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A Critical Analysis of the Evidence Regarding the Impact of Obesity on Male Fertility and Its Implications in Assisted Reproductive Technology Treatment. Literature Review

Dr Aloy Okechukwu UGWU[1,2*], Sunday Isaac Omisakin, Kehinde Elizabeth Adeyemo[3], Adebayo Williams Awoniyi[1], Chidinma Magnus Nwogu[4]

[1]Department of Obstetrics and Gynaecology, Lagos University Teaching Hospital, Nigeria.
[2]Atlantic fertility, Halifax, Nova Scotia, Canada
[3]Department of Nursing Science and Ward Manager at Surrey and Sussex Healthcare NHS Trust, United Kingdom
[4]Assisted conception unit, Kingswill Specialist Hospital, Lagos, Nigeria

ABSTRACT

Background:

Obesity is increasingly recognized as an important modifiable factor in male infertility. It may impair male reproductive function through disruption of the hypothalamic–pituitary–gonadal axis, altered sex hormone balance, insulin resistance, oxidative stress, chronic low-grade inflammation, increased scrotal temperature, and adipokine-mediated effects, particularly involving leptin and inhibin B. These mechanisms may adversely affect spermatogenesis, semen quality, sexual function, and outcomes of assisted reproductive technology treatment.

Methods:

This literature review critically analysed published evidence on the relationship between obesity and male fertility, with particular focus on hormonal alterations, inflammatory pathways, oxidative stress, scrotal thermoregulation, adipokines, and the implications of male obesity for assisted reproductive technology outcomes.

Results:

The evidence suggests that obesity negatively affects male fertility through multiple interacting mechanisms. Increased aromatization of testosterone to oestrogen in adipose tissue may suppress gonadotropin-releasing hormone, luteinizing hormone, and follicle-stimulating hormone secretion, resulting in reduced testosterone production and impaired spermatogenesis. Obesity-associated insulin resistance and reduced sex hormone-binding globulin further worsen androgen deficiency. Chronic inflammation, oxidative stress, raised scrotal temperature, and elevated leptin levels may damage sperm membranes and DNA, impair sperm concentration, motility, morphology, and reproductive potential. Evidence on the effect of male obesity on ART outcomes remains conflicting, although some studies suggest poorer embryo quality and reduced clinical pregnancy and live birth rates.

Conclusion:

Obesity has a significant adverse impact on male reproductive health through hormonal, metabolic, inflammatory, and oxidative mechanisms. It may contribute to male subfertility and may influence ART outcomes, although further studies are needed to clarify the independent effect of male obesity after controlling for confounders such as female BMI, age, and other causes of infertility.

Recommendation:

Men presenting for fertility care should be assessed for obesity and related metabolic risk factors. Weight optimization, lifestyle modification, and management of obesity-related comorbidities should be incorporated into preconception and fertility counselling. Further well-designed systematic studies meta-analysis are recommended to better define the mechanisms linking obesity with impaired male fertility and to clarify its independent effect on assisted reproductive technology outcomes

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Corresponding Author: Dr Aloy Okechukwu UGWU.
Email: okeyugwu92@gmail.com
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Background

Recently, there have been an increasing number of men with inability to achieve pregnancy with a fertile female despite regular unprotected, penetrative, penovaginal intercourse.1, 2, 3, 4 In many countries, especially the developing nations, aspersions are usually cast on the female partner for barren marriages.3, 4, 5 On one hand, this may be because the majority of the populace are ignorant of the causes and pattern of distribution of the probable causes of infertility, therefore, attribute almost all causes to the female partner3, 4, 5 while on the other hand, it may also be because most men don't present themselves for medical examination considering the fact, that some men equate adequate erection and ejaculation with ability to reproduce.3, 4 Furthermore, with increasing number of infertile men and decline in semen quality, literature abound to support that men having difficulty with conception contributes about 30-50% of infertility in humans.3, 4, 6, 7 Generally, the differences in quantity and quality of the semen parameters are used as a surrogate marker of male fecundity.2, 3, 6, 7

Obesity is a complex medical disorder resulting from excessive deposition of adipose tissue in the body.8 It is "defined as the body mass index (BMI) greater than or equal to 30 kilograms per square meter" (BMI ≥30Kg/m-2).8 The prevalence has been on the increase worldwide, with an estimate that it may have doubled since the late 20th Century.8 It has both genetic and environmental components as its risk factors.8 The proponents of environmental influence in the development of obesity believe that a high-calorie diet, rich in carbohydrates and fat, with little or no fruits and vegetables, has a central role in the development of obesity.9 Other authors, however, have also proposed that, notwithstanding the imbalance between dietary intake and body metabolism, there is also enough evidence to show that obesity has a strong genetic predisposition,10, 11, and these genes (single or multiple) can be inherited from one's parents.12 Obesity has been fingered as one major risk factor implicated in the aetiopathogenesis of many diseases through the secretion of different kinds of adipokines and numerous other mechanisms. 8

The aetiology of male infertility is "multi-factorial and polygenic in nature".3, 13 They are broadly classified into pre-testicular (hypothalamic-pituitary), testicular, and post-testicular (obstructive) causes.3, 14, 15 It has been suggested that genetic changes, lifestyle such as diet and obesity have a role to play in the aetiopathogenesis of male infertility especially the pre-testicular and testicular causes.13, 14, 15 This essay therefore, aims to critically evaluate the impact of obesity (hormonal and inflammatory changes) on male fertility and its implications in assisted reproductive technology (ART) treatment.

Effects of obesity on Hormonal changes-implications for male fertility

There is emerging evidence of the harmful effects of obesity on male reproductive health from changes in hormonal secretion and action.14, 15 It's common knowledge that male fertility is mostly determined by efficient spermatogenesis, which, analysis of its end product (sperm cells and seminal plasma produced by accessory male reproductive organs), for now, has remained the gold standard in evaluating the male partner in the infertile couple.3 Spermatogenesis requires tightly controlled interrelated mechanisms dependent on hormonal actions, cytokines, functional internal biochemical milieu, and "immune-privileged environment".16

At puberty, there is increased pulsatile production of Gonadotropin hormone-releasing hormone (GnRH) in the hypothalamus, leading to the maturation of the hypothalamic-pituitary-gonadal axis (HPG).16, 17 The secreted GnRH is transported to the pituitary gland through the hypophyseal portal venous system, stimulating it to release luteinizing and follicle-stimulating hormones (FSH and LH).17 These hormones act on their receptors on Leydig and Sertoli cells of the testis, respectively, thereby allowing the production of testosterone from the Leydig cells, the main driver for pubertal development and spermatogenesis. FSH, on the other hand, stimulates the proliferation of Sertoli cells, which act as a source of nourishment, protection, and support for proliferating and differentiating germ cells.17

Serum levels of testosterone and its metabolite (oestradiol) are the major regulators of FSH and LH secretion by acting as negative feedback on the hypothalamus.18-21 The amount of testosterone (both free and total) in males is not only dependent on its production from the Leydig cells, but also on its metabolism by the aromatase enzyme. 19, 20, 21 Metabolism of testosterone yields oestrogen, originally thought to be a female hormone. 18, 19, 20 Oestrogen has been shown to have different effects on male reproductive health.18, 20 The effect of which is dependent on its serum concentration. 18, 20

It's been demonstrated in obese men that there is a defective hypothalamic-pituitary-gonadal axis (HPG).20 These authors postulated that because of the excessive adiposity associated with obesity, that there is increased aromatization of oestrogen from testosterone in the adipose tissue.20, 21 The excess oestrogen produced from aromatization being more potent than testosterone acts via the negative feedback on the hypothalamus to decrease the pulsatile secretion of GnRH, it also reduces the response of pituitary to already produced GnRH thereby leading to decreased FSH and LH secretion.19, 20, 21 This hyper-oestrogenic state and low testosterone level will alter the normal physiologic (hormonal) balance required for testicular

steroidogenesis, spermatogenesis and sexual function.18, 20, 21

In addition, under normal physiological conditions, sex hormone binding globulin (SHBG), which is synthesized by the hepatic cells, binds to testosterone and oestrogen, reducing their potency by decreasing the amount in circulation.20, 22-24 In obese men, elevated levels of cytokines and adipokines cause abnormal signalling, thereby resulting in dyslipidemia, insulin resistance, hyperglycemia, and hyperinsulinemia. 20, 22-24 High serum levels of insulin inhibit SHBG production from the hepatocytes.23 Reduced SHBG aggravates the hyperestrogenic state, further depressing the testosterone level.20-23 It has also been suggested that high serum insulin levels may have direct adverse effects on sperm production and may also cause spermatozoa Deoxyribonucleic acid (DNA) damage.25 Furthermore, this exaggerated hyperinsulinaemia, hyperestrogenemia, and low testosterone may result in secondary hypogonadism, erectile dysfunction, and type-2 diabetes mellitus. 26, 27 The vicious cycle continues, resulting in abnormal sperm parameters and male subfecundity. 26, 27

A peptide hormone, Inhibin B, has also been shown to have a regulatory effect on testosterone synthesis (20, 27. It has been proposed that its serum level may have a direct relationship with testicular volume and that it may also serve as a surrogate marker for adequate sperm formation. 20, 28 It stimulates testicular testosterone secretion and also decreases FSH production from the anterior pituitary via a negative feedback. 14, 28, 29. Low Inhibin B in obese men has been shown to play a contributory role in the dysregulation of the HPG axis via downregulation of FSH.14, 20, 28, 29

Lastly, another peptide hormone, kisspeptin, has also been shown to exert its effect on the HPG axis.14 It stimulates GnRH secretion in the hypothalamus and enhances its transport via the portal vessels to the pituitary.14, 20 Therefore, decreased production of kisspeptin in obese men will inhibit GnRH release, thereby leading to hypogonadotropic hypogonadism (low FSH, LH, and testosterone) with resultant effects of low libido, erectile dysfunction, and defective spermatogenesis. 14, 20, 29, 30.

Obesity, inflammation, and male infertility.

Several mechanisms have been put forward to explain the link between obesity, chronic inflammatory conditions, and male reproductive health (14, 23, 31-39 Some of these explanations include the role of oxidative stress and reactive oxygen species (ROS), pro-inflammatory cytokines, leptin, and increased scrotal temperature.31-39

Reactive oxygen species (ROS) are free radicals produced during daily cellular metabolism.22, 23 In the testis, these free radicals are usually produced by seminal leucocytes and sperm cells, and they have been hypothesized to play a role in sperm function.23, 31, 32, 33 In obese men, there is increased catabolism to meet up with normal daily requirement due to large body surface area.8, 9 The rise in metabolic rate invariably generates more ROS than the antioxidant function of normal cells. The oxidant-antioxidant imbalance causes damage to the phospholipid membrane of sperm cells, thereby affecting their functional capacity. 32, 33 It also makes the DNA of spermatozoa vulnerable to damage. 23, 32, 33

Current evidence also suggests that there is a link between systemic immune response, obesity, and a chronic low-inflammatory state.33, 34, 35 Normal physiologic processes in humans are influenced by both innate and acquired immunity.35 The immune system protects the body from pathogenic organisms, and it also helps in eliminating apoptotic cells.35-37 This is usually maintained by the balance between pro- and anti-inflammatory macrophages (M1 and M2, respectively).36 In obese males, there is an imbalance in cytokines produced in adipocytes and adipose tissue macrophages.33, 35-37 Pro-inflammatory macrophages dominate with increased secretion of interleukin six and Tumour Necrosis Factor- alpha (IL-6 and TNF-α).20, 33, 35-37 These pro-inflammatory cytokines inhibits insulin action in adipose tissues through either "autocrine and or paracrine actions".35-37 This contributes to the overall systemic insulin resistance and disruption of HPG axis inhibiting LH/FSH production leading to decrease testosterone production, inhibits testosterone effect on spermatogenesis, sexual desire, erectile function and male fertility.20, 34

Spermatogenesis is a highly regulated physiologic process that is sensitive to body temperature changes.14, 38 It usually occurs in the seminiferous tubules of the testes enclosed in the scrotum with a lower temperature of about 2 – 4 degrees Celsius lower than the normal core body temperature (32-35 degrees Celsius). 38, 39 It has been argued that it is because of this optimal temperature that the testis is located in the scrotum, outside the abdominal cavity.38, 39, 40 Testicular temperature is maintained by conventional heat losses from thin scrotal skin and abundant sweat glands in the scrotum, heat exchange from the testicular pampiniform venous plexus or by the activity of cremaster muscle and Dartos fascia.38, 39 There is an associated increase in scrotal temperature in obese men because of abundant fat deposition in the scrotum, (changing the texture to a thick scrotal wall), fat deposition in lower abdominal wall, and thighs.38-40 Elevated scrotal temperature has been postulated to affect sperm motility, concentration, and morphology via alterations in testicular signalling mechanisms.34, 38-40 This also causes accelerated damage to the DNA of spermatozoa either by direct effect, or by inducing a hypoxic environment, or via changes in testicular microcirculation, or via increased generation of ROS.34, 38, 39. 40 These have been shown to hurt a man's ability

to procreate. 34, 40 Historically, Robinson and co-workers were the first researchers to demonstrate the effect of external scrotal cooling using a device on sperm parameters. They noticed that cooling the testis for a few weeks resulted in an increase in sperm count in both the normospermic and oligospermic men.41 This further supports the fact that elevated scrotal temperature hurts male fertility.

It is also fascinating to know that obesity has been found to have a beneficial effect on an aspect of male fertility.42 There has been a long-standing association between varicocele and male infertility, which is most likely because of increased oxidative damage of sperm cells in men with high-grade varicocele, leading to a decrease in the quality of sperm produced.43 Handel and colleagues in their study found that the "prevalence of varicocele decreases with increasing body mass index".42 They hypothesized that this may be because of the associated decreased pressure in the left renal vein from fat deposition.42 The left renal vein is the major vessel that drains the left testicular vein and whose compression is implicated in varicocele- the so-called "nutcracker phenomenon".44, 45 They also argued that increased deposition of fat in the scrotum and spermatic cord may stabilize those vessels, thereby preventing them from dilatation, which invariably decreases their incidence too. 42

Leptin, a hormone produced in the adipose tissues, also affects male reproductive function.46-50 The serum level of leptin is directly proportional to the amount of adipose tissue in the body.46 The role as a satiety hormone has been established.46 However, evidence also suggests that it has a part to play in cellular and humoral immunity as well as pro-inflammatory conditions associated with certain diseases. 46, 47, 48, 49. The serum level of leptin rises just before puberty when it helps in testicular development, after which it falls.50, 51, 52 The unexpected rise of leptin in obese men inhibits androgen secretion from Leydig cells.50-52 Also, through several mechanisms that are not well understood, it enhances oxidative damage to sperm DNA, disrupts GNRH secretion, and increases apoptosis of sperm cells.14, 34, 50, 51, 52. Additionally, leptin, via its pro-inflammatory and immunomodulatory effects, has been proposed to have a deleterious effect on the blood-testis barrier, thereby affecting spermatogenesis by predisposing differentiating germ cells to immune damage.14, 34, 50, 51

Obesity, therefore, affects male fertility via "low-grade, sterile, chronic inflammatory Process,"53. This is because its effect is mainly from metabolic stimulus, that is, long-lasting with no offending microbial agent.

Obesity and male infertility: Implications for ART

Considering all the effects of obesity on male fertility are enumerated. It's arguable that with the rising incidence of obesity, the cost and burden imposed on ART treatment most likely will tend to increase in the same proportion. This cost may be a cumulative effect from the treatment of co-morbidities associated with obesity, to the cost of assessing fertility care. It has been postulated that men living with obesity have a "poor quality embryo" post-fertilization compared to their non-obese counterparts.54 However, Liu and colleagues found no difference in the quality of embryos between the obese and non obese men55 while Schliep *et al. believe* that the effect of obesity on ART treatment may be due to the combined effects of male and female obesity.56 Furthermore, there is a conflicting result on the effect of male obesity and the rates of live birth and clinical pregnancy following ART. While some authors found no difference, 55-57, Anifandis and colleagues in their study revealed that, despite the BMI of the female partner, most outcomes of *in vitro* fertilization are influenced by the BMI of the male partner.58 Interestingly, Mushtaq *et al.,* in their systematic review, affirmed that obesity reduces both clinical pregnancy rate and live birth rate.59 However, the confounding variables, such as the age of both partners, other causes of infertility, and the BMI of the female partner, need to be considered in future studies.59 There are also social and other medical issues associated with obesity; these men tend to have low self-esteem, low mood, and other co-morbidities such as diabetes, hypertension, and cardiovascular diseases, which may also be a hindrance to accessing fertility treatment that is available to the entire citizenry.60, 61

Conclusion

Obesity presents a myriad of problems regarding male sexuality and fertility. This essay has discussed several aspects of these problems and how they can affect male reproductive health. It explored how obesity can impact male fertility via its numerous effects on male reproductive hormones and the negative effects of a low-inflammatory environment induced by obesity. It also explored how this complex entity can affect ART treatment. More studies are required to further understand the mechanisms through which leptin and Inhibin B influence male reproduction.

Disclaimer

practices, drug dosages, procedures, and research findings before application in professional practice.

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