How can obesity and insulin resistance impact on implantation failure and / or miscarriage

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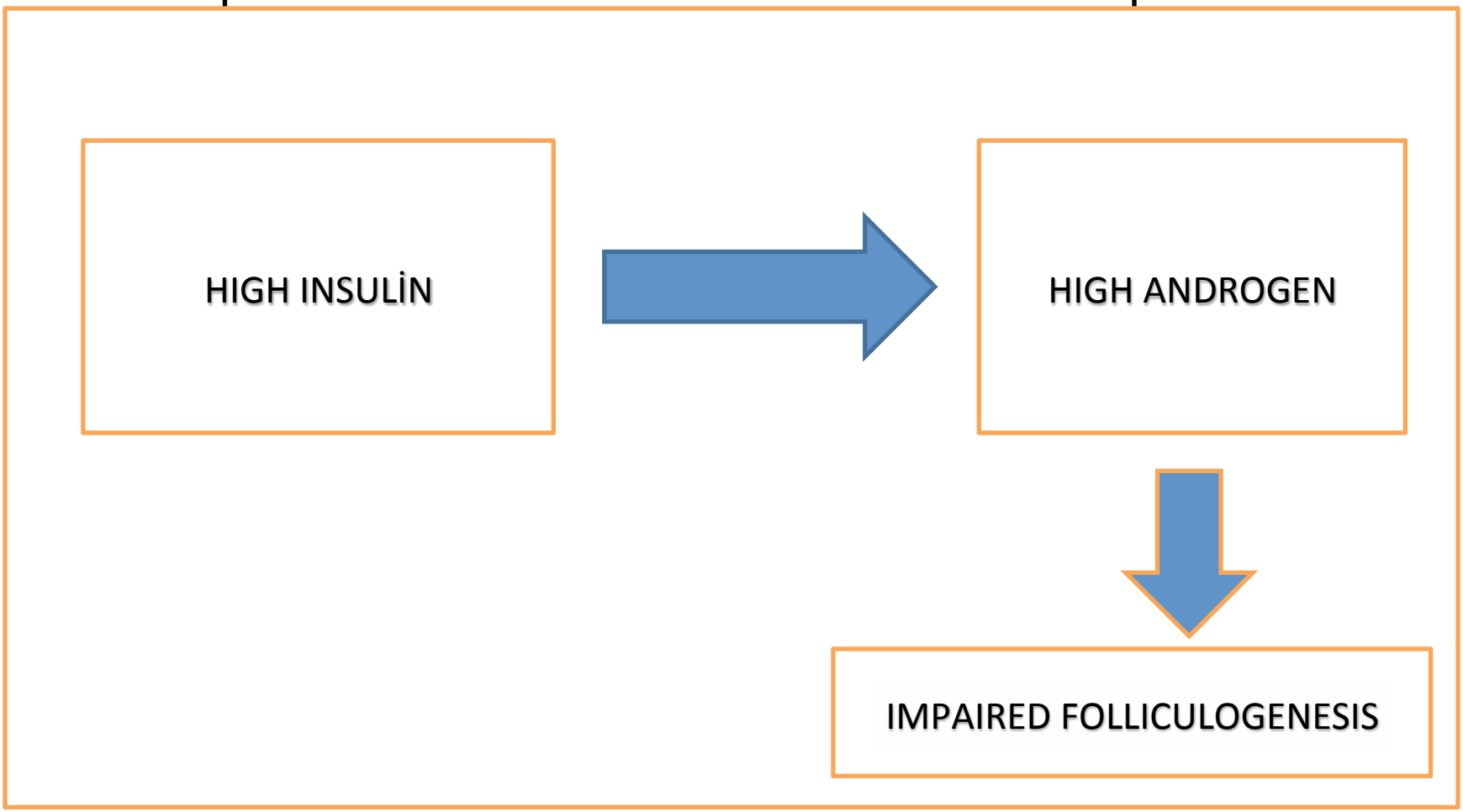
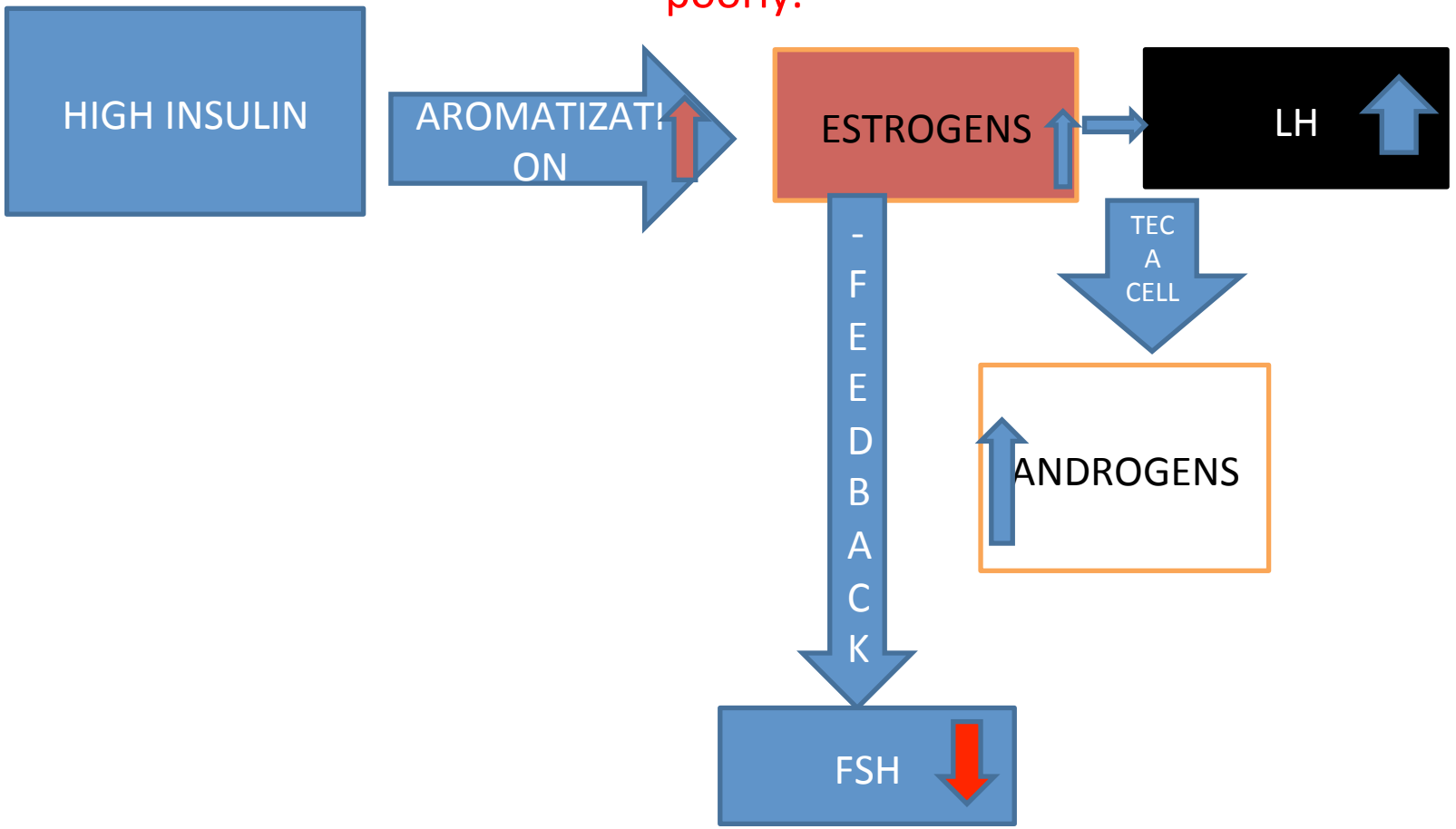
HOW DOES INSULİN RESISTANCE AND OBESITY AFFECT FERTILITY

In polycystic ovary syndrome and obesity high insulin levels cause the follicules in the ovary to produce male hormones. These male hormones (androgens) slow down the development of the follicules and can even stop ovulation.

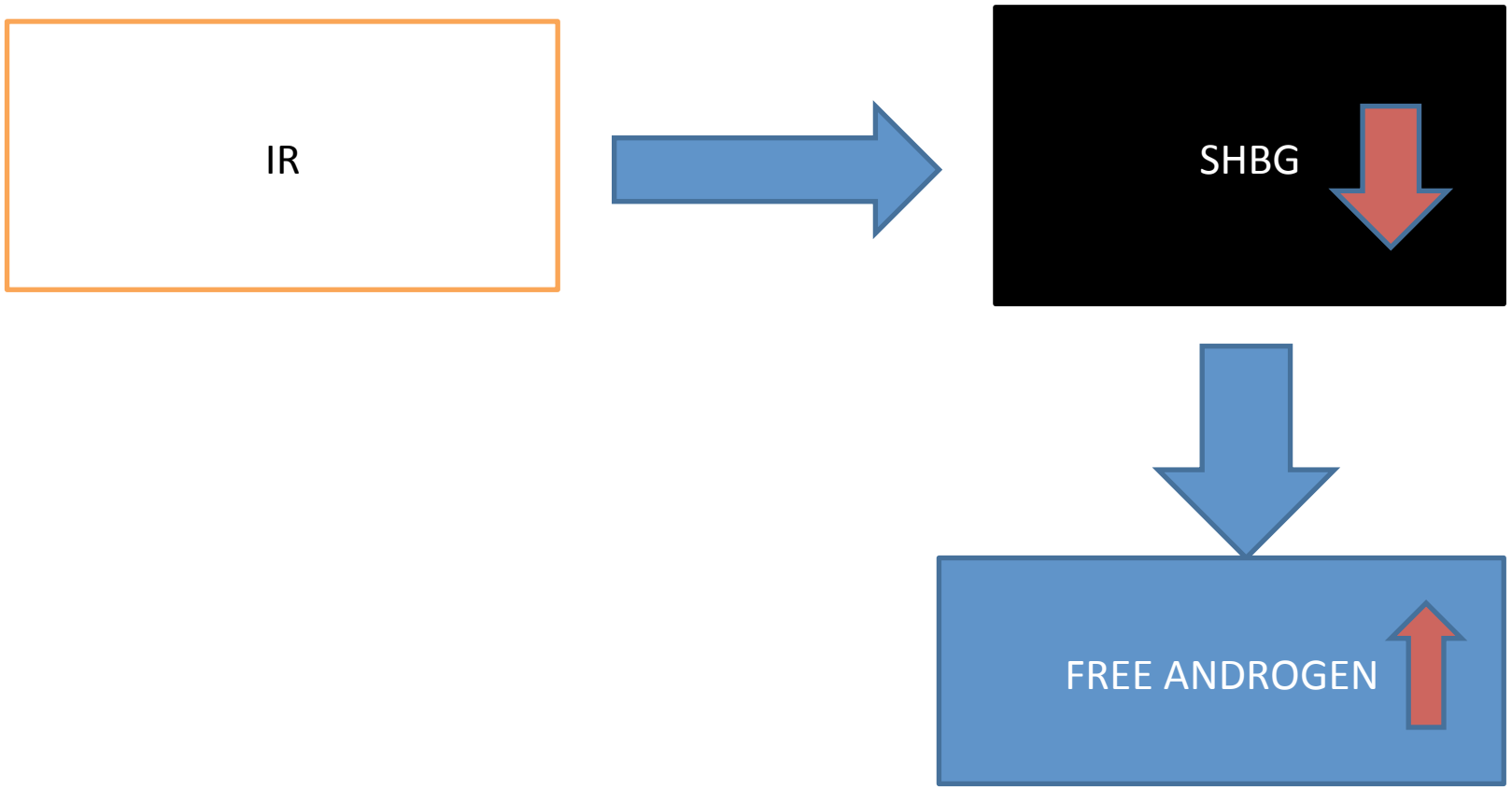


High amounts of insulin also cause fat cells to convert testosterone into estrogen, with aromatization process. High estrogen levels increase the pituitary gland's secretion of Luteinizing Hormone (LH) which result in even more testosterone release from the ovary. ''vicious cycle'' .High estrogen also suppresses Follicule Stimulating Hormone (FSH), causing the eggs to develop poorly.



Insulin Resistance (IR)

Lowers sex hormone binding globulin (SHBG) which normally binds up hormones and keeps them from activating tissue receptors. When SHBG is low there are more androgens freely floating in the bloodstream available to act on tissues and therefore produce androgenic effects.

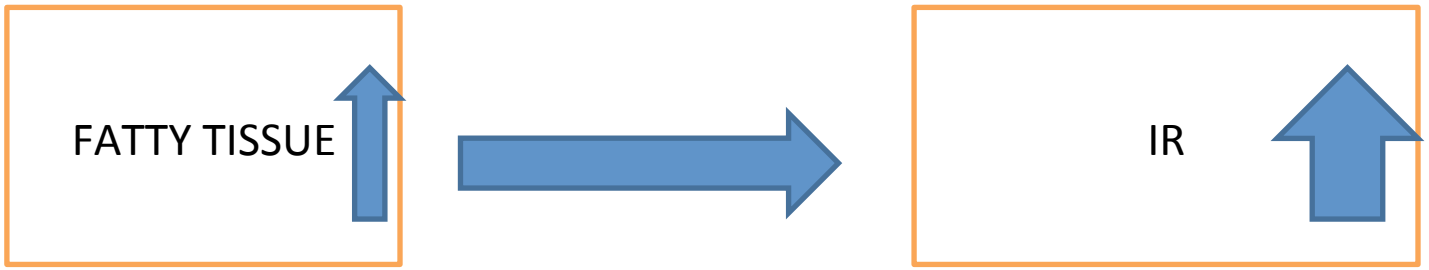


IN PCOS

- Regardless Slim or overweight IR is always a part of condition.

Obese or overweight Pcos

- More fatty tissue further aggrevates IR.



IR is associated with inflamation

- Certain inflammatory factors have been found to be high like CRP and homocysteine are also potential factors in miscarriage and implantation failure.

IR

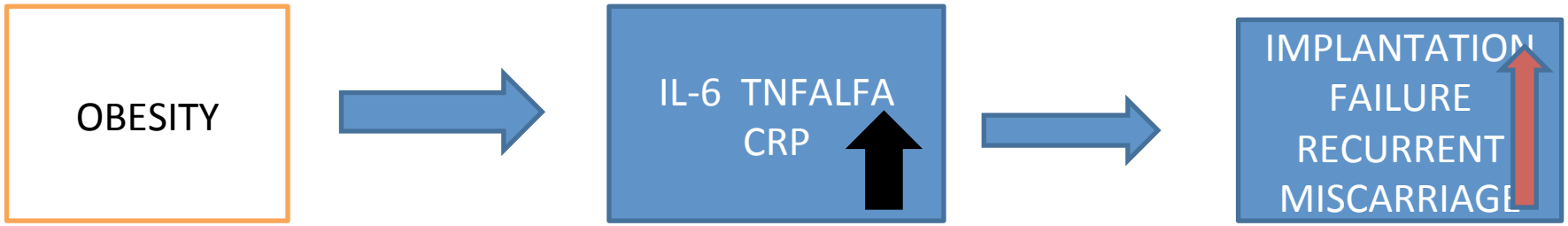
- Another large study suggested that insulin resistance was an independent risk factor for recurrent miscarriages, even when controlled for PCOS.

OBESITY

- Insulin resistance increases sharply at a BMI . level of 27 and above. Obese women with pcos have even more problems with fertility when compared to lean pcos women.This is because high BMI greatly agrevates the underlying insulin resistant state that is already present in pcos.

OBESITY

- Obesity also produces chronic low-grade inflammation. Inflammation has been associated with different fertility conditions such as implantation failure and recurrent miscarriage. A study on mouse models of obesity found elevated inflammatory markers interleukin-6, TNF-alpha and CRP, all of which have been associated with infertility.



21. Jungheim ES, Louden ED, Chi MM, Frolova AI, Riley JK, Moley KH. Preimplantation exposure of mouse embryos to palmitic acid results in fetal growth restriction followed by catch-up growth in the offspring. Biology of reproduction. 2011 Oct;85(4):678–683.

- In an in vitro model of obesity, pre-implantation embryos exposed to excess amounts of palmitic acid—a fatty acid that has been detected in uterine and tubal fluid. This exposure resulted in abnormal embryonic expression of the IGF-1 receptor, which is responsible for insulin signalling in the embryo. When transferred back into normal recipient mice, the palmitic acid-exposed embryos resulted in growth-restricted fetuses and offspring demonstrated a metabolic-like syndrome. Data from a similar model of type II diabetes demonstrate that embryonic insulin resistance is associated with increased risk of miscarriage, and that metformin, an insulin sensitizer, reverses this risk.

- Pathogenetically, the insulin resistance in at least 50% of PCOS women is believed to be related to excessive serine phosphorylation of the insulin receptor. Increased insulin receptor serine phosphorylation decreases its protein tyrosine kinase activity and is one mechanism for the post-binding defect in insulin action characteristic of PCOS.

Presumably, a serine/threonine kinase, that phosphrylates serine residues of insulin receptor β-subunit, causes this abnormality and is an example of an important mechanism for human insulin resistance related to factors regulating insulin receptor signaling. The serine/threonine kinase also increases the serine phosphorylation of P450c17α, the key enzyme of controlling androgen biosynthesis, leading to increased production of androgens.

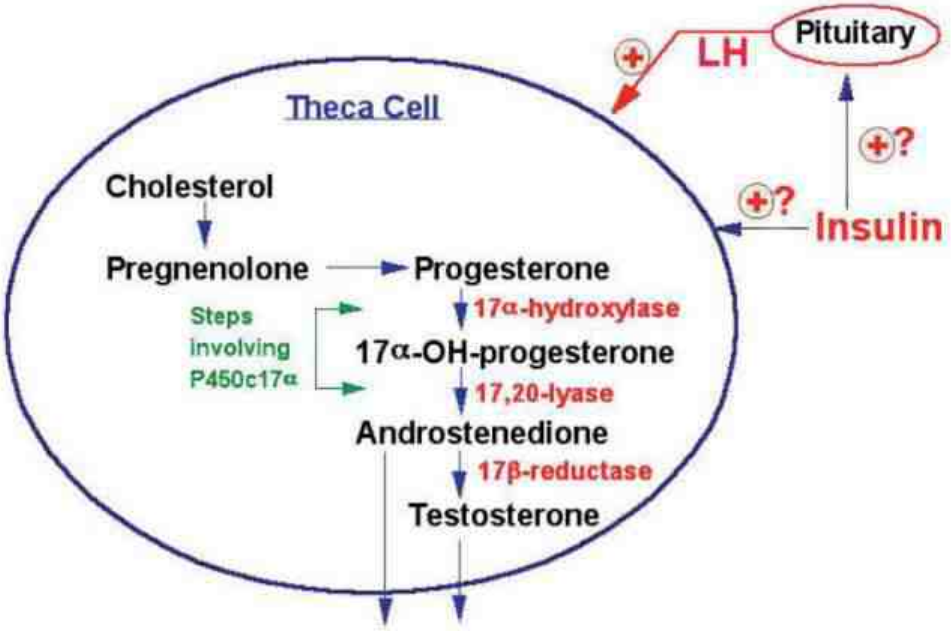


Fig. 3 Possible mechanisms of insulin stimulation of ovarian cytochrome P450c17α activity and androgen production. Insulin may stimulate the production of androgens through direct action on thecal cells and/or indirect enhancement of pituitary luteinizing hormone (LH) secretion. The enzyme, 17,20-lyase, is also named 17,20-desmolase.

LEPTIN

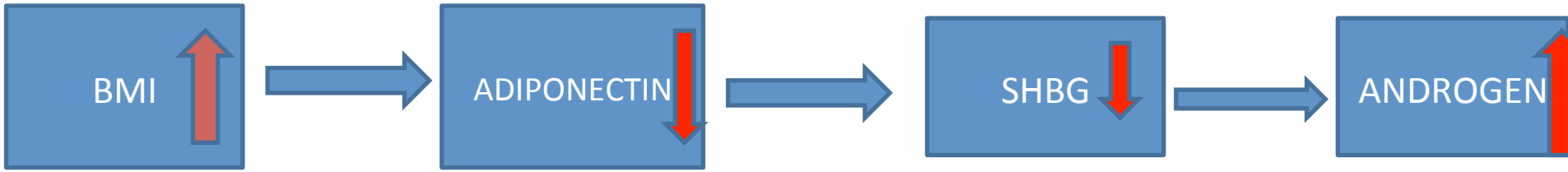
- A high BMI is also associated with blood and follicular leptin concentration. Leptin is a hormone that inhibits appetite and regulate calori expenditure. Leptin typically is higher in overweight people, and lower in those who are lean. It inhibits appetite by acting on the hypothalamus. In cases of obesity however , it is thought that the cells become resistant to leptin. High levels of leptin without the corresponding reduction in appetite contribute to even more weight gain.

Leptin Granulosa cells

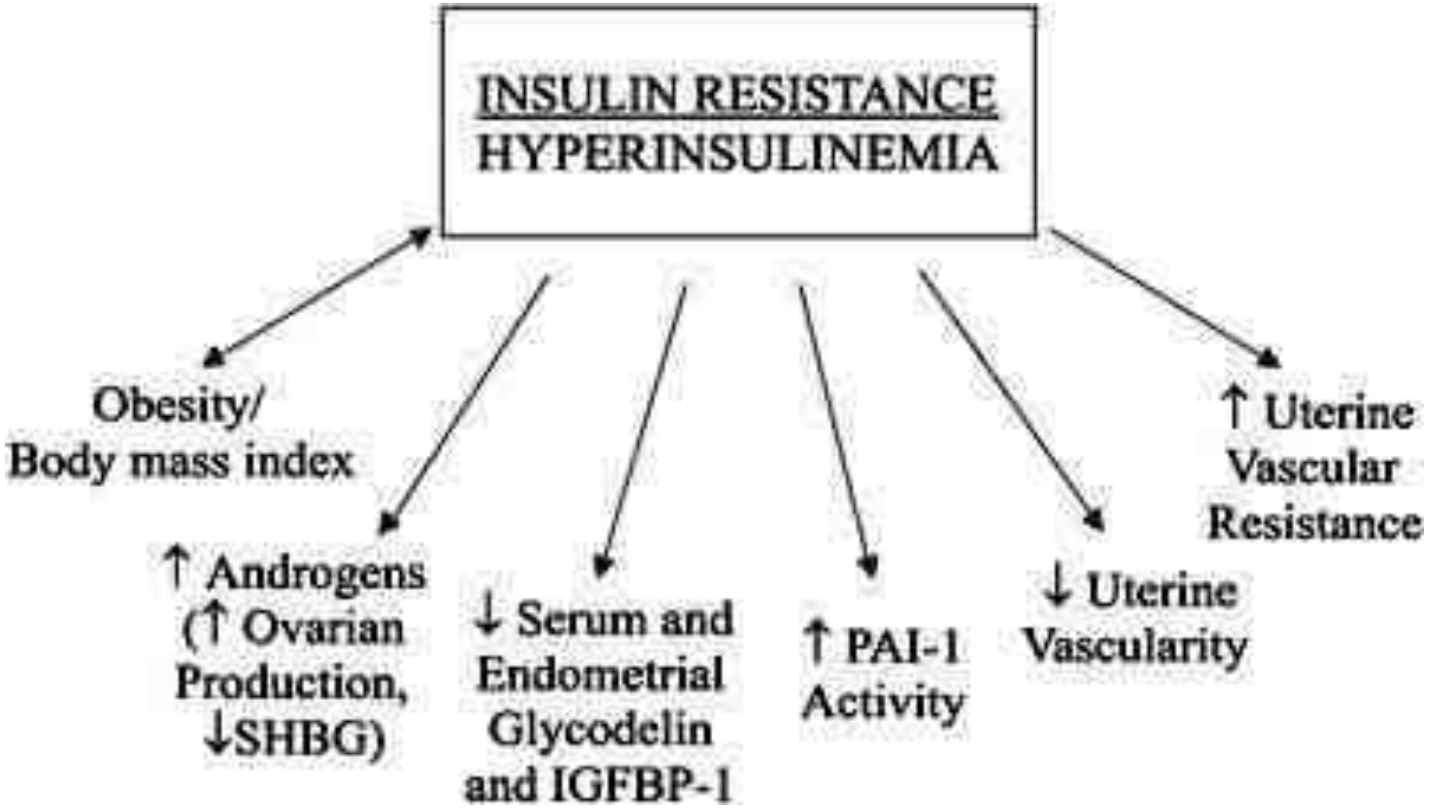
- Leptin by inhibiting the ovary hormone production affects the function and quality of the follicules.

High BMI Adiponectin

- High BMI is also associated with lower serum adiponectin levels. Adiponectin is a fat specific protein that prevents arterial plaques and is anti-inflammatory. Adiponectin is lower in patients with obesity, type 2 diabetes and cardiovascular disease.
- Low adiponectin levels in obese women also decrease Sex Hormone Binding Globulin (SHBG), and thereby increase free male hormones in a similar fashion to PCOS. High free androgens disrupt the normal ovarian cycle, and impair egg quality.



obesity: epidemiology



Body mass index

In general, the risk of obesity-related reproductive morbidity is associated with increasing BMI. BMI categories are as follows:

- Overweight 25–29.9 kg/m^2: increased disease risk
- Class I obesity 30–34.9 kg/m^2: high disease risk
- Class II obesity 30–34.9 kg/m^2: very high disease risk
- Class III obesity $\geq$ 40 kg/m^2: extremely high disease risk[3]

obesity: epidemiology

- Obesity → new worldwide epidemic
- in USA and Europe
  - 60% of all women are overweight (BMI>25 kg/m^2)
    - 30% of them are obese (BMI>30 kg/m^2)
    - 6% of them are morbidly obese (BMI>40 kg/m^2)
- definition
  - Body Mass Index (BMI): 18.5 – 25 – 30 – 35 – 40 kg/m^2
  - waist circumference to define truncal/abdominal obesity

According to the WHO, one billion adults are overweight and more than 300 million are obese. Once associated with high-income countries, obesity is now also prevalent in low- and middle-income countries. Approximately one third of U.S. adults are obese and in 2010, 12 states had an obesity prevalence of 30% or more

obesity and infertility (1)

- obese women: x3 times at risk of infertility
  - in the presence of irregular cycles
    - associated with oligo-anovulation
  - in the presence of regular cycles
    - probability of pregnancy is reduced by 5% for every BMI unit that exceeds 29 kg/m^2
      - anovulation even with regular cycles
      - release of oocytes with reduced fertilization potential
      - endometrial abnormalities

obesity and infertility (2)

- underlying mechanisms
  - insulin resistance
  - hyperandrogenism
  - elevated leptin levels and leptin resistance

Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome

José Bellver, M.D., José Antonio Martínez-Conejero, Ph.D., Elena Labarta, M.D., Pilar Alamá, M.D., Marco Antonio Barreto Melo, M.D., José Remohí, M.D., Antonio Pellicer, M.D., José Antonio Horcajadas, Ph.D.

Result(s)

One hundred and fifty-one genes were dysregulated in obese groups compared with controls. This dysregulation was more pronounced when infertility was associated. The biologic processes of these genes belonged mainly to development and regulation of different biological functions such as transcription and biosynthesis. The molecular functions overrepresented were transcription and peptide receptor activity. The endometrium of obese women with PCOS showed dysregulated genes related to biologic processes such as development, morphogenesis, and the immune system, as well as different molecular functions such as protein binding, binding, growth factor activity, and carboxylic acid transmembrane transporter activity. Some of these genes have been previously related to implantation and unexplained infertility.

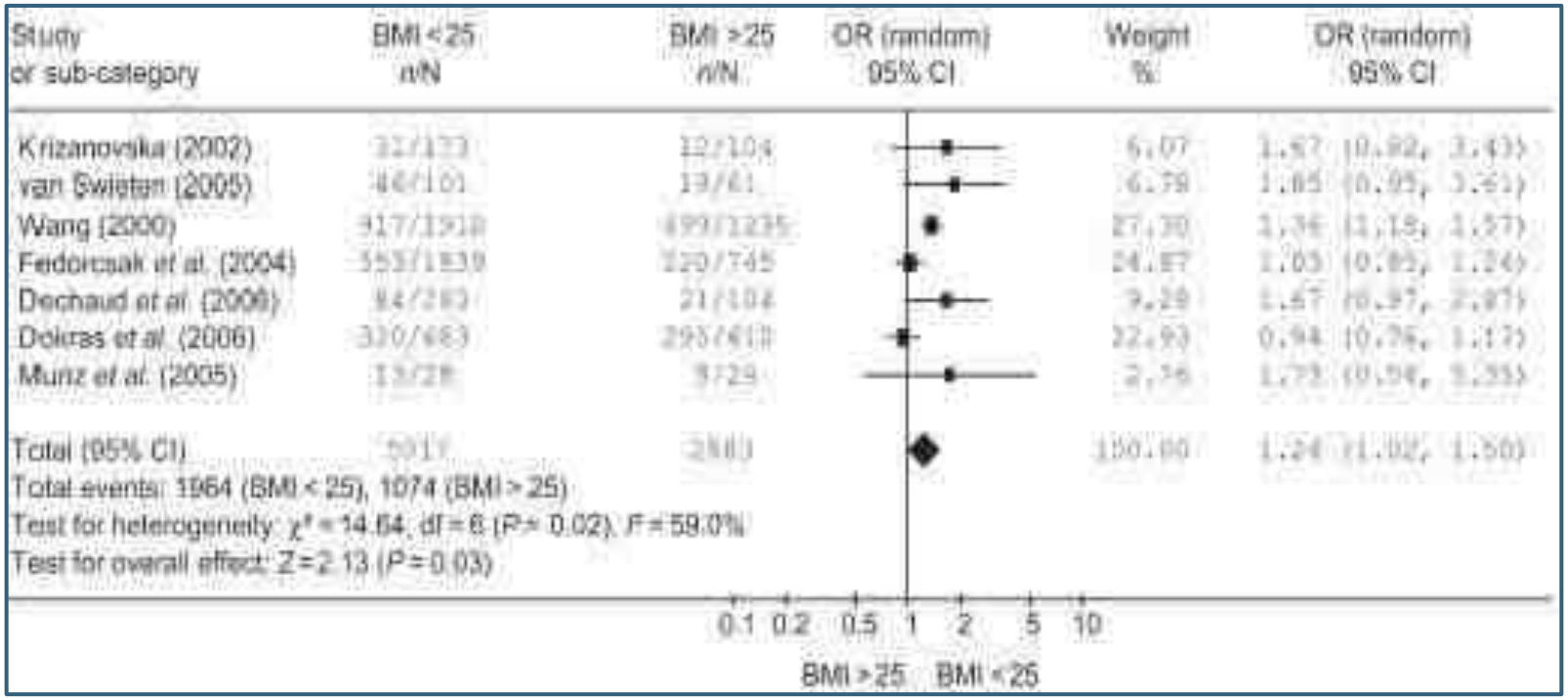
Conclusion(s)

Obese women present a different endometrial gene expression than controls during the WOI, which is more pronounced when infertility or polycystic ovary syndrome are associated.

- *British Fertility Society guidelines* infertility treatment should be deferred until BMI<35 kg/m^2 or even until BMI<30 kg/m^2 in young women with good ovarian reserve

Obesity and Pregnancy Rates (1)

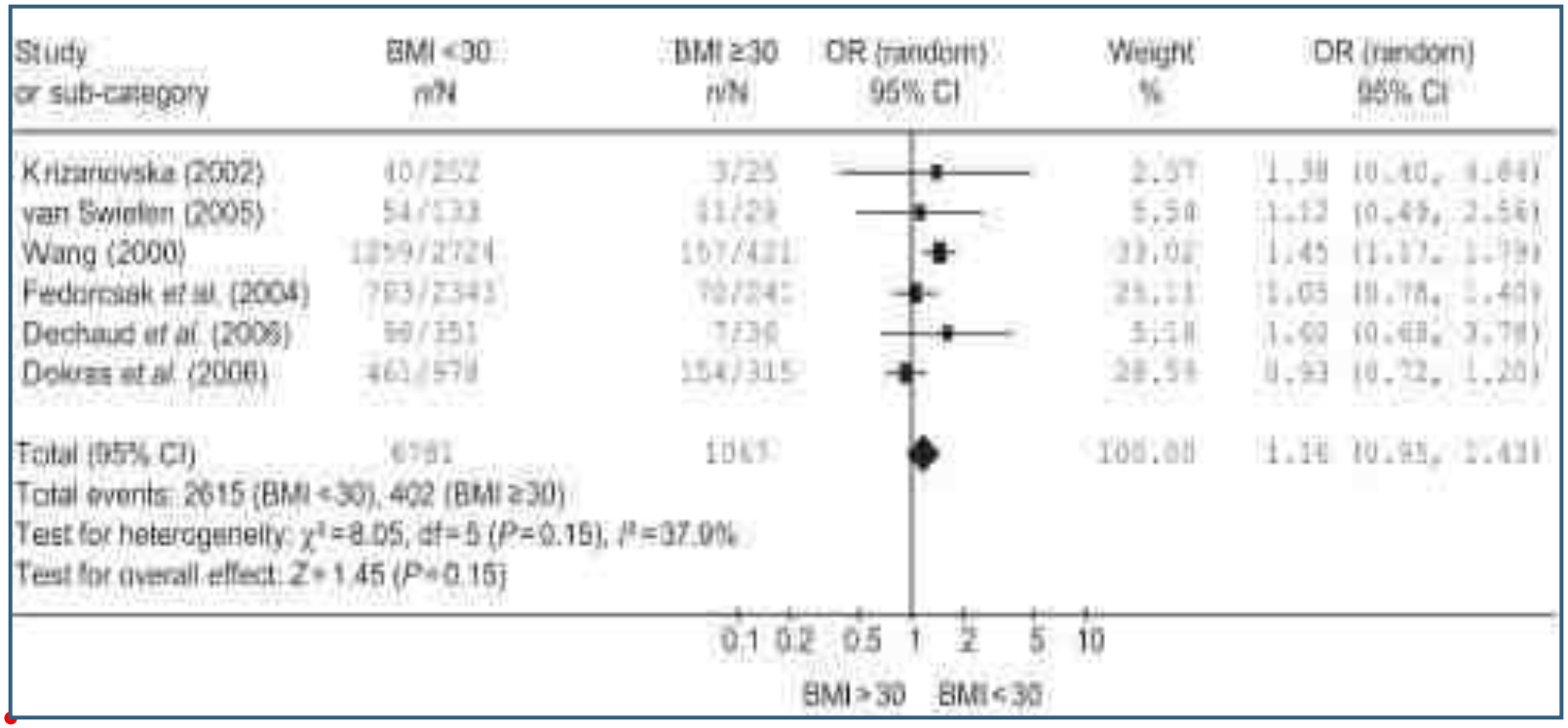
- BMI >25 vs <25: lower pregnancy rates



Maheshwari et al, 2007: 37 papers for effects of obesity on ART- 12 papers actually included

Obesity and Pregnancy Rates (2)

- BMI >30 vs <30: lower pregnancy rates



Maheshwari et al, 2007

IVF outcome stratified by BMI.

Characteristic	All cycles	BMI <20	BMI 20–24.9	BMI 25–29.9	BMI 30–34.9	BMI >35	*P* value
n (total)	6827	466	3605	1632	724	400	
Age (y), mean	36.5	36.3	36.6	36.6	36.2	35.2	<.0001[a]
BMI, mean	24.9	18.9	22.1	26.8	31.8	37.4	N/A
Cycles/patient	2.7	2.6	2.6	2.7	2.7	2.6	.14
Peak estradiol	1290	1424	1333	1222	1233	1135	<.0001[b]
No. of mature follicles	6.1	6.0	6.1	6.0	6.2	6.2	.34
No. of oocytes retrieved	9.4	9.5	9.4	9.4	9.4	8.7	.18
No. of mature oocytes	7.7	7.7	7.8	7.7	7.8	7.2	.35
No. of embryos transfered	2.6	2.5	2.6	2.6	2.6	2.5	.56
Implantation rate (%)	18	20	19	20	18	13	<.0001[a]
Clinical pregnancy rate (%)	28.3	32.9	31.4	27.6	27.9	21.8	<.0001[a]

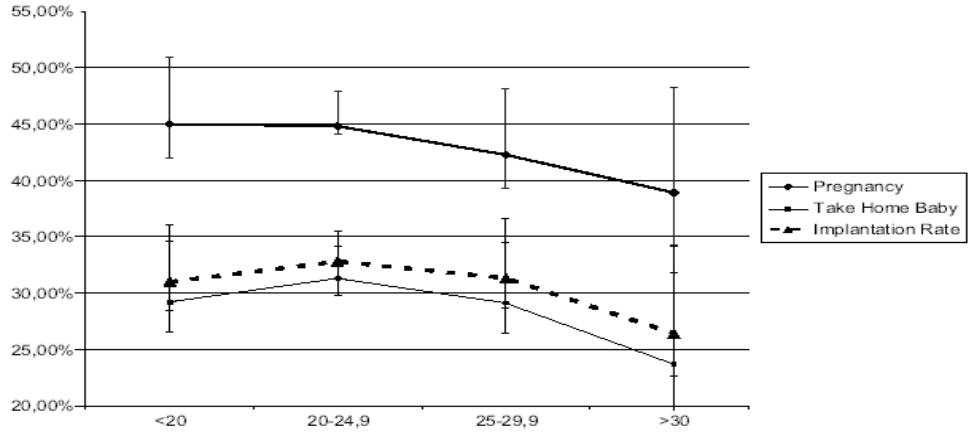
[a] BMI >35 group vs. all other groups.
[b] BMI >35 group vs. all groups with BMI 25 and higher.

Perkins. Recurrent IVF failure. Fertil Steril 2012.

Obesity and Pregnancy Rates (4)

- in obese: lower implantation, pregnancy, livebirth rates
- in overweight: lower implantation, pregnancy, livebirth rates
- raising BMI by 1 unit: odds for pregnancy decrease by 0.98
- reducing BMI by 1 unit: odds for pregnancy increase by 1.19

Implantation, pregnancy, and live birth rates in IVF-ICSI cycles according to the women's BMI. Each point represents percentages and 95% CI.



Bellver et al, 2009

Obesity and Fertilization Rates

Salha et al, 2001	•reduced FR in BMI >26(26.6%) vs. BMI 18-25(37.1%)
van Swieten et al, 2006	•reduced (by 45%) FR in BMI≥30
Matalliotakis et al, 2008	•reduced FR in BMI >24(51.7%) vs. BMI <24(58.9%)

Lashen et al, 1999	•no effect of increased BMI
Whittemer et al, 2000	•no effect of increased BMI
Fedorcsak et al, 2004	•no effect of increased BMI
Dokras et al, 2006	•no effect of increased BMI
Esinler et al, 2006	•no effect of increased BMI
Dechaud et al, 2006	•no effect of increased BMI
Metwally et al, 2007	•no effect of increased BMI
Martinuzzi et al, 2008	•no effect of increased BMI
Bellver et al, 2009	•no effect of increased BMI

Mechanisms for Impaired Endometrium (1)

- hyper-estrogenic state
  - due to
    - high activity of aromatase system: increased E production
    - decreased SHBG: increased free E2 delivered to target tissues
    - increased estrone – decreased inactive metabolites
  - results in
    - extremely thick endometrium: if>14mm is associated with lower PR (controversial)
    - more endometrial polyps and more multiple polyps

- defective endometrium
  - due to inverse correlation between BMI and
    - E and PR receptors in endometrium
    - LIF in endometrial glands
    - leukocyte subpopulations

Mechanisms for İmpaired Endometrium (2)

- leptin resistance in peripheral tissues

- insulin resistance and hyperinsulinemia
  - reduced glycodelin in endometrium: associated with recurrent pregnancy loss
  - reduced IGF-binding protein (facilitates adhesion at maternal-fetal surface)

- increased acute phase proteins & pro-inflammatory cytokines (IL6, PAI-1, TNFa)
  - negative effect on endometrium and early embryonic development

Obesity and Endometrium (1)

oocyte donation models

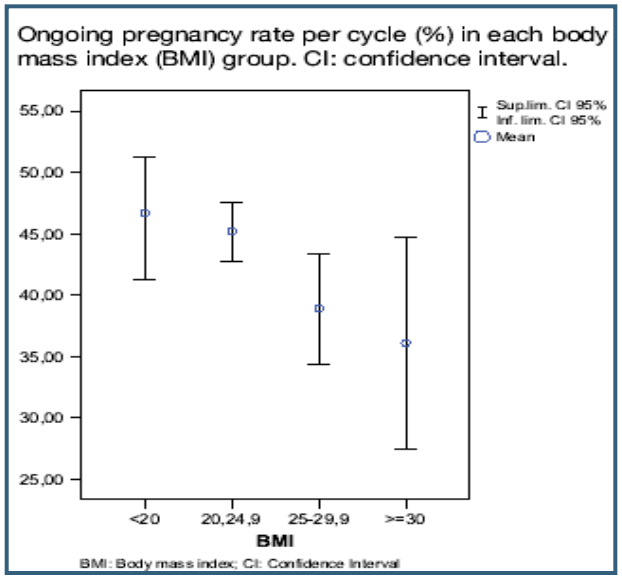
- use of oocytes from young donors with normal weight
- transfer to recipient and analysis according to their BMI
- effects on pregnancy rates (if any) should be attributed to endometrial factors

Wattanakumtornkul et al, 2003	•no effect of increased BMI on pregnancy rates •BUT very small sample (7 lean, 12 obese, 97 cycles)
Bellver et al, 2003	•trend towards reduced implantation and pregnancy rates •x4 increase in miscarriages •BUT small sample and not only the 1st cycles included
Styne-Gross et al, 2005	•no effect of increased BMI on pregnancy rates •BUT very high miscarriage rate for unknown reasons

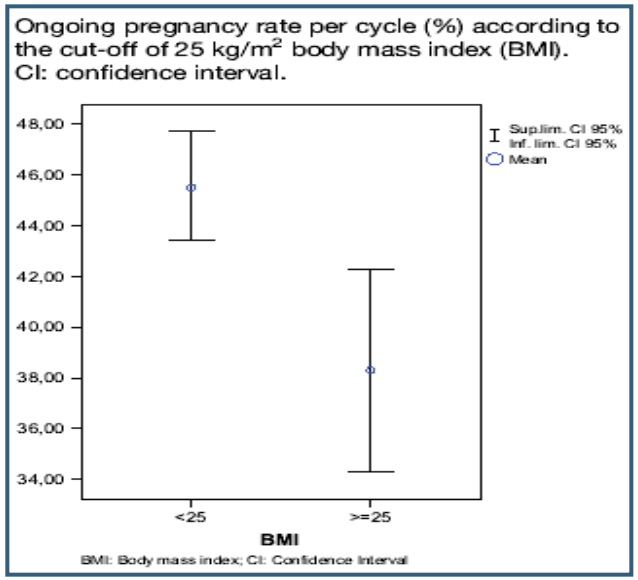
Obesity and Endometrium (2)

Bellver et al, 2007
2656 first oocyte donation cycles

- lower implantation and pregnancy rates as BMI increases
- higher miscarriage rate as BMI increases
- lower ongoing pregnancy rate in OW and OB



ongoing PR
in BMI<25: **45.5%**
in BMI>25: **38.3%**



Obesity and Endometrium (3)

Bellver et al, 2007
2656 first oocyte donation cycles

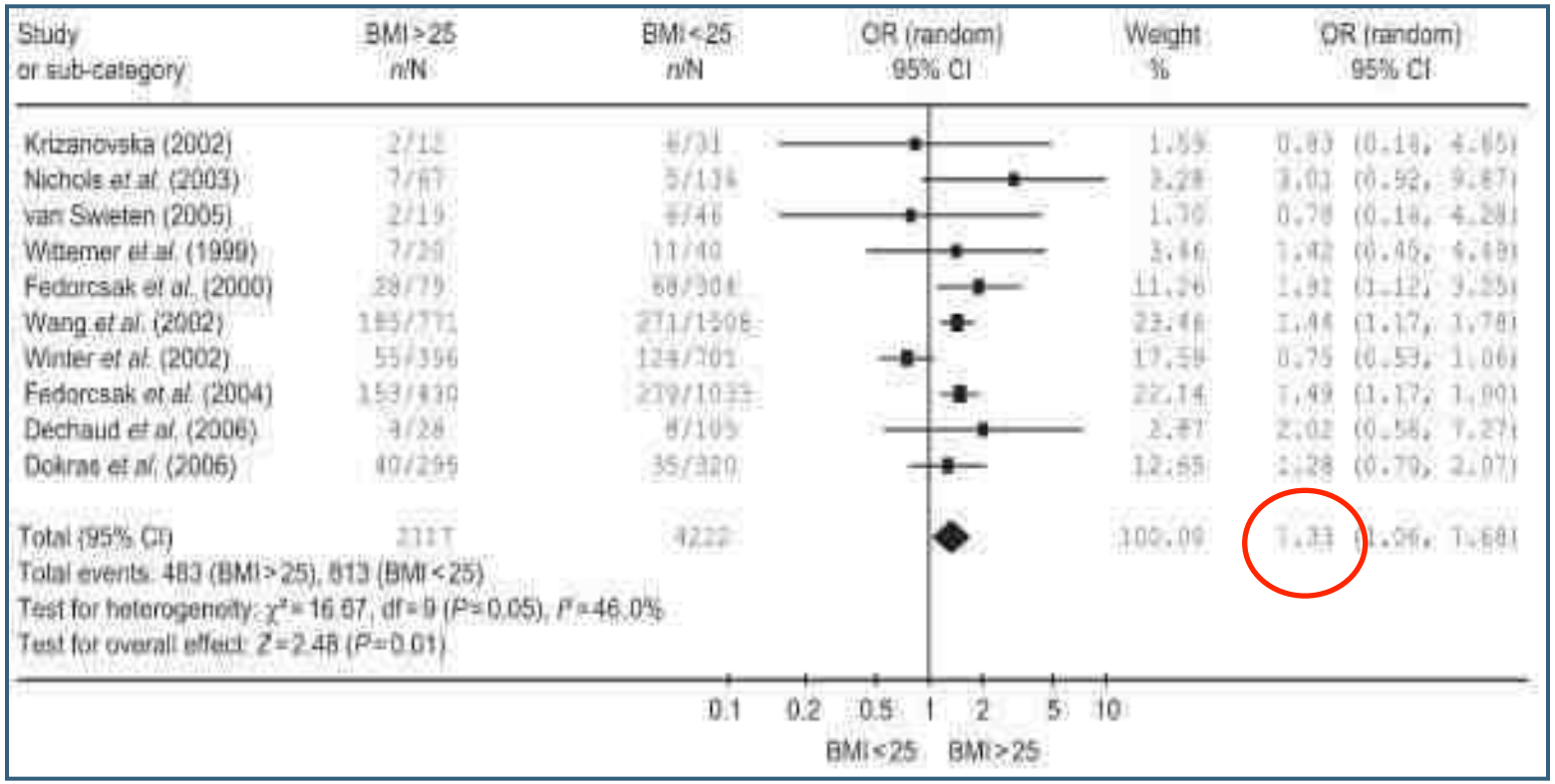
- excess weight may exert an extra-ovarian detrimental effect
- the effect on the endometrium seems subtle
  but should be taken into account
- being overweight implies negative impact as being obese
- underweight women do not experience poorer outcomes in donation models
  - the theory of inverted U is applied only to native oocyte conceptions, based on the ovarian effect of underweight

Mechanisms for Increased Miscarriages

- hormonal alterations
  - –endometrial receptivity
  - –trophoblast function
  - –early embryo development
- insulin resistance
  - –impaired progesterone release: inhibits normal corpus luteum function
  - –reduced IGF binding protein
  - –reduced avb3 integrin
  - –reduced adhesion molecules
  - –reduced glycodelin in endometrium
- leptin
  - –when high or resistance: leads to insulin resistance state
  - –when low: detrimental to early embryo development and trophoblast invasion

Obesity and Miscarriages (1)

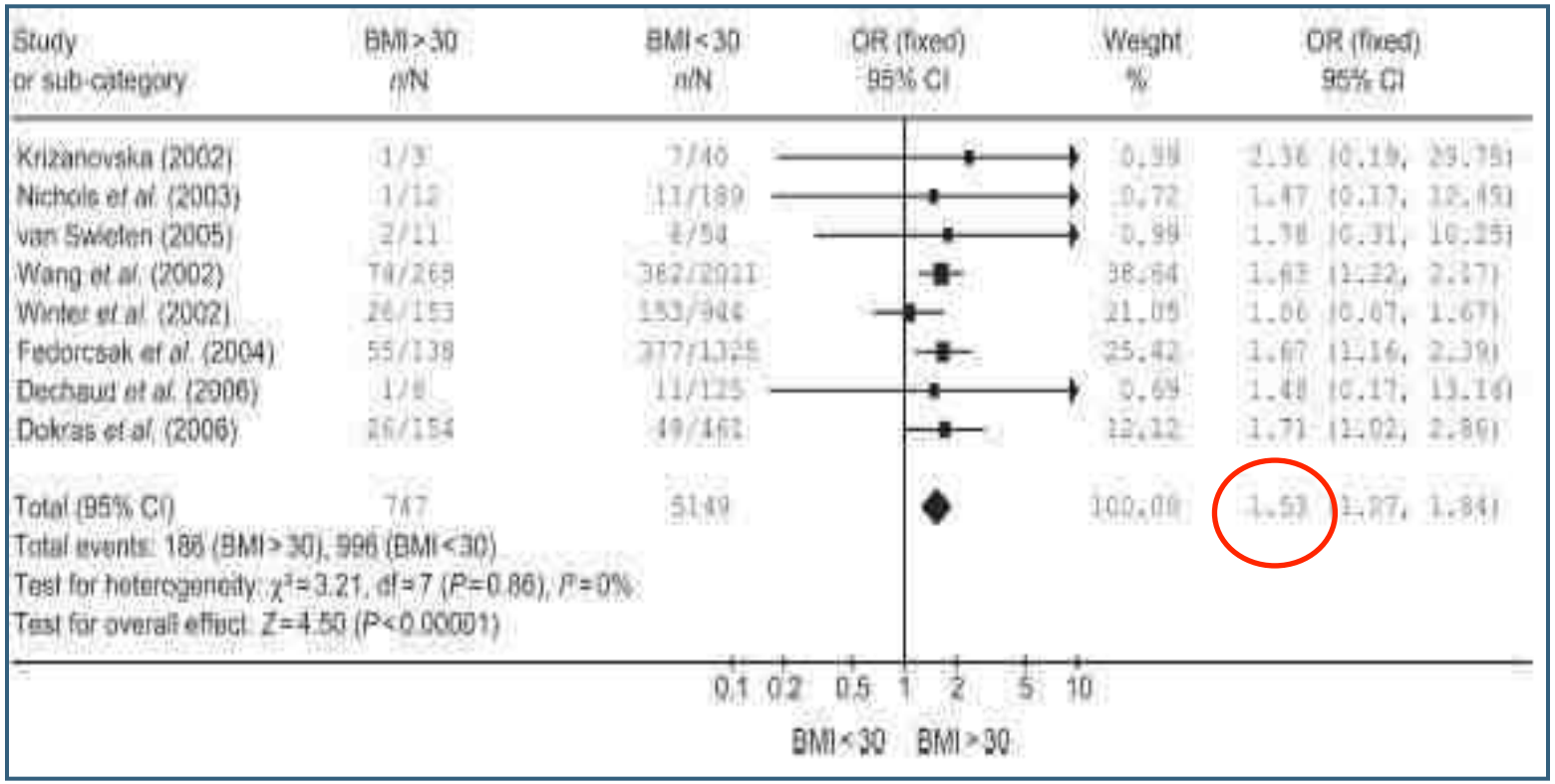
BMI >25 vs <25: higher miscarriage rates



Maheshwari et al, 2007

Obesity and Miscarriages (2)

BMI >30 vs <30: higher miscarriage rates

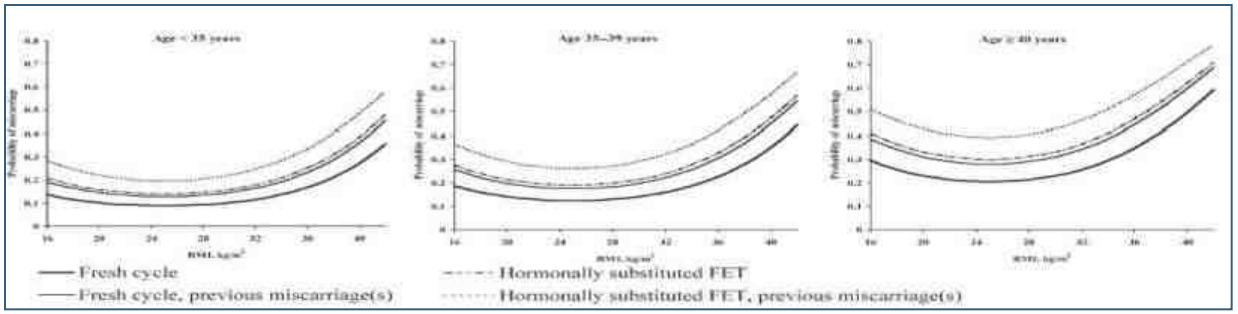


Maheshwari et al, 2007

Obesity and Miscarriages (3)

Veleva et al, 2008

- U-shaped effect of BMI on miscarriage rates after IVF (p=0.01)
- in fresh cycles: 13.4%
- in natural thaw cycles 11.4%
- in hormonal thaw cycles: 23% (risk x 1.7, p= 0.002)



Bellver et al, 2009

- no effect of BMI on miscarriage rates
- perhaps because no differences to embryo quality were noted

Semin Reprod Med. 2011 Nov;29(6):507-13. doi: 10.1055/s-0031-1293204. Epub 2011 Dec 8.

Does obesity increase the risk of miscarriage in spontaneous conception: a systematic review.

Boots C[1], Stephenson MD.

Author information

Abstract

Obesity has become an epidemic in developed societies. Retrospective studies suggest that obesity is associated with miscarriage in assisted reproduction. The objective of this study was to evaluate whether obesity is associated with miscarriage in spontaneous conception. We conducted systematic review of published studies with pooled analysis. A literature review was performed. Studies in which fertility drugs or in vitro fertilization were used were excluded, unless data could be extracted for spontaneous conception. Data were compared for obese (body mass index [BMI]: ≥28 or 30 kg/m (2)), overweight (BMI: 25 to 29 kg/m (2)), and normal-weight (BMI: <25 kg/m (2)) women, with pooled odds ratios (ORs). Recurrent miscarriage data were analyzed separately. Six studies met the criteria for a cohort of 28,538 women. Pooled analysis revealed a higher miscarriage rate of 13.6% in 3800 obese versus 10.7% in 17,146 normal-BMI women (OR: 1.31; 95% confidence interval [CI], 1.18 to 1.46). Although the cohort was small, there was a higher prevalence of recurrent early miscarriage in obese versus normal-BMI women (0.4% versus 0.1%; OR: 3.51; 95% CI, 1.03 to 12.01). In women with recurrent miscarriage, there was a higher miscarriage rate in the obese versus nonobese women (46% versus 43%; OR: 1.71; 95% CI, 1.05). Based on retrospective studies, we concluded that obesity is associated with a higher miscarriage rate in women who conceive spontaneously. Larger prospective studies are urgently needed to verify these preliminary results.

Fertil Steril. 2008 Sep;90(3):714-26. Epub 2008 Feb 6.

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

Metwally M[1], Ong KJ, Ledger WL, Li TC.

Author information

Abstract

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 > or =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.

Obesity and IVF: Most Recent Studies (1)

Kupka et al, 2010

- retrospective analysis of 706360 cycles from German registry dataset
- inclusion of female and male weights
- the combination of obese male and normal-weight female is positively related to increased implantation rates after IVF/ICSI
- this combination is more likely in couples with higher social status: the result may be related to lifestyle factors

Keltz et al, 2010

- retrospective analysis of 290 cycles
- male overweight status was associated with significantly lower clinical pregnancy rate after IVF (53.2% vs 33.6%), but not after ICSI
- ICSI may overcome some obesity-related impairement of sperm-egg interaction

Obesity and IVF: Most Recent Studies (2)

Zhang et al, 2010

- retrospective analysis of 2628 cycles in Chinese couples
- obese women
  - higher FSH dose – more stimulation days – fewer oocytes – lower fertilization rates
- overweight women
  - fewer oocytes – lower fertilization rates – fewer cleavaged, high-grade and cryopreserved embryos
- no differences in pregnancy/miscarriage/live birth rates

Vilarino et al, 2010

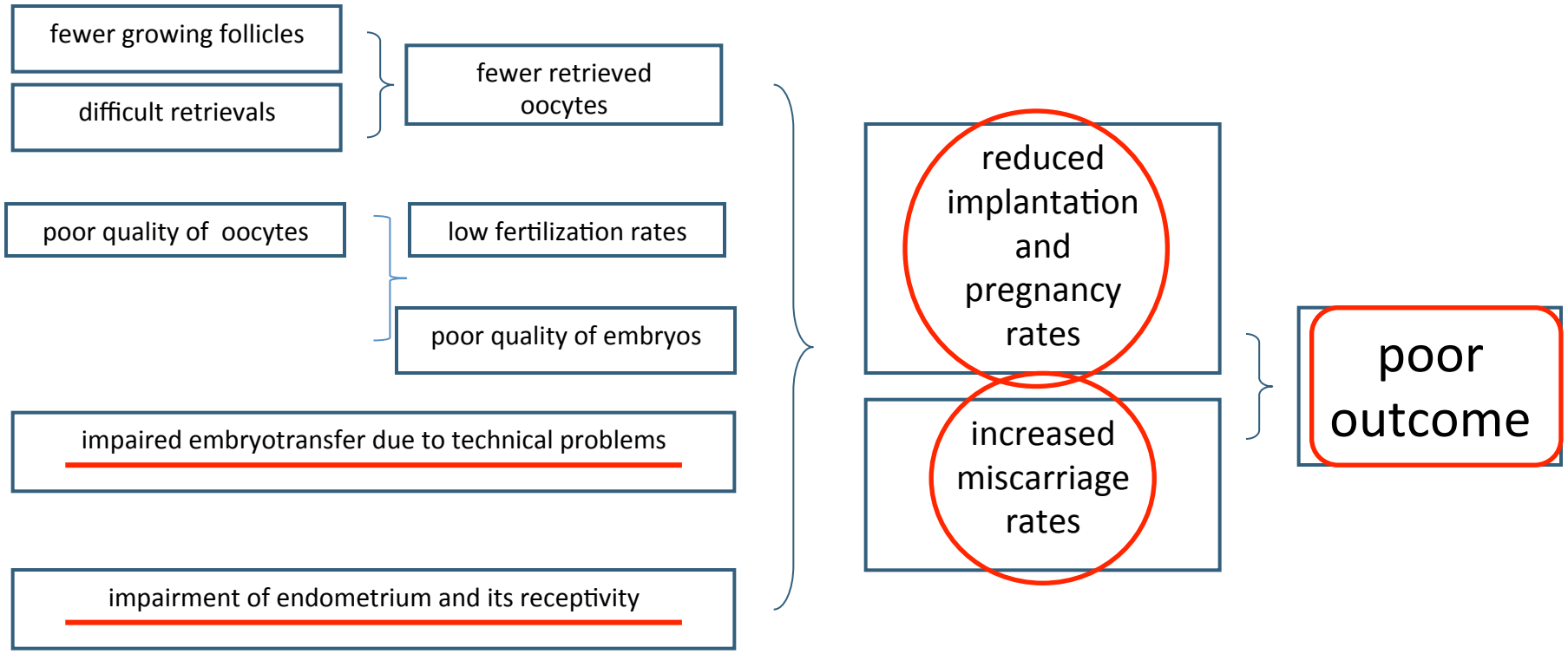
- retrospective analysis of 208 cycles
- no differences in
  - FSH dose-number of oocytes-fertilization rate-embryo quality-frozen embryos
  - clinical pregnancy/miscarriage/live birth rates

obesity and IVF: conclusions

even though no evidence-based consensus obesity may have negative effects on

- ovarian stimulation parameters
- oocyte and embryo quality
- fertilization rates
- embryo transfer
- implantation rates
- pregnancy rates
- miscarriage rates

obesity and IVF: conclusions




MERAM TIP FAKÜLTESİ HASTANESİ