Article published online: 2023-11-01

Obesity and In Vitro Fertilization

Emily L. Ferrell, MD[1] Abira A. Choudhry, MD[2] Samantha B. Schon, MD, MTR[1]

[1] Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, Michigan
[2] University of Michigan Medical School, Ann Arbor, Michigan

Address for correspondence Samantha B. Schon, MD, MTR, Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Michigan, Ann Arbor, MI 48109 (e-mail: sschon@med.umich.edu).

Semin Reprod Med 2023;41:87–96

Abstract

Obesity is a highly prevalent chronic disease with a significant effect on reproductive-age women. The clinical implications of obesity on fertility and pregnancy are well studied citing ovulatory dysfunction, hormonal imbalances, higher miscarriage rates, and increased maternal and neonatal risks. For this reason, many patients with obesity seek reproductive specialists to help build their families. Despite this literature base, the effect of weight loss interventions prior to assisted reproductive technology (ART) is lacking. This review aims to outline the impact of obesity on ART, specifically in vitro fertilization (IVF). Response differences to treatment protocols compared with normal weight counterparts, limitations of access to care, and the mixed results of weight-reduction strategies prior to fertility treatment will be addressed. The known data surrounding benefits of lifestyle modification, pharmacologic therapies, and surgical interventions for obesity prior to IVF are outlined and found to emphasize a need for further research to determine the optimal approach for infertility patients with obesity.

Keywords
► obesity
► in vitro fertilization
► assisted reproductive technology
► infertility

Obesity is a highly prevalent chronic disease that affects over 600 million adults worldwide. Within developed nations, the United States experiences significantly higher obesity rates, with over 40% of American adults meeting criteria for obesity based on 2018 data.[1] Since 1960, the number of individuals with obesity in the United States has doubled. This trend also extends to women of reproductive age, with nearly 30% of U.S. women found to have obesity immediately prior to pregnancy. Additionally, the prevalence in this group increased by 11% over just a 3-year time period.[2]

The impact of obesity on reproductive-aged women is profound and is correlated with numerous reproductive risks and complications both prior to and during pregnancy. Obesity is associated with anovulation, longer-time to pregnancy, infertility, increased rates of miscarriage, and several obstetrical risks, both maternal and fetal.[3,4] While the clinical impact of obesity on female reproduction is well reported, the effect of weight loss on improving fertility outcomes beyond improvements in ovulation is less clear.[3,4]

Reproductive care specialists are faced with the challenge of treating infertility in the setting of steadily increasing rates of obesity. There are several fertility treatments available to women with infertility ranging from oral and injectable medications, intrauterine insemination, and in vitro fertilization (IVF). This review will focus on the impact of obesity on IVF including clinical outcomes, limitations to care, and data regarding how various weight-loss strategies may or may not impact IVF outcomes.

Pathophysiology

It is estimated by the World Health Organization that approximately one in every six people of reproductive age worldwide experiences infertility in their lifetime.[5] Many women with obesity can achieve pregnancy naturally despite their weight. However, women with overweight and obesity often have a longer time to pregnancy, and increased rates of infertility.[6]

The relationship between excess adipose accumulation and infertility is complex and multifactorial. The most comprehensively understood link between obesity and reduced fertility lies in the distinction between regular

Issue Theme Obesity and Reproduction; Guest Editor, Wendy S. Vitek, MD

DOI https://doi.org/10.1055/s-0043-1776420.
ISSN 1526-8004.

ovulation and irregular or absence of ovulation. Hormonal imbalances, along with a combination of disorders related to insulin, low levels of sex hormone binding proteins, and elevated androgen levels, contribute to this phenomenon. Collectively, these factors disrupt the secretion of hypothalamic gonadotropin hormones, leading to a decrease in both the quantity of mature ovarian follicles and progesterone levels during the menstrual cycle.[7]

Adipose tissue serves as a multifunctional endocrine organ responsible for storage and secretion of several factors.[8] Adipose-derived cytokines, called adipokines, have an important function in metabolism and are increasingly being studied for their roles in adiposity-induced subfertility. These adipokines, including leptin, ghrelin, resistin, visfatin, chemerin, omentin, and adiponectin, play a significant role in the regulation of reproductive hormones from the brain as well as ovarian function.[9,10] Disruptions or abnormalities in these adipokines can impact reproductive health, such as the exacerbation of polycystic ovary syndrome (PCOS) often seen in women with high adipose tissue levels. Adiponectin receptors, which are ubiquitously expressed in reproductive tissues like the ovaries, endometrium, and placenta, have been associated with recurrent implantation failure when their expression is reduced.[11] Reduced adiponectin may also contribute to decreased endometrial receptivity and an increased risk of diabetes, as adiponectin is involved in glucose uptake in the liver. This impairment affects insulin sensitivity, further linking obesity to insulin resistance and risk of type 2 diabetes mellitus.[12]

Obesity affects ovarian follicles in various ways, often resulting in an altered composition of the follicular fluid in which the oocyte develops. These changes to the follicle environment have been associated with poor follicular development, as well as inhibition of normal ovulation and alterations of follicular function.[13,14] Lipolysis, the breakdown of fat, influences the composition of non-esterified fatty acids in follicular fluid. Follicular fluid in individuals with a high body mass index (BMI) contains elevated levels of oleic acid, which is associated with increased embryo fragmentation.[13] At the blastomere stage, elevated levels of stearic acid, also found in the follicular fluid of women with a high BMI, are associated with poor blastomere scores. Leptin, a hormone found in high concentrations in individuals with obesity, has been shown to impair folliculogenesis and reduce ovulation rates. In vitro models also demonstrate direct inhibition of estriol production by granulosa cells.[15] Leptin-rich mice models have also demonstrated impaired folliculogenesis, decreased ovulation rates, and increased apoptosis in granulosa cells.[15]

Impact of Obesity on Assisted Reproduction

Given the steady increase in obesity rates among reproductive-aged women, reproductive care providers are encountering an increasing number of women with obesity and infertility who require assisted reproductive technology (ART) to build their families. Early studies suggest that women with infertility and obesity may experience overall poorer outcomes when undergoing IVF, ultimately resulting in decreased live birth rates (LBRs).[16] These findings have recently been challenged in some studies as outlined below.

Ovarian Response

Notable ovarian response differences have been reported for women with higher BMIs undergoing IVF. Specifically, women with obesity often require higher starting and overall gonadotropin doses, as well as longer duration of injections for adequate follicular development.[17] Early studies further found that despite higher gonadotropin doses, ovarian stimulation resulted in fewer mature follicles leading to either more frequent cycle cancelations or a decrease in the number of oocytes obtained during egg retrieval.[18–20] There are different proposed mechanisms for the observed decreased response in the setting of obesity. These include a distributional effect given the increased body mass, versus a decrease in ovarian reserve as noted by anti-mullerian hormone (AMH) levels. Indeed, several studies demonstrate that obesity is associated with lower AMH levels.[21,22]

Oocyte Quality

In addition to oocyte number, obesity has also been shown to impact oocyte quality. Several studies show that with increasing BMI, graded oocyte quality is reduced, resulting in lower fertilization rates.[18,23] Recent research aimed at evaluating the etiology of altered oocyte quality have shown that obesity is associated with dysregulation at the level of the follicle, including altered proteins related to inflammation and metabolism.[24–26] This is a suggested contributor to the finding that women with obesity are also less likely to achieve clinical pregnancy even after IVF embryo transfer.[27]

Donor oocyte models have also suggested intrinsic oocyte quality alterations in the setting of obesity.[28,29] For example, Coyne et al found no difference in pregnancy outcomes when oocytes from normal weight donors were transferred to women with obesity. Specially, there were no statistically significant differences in the implantation rates, clinical pregnancy rates, or LBRs per embryo transfer among patients in the three BMI groups.[28]

Embryo Quality

Once fertilized, it has been suggested that resultant embryos may also be of poorer quality, which may ultimately result in an increased risk of miscarriage.[29,30] Metwally et al conducted a retrospective analysis of 426 IVF cycles undergoing intracytoplasmic sperm injection (ICSI) with patients stratified by age.[31] They found that while oocyte grade/quality was not compromised in the setting of obesity, embryo quality was significantly decreased in women younger than 35 years with obesity compared with overweight and normal BMI groups of the same age. It is important to note that studies do not appear to show a difference in euploidy/aneuploidy rates in women with obesity.[21,32] However, some research suggest that women with obesity do experience an increased risk of miscarriage, even in the setting of chromosomally normal pregnancies.[33,34]

Endometrial Receptivity

It is well established that the hyperestrogenic environment associated with obesity leads to a significantly increased risk of complex hyperplasia and endometrial cancer.[35] With obesity having such a pronounced impact on the endometrium, additional studies have investigated the impact of obesity on the endometrium as it relates to implantation. It has been reported that an elevated BMI alters gene expression in the endometrium during the window of implantation. This altered expression was even more evident in women with obesity who also have infertility or PCOS.[36] Bellver et al also assessed whether the use of donor oocytes from women with normal weight would change the observed differences in fertility outcomes between women with and without obesity. They found that implantation, pregnancy, clinical pregnancy, twin pregnancy, and live-birth rates were all significantly reduced as BMI increased.[37] However, similar to the Coyne's study discussed above, a systematic review and meta-analysis found no difference in implantation, clinical pregnancy rates, miscarriage, or live birth according to BMI status when donor oocytes from women with normal weight were used.[28,29]

Pregnancy and Live Birth

There is conflicting evidence regarding clinical pregnancy and LBRs in women with obesity undergoing IVF. Some studies report reduced pregnancy and LBRs between 15 and 30% in women with obesity, while others report no difference compared with patients with normal BMIs.[38–41]

A 2011 meta-analysis of 33 studies was performed to analyze the effect of elevated BMI on clinical pregnancy, miscarriage, and live-birth rates following IVF and ICSI ART cycles. The authors found that women with overweight, defined as BMI $>$ 25, had lower pregnancy outcomes, decreased LBRs, and higher miscarriage rates.[30] One of the largest studies conducted by Provost et al included 239,127 fresh IVF cycles analyzed between 2008 and 2010 from the Society for Assisted Reproductive Technology (SART) registry data, and found progressively worsening rates of implantation, clinical pregnancy live birth with increasing BMI.[42]

More recent data contradict these previous findings and highlights the complexity and heterogeneity of obesity. Akpinar et al found that while patients with obesity required higher doses of gonadotropins and had fewer oocytes, there was no difference in implantation and clinical pregnancy rates.[43] Similarly, the recent Appraisal of Body Content study found no difference in IVF outcomes based on obesity status.[21] This prospective cohort study analyzed nearly 1,900 couples with infertility undergoing IVF and performed bioelectric impedance analysis for body fat percentage and BMI calculations at the time of egg retrieval. Their findings suggest nearly equivalent outcomes between women with obesity and normal weight with the exception of a small increased risk for very low birth weight infants in the maternal obesity category.[21] Specifically, there was no difference in number of oocytes retrieved, mature oocytes, fertilization rates, euploidy rates, implantation rates, and LBRs. Additionally, Kim et al found higher blastocyst formation rates in patients with obesity compared with overweight and normal weight patients. It is important to note that all oocytes in this study were fertilized via ICSI and all patients underwent a frozen embryo transfer; thus, the authors hypothesized that ICSI may have overcome intrinsic oocyte quality issues and that the use of frozen embryos may also have improved outcomes due to improved uterine synchrony and increased progesterone levels.[21] These findings suggest that through further research, ART has the potential to overcome many of the biological limitations associated with obesity and infertility. In conclusion, elevated BMI is associated with adverse reproductive outcomes in women undergoing IVF treatment, including higher miscarriage rates and lower birth rates in some, but not all studies. More research with larger and diverse cohorts are needed to further clarify these observations and identify the intrinsic factors affected by obesity.

Limited Access to Care

Aside from altered responses to medications, an elevated BMI can pose technical challenges to performing IVF including difficult ultrasound monitoring, challenging oocyte retrievals, and anesthetic risks.[44] In response to these as well as maternal–fetal risks, BMI cutoffs have been imposed at many fertility clinics worldwide. However, most national professional organizations around the world remain ambiguous in their recommendations, spurring controversies and a range of individualized practices between clinics. In New Zealand and Australia, a BMI over 35 kg/m^2 is considered an absolute contraindication to IVF and publicly funded IVF is limited to those with a BMI less than 32 kg/m^2.[45] The UK National Institute for Health and Care Excellence (NICE) guidelines do not explicitly advise against providing IVF to women with obesity but point out that obesity may impact fertility and recommend providing weight loss advice to those women. The British Fertility Society published guidelines in 2007, stating that severely obese women should have their fertility treatment deferred until they have lost weight.[46] Furthermore, in the United Kingdom publicly funded IVF is limited to those with a BMI below 30 to 35 kg/m^2.

In the United States, no such formal restrictions exist. However, a 2014 study surveying U.S. fertility clinics found that 35% reported using a BMI or body weight cutoff points to determine eligibility for IVF treatment. The mean BMI cutoff point was $\sim$38.5 kg/m^2. Importantly, 46% of these clinics implemented a BMI limit yet did not offer weight loss treatment recommendations.[47] A more recent study found that now 65% of surveyed clinics enforce BMI cutoffs.[48]

Major arguments for imposing BMI cutoff include the technical difficulty of the retrieval and anesthesia safety concerns among women with obesity. However, a study specifically investigating the safety of transvaginal oocyte retrieval in women with obesity undergoing ART found that overall, serious complications were in fact uncommon. None of the patients with BMI $>$40 kg/m^2 required converting to endotracheal intubation during the procedure or hospital admission following. 6.25% of the patients with obesity required an oral or nasal airway for improved oxygen saturation compared with only 1% of those with BMI $<$ 40 kg/m^2.

They concluded that transvaginal oocyte retrievals can be performed safely on individuals with obesity in the outpatient setting.[49] Notably, the American Society of Reproductive Medicine recently stated that "on the basis of available evidence, there is no medical or ethical directive for adopting a society-wide BMI threshold for offering fertility treatment; rather, there is considerable evidence arguing against such a policy."[3]

As obesity rates are highest among Black and Hispanic populations, it is important to highlight that BMI cutoffs disproportionally limit access to ART among minority populations.[50] Furthermore, in the United States where IVF is not publicly funded, much of the fertility care provided in the country is paid out-of-pocket by patients, further compounding the barriers to care among those with lower socioeconomic status who also have higher rates of obesity.[51]

Treatment Strategies

Given concern for poorer reproductive outcomes as well as lower BMI requirements enforced to access care, women are commonly counseled toward weight loss prior to fertility treatment. The evidence, however, is mixed as to how weight loss may or may not improve outcomes. The studies discussed below are outlined in ►**Table 1**.

Lifestyle Modifications

In women with obesity, a reduced-calorie diet and exercise interventions are often the first recommended treatment strategy. As previously discussed, obesity affects ovulation and menstrual cycles, response to fertility treatment, pregnancy rates, and outcome. Weight reduction is an effective strategy for resumption of ovulation among women with irregular menses. Regarding IVF specifically, outcomes are varied.

A 2012 cohort study of 170 women undergoing IVF observed patient-driven weight changes prior to treatment and found short-term weight loss was associated with an improved number of mature oocytes retrieved but no difference in clinical pregnancy or LBRs.[52] Conversely, higher LBRs have been observed in randomized control trials with patients undergoing lifestyle intervention for weight loss before IVF treatments.[53,54] A more recent 2022 study out of China found that weight loss of more than 5 kg in patients with obesity and PCOS resulted in improved implantation, clinical pregnancy, and LBRs.[55] However, the presence of PCOS diagnosis offers a confounding pathophysiology compared with patients with obesity alone.

Several studies have not shown clinical improvements with lifestyle modifications prior to IVF. Moran et al randomized patients to a 5- to 9-week diet and exercise intervention before IVF or a control group without lifestyle interventions. They found no difference in LBRs between the groups despite more weight loss observed in the intervention arm.[56] Another randomized trial out of Sweden divided 317 women with infertility to either 16 weeks of weight reduction followed by IVF or immediate IVF treatment. The weight reduction group followed a strict low-

Table 1 IVF outcomes after weight loss interventions

Author (year)	Study type	Population and intervention	Major findings
Moran et al[56] (2011)	Lifestyle modification Randomized controlled trial	46 women with infertility and BMI $\geq$28 but <45 kg/m^2 undergoing IVF. Randomized to: Diet and exercise for 5–9 wk before IVF ($n = 21$) Control group ($n = 25$)	No difference in live birth rate (38.8% in the lifestyle intervention vs. 25% in the control group; $p = 0.48$)
Chavarro et al[52] (2012)	Lifestyle modification Cohort study	170 women with infertility followed up for change in body weight between baseline and the last clinical appointment prior to an IVF cycle	Short-term weight loss was associated with a higher proportion of metaphase II (MII) oocytes retrieved: 91% for women who lost 3 kg or more and 86% for women whose weight remained stable ($p = 0.002$) No difference in clinical pregnancy ($p = 0.09$) or live birth rates ($p = 0.12$)
Sim et al[53] (2014)	Lifestyle modification Randomized controlled trial	49 women with infertility and obesity undergoing IVF. Randomized to: 12-wk of very-low-energy diet for the initial 6 wk followed by a hypocaloric diet, plus a weekly group program ($n = 26$) Control group received recommendations for weight loss and the same printed material ($n = 22$)	Clinical pregnancy rate was higher in the intervention group (48 vs. 14%, $p = 0.007$) and higher live births (44 vs. 14%; $p = 0.02$)

Table 1 (*Continued*)

Author (year)	Study type	Population and intervention	Major findings
Espinós et al[54] (2017)	Lifestyle modification Randomized controlled trial	41 women with infertility and BMI ≥30 but <40 kg/m^2 undergoing IVF. Randomized to: Intervention ($n = 21$) with 12-wk diet and exercise pre-IVF Control group ($n = 20$)	No difference in clinical pregnancy rate after fresh embryo transfer (66.7 vs. 41.2%) (OR with 95% CI = 2.85 [0.7–11.3]). Significantly higher cumulative live birth rate in intervention group (61.9 vs. 30%: $p = 0.045$)
Einarsson et al[57] (2017)	Lifestyle modifications Randomized controlled trial	317 women with infertility and BMI ≥30 but <35 kg/m^2 undergoing IVF. Randomized to: 16-wk weight reduction program with strict diet and dietitian counseling before IVF ($n = 152$) Immediate IVF ($n = 153$)	No difference in overall live birth rate (difference: 2.2%, 95% CI: 12.9 to −8.6, $p = 0.77$) Significantly greater weight reduction for intervention group (−9.44 kg vs. +1.95 kg; $p < 0.0001$) Increased spontaneous pregnancy in weight loss group (10.5 vs. 2.6%; $p = 0.009$)
Wu et al[55] (2022)	Lifestyle modification Case–control study	352 patients with PCOS infertility and overweight/obesity, defined by BMI >25 kg/m^2, undergoing IVF. Cases: 6-mo pretreatment of weight loss prior to IVF. Further divided into 4 groups based on amount of weight lost (0, 1–5, 5–10, and >10 kg). Controls: 75 tubal factor infertility patients	PCOS patients with less weight loss required more gonadotropins and days of stimulation ($p < 0.05$), fewer oocytes retrieved (11.76 ± 7.12 vs. 16.64 ± 7.28; $p < 0.05$) and fewer high-quality embryos (36.32 vs. 43.11%; $p < 0.05$) than patients with more weight loss. Patients in groups with 5–10 kg weight loss and >10 kg weight loss had significantly increased implantation rates (64.37 and 62.9% vs. 42.82%; $p < 0.05$), clinical pregnancy rate (63.22 and 61.29% vs. 40.95%; $p < 0.05$) and live birth rates (56.32 and 54.83% vs. 29.5%; $p < 0.05$) compared with the group without weight loss. Significantly decreased miscarriage rates for patients with weight loss over 5 kg compared with 0 kg weight loss (12.73 and 13.16% vs. 32.56%; $p < 0.05$)
Salamun et al[68] (2018)	Pharmacologic treatment Randomized open-label study	28 women with infertility, PCOS and obesity (BMI ≥ 30 kg/m^2) undergoing IVF. Randomized to: Metformin for 12 wk ($n = 14$) Metformin and low-dose liraglutide for 12 wk ($n = 14$)	Significantly increased pregnancy rates per embryo transfer (85.7 vs. 28.6%; $p = 0.03$) and cumulative pregnancy rates over 12 mo (69.2 vs. 35.7%) in the intervention group with addition of low-dose liraglutide
Wang et al[60] (2021)	Pharmacologic treatment Randomized controlled trial	877 infertile women with overweight/obesity, defined by BMI >25 kg/m^2, undergoing IVF Randomized to: Orlistat ($n = 439$) for 4–12 wk Placebo ($n = 438$) for 4–12 wk	No significant difference in rates of conception (36.9 vs. 36.3%; $p = 0.854$), clinical pregnancy (31.7 vs. 30.4%; $p = 0.678$), pregnancy loss (19.4 vs. 15%; $p = 0.339$), or live birth rate (25.5 vs. 25.6%; $p = 0.984$) Orlistat was beneficial for weight reduction (−2.49 kg vs. −1.22 kg; $p = 0.005$)
Tong et al[61] (2022)	Pharmacologic treatment Retrospective	29 women with overweight/obesity, defined by BMI > 25 kg/m^2, undergoing IVF/ICSI Cases: Orlistat intervention (29	Significantly higher clinical pregnancy rate of the orlistat group (59.46 vs. 39.47%; $p = 0.004$) No significant difference in the live

(*Continued*)

Table 1 (*Continued*)

Author (year)	Study type	Population and intervention	Major findings
	case–control study	patients underwent 37 embryo transfers) Controls: age and BMI matched (29 patients underwent 38 embryo transfers)	birth rate between the two groups (54.05 vs. 36.84%; $p > 0.05$)
Tsur et al[72] (2014)	Bariatric surgery Retrospective case series	7 women with infertility who underwent IVF treatment before and after bariatric surgery	Surgery reduced treatment costs through reduced number of gonadotropins required during stimulation ($p = 0.043$) No between-cycle differences in number of oocytes retrieved (10.1 ± 6.3 vs. 8.7 ± 6.5; $p = 0.6$), percentage of mature oocytes (79 vs. 90.9%; $p = 0.1$), or percent of high-quality embryos (28.2 vs. 37.2%; $p = 0.78$)
Milone et al[73] (2017)	Bariatric surgery Retrospective case series	40 women with infertility who underwent IVF before and after bariatric surgery	Significantly lower gonadotropin units and length of stimulation after surgery ($p = 0.001$) Significantly increased follicles ($p = 0.005$), mature oocytes retrieved ($p = 0.008$), and high-quality embryos (0.5 ± 0.6 vs. 1.1 ± 0.9; $p = 0.003$) after surgery. Significantly increased pregnancy rate (37.5 vs. 0%; $p < 0.001$) and live birth rate (35 vs. 0%; $p < 0.001$) after surgery
Grzegorczyk-Martin et al[74] (2020)	Bariatric surgery Retrospective cohort study	332 patients divided into 3 age-matched groups undergoing IVF Groups: Bariatric surgery patients (83 patients, mean BMI 28.9 kg/m^2) BMI-matched nonoperated patients (166 patients, mean BMI 28.8 kg/m^2) Nonoperated patients with obesity (83 patients, mean BMI 37.7 kg/m^2)	No significant difference in cumulative birth rates between the surgery patients and the two nonoperated groups (22.9, 25.9, and 12.0%) Live birth rate per transfer in obesity group was significantly lower compared with the other two groups (9.3 vs. 20% and 18%; $p = 0.0167$) No difference in miscarriage rates between the three groups (38.7, 35.8, 56.5%; $p = 0.256$) No significant difference in average number of mature oocytes and embryos obtained among the three groups
Nilsson-Condori et al[75] (2022)	Bariatric surgery Case–control study	153 patients undergoing IVF after bariatric surgery Cases: 153 patients underwent bariatric surgery before IVF Controls: up to 5 nonoperated control patients selected for each surgery case matched by age, parity, and BMI at treatment	No significant difference in the cumulative pregnancy rate (40.5 vs. 49.1%; $p = 0.062$) or cumulative live birth rates (29.4 vs. 33.1%; $p = 0.395$) between the surgery group and the matched controls Significantly fewer number of retrieved oocytes (7.6 vs. 8.9; $p = 0.005$) and frozen embryos (1.0 vs. 1.5; $p = 0.041$) in the surgery group Significantly lower birth weight in children born to bariatric surgery patients ($p = 0.037$)

Abbreviations: BMI, body mass index; ICSI, intracytoplasmic sperm injection; IVF, in vitro fertilization; PCOS, polycystic ovary syndrome.

calorie diet with counseling by a dietitian. While weight reduction in the intervention group was significantly higher, they did not find a statistically significant difference in overall LBR. They did, however, find increased spontaneous pregnancy in the weight loss group.[57]

Pharmacological Treatments

There are currently four anti-obesity medications approved in the United States for chronic weight management. Anti-obesity medications can facilitate weight loss by decreasing nutrient absorption or altering gut–brain regulation, ultimately resulting in decreased appetite and/or increased satiety.

Orlistat

Orlistat is an oral medication that works by decreasing nutrient absorption and is typically associated with ~3 to 6% weight loss.[58,59] Orlistat treatment is beneficial for weight loss; however, it has not been shown to significantly improve reproductive outcomes in women with obesity prior to IVF. Wang et al conducted a randomized controlled trial across 19 reproductive medical centers in China from 2017 to 2019. Approximately 900 women with infertility and a BMI > 25 scheduled for IVF were enrolled and randomly allocated to receive orlistat or placebo treatment for 4 to 12 weeks. Live birth rates were not found to be significantly different between the two groups. It was concluded that no significant differences existed between the groups in terms of rates of conception, clinical pregnancy, or pregnancy loss.[60] A smaller scale study, also out of China, found increased clinical pregnancy rates with the use of Orlistat compared with age and BMI-matched controls, but no difference in LBRs between groups.[61]

Phentermine/Topamax

Phentermine is a stimulant medication approved for short-term (3 months) treatment which has been shown to induce over 7% weight loss at 6 months.[62] The combination of phentermine plus topiramate, a traditionally anticonvulsant medication, has been approved by the FDA for chronic management of obesity and has shown improved weight loss when used in combination, with an average expected weight loss of 5 to 11% over 1 year.[63] There are no trials that have assessed phentermine or phentermine/Topamax use prior to IVF.

Bupropion/Naltrexone

Bupropion reduces appetite through stimulation of proopiomelanocortin (POMC) neurons for melanocyte stimulating hormone release responsible for regulation of food intake and energy expenditure. It is used in combination with an opioid antagonist, naltrexone, that blocks inhibitory feedback on POMC cells.[64] There are no trials that have assessed the combination of bupropion/naltrexone use prior to IVF.

Glucagon-Like Peptide-1 Receptor Agonists

The glucagon-like peptide-1 (GLP-1) agonists, Semaglutide and Liraglutide, are injectable medications administered either once weekly or once daily and are FDA approved for chronic weight management. GLP-1 receptor agonists improve glycemic control by stimulating insulin secretion from the β-pancreatic cells and suppressing glucagon release from the α-pancreatic cells.[65] GLP-1 is a gut-derived incretin hormone that inhibits gastric emptying, increases feelings of satiety, and reduces appetite ultimately resulting in significant weight loss. O'Neil et al conducted a comparison study between the degree of weight reduction in adults with a BMI > 30 kg/m^2 using liraglutide and those using Semaglutide. They reported that liraglutide 3.0 mg daily showed an estimated mean weight loss of 7.8% after a year.[66] In more recent studies, Semaglutide is notable for even further reduction in body weight by 15% or more after 1 year of use.[67] Weight loss observed with Semaglutide is greater than that reported for other approved anti-obesity medications: orlistat (6%), phentermine–topiramate (8–10%), and naltrexone–bupropion (5%).[59]

In a prospective study by Salamun et al, 28 women with infertility and PCOS received a 12-week preconception intervention of metformin alone or liraglutide plus metformin before undergoing IVF treatment. The authors found that those who received liraglutide had a significantly higher pregnancy rate after IVF compared with metformin.[68] It is important to note that few studies have been performed with these medications in the setting of fertility treatments given contraindications in pregnancy.

Bariatric Surgery

Bariatric surgery remains the most effective strategy for weight loss in patients with severe obesity.[69] Today, laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass are most commonly performed.[70] Observational studies show that surgical intervention for obesity is associated with increased rates of spontaneous conception,[71] but improvements in LBR associated with IVF treatments have yet to be clearly established.

There have been a handful of studies investigating IVF outcomes after bariatric surgery. Two studies assess outcomes in patients who had IVF treatments both before and after bariatric surgery. One of these studies assessed seven patients and found that, while patients required less gonadotropins after surgery, there was no difference in oocytes retrieved or maturity rates.[72] Milone et al also noted reduced gonadotropin dosing when comparing IVF cycles before and after bariatric surgery in their study of 40 women with idiopathic infertility. Additionally, they reported a significantly increased number of oocytes retrieved, higher oocyte maturity, increased embryo quality, as well as increased pregnancy and LBR after surgery.[73]

Grzegorczyk-Martin et al assessed first-time IVF cycle outcomes in three groups: bariatric surgery patients, BMI-matched nonoperated patients, and nonoperated patients with obesity.[74] They noted no significant difference in cumulative LBRs comparing the bariatric surgery group to the nonoperated groups. However, the LBR per transfer in the obesity group was significantly lower. There was also a significantly smaller weight for gestational age observed in newborns of the bariatric surgery group.[74]

A recent case–control study out of Sweden utilized data from a national registry to analyze 153 women undergoing

IVF after bariatric surgery with up to 5 nonoperated control patients matched by age, parity, and BMI at treatment. They found no significant difference in the cumulative LBR between the bariatric surgery group and the matched controls group.[75] Similar to the study of Grzegorczyk-Martin et al, birth weight was significantly lower in the children born to patients having undergone bariatric surgery suggesting a potential nutritional impact on pregnancy for this population.

Conclusions

From this review of the literature, it is evident that studies of IVF and obesity are limited. Obesity has a significant impact on reproduction as demonstrated by reduced fertility, increased miscarriages, and poorer outcomes with assisted reproductive treatments. However, recent large-scale studies question several prior findings regarding the specific impact of obesity on IVF. Furthermore, access to fertility treatments is often restricted in this population, reducing trials and assessments among women with severe obesity. Women with obesity are often counseled to utilize weight loss therapies including lifestyle modifications, pharmacotherapies, or surgical approaches prior to ART treatments with little evidence basis. This review found limited and mixed data for the various treatment strategies for obesity prior to IVF. In summary, while obesity may impact IVF outcomes, further research is still needed to determine the optimal approach for women with infertility and obesity planning IVF.

Conflict of Interest
None declared.

References

1 Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017-2018. NCHS Data Brief 2020;(360):1–8
2 Driscoll AK, Gregory ECW. Increases in prepregnancy obesity: United States, 2016-2019. NCHS Data Brief 2020;(392):1–8
3 Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org Practice Committee of the American Society for Reproductive Medicine. Obesity and reproduction: a committee opinion. Fertil Steril 2021;116 (05):1266–1285
4 Obesity in pregnancy: ACOG Practice Bulletin, Number 230. Obstet Gynecol 2021;137(06):e128–e144
5 World Health Organization. Infertility. Published April 3, 2023. Accessed October 13, 2023 at: https://www.who.int/news-room/fact-sheets/detail/infertility
6 Wise LA, Rothman KJ, Mikkelsen EM, Sørensen HT, Riis A, Hatch EE. An internet-based prospective study of body size and time-to-pregnancy. Hum Reprod 2010;25(01):253–264
7 Itriyeva K. The effects of obesity on the menstrual cycle. Curr Probl Pediatr Adolesc Health Care 2022;52(08):101241
8 Wang P, Mariman E, Renes J, Keijer J. The secretory function of adipocytes in the physiology of white adipose tissue. J Cell Physiol 2008;216(01):3–13
9 Silvestris E, de Pergola G, Rosania R, Loverro G. Obesity as disruptor of the female fertility. Reprod Biol Endocrinol 2018; 16(01):22
10 Tersigni C, Di Nicuolo F, D'Ippolito S, Veglia M, Castellucci M, Di Simone N. Adipokines: new emerging roles in fertility and reproduction. Obstet Gynecol Surv 2011;66(01):47–63
11 Dos Santos E, Serazin V, Morvan C, et al. Adiponectin and leptin systems in human endometrium during window of implantation. Fertil Steril 2012;97(03):771–8.e1
12 Kawano J, Arora R. The role of adiponectin in obesity, diabetes, and cardiovascular disease. J Cardiometab Syndr 2009;4(01). Doi: 10.1111/j.1559-4572.2008.00030.x
13 Shi M, Sirard MA. Metabolism of fatty acids in follicular cells, oocytes, and blastocysts. Reprod Fertil 2022;3(02):R96–R108
14 Wołodko K, Castillo-Fernandez J, Kelsey G, Galvão A. Revisiting the impact of local leptin signaling in folliculogenesis and oocyte maturation in obese mothers. Int J Mol Sci 2021;22(08):4270
15 Gautam D, Purandare N, Maxwell CV, et al; FIGO Committee on Impact of Pregnancy on Long-term Health and the FIGO Committee on Reproductive Medicine, Endocrinology and Infertility. The challenges of obesity for fertility: a FIGO literature review. Int J Gynaecol Obstet 2023;160(Suppl 1, Suppl 1):50–55
16 Sermondade N, Huberlant S, Bourhis-Lefebvre V, et al. Female obesity is negatively associated with live birth rate following IVF: a systematic review and meta-analysis. Hum Reprod Update 2019;25(04):439–451
17 Souter I, Baltagi LM, Kuleta D, Meeker JD, Petrozza JC. Women, weight, and fertility: the effect of body mass index on the outcome of superovulation/intrauterine insemination cycles. Fertil Steril 2011;95(03):1042–1047
18 Wittemer C, Ohl J, Bailly M, Bettahar-Lebugle K, Nisand I. Does body mass index of infertile women have an impact on IVF procedure and outcome? J Assist Reprod Genet 2000;17(10): 547–552
19 Tamer Erel C, Senturk LM. The impact of body mass index on assisted reproduction. Curr Opin Obstet Gynecol 2009;21(03):228–235
20 Fedorcsák P, Dale PO, Storeng R, et al. Impact of overweight and underweight on assisted reproduction treatment. Hum Reprod 2004;19(11):2523–2528
21 Kim J, Patounakis G, Juneau C, et al. The Appraisal of Body Content (ABC) trial: Increased male or female adiposity does not significantly impact in vitro fertilization laboratory or clinical outcomes. Fertil Steril 2021;116(02):444–452
22 Bernardi LA, Carnethon MR, de Chavez PJ, et al. Relationship between obesity and anti-Müllerian hormone in reproductive-aged African American women. Obesity (Silver Spring) 2017;25 (01):229–235
23 Shah DK, Missmer SA, Berry KF, Racowsky C, Ginsburg ES. Effect of obesity on oocyte and embryo quality in women undergoing in vitro fertilization. Obstet Gynecol 2011;118(01):63–70
24 Schon SB, Yang K, Schindler R, et al. Obesity-related alterations in protein expression in human follicular fluid from women undergoing in vitro fertilization. F S Sci 2022;3(04):331–339
25 Gonzalez MB, Lane M, Knight EJ, Robker RL. Inflammatory markers in human follicular fluid correlate with lipid levels and Body Mass Index. J Reprod Immunol 2018;130:25–29
26 Robker RL, Akison LK, Bennett BD, et al. Obese women exhibit differences in ovarian metabolites, hormones, and gene expression compared with moderate-weight women. J Clin Endocrinol Metab 2009;94(05):1533–1540
27 Jungheim ES, Lanzendorf SE, Odem RR, Moley KH, Chang AS, Ratts VS. Morbid obesity is associated with lower clinical pregnancy rates after in vitro fertilization in women with polycystic ovary syndrome. Fertil Steril 2009;92(01):256–261
28 Coyne K, Whigham LD, O'Leary K, Yaklic JK, Maxwell RA, Lindheim SR. Gestational carrier BMI and reproductive, fetal and neonatal outcomes: are the risks the same with increasing obesity? Int J Obes 2016;40(01):171–175
29 Jungheim ES, Moley KH. Current knowledge of obesity's effects in the pre- and periconceptional periods and avenues for future research. Am J Obstet Gynecol 2010;203(06):525–530

30 Rittenberg V, Sobaleva S, Ahmad A, et al. Influence of BMI on risk of miscarriage after single blastocyst transfer. Hum Reprod 2011; 26(10):2642–2650
31 Metwally M, Cutting R, Tipton A, Skull J, Ledger WL, Li TC. Effect of increased body mass index on oocyte and embryo quality in IVF patients. Reprod Biomed Online 2007;15(05):532–538
32 Goldman KN, Hodes-Wertz B, McCulloh DH, Flom JD, Grifo JA. Association of body mass index with embryonic aneuploidy. Fertil Steril 2015;103(03):744–748
33 Boots CE, Bernardi LA, Stephenson MD. Frequency of euploid miscarriage is increased in obese women with recurrent early pregnancy loss. Fertil Steril 2014;102(02):455–459
34 Lee JC, Bernardi LA, Boots CE. The association of euploid miscarriage with obesity. F S Rep 2020;1(02):142–148
35 Wise MR, Jordan V, Lagas A, et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: a systematic review. Am J Obstet Gynecol 2016;214(06):689.e1–689.e17
36 Bellver J, Martínez-Conejero JA, Labarta E, et al. Endometrial gene expression in the window of implantation is altered in obese women especially in association with polycystic ovary syndrome. Fertil Steril 2011;95(07):2335–2341, 2341.e1–2341.e8
37 Bellver J, Pellicer A, García-Velasco JA, Ballesteros A, Remohí J, Meseguer M. Obesity reduces uterine receptivity: clinical experience from 9,587 first cycles of ovum donation with normal weight donors. Fertil Steril 2013;100(04):1050–1058
38 Pinborg A, Gaarslev C, Hougaard CO, et al. Influence of female bodyweight on IVF outcome: a longitudinal multicentre cohort study of 487 infertile couples. Reprod Biomed Online 2011;23 (04):490–499
39 Luke B, Brown MB, Stern JE, Missmer SA, Fujimoto VY, Leach RSART Writing Group. Female obesity adversely affects assisted reproductive technology (ART) pregnancy and live birth rates. Hum Reprod 2011;26(01):245–252
40 Petersen GL, Schmidt L, Pinborg A, Kamper-Jørgensen M. The influence of female and male body mass index on live births after assisted reproductive technology treatment: a nationwide register-based cohort study. Fertil Steril 2013;99(06):1654–1662
41 Moragianni VA, Jones SML, Ryley DA. The effect of body mass index on the outcomes of first assisted reproductive technology cycles. Fertil Steril 2012;98(01):102–108
42 Provost MP, Acharya KS, Acharya CR, 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. Fertil Steril 2016;105(03):663–669
43 Akpınar F, Demir B, Dilbaz S, Kaplanoğlu I, Dilbaz B. Obesity is not associated with the poor pregnancy outcome following intracytoplasmic sperm injection in women with polycystic ovary syndrome. J Turk Ger Gynecol Assoc 2014;15(03):144–148
44 Kaye L, Sueldo C, Engmann L, Nulsen J, Benadiva C. Survey assessing obesity policies for assisted reproductive technology in the United States. Fertil Steril 2016;105(03):703–706.e2
45 Gillett WR, Peek JC, Herbison GP. Development of clinical priority access criteria for assisted reproduction and its evaluation on 1386 infertile couples in New Zealand. Hum Reprod 2012;27(01): 131–141
46 Balen AH, Anderson RAPolicy & Practice Committee of the BFS. Impact of obesity on female reproductive health: British Fertility Society, Policy and Practice Guidelines. Hum Fertil (Camb) 2007; 10(04):195–206
47 Turner-McGrievy GM, Grant BL. Prevalence of body mass index and body weight cut-off points for in vitro fertilization treatment at U.S. clinics and current clinic weight loss strategy recommendations. Hum Fertil (Camb) 2015;18(03):215–219
48 Kelley AS, Badon SE, Lanham MSM, Fisseha S, Moravek MB. Body mass index restrictions in fertility treatment: a national survey of OB/GYN subspecialists. J Assist Reprod Genet 2019;36(06): 1117–1125
49 Romanski PA, Farland LV, Tsen LC, Ginsburg ES, Lewis EI. Effect of class III and class IV obesity on oocyte retrieval complications and outcomes. Fertil Steril 2019;111(02):294–301.e1
50 Petersen R, Pan L, Blanck HM. Racial and ethnic disparities in adult obesity in the United States: CDC's tracking to inform state and local action. Prev Chronic Dis 2019;16:E46
51 Slocum B, Schon SB. Body size, fertility, and reproductive justice: examining the complex interplay between BMI, reproductive health, and access to care. Women 2022;2(02):93–101
52 Chavarro JE, Ehrlich S, Colaci DS, et al. Body mass index and short-term weight change in relation to treatment outcomes in women undergoing assisted reproduction. Fertil Steril 2012;98(01): 109–116
53 Sim KA, Dezarnaulds GM, Denyer GS, Skilton MR, Caterson ID. Weight loss improves reproductive outcomes in obese women undergoing fertility treatment: a randomized controlled trial. Clin Obes 2014;4(02):61–68
54 Espinós JJ, Polo A, Sánchez-Hernández J, et al. Weight decrease improves live birth rates in obese women undergoing IVF: a pilot study. Reprod Biomed Online 2017;35(04):417–424
55 Wu L, Fang Q, Wang M, et al. Effect of weight loss on pregnancy outcomes, neuronal-reproductive-metabolic hormones and gene expression profiles in granulosa cells in obese infertile PCOS patients undergoing IVF-ET. Front Endocrinol (Lausanne) 2022; 13:954428
56 Moran L, Tsagareli V, Norman R, Noakes M. Diet and IVF pilot study: short-term weight loss improves pregnancy rates in overweight/obese women undertaking IVF. Aust N Z J Obstet Gynaecol 2011;51(05):455–459
57 Einarsson S, Bergh C, Friberg B, et al. Weight reduction intervention for obese infertile women prior to IVF: a randomized controlled trial. Hum Reprod 2017;32(08):1621–1630
58 Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA 2014;311(01):74–86
59 Novograd J, Mullally J, Frishman WH. Semaglutide for weight loss: Was it worth the weight? Cardiol Rev 2022;30(06):324–329
60 Wang Z, Zhao J, Ma X, et al. Effect of orlistat on live birth rate in overweight or obese women undergoing IVF-ET: a randomized clinical trial. J Clin Endocrinol Metab 2021;106(09):e3533–e3545
61 Tong J, Xiang L, Niu Y, Zhang T. Effect of orlistat intervention on *in vitro* fertilization/intracytoplasmic sperm injection outcome in overweight/obese infertile women. Gynecol Endocrinol 2022;38 (03):253–257
62 Aronne LJ, Wadden TA, Peterson C, Winslow D, Odeh S, Gadde KM. Evaluation of phentermine and topiramate versus phentermine/ topiramate extended-release in obese adults. Obesity (Silver Spring) 2013;21(11):2163–2171
63 Khera R, Murad MH, Chandar AK, et al. Association of pharmacological treatments for obesity with weight loss and adverse events: a systematic review and meta-analysis. JAMA 2016;315 (22):2424–2434
64 Vitek WS, Hoeger KM. Worth the wait? Preconception weight reduction in women and men with obesity and infertility: a narrative review. Fertil Steril 2022;118(03):447–455
65 Chao AM, Tronieri JS, Amaro A, Wadden TA. Semaglutide for the treatment of obesity. Trends Cardiovasc Med 2023;33(03):159–166
66 O'Neil PM, Birkenfeld AL, McGowan B, et al. Efficacy and safety of semaglutide compared with liraglutide and placebo for weight loss in patients with obesity: a randomised, double-blind, placebo and active controlled, dose-ranging, phase 2 trial. Lancet 2018; 392(10148):637–649
67 Wilding JPH, Batterham RL, Calanna S, et al; STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384(11):989–1002
68 Salamun V, Jensterle M, Janez A, Vrtacnik Bokal E. Liraglutide increases IVF pregnancy rates in obese PCOS women with poor response to first-line reproductive treatments: a pilot randomized study. Eur J Endocrinol 2018;179(01):1–11

69 Gosman GG, King WC, Schrope B, et al. Reproductive health of women electing bariatric surgery. Fertil Steril 2010;94(04):1426–1431
70 Estimate of Bariatric Surgery Numbers. 2011–2021. American Society for Metabolic and Bariatric Surgery. Published June 27, 2022. Accessed August 13, 2023 at: https://asmbs.org/resources/estimate-of-bariatric-surgery-numbers
71 Milone M, De Placido G, Musella M, et al. Incidence of successful pregnancy after weight loss interventions in infertile women: a systematic review and meta-analysis of the literature. Obes Surg 2016;26(02):443–451
72 Tsur A, Orvieto R, Haas J, Kedem A, Machtinger R. Does bariatric surgery improve ovarian stimulation characteristics, oocyte yield, or embryo quality? J Ovarian Res 2014;7:116
73 Milone M, Sosa Fernandez LM, Sosa Fernandez LV, et al. Does bariatric surgery improve assisted reproductive technology outcomes in obese infertile women? Obes Surg 2017;27(08):2106–2112
74 Grzegorczyk-Martin V, Fréour T, De Bantel Finet A, et al. IVF outcomes in patients with a history of bariatric surgery: a multicenter retrospective cohort study. Hum Reprod 2020;35(12):2755–2762
75 Nilsson-Condori E, Mattsson K, Thurin-Kjellberg A, Hedenbro JL, Friberg B. Outcomes of in-vitro fertilization after bariatric surgery: a national register-based case-control study. Hum Reprod 2022;37(10):2474–2481

