ART and The Obese Patient

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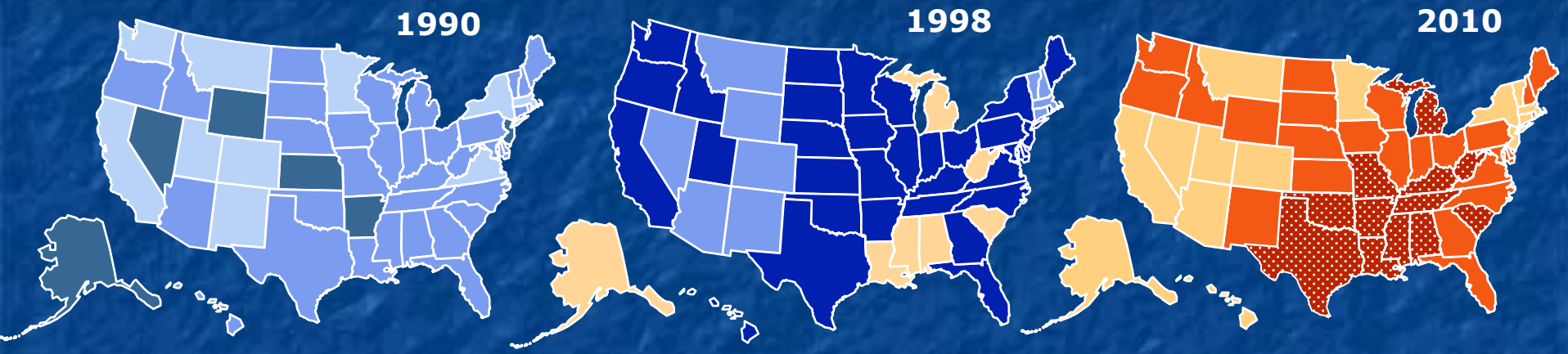
Obesity Pandemic "Globesity"

- Obesity is a worldwide epidemic
- In 2013, 2.3 billion adults were overweight or obese[1]
- In Europe, over half of women of reproductive age are either overweight or obese [2, 3]

1 Ng et al, 2014; 2 Balen and Anderson 2007; 3 Koning et al. 2010

Obesity Trends Among U.S. Adults
1990 - 2010



- In 1990, no states had prevalence of obesity >14%
- In 2010, no states had prevalence of obesity <20%
- In 2013, 71% were either overweight or obese

No Data | <10% | 10%–14% | 15%–19% | 20%–24% | 25%–29% | ≥30%

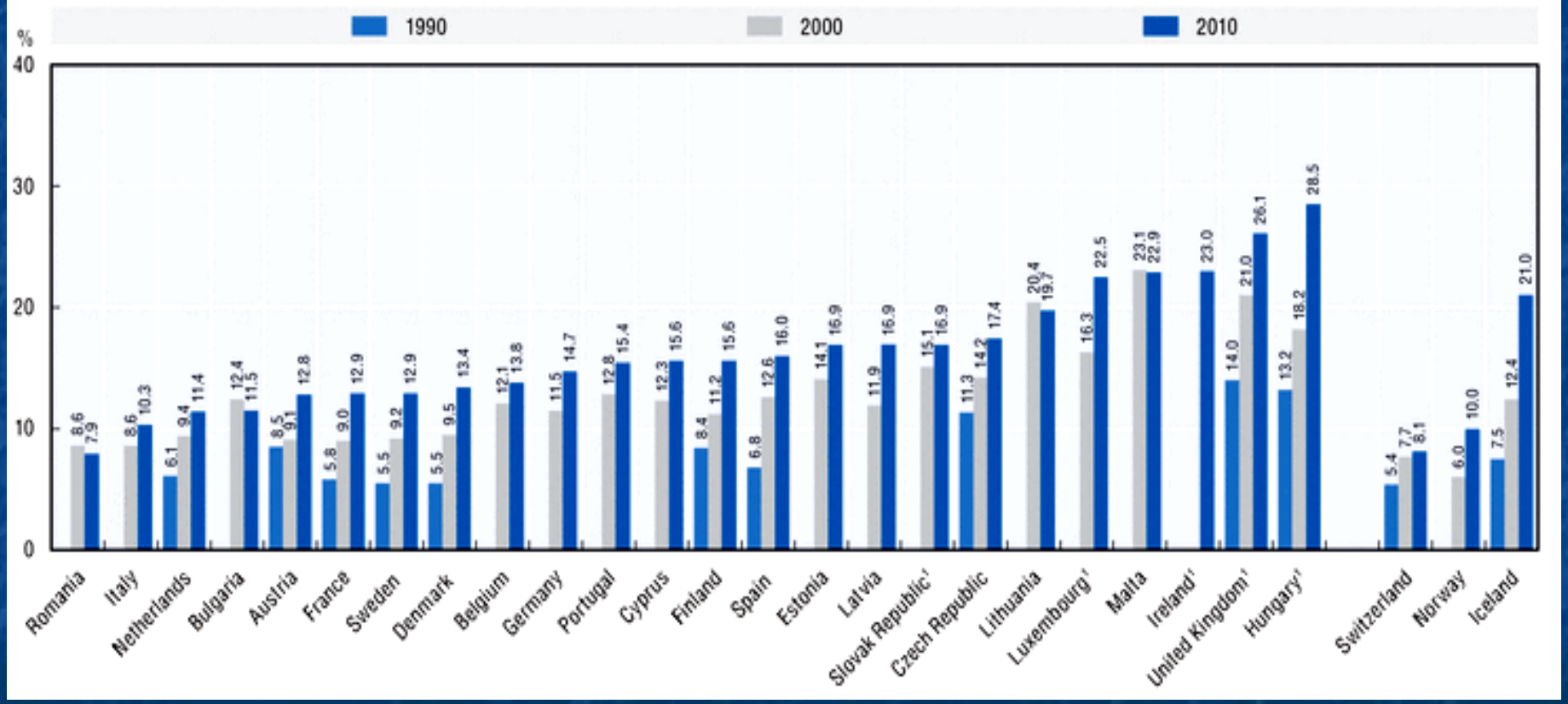
CDC, 2013

Obesity in Europe (WHO, 2014)

- Obesity rates **quadrupled** in the last 25 years
- **23%** are obese
- **In 2013, 68%** were either overweight or obese
- In the UK, obesity causes **3000 deaths** & costs NHS **£7.4b** / year

Obesity in Europe (WHO, 2014)

Figure 2.7.2 **Increasing obesity rates among adults in European countries, 1990, 2000 and 2010 (or nearest years)**



OECD, 2012

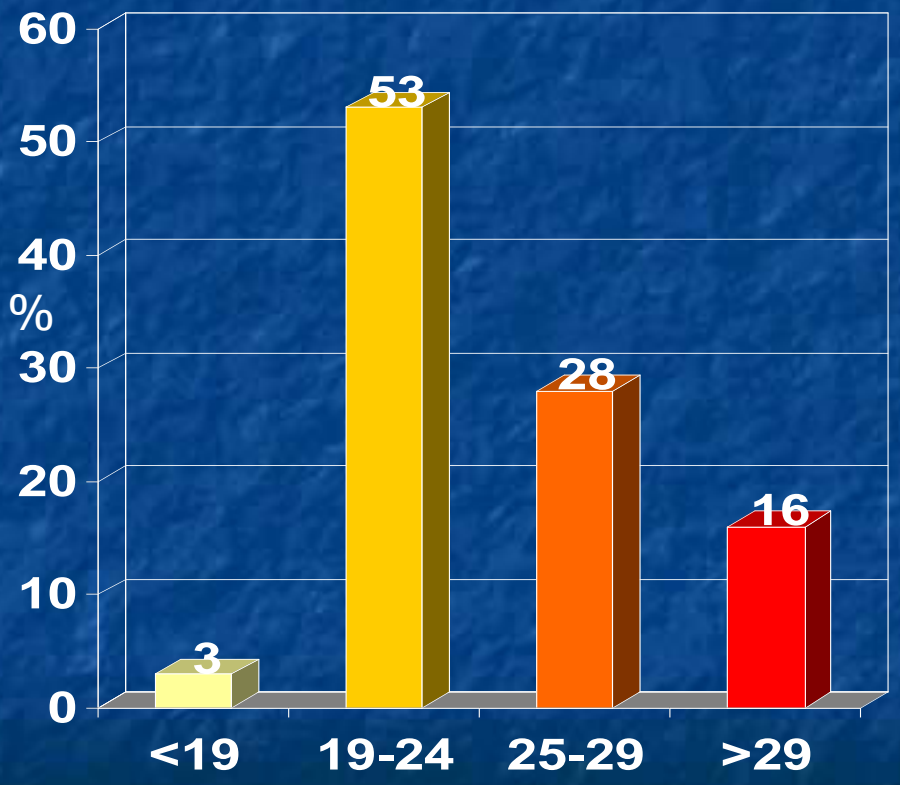
Does Obesity Impair Fertility?

- **Obese women have a 34% lower fecundability**
- **Obese women have a 3-fold increased risk of infertility**
- **Obesity detrimental to IVF outcome**
  - own data
  - literature review

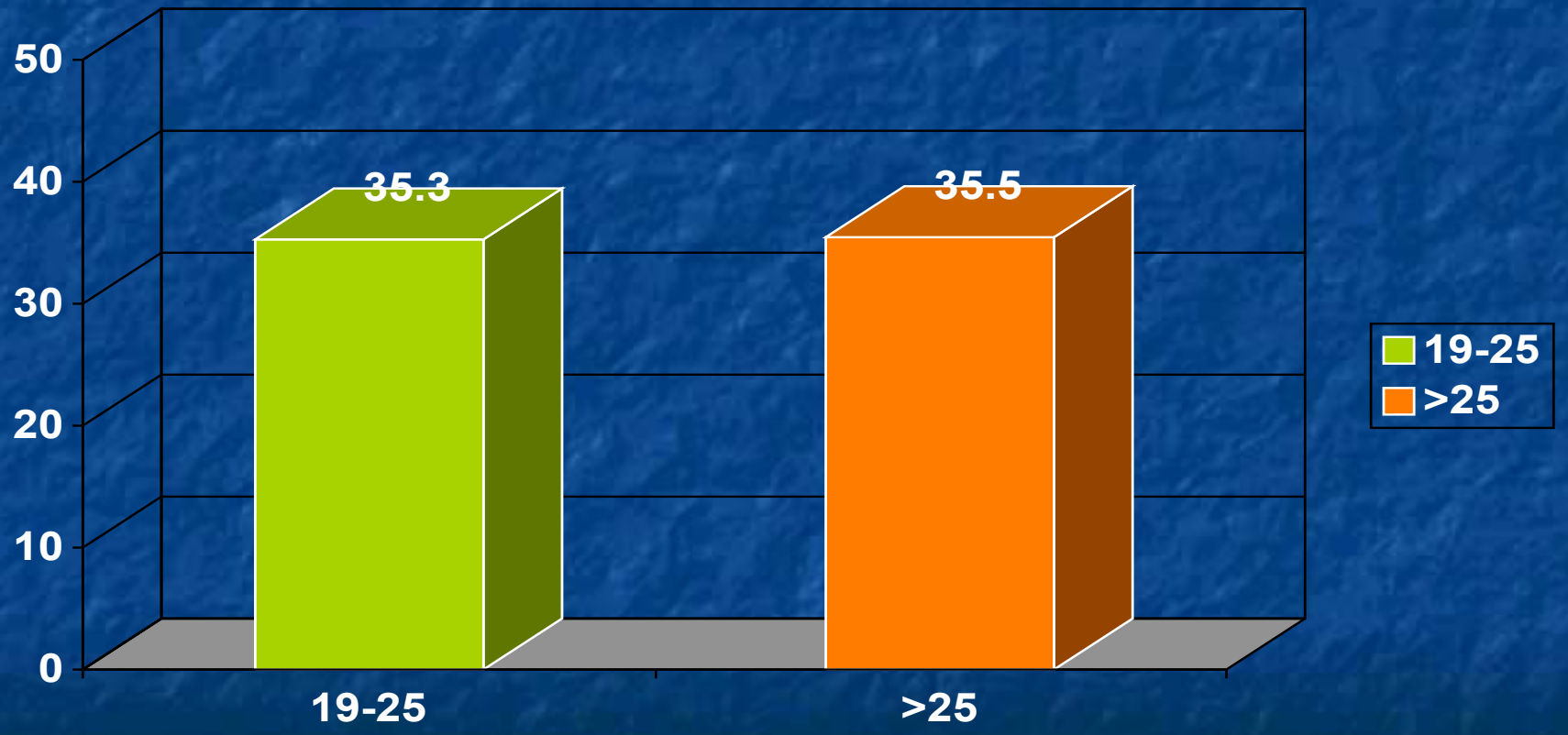
(Gesink Law et al, 2007)

Obesity and IVF outcome 2002-2014

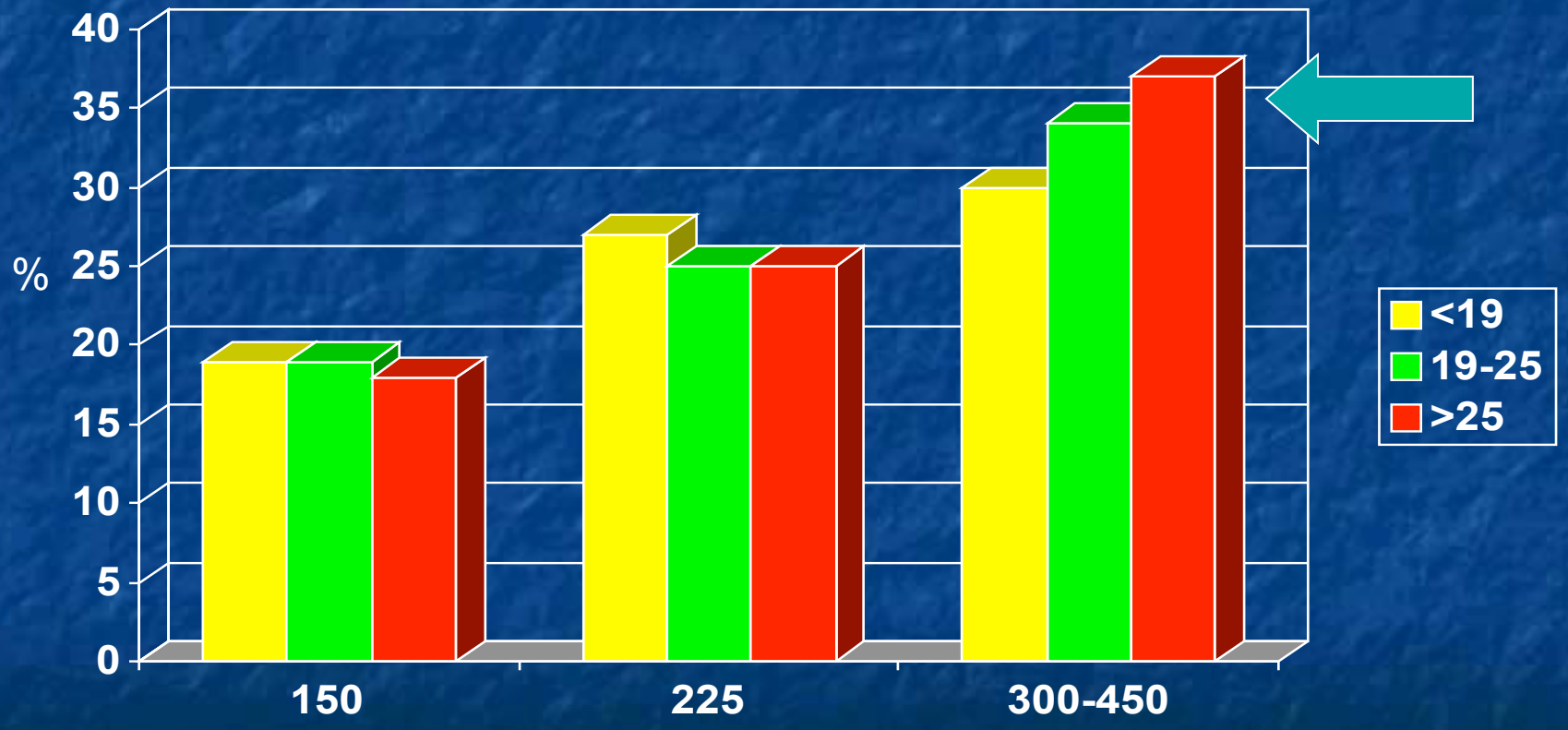
- Started collecting BMI data in 2002
- Have >10,500 IVF cycles with verified BMI data
- 44% of cycles were performed for overweight or obese patients



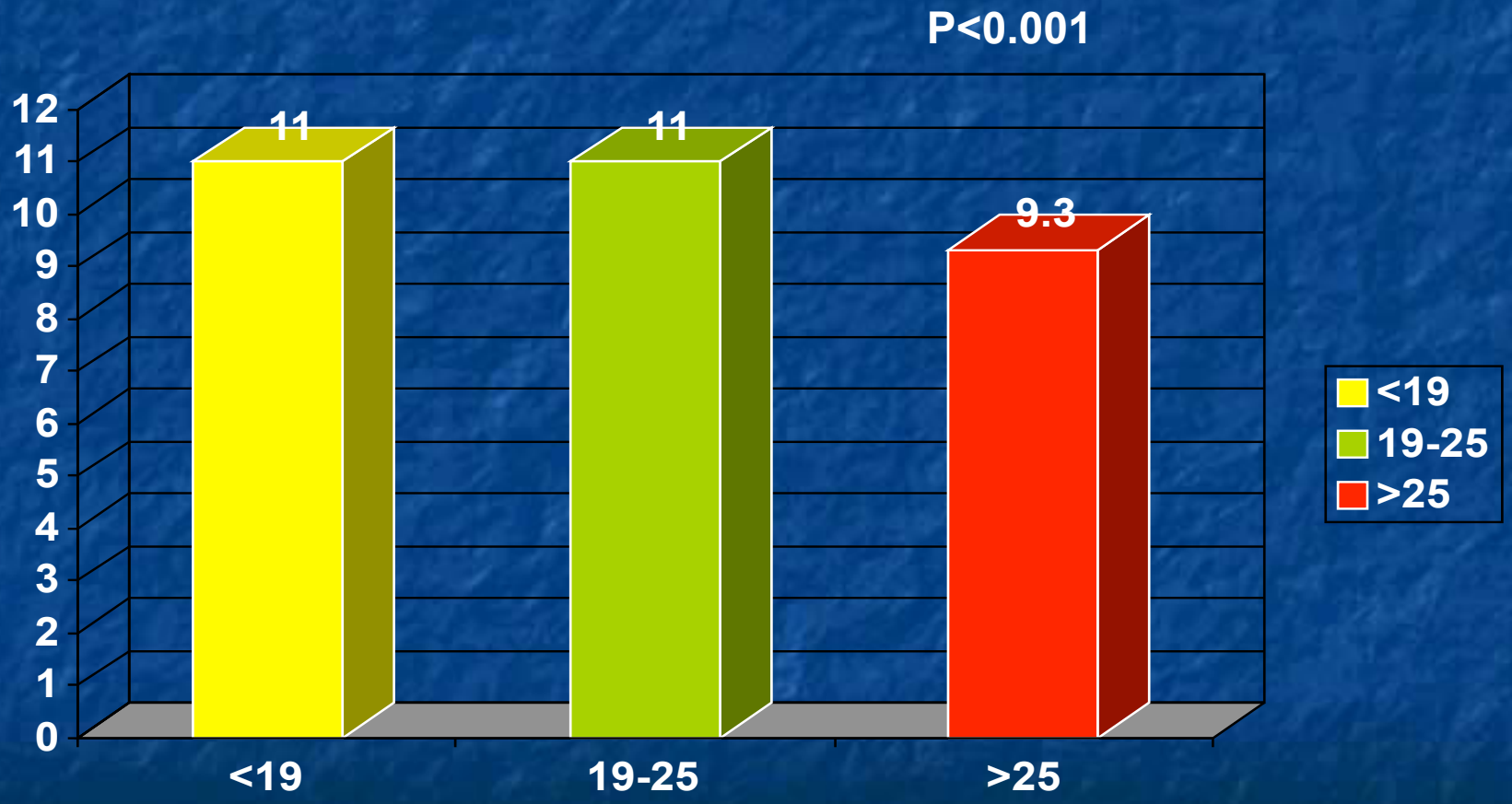
Patient Age



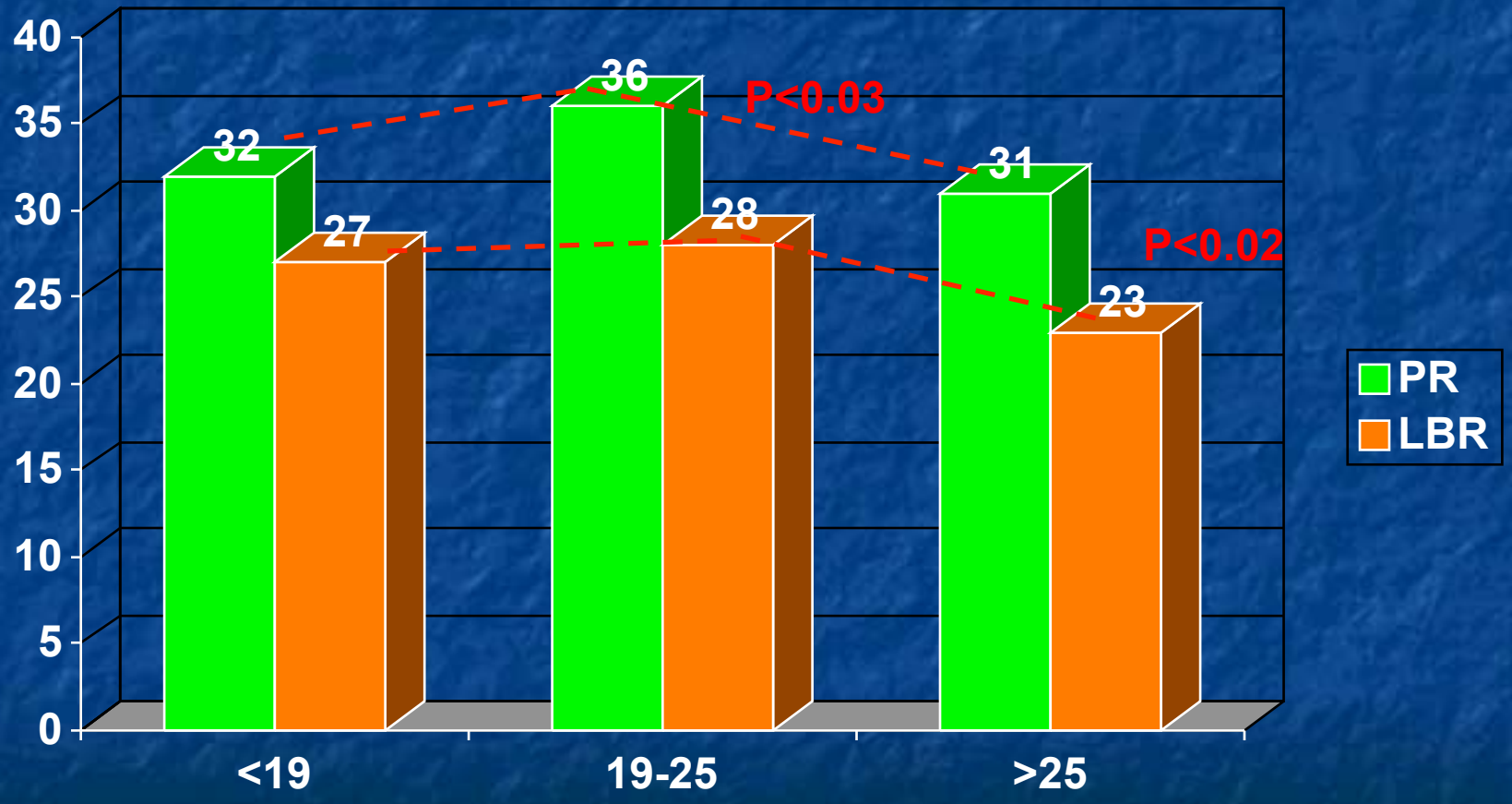
FSH dose of stimulation



Mean Number of Eggs Retrieved



IVF outcome



Literature Evidence

- Two systematic reviews in 2007-2008 found insufficient evidence that raised BMI affects IVF outcome [1,2]
- Since their publication, numerous relevant studies had been published

Human Reproduction Update, Vol.13, No.5 pp. 433–444, 2007 doi:10.1093/humupd/dmm017
Advance Access publication June 21, 2007

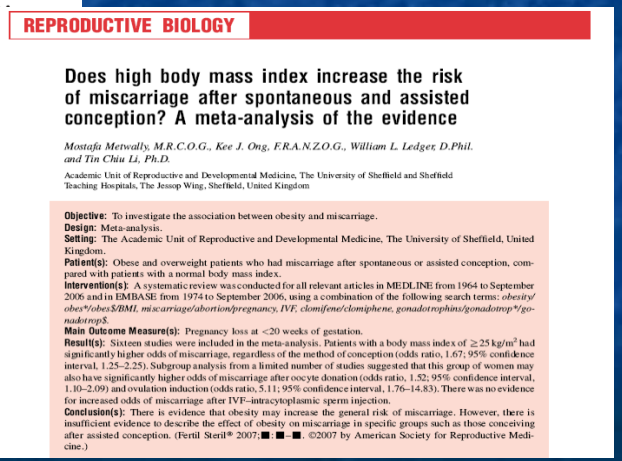
Effect of overweight and obesity on assisted reprodu technology—a systematic review

A. Maheshwari[1,4], Lawrize Stofberg[2] and S. Bhattacharya[3]

[1]Assisted Reproduction Unit, University of Aberdeen, Aberdeen Maternity Hospital, Aberdeen AB25 2ZL, UK; [2]Ob Gynaecology, Aberdeen Royal Infirmary, Aberdeen AB25 2ZL, UK; [3]Department of Obstetrics and Gynaecology, Dug Research on Women's Health, School of Medicine University of Aberdeen, Aberdeen AB25 2ZD, UK

[4]Correspondence address. Tel: +44-1224-553582; Fax: +44-1224-551072; E-mail: abha.maheshwari@abdn.ac.uk

Obesity is known to be associated with sub-optimal reproductive performance but its direct effect o assisted reproduction techniques (ART) is less clear. This present study aimed to perform a system available evidence to assess the effects of obesity on the outcome of ART. A number of observatio identified. Interpretation of the results was compromised by variations in the methods used to d and obese populations and inconsistencies in the choice and definition of outcome measures. women with a BMI of 25 kg/m^2 or less, women with a BMI ≥25 kg/m^2 have a lower chance of pre IVF [odds ratio (OR) 0.71, 95% CI: 0.62, 0.81], require higher dose of gonadotrophins (weighed 210.08, 95% CI: 149.12, 271.05) and have an increased miscarriage rate (OR 1.33, 95% CI: 1.06, 1.68 cient evidence on the effect of BMI on live birth, cycle cancellation, oocyte recovery and ovarian syndrome. Further studies with clear entry criteria and uniform reporting of outcomes are need the true impact of weight on the outcome of ART.



REPRODUCTIVE BIOLOGY

Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence

Mostafa Metwally, M.R.C.O.G., Kee J. Ong, F.R.A.N.Z.O.G., William L. Ledger, D.Phil. and Tin Chiu Li, Ph.D.

Academic Unit of Reproductive and Developmental Medicine, The University of Sheffield and Sheffield Teaching Hospitals, The Jessop Wing, Sheffield, United Kingdom

Objective: To investigate the association between obesity and miscarriage.
Design: Meta-analysis.
Setting: The Academic Unit of Reproductive and Developmental Medicine, The University of Sheffield, United Kingdom.
Patient(s): Obese and overweight patients who had miscarriage after spontaneous or assisted conception, compared with patients with a normal body mass index.
Intervention(s): A systematic review was conducted for all relevant articles in MEDLINE from 1964 to September 2006 and in EMBASE from 1974 to September 2006, using a combination of the following search terms: *obesity/obes*/obes$/BMI, miscarriage/abortion/pregnancy, IVF, clomifene/clomiphene, gonadotrophins/gonadotrop*/gonadotrop$.*
Main Outcome Measure(s): Pregnancy loss at <20 weeks of gestation.
Result(s): Sixteen studies were included in the meta-analysis. Patients with a body mass index of ≥25 kg/m^2 had significantly higher odds of miscarriage, regardless of the method of conception (odds ratio, 1.67; 95% confidence interval, 1.25–2.25). Subgroup analysis from a limited number of studies suggested that this group of women may also have significantly higher odds of miscarriage after oocyte donation (odds ratio, 1.52; 95% confidence interval, 1.10–2.09) and ovulation induction (odds ratio, 5.11; 95% confidence interval, 1.76–14.83). There was no evidence for increased odds of miscarriage after IVF–intracytoplasmic sperm injection.
Conclusion(s): There is evidence that obesity may increase the general risk of miscarriage. However, there is insufficient evidence to describe the effect of obesity on miscarriage in specific groups such as those conceiving after assisted conception. (Fertil Steril® 2007;■:■–■. ©2007 by American Society for Reproductive Medicine.)

1 Maheshwari et al. 2007

2 Metwally et al. 2008

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Objective

- **Perform an up-to-date systematic review**
- **Evaluate the impact of BMI on IVF outcome**
  - **live birth rate (LBR)**
  - **miscarriage rate (MR)**

Literature Search

- Literature Searches on MEDLINE, EMBASE and the Institute for Scientific Information conference proceedings from 1966-2010

- Study group:
  - BMI < 25 versus BMI ≥ 25 (overweight + obese)

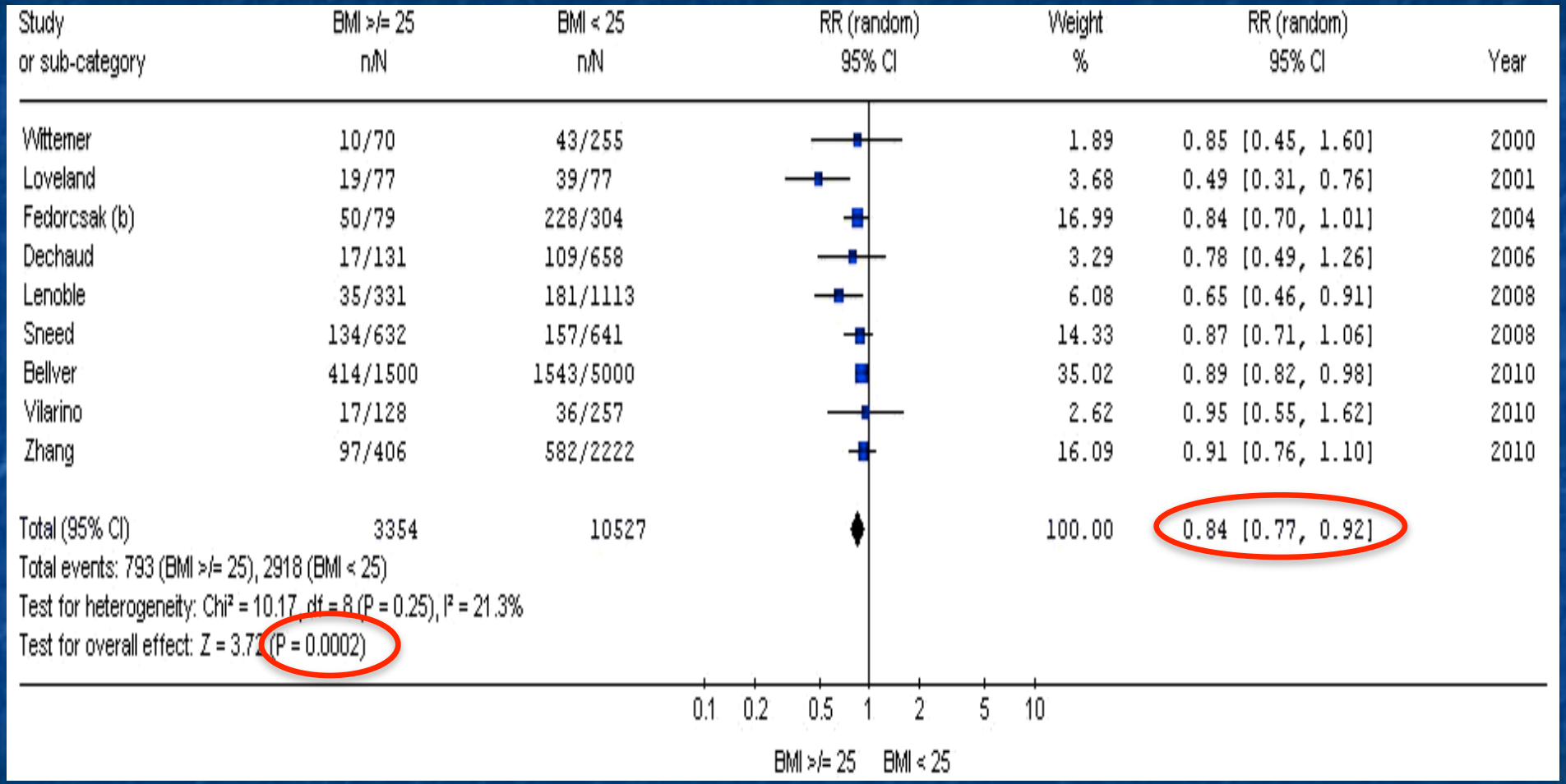
- Subgroup analysis:
  - BMI < 25 versus overweight (BMI ≥ 25–29.9)
  - BMI < 25 versus obese (BMI ≥30)

Results

- 33 studies
  - 25 studies: BMI <25 vs BMI ≥ 25
  - 16 studies: BMI <25 vs BMI 25-29.9
  - 15 studies: BMI <25 vs BMI ≥ 30

- 47967 treatment cycles
  - BMI < 25 n = 32496
  - BMI ≥ 25 n = 15471

LBR: BMI < 25 vs ≥ 25



Study or sub-category	BMI >/= 25 n/N	BMI < 25 n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI	Year
Wittemer	10/70	43/255		1.89	0.85 [0.45, 1.60]	2000
Loveland	19/77	39/77		3.68	0.49 [0.31, 0.76]	2001
Fedorcsak (b)	50/79	228/304		16.99	0.84 [0.70, 1.01]	2004
Dechaud	17/131	109/658		3.29	0.78 [0.49, 1.26]	2006
Lenoble	35/331	181/1113		6.08	0.65 [0.46, 0.91]	2008
Sneed	134/632	157/641		14.33	0.87 [0.71, 1.06]	2008
Bellver	414/1500	1543/5000		35.02	0.89 [0.82, 0.98]	2010
Vilarino	17/128	36/257		2.62	0.95 [0.55, 1.62]	2010
Zhang	97/406	582/2222		16.09	0.91 [0.76, 1.10]	2010
Total (95% CI)	3354	10527		100.00	0.84 [0.77, 0.92]	

Total events: 793 (BMI >/= 25), 2918 (BMI < 25)

Test for heterogeneity: Chi² = 10.17, df = 8 (P = 0.25), I² = 21.3%

Test for overall effect: Z = 3.72 (P = 0.0002)

LBR: overweight and obese

BMI <25 versus BMI 25-29.9

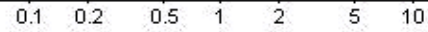
Study or sub-category	BMI 25 - 29.9 n/N	BMI Normal n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Year
Fedorcsak (b)	183/963	718/3457		27.39	0.91 [0.79, 1.06]	2004
Dechaud	11/83	76/394		2.32	0.69 [0.38, 1.23]	2006
Sneed	68/325	148/613		8.98	0.87 [0.67, 1.12]	2008
Bellver	315/1081	1230/3930		46.46	0.93 [0.84, 1.03]	2010
Zhang	90/379	582/2222		14.85	0.91 [0.75, 1.10]	2010
Total (95% CI)	2831	10616		100.00	0.91 [0.85, 0.98]	

Total events: 667 (BMI 25 - 29.9), 2754 (BMI Normal)
Test for heterogeneity: Chi² = 1.21, df = 4 (P = 0.88), I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)

BMI <25 versus BMI ≥30

Study or sub-category	BMI > 30 n/N	BMI Normal n/N	RR (fixed) 95% CI	Weight %	RR (fixed) 95% CI	Year
Fedorcsak (b)	78/463	718/3457		31.65	0.81 [0.66, 1.00]	2004
Dechaud	99/419	1230/3930		44.23	0.75 [0.63, 0.90]	2006
Sneed	66/307	148/613		18.43	0.89 [0.69, 1.15]	2008
Bellver	6/48	76/394		3.08	0.65 [0.30, 1.41]	2010
Zhang	7/27	582/2222		2.61	0.99 [0.52, 1.88]	2010
Total (95% CI)	1264	10616		100.00	0.80 [0.71, 0.90]	

Total events: 256 (BMI > 30), 2754 (BMI Normal)
Test for heterogeneity: Chi² = 1.89, df = 4 (P = 0.77), I² = 0%
Test for overall effect: Z = 3.72 (P = 0.0002)



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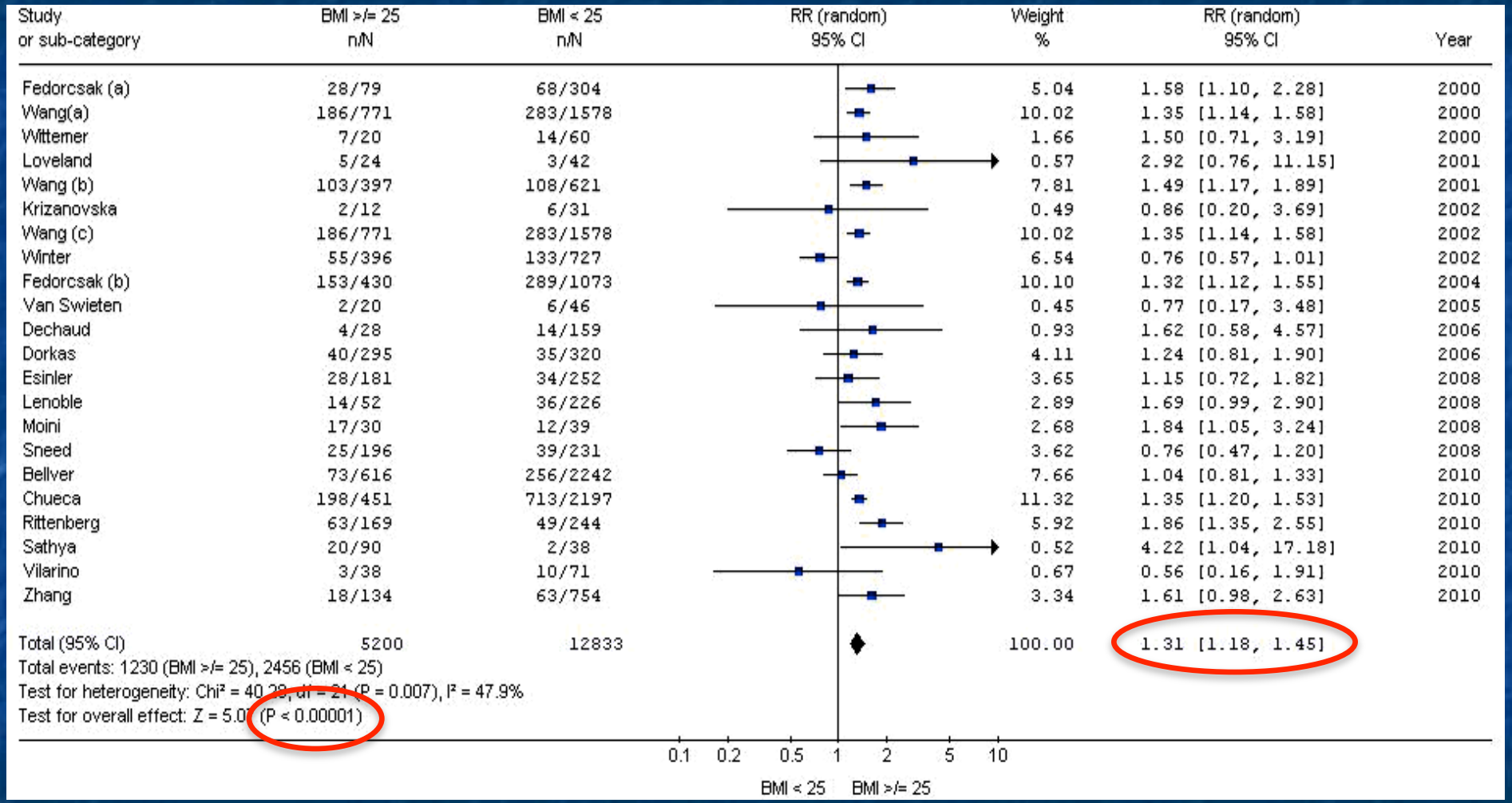
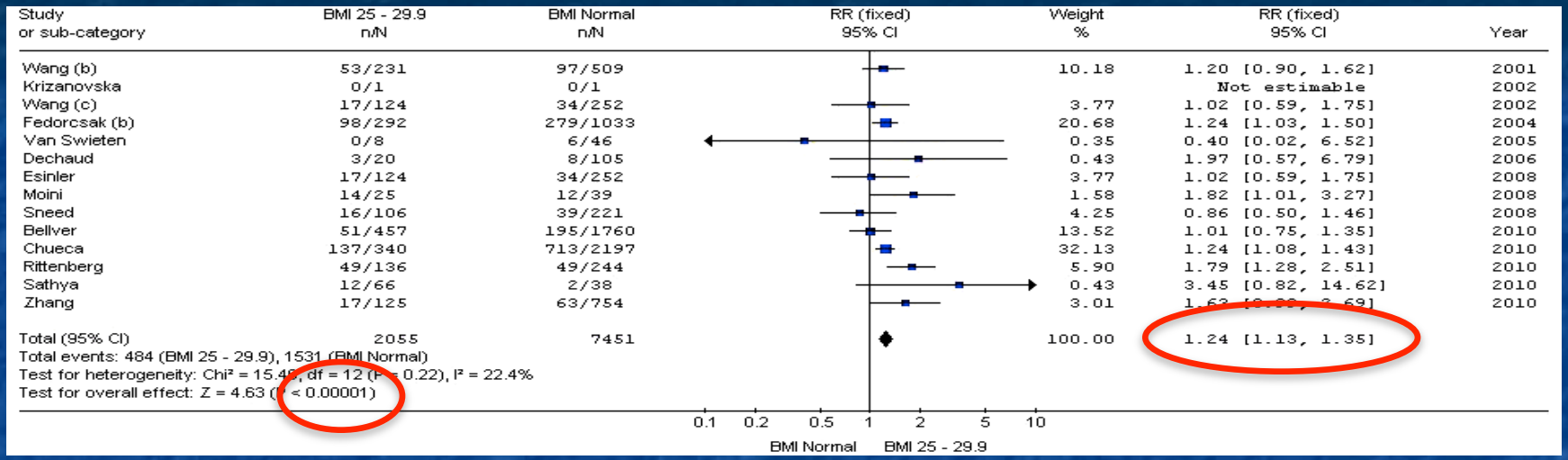
Miscarriage: BMI < 25 vs ≥ 25

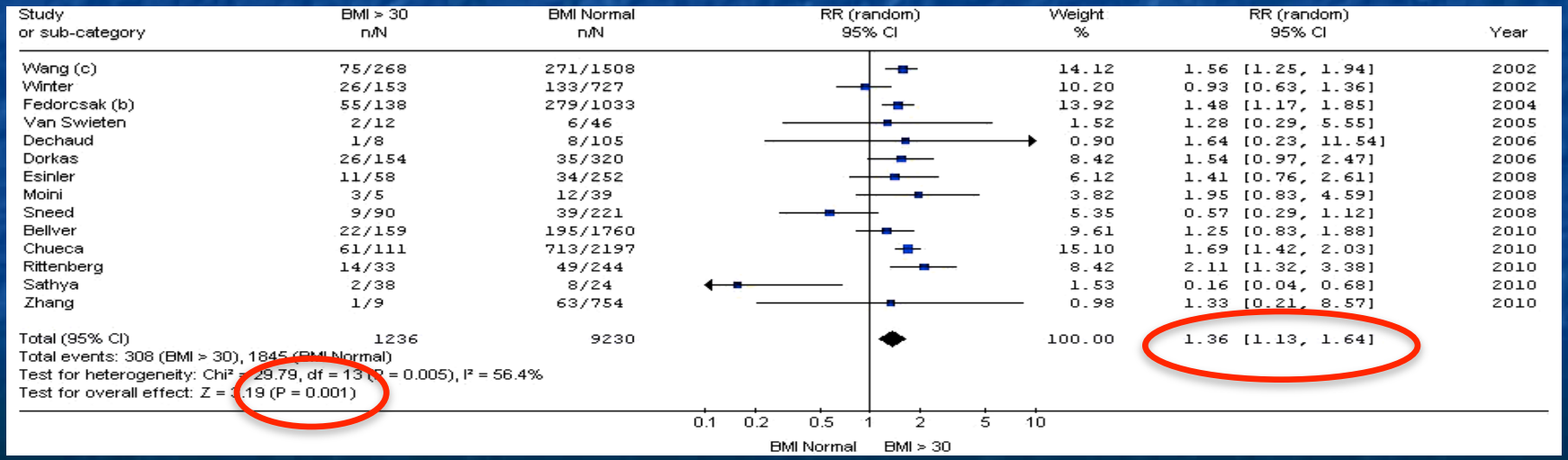


Miscarriage: overweight and obese

BMI <25 versus BMI 25-29.9



BMI <25 versus BMI ≥30



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Influence of BMI on risk of miscarriage after single blastocyst transfer

Vivian Rittenberg[1], Sviatlana Sobaleva[1], Alyaa Ahmad[1], Eugene Oteng-Ntim[1], Virginia Bolton[1], Yacoub Khalaf[1], Peter Braude[1,2], and Tarek El-Toukhy[1,*]

- More homogeneous study model
- Better selection of embryos, higher implantation potential [1]
- Potentially reduced miscarriage rate [2]

1 Papanikolaou et al. 2008 2 Papanikolaou et al. 2006

Material & Methods

- All pregnancies after SBT in 2006-2010
- Two groups according to WHO classification:
  - BMI 18.5-24.9
  - BMI ≥25
- Fresh (***f***) + Cryo-thawed (***c***) cycles
- Excluded:
  - oocyte donation
  - PGD cycles
  - BMI < 18.5
  - > 40 years old

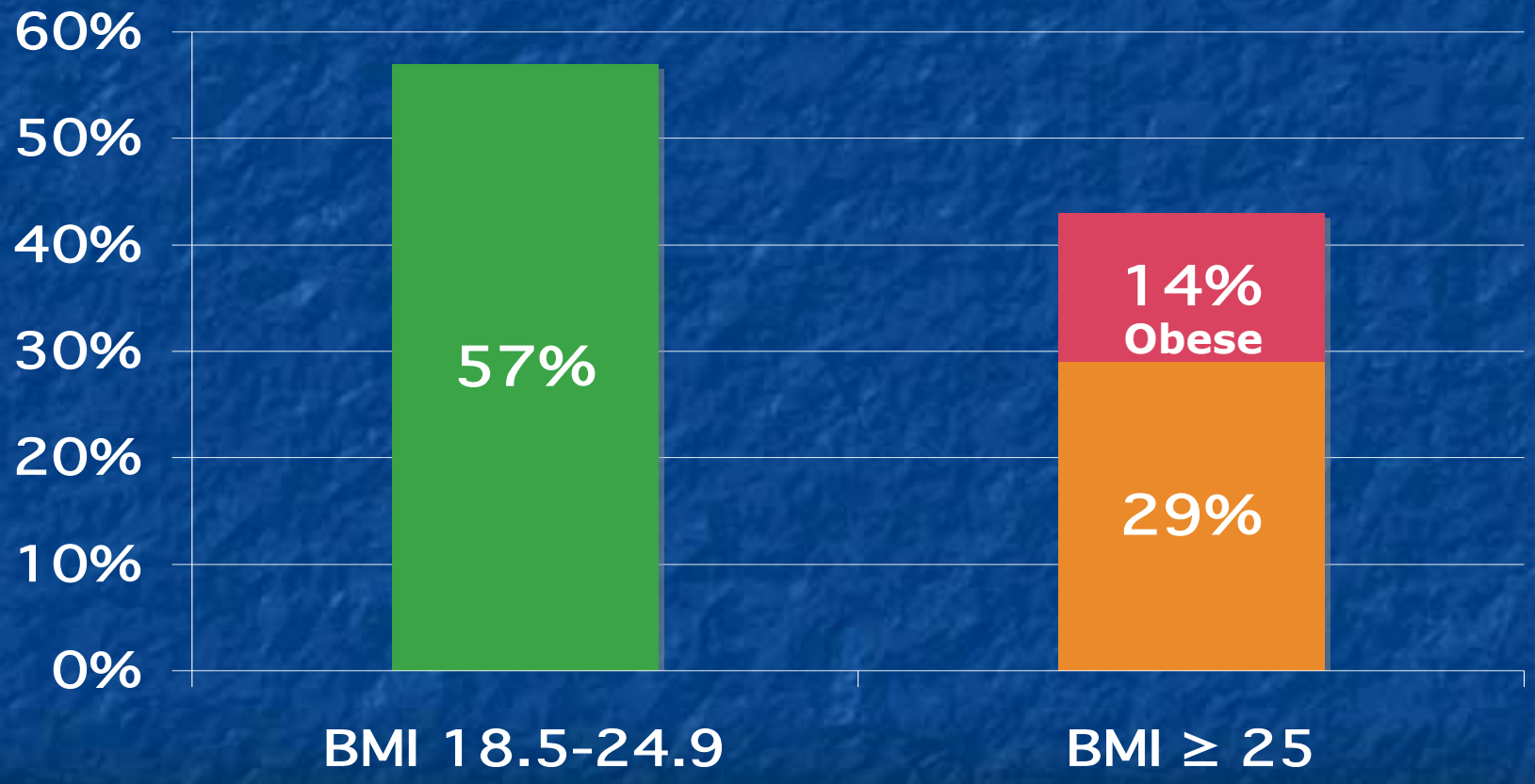
Results

- **Fresh (f)** IVF/ICSI cycles
  - 502 had SBT and 267 (53%) conceived

  Cryo-thawed (c) cycles:
  - 186 had SBT and 64 (34%) conceived

- **Total of 323 women conceived after SBT**

BMI distribution



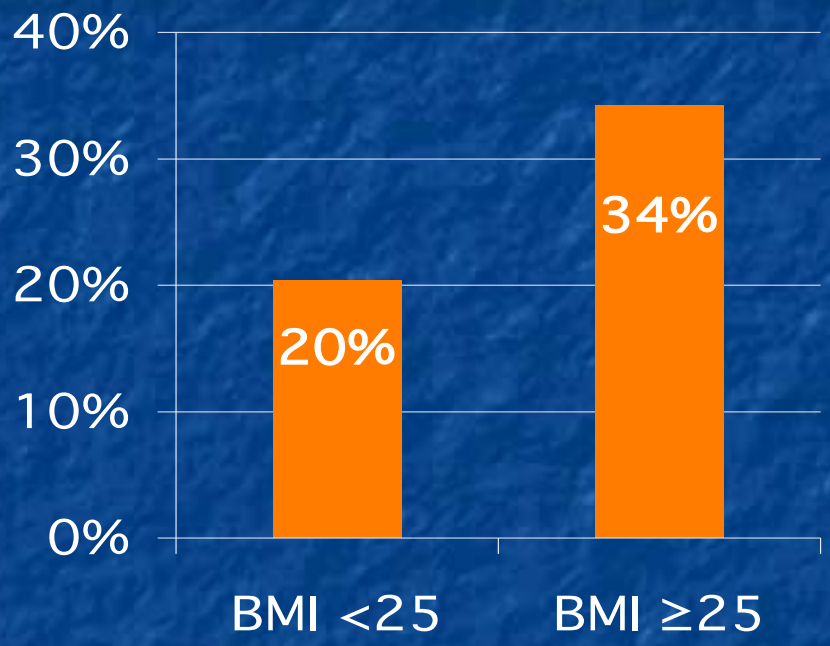
Fresh IVF cycle characteristics

	BMI <25	BMI≥25	P value
Duration of stimulation (days)	**10.4 ±1.7**	**11.3 ±2.3**	**<0.0003**
Daily dose of stimulation (FSH)	191±70	186±69	NS
N° oocytes	16.3±6.6	16.2±7.0	NS
Fertilisation rate	66%	66%	NS
2PN	10.3±4.7	10.4±3.9	NS
N° 8 cell embryos day 3	4.1±2.5	3.9±2.5	NS
N°blastocysts	6.4±3.3	6.7±3.0	NS
Blastocysts high quality	68%	62.2%	NS
freezing	88%	87%	NS
N°frozen	4±2.3	4±2.7	NS

Characteristics of frozen cycles

	BMI<25	BMI≥25	P value
Number	32	28	
Age at cryopreservation	32.7±4.4	32.9±3.65	NS
Previous miscarriage	28%	21.4%	NS
Dose of FSH	229.3±73.4	217.4±90.2	NS
N° of oocytes	16.6±7.2	17.7±9.7	NS
2PN	9.4±4.2	10.8±5.9	NS
N°frozen	2.8±2.1	2.96±2.5	NS
Primary cause of infertility:			
-unexplained	18.8%	7.1%	NS
- tubal	9.4%	17.9%	NS
- male	34.4%	42.9%	NS
-anovulation	9.4%	10.7%	NS
-other/mixt	28.1%	21.4%	NS

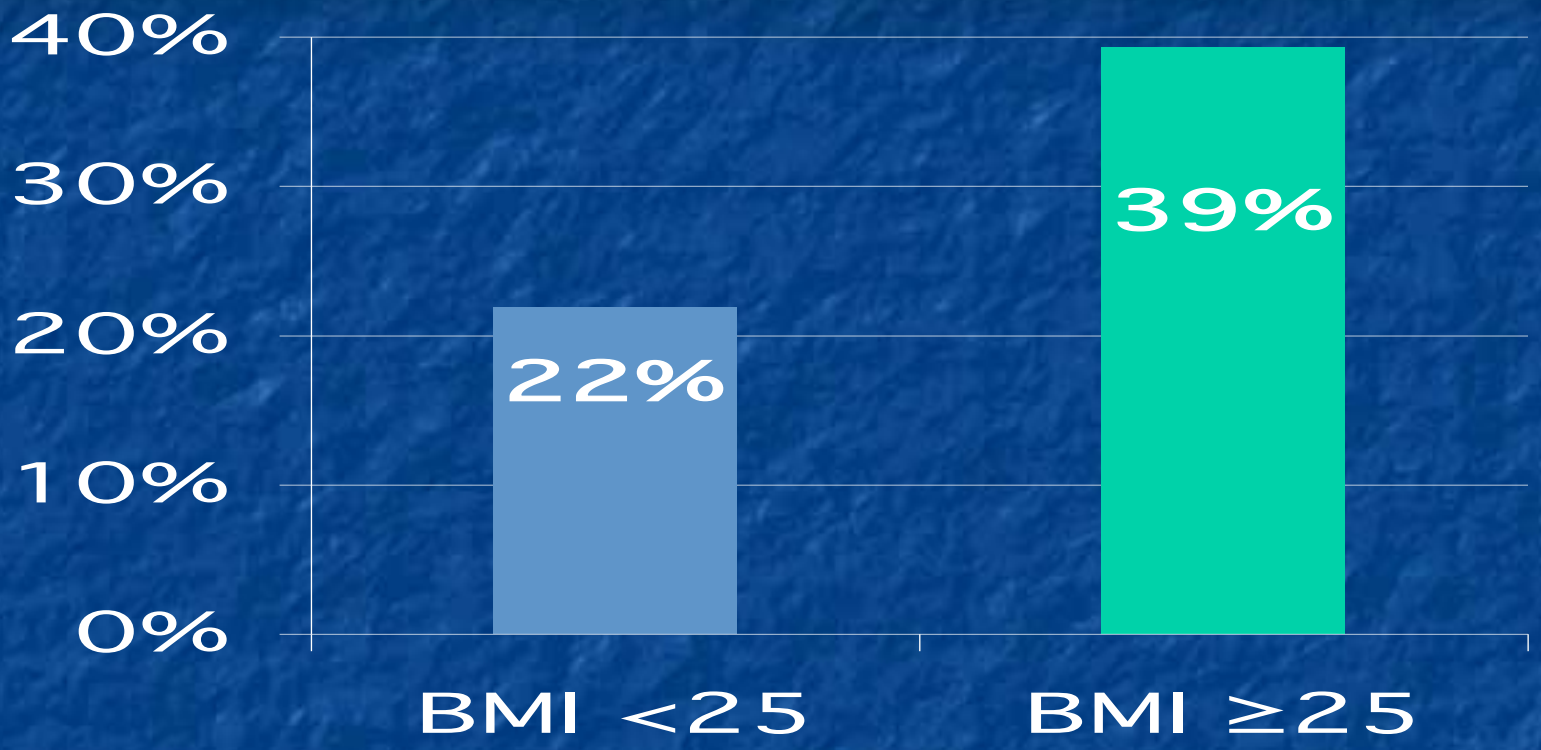
Miscarriage rates for fresh cycles



- **BMI 18.5-24.9 Miscarriage rate 20% (31/152)**
- **BMI ≥25 Miscarriage rate 34% (38/11**

OR: 2.03 (95% CI: 1.16-3.54) P=0.017

Results for Frozen cycles



- **BMI 18.5-24.9: miscarriage rate 22% (7/32)**
- **BMI ≥25 : miscarriage rate 39% (11/28)**

OR: 2.31 (95% CI: 0.7-7.2) p=0.14

Overall miscarriage rates (f+c) cycles

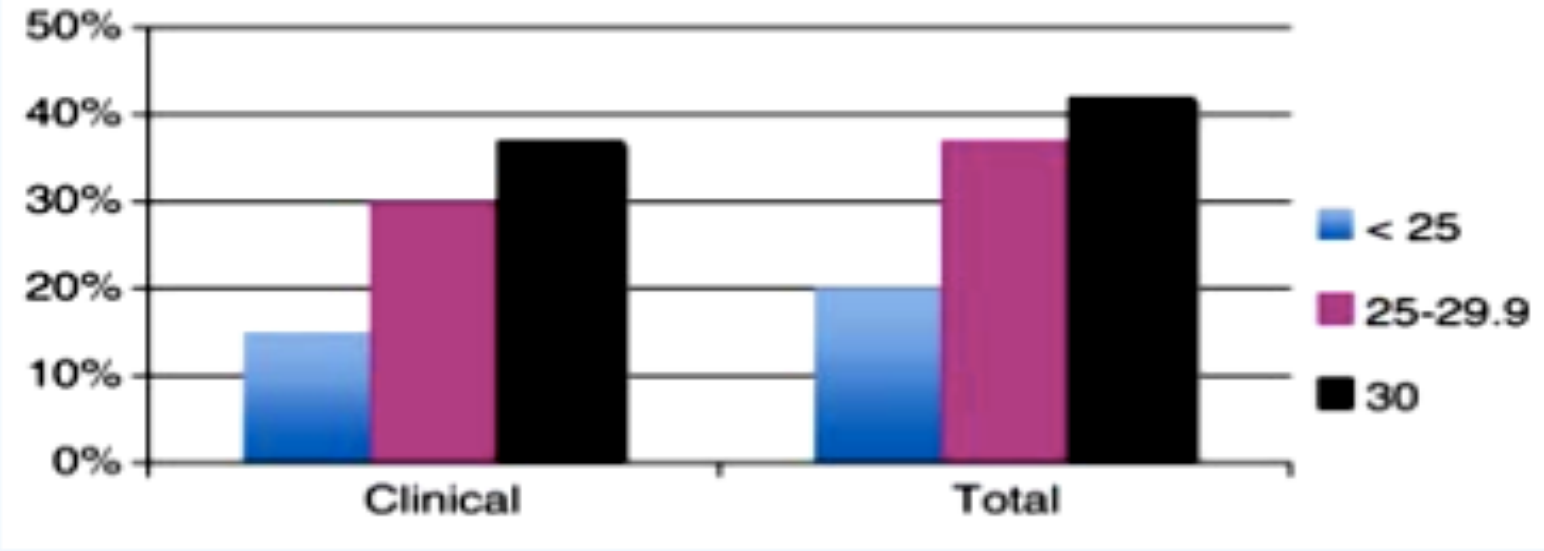


Figure 1 Miscarriage rates in the three BMI groups.

- **BMI 18.5-24.9: miscarriage rate 21% (38/184)**
- **BMI ≥25: miscarriage rate 35% (49/139)**

OR:2.09 (CI: 1.27-3.44, p=0.005)

Adjusted risk of miscarriage

- female age
- duration and cause of infertility (PCOS)
- smoking status
- previous miscarriage
- ovarian reserve
- blastocyst grade

BMI≥25

OR: 2.18 (95% CI 1.16-4.10, P<0.001)

Obesity and Poor IVF Outcome

Effects of obesity upon ART

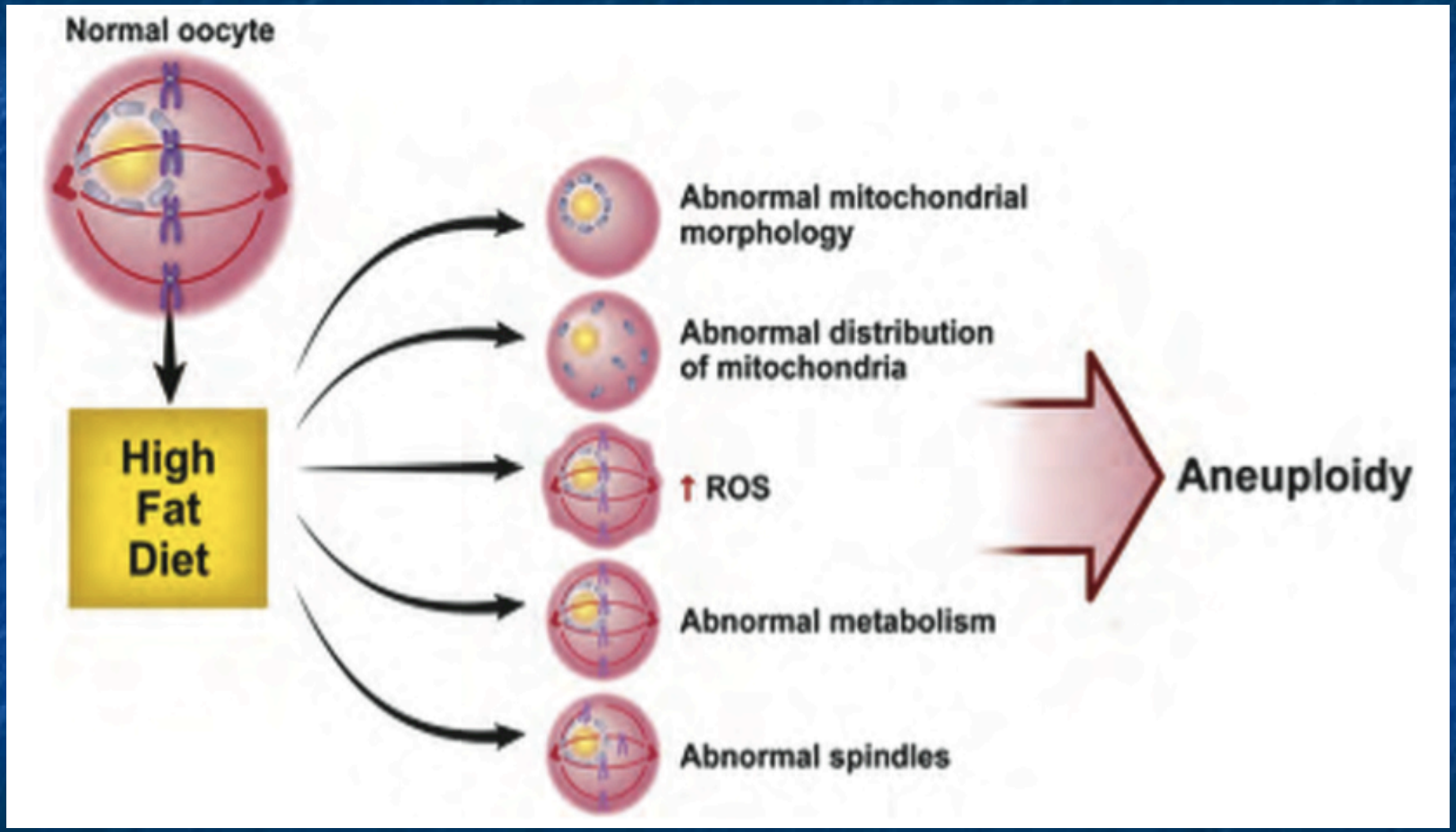
Impaired USS image quality due to adipose tissue[a]
Increased duration of stimulation
Increased total gonadotrophin dose required (WMD 361.94, 95% CI: 156.47, 567.40; BMI <30 vs >30)[b]
Increased follicular asynchrony[c]
Increased cycle cancellation (OR 1.35, 95% CI: 0.99, 1.84; BMI >30 vs <30)[d]
Poor response to superovulation[e]
Reduced follicular hCG concentration on day of ovum pickup (inverse correlation with BMI ($r = -0.353$, $P < 0.001$)
Relative reduction in number of cumulus–oocyte complex recovered at ovum pickup[g]
Relative reduction in metaphase II oocytes recovered at ovum pickup[h]
Reduced number of surplus good quality embryos available for cryopreservation[i]
Reduced pregnancy rates (OR 1.47, 95% CI: 1.20, 1.80; BMI <30 vs >30)[j]
Increased miscarriage rates (OR=1.53, 95% CI: 1.27, 1.84; BMI >30 vs <30)[k]

Brewer & Balen, 2010

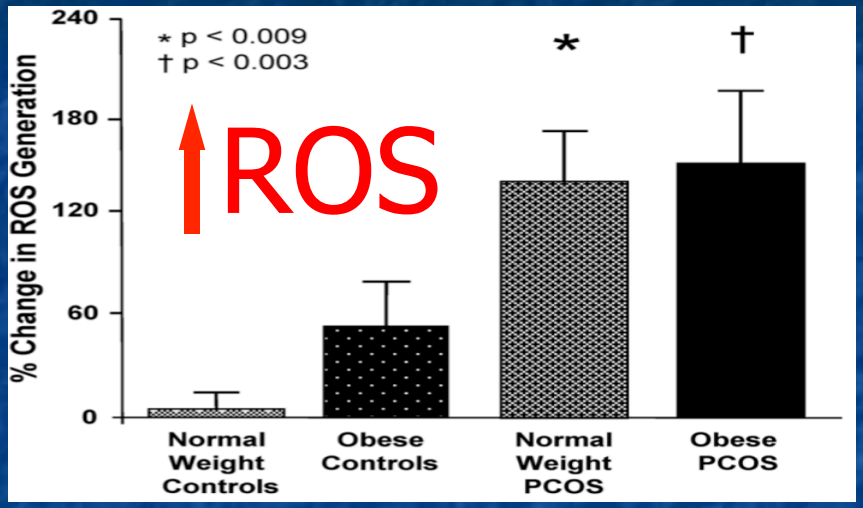
Link Between Obesity and Poor IVF Outcome

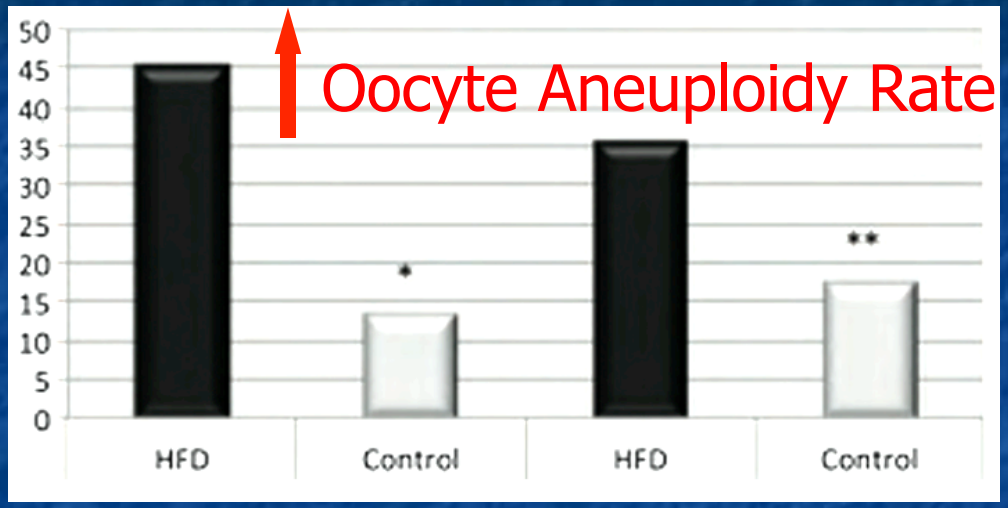
- Poor oocyte development
- Poor embryo development
- Deficient endometrial receptivity

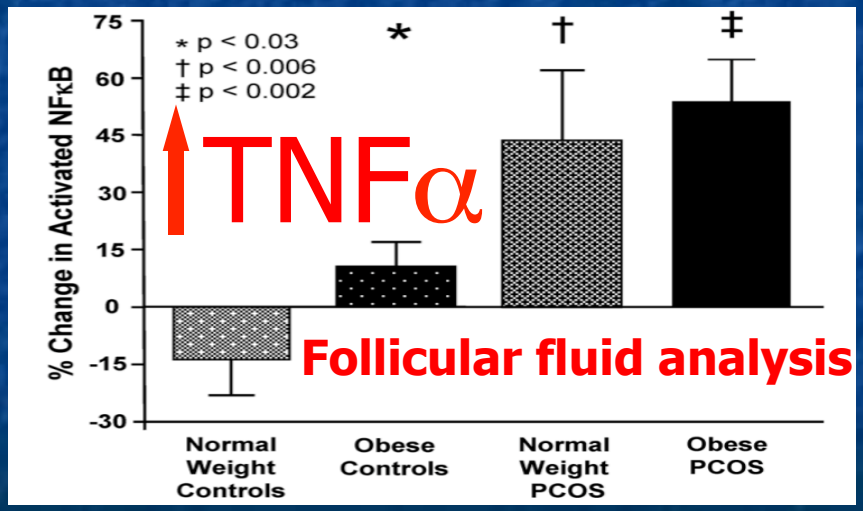
Obesity and Poor Oocyte Quality

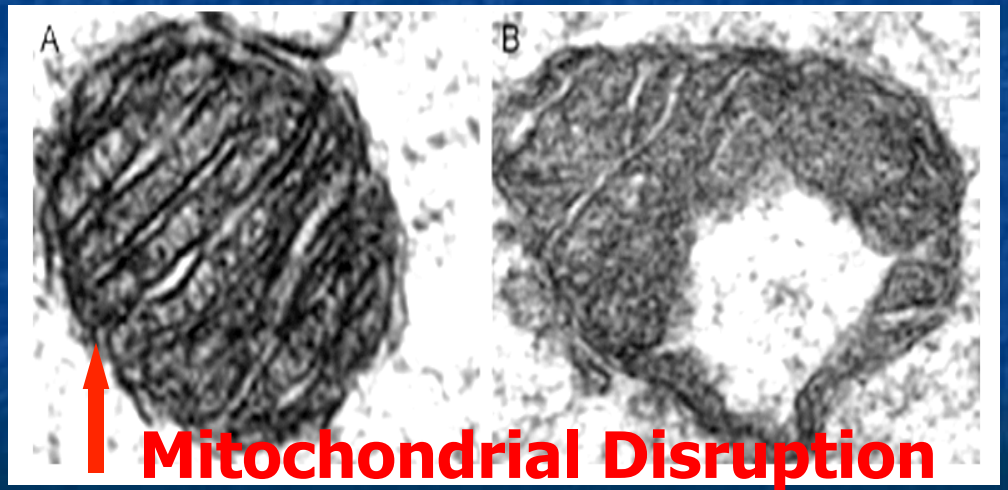


Obesity and Poor Oocyte Quality



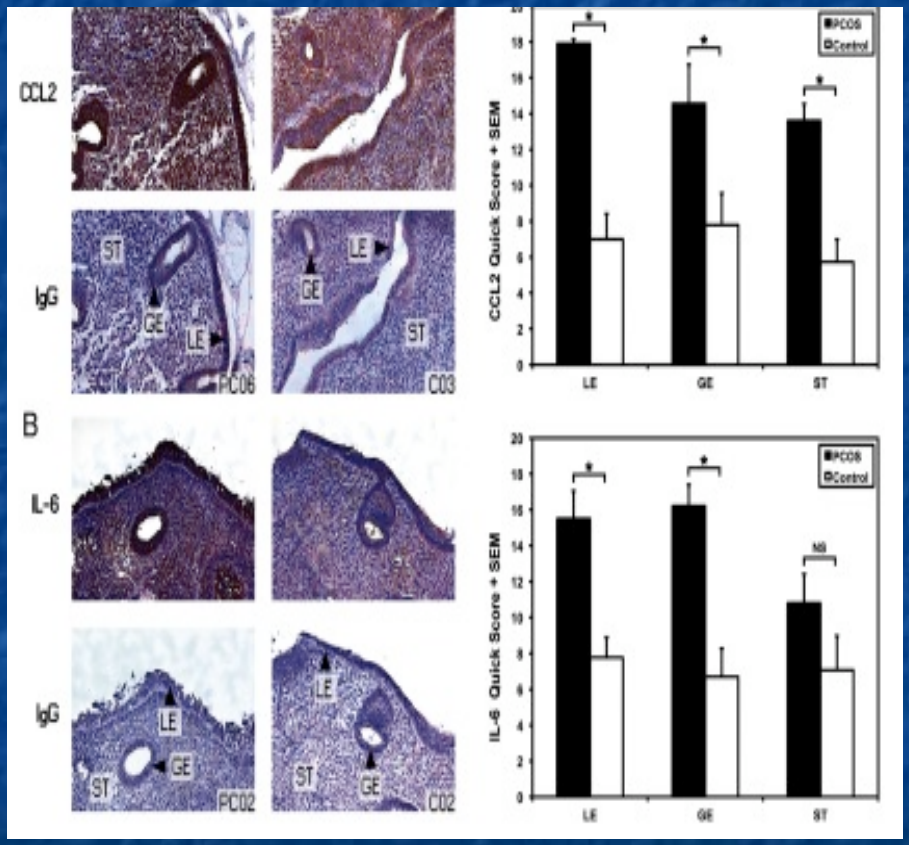






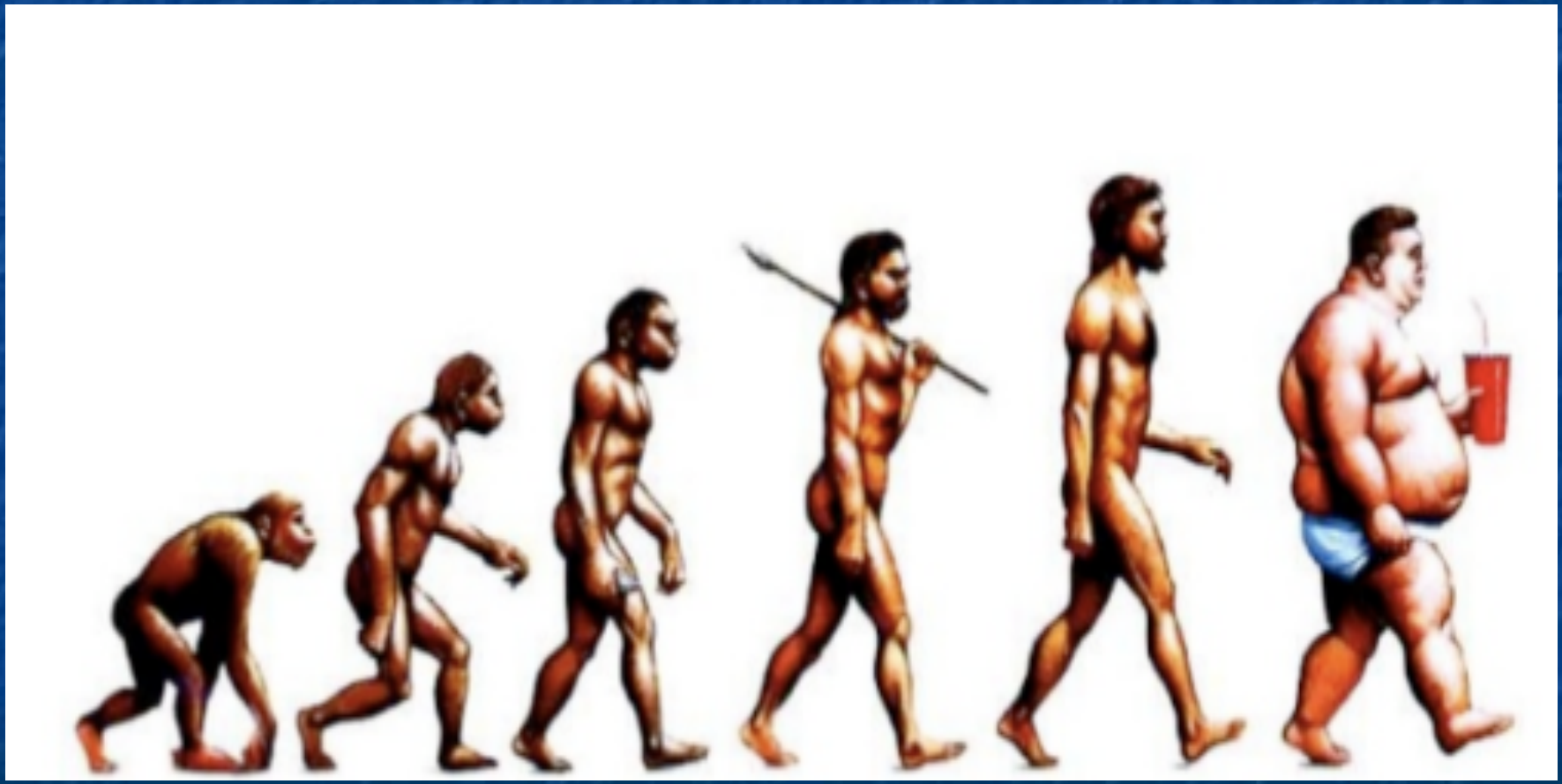
Obesity and Endometrial Receptivity

- Increased pro-inflammatory markers
- Increased Leptin level impairs trophoblastic invasion
- Increased likelihood of luteal-phase defect

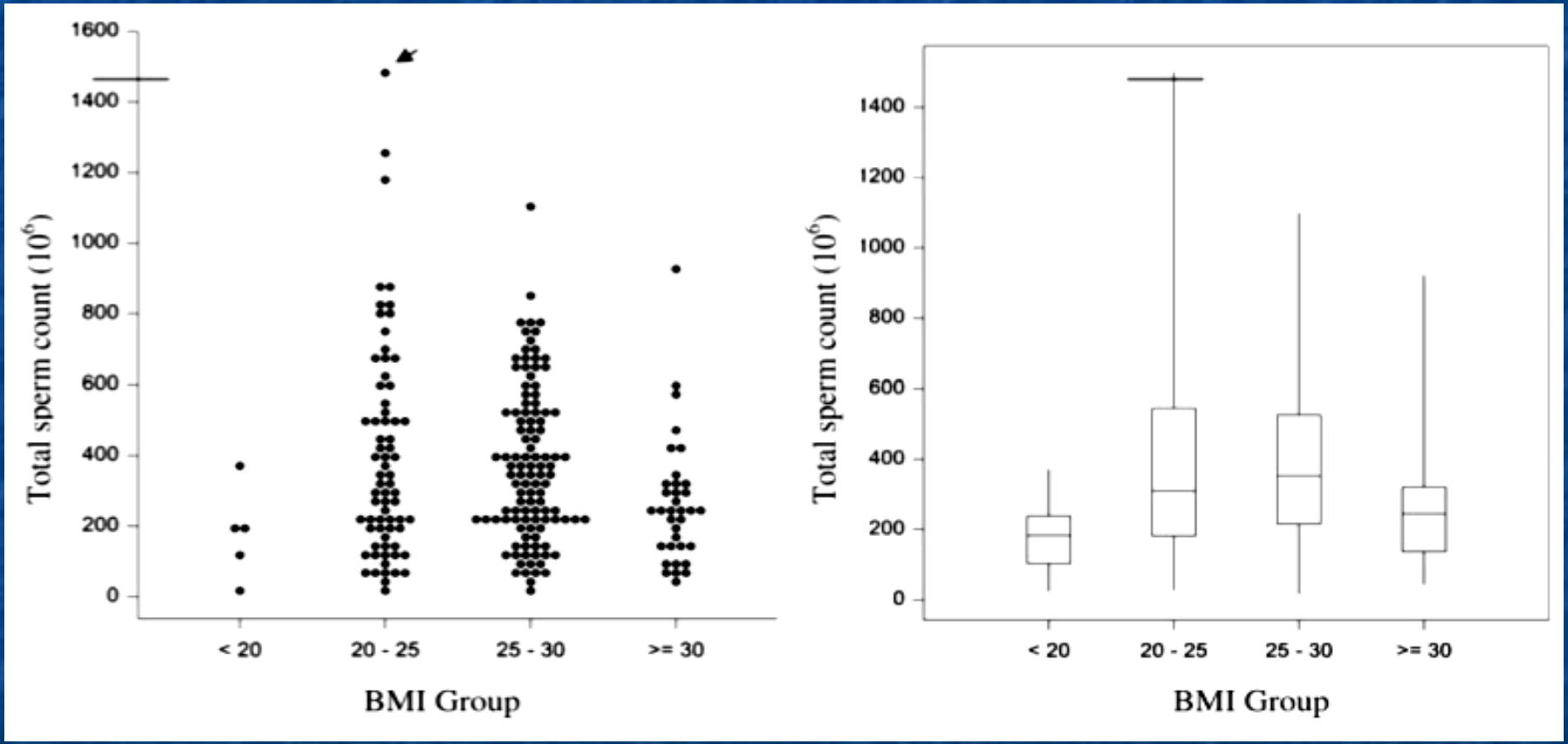


Piltonen et al, 2013

ART and Male Obesity



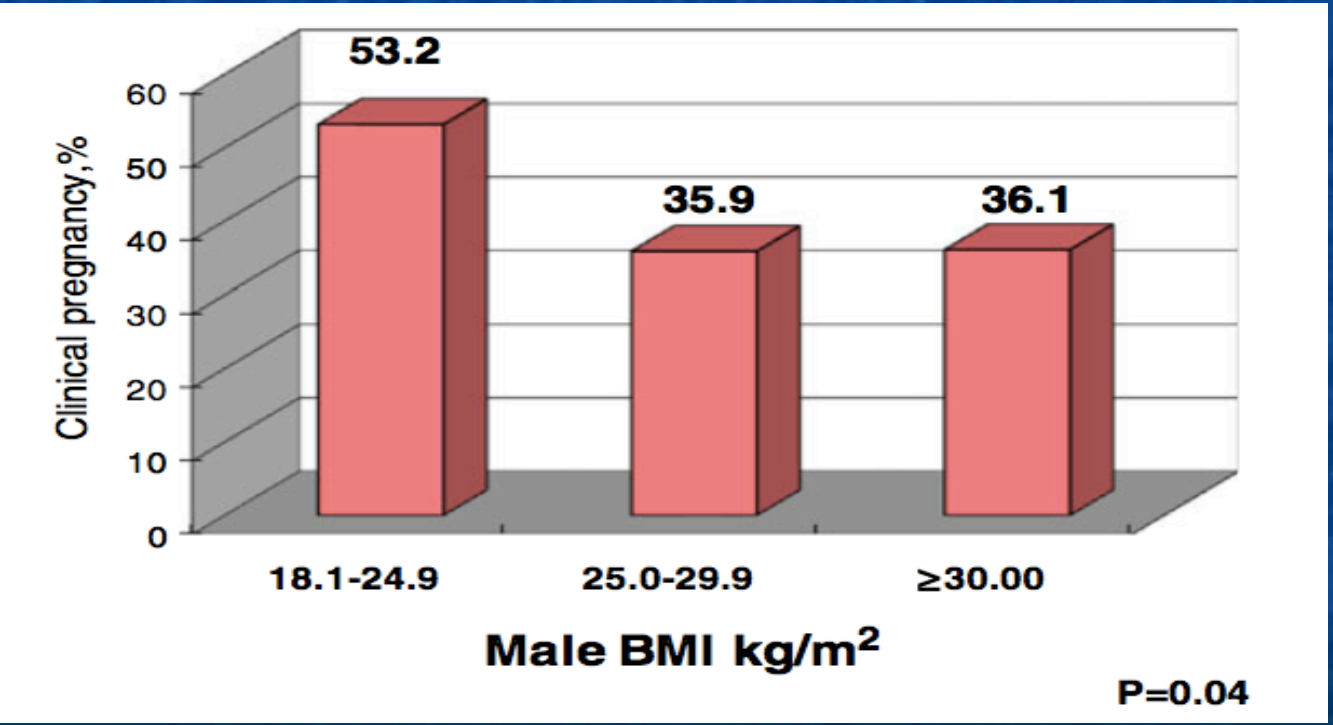
Obesity Reduces Sperm Count



Stewart et al, 2009

Male Obesity and ART Outcome

Between 2010-2015, six studies (n = 4497) reported lower CPR with increased male BMI



(Keltz 2010; Colaci 2012; Ramasamy 2013; Petersen 2013; Merhi 2013; Umul 2015)

Male Obesity and ART Outcome

Poorer ART outcome was most significant in IVF, but not ICSI, cycles (synergistic effect)

Table 3 Likelihood of clinical pregnancy after ART, presented as odds ratio (95% confidence interval)

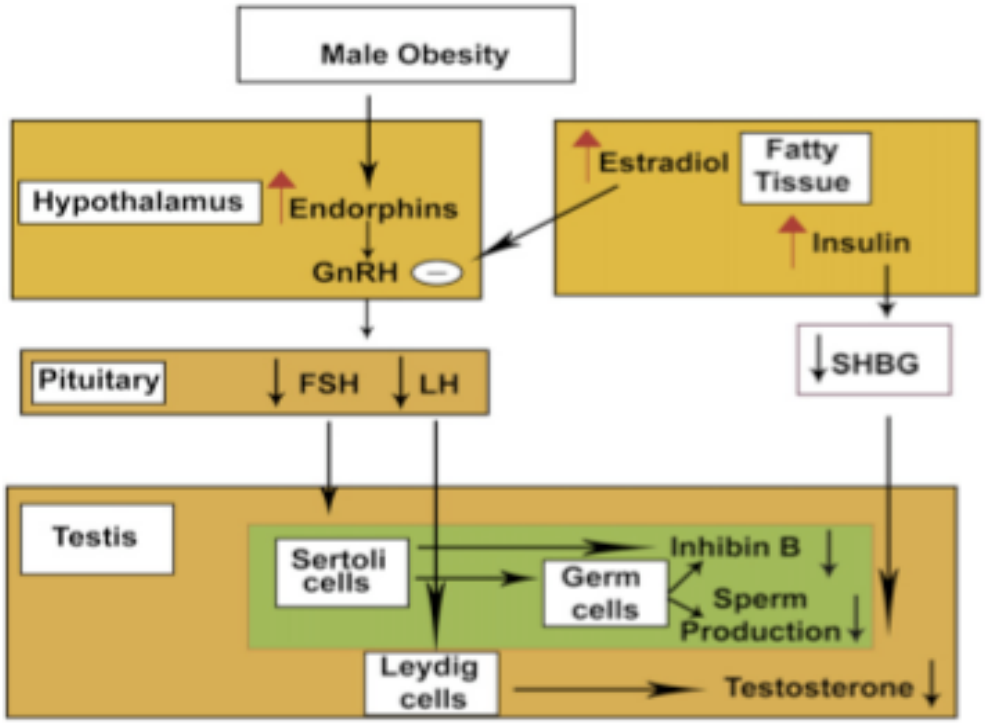
Determinant	IVF	ICSI
Male BMI ≥25 kg/m2		
Unadjusted	0.20 (0.06–0.66)[b], p=0.01	0.74 (0.37–0.45), p=0.38
Adjusted[a]	0.21 (0.07–0.69)[b], p=0.01	0.75 (0.38–1.49), p=0.41

(Keltz 2010)

Poor ART outcome with male obesity

FIGURE 1

Proposed pathways for hormonal alterations associated with male obesity.



Hammoud. Obesity and male infertility. Fertil Steril 2008.

- Reduced count
- Reduced motility
- Reduced morphology
- Increased DNA fragmentation
- Increased ROS

Male BMI and ICSI Outcome

- Prospective study of 800 couples having 1st or second ICSI cycles - BMI calculated in clinic using a standardised method
- Single blastocyst transfer
- Adjusted for female BMI and all important confounding variables
- Live birth rate is primary outcome

Does weight loss improve ART outcome?

Sim KA, Partridge SR, Sainsbury A

Weight loss in overweight and/or obese women via:

- Low-energy diet and lifestyle changes
- Non-surgical medical interventions, including Metformin
- Bariatric surgery

1 - significantly increased pregnancy and/or live birth rates

2 - increased number of embryos available for transfer

3 - reduced number of cycles required to achieve pregnancy

4 - decreased miscarriage rate

Obes Rev 2014; 15: 839-50

Conclusion

- The obesity epidemic presents a challenge to fertility specialists
- Obesity increases miscarriage and reduces live birth rates after ART
- Weight loss should be encouraged for obese and overweight women and men
- This information should be provided to all couples before starting IVF


THANK YOU
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Guy's and St Thomas' NHS
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