Available online at **www.ijmrhs.com**

ISSN No: 2319-5886

International Journal of Medical Research & Health Sciences, 2016, 5, 11:157-170

Female Obesity and Clinical Outcomes of Assisted Reproductive Technologies (ART): an Updated Systematic Review and Meta-analysis

Heidar Heidari Khoei[1], Leila Dehdehi[2], Milad Moloudizargari[3], Zahra Baninameh[4], Sedighe Rezaie-Chamani[5], Gea Oliveri Conti[6], Shokoofe Azarbahra[7] and Kolsoom Mohammadmoradi[8]*

[1]Student Research Committee, Department of Biology and Anatomical Sciences, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Biology and Anatomical Sciences, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[3]Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Sina Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[5]Department of Midwifery, Faculty of Nursing and Midwifery, Guilan University of Medical Sciences, Rasht, Iran
[6]Environmental and Food Hygiene Laboratories (LIAA), 'G.F. Ingrassia' Department, Hygiene and Public Health, University of Catania, Catania, Italy
[7]Student's Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran
[8]Food and Cosmetic Health Research Center, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
**Corresponding Email: dli.moradi@gmail.com*

ABSTRACT

Assisted Reproductive Technology (ART) has been developed to be used for reproductive-age women with primary and secondary infertilities. Obesity is a worldwide epidemic for both women and men and a major global health concern. The direct effect of Body Mass Index (BMI) increase on the outcomes of ART is still unclear. This study aimed to carry out a systematic review of the available scientific evidence to assess the effects of obesity on the clinical outcome of ART treatment. Numerous studies have shown failure in ART due to increased BMIs in infertile women; however, the impact of increased BMI on clinical effectiveness of ART still remains inconclusive. Using results from 44 studies (831616 subjects) we conducted an updated systematic review and meta-analysis to highlight this subject (clinical pregnancy rate, miscarriage rate and live-birth rate). Compared to the women with BMIs of 25 kg/m^2 or less, women with BMI ≥ 25 kg/m^2 have a lower chance of pregnancy [risk ratio 0.91, 95% CI: 0.89-0.94] as well as lower live-birth rates [risk ratio 0.81, 95% CI: 0.70-0.94], and show increased miscarriage rates [risk ratio 1.35, 95% CI: 1.28-1.46]. Our findings indicate that elevated BMI and obesity requires more recognition as a potential contributor to negative pregnancy outcomes and reduced live-birth following ART. The results of our meta-analysis suggest that weight loss should be considered in overweight and obese women before the initiation of infertility treatment.

Key words: Obesity, Assisted Reproductive Technology, systematic review, clinical pregnancy rate, live-birth rate, miscarriage rate.

INTRODUCTION

In vitro fertilization (IVF), frozen embryo transfer (FET) and intra-cytoplasmic sperm injection (ICSI) were first reported in 1978, 1984, and 1992, respectively. [1-3]. The Assisted Reproductive Technology (ART) has been developed to be used for reproductive-age women with primary and secondary infertilities. Recent estimates indicate that 1.7% to 4.0% of pregnancies in industrialized and developed countries had positive outcomes of ART [4]. Most of the pregnancies resulting from ART process did not show any complications and resulted in healthy children [5]. Therefore, ART represents an important and useful tool and that could be used more widely in the future. Obesity is a worldwide epidemic for both women and men and represents still today a major global health concern. Rates of obesity have more than doubled since 1980. In 2014 more than 1.9 billion adults were overweight and 600 million were obese [6].

The World Health Organization (WHO) defined the obesity as Body Mass Index (BMI=weight/height^2 and expressed as kg/m^2) $\geq$ 30 kg/m^2 [Table 1], however, many authors used variable body mass index (BMI) cut-off values to define obesity. Obesity is associated with cardiovascular disease, diabetes, osteoarthritis and malignancies [6]. It is increasingly being recognized that this current obesity epidemic has also contributed to fertility problems. Both populations in developing and developed countries show an increase of overweight or obese people and 0.5% of the population in some developing countries to 50% or more in some developed countries is overweight or obese [7-9].

Table 1: The international classification of adult underweight, overweight and obesity according to BMI

Classification	BMI (kg/m^2) cut-off points
Underweight	<18.50
Normal range	18.50 - 24.99
Overweight	25.00- 29.99
Obese	≥30.00

Source: Adapted from WHO, 1995, WHO, 2000 and WHO 2004.

For the women undergoing ART, although there are contradictory results regarding the effect of raised BMI on the outcomes of ART, several meta-analyses studies have recently demonstrated that excess weight and elevated BMI is associated with: decreased pregnancy rate, lower Birth Rate (LBR), lower Implantation Rate (IR), higher Miscarriage Rate (MR) and with the possibility of reduction of follicle development as also of oocyte's numbers as well as an increased gonadotropin requirement following the ART [10-12]. However, several studies have been unable to find any negative impact of obesity on ART outcomes [13, 14].

Available studies on the obesity effects on women on following in ART treatments show variable results. The aim of our study is to carry out an updated systematic review of literature in order to definitively verify whether excessive weight and the increased BMI adversely affect on the clinical outcomes (LBR, IR, MR) of ART, and if so, to assess the size of this effect.

MATERIALS AND METHODS

Literature search

We conducted a comprehensive review of all studies containing data on overweight and BMI and clinical outcomes for patients treated with any form of ART. We used a systematic approach to search the literature according to PRISMA method [15]. On October 29, 2016, we carried out searches through PubMed, Web of Science and Scopus by using the search string: "(body mass index OR obesity OR overweight) AND (assisted reproductive techniques OR in vitro fertilization or intracytoplasmic sperm injection) AND (women or female) AND (live birth rate OR pregnancy rate OR miscarriage)". In addition, manual reference checks were performed of references of accepted articles and reviews published within the last 2 years. No language restrictions were used in our search. After removing duplicates, 458 potentially relevant articles remained (Fig. 1). Titles and abstracts were then screened (by HHK and ZB) and reviews and irrelevant studies were removed, leaving us finally with 85 potentially relevant studies (Fig. 1).

2.2. Study selection, eligibility criteria and Data extraction

Two authors (KM, SRC) independently searched the eligible studies and a final study set for data extraction was identified by consensus. Studies were included if they investigated the effect of BMI on pregnancy outcome (Table 1) in women undergoing ART treatment. From each relevant study one author (SA) abstracted the following information (population size, study design, BMI categories used and population numbers in each category and outcome measures) which was checked by two others colleagues (HHK and LD) (see Table 2).

Statistical analysis

We pooled outcome data from each study and expressed as risk ratio (RR) with 95% confidence interval (CI) by using either a fixed-effect model [16] or a random-effect model [17] through a statistical software program Comprehensive Meta-Analysis V2.0 (Biostat, Englewood, NJ). We assessed heterogeneity of treatment effects in our meta-analytic model using the I^2 statistic [18] and described graphically through the forest plots [19] to quantify the variation across studies caused by heterogeneity. If significant heterogeneity was observed ($p < 0.10$ or $p > 0.10$ but $I2 > 50\%$), the meta-analyses were conducted using a random effect model. A fixed effect model was used for the meta-analysis where heterogeneity was acceptable ($p > 0.10$, or $p < 0.10$ but $I2 < 50\%$).

RESULTS

Analysis and pooling of data

The literature analysis was presented as a PRISMA diagram (Fig. 1) . From 85 studies fulfilling the inclusion criteria only 44 studies had cut-off values for BMI according to the WHO criteria, which included data for meta-analysis (Table 2).

Out of the 44 studies, only four studies were prospective observational, the remaining were retrospective studies. All the included studies were cohort studies except for one case control study [20]. Of the 44 studies included in the final meta-analysis, 28 studies reported on the miscarriage rates in pregnancies conceived following ART, 19 and 35 studies reported on live birth rate and pregnancy rate following ART, respectively.

In total, 44 studies including 831616 IVF/ICSI cycles were included in the review with a total of BMI<25 kg/m2, n=505475; and BMI ⩾25 kg/m2, n=831616.

A random effect model was used to calculate risk ratios (RR) (95% CI). Tests of heterogeneity were performed before to pooling of data.

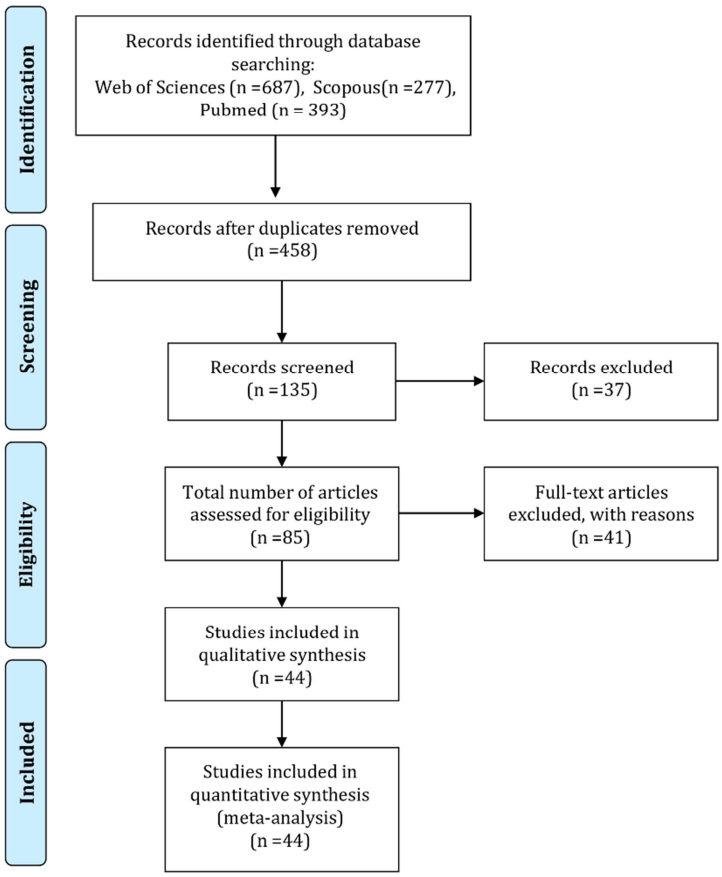

Fig 1. Flow diagram detailing the search and inclusion of studies in our review, as suggested by the PRISMA statement

Results of the aggregated data

Pooled results were described separately for BMI ≥ 25 versus < 25. In addition, outcomes per cycle were aggregated together and described separately.

Live birth rate

In women with BMI of < 25, the risk ratio of pooled results from 19 studies was 0.81 (95%: CI 0.70-0.94), when compared with women with BMI of ≥ 25 (Figure 2). The pooled results showed a statistically significant reduction in the live-birth rate in women with BMI ⩾25 kg/m^2 compared with women with BMI < 25 kg/m^2. The live birth rate is reduced by approximately 18 % (95 %: CI 5.6-29.2) in women BMI ⩾25 kg/m^2 when compared with women with BMI < 25 kg/m^2. There was significant statistical heterogeneity between the included studies (I^2=99.35%. P = 0.000).

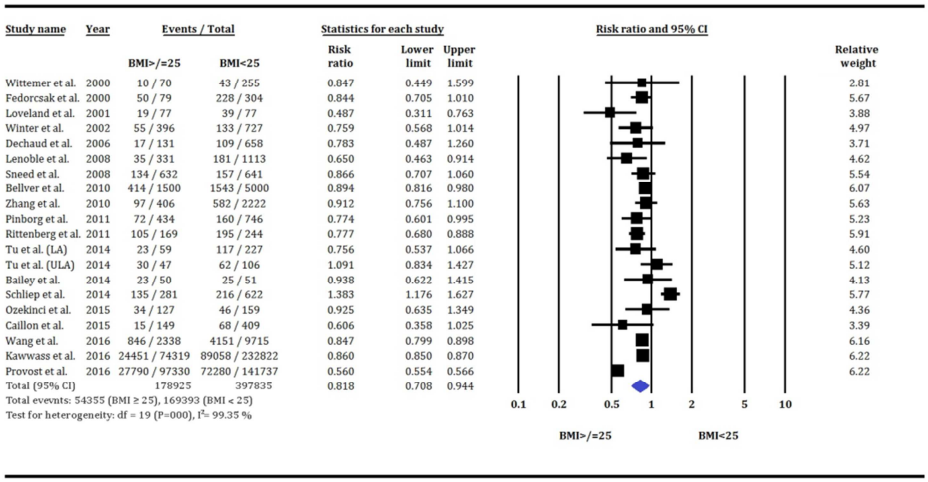

Fig 2. Forest plot of risk ratio live-birth rate in women with BMI < 25 versus BMI ≥ 25

Pregnancy rate

In women with BMI of < 25, the risk ratio of pooled results from 35 studies was 0.91 (95%: CI 0.89-0.94) when compared with women with BMI of ≥ 25. The pooled results showed a statistically significant reduction in the pregnancy rate in women with BMI ⩾25 kg/m^2 compared with women with BMI < 25 kg/m^2. The pregnancy rate is reduced by 8.4 % (95 %: CI 6-10.7) in women BMI ⩾25 kg/m^2 when compared with women with BMI < 25 kg/m^2. Again there was significant statistical heterogeneity between the included studies (I^2=60.91 %. P = 0.000).

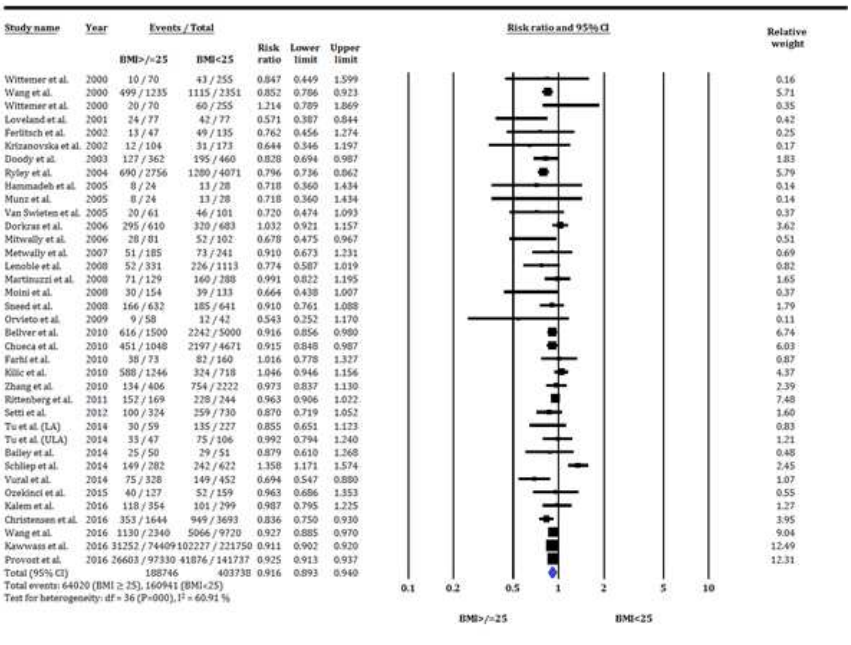

Fig 3. Forest plot of pregnancy rate in women with BMI < 25 versus BMI ≥ 25

Table 2. Characteristics of the included studies

Authors	Year	Study design	Participant groups	*BMI group (kg/m^2) and numbers of cycles/patients*	Outcome measures	Reference
Wittemer et al.	2000	Retrospective	All couples referred for IVF/ICSI Excluded PCOS	<20: 87 Women 20–25: 222 Women ⩾25:, 89 Women	Pregnancy rate Miscarriage rate Delivery rate	[21]
Wang et al.	2000	Retrospective	All women undergoing ART (IVF/ ICSI/GIFT)	< 20: 441 women 20–24.9: 1910 women 25–29.9: 814 women 30–34.9: 304 women ≥ 35: 117 women	Clinical pregnancy rate	[22]
Fedorcsak et al.	2000	Cohort study	Women pregnant as a result of IVF or ICSI	< 25: 304 pregnancies ≥ 25: 79 pregnancies	Miscarriage rate	[23]
Loveland et al.	2001	Retrospective	All women undergoing IVF/ICSI cycles	≤25: 87 cycles, 70 women >25: 93 cycles, 69 women	Clinical pregnancy rate Spontaneos abortion Ongoing pregnancy rate	[24]
Wang et al.	2001	Cohort	All women undergoing ART (IVF/ ICSI/GIFT)	<20: 112 Women 20–24.9: 509 Women 25–29.9: 231 Women 30–34.9: 116 Women ⩾35: 50 Women	Spontaneous abortion	[25]
Ferlitsch et al.	2002	Retrospective	All women undergoing IVF	<20: 31 Women 20–24.9: 104 Women 25–30: 31 Women >30: 16 Women	pregnancy rate	[26]
Krizanovska et al.	2002	Retrospective	Women undergoing IVF and ICSI	<16: 2 Women 18–20: 30 Women 20–25: 173 Women 25–30: 79 Women ⩾30: 25 Women	Clinical pregnancy Miscarriage rate	[27]
Wang et al.	2002	Retrospective	All women undergoing ART (IVF/ ICSI/GIFT)	<18.5: 70 Women 18.5–24.9: 1508 Women 25–29.9: 503 Women 30–34.9: 198 Women ⩾35: 70 Women	Spontaneous miscarriage	[28]
Winter et al.	2002	Cohort	All women undergoing ART (IVF/ ICSI/GIFT)	<18.5: 26 Women 18.5–25: 701 Women 25.1–30: 243 Women 30.1–35: 107 Women >35: 46 Women	Early pregnancy loss	[29]
Doody et al.	2003	Retrospective	Women undergoing IVF and ICSI	<25: 460 Women 25–29.9: 194 Women 30–34.9: 89 Women >35: 79 Women	Ongoing pregnancy rate	[30]
Ryley et al.	2004	Retrospective	Women undergoing IVF	<20: 466 Cycles 20–24.9: 3605 Cycles	Clinical pregnancy rate	[31]

				25–29.9: 1632 Cycles 30–34.9: 724 Cycles >35: 400 Cycles		
Fedorcsak et al.	2004	Retrospective	Women undergoing IVF and ICSI	<18.5: 76 Women, 136 cycles 18.5–24.9,: 1839 Women, 3457 cycles 25–29.9: 504 Women, 963 cycles ⩾30: 241 Women, 463 cycles	Pregnancy rate Miscarriage rate Live birth rate	[32]
Hammadeh et al.	2005	Prospective	Women undergoing IVF	⩽25: 28 Women >25: 24 Women	Pregnancy rate	[33]
Munz et al.	2005	Retrospective case–control	Women undergoing IVF and ICSI	<25: 28 Women >25: 24 Women	Pregnancy rate	[20]
Van Swieten et al.	2005	Observational study	Women undergoing IVF and ICSI	< 25: 683women 25–29.9: 295 women 30-39.9: 236 women ≥ 79: 29 women	Clinical pregnancy rate Miscarriage rate	[34]
Dokras et al.	2006	Retrospective	Women undergoing IVF	< 25: 101women 25–30: 32 women ≥ 30: 29 women	Pregnancy rate Miscarriage rate Delivery rate	[35]
Mitwally et al.	2006	Cohort	Women undergoing IVF	<25: 102 Cycles ⩾25: 81 Cycles	Clinical pregnancy rate	[36]
Dechaud et al.	2006	Retrospective	Women undergoing IVF and ICSI	<20: 186 Women, 264 cycles 20–25: 283 Women, 394 cycles 25–30: 68 Women, 83 cycles ⩾30: 36 Women, 48 cycles	Clinical pregnancy rate Miscarriage rate	[14]
Metwally et al.	2007	Retrospective	Women undergoing IVF and ICSI	19–24.9: 241 Women 25–29.9: 113 Women ⩾30: 72 Women	Clinical pregnancy rate	[37]
Lenoble et al.	2008	Retrospective	Women undergoing IVF and ICSI	⩽18: 43 Women, 68 cycles 18–25: 607 Women, 1045 cycles ⩾25: 196 Women, 331 cycles	Clinical pregnancy rate Miscarriage rate	[38]
Martinuzzi et al.	2008	Retrospective	Women undergoing IVF and ICSI	<18.5: 21 Women 18.5–24.9: 267 Women 25–29.9: 77 Women ⩾30: 52 Women	Clinical pregnancy rate	[39]
Moini et al.	2008	Cross-sectional	Women undergoing IVF and ICSI	20–25: 133 Women >25–30: 117 Women >30: 37 Women	Clinical pregnancy rate Miscarriage rate	[40]
Sneed et al.	2008	Retrospective	Women undergoing IVF	<18.5: 28 Women >18.5–24.9: 613 Women >25–29.9: 325 Women >30: 307 Women	Spontaneous abortion Clinical pregnancies Live births	[41]
Esinler et al.	2008	Retrospective	Women undergoing ICSI	18.5–24.9: 451 Women, 627 cycles 25–29.9: 222 Women, 339 cycles ⩾30: 102 Women, 147 cycles	Clinical pregnancy rate miscarriages rate	[42]
Orvieto et al.	2009	Retrospective	Women undergoing IVF	⩽25: 42 Women >25: 58 Women	Pregnancy rate	[43]
Bellver et al.	2010	Retrospective	Women undergoing IVF and ICSI	<20: 1070 Cycles	Pregnancy rate	[44]

				20–24.9: 3930 Cycles 25–29.9: 1081 Cycles ⩾30: 419 Cycles	Early pregnancy loss rate Clinical miscarriage rate Live-birth rate	
Chueca et al.	2010	Retrospective	Women undergoing IVF	<20: 1289 Cycles 20–25: 3382 Cycles >25–30: 755 Cycles >30: 293 Cycles	Clinical Pregnancy rate miscarriage rate	[45]
Farhi et al.	2010	Retrospective	Women undergoing IVF	⩽25: 160 Cycles >25: 73 Cycles	Pregnancy rate	[46]
Kilic et al.	2010	Retrospective	Women undergoing ART	18–24.9: 718 Women 25–29.9: 470 Women ⩾30: 782 Women	Clinical Pregnancy rate	[47]
Zhang et al.	2010	Cohort study	Women undergoing IVF and ICSI	18.5–25: 2222 Women >25–29.9: 379 Women ⩾30: 27 Women	Pregnancy rate Miscarriage rate Ongoing pregnancy rate Live-birth rate	[48]
Rittenberg et al.	2011	Cohort study	Women undergoing IVF and ICSI	18.5–24.9: 244 Women ⩾25: 169 Women	Clinical pregnancy rate Implantation rate Miscarriage rate Ongoing pregnancy rate	[49]
Pinborg et al.	2011	Cohort study	Women undergoing IVF and ICSI	<18.5: 24 Women 18.5–24.9: 305 Women 25–29.9: 103 Women ⩾30: 59 Women	Pregnancy rate Miscarriage rate Ongoing pregnancy rate Live-birth rate	[50]
Setti et al.	2012	Retrospective	Women undergoing ICSI	<19: 39 Women 19–24.9: 738 Women 25–29.9: 242 Women ⩾30: 86 Women	Pregnancy rate Miscarriage rate	[51]
Tu et al.	2014	Retrospective	Women undergoing IVF and ICSI	⩽25: 387 Women >25: 112 Women	Clinical PR per experimental therapeutics Miscarriage rate Live birth rate per ET	[52]
Bailey et al.	2014	Retrospective cohort	PCOS women undergoing IVF	18.7-24.9: 51 Women 25–29.9: 19 Women ⩾30: 31 Women	Clinical pregnancy per ET Miscarriage Live-birth rate per cycle start and ET	[53]
Schliep et al.	2014	Prospective cohort	All couples undergoing first fresh IVF cycles	<18.5: 32 Women 18.5–24.9: 407 Women 25–29.9: 147 Women 30-34.9: 72 Women ⩾35: 63 Women	pregnancy rate Live-birth rate	[54]
Vural et al.	2014	Retrospective cohort	Women undergoing IVF	<25: 452 Women 25–30: 230 Women ⩾30: 98 Women	Clinical Pregnancy rate	[55]
Ozekinci et al.	2015	Retrospective cohort	Women younger than 38 years old undergoing Ivf-icsi	18.5-24.9: 164 Cycles 25–29.9: 70 Cycles ⩾30: 64 Cycles	Clinical pregnancy rate Spontaneous abortion Ongoing pregnancy	[56]

Caillon et al.	2015	Retrospective	Women undergoing IVF and ICSI	20-24.9: 409 Women ⩾25: 149 Women	Miscarriage rate Live-birth rate per cycle	[57]
Kalem et al.	2016	Retrospective cohort	PCOS women undergoing IVF	18.5–24.9: 299 Women 25–29.9: 208 Women ⩾30: 146 Women	Clinical pregnancy rate	[58]
Christensen et al.	2016	Historical cohort	Women undergoing IVF and ICSI	<18.5: 159 Cycles 18.5–24.9: 35339 Cycles 25–29.9: 1171 Cycles ⩾30: 474 Cycles	Clinical pregnancy rate	[59]
Wang et al.	2016	Retrospective cohort	Women undergoing IVF and ICSI	<25: 7097 Cycles ⩾25: 1768 Cycles	Clinical pregnancy rate Abortion Live-birth rate	[60]
Kawwass et al.	2016	Retrospective cohort	Women undergoing IVF	<18.5: 13678 Cycles 18.5–24.9: 271985 Cycles 25–29.9: 116788 Cycles ⩾30: 91646 Cycles	Intrauterine pregnancy rate Miscarriage rate Live-birth rate	[61]
Provost et al.	2016	Retrospective cohort	Women undergoing IVF	<18.5: 7149 Cycles 18.5–24.9: 134588 Cycles 25–29.9: 54822 Cycles 30–34.9: 24992 Cycles 35–39.9: 11747 Cycles 40–44.9: 4084 Cycles 45–49.9: 1292 Cycles ⩾50: 463 Cycles	Clinical pregnancy rate Pregnancy loss rate Live birth rate	[62]

Miscarriage rate

In women with BMI of < 25, the risk ratio of pooled results from 28 studies was 1.35 (95%: CI 1.28-1.46), when compared with women with BMI of ≥ 25 (Figure 4). The pooled results showed a statistically significant increase in the miscarriage rate in women with BMI ⩾25 kg/m^2 compared with women with BMI<25 kg/m^2. The miscarriage rate is increased by approximately 35 % (95 %: CI 25-45) in women BMI ⩾25 kg/m^2 when compared with women with BMI < 25 kg/m^2. The results showed evidence of statistical heterogeneity (I^2=71.5 %. P = 0.000).

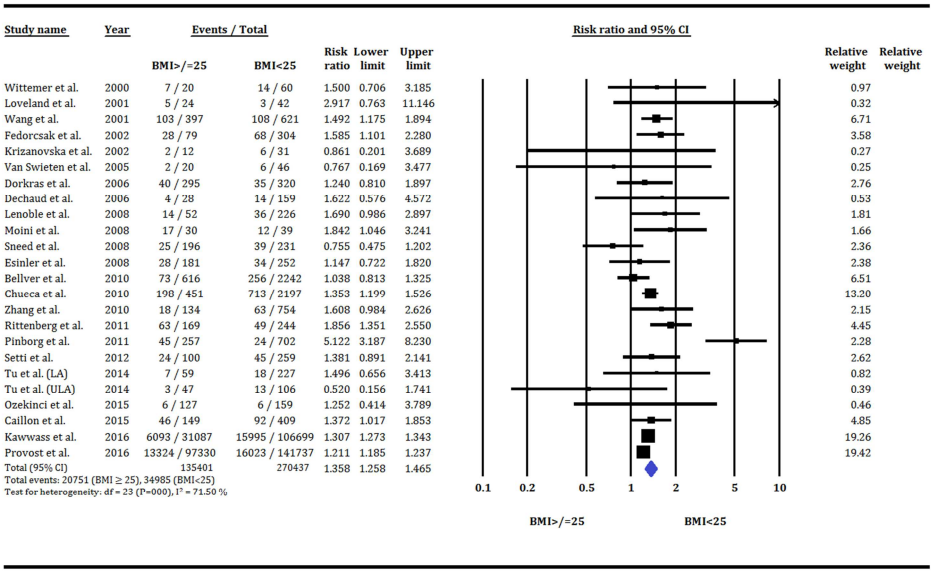

Fig 4. Forest plot of miscarriage rate in women with BMI < 25 versus BMI ≥ 25

Publication bias

The funnel plot for all outcome measures of ART that evaluated in this study, was asymmetric (Fig. 5) and with the results of Egger test (Table 3) suggesting small-study bias.

DISCUSSION

Obesity is an expensive and increasingly prevalent health burden upon modern society [63]. Obesity is an abnormal accumulation of body fat, generally 20% or more over an individual's ideal body weight. Obesity is associated with increased risk of illness, disability, and death. Obesity is often a comorbidity of other pathologies such as cardiovascular disease, hypertension, type 2 diabetes, gastrointestinal disease, arthritis, and cancer, also obese women are more likely to experience reproductive problems [6, 64-66]. Obesity has been attributed to menstrual and hormonal disorders, loss of fertility, miscarriage, undesired obstetric consequences (such as congenital defects and premature birth) and obstetric complications (e.g. increased blood pressure, pregnancy diabetes and wound infection) [67-70]. In addition, obesity is encountered in 30% to 70% of women with polycystic ovary syndrome [71]. Consequently, number of infertile overweight and obese women who are subjected to ART as a treatment for infertility is increasing steadily in worldwide [11, 72], thus, the impact of overweight and increased BMI on the outcome of ART treatment is of interest to patients, clinicians and makers of public health.

Our meta-analysis included data on 831616 subjects treated with ART, extracted from 44 studies. The result of our meta-analysis suggests that overweight women face a lower likelihood of: pregnancy , a live birth and an increased risk of miscarriage after IVF.

The results of our review are in accordance with a previous review and meta-analysis [11] and indicate that women who are overweight or obese (BMI ⩾25 kg/m^2) have adverse outcomes following ART treatment compared with women with normal BMI. Unlike the previous systematic reviews [10, 37] our data demonstrate that positive clinical outcomes of ART treatment decrease in women overweight and with an increased BMI of and also, the raised BMI is associated significantly with a reduced live-birth rate and increased miscarriage rate after ART treatment.

It is, however, possible to deduce from the available data that an apparent decrease in implantation rate and higher miscarriage in overweight and obese women it reflects in a reduced expectation of live birth rate.

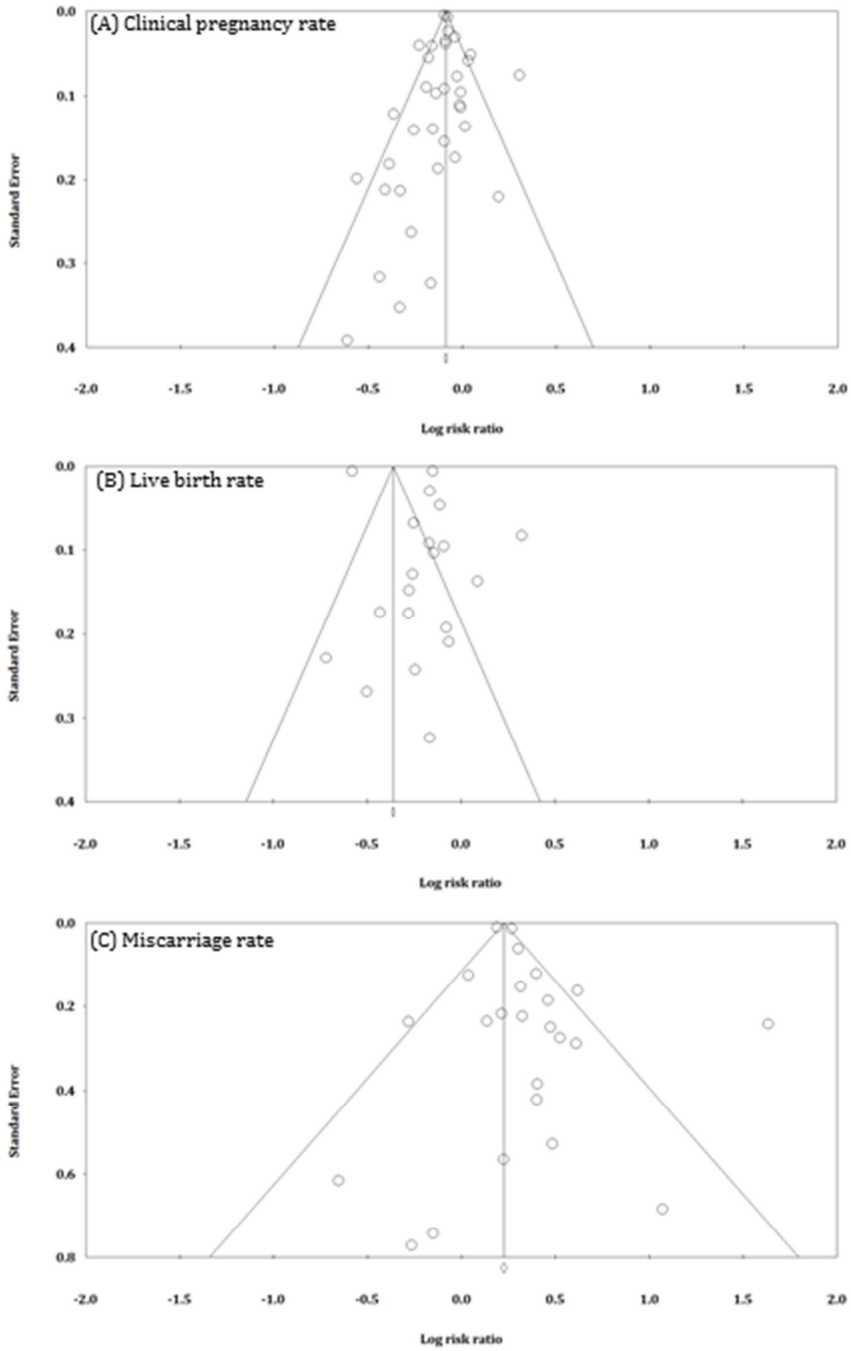

Fig 5. Funnel plot of (A) clinical pregnancy rate, (B) miscarriage rate and (C) live birth rate for assessing potential publication bias. The diagonal lines indicates approximate 95% confidence intervals for estimates.

Table 3. The results of Egger test for funnel plot asymmetry.

Outcome of ART	*t* value	*df*	*p* value (1-tailed)	*p* value (2-tailed)
Pregnancy rate	0.791	35	0.217	0.434
Live-birth rate	0.663	18	0.257	0.515
Miscarriage rate	1.535	22	0.069	0.138

While give in consultation to the infertile obese women who require ART to conceive, it is of note to know that pregnancy rate in overweight and obese women is still good, and age is the overriding factor in predicting success following ART [73].

The results of this study show that the live-birth rate and pregnancy rate is reduced by 19 % (95% CI 6–30%) and 8.4 % (95 %: CI 6-10.7), respectively, in women with BMI⩾25 kg/m^2 when compared with women with BMI lower

than 25 kg/m^2 following infertility treatment. Also the miscarriage rate is increased by approximately 35 % (95 %: CI 25-45) in women BMI ⩾25 kg/m^2 when compared with women with BMI < 25 kg/m^2.

Waist-to-hip ratio (WHR) is a value derived from the waist measurement and hip measurement and calculated as waist measurement divided by hip measurement (W ÷ H). The WHR may be used as a possible indicator of health issues, but also as risk of developing serious health conditions. WHR is correlate with infertility problem in males and females, but with different optimal values. There are suggestions that WHR is a better predictor of reproductive outcome than BMI [10, 74, 75] because the BMI does not differentiate between android and gynaecoid fat distribution, although in this review, we have used BMI as a marker of overweight and obesity.

Underlying mechanisms that linking the elevated BMI with the poorer outcomes after ART are not fully understood, though three hormonal systems—the insulin and insulin-like growth factor (IGF) axis (insulin resistance), sex steroids (hyperandrogenism and LH hypersecretion) and adipokines (elevated leptin levels and leptin resistance)—are the most studied candidates [65, 76-79]. All three systems are interlinked through insulin.

Adiponectin is a ubiquitous fat tissue hormone which is mainly produced from the cells of visceral fat and has been shown to have an inverse association with BMI. Mean circulating concentrations are higher in women than men [65, 80]. Beyond these mechanisms, other candidate systems include obesity-related inflammatory cytokines, altered immune response, oxidative stresses and lipid peroxidation [81, 82]. We do not yet know what mechanisms might link the clinical outcomes of ART with obesity.

Raised BMI through mechanisms that were mentioned above could adversely affect folliculogenesis, oocyte maturation and embryonic competence. Elevated BMI could be also associated with impaired implantation and increased risk of miscarriage; thus affecting ART outcome [81-86].

The results of our review are not completely free from bias and should be interpreted with caution. Methodological and clinical heterogeneity arises through the use of different study designs, particularly in relation to study population characteristics and definition of the relevant outcome measures. More study in this field is needed with clearly defined patient populations, using WHO criteria for BMI and uniform outcome measures to determining effect of raised BMI on reproductive outcomes following the ART treatment.
The findings of our review and other systematic review and meta-analysis studies permit clinicians to provide more detailed advice regarding the impact of elevated BMI and obesity on outcome of treatment before initiating an ART cycle. The obese infertile patients with abnormal BMI should be encouraged to lose weight and improve exercise tolerance to improve the clinical outcomes after ART treatment and to prepare for the stresses during pregnancy and at the moment of labour.

CONCLUSION

In conclusion, this systematic review and meta-analysis clearly demonstrates that raised BMI has an adverse effect on the outcome of ART. Obesity and overweight is associated with decreased pregnancy as well as higher miscarriage rates and decreased live birth rate following infertility treatment. Weight loss should be strongly considered in overweight and obese women before initiating infertility treatments. This will result in better health conditions of women undergoing infertility treatment, improving their chances of pregnancy and minimizing the costs of infertility treatment.

Conflict of interest
The authors have no conflict of interest to declare.

Acknowledgements
This work was supported by a grant from Students Research office, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

REFERENCES

[1] Steptoe, P.C. and R.G. Edwards, Birth after the reimplantation of a human embryo. The Lancet, 1978. 312(8085): p. 366.
[2] Zeilmaker, G.H., et al., Two pregnancies following transfer of intact frozen-thawed embryos. Fertility and sterility, 1984. 42 :(2)p. 293.
[3] Palermo, G., et al., Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte. The Lancet, 1992. 340(8810): p. 17-18.

[4] Talaulikar, V.S. and S. Arulkumaran, Reproductive outcomes after assisted conception. Obstetrical & gynecological survey, 2012. 67(9): p. 566-583.
[5] Okun, N., et al., Pregnancy outcomes after assisted human reproduction. Journal of Obstetrics and Gynaecology Canada, 2014. 36(1): p. 64-83.
[6] Facts about overweight and obesity. June 2016; Available from: http://www.who.int/mediacentre/factsheets/fs311/en./
[7] Koning, A., et al., Economic consequences of overweight and obesity in infertility: a framework for evaluating the costs and outcomes of fertility care. Human reproduction update, 2010. 16 :(3)p. 246-254.
[8] Laing, S.T. and C.L. Rochester, PREVALENCE OF OVERWEIGHT AND OBESITY IN THE UNITED STATES, 1999-2004. Journal of Cardiopulmonary Rehabilitation and Prevention, 2006. 26(5): p. 341-342.
[9] Prentice, A.M., The emerging epidemic of obesity in developing countries. International journal of epidemiology, 2006. 35(1): p. 93-99.
[10] Maheshwari, A., L. Stofberg, and S. Bhattacharya, Effect of overweight and obesity on assisted reproductive technology—a systematic review. Human reproduction update :(5)13 .2007 ,p. 433-444.
[11] Rittenberg, V., et al., Effect of body mass index on IVF treatment outcome: an updated systematic review and meta-analysis. Reproductive biomedicine online, 2011. 23(4): p. 421-439.
[12] Moragianni, V.A., S.-M.L. Jones, and D.A .Ryley, The effect of body mass index on the outcomes of first assisted reproductive technology cycles. Fertility and sterility, 2012. 98(1): p. 102-108.
[13] Lashen, H., et al., Extremes of body mass do not adversely affect the outcome of superovulation and in-vitro fertilization. Human Reproduction, 1999. 14(3): p. 712-715.
[14] Dechaud, H., et al., Obesity does not adversely affect results in patients who are undergoing in vitro fertilization and embryo transfer. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2006. 127(1): p. 88-93.
[15] Moher, D., et al., Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine, 2009. 151(4): p. 264-269.
[16] Mantel, N. and W. Haenszel, Statistical aspects of the analysis of data from retrospective studies. J natl cancer inst, 1959. 22(4): p. 719-748.
[17] DerSimonian, R. and N. Laird, Meta-analysis in clinical trials. Controlled clinical trials, 1986. 7(3): p. 177-188.
[18] Higgins, J. and S.G. Thompson, Quantifying heterogeneity in a meta-analysis. Statistics in medicine, 2002. 21(11): p. 1539-1558.
[19] Lewis, S. and M. Clarke, Forest plots: trying to see the wood and the trees. British Medical Journal, 2001. 322(7300): p. 1479.
[20] Munz ,W., et al., [Body mass index, protein metabolism profiles and impact on IVF/ICSI procedure and outcome]. Zentralblatt fur Gynakologie, 2005. 127(1): p. 37-42.
[21] Wittemer, C., et al., Does body mass index of infertile women have an impact on IVF procedure and outcome? Journal of assisted reproduction and genetics, 2000. 17(10): p. 547-552.
[22] Wang, J.X., M. Davies, and R.J. Norman, Body mass and probability of pregnancy during assisted reproduction treatment: retrospective study. BMJ : British Medical Journal, 2000. 321(7272): p. 1320-1321.
[23] FEDORCSÁK, P., et al., Obesity is a risk factor for early pregnancy loss after IVF or ICSI. Acta obstetricia et gynecologica Scandinavica, 2000. 79(1): p. 43-48.
[24] Loveland, J.B., et al., Clinical Assisted Reproduction: Increased Body Mass Index Has a Deleterious Effect on In Vitro Fertilization Outcome. Journal of Assisted Reproduction and Genetics, 2001. 18(7): p. 382-386.
[25] Wang, J.X., M.J. Davies, and R.J. Norman, Polycystic ovarian syndrome and the risk of spontaneous abortion following assisted reproductive technology treatment. Human Reproduction, 2001. 16(12): p. 2606-2609.
[26] Ferlitsch, K., et al., The significance of the body weight in assisted reproduction. J. Fertil. Reprod, 2002. 12: p. 7-12.
[27] Krizanovska, K., et al., [Obesity and reproductive disorders]. Sbornik lekarsky, 2001. 103(4): p. 517-526.
[28] Wang, J.X., M.J. Davies, and R.J. Norman, Obesity increases the risk of spontaneous abortion during infertility treatment. Obesity research :(6)10 .2002 ,p. 551-554.
[29] Winter, E., et al., Early pregnancy loss following assisted reproductive technology treatment. Human Reproduction, 2002. 17(12): p. 3220-3223.
[30] Doody, K.M., et al., Morbid obesity adversely impacts outcomes with IVF. Fertility and Sterility, 2003. 80: p. 160.
[31] Ryley, D., et al., Influence of body mass index (BMI) on the outcome of 6,827 IVF cycles. Fertility and Sterility, 2004. 82: p. S38-S39.
[32] Fedorcsák, P., et al., Impact of overweight and underweight on assisted reproduction treatment. Human Reproduction, 2004. 19(11): p. 2523-2528.
[33] Hammadeh, M., et al., Relationship between body mass index (BMI) and plasma lipid concentration and their effect on IVF/ICSI outcome. Fertility and Sterility, 2005. 84: p. S422.

[34] van Swieten, E.C., et al., Obesity and clomiphene challenge test as predictors of outcome of in vitro fertilization and intracytoplasmic sperm injection. Gynecologic and obstetric investigation, 2005. 59(4): p. 220-224.
[35] Dokras, A., et al., Obstetric outcomes after in vitro fertilization in obese and morbidly obese women. Obstetrics & Gynecology, 2006. 108(1): p. 61-69.
[36] Mitwally, M.F., et al., The effect of Body Mass Index (BMI) on the outcome of IVF and embryo transfer in women of different ethnic backgrounds. Fertility and Sterility, 2006. 86(3): p. S68-S69.
[37] Metwally, M., et al., Does high body mass index increase the risk of miscarriage after spontaneous and assisted conception? A meta-analysis of the evidence. Fertility and sterility, 200 :(3)90 .8p. 714-726.
[38] Lenoble, C., et al., [Effect of women's weight on the success rate of in vitro fertilization]. Gynecologie, obstetrique & fertilite, 2008. 36(9): p. 940-944.
[39] Martinuzzi, K., et al., Elevated body mass index (BMI) does not adversely affect in vitro fertilization outcome in young women. Journal of assisted reproduction and genetics, 2008. 25(5): p. 169-175.
[40] Moini, A., et al., The effect of body mass index on the outcome of IVF/ICSI cycles in non-polycystic ovary syndrome women. Int J Fertil Steril, 2008. 2(2): p. 82-85.
[41] Sneed, M.L., et al., Body mass index: impact on IVF success appears age-related†. Human reproduction, 2008. 23(8): p. 1835-1839.
[42] Esinler, I., G. Bozdag, and H. Yarali, Impact of isolated obesity on ICSI outcome. Reproductive biomedicine online, 2008. 17(4): p. 583-587.
[43] Orvieto, R., et al., Ovarian stimulation in polycystic ovary syndrome patients: the role of body mass index. Reproductive biomedicine online, 2009. 18(3): p. 333-336.
[44] Bellver ,J., et al., Female obesity impairs in vitro fertilization outcome without affecting embryo quality. Fertility and sterility, 2010. 93(2): p. 447-454.
[45] Chueca, A., et al., Should BMI limit patient access to IVF? Hum. Reprod, 2010. 25: p. i283.
[46] Farhi ,J., et al., High-quality embryos retain their implantation capability in overweight women. Reproductive biomedicine online, 2010. 21(5): p. 706-711.
[47] Kilic, S., et al., Obesity alters retrieved oocyte count and clinical pregnancy rates in high and poor responder women after in vitro fertilization. Archives of gynecology and obstetrics, 2010. 282(1): p. 89-96.
[48] Zhang, D., et al., Overweight and obesity negatively affect the outcomes of ovarian stimulation and in vitro fertilisation: a cohort study of 2628 Chinese women. Gynecological Endocrinology, 2010. 26(5): p. 325-332.
[49] Rittenberg, V., et al., Influence of BMI on risk of miscarriage after single blastocyst transfer. Human reproduction, 2011: p. der254.
[50] Pinborg, A., et al., Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples. Reproductive biomedicine online, 2011. 23(4): p. 490-499.
[51] Setti, A.S., et al., Body mass index is negatively correlated with the response to controlled ovarian stimulation but does not influence oocyte morphology in ICSI cycles. European Journal of Obstetrics & Gynecology and Reproductive Biology, 2012. 163(2): p. 175-179.
[52] Tu, J., et al., A novel modified ultra-long agonist protocol improves the outcome of high body mass index women with polycystic ovary syndrome undergoing IVF/ICSI. Gynecological Endocrinology, 2014. 30(3): p. 209-212.
[53] Bailey, A.P., et al., Effect of body mass index on in vitro fertilization outcomes in women with polycystic ovary syndrome. American journal of obstetrics and gynecology, 2014. 211(2): p. 163. e1-163. e6.
[54] Schliep, K.C., et al., Effect of male and female body mass index on pregnancy and live birth success after in vitro fertilization. Fertility and sterility, 2 :(2)103 .015p. 388-395.
[55] Vural, F., B. Vural, and Y. Çakiroglu, In vitro fertilization outcomes in obese women under and above 35 years of age. Clin. Exp. Obstet. Gynecol, 2016. 43(2): p. 2016.
[56] Ozekinci, M., et al., Does obesity have detrimental effects on IVF treatment outcomes? BMC women's health, 2015. 15(1): p. 1.
[57] Caillon, H., et al., Effects of female increased body mass index on in vitro fertilization cycles outcome. Obesity research & clinical practice, 2015. 9(4): p. 382-388.
[58] Kalem ,M.N., et al., Effect of body mass index and age on in vitro fertilization in polycystic ovary syndrome. 2016.
[59] Christensen, M.W., et al., Effect of Female Body Mass Index on Oocyte Quantity in Fertility Treatments (IVF): Treatment Cycle Number Is a Possible Effect Modifier. A Register-Based Cohort Study. PloS one, 2016. 11(9): p. e0163393.
[60] Wang, X., et al., Effects of female and male body mass indices on the treatment outcomes and neonatal birth weights associated with in vitro fertilization/intracytoplasmic sperm injection treatment in China. Fertility and sterility, 2016.
[61] Kawwass, J.F., et al., Extremities of body mass index and their association with pregnancy outcomes in women undergoing in vitro fertilization in the United States. Fertility and Sterility, 2016.

[62] Provost, M.P., et al., Pregnancy outcomes decline with increasing body mass index: analysis of 239,127 fresh autologous in vitro fertilization cycles from the 2008–2010 Society for Assisted Reproductive Technology registry. Fertility and sterility, 2016. 105(3): p. 663-669.
[63] Norman, R. and A. Clark, Obesity and reproductive disorders: a review. Reproduction, fertility, and development, 1997. 10(1): p. 55-63.
[64] Clark, A., et al., Weight loss in obese infertile women results in improvement in reproductive outcome for all forms of fertility treatment. Human Reproduction, 1998. 13(6): p. 1502-1505.
[65] Kadivar, A., et al., Correlation of adiponectin mRNA abundance and its receptors with quantitative parameters of sperm motility in rams. International journal of fertility & sterility, 2016. 10(1): p. 127.
[66] Calle, E.E., et al., Body-mass index and mortality in a prospective cohort of US adults. New England Journal of Medicine, 1999. 341(15): p. 1097-1105.
[67] Edwards, L.E ,.et al., Pregnancy complications and birth outcomes in obese and normal-weight women: effects of gestational weight change. Obstetrics & Gynecology, 1996. 87(3): p. 389-394.
[68] HAMILTON-FAIRLEY, D., et al., Association of moderate obesity with a poor pregnancy outcome in women with polycystic ovary syndrome treated with low dose gonadotrophin. BJOG: An International Journal of Obstetrics & Gynaecology, 1992. 99(2): p. 128-131.
[69] Lucas, A., et al., Maternal fatness and viability of preterm infants. BMJ :(6635)296 .1988 ,p. 1495-1497.
[70] Bellver, J., et al., Obesity and poor reproductive outcome: the potential role of the endometrium. Fertility and sterility, 2007. 88(2): p. 446-451.
[71] Vrbikova, J. and V. Hainer, Obesity and polycystic ovary syndrome .Obesity facts, 2009. 2(1): p. 26-35.
[72] Ferraretti, A.P., et al., Assisted reproductive technology in Europe, 2009: results generated from European registers by ESHRE. Human Reproduction, 2013: p. det278.
[73] Jungheim, E.S., J.L. Travieso, and M.M. Hopeman, Weighing the impact of obesity on female reproductive function and fertility. Nutrition reviews, 2013. 71(suppl 1): p. S3-S8.
[74] Wass, P., et al., An android body fat distribution in females impairs the pregnancy rate of in-vitro fertilization-embryo transfer. Human Reproduction, 1997. 12(9): p. 2057-2060.
[75] Zaadstra, B.M., et al., Fat and female fecundity: prospective study of effect of body fat distribution on conception rates. Bmj, 1993. 306(6876): p. 484-487.
[76] Sharpe, R.M. and S. Franks, Environment, lifestyle and infertility--an inter-generational issue. Nature cell biology, 2002. 4.
[77] Brewer, C.J. and A.H. Balen, The adverse effects of obesity on conception and implantation. Reproduction, 2010. 140(3): p. 347-364.
[78] Dumesic, D.A., V. Padmanabhan, and D.H. Abbott, Polycystic ovary syndrome and oocyte developmental competence. Obstetrical & gynecological survey, 2008. 63(1): p. 39.
[79] Qiao, J. and H.L. Feng, Extra-and intra-ovarian factors in polycystic ovary syndrome: impact on oocyte maturation and embryo developmental competence. Human reproduction update, 2010: p. dmq032.
[80] Deng, Y. and P.E. Scherer, Adipokines as novel biomarkers and regulators of the metabolic syndrome. Annals of the New York Academy of Sciences, 2010. 1212 :(1)p. E1-E19.
[81] Lee, Y. and K. Loke, The molecular pathogenesis of obesity: an unfinished jigsaw puzzle. Annals of the Academy of Medicine, Singapore, 2000. 29(3): p. 388-395.
[82] Gosman, G.G., H.I. Katcher, and R.S. Legro, Obesity and the role of gut and adipose hormones in female reproduction. Human reproduction update, 2006. 12(5): p. 585-601.
[83] Wang, T.-H., et al., Insulin-like growth factor-II (IGF-II), IGF-binding protein-3 (IGFBP-3), and IGFBP-4 in follicular fluid are associated with oocyte maturation and embryo development. Fertility and sterility, 2006. 86(5): p. 1392-1401.
[84] Fowke, J.H., et al., Racial differences in the association between body mass index and serum IGF1, IGF2, and IGFBP3. Endocrine-related cancer, 2010. 17(1): p. 51-60.
[85] Ma, Y., et al., Maternal obesity and overnutrition alter fetal growth rate and cotyledonary vascularity and angiogenic factor expression in the ewe. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 2010. 299(1): p. R249-R258.
[86] Dimitriadis, E., et al., Local regulation of implantation at the human fetal-maternal interface. International Journal of Developmental Biology, 2009. 54(2-3): p. 313-322.