Problems of Obesity and Early Pregnancy

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Obesity and Reproductive Problems

- Infertility
- Miscarriage
- Recurrent Miscarriage
- Ectopic pregnancy
- Late pregnancy complications
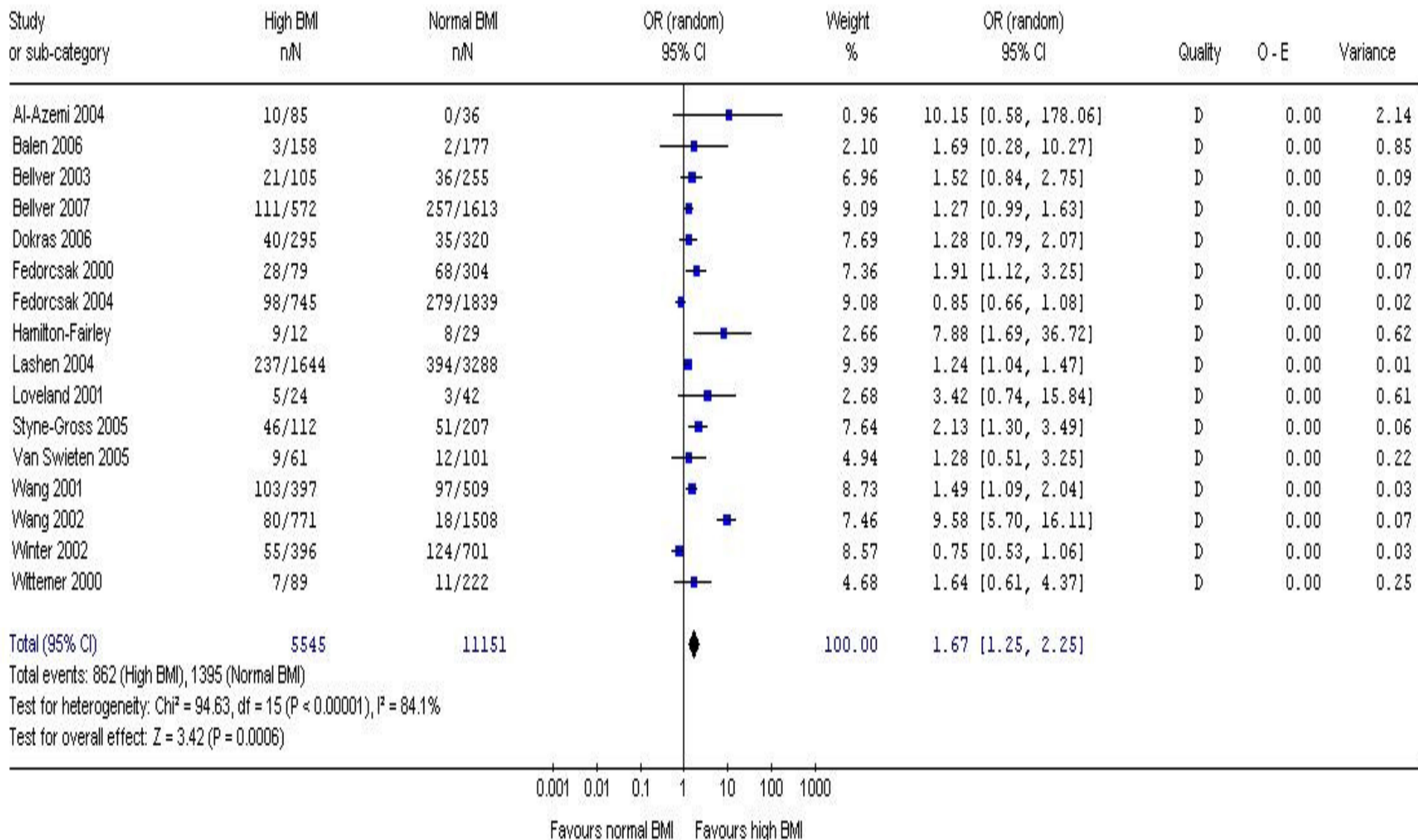
Study 1

Meta-analysis
BMI & miscarriage rate

Study design

- Meta analysis
- MEDLINE (1964 - 2006)
- EMBASE (1974 – 2006)
- All methods of conception
- Patients with a BMI of ≥ 25 kg/m^2 Vs Normal BMI
- 16 studies

Obesity & Miscarriage

Review:	obesity and miscarriage (Version 05)
Comparison:	01 obesity and miscarriage
Outcome:	01 risk of miscarriage

| Study or sub-category	High BMI n/N	Normal BMI n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI	Quality	O - E	Variance
Al-Azemi 2004	10/85	0/36		0.96	10.15 [0.58, 178.06]	D	0.00	2.14
Balen 2006	3/158	2/177		2.10	1.69 [0.28, 10.27]	D	0.00	0.85
Bellver 2003	21/105	36/255		6.96	1.52 [0.84, 2.75]	D	0.00	0.09
Bellver 2007	111/572	257/1613		9.09	1.27 [0.99, 1.63]	D	0.00	0.02
Dokras 2006	40/295	35/320		7.69	1.28 [0.79, 2.07]	D	0.00	0.06
Fedorcsak 2000	28/79	68/304		7.36	1.91 [1.12, 3.25]	D	0.00	0.07
Fedorcsak 2004	98/745	279/1839		9.08	0.85 [0.66, 1.08]	D	0.00	0.02
Hamilton-Fairley	9/12	8/29		2.66	7.88 [1.69, 36.72]	D	0.00	0.62
Lashen 2004	237/1644	394/3288		9.39	1.24 [1.04, 1.47]	D	0.00	0.01
Loveland 2001	5/24	3/42		2.68	3.42 [0.74, 15.84]	D	0.00	0.61
Styne-Gross 2005	46/112	51/207		7.64	2.13 [1.30, 3.49]	D	0.00	0.06
Van Swieten 2005	9/61	12/101		4.94	1.28 [0.51, 3.25]	D	0.00	0.22
Wang 2001	103/397	97/509		8.73	1.49 [1.09, 2.04]	D	0.00	0.03
Wang 2002	80/771	18/1508		7.46	9.58 [5.70, 16.11]	D	0.00	0.07
Winter 2002	55/396	124/701		8.57	0.75 [0.53, 1.06]	D	0.00	0.03
Wittemer 2000	7/89	11/222		4.68	1.64 [0.61, 4.37]	D	0.00	0.25
Total (95% CI)	5545	11151		100.00	1.67 [1.25, 2.25]			

Total events: 862 (High BMI), 1395 (Normal BMI)

Test for heterogeneity: Chi² = 94.63, df = 15 (P < 0.00001), I² = 84.1%

Test for overall effect: Z = 3.42 (P = 0.0006)

0.001 0.01 0.1 1 10 100 1000

Favours normal BMI   Favours high BMI

M Metwally, K Ong, WL Ledger , TC Li, Fertil Steril 2007

Subgroup analysis

Ovulation induction

Study or sub-category	High BMI n/N	Normal BMI n/N	OR (fixed) 95% CI	Weight %	OR (fixed) 95% CI	Quality	O - E	Variance
Al-Azemi 2004	10/85	0/36		16.89	10.15 [0.58, 178.06]	D	0.00	2.14
Hamilton-Fairley	9/12	8/29		32.20	7.88 [1.69, 36.72]	D	0.00	0.62
Balen 2006	3/158	2/177		50.91	1.69 [0.28, 10.27]	D	0.00	0.85
Total (95% CI)	255	242		100.00	5.11 [1.76, 14.83]			

Total events: 22 (High BMI), 10 (Normal BMI)

Test for heterogeneity: Chi² = 1.97, df = 2 (P = 0.37), I² = 0%

Test for overall effect: Z = 3.00 (P = 0.003)

0.001 0.01 0.1 1 10 100 1000

Favours normal BMI   Favours high BMI
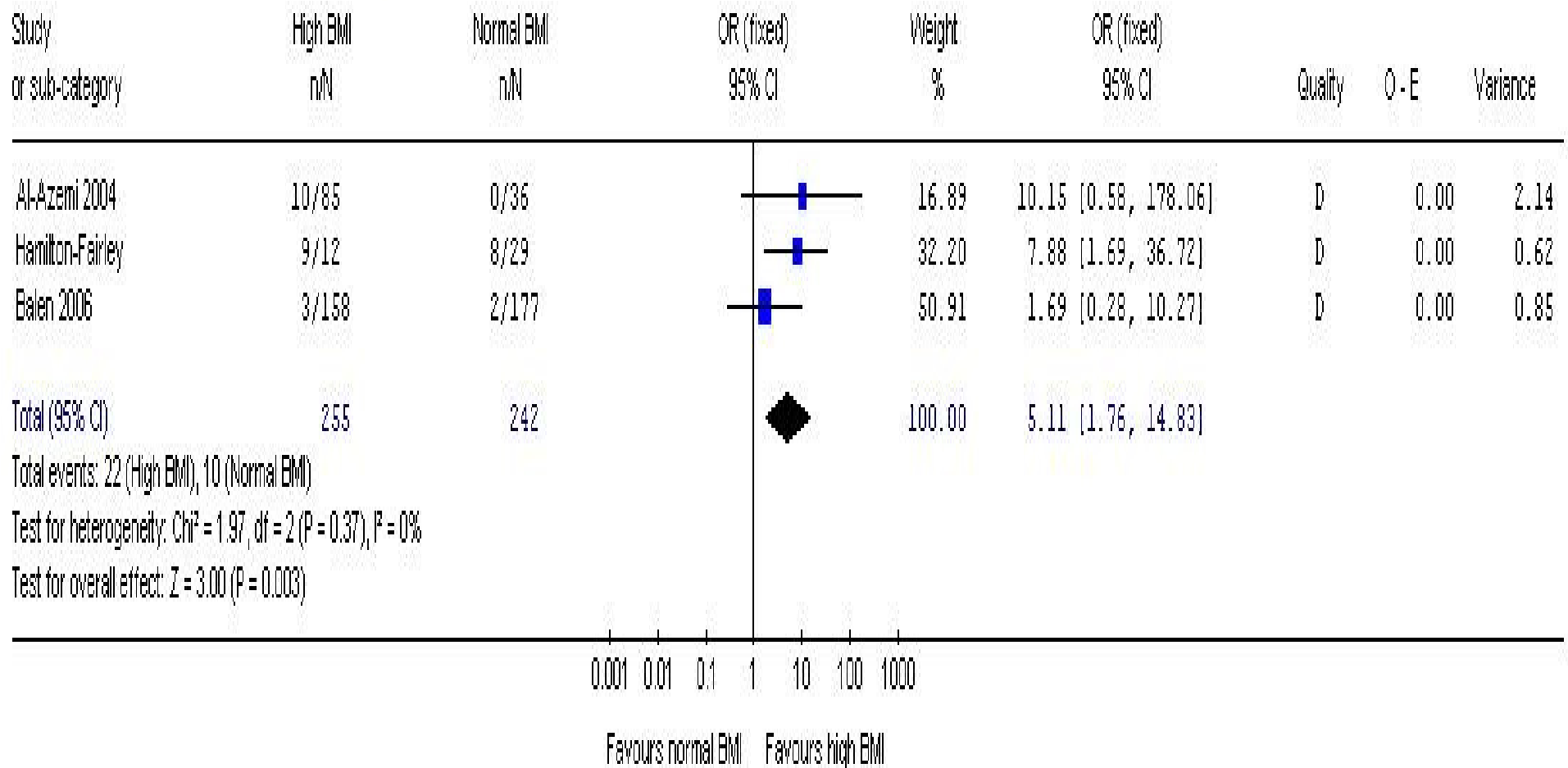
IVF/ICSI

Review: obesity and miscarriage (Version 05)
Comparison: 01 obesity and miscarriage
Outcome: 02 miscarriage after IVF/ICSI

Study or sub-category	High BMI n/N	Normal BMI n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI	Quality	O - E	Variance
Dokras 2006	40/295	35/320		12.13	1.28 [0.79, 2.07]	D	0.00	0.06
Fedorcsak 2000	28/79	68/304		11.88	1.91 [1.12, 3.25]	D	0.00	0.07
Fedorcsak 2004	98/745	279/1839		13.06	0.85 [0.66, 1.08]	D	0.00	0.02
Loveland 2001	5/24	3/42		6.47	3.42 [0.74, 15.84]	D	0.00	0.61
Van Swieten 2005	9/61	12/101		9.62	1.28 [0.51, 3.25]	D	0.00	0.22
Wang 2001	97/509	103/397		12.84	0.67 [0.49, 0.92]	D	0.00	0.03
Wang 2002	80/771	18/1508		11.95	9.58 [5.70, 16.11]	D	0.00	0.07
Winter 2002	55/396	124/701		12.74	0.75 [0.53, 1.06]	D	0.00	0.03
Wittemer 2000	7/89	11/222		9.32	1.64 [0.61, 4.37]	D	0.00	0.25
Total (95% CI)	2969	5434		100.00	1.52 [0.88, 2.61]			

Total events: 419 (High BMI), 653 (Normal BMI)
Test for heterogeneity: Chi² = 93.05, df = 8 (P < 0.00001), I² = 91.4%
Test for overall effect: Z = 1.51 (P = 0.13)

0.01   0.1   1   10   100

Favours normal BMI   Favours high BMI

Oocyte donation

Study or sub-category	High BMI n/N	Normal BMI n/N	OR (random) 95% CI	Weight %	OR (random) 95% CI	Quality	O - E	Variance
Bellver 2003	21/105	36/255		20.89	1.52 [0.84, 2.75]	D	0.00	0.09
Bellver 2007	111/572	257/1613		52.05	1.27 [0.99, 1.63]	D	0.00	0.02
Styne-Gross 2005	46/112	51/207		27.06	2.13 [1.30, 3.49]	D	0.00	0.06
Total (95% CI)	789	2075		100.00	1.52 [1.10, 2.09]			

Total events: 178 (High BMI), 344 (Normal BMI)

Test for heterogeneity: Chi² = 3.46, df = 2 (P = 0.18), I² = 42.2%

Test for overall effect: Z = 2.56 (P = 0.01)

0.1 0.2 0.5 1 2 5 10

Favours normal BMI   Favours high BMI

Obesity and Reproductive Problems

- Infertility
- Miscarriage
- Recurrent Miscarriage
- Ectopic pregnancy
- Late pregnancy complications

Study 2

Impact of BMI on miscarriage rate in women with recurrent miscarriage

FIGURE 1

Miscarriage rates for different BMI categories for all pregnancies (n = 844; $P > 0.05$) and the first pregnancy after referral (n = 491; $P > 0.05$).
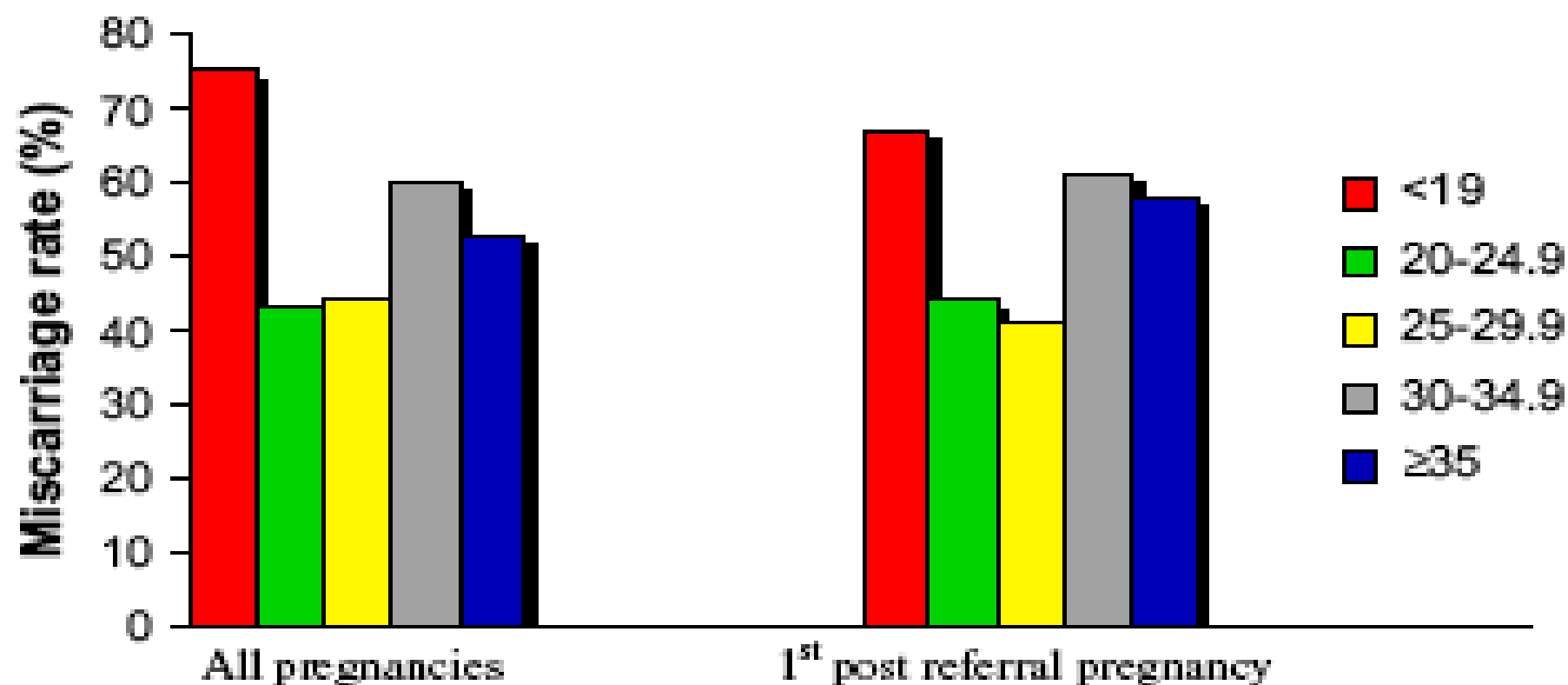
Metwally. BMI and recurrent miscarriage. Fertil Steril 2010.

Where is the problem?
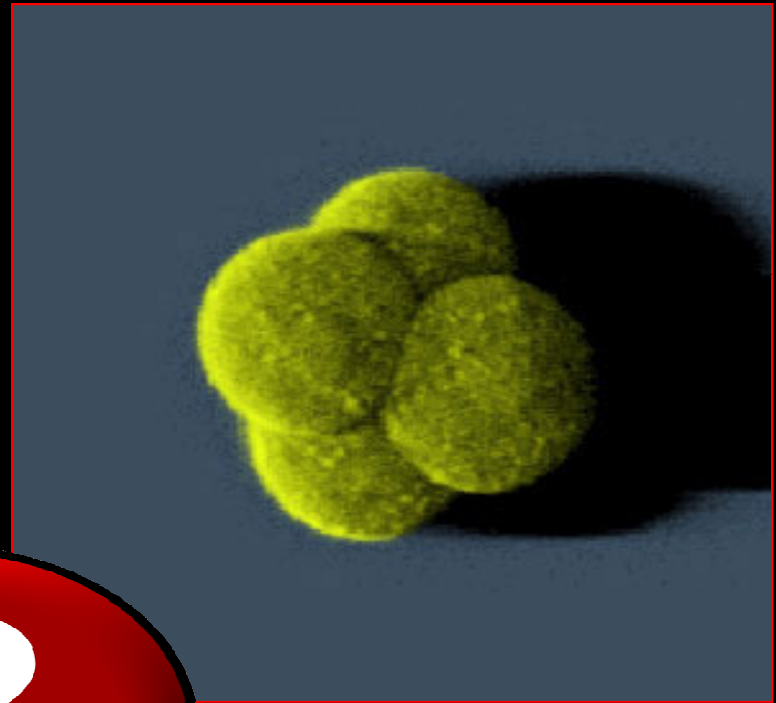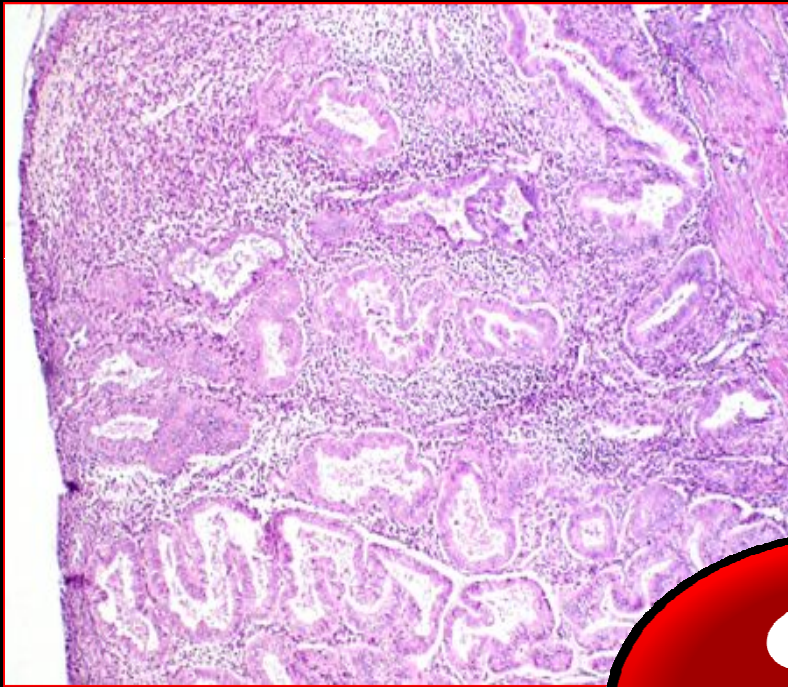
Study 3

Impact of BMI on Endometrial function in women with recurrent miscarriage :

a retrospective study

M Metwally, E Tuckerman, SM Laird, WL Ledger , TC Li, RBM Online 2007

Subjects

145 unexplained RM

BMI

BMI <25
n=74

BMI>25
n= 71

Methodology

- Morphology: dating criteria of Noyes
- Immunohistochemistry
  - Steroid receptors
  - LIF
  - Leucocyte subpopulations

Aim
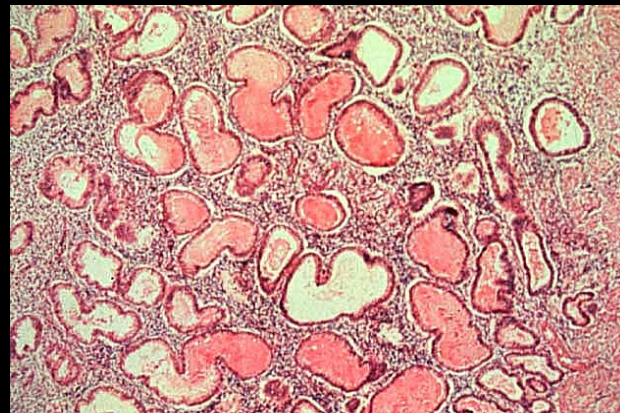
	BMI<25 n=74	BMI ≥25 n= 71
LPD	15	17
Normal development	59	54

P>0.05

Receptor	BMI<25 n= 16	BMI>25 n= 17	p
Stromal P	270.0 (53.0)	260 (68.0)	NS
Glandular P	240.0 (139.0)	225.0 (340.0)	NS
Luminal P	255.0 (148.0)	220.0 (148.0)	NS
Stromal E	119.0 (114.0)	145.0 (130.0)	NS
Glandular E	170.0 (141.0)	110.0 (133.0)	NS
Luminal E	146.5 (125.0)	125.0 (135.0)	NS

	BMI<25 N=13	BMI>25 n=16	p
CD45	23.3 (13-35)	21.0(14-29)	NS
CD56	8 .4(5-28)	8.3 (4-16)	NS
CD4	2.5 (1-5)	2.5(0.5-7)	NS
CD3	3.6 (2-7)	3.9 (0-8)	NS

LIF
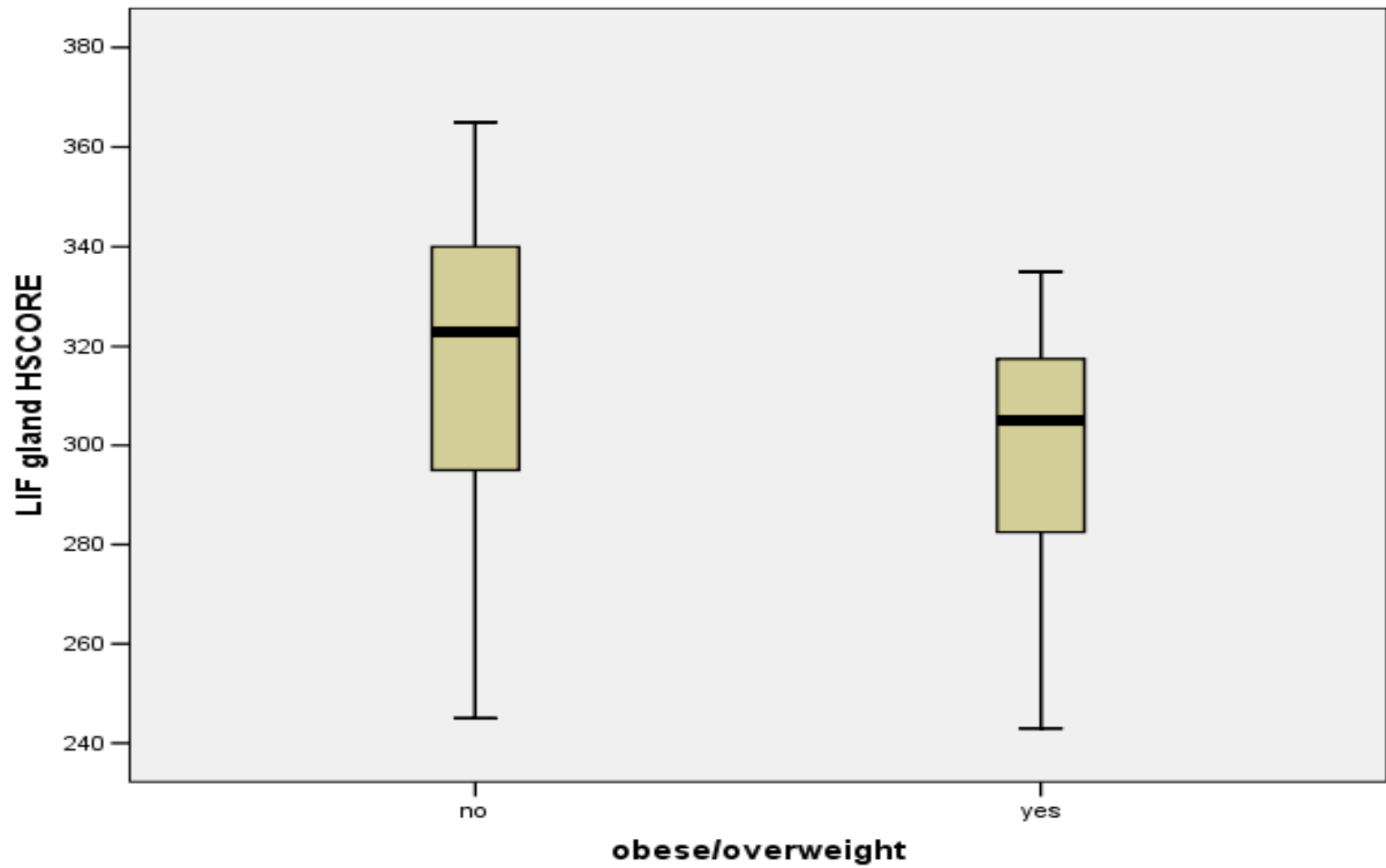
LIF
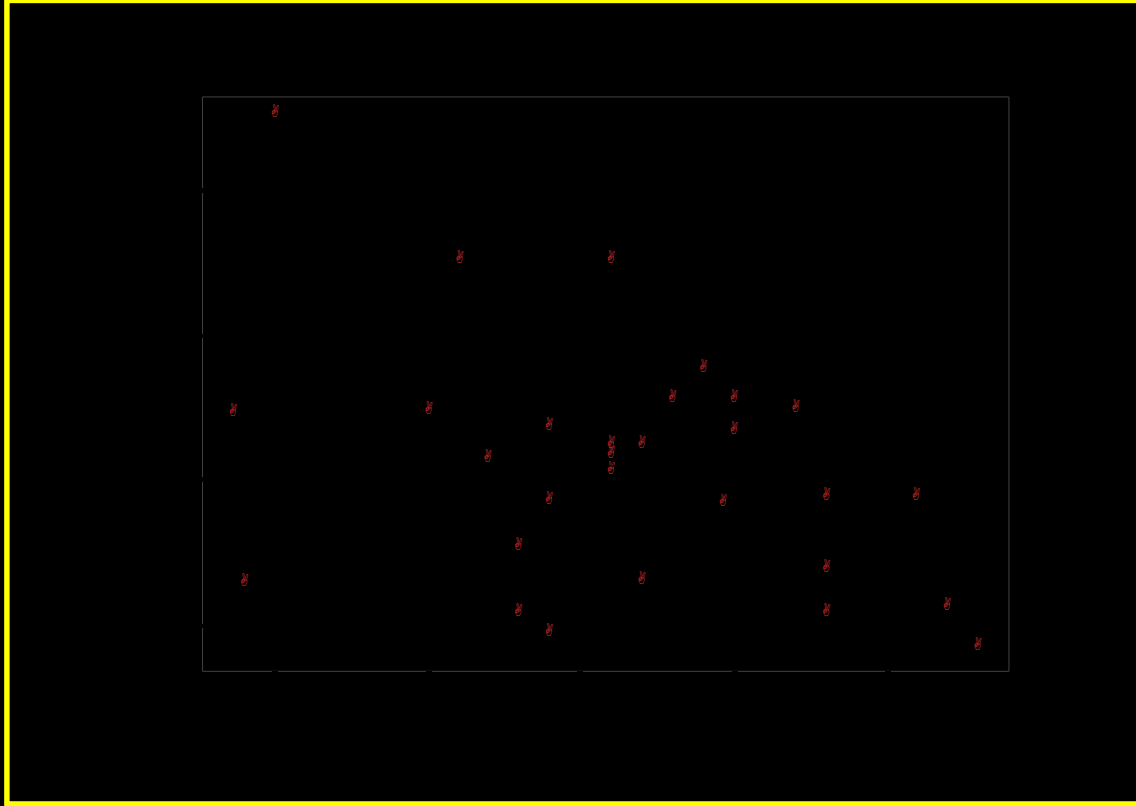
Conclusion

- A modest increase in BMI does not appear to have a major adverse effect on:
  - Endometrial morphology
  - Oestrogen and progesterone receptors
  - Leucocyte populations
- Negative correlation between BMI and LIF expression
- a strong case to conduct a prospective study to further examine LIF expression in women with high BMI, especially in women who are severely or morbidly obese

Study 4

Impact of BMI on endometrial protein profile (Proteomic) of women with recurrent miscarriage :

a prospective study

Proteomics: the way forward?
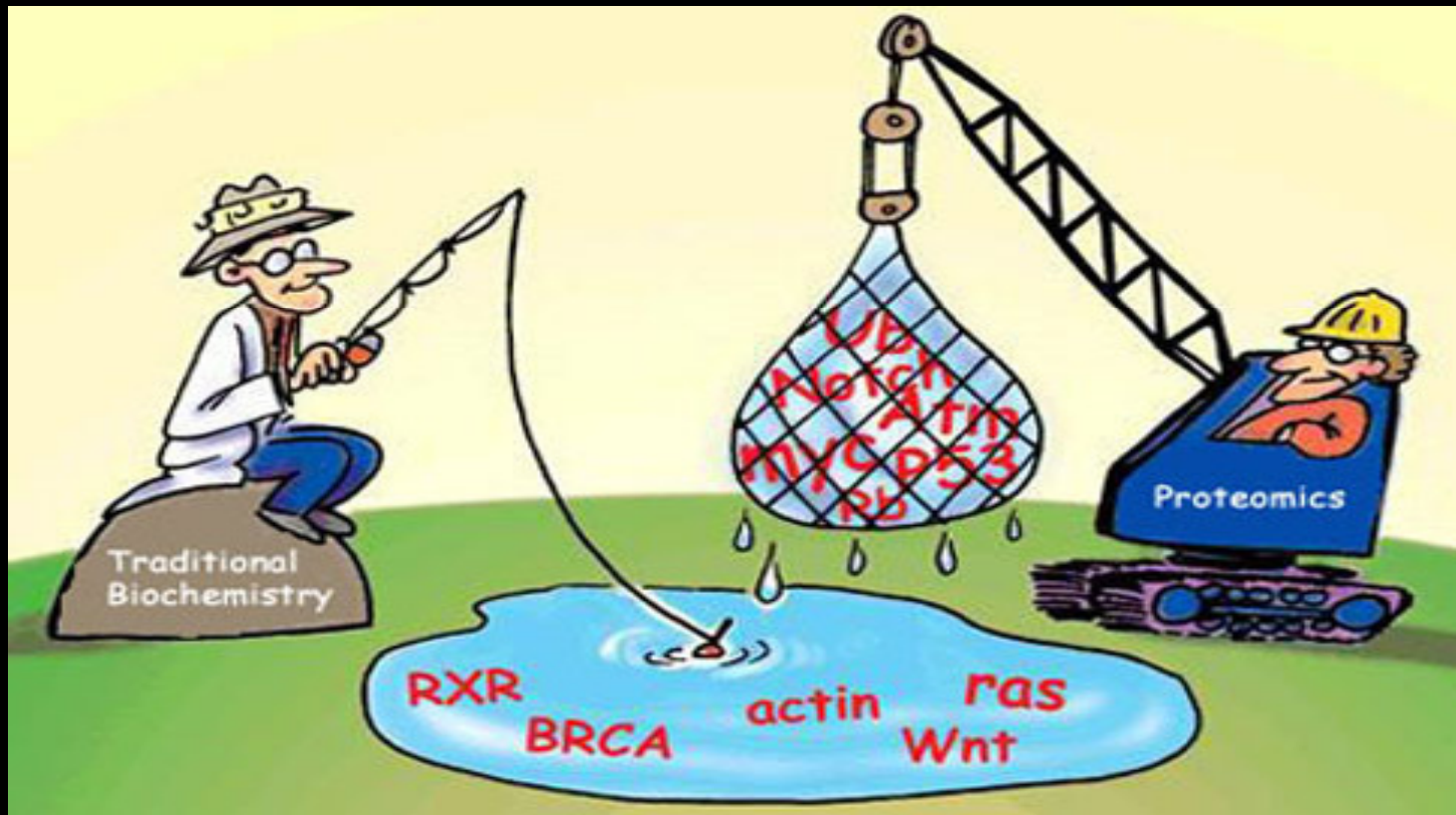
Is obesity associated with an endometrial defect? An endometrial proteomic analysis of obese women with recurrent miscarriage

M Metwally, WL Ledger, TC Li

The Jessop Wing, Sheffield, UK

Obesity and the endometrium

- Suggested from clinical studies using the oocyte donation model Bellver et al, F&S, 2007

- Suggested from tissue studies:
  - Steroid receptors
  - Endometrial leukocytes
  - Endometrial morphology
  - Leukemia inhibitory factor

  Metwally et al, RBM online, 2006

Aim of study

- To map the protein structure of the endometrium in women with increased BMI and recurrent miscarriage.

- To determine if an alteration in the endometrial protein profile may reflect an endometrial cause for the increased risk of miscarriage in women with this condition.

Materials and methods

Recurrent miscarriage	Controls

Obese
12

Normal
4

Obese
2

Normal
3

Mid-luteal endometrial biopsy

Proteomics

- Extraction and labelling of proteins

- 2D gel electrophoresis

- Image Analysis: quantification of differences in protein expression

- Principle components analysis

- Protein identification: mass spectrometry

2D gel electrophoresis
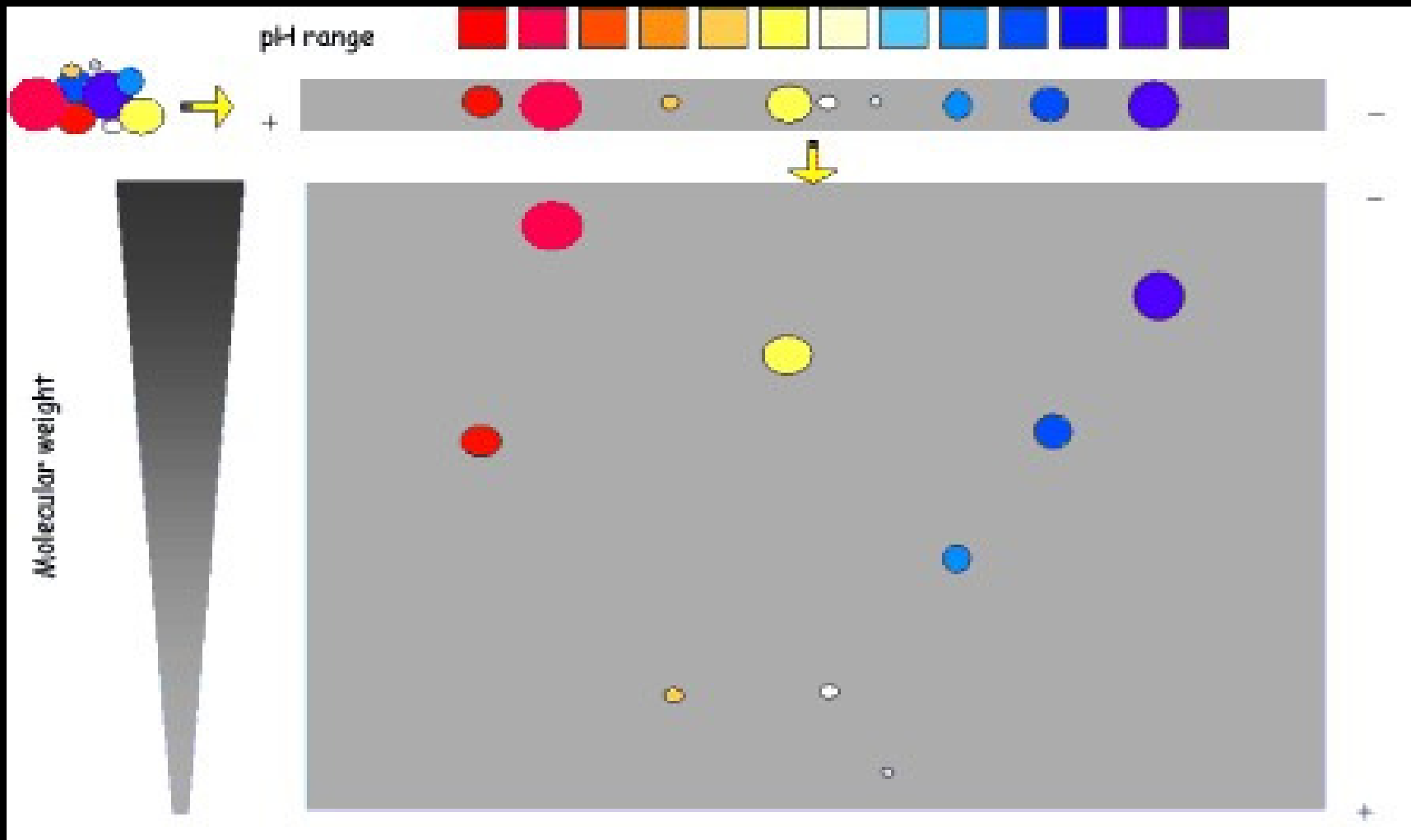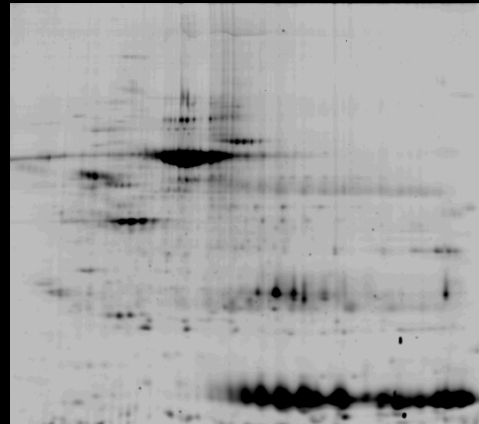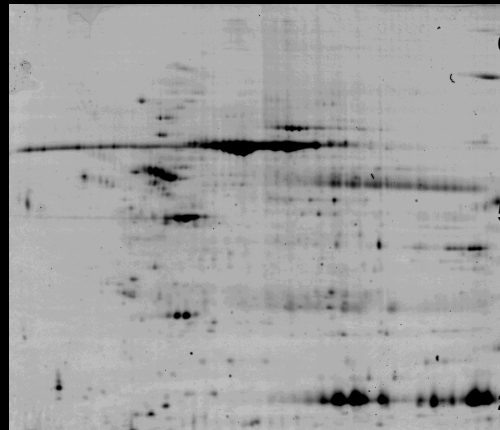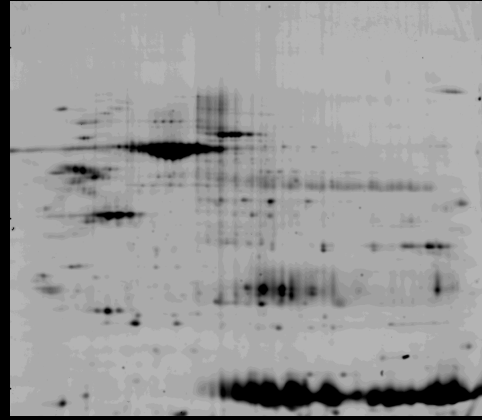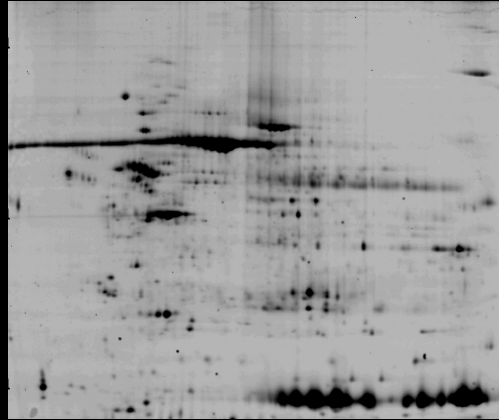
Proteomics

- Extraction and labelling of proteins

- 2D gel electrophoresis

- Image Analysis: quantification of differences in protein expression

- Principle components analysis

- Protein identification: mass spectrometry

Interpretation

- Obesity has a positive impact on Haptoglobin
  - glycoprotein synthesised in the liver
  - binds excess haemoglobin protecting the kidneys in cases of intravascular haemolysis
  - important component of the body's response to inflammatory conditions
  - Mediator of endothelial dysfunction
- Chain A pre albumin and beta globulin: Markers of endothelial dysfunction
- Evidence for a local inflammatory reaction

Study 5

Impact of BMI on embryo quality in women undergoing assisted conception :

a retrospective study

The embryo?

Difficult to assess
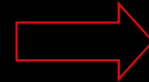
Many grading systems
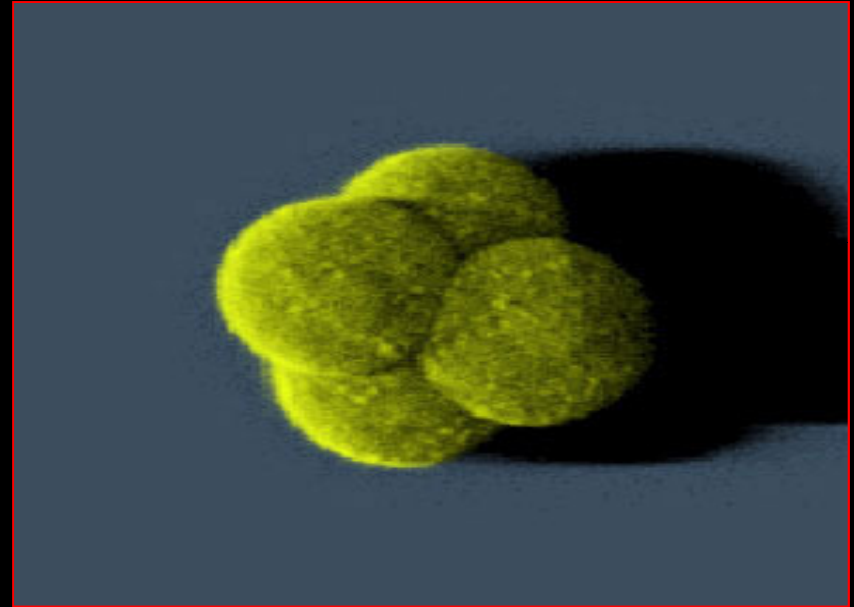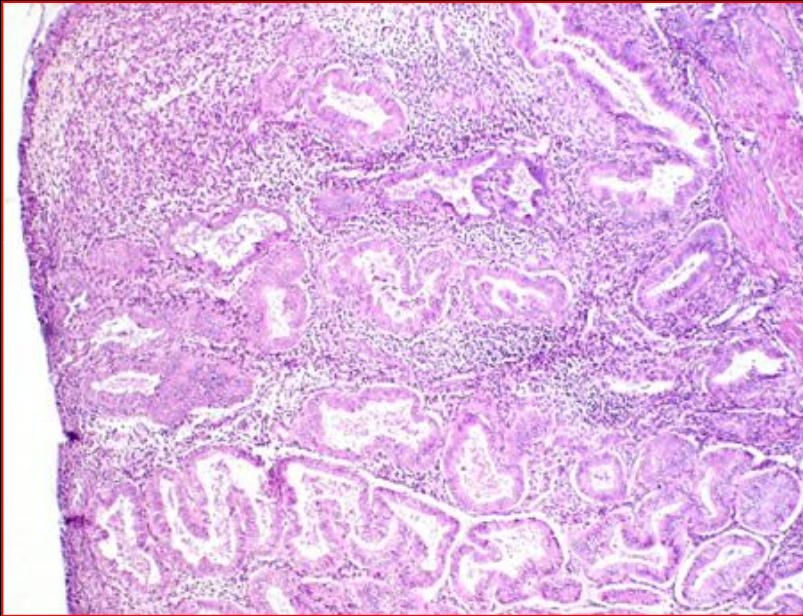
Inter and intra-observer variability
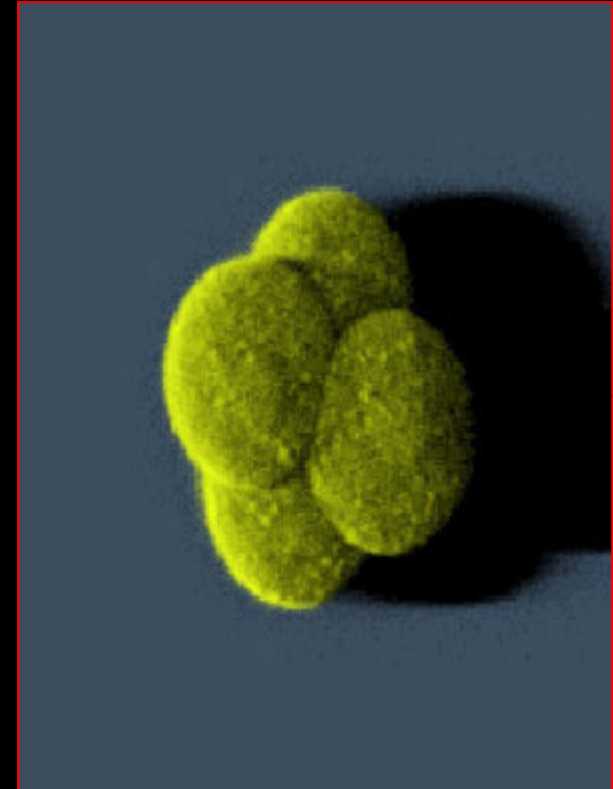
Baxter Bendus *et al.*, 2006

Embryo quality markers

	Normal	Overweight	obese	p
Embryo grade	2	1.9	2.3	0.02
Embryos discarded	4.5	4.0	6.4	0.007
Utilisation rate	49%	50%	31%	0.01
Embryos cryopreserved	1.1	0.9	0.2	0.04

Metwally et al, RBM Online, 2007

Where is the problem?

Both

Obesity and Reproductive Problems

- Infertility
- Miscarriage
- Recurrent Miscarriage
- Ectopic pregnancy
- Late pregnancy complications

Conclusions

- Obesity increases the risk of miscarriage and recurrent miscarriage

- Obesity affects embryo quality

- Obesity adversely affect endometrial function

Thank you