Obesity and PCOS

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Disclosures

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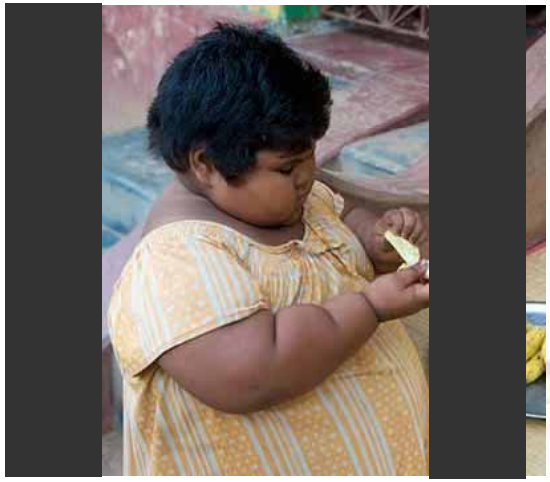
Outline of talk

- Nutrition, obesity and reproduction
- Obesity and the egg
- The effect of obesity on PCOS
- The effect of PCOS on obesity
- Intervention strategies in PCOS and obesity

Nutrition and reproduction

An appropriate diet and fat stores are essential for healthy reproduction



Obesity and reproduction – bad synergies

Prior to pregnancy

Increases length of time to pregnancy, menstrual disorders, more drugs needed

Early pregnancy

Miscarriage, fetal anomalies

During pregnancy

Increased gestational diabetes, high blood pressure, PET, DVT, instrumental and operative delivery

Postpartum

Haemorrhage, infection, DVT

After pregnancy

Increases diabetes mellitus, high blood pressure, endometrial cancer, cardiovascular disease, musculoskeletal problems

Obesity may lead to infertility

Abundant evidence for infertility in overweight women on natural cycles regardless of menstrual regularity:

Green et al 1988, Zaadstra et al 1993, Rich-Edwards et al 1994, Lake et al 1997, Bolumar et al 2000, Hassan and Killick 2004, Gessink Law et al 2007

Evidence for reduced success of ovulation induction and ART in overweight women:

Wang et al 2000, Bellver et al 2003, Legro et al 2007

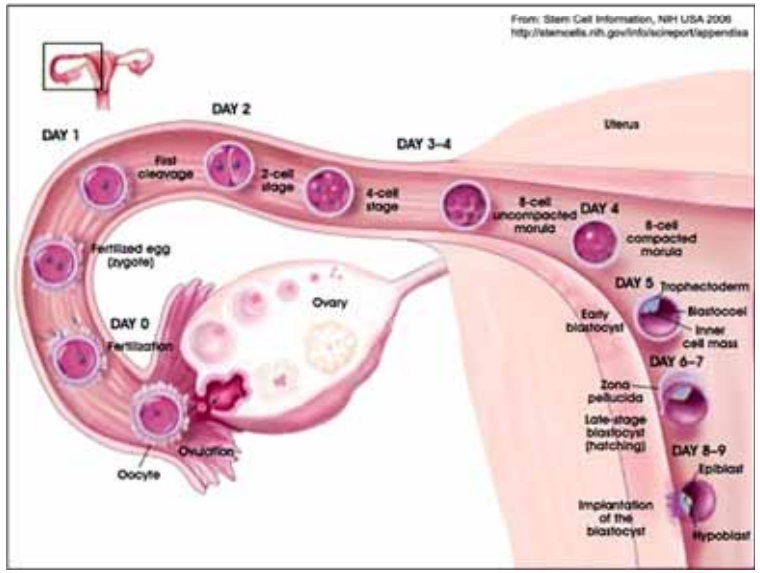
Evidence for increased success in reproductive outcomes in overweight women with lifestyle intervention:

UK (Franks), Italy (Pasquali), Australia (Norman), USA (Hoeger, Legro)

Overweight and infertility

Extra- gonadal effects eg
hyperinsulinaemia, male factor issues

Ovarian and oocyte development impairment



Uterine endometrial impairment

Sexual intercourse impaired by high
BMI in woman or partner

Intercourse frequency same in RM PPCOS trial Fertility and Sterility 2009

Effect of uterus vs egg on pregnancy

Egg donation program

- 2656 egg donor cycles
- All donors had normal BMIs
- Recipients had different BMIs
- Allows comparison of egg vs uterine contribution
- Appears as if there is also an effect of the uterus

Pregnancy rates

Pregnancy and live birth rates reduced according to BMI of recipient

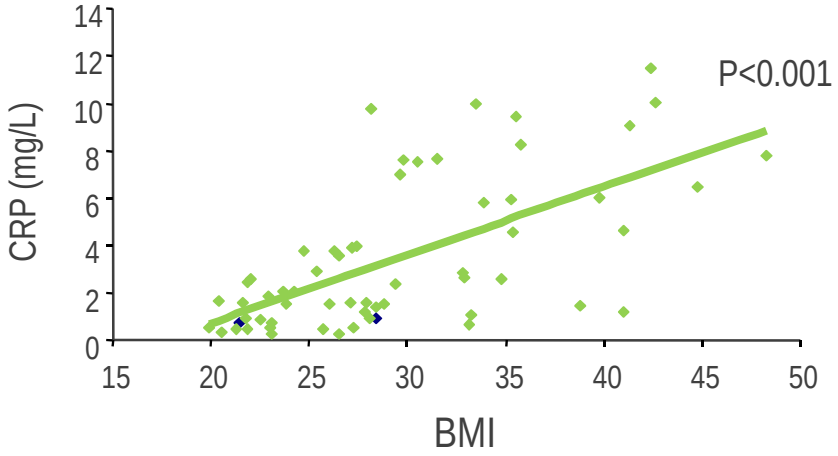
BMI	Ongoing pregnancy (%)
<20	45
20-25	45
25-29	37
>30	35

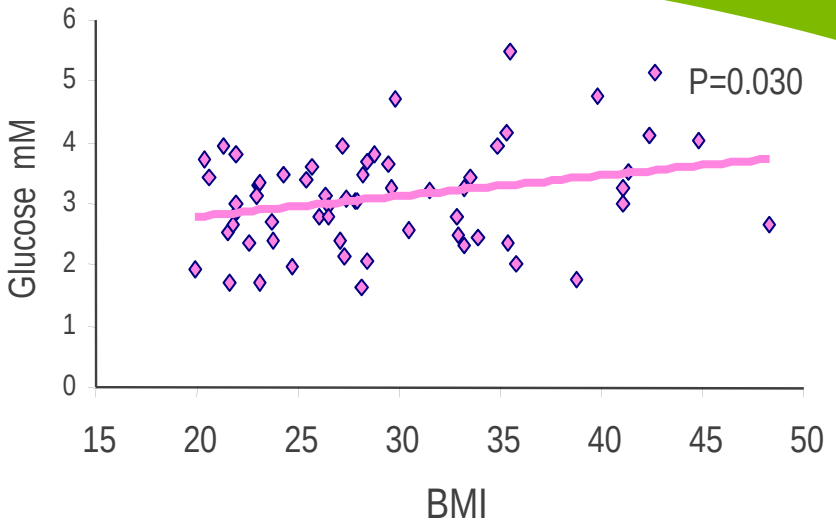
Bellver et al 2007

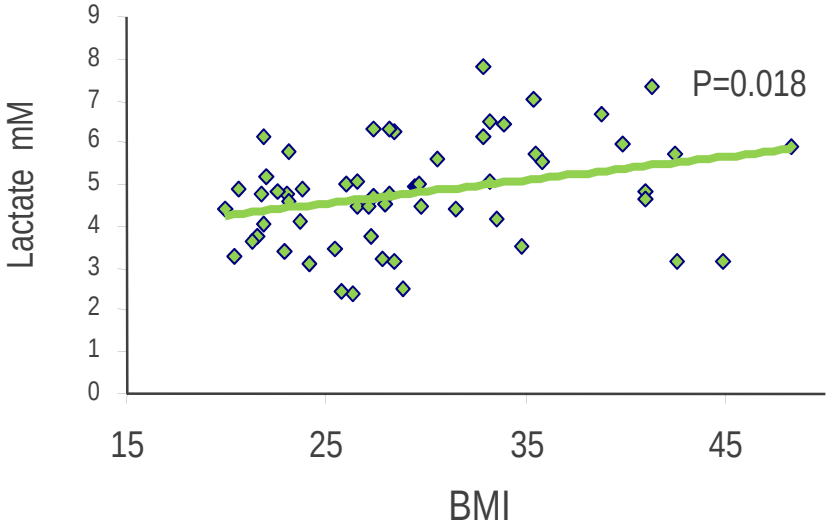
Influence of insulin on obesity effects

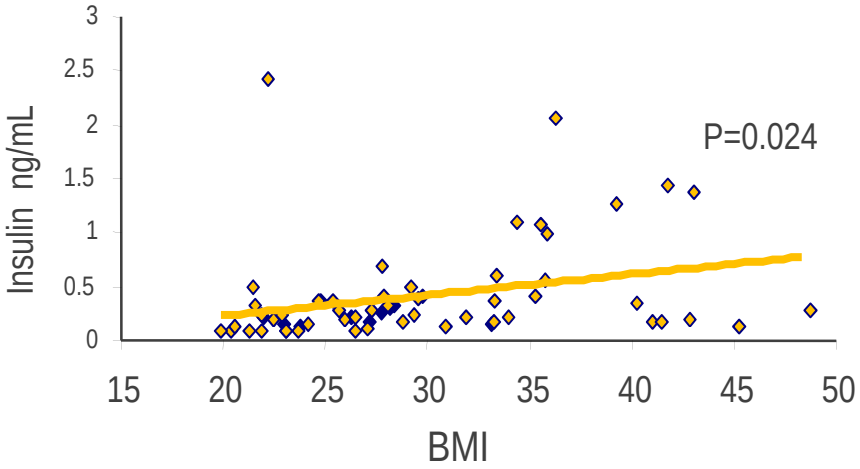
- Diet and exercise programs reducing weight by >5% lead to restoration of menstrual cycles and fertility *(Kiddy et al, Clark et al, Moran et al, Pasquali et al)*
- Caloric restriction more important than dietary composition *(Moran et al)*
- Insulin sensitisers eg metformin or PPAR agonists restore menstrual cycles and fertility despite weight *(Nestler et al, Legro et al, Azziz et al, Norman et al, Zain et al)*
- Associated with improved insulin sensitivity and altered body composition *(Robinson et al, Huber-Bucholz et al, Pasquali et al)*

Follicular fluid analytes



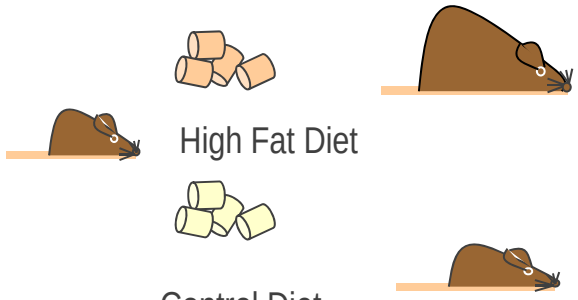






Obesity and fertility in mice

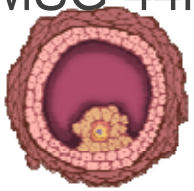
4 weeks



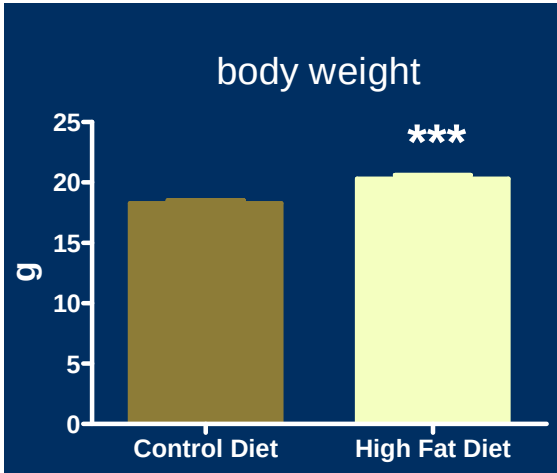
High Fat Diet

Control Diet

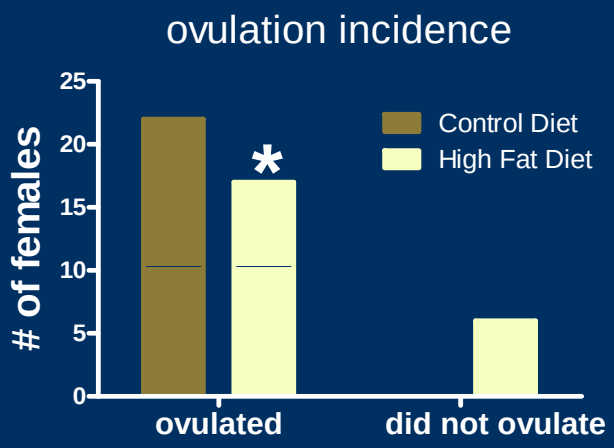
PMSG 44h → hCG 13h → Mated



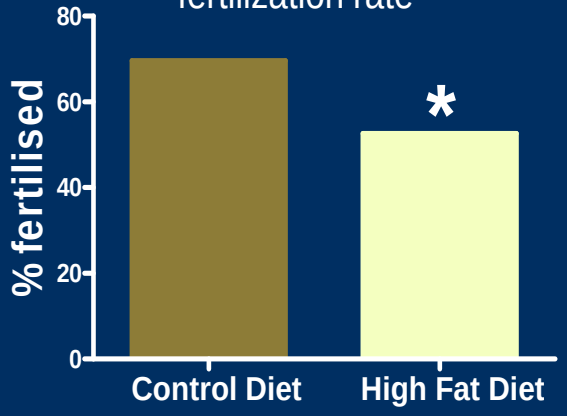
GCs COCs COCs



T test. (means± SEM, n=10)
* * * P<0.0001

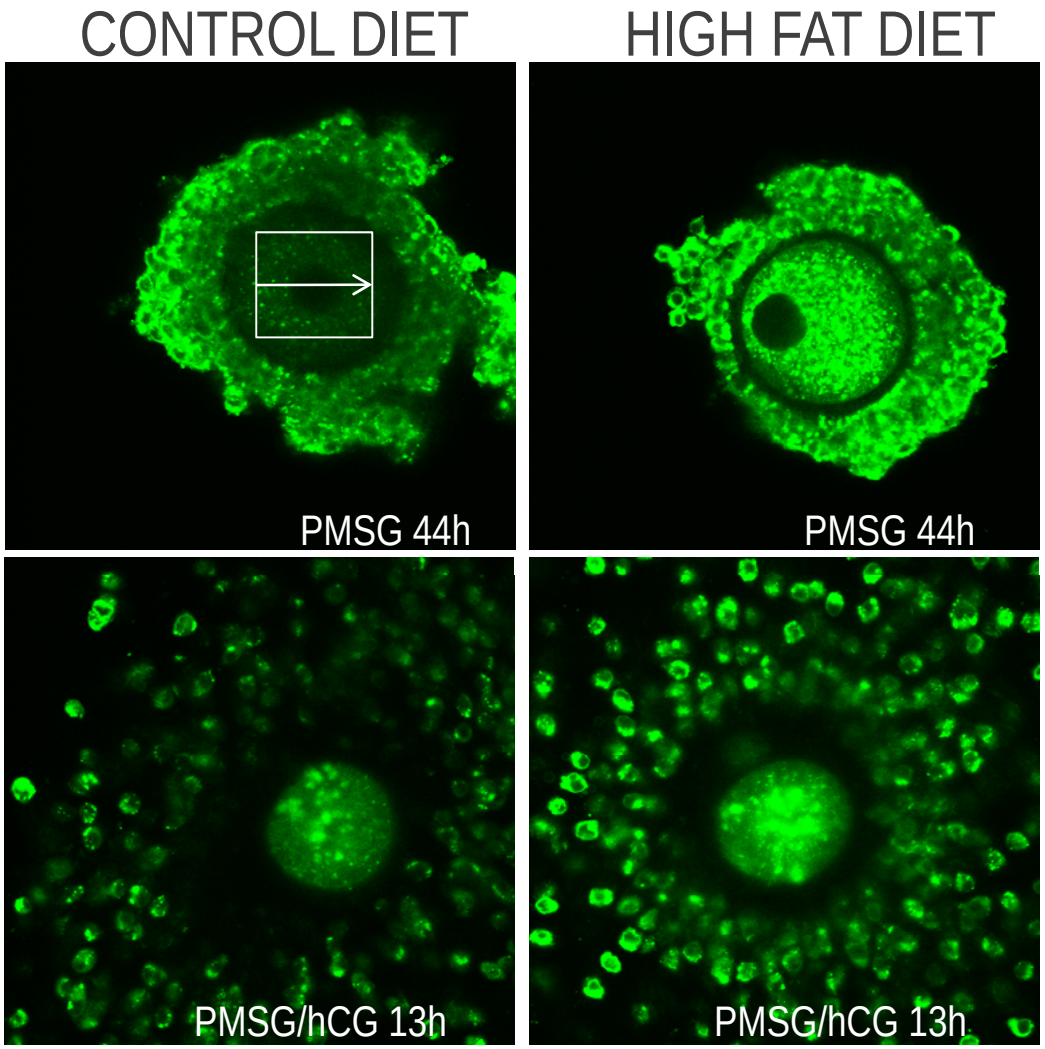


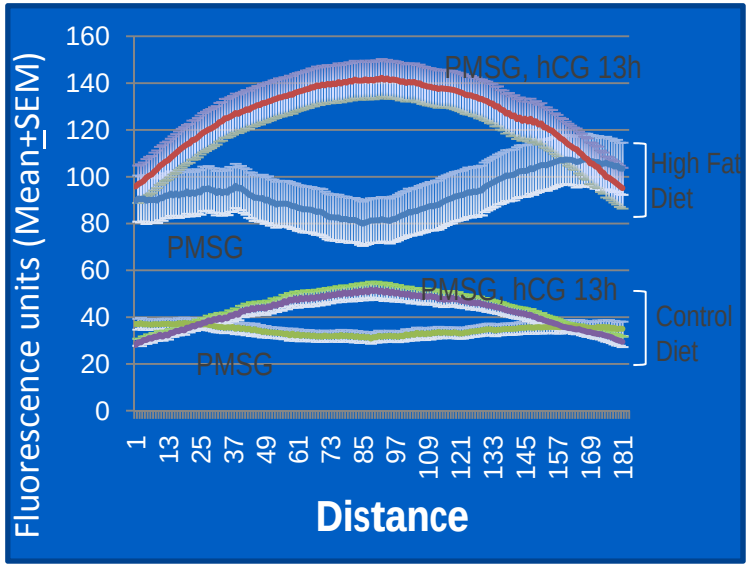
* P<0.05; Fisher's Exact Test.

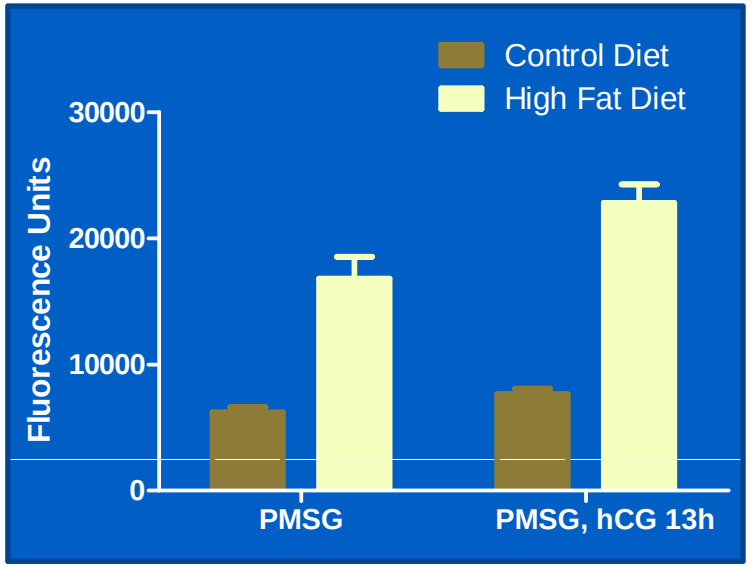


Robker et al 2010

Mouse COC lipid localization







Xing Yang

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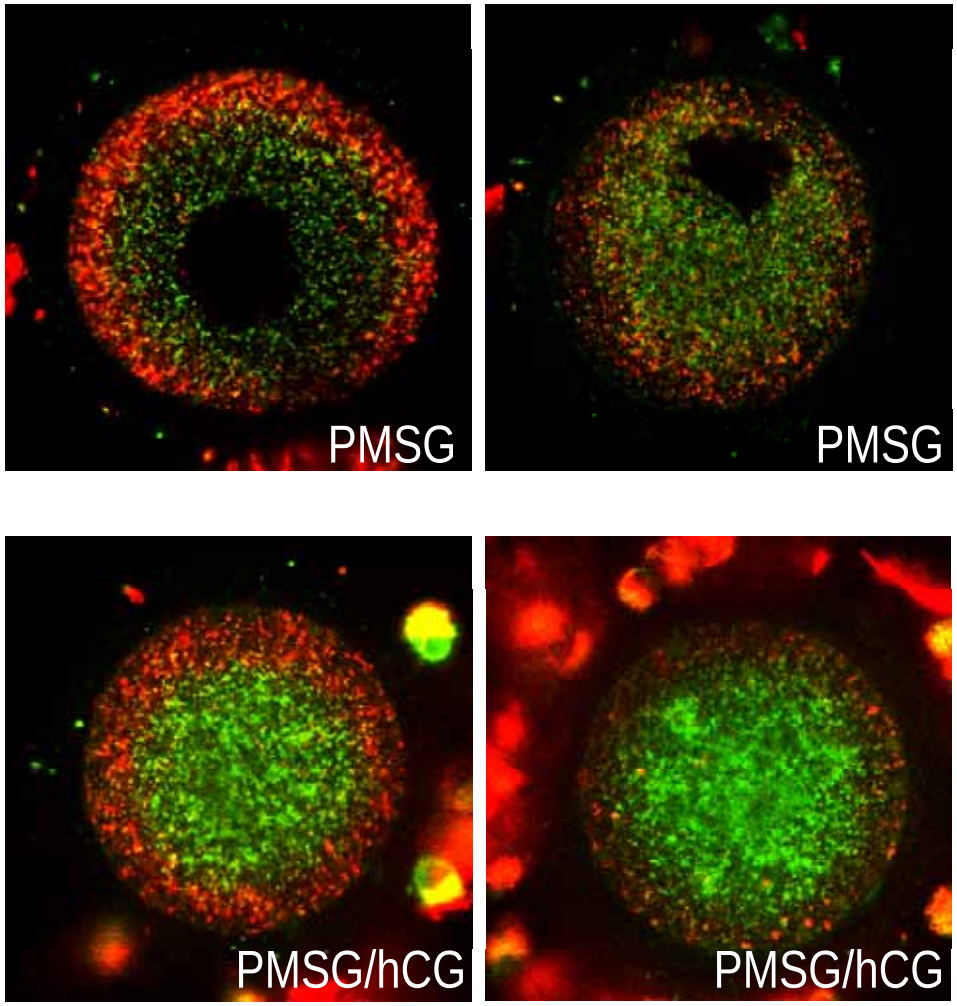
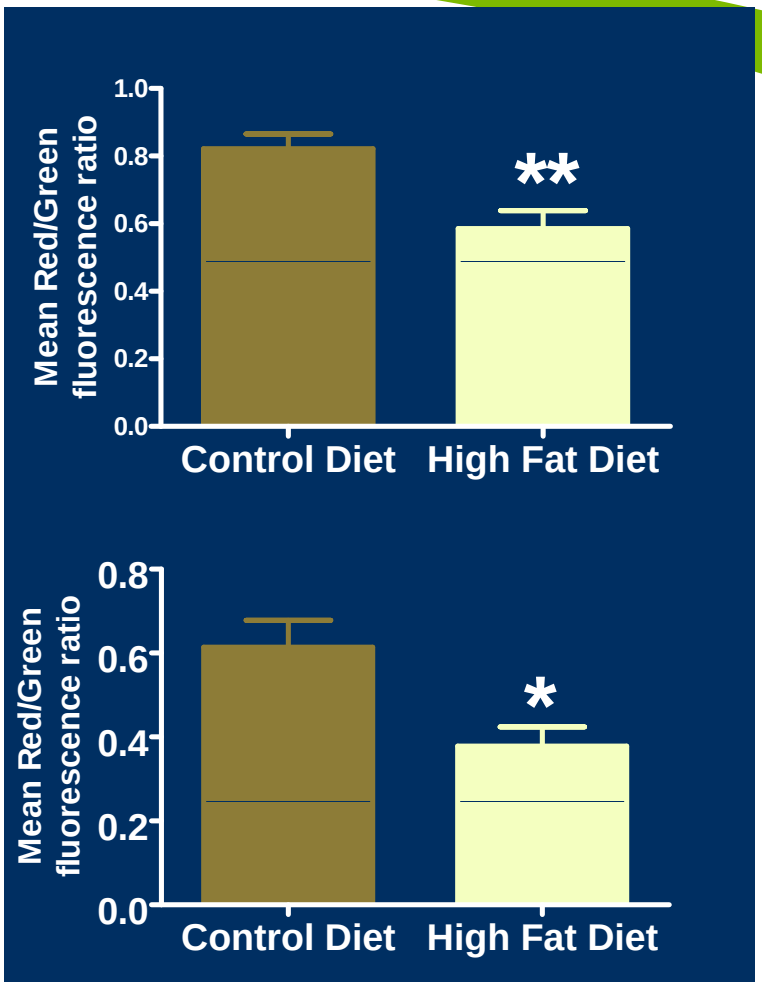
Oocyte Mitochondrial Membrane Potential

CONTROL DIET HIGH FAT DIET





Linda Wu

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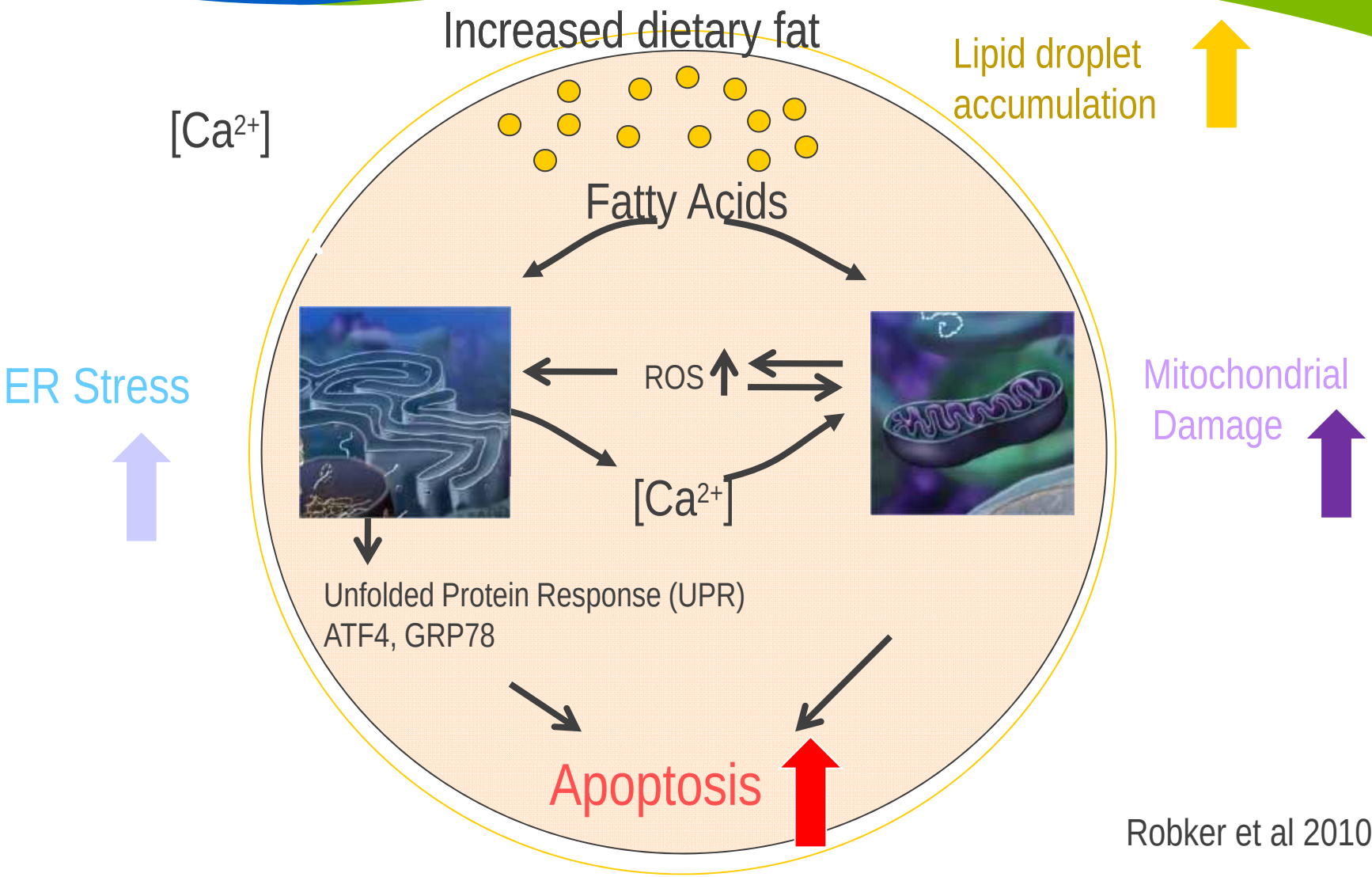
T test. (means± SEM, n=30) **P<0.001, *P<0.05

Lipotoxicity in response to high fat diet



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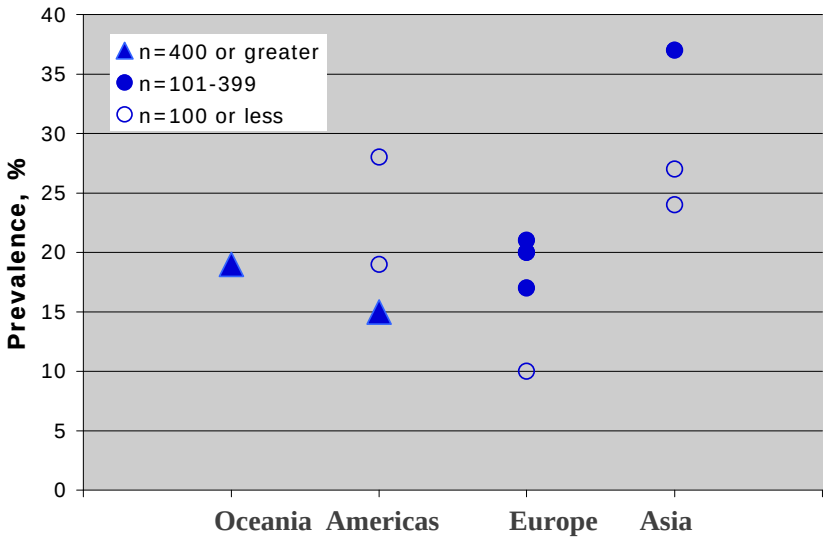
Effect of obesity in PCOS

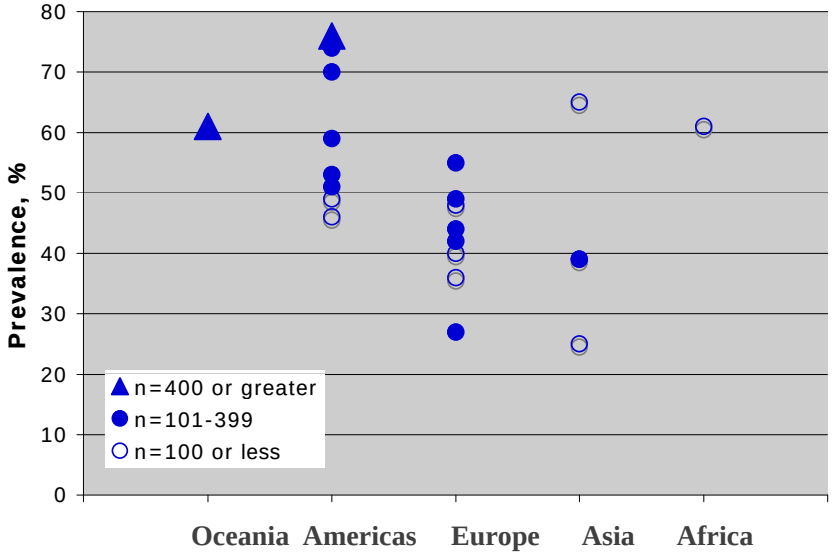
- Does obesity increase the prevalence of PCOS?
- Does obesity affect treatment of infertility in PCOS?
- Does obesity increase the prevalence of diabetes?
- Does obesity increase the prevalence of impaired glucose tolerance?
- Does obesity increase the prevalence of metabolic syndrome?

Prevalence of obesity in PCOS

Prevalence of overweight (BMI 25-29.9)



Prevalence of obesity (BMI >30)

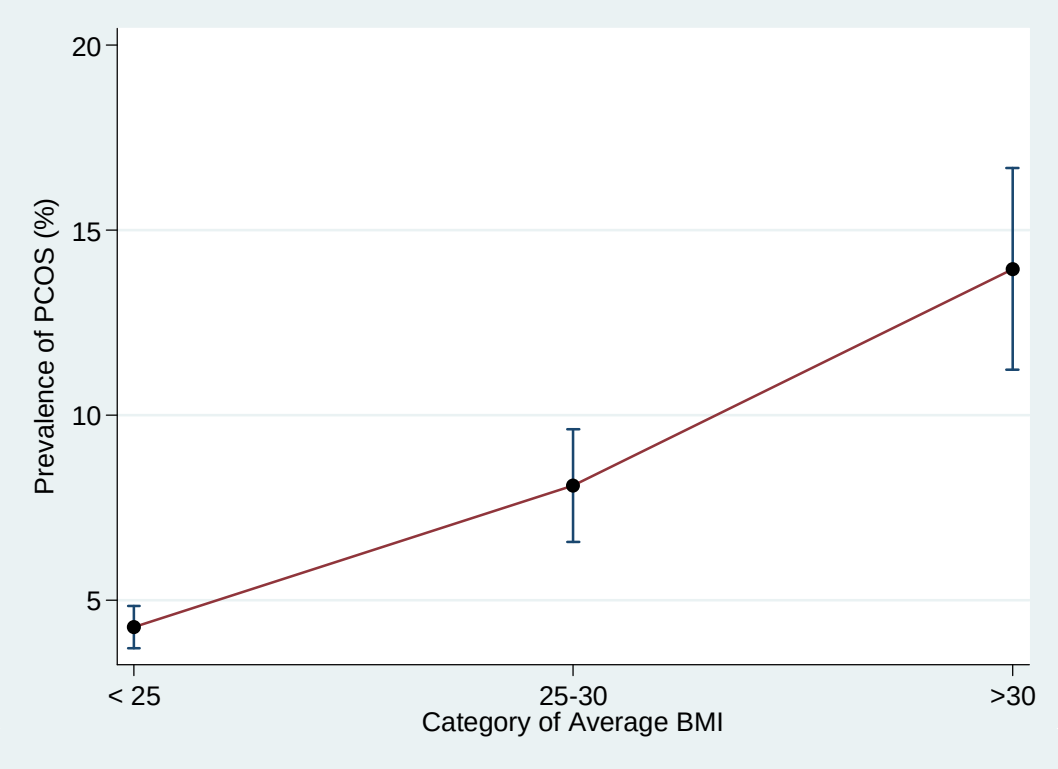


Siew Lim unpublished

Obesity and PCOS

Prevalence of PCOS

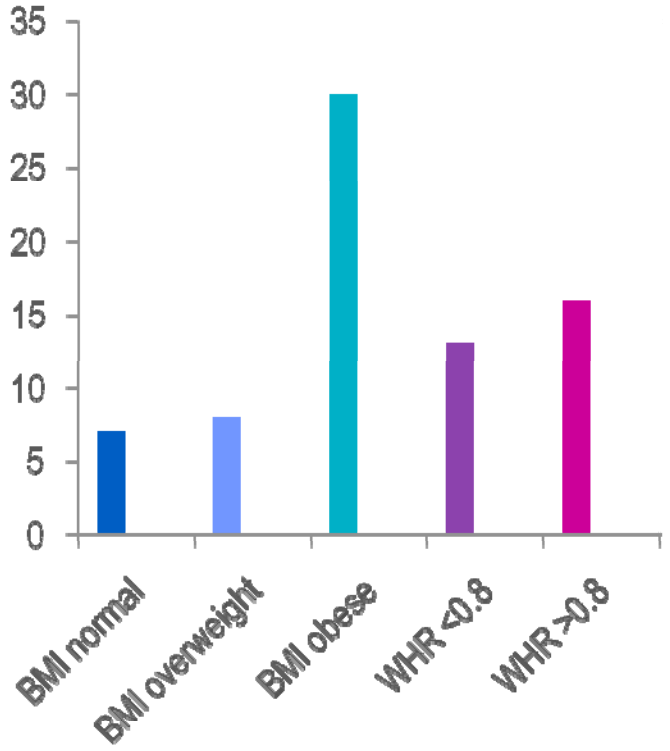
8600 Australian women followed longitudinally



Teede et al 2010

Prevalence of PCOS

Aboriginal women in Australia



Boyle et al 2010

Effect of obesity on treatment of PCOS

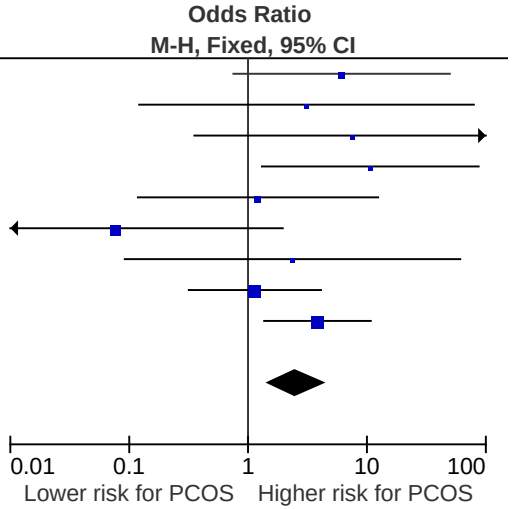
- Less spontaneous ovulation
- Less response to clomiphene
- Less response to gonadotrophins
- Greater danger with laparoscopic ovarian drilling
- Less pregnancies with IVF
- Worse outcomes of pregnancies
- Greater risk for long-term health of babies born

Prevalence of impaired glucose tolerance (BMI matched)

Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Rajkhowa 1996	10	72	1	39	6.9%	6.13 [0.75, 49.80]	1996
Yarali 2001	1	30	0	30	2.9%	3.10 [0.12, 79.23]	2001
Dunaif 2001	3	14	0	12	2.5%	7.61 [0.35, 163.82]	2001
Phy 2004	4	7	2	18	3.0%	10.67 [1.31, 86.93]	2004
Faloia 2004	3	50	1	20	8.3%	1.21 [0.12, 12.40]	2004
Sawathiparnich 2005	0	6	3	6	20.0%	0.08 [0.00, 1.96]	2005
Diamanti-Kandarakis 2005	1	29	0	22	3.3%	2.37 [0.09, 60.96]	2005
Alvarez-Blasco 2006	4	32	8	72	26.6%	1.14 [0.32, 4.11]	2006
Attuoua 2008	18	107	5	100	26.5%	3.84 [1.37, 10.79]	2008
Total (95% CI)		**347**		**319**	**100.0%**	**2.54 [1.44, 4.47]**	
Total events	44		20				

Heterogeneity: Chi² = 9.97, df = 8 (P = 0.27); I² = 20%

Test for overall effect: Z = 3.22 (P = 0.001)



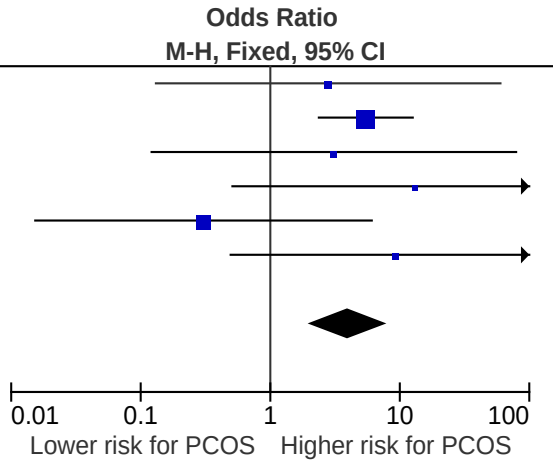
Moran et al 2010

Prevalence of diabetes mellitus in PCOS (BMI matched)

Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Rajkhowa 1996	2	72	0	39	9.0%	2.80 [0.13, 59.82]	1996
Cibula 2000	9	28	60	752	42.3%	5.46 [2.37, 12.60]	2000
Yarali 2001	1	30	0	30	6.9%	3.10 [0.12, 79.23]	2001
Sawathiparnich 2005	3	6	0	6	3.6%	13.00 [0.51, 330.48]	2005
Alvarez-Blasco 2006	0	32	3	72	31.1%	0.31 [0.02, 6.09]	2006
Moini 2009	4	273	0	276	7.1%	9.23 [0.49, 172.33]	2009
Total (95% CI)		**441**		**1175**	**100.0%**	**4.00 [1.97, 8.10]**	
Total events	19		63				

Heterogeneity: Chi² = 4.27, df = 5 (P = 0.51); I² = 0%

Test for overall effect: Z = 3.84 (P = 0.0001)



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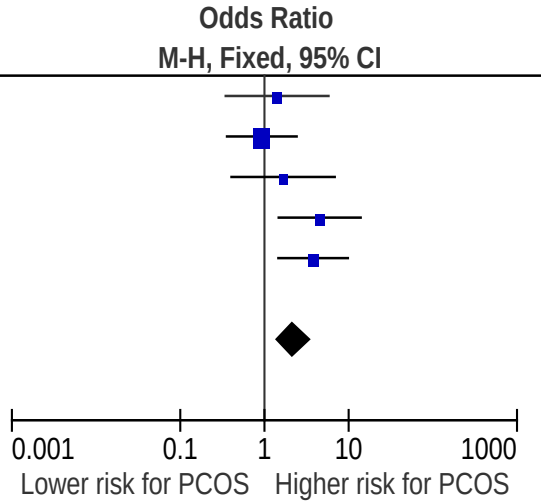
Prevalence of metabolic syndrome in PCOS (BMI matched)

Study or Subgroup	PCOS Events	PCOS Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Faloia 2004	10	50	3	20	14.7%	1.42 [0.35, 5.80]	2004
Alvarez-Blasco 2006	8	32	19	72	37.6%	0.93 [0.36, 2.42]	2006
Shroff 2007b	6	24	4	24	12.9%	1.67 [0.40, 6.87]	2007
Attuoua 2008	17	107	4	100	14.9%	4.53 [1.47, 13.98]	2008
Gulcelik 2008	20	60	7	60	20.0%	3.79 [1.46, 9.82]	2008
Total (95% CI)		**273**		**276**	**100.0%**	**2.20 [1.36, 3.56]**	
Total events	61		37				

Heterogeneity: $Chi^2 = 6.47$, df = 4 (P = 0.17); $I^2 = 38\%$

Test for overall effect: Z = 3.23 (P = 0.001)



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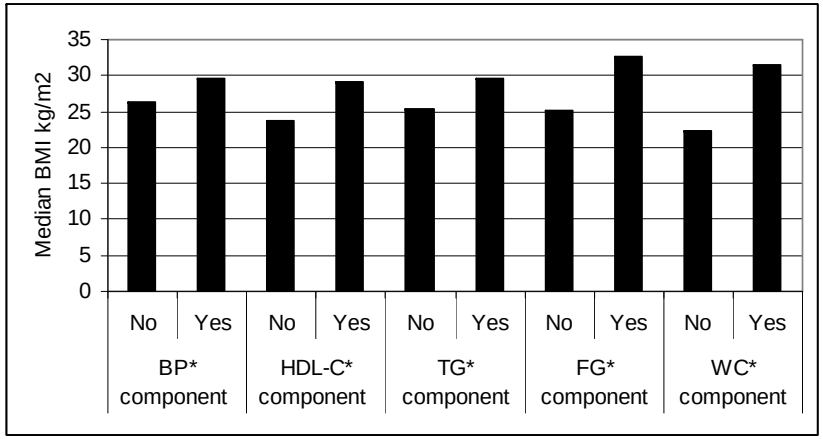
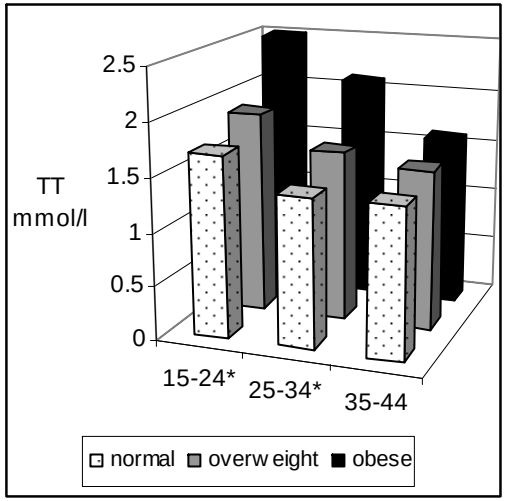
Metabolic syndrome related to obesity

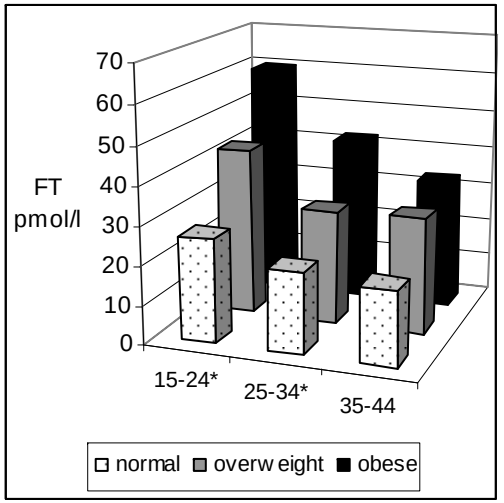
BMI and metabolic syndrome

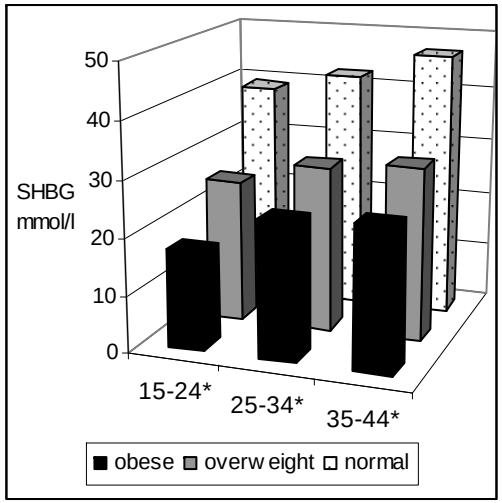


All metabolic features of PCOS were explained by increased BMI and central adiposity rather than PCOS itself

BMI and androgens







Boyle et al 2010

*p<0.05 between normal BMI and obese BMI category

Effect of PCOS on obesity

- Abnormal appetite regulation (Moran et al 2007)
- Impaired quality of life and greater depression
- Added problem of insulin resistance
- Increased androgens and hirsutism
- Increased risk of menstrual disorders and cancer
- Increased risk of infertility

Intervention strategies

- Lifestyle management better than drugs
  - Few randomised trials
  - Dropouts major problem
  - Almost impossible to maintain
  - May change oocyte lipid
- Metformin addition has little value on weight
- Bariatric surgery may be required in some people

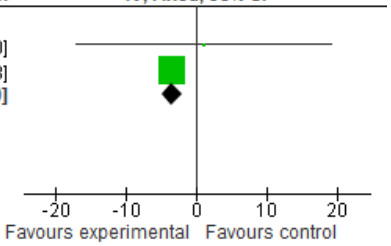
Intervention strategies

Weight

Study or Subgroup	Experimental Mean	SD	Total	Minimal treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.13.3 Weight (endpoint) (kg)								
Hoeger 2008	95.2	19.2	8	94.2	19.8	10	0.7%	1.00 [-17.10, 19.10]
Vigorito 2007	68	3.2	45	71.5	3.9	45	99.3%	-3.50 [-4.97, -2.03]
Subtotal (95% CI)			**53**			**55**	**100.0%**	**-3.47 [-4.94, -2.00]**

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 4.63 (P < 0.00001)

Test for subgroup differences: Not applicable

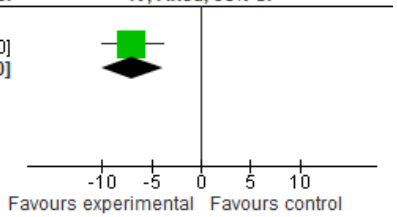


Weight change %

Study or Subgroup	Experimental Mean	SD	Total	Minimal treatment Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.14.4 Weight (% change)								
Hoeger 2004	-6.8	3.8	6	0.2	0.8	7	100.0%	-7.00 [-10.10, -3.90]
Subtotal (95% CI)			**6**			**7**	**100.0%**	**-7.00 [-10.10, -3.90]**

Heterogeneity: Not applicable
Test for overall effect: Z = 4.43 (P < 0.00001)

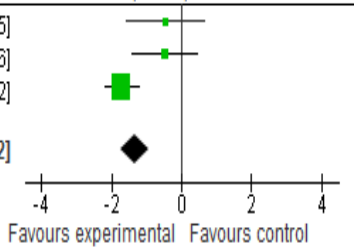
Test for subgroup differences: Not applicable



Insulin with GTT

Study or Subgroup	Lifestyle treatment Mean	SD	Total	Minimal treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Hoeger 2004	15,625	4,265	6	19,808	10,713	7	13.1%	-0.46 [-1.57, 0.65]
Hoeger 2008	20,726	16,153	8	32,538	27,386	10	18.1%	-0.49 [-1.43, 0.46]
Vigorito 2007	14,750	992	45	16,455	985	45	68.8%	-1.71 [-2.20, -1.22]
Total (95% CI)			**59**			**62**	**100.0%**	**-1.32 [-1.73, -0.92]**

Heterogeneity: Chi² = 7.75, df = 2 (P = 0.02); I² = 74%
Test for overall effect: Z = 6.44 (P < 0.00001)



Moran et al Cochrane 2010

Acknowledgements

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