ABSTRACT

As the global mean Body Mass Index (BMI) is on the rise, the importance of understanding exactly how female fertility is impacted by once outlier BMI values, becomes ever more important. Studies have implicated abnormal BMI on the female reproductive system by contributing to anovulation, irregular menses, adverse oocyte quality, endometrial alterations, and hormonal imbalances. These well ultimately result in female infertility, which could complicate natural conception efforts and request considering assisted reproductive technology (ART) in such couples. With an increase in the demand for ART, it is crucial to understand what factors can be altered by the female BMI in order to maximize the opportunity for successful pregnancy. The current manuscript aimed to review the information about the effect of BMI on the female fertility and ART outcomes. The complex nature of the female reproductive system leaves space for multiple factors to adversely affect its processes. Imbalances in the hypothalamus-pituitary-ovarian axis can impede efforts for couples to conceive. Leptin and estrogen are two hormones that have been implicated in regulating BMI as well as reproductive physiology. Lifestyle modifications prior to, and during ART have shown promise in enhancing fecundity. The intricacies in female reproductive system leaves much to the unknown, and often with conflicting results. Further research is required to fully elucidate what aspects of female fertility are influenced by BMI, and how the healthcare provider can facilitate successful outcomes. The current review will enable a better consultation and treatment.


KEY WORDS: Fertility - Infertility - Body Mass Index - Estrogens - Insulin - Life style.
Overview of BMI

Epidemiology

BMI is a simple calculation using a person's height and weight in order to quantify an individual's amount of tissue mass. BMI > 25.0 kg/m² is considered overweight, and < 18.5 kg/m² is underweight. An individual with a BMI greater than 30.0 kg/m² is obese, and those over 40.0 kg/m², or are 35.0 kg/m² and suffer from obesity related hypertension or diabetes, are defined as morbidly obese. Though this measurement does not consider distribution of weight in terms of muscle or fat, it has long been used as a standardized measurement of health.

Increased BMI and obesity has plagued the modern world and has become an international public health concern. Over the past three decades, the average BMI rose dramatically in 200 countries worldwide. Data collected from 1980 and 2000, showed the BMI to have increased at an annual rate of 0.4 kg/m² per decade for men and 0.5 kg/m² for women. In 2008, the prevalence of overweight adults reached alarming 1.47 billion people across the globe. Another assessment of 1698 population-based data sets that involved more than 19 million adults, showed global age-standardized mean BMI to have increased from 21.7 kg/m² in 1975 to 24.2 kg/m² in 2014 in men, and from 22.1 kg/m² in 1975 to 24.4 kg/m² in 2014 in women. For women of reproductive age in particular, the prevalence of morbid obesity has markedly increased within the past decade. A review by Jungheim et al., reported that 35.8 percent of menstruating women had a higher than normal BMI, with a mean BMI of 28.7 kg/m².

On the other end of the spectrum, low BMI (such as anorexia nervosa) is an important factor affecting fertility in women of reproductive age. This disorder is characterized by a tremendously low BMI, due to intense fear of gaining weight, and body image issues. Although its reported prevalence is between 0.9% and 4.3% in women, this value does not reflect the true severity of this disorder. In surveys completed by university aged women, 26% of them were reported to have abnormal attitudes about eating. Though recently there has been an increase in anorexia diagnoses in young women, it is unclear as to whether this is a true upward trend in the disorder, or whether the medical practice is changing to recognize this devastating mental illness more readily. Contrastingly, some large reviews conducted at multiple institutions failed to show any significant increase in the prevalence of this disorder.

Yet what is known is that there is indeed a minimum BMI required for regular menses. Below this level, the body's available energy to use towards cellular processes, growth, and reproduction is diminished. A study conducted by Loucks et al., defined energy availability as the energy intake minus the energy expenditure. In women suffering from anorexia who reduce the energy intake, less is available for health maintenance, including reproductive processes.

Pathways associating BMI and the reproductive system

Numerous pathways were suggested to associate an abnormal BMI and the reproductive system. Two major ones will be described.

Leptin

In humans, leptin has been shown to have a direct association with adipose density. Since leptin is produced by adipose tissue, circulating serum levels of leptin correlates with the amount of adipose tissue present in the body. In order to regulate energy expenditure and appetite homeostasis, leptin acts on the arcuate nucleus in the hypothalamus via a single transmembrane type 1 cytokine receptor. Additionally, leptin helps to control the levels of insulin, insulin-like growth factor, and growth hormone. In this way, leptin plays an integral role in monitoring the pathogenesis of obesity and other eating disorders. In obese women, there is an increased resistance to leptin, disrupting their ability to control energy intake, while in underweight women low energy availability dysregulates the diurnal leptin secretion.

Beyond its substantial central effects on the hypothalamic-pituitary axis, leptin has significant regulatory responsibilities in peripheral physiology as well. Leptin deficiency may lead to obesity, bone mineralization issues, and reproductive cycle changes. Ovulatory cycles in females are connected to energy stores, that as aforementioned, are represented by leptin levels. A study conducted in hypogonadal leptin-deficient transgenic mice, showed that administration of leptin corrected the amenorrhea and restored reproductive status. This study concluded that leptin helps to regulate hormone axis contributing to reproductive capabilities when in BMI extremes.

In healthy individuals, leptin was shown to have an effect on luteinizing hormone (LH) and estradiol levels, suggesting that leptin may have a distinct regulatory effect on hormones involved in reproductive processes. Thus, leptin has an integral role in maintaining normal homeostasis and body physiology beyond that of hunger.
**Estrogen**

Estrogen is the primary hormone of normal female reproductive physiology. Estrogen is responsible for inducing the development of secondary sex characteristics in females and controls the monthly menstrual cycle. This hormone is primary produced in the ovaries, and during pregnancy, by the placenta. Pulsatile secretion of gonadotropin releasing hormone (GnRH) stimulates the pituitary to release follicle stimulating hormone (FSH). This then acts on the ovaries to induce granulosa cells to produce estrogen from the androgen environment. Estrogen has multiple roles during the menstrual cycle, including regulating negative feedback on the hypothalamus to decrease GnRH and FSH secretion. Estrogen maintains a dominant follicle until ovulation. Altered estrogen levels or estrogen receptor (ER) could have a negative impact on female fertility.

Aside from clear reproductive effects, the ER was actually discovered in invertebrates that did not have sexual reproductive capacities, suggesting that the receptor may have played a role in energy balance and survival. There are two classes of estrogen receptor: ERα and ERβ, each with distinct physiological functions. ER deficient mice exhibited increased body weight and adiposity in both males and females. In mouse studies, ovariectomy led to increased adiposity, that was reversed by estrogen replacement therapies. Additionally, the ER has been densely localized in various nuclei of the hypothalamus. This brain region, as previously stated, helps to regulate food intake, energy balance and weight homeostasis. Specifically, ERs have been identified in remarkable quantities the pro-opiomelanocortin neurons within the arcuate nucleus. These neurons have distinct regulatory capacities regarding food intake, reproductive processes, and energy usage. In humans, this association has not been fully elucidated. However, in postmenopausal women, there is a decrease in circulating estrogens, and as a result these women display increased intraabdominal fat. BMI could also thus be dependent on the estrogen signaling pathway.

**Effects of BMI on fecundity**

Fecundity is defined as the probability of achieving at least one pregnancy during one’s lifetime. The effect of BMI on fecundity is controversial. It has been suggested that a low (<18.5 kg/m²) or high (>25 kg/m²) BMI can adversely affect reproductive ability and reduce fecundity. The main mechanism by which BMI may affect fecundity is menstrual dysfunction resulting in anovulation. Other putative hypotheses implicate the negative impact BMI has on embryo quality and endometrial function.

A study conducted by Gaskins et al. found that in females of 18 years of age, both a BMI>25, and a BMI<18.5 were associated with reduced fecundity. A systematic review of the literature was consistent with previous observations that the association between exercise, BMI, and ovulation is U-shaped, with women at the extremes (sedentary with high BMI as well as over-trained with low BMI) more likely to suffer from hormonal impairment and disturbances in their menstrual cycle.

**Obesity**

**Background**

Over the past decades, attention has been directed toward the inverse relationship between obesity and fertility. A high BMI is known to be associated with several comorbidities including type 2 diabetes mellitus and dyslipidemia, which may indirectly have negative impacts on fertility. Moreover, obesity is strongly correlated with polycystic ovarian syndrome (PCOS), the most common hyperandrogenic disorder, further complicating the female’s fertility success mostly by causing anovulation.

Still, the effects of obesity on fertility appear to be complex and multifactorial. Though the mechanisms are not fully elucidated, it is well established that obese women are at higher risk for infertility due to anovulation, menstrual cycle disorder, reduced implantation rates, and adverse peri- and postpartum outcomes. Rich-Edwards et al. reported that obese women with a BMI>32 were three times greater relative risk for infertility (RR 2.7 CI 95% 2.0-3.7) as compared normal weight women (BMI 20-22), while overweight women with BMIs between 24 and 26 were still at an infertility increased relative risk of 1.3 (CI 95% 1.2-1.6). This was attributed to obesity induced ovulatory and menstrual cycle dysfunction. In a case control study on ovulatory infertility, Green et al. found a relative risk of 2.1 (CI 95% 1.0-4.3) for women with BMI>24.6. Several other mechanisms are possible for the negative effect of obesity on fertility including elevated free androgens related to depressed sex hormone binding protein synthesis and an accentuated insulin response related higher mass of adipose tissue.

Other reports suggest that obesity detrimentally affects oocyte quality by altering oocyte maturity and developmental competence. Wittmer et al. found a significantly reduced ratio of good quality oocytes (at metaphase I or II) in obese women as compared to ratios in normal weight
women (BMI 20-24). Another study of unique design also concluded that increased BMI and the associated insulin resistance in particular, have detrimental effects on the oocyte quality. However, despite the abundant research efforts dedicated to elucidating these pathways, the details of cellular mechanisms and the exact nature of the oocyte quality impairment in abnormal BMI humans remains unclear. In animal models, oocytes from obese mice demonstrated delayed oocyte maturation and higher rates of aneuploidy. This was due to the lipotoxic effects on oocyte maturation, which severely impaired mitochondrial and endoplasmic reticulum function, and increased apoptosis in the cumulus oocyte complex.

Additionally, diabetes mellitus is a common comorbidity in obese women. Such patients suffer from insulin resistance, which causes a state of chronic hyperglycemia along with hyperinsulinemia. Insulin has long been implicated in the regulation of endometrial development, metabolism, and receptivity. Hence, insulin resistance, commonly exhibited by obese women, may have a negative influence on implantation, further compounding hopes of subsequent pregnancy. Beyond insulin, the production of reactive oxygen species and decreased efficiency of antioxidants, also known as oxidative stress, is a key mechanism behind infertility in diabetic women. Oxidative stress leads to mitochondrial damage and serves as a trigger for many alterations in sexual function. Furthermore, the excess of radical oxygen species production may also disturb oocyte maturation, oocyte fertilization, embryogenesis, and pregnancy.

**Impact on ovulation**

Multiple processes of ovarian physiology are altered in obese women, including the hypothalamic-pituitary-ovarian axis. Obesity is associated with greater adipose tissue levels in the body, thereby affecting the gonad hormonal balance. This leads to increased plasma insulin levels, ultimately resulting in hyperandrogenism and anovulation. The elevated adipose tissue aromatizes androgens to estrogens at high rates in the periphery, leading to negative feedback on the hypothalamic-pituitary-ovarian axis and downregulating gonadotropin production. This impaired pulsatile secretion of pituitary gonadotrophins leads to impaired folliculogenesis.

As aforementioned, the lipotoxicity, also known as adiposity, associated with obesity serves as yet another potential mechanism causing oocyte organelle damage. Obese women have higher levels of circulating free fatty acids that damage non-adipose cells by increasing the formation of reactive oxygen species. This induces mitochondrial and endoplasmic reticulum stress that ultimately activates the apoptotic pathways in these cells. Furthermore, the chronic low-grade inflammatory state and high levels of circulating serum leptin in obese women have detrimental effects on the follicle fluid milieu.

**Endometrium receptivity**

There is no paucity of literature on the hypothesis that excess body weight adversely impacts the endometrium and its environment. Yet, exactly how obesity influences endometrial receptivity to the embryo is not well understood. The negative effects of obesity may be manifested in changes in endometrial thickness, through metabolic and hormonal disturbances, and by the embryo-uterine dialogue, the complex "cross-talk" that occurs as part of the implantation process. Obesity may affect trophoblast cell invasion and endometrial receptivity through hormonal alterations, leading to increased spontaneous abortion rates in the first trimester. Moreover, gene expression analyses during the implantation window have revealed endometrial dysregulation in obese women, especially in women also suffering from PCOS.

Genetic mechanisms that may contribute to endometrial function are also being studied to determine whether there are genetic predispositions to suboptimal fecundity. Comstock et al. observed that obesity appeared to be associated with significant alterations in endometrial gene expression during the optimal window of implantation, especially in patients with underlying metabolic syndrome. As BMI increased, exponential variations in gene expression were found along with an increased incidence of a nonreceptive endometrium. This endometrial gene dysregulation could contribute to the increased risk of infertility, adverse pregnancy events, and poor in vitro fertilization (IVF) outcomes seen in obese women.

Another study conducted by Souter et al. reported a positive association between endometrial thickness and both BMI and pregnancy. Perhaps the most effective study model for these correlations is ovum donation. However, while Bellvet et al. did report poorer ongoing pregnancy rates per oocyte donation cycle in women with high BMI, they were unable to show a significant difference in the thickness of the endometrium and implantation rate among the different BMI groups.

Other reports have shown an increased risk of spontaneous abortion among obese women after IVF with autologous or donated oocytes. Luke et al. conducted a retrospective analysis on 45,163 embryo transfers performed in 345 clinics in the USA. They described a statistically
significant reduction in clinical intrauterine gestation and live-birth rates in obese women using autologous oocytes, but not when donated oocytes were considered. This finding suggested an impaired embryo quality but not reduced endometrial receptivity in obese women. The complicated nature of how obesity impacts the endometrium and successful oocyte implantation is complex, often yielding contrasting results.

**Low BMI**

Low BMI is a well-recognized risk factor for infertility and adverse pregnancy outcomes. Low body weight, exercise and psychogenic stress are the leading reasons for functional hypothalamic failure, potentially causing a shortened luteal phase, or anovulatory menstrual cycles, and in the severe cases even amenorrhea. Another known mechanism contributing to reproductive system malfunction is that the decreased amount of adipose tissue in underweight women causes estrogen to be metabolized into a less potent form, the catechol estrogen. Furthermore, low BMI may indicate inadequate energy intake and status, thereby impacting gonadotropin concentration, follicle growth, and oocyte quality.

Leptin, a molecule secreted in response to adipose tissue mass, influences numerous neuro-endocrine systems including those involved with fertility. As previously mentioned, leptin plays a critical role in the regulation of hypothalamic hormonal axes and oocyte implantation time. Specifically, low expression of leptin in the endometrium has been associated with higher implantation failure rates. Decreased leptin mRNA expression (0.76 fold down) was reported to lead to infertility. The reduced leptin levels observed in underweight women could therefore be further implicated as a factor contributing to reduced fecundity.

Similarly, Cai et al. found a significant increased incidence of miscarriage in underweight women (BMI<18.5) compared with normal weight (BMI 18.5-25) women (13.8% vs. 10.7%, OR per pregnancy 1.51, 95% CI 1.13-2.07, P=0.049). This study also reported reduced live birth rates (OR 0.9, CI 95% 0.75-1.1), particularly for women above the age of 35 (24.6% vs. 38.1%, P=0.003). Excessively low body weight affects hormonal balances as well as reproductive physiology at the organ level, thus disrupting fertility.

**Pregnancy complication risks**

A systematic review by McDonald et al. demonstrated that obese women undergoing natural pregnancies have increased risks of several adverse pregnancy complications, such as preterm birth before 37 weeks, leading to significant neonatal morbidity and mortality. Further, a recent meta-analysis suggested that even modest increases in maternal BMI are associated with an increased risk of fetal death (95% CI: 1.09-1.35), stillbirth (95% CI: 1.18-1.30) and infant death (95% CI: 1.09-1.28).

**ART**

**Background**

Infertility is defined as one or more years of unprotected intercourse without pregnancy. An analysis from 2007 suggested that approximately 72.4 million women are infertile, with 40.5 million of them seeking treatment. Reports explaining the need for infertility treatments showed these values to be equal across less developed and more developed countries. However, the means by which to pay for these services is lacking in resource poor areas. ART includes special techniques used to help infertile couples conceive and mainly refers to IVF and intracytoplasmic sperm injection (ICSI). These treatment modalities are the most advanced fertility treatment available and usually include controlled ovarian simulation prior to ovum pickup.

**Indications for treatment**

Consideration for ART is not a decision to be made lightly. Indications for treatment are strict in order to maximize the potential for successful conception. Aside from physical stress on the female, the mental and emotional tolls taken while undergoing ART are significant and cannot be ignored. As aforementioned, a couple must have difficulty getting pregnant for 12 months to be defined as infertile.

Metabolic factors affecting ART results

The most important factor associated with ART success is the women's age. Women above the age of 35 had lower success rates than younger patients. However, success rates improved in older patients when using donated embryos. Predictably, livebirth rate significantly decreased as the number of infertility years increased.

Diabetes mellitus is defined as an absence or insufficient response to insulin and a chronic state of hyperglycemia, is
the most common medical complication of pregnancy, and dramatically affects female fertility. Over 371 million people have been diagnosed with diabetes worldwide, with many more unaware of their potential diagnosis. Type 1 diabetes results from an autoimmune mediated destruction of insulin secreting beta-cells in the pancreas. Insulin receptors are abundant throughout the ovary on theca cells, granulosa cells, and stromal components, alike, as well as in the uterus. As such, impaired insulin signaling can dramatically affect normal reproductive processes and fertility. In 1954, it was documented that 30% of women with type 1 diabetes had irregular menses. The prevalence of secondary amenorrhea in diabetic women is measured at 8.2% as compared to 2.8% in non-diabetic women. These diabetic women have enhanced as well as diminished responses to LH, impairing the normal reproductive cycle. Women with type II diabetes are hyperinsulinemic, and as such, have increased ovarian steroidogenesis that contributes to the development of PCOS.

Thyroid disease has also been shown to have an effect on female fertility. Thyroid hormone receptor has been found on reproductive cells in the female and male reproductive organs, in addition to direct action on the oocyte and sperm. The processes of embryo fertilization, implantation, and placental formation can all be affected by dysregulation of this hormone as a result. Furthermore, this hormone can also alter androgen and estrogen concentrations. A study conducted by Joshi et al. showed that reproductive failure which includes fertility was documented in 37.5% of women with hypothyroidism, and in 36.5% of women with hyperthyroidism. Interestingly, they showed irregularity in menses to precede symptoms of thyroid disorder and suggested that menstrual signs may be indicative of an iodinent thyroid problem. In considering ART, women requiring thyroid stimulation by levothyroxine therapy showed two times the risk for primary ovulatory infertility. Successful pregnancy rates in women undergoing ART are lower in when thyroid autoantibodies are present. This could be due to complications with oocyte fertilization, or embryo quality in these women. Rates of miscarriage are also elevated in these cases. Yet this connection between the minutiae of impaired thyroid function and ART protocols is still highly debated in the literature.

Effects of BMI on ART outcomes
As reflected by conflicting study results, there is still a great deal of controversy regarding the overall impact of BMI on ART outcome. Wang et al. reported that both low and high BMI are associated with reduced fecundity in women receiving ARTs (OR 0.81 for low and 0.5-0.81 for high BMI, respectively). Kanwass et al. postulated that pre-pregnancy BMI affects pregnancy and obstetric outcomes. Underweight status may have a limited impact on pregnancy and live-birth rates but is associated with increased preterm and low-birth-weight delivery. Dokras et al. reported that obese women undergoing IVF treatment demonstrated higher rates of second and the third trimester risk factors including hypertension and pre-eclampsia. They also observed higher rates of cesarean section, endangering both mother and fetus. These complications could be explained by the defect of decidualization and implantation that negatively impacts the placenta tion process. Many of the pregnancy complications seen in obese women are linked to placental dysfunction, including stillbirth and pregnancy-induced hypertension.

Modifications in ART protocols also illustrate the potential effects of BMI. Previous studies have shown an increased duration of ovarian stimulation, higher total dose of gonadotrophin administered, lower ovarian response to ovarian stimulation, with reduced oocyte retrieval and higher cycle cancellation, poorer embryo quality and lower fertilization rates in obese women undergoing IVF compared with normal weight infertile women. A prospective study by Alumun et al. found significantly smaller oocyte size, a known independent predictor of embryo quality after adjustment for age and less mature oocyte numbers in obese women who underwent ART.

BMI is inversely associated with the estradiol level per follicle in women that underwent ART. Maheshvari et al. reported that overweight women faced a lower likelihood of pregnancy after IVF and had lower retrieved oocyte numbers despite higher gonadotropin doses. In a Danish cohort study, Ramlau-Hansen et al. discovered a relationship between high female BMI and prolonged time to pregnancy. The time taken to successful conception was 2.8 days per 1 kg in body weight and was greater than one year amongst obese couples.

Pregnancy rate after ART was reported to be 10% lower among women with high BMI. Nonetheless, literature to the contrary included several studies which did not find any effect of increased BMI on pregnancy rate after IVF, ovulation induction or intrauterine insemination cycles, or on delivery rate after IVF/ICSI. Another newer ART technique is ICSI, which appears to be less negatively impacted by BMI. Possible explanations include that this technology bypasses the direct adverse effect of fat tissue on the oocyte, and because the male
Do lifestyle modifications affect ART outcome?

Study evidence suggests that physical activity may decrease systemic inflammatory mediators and contribute to improvement in fertility. Losing weight prior to ART initiation correlates with a higher yield of metaphase oocytes, particularly among women who were overweight or obese at baseline. Although short-term weight change was not consistent with clinical outcomes among women who underwent ART, it has been demonstrated that a 5% weight loss can improve menstrual cyclicity and reproductive outcomes.

The British Fertility Society recommends withholding IVF treatment for women with BMIs >35 and advises a weight loss program for BMIs >30. However, literature detailing the effect of bariatric surgery on reproductive health outcomes is limited. Clark et al. have shown that weight loss in overweight women is associated with return of spontaneous ovulation. They compared the pregnancy rates between obese women who underwent a lifestyle modification program with women who failed to complete the course. Among the women who were unable to conceive naturally during the program and went on to receive infertility treatment, 26 of the 47 women who completed the program and underwent IVF became pregnant, compared to none of the 35 women who dropped out of the program and underwent IVF.

Moran et al. completed a pilot randomized trial of weight loss among obese women undergoing ART; yet showed there were no differences in pregnancy or live births between women randomized to lifestyle intervention and women randomized to control. Clearly, the data available to date do not clarify whether losing weight before initiating ART has any statistically significant beneficial effects on clinical outcomes.

Conclusions

The objective of this review was to offer an inclusive accrual of the published literature concerning the numerous and complex effects of abnormal BMI of the female reproductive system. We can conclude that there are various modes by which this occurs (Figure 1). Leptin has been shown to be an integral regulatory component in the processes controlling BMI as well as reproduction. Because leptin correlates with adipose density, it has been used as a marker for the energy balances, and therefore imbalances, within the human body. Energy homeostasis is crucial for normal reproductive processes to occur, and as such, states of elevated BMI or low BMI can unfavorably affect the female reproductive environment. Estrogen is well documented to be the most important control for female reproduction. Its roles in female reproductive pathophysiology and its well elucidated roles in modulating BMI make it an important consideration when consulting couples diagnosed with infertility. These factors have all been shown to affect normal ovulation and endometrial receptivity, components that must be accounted for when consulting for ART. States of insulin imbalance leading to diabetes mellitus or thyroid hormone discrepancies can also impact female fertility and therefore ART outcomes. Yet despite this, there is no consensus on whether lifestyle modifications in efforts to change BMI have any benefits towards increasing the chances for successful conception naturally or via ART. Future studies should hope to further elucidate how couples can adjust behavior or lifestyle to enhance the chances for successful conception. Other research should also look into the intricacies of the pathways controlling fertility, in the hopes of further elucidating just how well these are able to be changed to increase fecundity.
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