# Female Obesity and Assisted Reproductive Technologies

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**Abstract**

Obesity has grown to epidemic proportions, and currently nearly half of the reproductive-age women are overweight or obese. Risks, success rates, and economic aspects of infertility treatments in obese women have been extensively investigated. Unfavorable ovarian stimulation characteristics like increased gonadotropin consumption, fewer selected follicles, and lower number of retrieved oocytes have been observed in obese women undergoing assisted reproductive technologies (ART). There seems to be a strong association between increased body mass index and lower pregnancy and live-birth rates and increased miscarriage rate. Coexisting factors like age and polycystic ovary syndrome status have also been blamed for these adverse effects. The mechanisms underlying those adverse outcomes, whether ovarian or endometrial, still remain to be fully elucidated. Moreover, maternal, perinatal, and neonatal complications have also been reported to be higher in obese pregnant women. Hence in some countries strict restrictions exist for access to elective fertility treatment in obese women. However, it is controversial if these policies are socially and ethically acceptable. Furthermore, because weight reduction is not an easy task, it may lead to the decreased probability of conception due to the advancing reproductive age for many obese women. Thus weight reduction should be encouraged and patients counseled accordingly, but whether restriction for fertility treatment is implemented in obese women remains a matter of debate. There remains much to be known regarding the association between obesity and ART.

**Keywords**
- obesity
- body mass index
- ART
- IVF
- outcome



## Definition of Obesity

Obesity is a worldwide epidemic both for women and men. Approximately 30% of women age 25 to 44 years are overweight, and 20% are obese.[1,2] The prevalence of overweight and obesity varies in populations and is estimated to be ~5% in some developing countries and >50% in some developed countries.[3]

Although the World Health Organization (WHO) classified obesity precisely, many authors used variable body mass index (BMI) cutoff values to define obesity (►**Table 1**).[4,5] BMI is calculated using the formula weight/height$^2$ and expressed as kg/m$^2$. However, some researchers are against the consideration of BMI as a marker of obesity and have suggested that waist-to-hip ratio might be a better predictor of health and fertility outcomes.[6,7] However, BMI is the most

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**Table 1** Body Mass Index Thresholds Used in Various Studies as Compared with World Health Organization Classification

| Study Definitions | BMI Threshold | WHO Classification | WHO BMI Thresholds |
|---|---|---|---|
| Underweight | <18.5 | Underweight | <18.5 |
| Lean | <20 | Normal | 18.5–24.9 |
| Normal | 20–24.9 or 18.5–23.9 | Overweight | 25–29.9 |
| Overweight | 25–29.9 or ≥24 | Obesity class I | 30–34.9 |
| Obese | ≥30 | Obesity class II | 35–39.9 |
| Morbidly obese | ≥35 or ≥40 | Obesity class III | ≥40 |

BMI, body mass index; WHO, World Health Organization.

commonly used measure of obesity, which might be due to its ease of measurement and lack of susceptibility to inter- and intraobserver variations.

Regarding the effects of obesity on fertility, various terms like *overweight, obese,* and *morbidly obese* have been used in the literature. Definitions of overweight, obesity, and underweight differ in various reports.[5] Overweight has been defined as BMI ≥24 kg/m$^2$ by some, or BMI 25–29.9 kg/m$^2$ by others, and obesity has been usually defined as BMI ≥30 kg/m$^2$.[6] Women with a BMI >35 kg/m$^2$ by some and with a BMI >40 kg/m$^2$ by others were categorized as morbidly obese.[8,9] In the relevant studies, patients have been mostly stratified into groups like BMI <19 kg/m$^2$, 19 to 25.9 kg/m$^2$, 26 to 30.9 kg/m$^2$, 31 to 35.9 kg/m$^2$, and >36 kg/m$^2$. Because some researchers used different cut-off values for BMI instead of the WHO classification, the comparisons of the findings from those studies may not be possible, which leads to inconclusive data in the literature. Thus it is necessary to use single standardized BMI criteria. The National Institutes of Health and the International Obesity Task Force have defined overweight (or preobese) as a BMI of 25 to 29.9, and obese as BMI ≥30.[10] Morbid obesity is defined as a BMI ≥40. Nevertheless, patients with a BMI >35 kg/m$^2$ have been suggested as a high-risk group for assisted reproductive technologies (ART). Maternal age and the existence of polycystic ovary syndrome (PCOS) were further suggested as important variables in assessing the effects of obesity on ART. For the purpose of this review, ART is defined as all fertility treatments in which both eggs and sperm are handled, which includes in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), either by utilizing autologous or donor eggs or sperm, frozen thawed embryo transfer, and gestational surrogacy. ART does not include treatments in which only sperm are handled such as superovulation with intrauterine insemination.

## The Effects of Obesity on Reproduction

As widely accepted, obesity is associated with diabetes, hypertension, hypothyroidism, and cardiovascular and musculoskeletal diseases.[11] In addition, female obesity might lead to menstrual irregularity, chronic oligoanovulation, hirsutism, infertility, and an increased rate of miscarriages.[12]

Infertility in obese women has mostly been associated with anovulation that was shown to improve after weight loss.[13,14] Obesity is associated with the alterations of pulsatile gonadotropin-releasing hormone secretion, the levels of sex hormone-binding globulin (SHBG), ovarian and adrenal androgens, and luteinizing hormone (LH) that may potentially interfere with ovulatory function.[2,14]

With obesity, peripheral aromatization of androgens to estrogens are increased and SHBG levels are decreased, both of which may lead to increased free estradiol and testosterone levels. Obesity is associated with hyperinsulinemia leading to decreased SHBG synthesis and stimulation of ovarian androgen production.[15] The resultant hypersecretion of LH and increased androgen-to-estrogen ratio may lead to impaired folliculogenesis and follicular atresia.[16,17] In fact, the major factor implicated in the association between obesity and reproductive problems is insulin resistance and accompanying hyperinsulinemia. Obesity-associated hyperleptinemia is an additional factor causing anovulation by both inducing hyperinsulinemia and directly impairing ovarian function.[18]

PCOS is the most common endocrinopathy in women. The prevalence of PCOS among obese women with menstrual irregularities is not clear yet due to the various criteria used for PCOS. However, obesity may promote the development of the PCOS phenotype in susceptible women. The adverse effects of obesity seem to be more evident in women with PCOS. In a 2009 study investigating the possible alterations in ovarian function in obese women, significant changes were found in the follicular fluid levels of insulin, lactate, C-reactive protein, and androgens that might support that poorer reproductive outcome in obese women may be ovarian in origin.[19]

Some studies have suggested that the fecundity can be lower among ovulatory obese women as well. In a cohort of ovulatory subfertile women, it was reported that the probability of natural conception over 12 months declined by 4% per kg/m$^2$ with a BMI >29 kg/m2.[20,21]

## Treatment of Infertility

Obesity has been shown to impair ovarian response to ovulation induction with clomiphene citrate and gonadotropins.[22–24] Furthermore, higher poor response rates were demonstrated in obese women undergoing ART.[25]

In addition to insulin resistance, adiposity is also associated with inflammation, coagulation, and fibrinolysis.[26]

Inflammatory markers such as C-reactive protein, interleukin-6, tumor necrosis factor-α, and plasminogen activator inhibitor type-1 are found to be increased in the serum of obese subjects, and those markers are thought to exert a negative impact on implantation and early embryonic development.[26] Hence extraovarian factors may also play a role in adverse ART outcomes.[17] However, the exact mechanisms for this negative impact remain to be elucidated.

To minimize the ovarian effects and to reveal the extraovarian factors as causes of the adverse affects of obesity on reproductive outcomes, the oocyte donation-recipient model was investigated.[27–30] The results were controversial regarding implantation and miscarriage rates, which were mainly due to small sample size. When donors versus autologous oocytes were considered, most studies reported no change in pregnancy rates.[29,30] However, some other studies suggested lower ongoing pregnancy rates with increased recipient BMI.[27,28,31] The authors of one of the largest studies concluded that extraovarian factors contributed to the assumed detrimental effects of overweight/obesity on reproductive performance.[28] However, the role of the endometrium has been suggested to be small.[28] Obesity and associated metabolic and endocrinological alterations affect not only the ovary but also the endometrium, both together leading to poor reproductive outcome in overweight/obese women. Further studies incorporating the actions of insulin, leptin, ghrelin, resistin, adiponectin, and other relevant hormones on the endometrium would help to elucidate this issue further.[32]

## Obesity and ART Outcome

The effect of female obesity on the ART outcome has been controversial. Various researchers have focused on different aspects of fertility outcomes in obese women that included follicular development, number of oocytes retrieved, gonadotropin requirement, oocyte quality, embryo quality, endometrial alteration, implantation rates, pregnancy rates, miscarriage rates, and live-birth rates. In obese women who already started ART cycle, the general aim is to obtain the best quality embryos to overcome presumed endometrial contribution to poor reproductive outcome. Nearly all the studies have concluded that whether the mechanism of negative impact of obesity on in vitro fertilization outcome is ovarian, endometrial, or a combination of the two is unknown.

Although some reviews and observational studies suggested that women with a BMI $\geq$25 kg/m$^2$ require higher doses of gonadotropins to achieve adequate ovarian response, have lower pregnancy rates, and experience higher miscarriage rates after ART, the evidence regarding the effect of BMI on cycle cancellation and live birth was weak.[33]

The data from the Society for Assisted Reproductive Technology (SART) Clinic Online Reporting System (SART CORS) was recently analyzed to assess the relation between obesity and ART outcomes in a large population that includes >90% of the ART cycles performed in the United States. The crude data are expected to be entered prospectively by each member ART clinic. Since 2007, height and cycle baseline weight were added to SART CORS. Therefore the calculation of female BMI became possible. The dataset did not include parameters like waist circumference, waist-to-hip ratio, donor BMI, or the paternal BMI.

The initial article on obesity from SART CORS included 45,163 ART cycles performed in 2007, resulting in transfer of one or more embryos. The BMI classification reflects WHO criteria, and the highest BMI category was the class III group between 40.0 and 46 kg/m$^2$. The outcome variables included odds of failure to achieve a clinical intrauterine gestation and failure to achieve a live birth.[34] Proportion of blastocyst-stage embryos decreased with higher BMIs. In general, failure to achieve clinical intrauterine pregnancy increased significantly with advancing age. The rates of clinical intrauterine pregnancy, live births, and length of gestation by plurality declined with increasing BMI. The adverse effects of increasing BMI was greater among women <35 years of age than in women $\geq$35 years using autologous oocytes. Therefore advancing female age was a more important factor than obesity itself. Because of small numbers, the effect of using donor oocytes with increasing BMI was analyzed only among women $\geq$35 years, and it was not found to be significant. Because the study only included those cycles resulted in embryo transfers rather than cycle starts, no information can be obtained regarding cycle cancellation with increasing BMI. Furthermore, PCOS was grouped with all ovulatory disorders in the dataset, which may account for some of the adverse outcomes of increasing BMI.[34]

The second study from SART CORS included 152,500 cycle starts performed in 2007 and 2008.[35] Cycles using gestational carriers and embryo banking were excluded, and each cycle was treated as an independent observation. This time, cycle cancellation and cycle cancellation due to low response were also assessed, although those women who had repeat cycle failures might be overrepresented. The BMI categories also included 40 to 44.9, 45.0 to 49.9, and $\geq$50 kg/m$^2$. The coded rates of ovulation disorders including PCOS, tubal, and uterine factors increased with rising BMI. The mean follicle-stimulating hormone (FSH) dosage increased significantly as BMI increased. The odds ratios of cycle cancellation increased significantly for cycles with higher BMIs starting in the overweight group with BMIs between 25.0 and 29.9 kg/m$^2$. A similar pattern was observed for cycle cancellation due to low response. Increasing BMI above normal range (18.5 to 24.9) was associated with progressively increased odds ratios for failure to achieve clinical intrauterine pregnancy and live birth with autologous oocytes. The same pattern was observed to a lesser extent in donor egg cycles and thawed embryos.

## ART in Obese Women with PCOS

In the studies about obesity and ART, the incidence of anovulation was found to be higher in obese women.[2,35] Female obesity can play a key role in the pathophysiology of hyperandrogenism, hyperinsulinemia, and metabolic abnormalities that characterize PCOS.

Obesity is actually a hyperandrogenic state and exists in 35 to 60% of women with PCOS.[12,36] PCOS is further exacerbated by insulin resistance associated with overweight/obesity.[37] Insulin resistance is highly prevalent in obese or PCOS patients. Insulin resistance is rarely detected in women with BMIs $<27$ kg/m$^2$.[36] PCOS status, obesity, and insulin resistance are interrelated conditions. The clinical characteristics of PCOS are heterogeneous and may present in various phenotypes at different ages depending mainly on the presence of obesity and metabolic alterations. PCOS, obesity, and insulin resistance are all associated with lower clinical pregnancy rates in assisted conception cycles, increased miscarriage rates, and decreased live-birth rates.[33,38] Mechanisms for these adverse outcomes are unclear. Some researchers claimed that insulin resistance was an independent risk factor for miscarriage.[39] PCOS was also shown to have an independent effect on fecundity and spontaneous abortion rate.[40–42]

Obesity has been assumed to potentiate the negative impact of PCOS on fertility. In a recent study, outcomes of IVF were compared between PCOS women with a BMI $<40$ kg/m$^2$ and those with a BMI $\geq 40$ kg/m$^2$ that revealed morbid obese PCOS women had significantly lower pregnancy rates.[38] Similarly, Ozgun et al compared ICSI outcome between obese PCOS women (BMI $\geq 30$ kg/m$^2$; $n = 18$ women) and nonobese PCOS women (BMI $<30$ kg/m$^2$; $n = 26$ women).[43] Obese women were found to consume higher amounts of gonadotropins, and the miscarriage rate was significantly higher in obese PCOS women. In another study, BMI impact on the IVF outcomes of women with PCOS has been investigated, and it was concluded that as the BMI increased, gonadotropin consumption increased and the retrieved oocyte numbers decreased, but clinical outcomes did not differ. Therefore, obesity was claimed to confer relative gonadotropin resistance.[44] Another study found no effects of PCOS and BMI on early pregnancy loss in ART conceptions.[45] Discrepancies among these studies might be the result of small sample sizes or methodological differences.

Considering all potential adverse outcomes in ART, insulin sensitivity should be improved through lifestyle modifications or pharmacological intervention before fertility treatment in obese or PCOS women. Nonrandomized studies have demonstrated that the reduction in insulin levels with metformin in insulin-resistant women might reduce spontaneous abortion risk by improving the endometrial milieu.[46] Similarly, metformin was claimed to improve ovulation and clinical pregnancy rates in women with PCOS.[47] However, in a 2009 Cochrane review, the effectiveness of metformin as a cotreatment during ART in women with PCOS was evaluated, and no evidence was found for metformin in improving pregnancy or live-birth rates but was found to reduce the risk of OHSS.[48]

The weight reduction can improve hormonal abnormalities, menstrual pattern, and fertility rates in anovulatory obese women.[49] In a recent study, addition of metformin to lifestyle changes (diet and exercise) was evaluated in PCOS women, and no significant difference was found in ovulation rates, but dropout rates were high in the study.[50] Weight loss of at least 5% of the initial weight in obese hyperandrogenic, anovulatory women causes reduction in insulin and free testosterone levels and may lead to normal ovulatory cycles.[11,51] Dietary restriction and exercise will result in normal ovulatory cycles and improved fertility in most anovulatory obese PCOS women.[36] Therefore, weight reduction should be the first therapeutic measure in women with PCOS before a planned ART cycle. This may be difficult and time consuming but somewhat inexpensive and may provide better obstetric outcomes. Recently the role of bariatric surgery was also investigated in morbidly obese infertile women, and further research has been recommended to reveal the impact of bariatric surgery on pregnancy and miscarriage rates.[52]

## ART in Obese Non-PCOS Women

Because the prevalence of obesity is rising, more and more women with a high BMI will present for fertility treatment. Although an overall negative effect is seen in the literature, the definition of obesity, cause of infertility, ovarian stimulation protocols used, initial gonadotropin dose, and oocyte/embryo quality criteria are not uniform among the studies related to obesity and assisted reproduction. Coexisting factors like PCOS status, male BMI, and maternal age might be contributing to the adverse effect. Available evidence suggests that age has a stronger negative impact on fertility and obstetric outcomes.[34,53]

Assisted reproductive treatments are already costly. Obese women require higher amounts of gonadotropins for ovarian stimulation,[2,54,55] have prolonged duration of stimulation,[54] have a higher risk for miscarriage,[40,54,56,57] and have pregnancies with higher complication rates.[58–60] In an oocyte donation program, the link between obesity and abortion rate was evaluated, and fourfold increase in the risk of spontaneous abortion was found in recipient women with BMI $\geq 30$ kg/m$^2$ compared with those with normal weight (BMI 20 to 24.9 kg/m$^2$).[27] Similarly, in a meta-analysis investigating the association between obesity and miscarriage after spontaneous or assisted conception, an increased risk of miscarriage was found in women with a BMI $\geq 25$ kg/m$^2$ regardless of the method of conception.[5] However, the same authors suggested that in subgroup analysis there was no evidence for increased miscarriage rate after IVF and ICSI as compared with spontaneous conception. Because of these adverse effects, fertility treatments will probably be less successful and even more expensive in obese women. That is the reason why there are strict upper BMI limits for access to IVF in some health-care settings.[61–63]

The British Fertility Society suggests that infertility treatment should better be delayed until BMI is $<35$ kg/m$^2$.[1,2,64] A woman's age is an important determinant, for younger women ($<37$ years), with good ovarian reserve (normal FSH), a reduction in BMI even to $<30$ kg/m$^2$ has been recommended.[1] The National Institute of Clinical Excellence (NICE) guideline in the United Kingdom suggests it is ideal to achieve a BMI $<29$ kg/m$^2$ prior to fertility treatment.[53] Similarly, in New Zealand, there is restriction for women with BMIs $>32$ kg/m$^2$ to apply for fertility treatment.[53] However, those BMI cutoff values are still considered arbitrary and based on expert opinion only. Given the lack of consensus on threshold BMI values for increased obstetric risks, decreased effectiveness of fertility treatments, and increased costs, it may not be justifiable yet to restrict some patients from accessing fertility treatment. Moreover, restriction of obese women from accessing fertility treatment may result in psychological stress leading to depression, anxiety, low self-esteem, social isolation, and sexual dysfunction that are already known to be more common in infertile women.[65,66]

Because pregnancy in obese women is associated with increased risks, recommendations for weight loss before attempted pregnancy would be reasonable in young women. For women with advanced reproductive age, the benefits of postponing pregnancy must be balanced against declining fertility with advancing age.

Some researchers have explored health-care costs of ART in obese women.[2] The results revealed that the mean cost of IVF treatment cycle was similar across the BMI groups.[2] It was found that the cost of an IVF cycle in a woman with BMI $\geq$35 kg/m$^2$ was £2719 and £2685 in a woman with normal BMI (18.5 to 24.9 kg/m$^2$). However, in that study, the initial gonadotropin dose was determined by the age of the woman alone, and BMI was not taken into consideration (150 IU <37 years, 225 IU 37 to 39 years, 300 IU $\geq$40 years). Women with polycystic ovaries were started with 150 IU. Although the author claimed that there were no randomized controlled trials evaluating whether overweight and obese women had better outcomes with higher dose of gonadotropins, one of the determinants of the initial gonadotropin dose is BMI.[67]

Many studies have demonstrated higher poor response rates in obese women undergoing ART.[35,54] Starting a gonadotropin dose might have an impact on ovarian response or cycle cancellation rate, and it was adjusted according to age and BMI in some studies[54,68] but not in others.[69] Cycle cancellation rate including both due to poor response and ovarian hyperstimulation syndrome (OHSS) was given together in the study by Maheshwari et al.[2] However, poor response rate would be better reported individually, which would be more meaningful. Fedorcsák et al stated that obese women had fewer selected follicles, fewer oocytes collected, fewer embryos to select for transfer, and fewer cycles that proceeded to transfer.[54] These adverse ART cycle outcomes might be improved by the use of alternative stimulation protocols and BMI-adjusted initial gonadotropin dose to increase the number of available oocytes and reduce cancellation rates in obese women. Stimulation protocols used might also have an impact on ovarian response and cycle cancellation rates.[70] In a relevant study, two stimulation protocols, agonist long and antagonist protocols, were compared in women with BMI >40 kg/m$^2$, but no difference was found between the two with regard to the treatment outcomes.[71]

The studies on ART in overweight/obese women have reported conflicting results with regard to cycle cancellation rate, the number of oocytes retrieved, the number of embryos obtained, or outcome measures like implantation, pregnancy, and live-birth rates (►**Tables 2** and **3**). Some researchers found increased cycle cancellations,[35,72] decreased implantation and clinical pregnancy rates,[73,74] lower fertilization rate,[75] lower ongoing pregnancies,[73] lower live births,[34,35,54,74] whereas others showed no impact.[45,68,76–78] Fedorcsák et al found that increased BMI was related to lower live-birth rate, higher miscarriage rate, increased gonadotropin requirement, longer stimulation period, insufficient follicular development, and fewer collected oocytes.[54] Similarly, Sneed et al[79] suggested that overweight and obese women had a lower live-birth rate after IVF/ICSI, especially those $\leq$36 years of age, almost similar findings to those of Luke et al.[35] In a recent study including 419 ART cycles in obese women (BMI $\geq$30 kg/m$^2$), implantation, pregnancy, and live-birth rates were found to be significantly impaired in obese women, but the embryo quality did not differ. Hence the alteration of the uterine environment was suggested as the cause of observed adverse effects.[74] On the contrary, in a large cohort of women undergoing IVF, no association was found between BMI and clinical pregnancy and live-birth rates.[80] Maheshwari et al noted no significant difference in live-birth rates among women in different BMI categories.[2,33] In another study, obese women (BMI >30 kg/m$^2$) who responded normally to ovarian stimulation were found to have similar conception rates to those with BMIs < 30 kg/m$^2$.[25]

The published literature in women with BMIs >35 kg/m$^2$ has been limited to reach reliable conclusions on the ART cycle characteristics and outcomes in this group. In a large patient group with BMI $\geq$35 kg/m$^2$ ($n$ = 117), pregnancy rate was found to be half that of the moderate (BMI 20 to 25 kg/m$^2$) group.[40] Dokras et al reported on 76 morbidly obese women (BMI $\geq$40 kg/m$^2$) who had significantly higher cycle cancellation rate (25%) but similar clinical pregnancy rates compared with those in normal-weight women.[80] Miscarriage rate was found to be significantly higher in women with BMI $\geq$35 kg/m$^2$.[2] The largest study in that regard included 10,528 cycles in women with BMIs $\geq$35 kg/m$^2$ and showed increased cycle cancellation and increased odds of failure to achieve clinical intrauterine pregnancy and live birth as the BMI increased.[35] The adjusted odds ratios for cycle cancellation with autologous oocytes (1.97; 95% confidence interval [CI], 1.42 to 2.74), failure to achieve clinical intrauterine pregnancy (1.53; 95% CI, 1.13 to 2.06), and failure to achieve live birth in fresh cycles (2.29; 95% CI, 1.37 to 3.83) were highest in the group with BMI $\geq$50 kg/m$^2$.[35]

Another issue regarding the effects of obesity on ART is the anesthetic impact of obesity in women who undergo ART procedures. Because the patients with high BMI have a greater prevalence of comorbid conditions such as gastroesophageal reflux disease, depression/anxiety, hypothyroidism, diabetes, and hypertension, they more commonly require an alteration in anesthetic and oocyte retrieval techniques.[81] The method of oocyte retrieval may also be influenced by BMI value.[81] The transabdominal approach might be used when the transvaginal route fails or is not anatomically possible. Procedure time has been observed to be longer in women with high BMI reflecting greater anatomical difficulty in performing the oocyte retrieval. In addition, patients with high BMI experience more frequent intraoperative and postoperative events

**Table 2** Studies Revealing Adverse Effects of Obesity in Women Undergoing Assisted Reproductive Technologies

| Author | Design | Outcome | No of Cycles/Patients (*n* with Maximum BMI) |
|---|---|---|---|
| Wang[40] | Retrospective | ↓PR | N = 3,586 women/8,822 ART cycles (n = 117 ≥35 kg/m$^2$) |
| Wang[56] | Retrospective | ↑Miscarriage | N = 2,349 pregnancies achieved by fertility treatment (n = 70 pregnancies ≥35 kg/m$^2$) |
| Bellver[27] | Retrospective | ↑Miscarriage | N = 712 cycles using donor oocytes (n = 50 ≥30 kg/m$^2$) Donors with normal weight |
| Fedorcsak[54] | Retrospective | ↑EPL; ↑Cycle cancellation; ↓Ovarian response | N = 5019 ART cycles in 2660 couples (n = 241 ≥30 kg/m$^2$) |
| van Swieten EC[69] | Prospective cohort | ↓Fertilization | N = 162 patients undergoing ART (n = 29 >30 kg/m$^2$) |
| Dokras[80] | Retrospective | ↑Cycle cancellation | N = 1,293 women <38 years, first fresh IVF cycles (n = 79 ≥40 kg/m$^2$) |
| Bellver[28] | Retrospective | ↓OPR | N = 2,656 first cycles using donor oocytes (n = 122 ≥30 kg/m$^2$) Donors with normal weight |
| Thum[57] | Prospective cohort | ↑Miscarriage ↓LBR | N = 8,145 consecutive ART cycles (n = 76 >36 kg/m$^2$) |
| Egan[81] | Retrospective | ↑Oxygen desaturation; ↑retrieval duration | N = 1,289 patients undergoing oocyte retrievals (n = 176 >30 kg/m$^2$) |
| Bellver[74] | Retrospective | ↓IR, PR, LBR Embryo quality not affected | N = 6,500 ART cycles (n = 419 ≥30 kg/m$^2$) |
| Zhang[75] | Retrospective | ↓Fertilization ↓Ovarian response | N = 2,628 first ART cycles (n = 27 ≥30 kg/m$^2$) |
| Luke[34] | Prospective cohort | ↓CPR ↓LBR | N = 45,163 embryo transfer cycles (n = 863, 40–46 kg/m$^2$) |
| Luke[35] | Prospective cohort | ↑Cycle cancellation ↓CPR; ↓LBR | N = 152,500 cycle starts (n = 290 ≥50 kg/m$^2$) |

BMI, body mass index; PR, pregnancy rate; ART, assisted reproductive technologies; EPL, early pregnancy loss; IVF, in vitro fertilization; OPR, ongoing pregnancy rate; LBR, live-birth rate; IR, implantation rate; CPR, clinical pregnancy rate.

like desaturation, need for oxygen, and postoperative pain.[81] Awareness of these problems may help prevent adverse outcomes in obese women undergoing oocyte retrieval for ART.

In summary, the majority of studies on obesity and ART are retrospective in data collection and analysis, and few studies reported the analysis of prospectively collected information (►**Tables 2** and **3**). Furthermore, the sample sizes are also limited, especially the obese patient population. There are also a limited number of patients in trials analyzing various BMI subgroups of obesity (►**Tables 2** and **3**). Therefore, all of the studies are observational and prospective randomized clinical trials including obese and nonobese women, and matching for other infertility factors and male BMI are lacking.

Conflicting results in the studies are possibly due to the biases inherent in many observational studies that may also include the use of different terminology while reporting outcomes like per cycle or per woman.[33] Moreover, there are wide variations in the definitions used for clinical/ongoing pregnancy rates and early pregnancy loss/miscarriage rates in many studies.[33] For instance, some studies defined clinical pregnancy per the appearance of fetal heartbeat, and some others use the definition depending on the presence of a gestational sac at 6 to 7 weeks identified by transvaginal ultrasound. Miscarriage rate was defined as an early pregnancy loss before 6 weeks, before 12 weeks, or up to 20 weeks. Additionally, there is no consensus on the definition of poor response or clear criteria for cancellations.[68,69,80] The lack of uniform definitions for overweight and obesity further makes the comparison of findings across studies challenging.

## Weight Loss

It is strongly suggested that weight loss improves reproductive outcomes.[12,14] However, the effectiveness of weight reduction is still debatable due to the lack of large controlled studies.[3,20] Furthermore, effectiveness of weight reduction preceding ART has not yet been established.[3] At present, there are no evidence-based guidelines for fertility treatment in overweight/obese subfertile women. Methods like lifestyle modification, dietary restriction, increased physical activity, and pharmacological/surgical intervention produce variable results.[3,20] The currently available data on the effects of weight loss on ART outcome will be discussed on a separate article.

**Table 3** Studies Revealing No Effect of Obesity in Women Undergoing Assisted Reproductive Technologies

| Author | Design | Reported Parameters | No. of Cycles/Patients (*n* with Maximum BMI) |
|---|---|---|---|
| Winter et al[45] | Retrospective | EPL | $N = 1196$ ART pregnancies ($n = 46$ pregnancies $>35$ kg/m$^2$) |
| Wattanakumtornkul et al[29] | Retrospective | IR | $N = 97$ first cycle recipients ($n = 12$ $\geq 30$ kg/m$^2$) Donors with normal weight |
| Styne-Gross et al[30] | Retrospective | IR<br>OPR<br>Miscarriage rate | $N = 536$ first cycle recipients ($n = 77$ $\geq 30$ kg/m$^2$) Donors with normal weight |
| Dechaud et al[68] | Retrospective | Cycle cancellation<br>IR<br>PR | $N = 573$ women and 789 ART cycles ($n = 48$ cycles $\geq 30$ kg/m$^2$) |
| Metwally et al[77] | Retrospective | Oocyte quality<br>CPR | $N = 426$ ART cycles ($n = 72$ $\geq 30$ kg/m$^2$) |
| Esinler et al[78] | Retrospective | Fertilization rate<br>CPR<br>IR<br>MPR<br>Miscarriage rate | $N = 1113$ ICSI cycles ($n = 147$ cycles $\geq 30$ kg/m$^2$) |

BMI, body mass index; EPL, early pregnancy loss; ART, assisted reproductive technologies; IR, implantation rate; OPR, ongoing pregnancy rate; PR, pregnancy rate; CPR, clinical pregnancy rate; MPR, multiple pregnancy rate.

For older overweight/obese women, losing a significant amount of weight preconceptionally may require a valuable time frame that can result in decreased chance of conception with fertility treatment. Although women with a BMI $>35$ kg/m$^2$ should be counseled about initial weight reduction, the evidence is not as strong whether the weight loss per se improves spontaneous and treatment-related pregnancy chances or decreases obesity-related pregnancy complications.[3,20] Moreover, many ART studies did not consider the influence of male body composition on the pregnancy outcome, although there is both evidence in animal and human studies that increased paternal BMI may adversely affect embryo quality and implantation and sperm parameters.[82,83] Therefore, restricting access of women to fertility treatment based on BMI values is controversial and debatable in terms of medical ethics as well.[2,3,53,84,85]

## Pregnancies Following ART in Obese Women

In developed countries obesity is a major health problem, and the incidence of obesity in pregnancy has been reported to be 18 to 38% according to the definition used.[9] In the United Kingdom, 35% of all maternal deaths between 2000 and 2002 were observed in obese women with BMIs $>30$ kg/m$^2$.[9]

Prepregnancy BMI seems to influence adverse obstetric and neonatal outcomes.[86] Obesity is strongly associated with complicated pregnancies and increased obstetric interventions.[9] Moreover, maternal and neonatal morbidity and mortality are increased, and there are more neonatal admissions and higher costs of care.[87,88] However in a cost analysis study, the median costs for antenatal and peripartum care were found to be similar across BMI groups.[2] The mean cost per positive pregnancy, per ongoing pregnancy, and per live birth was similar across BMI groups as well. Total cost of an IVF liveborn baby was nearly £20,300 in an obese woman and £16,500 in a normal-weight woman.

Obese women were shown to have a significantly higher risk for obstetric complications like preeclampsia, gestational diabetes, prolonged duration of labor, unsuccessful induction of labor and resultant cesarean delivery, macrosomia, increased blood loss, and unexplained stillbirth.[2,9,80,89,90] The risk of preeclampsia has been shown to double with each 5 to 7 kg/m$^2$ increase in prepregnancy BMI.[91] It has been suggested that rapid fetal growth induced by hyperinsulinemia may be coupled with placental insufficiency, which consequently might result in intrauterine fetal demise in obese pregnant women.[59,90]

In a previous study of $\sim$350 obese and morbidly obese women who achieved pregnancy following ART, obstetric complications like preeclampsia, gestational diabetes, and cesarean delivery were observed to be significantly higher.[80] This increased risk is most evident in women with BMIs $\geq 35$ kg/m$^2$.[2,9] Although some researchers suggested that all pregnancies in obese women should be considered high risk and managed accordingly, no upper limit exists for BMI in a pregnant woman to define her pregnancy as a low-risk pregnancy.[92]

Overall, to prevent these adverse obstetric events, it is still prudent to counsel obese women for weight loss before the initiation of fertility therapy.

## Conclusion

The influence of female obesity on ART has been the subject of many observational studies. Although strong evidence is lacking from prospective randomized controlled studies, it is widely accepted that the probability of a successful pregnancy outcome is reduced in obese women. Obesity adversely affects the chance of conception through a variety of mechanisms that need to be further elucidated. Due to its potential negative impact on ART outcome and also on pregnancy outcomes, there are restrictions in some countries for ART for those women with a BMI $>35$ kg/m$^2$, which is being highly debated. For older women, the benefits of postponing pregnancy to achieve weight loss must be balanced against the risk of declining fertility with advanced reproductive age.

Overweight and obese women have fewer collected oocytes despite requiring higher doses of gonadotropins. Overweight and obese women have a lower likelihood of achieving clinical pregnancy and a live birth, and an increased risk of miscarriage was observed following ART. These adverse outcomes are evident even at BMIs $\geq 25$ kg/m$^2$. In future studies, uniform reporting of outcomes is essential to investigate the true effects of obesity on ART outcomes.

Maternal BMI is strongly associated with pregnancy complications and outcomes. Obesity is associated with increased incidence of preeclampsia, gestational diabetes, macrosomia, stillbirth, induction of labor, and cesarean delivery. This is particularly important for women who will start ART with morbid obesity. Weight loss before ART is an important part of infertility counseling in obese women. Various strategies for weight reduction like diet, exercise, pharmacological and surgical intervention exist; however, lifestyle modification has the utmost importance. Weight loss is associated with significant improvement in menstrual cyclicity in anovulatory women; however, the evidence is lacking for the positive impact of weight loss on ART-treatment-related pregnancy outcome. Extrapolating the data obtained from infertility studies other than ART, weight reduction may lead to decreased pregnancy complications and consequently better maternal and neonatal outcomes.

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