ARAB JOURNAL OF UROLOGY
https://doi.org/10.1080/20905998.2025.2473219

Obesity and male infertility - a tenuous relationship: Facts discerned for the busy clinicians

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ABSTRACT

Obesity is a common health problem affecting over a third of the population worldwide. Obesity has been correlated with many diseases, including cardiovascular disorders, diabetes, cancer, brain degeneration, and premature aging. In men, obesity can also cause issues like erectile dysfunction, poor sperm quality, and prostate problems. Factors like high insulin levels, chronic inflammation, and oxidative stress may play a role in how obesity affects male fertility. Obesity can disrupt the male reproductive system by changing hormone levels, affecting sperm production, and causing problems with metabolism. This can result in a reduction of sperm count, motility, and normal forms. Obesity can also cause sperm DNA fragmentation, increase cell death, and impact the genetic information that can be passed on to future generations. This narrative review explores how obesity impacts male reproductive health and fertility, as well as possible treatment options like weight management, lifestyle changes, medications, and alternative therapies.

KEY POINTS

- Obesity can negatively affect male fertility by reducing testosterone levels and sperm count, compromising DNA integrity, and diminishing overall sperm quality.
- When addressing sperm issues related to obesity and male infertility, it is crucial to consider lifestyle changes, medical interventions, surgical options and ART.
- Weight loss through lifestyle changes has been shown to enhance testosterone levels; however, it remains uncertain whether this leads to improved fertility outcomes.
- Bariatric surgery may serve as a complement to lifestyle changes and medical treatments for obesity, yet more studies are needed to clarify the long-term implications of such surgeries on male reproductive health.
- New high-quality research is needed to explore the relationship between obesity and male infertility.
- While obesity has been linked to an increased risk of infertility, it is essential to recognize that many obese men are still able to father children without the help of ARTs.

ARTICLE HISTORY
Received 27 December 2024
Accepted 22 February 2025

KEYWORDS
Male infertility; obesity; semen quality; oxidative stress; Mediterranean diet

Introduction

Obesity is defined as increased body mass index (BMI) above 30 kg/m2 and above 35 kg/m2 for morbid obesity [1].

Obesity is a global health crisis with a notably increased incidence between 1980 and 2013 (in men between 28% and 36%) [2], and affection of over 1.4 billion people worldwide. In 2013, the American Medical Association recognized obesity as a disease, highlighting the need for prevention and management due to its associated health risks. This rise in obesity is attributed to environmental factors such as energy-dense food, sedentary lifestyles, and societal structures that promote inactivity. It is estimated that obesity will affect more than 40% of the world's population by 2030 [3].

Risk factors of obesity include polygenetic predisposition, epigenetic inheritance, aging, and female gender [4]. Low socio-economic standards, psychological factors, and sleep disturbances also contribute to obesity. The most crucial risk factors are poor nutritional choices and a sedentary lifestyle in an obesogenic environment, particularly in Westernized regions. Certain prescription medications increase the risk of obesity. Excessive adiposity complications include cardiovascular disease, diabetes, cancer, accelerated aging, neurodegeneration, and reproductive issues. These complications have been correlated to insulin resistance, inflammation, and oxidative stress (OS) [5] (Figure 1).

Obesity hurts men's health, affecting both sexual function and fertility potential [6]. Studies suggest that overweight and obese men have lower sperm counts compared to those with a normal body

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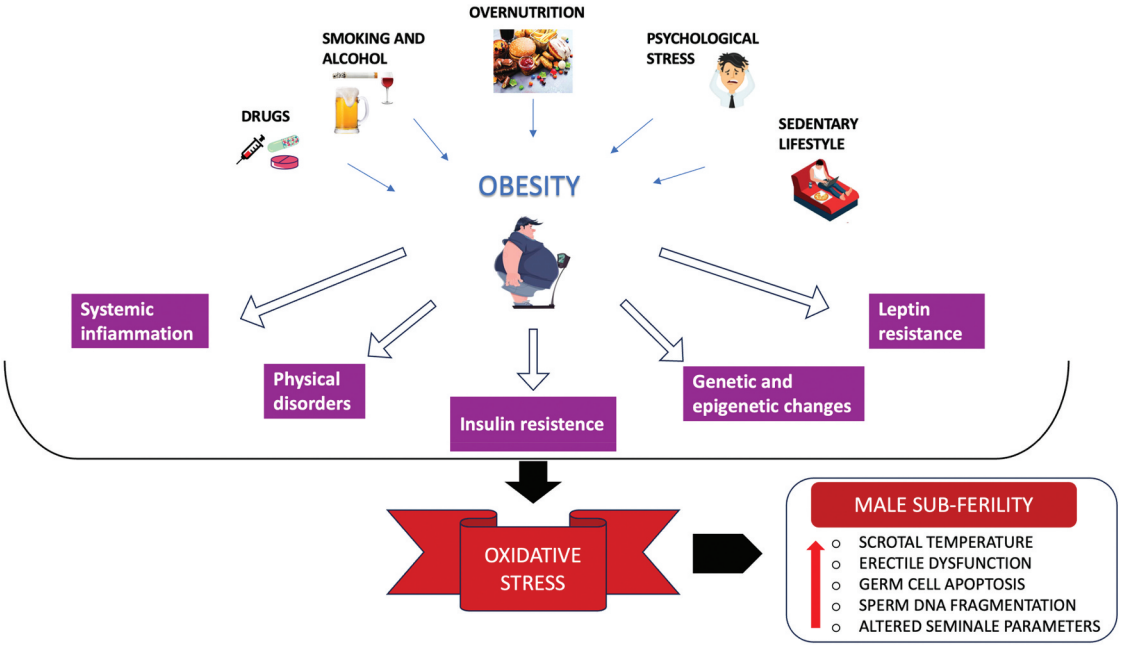

Figure 1. Risk factors, mechanisms and male reproductive outcomes in obesity. E2, 17β-estradiol; T, testosterone.

weight [7–9]. High BMI can also reduce sperm count, motility, morphology, and testosterone levels [10,11], and is associated with reduced fertility potential [12]. It is believed that obesity impacts male fertility by decreasing testosterone levels and semen quality [11]. Progressive sperm motility, which is closely linked to pregnancy rates [13], is often affected in obese men [14]. Additionally, obese men are more likely to suffer from erectile dysfunction and decreased libido [15].

This review aims to provide an overview of the current scientific evidence on the relationships between obesity and male infertility. We seek to understand how obesity can influence male fertility and highlight the interventions and treatment strategies for obesity-associated male infertility.

Pathogenesis of infertility in obese men

Obesity-related hormonal changes

Reduced serum levels of total testosterone were found to negatively influence sperm quality in obese men [16]. Functional hypogonadism and relative hyperestrogenism have been linked to abnormalities in spermatogonial stem cell proliferation and maturation. Additionally, changes in hormone levels can impact germ cell development and maturation. Insulin resistance, hyperinsulinemia, and chronic low-grade inflammation, commonly associated with obesity, can further disrupt the regulation of testicular functions [17]. A mechanism by which the chronic inflammatory process in obese patients can affect semen is shown in Figure 2.

Obesity and oxidative stress

Oxidative stress is a significant factor in male infertility among obese individuals [18]. Oxidative stress due to excess reactive oxygen species (ROS) is caused by several factors, including heat stress, environmental contaminants, alcohol consumption, smoking, consumption of high-fat and high-protein foods, use of anabolic steroids, some drugs, genital tract infections, aging, and obesity [19–23]. The most common ROS in sperm cells is O2-, which is produced through oxidative phosphorylation and the electron transport chain in the mitochondria. Additionally, H2O2 is a neutral biochemical molecule that can cause peroxidative damage to germ cell membranes by quickly passing through the plasma membrane [24].

During OS, NADPH (Nicotinamide adenine dinucleotide phosphate) Oxidase 5 (NOX5), a Ca^{2+}-dependent NADPH oxidase present in the midpiece and acrosomal region, is a major producer of ROS, leading to sperm DNA fragmentation (SDF) [25].

Epigenetic modifications

An increasing body of evidence suggests that obesity can negatively influence male fertility, with potential repercussions for future generations, due to genetic and epigenetic changes in germ cell DNA [24]. Specific infertility conditions such as Prader-Willi, Alström, Laurence-Moon-Bardet-Biedl, and Klinefelter syndromes are due to genetic defects affecting chromosomes or genes related to metabolism and endocrinology. For example, Prader-Willi syndrome is associated with abnormalities in

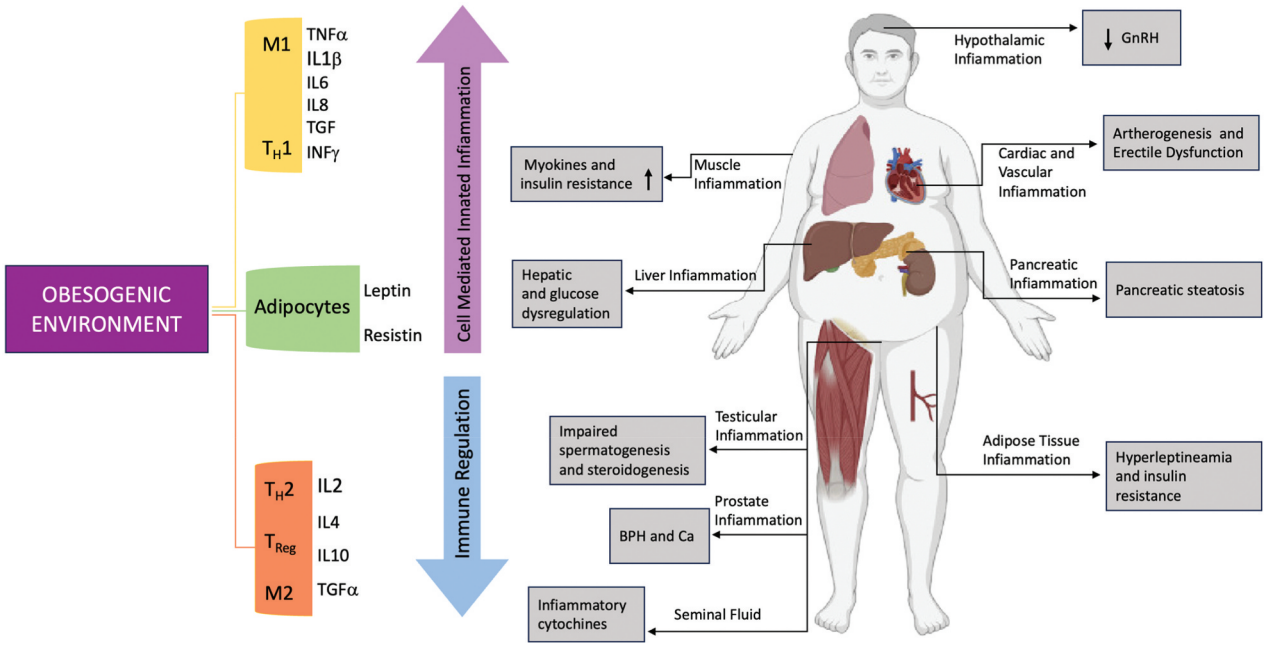

Figure 2. Low-grade systemic chronic inflammation associated with obesity. Abbreviations: TH1 and M1= TH1-lymphocyte and M1-macrophage driven pro-inflammatory responses; IL-1β = Interleukin-1β; IL6 = Interleukin-6; IL8= Interleukin-8; TNFα= tumor necrosis factor-alpha; IFNγ = interferon gamma; TGF= transforming growth factor; TH2 and M2= TH2-lymphocyte and M2-macrophage related to inflammatory responses; Treg= regulatory T cell; IL2 = Interleukin-2; IL4 = Interleukin-4; IL10 = Interleukin-10; TGFa = transforming growth factor alpha; GnRH= gonadotropin-releasing hormone; BPH = benign prostatic hyperplasia; Ca = cancer.

chromosome 15, while Alström syndrome results from mutations in the ALMS1 gene [26,27].

Moreover, DNA methylation patterns in obese men are different from those in non-obese men and can have lasting effects on offspring [28]. Children born to obese parents may exhibit altered sperm DNA methylation profiles, potentially influencing their own fertility and health [29]. Environmental factors, including diet and lifestyle, can also influence epigenetic changes that can be transmitted to future generations.

Despite the lack of a direct link between sperm DNA and BMI, factors such as smoking have been linked to changes in methylation levels [30]. Addressing the complex relationship between obesity, male fertility, and epigenetic changes is crucial for addressing potential health risks for current and future generations [24].

Impact of lifestyle factors

Infertility in obese males can be influenced by various lifestyle factors that can contribute to both obesity and reduced fertility. Here we reported some key lifestyle causes:

Poor Diet

Excess processed foods, sugars, and fats can contribute to obesity, while low nutrient intake can lead to hormonal imbalances that affect sperm production [31].

Physical inactivity

Sedentary lifestyles can lead to obesity. Regular physical activity is essential for maintaining a healthy weight and can also improve hormonal balance and sperm quality [4].

Alcohol consumption

Excessive alcohol intake can negatively influence testosterone levels and sperm production, potentially exacerbating infertility issues in obese men. A study suggested that alcohol consumption is linked to a decrease in semen volume without significantly affecting sperm parameters [32]. A meta-analysis points to alcohol as having a negative influence on the morphology of sperm (odds ratio of 1.87; 95% confidence interval, 0.86 to 2.88%) [33], suggesting that the quality of sperm is compromised by alcohol intake.

Additional investigations have highlighted that alcohol may disrupt several key processes in sperm development and maturation [34,35]. This impairment appears to be progressive; as alcohol intake increases, spermatogenesis seems to decline gradually [36].

Smoking

Cigarette smoking is recognized as a possible contributing factor to reduced fertility in men. It has been linked to leukocytospermia, which is an essential source of ROS [37].

Stress

A stressful lifestyle may lead to hormonal disturbances and adversely affect fertility [38].

Endocrine disruptors

Certain chemicals found in plastics and personal care products can interfere with hormonal balance and have been linked to changes in sperm quality [39].

Medical conditions

Conditions such as metabolic syndrome and diabetes, often associated with obesity, can also reduce male fertility potential [4].

Impact of obesity on male fertility potential

Obesity and semen parameters

Obesity has been correlated with a higher incidence of oligozoospermia [40,41] and asthenozoospermia [42]. A presumed and generally accepted mechanism underlying the reduction in sperm count is related to the aromatization of testosterone into estradiol in peripheral adipose tissue, leading to negative feedback mediated by estradiol and suppression of the hypothalamic-pituitary-testicular axis [43]. Additionally, increased abdominal adiposity in subfertile men has been linked to a reduction in sperm number and motility [44]. Obesity can also increase SDF [45–47], decrease sperm mitochondrial activity [48], and induce OS in seminal fluid [49].

Sperm DNA fragmentation refers to breaks or damage to genetic material, which can compromise fertility and the health of the embryo [24]. Studies indicated higher rates of SDF in obese men [50,51]. Sperm DNA fragmentation may increase the risk of miscarriages and genetic anomalies in the embryo [24].

Obesity and spontaneous pregnancy outcomes

The impact of fathers' BMI on pregnancy and children's health has not been adequately investigated [52], and many research criteria and analyses seem to operate under the presumption that paternal BMI has little significance. It has been demonstrated that higher paternal BMI at the time of fertilization can lead to changes in methylation patterns in fetal cord blood [29] and lower levels of neonatal immunoglobulin M [53]. It may also result in insulin resistance/type 2 diabetes and an increased risk of cardiovascular disease in offspring [54]. As such, most research on the effects of paternal obesity on pregnancy and child health has been performed using animal models, which allow for stricter control over maternal and environmental variables.

Animal models of obesity showed that paternal obesity at pregnancy could affect birth weights [55,56], heighten the offspring's risk of metabolic syndrome [57], lead to issues such as subfertility, fatty liver disease, kidney problems, and hypertension [58,59], while also diminishing cognitive function in offspring [60]. Additionally, direct epigenetic signals have been identified between sperm and the egg during fertilization, and from seminal plasma to the uterine environment [61]. These elements are widely recognized for their potential to affect early embryo and fetal development, suggesting that paternal obesity may affect pregnancy and childhood health outcomes through epigenetic modifications long after conception [61].

Obesity and assisted reproductive technique outcomes

Research indicates that overweight men tend to experience poorer outcomes with assisted reproductive techniques (ART). Paternal obesity has been negatively correlated with live birth rates following ART (odds ratio of 0.65; 95% confidence interval of 0.44–0.97) [62]. Specifically, the study indicated significantly higher probabilities of non-viable pregnancies in couples with obese male partners (odds ratio of 2.87; 95% confidence interval of 1.34 – 6.13). Conversely, another study suggests that male obesity might not substantially impact ART results [63]. Both meta-analyses display considerable variability among studies, highlighting the necessity for additional research to draw more solid conclusions [64].

Management of obesity-associated male infertility

A comprehensive strategy that integrates lifestyle modifications, medical interventions, psychological assistance, and continuous tracking is crucial for addressing male infertility linked to obesity. Working together, healthcare professionals like primary care doctors, nutritionists, and mental health specialists can boost the success of these treatments and enhance reproductive results for those impacted.

Influence of dietary choices on male fertility

Currently, extensive research supports the opinion that certain foods can positively impact semen parameters, such as fish, poultry, whole grains, fruits, vegetables, and low-fat dairy products [31,65,66]. Conversely, evidence suggests that preserved and processed meats, foods high in alcohol, sugary beverages, saturated fats,

and sweets may negatively affect semen quality [67–69]. Individual nutrients also play a crucial role, with low eating of saturated fatty acids and adequate consumption of omega-3 fatty acids and antioxidants linked to improved reproductive health [66,68,70,71]. A positive relationship has been found between higher dietary intake of vitamins, polyphenols, and carotenoids and enhanced sperm quality [72]. Furthermore, nutritional patterns have been shown to impact sperm quality, underscoring the potential importance of nutritional interventions in preserving male fertility [73].

Lifestyle modifications

Dietary change

Specific diets, such as the Mediterranean diet (MedDiet), were found to improve testosterone levels and reduce SDF [65]. MedDiet contains high amounts of vegetables, fruits, whole grains, legumes, nuts, and seafood, which are abundant in antioxidants and other bioactive compounds. Research indicates that this dietary pattern can significantly influence health outcomes at several biological levels, including genomic, epigenomic, transcriptomic, metabolomic, and metagenomic [65]. Recent studies have also explained the interaction between diet, epigenetics, and the gut microbiota [74]. Other investigations confirmed that the composition and diversity of gut microbiota can influence metabolic processes, inflammation, and hormonal balance, which are critical for maintaining healthy spermatogenesis [75].

Nutritional supplements

It has been suggested that dietary supplements rich in specific nutrients, vitamins and antioxidants can improve sperm motility and overall fertility potential [65].

Physical activity

Physical exercise is an essential tool in managing obesity and improving overall health. The relationship between exercise and testosterone levels is complex. Moderate exercise typically leads to an increase in testosterone levels, supporting positive outcomes. The mechanisms involved include stimulation of the hypothalamic-pituitary-gonadal axis, which enhances pituitary hormone release, improved function of Leydig cells in the testes, and decreased clearance of testosterone from the bloodstream [4].

Medical interventions

Hormonal treatments

Treatment of obese subfertile men may include therapies to adjust testosterone/estrogen ratios, such as aromatase inhibitors and selective estrogen receptor modulators [4].

Glucagon-like peptide-1 receptor agonists (GLP-1 RA) treatments

Recently, GLP-1 receptor agonists (GLP-1 RAs) have garnered significant interest for their multifaceted therapeutic applications, particularly in diabetes and obesity. Recent review articles have highlighted their effectiveness in weight management and emerging potential in improving male fertility [76,77]. In the management of obesity, GLP-1 RAs have demonstrated a robust capacity to facilitate weight loss, which is critical given the relationship between obesity and various health risks, including metabolic syndrome and cardiovascular diseases. Interestingly, while studies in high-fat diet-fed mice have shown that treatment with GLP-1 RAs did not restore serum testosterone levels, the treatment did improve critical sperm parameters. These improvements include enhanced sperm motility, increased mitochondrial activity, and reduced SDF, indicating that GLP-1 RAs may positively affect certain aspects of male fertility. The mechanism by which GLP-1 RAs exert these effects is linked to their action on GLP-1 receptors, distributed widely across various tissues such as the intestine, pancreatic islets, and immune cells [76,77].

Surgical options

Bariatric surgery can help reduce weight and enhance fertility potential in men with severe obesity or those who have not succeeded with other weight-loss methods [4]. Nevertheless, more studies need to examine the long-term effects of bariatric surgery on men's reproductive health [78].

Monitoring and follow-up

Regular monitoring of basic semen parameters and SDF can help assess the effectiveness of interventions and guide ongoing treatment [79]. It is always advisable to ask for an assessment from a fertility expert, mainly if there are concerns about potential underlying reproductive problems.

Future directions

While there is not yet a unanimous agreement, many studies indicate that male obesity negatively influences fertility through hormonal, genetic, physical, and environmental factors, leading to irregular semen quality. However, only a few studies involving human subjects demonstrate how various factors in obese men lead to infertility; therefore, more comprehensive trials are needed to establish a causal relationship. Currently, the primary approach to addressing male

infertility linked to obesity is through natural weight loss, with regular exercise being the initial recommended treatment. Although bariatric surgery tends to produce more significant weight loss results than non-surgical methods, additional research is needed to understand its effects on male fertility.

Additionally, well-structured and sufficiently large studies are warranted to measure the benefits of weight loss strategies on reproductive health in obese men and to determine whether these improved reproductive results have positive effects on their offspring as well.

Gaining clearer insight into how metabolic disorders influence the molecular signaling pathways related to sperm production and fertilization ability is crucial for developing new diagnostic methods and treatment approaches for managing infertility linked to obesity in men.

Given the rising prevalence of obesity and associated metabolic disorders, it is essential to further investigate the comprehensive benefits of GLP-1 RAs. Ongoing research will be vital in elucidating the exact role of GLP-1 RAs and optimizing their clinical application to enhance patient outcomes across these interconnected health fields.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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