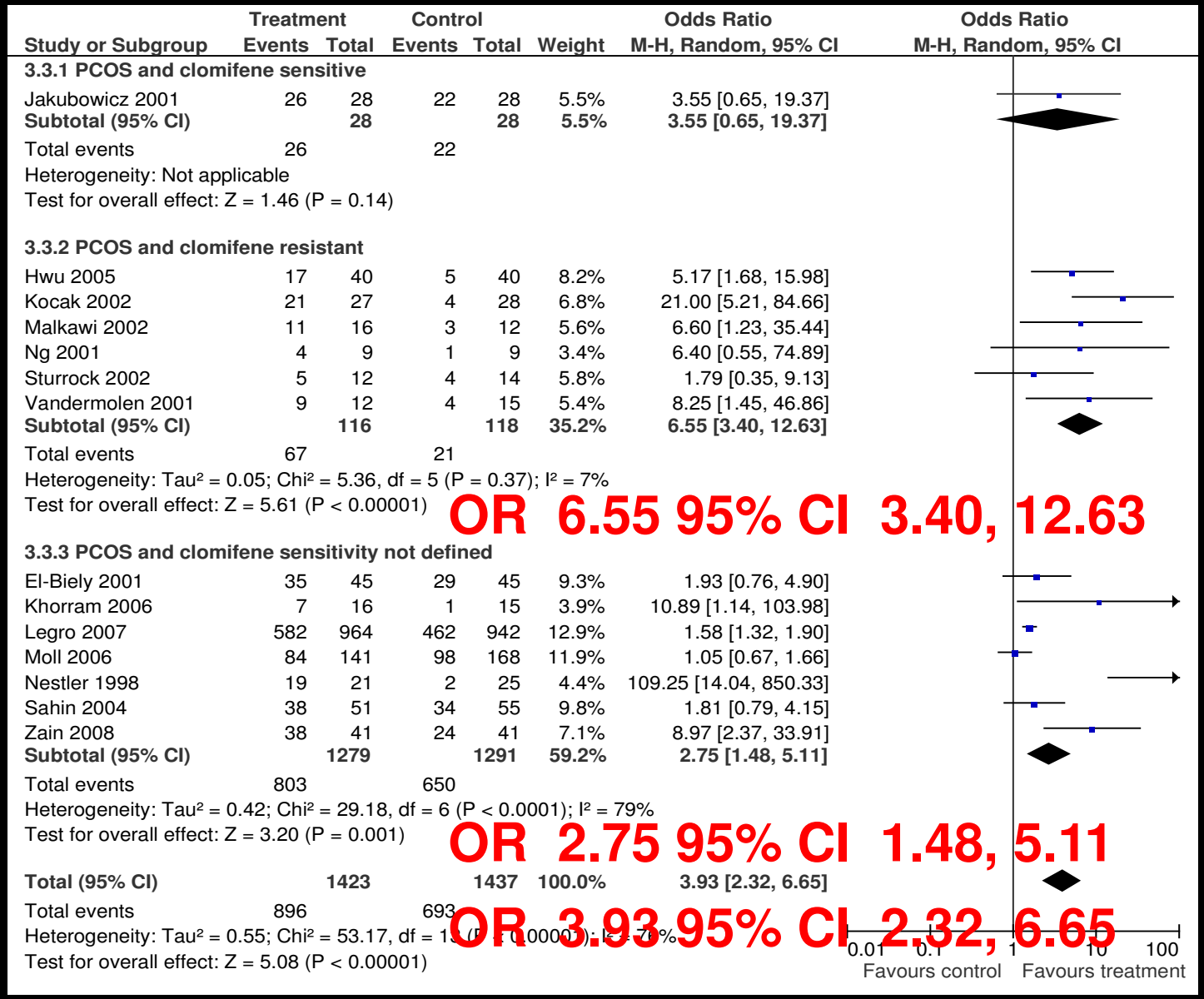
Test for overall effect: Z = 4.25 (P < 0.0001)



OR 0.30 95% CI 0.17, 0.52

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH.
sulin-sensitising drugs Cochrane Database of Systematic Reviews 2009 , Issue 3 .
Art. No.: CD003053. DOI:10.1002/14651858.CD003053.pub2 .

Metformin plus ovulation induction agent vs ovulation induction agent alone: Ovulation Rate



CC resistant — OR 6.55 95% CI 3.40, 12.63

CC sensitive — OR 2.75 95% CI 1.48, 5.11

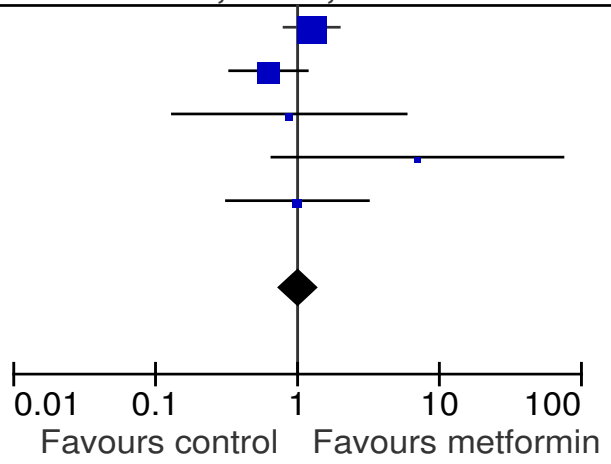
All — OR 3.93 95% CI 2.32, 6.65

Metformin plus ovulation induction agent vs ovulation induction agent alone: Live Birth Rate

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Legro 2007	56	209	47	209	50.7%	1.26 [0.81, 1.97]
Moll 2006	21	111	31	114	36.5%	0.62 [0.33, 1.17]
Sahin 2004	3	11	3	10	3.4%	0.88 [0.13, 5.82]
Vandermolen 2001	4	12	1	15	0.9%	7.00 [0.66, 73.93]
Zain 2008	7	41	7	41	8.6%	1.00 [0.32, 3.16]
Total (95% CI)		**384**		**389**	**100.0%**	**1.04 [0.75, 1.46]**
Total events	91		89			

Heterogeneity: Chi² = 5.79, df = 4 (P = 0.22); I² = 31%

Test for overall effect: Z = 0.25 (P = 0.80)



OR 1.04 95% CI 0.75, 1.46

Tang T, Lord JM, Norman RJ, Yasmin E, Balen AH.
sulin-sensitising drugs Cochrane Database of Systematic Reviews 2009 , Issue 3 .
Art. No.: CD003053. DOI:10.1002/14651858.CD003053.pub2 .

Cochrane Update: PCOS and Metformon

- There is no evidence that metformin improves live birth rates whether it is used alone (Pooled OR = 1.00, 95% CI 0.16 to 6.39) or in combination with clomiphene (Pooled OR = 1.48, 95% CI 1.12 to 1.95).
- However, clinical pregnancy rates are improved for metformin versus placebo (Pooled OR = OR 3.86, 95% C.I. 2.18 to 6.84) and for metformin and clomiphene versus clomiphene alone (Pooled OR =1.48, 95% C.I. 1.12 to 1.95)).

Tang et al, Cochrane Database, Jan 10, 2010

Insulin sensitising agents in PCOS: ESHRE/ASRM Consensus, 2007

- No clear role of metformin in management anovulatory infertility either alone or in combination
- No evidence of improvement in pregnancy outcome

Human Reproduction 2008; 23:462
Fertility & Sterility 2008; 89: 505

RCOG Scientific Advisory Committee Guideline, 2008

1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - mechanisms
   - polycystic ovary syndrome
   - miscarriage

3. Weight loss

4. Limits for treatment

Components of a healthy diet

National Audit Office Report.
Tackling Obesity in England. Reprinted with permission from the Foods Standards Agency. February 2001

Weight management in PCOS

Energy restriction lowers insulin

↑ IGFBP- 1 ∴ IGF-1 ↓

Androgen synthesis down-regulated

Kiddy et al 1992; Poretsky et al 1999

Weight management in PCOS

Abdominal (truncal) fat loss most significant in PCOS

A loss of weight of 5 - 10% → 30% reduction in visceral fat

↓ hyperandrogenism and hyperinsulinaemia
and restore reproductive function even if BMI still > 30 kg/m^2

↑ spontaneous ovulation
↑ response to ovulation induction
↓ miscarriage rate

Clark et al H. Rep 1995 10:2705 & 1998
Moran & Norman 2004
Holte et al JCEM 1995 80:2586

Weight loss and exercise

BMI > 30, > 2y anovulatory infertility, CC resistance

13/18 completed 6 month study:

- weight loss → improved endocrinology
- all ovulated
- 11 conceived (5 naturally)

Clark et al H. Rep 1995 10:2705

Weight loss in PCOS vs non-PCOS women

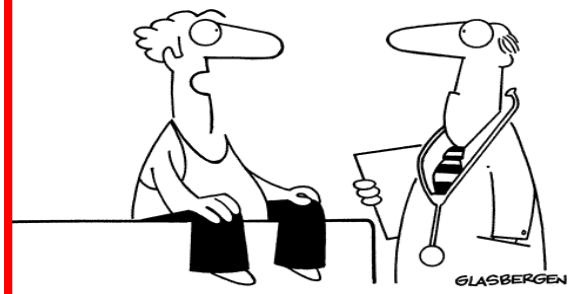
Women with PCOS may have reduced BMR and disturbed eating patterns

But no differences in weight loss in women with PCOS or normal ovaries following isocaloric 5000-6000 kj/day diets

for 2-7 months

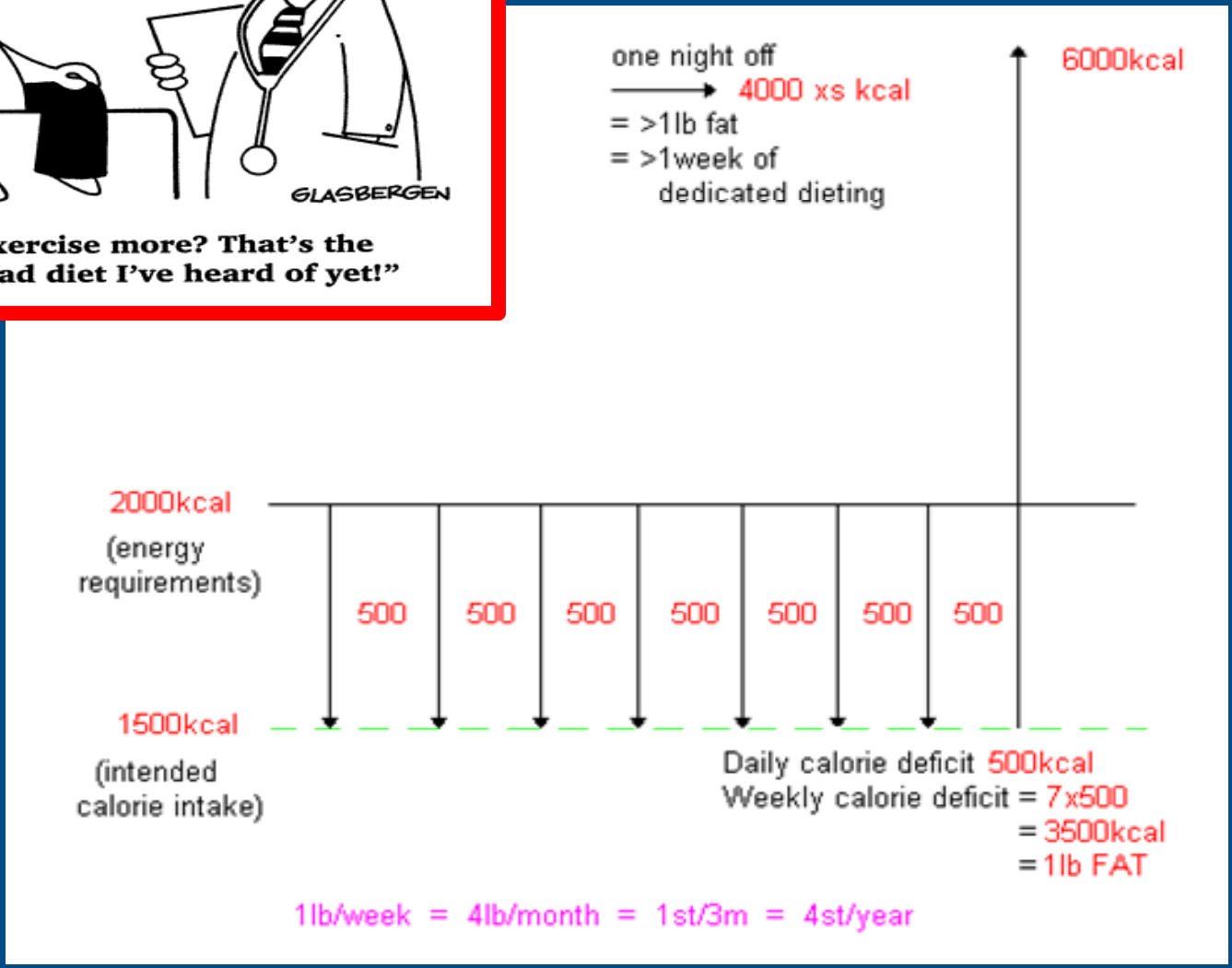
Jakubowitz & Nestler JCEM 1997; 82:556

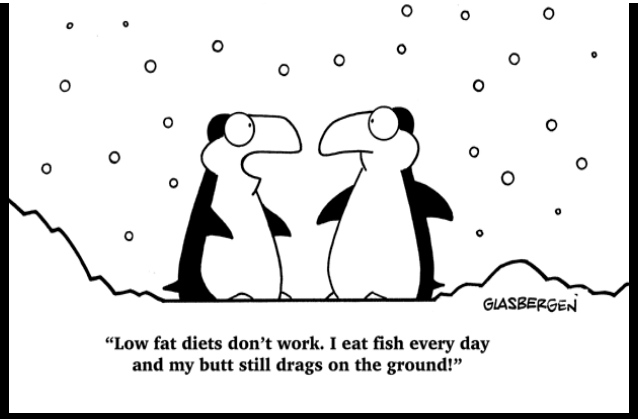
Pasquali et al JCEM 2000; 85:2767



"Eat less and exercise more? That's the most ridiculous fad diet I've heard of yet!"


Copyright 2002 by Randy Glasbergen. www.glasbergen.com
GLASBERGEN
"Eat less and exercise more? That's the most ridiculous fad diet I've heard of yet!"


one night off
4000 xs kcal
= >1lb fat
= >1week of dedicated dieting
6000kcal
2000kcal
(energy requirements)
500
500
500
500
500
500
500
1500kcal
(intended calorie intake)
Daily calorie deficit 500kcal
Weekly calorie deficit = 7x500
= 3500kcal
= 1lb FAT
1lb/week = 4lb/month = 1st/3m = 4st/year

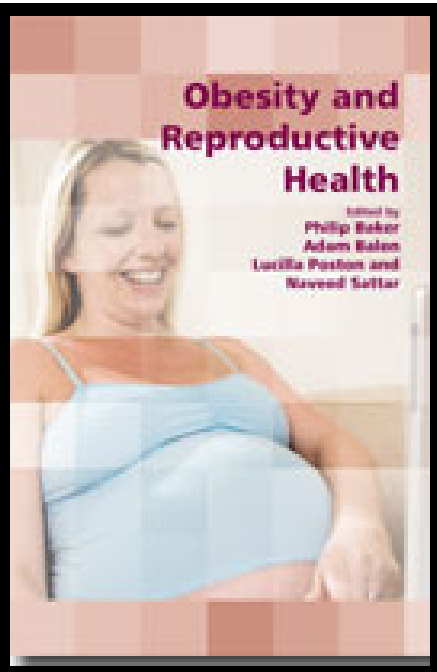


Types of Diet

	Fat	CHO	Protein	Alcohol	
Average	34	49	14	3	% kJ
Low-fat, high-CHO, low-protein	30	55	15	-	% kJ
Very-low-fat, very high-CHO	15	70	15	-	% kJ
Moderate-CHO, moderate-protein	30	40	30	-	% kJ
Moderate-protein, very-low-CHO	55	15	30	-	% kJ

Increasing dietary protein and reducing glycaemic index may be of benefit but still requires more evidence w.r.t. reproductive function

Weight Reduction: RCOG Guidelines, 2007



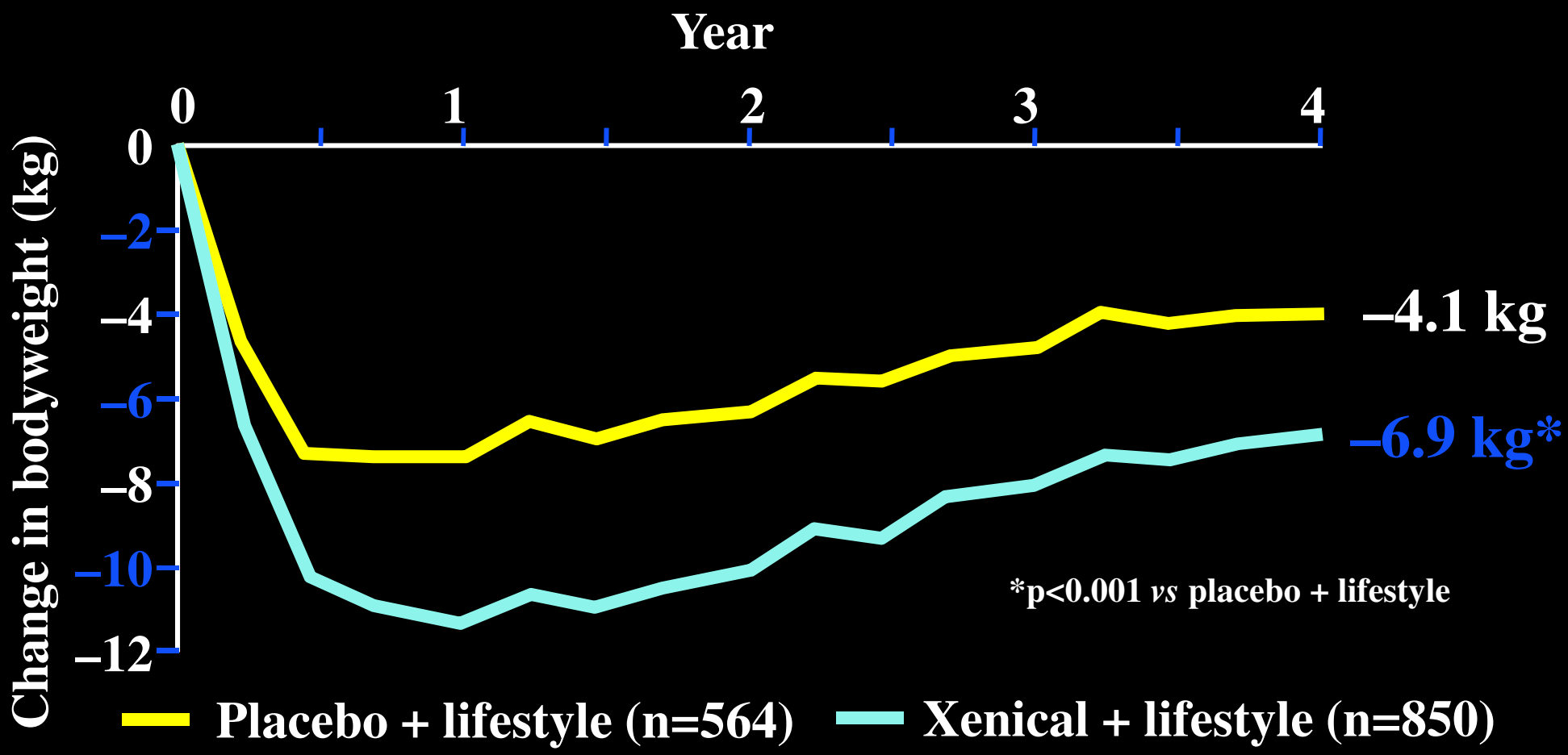
No evidence for one type of diet

Strategies may include pharmacotherapy (e.g. Orlistat)

Bariatric surgery

Avoid pregnancy during rapid weight loss

XENDOS: Xenical compared with placebo



Adapted from Torgerson JS et al. Diabetes Care 2004; 27: 155–161

Royal College of Obstetricians and Gynaecologists

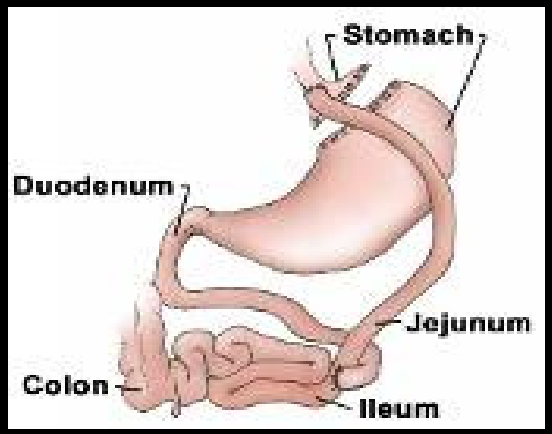
Setting standards to improve women's health

Scientific Advisory Committee
Opinion Paper 17
October 2009

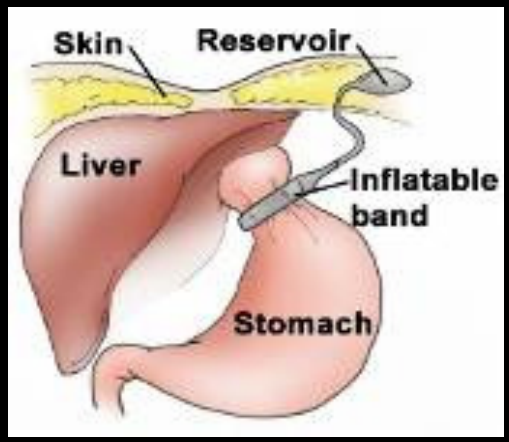
The role of bariatric surgery in the management of female fertility

Sam Scholtz, Carel Le Roux, Adam Balen

Roux-en-Y Gastric Bypass

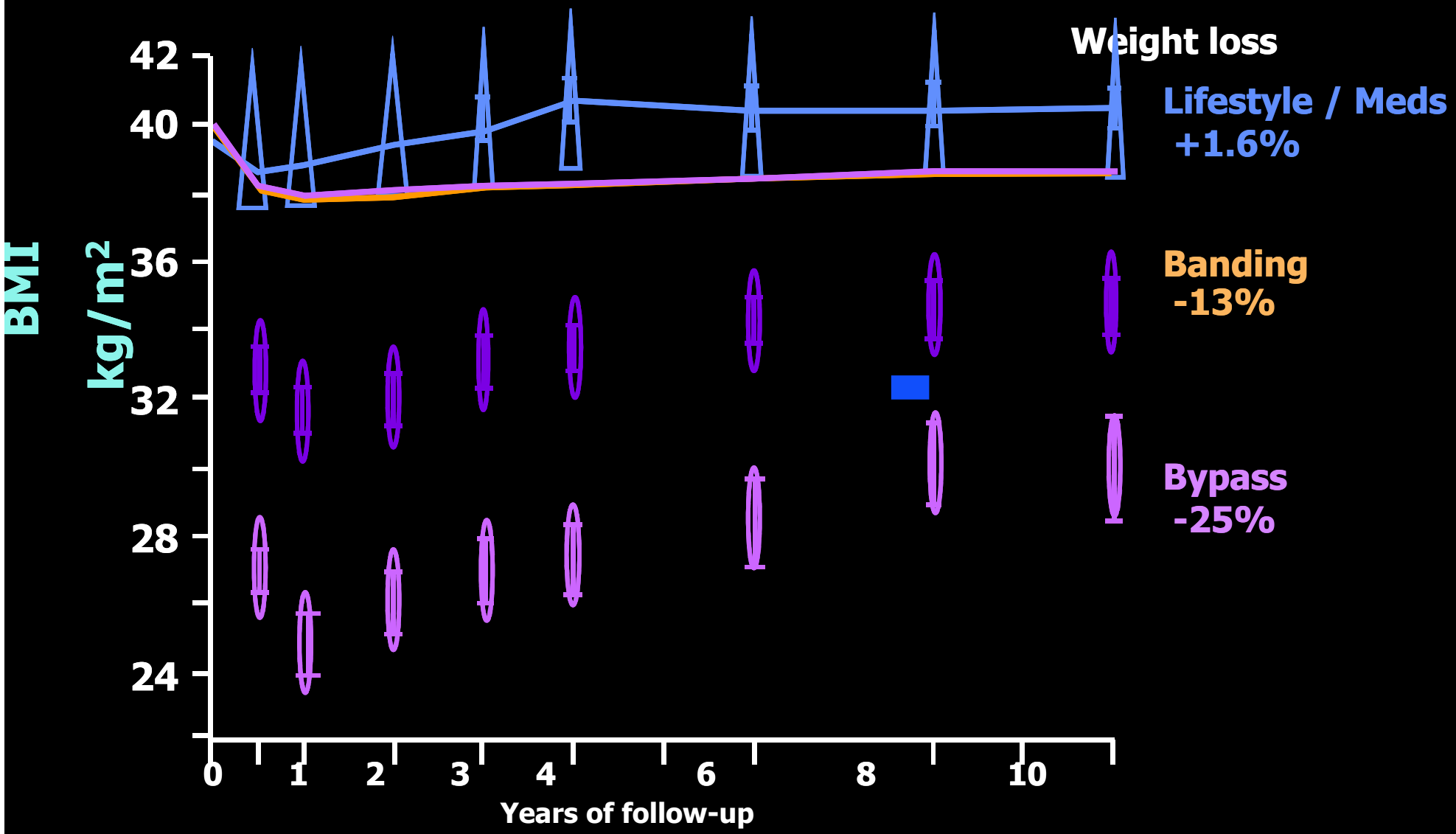


Gastric Banding



Avoid pregnancy during rapid weight loss

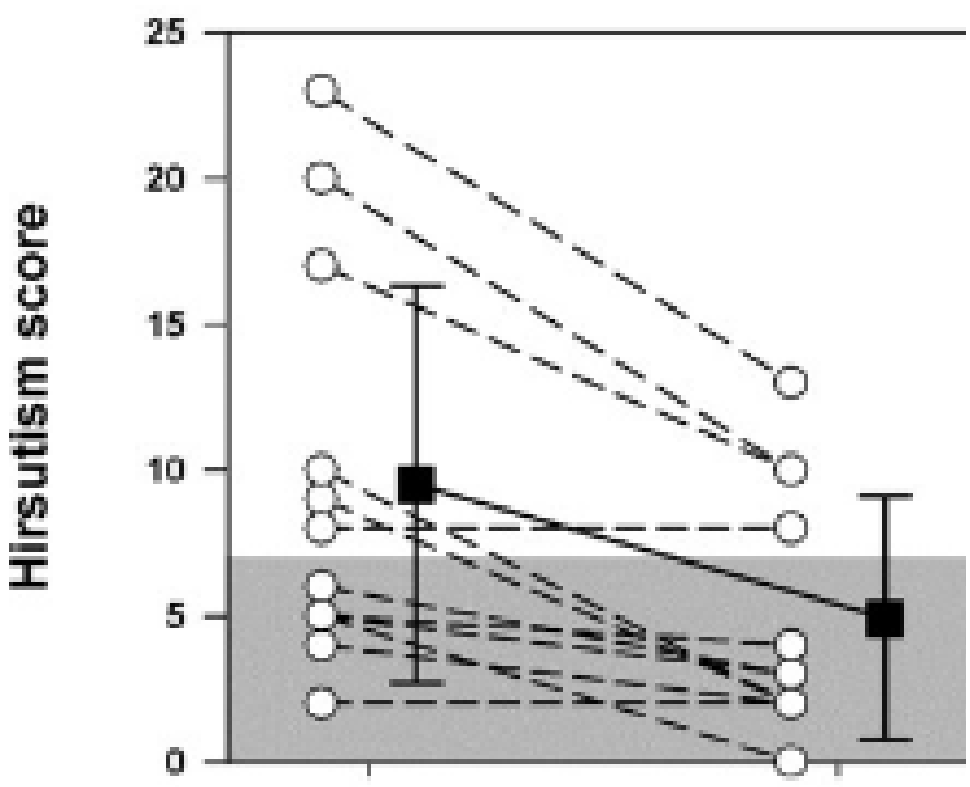
Long term weight loss maintenance

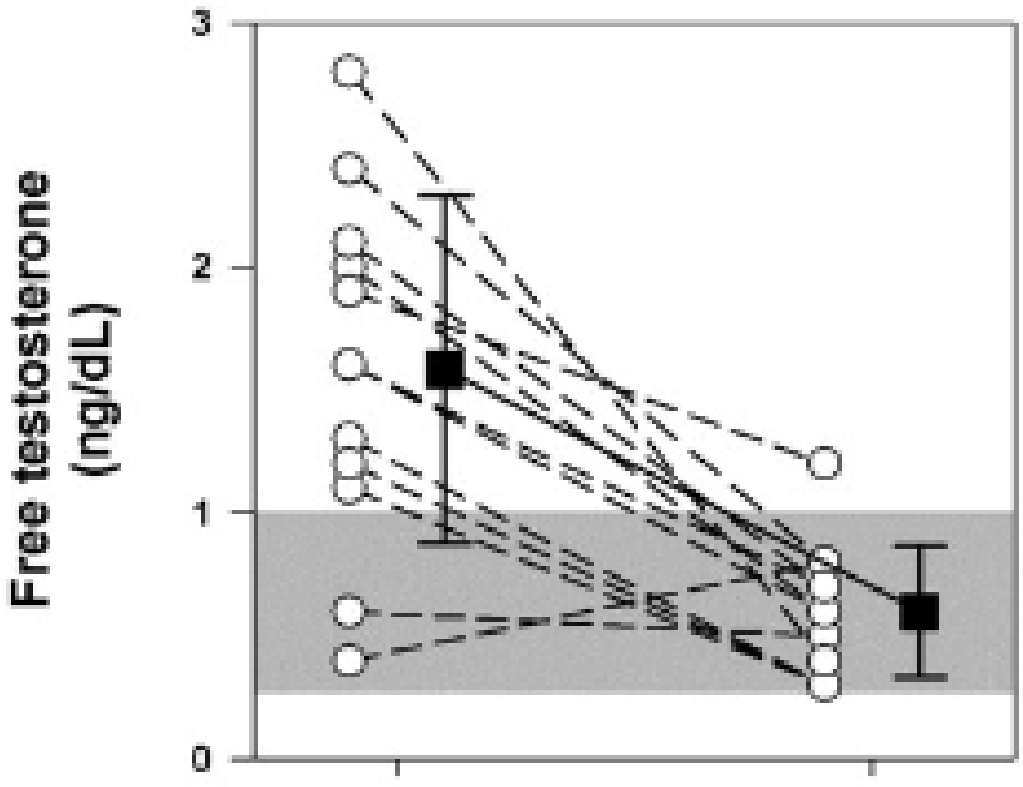


Sjöström, L. et al. N Engl J Med 2004

Obesity surgery and PCOS

- 12 patients: 100% resolution of menstrual abnormalities
- Normalisation of sex hormones and SHBG
- Significant improvements in hirsutism





Moreale et al, JCEM 2005

Pregnancy post obesity surgery

- Timing of conception controversial
- Less preeclampsia, GDM and macrosomia
- ? Fetal programming
- Higher rate of IUGR and C sections
- Low threshold for imaging / surgical exploration if maternal complications suspected
- Clinical trial needed for consensus (“*Bambini” RCT*)

Beard JH et al, Obes Surg. 2008 Aug;18(8):1023-7.
Guelinckx I et al, Hum Reprod Update. 2009 Mar-Apr;15(2):189-201.
Maggard MA et al, JAMA . 2008 Nov, 300(19)2286-96

1. Obesity – the modern epidemic

2. Obesity and reproduction
   - infertility / outcome of treatments
   - mechanisms
   - polycystic ovary syndrome
   - miscarriage

3. Weight loss

4. Limits for treatment

Obesity and Reproduction

- Should there be a cut-off?
- Is it possible to define a cut-off?
  Should this be based on BMI, waist circ, metabolic measurements, other “health parameters”?
- Should there be a different cut-off for different procedures/treatments?
- Should a defined cut-off come into play when placed on waiting list or should a patient not be allowed onto a list until weight has reduced?
- How absolute can we be?

BFS Guidelines, 2007

"Treatment should be deferred until BMI < 35 kg/m^2 although in those with more time (under 37y, normal ovarian reserve) a weight reduction to < 30 kg/m^2 is preferable"

Balen & Anderson, Human Fertility 2007; 10: 195-206

Conversion rates over time

67 obese PCOS,

mean age 32.5y & BMI 28.7 kg/m^2

Followed up with 75g GTT, mean time 6.2y

At start: 54 normal, 13 Impaired Glucose Tolerance

Normoglycaemic:	**9% IGT**	**8% Type 2 DM**
IGT:	**15% normal**	**54% Type 2 DM**

Relative risk of converting: If BMI < 25		**1**
	25-30	**7.1 (3.3-11.0)**
	> 30	**10.2 (3.9-16.5)**

Norman et al, Hum Reprod 2001; 16: 1995

Increased weight gain in women with PCOS

17,200 calories per annum ≡ 1.9 kg of fat
excess in PCOS versus normal

Increased weight and insulin resistance:

↓ SHBG
↑ androgens
anovulation
Gestational DM
Type 2 DM
Cardiovascular disease

Franks, 2006

PCOS and hyperinsulinaemia

30-50% Obese PCOS develop IGT or Type 2 DM by 30y

82% premenopausal women with Type 2 DM have PCO

- **52% of these had PCOS**
- **no difference in metabolic profile in those with or without symptoms**

Conn et al, Clin Endo 2000; 52: 81

Ethnicity and insulin resistance in PCOS

Comparison between Caribbean-Hispanic PCOS and non-Hispanic PCOS with controls

C-H had similar androgens but ↑ insulin resistance

Insulin resistance genetically transmitted, with ↑ prevalence in Pima Indians and Mexican Americans

Dunaif et al, Diabetes, 1993; 42: 1462

- **Ovulatory C-H women had normal reproductive function, despite same degree of insulin resistance as white PCOS women**

- **Susceptibility factors for PCOS extend beyond presence of insulin resistance**

Dunaif et al, Diabetes, 1993; 42: 1462

Insulin response to glucose load higher in Asian Indian women with PCOS than Caucasian PCOS

Norman et al, F & S 1995; 63:58