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The Dual Burden of Obesity and Infertility: The Role of Environmental Obesogens in Adipogenesis, Hypogonadism, and Sperm DNA Fragmentation

***[1]Oghenetega, O.B., [2]Okafor, C.P., [3]Oyovwi, M.O., [4]Oghenetega, E.G., [6]Ugwuishi, E.W., & [5]Ayegboyin, O.A.**

[1]Department of Physiology, Faculty of Basic Medical Science, Adeleke University, Ede, Osun State
[2]Department of Physiology, Babcock University, Ilisan-Remo, Ogun State
[3]Department of Physiology, Southern Delta University, Ozoro, Delta State, Nigeria
[4]Department of Biochemistry, Babcock University, Ilisan-Remo, Ogun State
[5]Department of Physiology, University of Ibadan, Nigeria
[6]Department of Physiology, College of Medicine, Enugu State University, Enugu, Nigeria

***Corresponding author email**: tegabonome@gmail.com

Abstract
The increasing rates of obesity and male infertility pose major public health challenges, with increasing evidence pointing to environmental obesogens—endocrine-disrupting chemicals (EDCs) that stimulate fat cell development and impaired metabolic function. This review consolidates the extant information on the mechanistic relationship between environmental obesogens and male infertility, highlighting the double role played by obesogens in inducing obesity and compromising reproductive health. Obesogens, a family of environmental chemicals such as bisphenol-A (BPA), phthalates, pesticides, and perfluorinated compounds, compromise the body's fat handling and contribute to male infertility via several inter-related mechanisms. Permanently activating peroxisome proliferator-activated receptor gamma (PPARγ), obesogens increase the development of fat cells and fat storage, upsetting the lipid balance. Concurrently, obesogens compromise the hypothalamic-pituitary-gonadal (HPG) axis, resulting in hypogonadotropic hypogonadism through disrupting hormone signal pathways via estrogenic or anti-androgenic pathways, leptin resistance, and alteration of kisspeptin signaling. The obesity further enhances these by boosting aromatase, converting testosterone to estrogen, which inhibits sperm production and quality, and reducing sex hormone-binding globulin (SHBG) levels, both of which inhibit sperm generation and quality. Moreover, obesogens cause direct testicular damage via oxidative stress, impaired mitochondria, and developmentally induced cell death (apoptosis) of Sertoli and Leydig cells, ultimately compromising blood testis barrier and germ cell survival. Population and laboratory data support the relationship between exposure to obesogens and adverse sperm features, such as diminished sperm movement and concentration, as well as enhanced sperm damage to DNA. Compounding these conditions, the thermal stress and chronic inflammation related to obesity further exacerbate testicular function. This review reflects the multifaceted ways in which environmental obesogens drive male infertility, the importance of minimizing exposure and a series of targeted policies to tackle these related health issues.

Keywords: Male Infertility, Obesogens, Testosterone, Obesity, Spermatogenesis

Introduction

According to World Health Organization (WHO), Obesity is a condition in which an individual has excessive weight, which is having a body mass index higher than 30kg/m2 (WHO, 2020). Mixtures that interfere with the body's natural hormones and disturb endocrine function are known as endocrine disrupting chemicals (EDC). Obesogens, a subset of EDC's, are xenobiotics that encourage obesity and adipogenesis directly or indirectly (Iva et al., 2022). They lead to abnormal alteration of lipid homeostasis, change metabolic set-points, disrupt energy

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balance, fat storage thereby promoting fat accumulation and resulting in obesity (Iva et al., 2022). Environmental obesogens are obesogens present in the environment acting as endocrine disruptors and interfering with normal endocrine functions.

Environmental obesogens can be found in most chemicals, most of which are usually used in manufacturing, agriculture and consumable goods. Some of which include: Bisphenol-A which is used in plastics and can be seen in food and beverages containers. A study showed that exposure to BPA results in obesity and alters the endocrine system controlling metabolism and weight gain (Masuno et al., 2007). Polycyclic aromatic hydrocarbons (PAHs) formed when substances are incinerated can also be found in coal-gasification sites and results in air pollution, Benzo(a)pyrene is a PAH compound has been reported by Irigaray et al. (2006) to inhibit fat breakdown and increase leptin in adult mice. An epidemiologic study carried out by Rundle et al. (2012) showed that higher exposure to PAHs during pregnancy was related to an increased body size of children between age 5 and 7.

The obesogen hypothesis, introduced in 2006, posits that environmental obesogens can contribute to the development of obesity by inducing adipogenesis, disrupting appetite and neuroendocrine homeostasis, and increasing energy storage (Grun & Blumberg, 2006). Since its inception, research has identified over 50 chemicals as potential environmental obesogens (Trasande, 2018). Sources of obesogens are shown in Fig. 1 below:

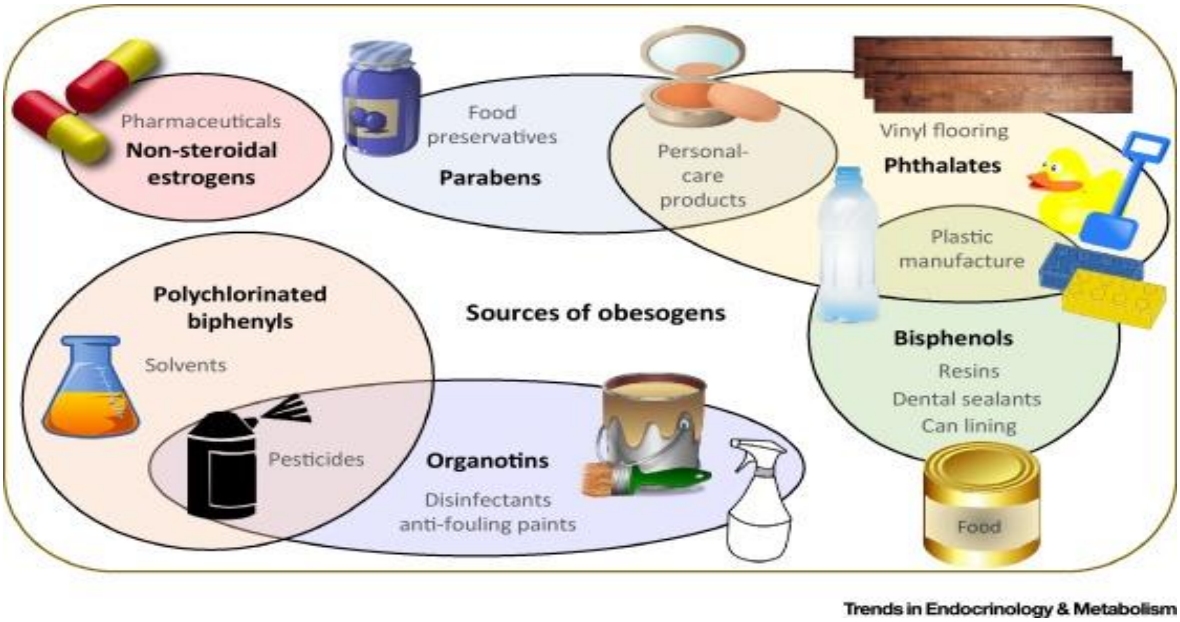

Figure 1: Diagram illustrating sources of obesogens (Almudena et al., 2018)

Route of Exposure of Obesogens to Human

Humans can come into contact with obesogens through breathing them in, absorbing them through the skin, or ingesting them. A common example is Bisphenol-A (BPA), a chemical found in polycarbonate plastics and beverage cans, which can seep into food and drinks from their containers (Fanny et al., 2015). Because BPA closely resembles estradiol in structure, it can easily bind to estrogen receptors in the body (Fanny et al., 2015). This interaction may lead to insulin resistance, an increase in fat production (lipogenesis), and heightened oxidative stress (Nicole et al., 2021). Phthalates, another class of obesogens, are found in a wide range of products, such as medical devices, food packaging, detergents, soaps, shampoos, and perfumes Tre et al. (2021). It has been revealed via in vitro studies that phthalates & its metabolites activate all three PPAR isoforms and could alter metabolism (Wang et al., 2024). Di-2-ethyhexyl-phthalate (DEHP) is a well-known phthalate which binds to the receptor of androgen, the main male sex hormone; this alters the synthesis of testosterone causing an anti-androgen effect which contributes to the development of obesity (Jerrold et al., 2018). The main form of exposure to obesogen is ingesting food or fluid

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that has been in contact with phthalate-containing products, another source of exposure is inhalation of phthalate particles in dust. Atrazine, a herbicide, is commonly found in surface and ground waters, atrazine is commonly found in waters of regions where it is used. Similarly to BPA, it also has anti-androgenic and estrogenic effects and reduces the production of luteinizing hormone (Gupta et al., 2020). It was observed that exposure to atrazine for a long time might enhance the risk of obesity and insulin resistance, especially in high fat diets (Gupta et al., 2020). Perfluorooctanoic acid (PFOA) is a surfactant used in waterproof clothing, non-stick cookware and microwaveable food items. Humans are exposed to PFOA through contaminated water; it stays in the body for an extended period of time once taken in (Lang, 2022). It has been demonstrated that mice exposed to PFOA before birth had higher chances of being obese when they reached adulthood, as well as increment in leptin, and body weight (Heindel et al., 2015).

Male Infertility

According to the World Health Organization (WHO), male infertility is a disease of the reproductive system marked by the failure to conceive after a year or more of regular sexual intercourse without contraception (World Health Organization, 2020). Infertility is classified as either primary, indicating no prior conceptions, or secondary, denoting the inability to conceive following a previous pregnancy (WHO, 2020). Male infertility, in particular, signifies a sexually mature man's inability to initiate a pregnancy in a fertile woman after a year of unprotected sex, and it can arise from diverse health problems that compromise his reproductive function, frequently related to sperm creation, density, or movement (Agarwal et al., 2021).

Male infertility presents with a range of symptoms, obvious and subtle, frequently stemming from hormonal imbalances, anatomical issues, or blockages in the reproductive tract. Key indicators include the inability to conceive after a year of unprotected sexual activity, a low sperm count (defined as fewer than 15 million sperm per milliliter), and erectile dysfunction potentially arising from neurological, psychological, or hormonal issues (Kumar & Singh, 2015). Discomfort, swelling, or lumps in the testicles can also indicate varicocele or an infection. Moreover, a reduction in body and facial hair can indicate chromosomal and endocrine anomalies, especially low levels of androgens (Kumar & Singh, 2015). Gynecomastia, a rare development of breasts, typically occurs as a result of discordance in the balance of estrogen and testosterone and can be related to disorders underlying the infertility of males (Nieschlag et al., 2013). Other indicators, including reduced sex drive, abnormal semen, anosmia (loss of smell), repeated respiratory infections, and small-sized testicles, can represent dysfunctional production of testosterone and genetic disorders affecting fertility (Nieschlag et al., 2013).

The cause of male infertility is multifactorial, encompassing a mix of environmental, chemical, biological, and lifestyle factors. Damage to the testicles due to infection, congenital anomalies, trauma, or undescended testicle can damage sperm production (spermatogenesis) and sperm storage, resulting in sperm parameter abnormalities (Agarwal et al., 2021). Some common terminologies in male infertility are presented in Fig. 2. Endocrine disorders such as hypogonadism, tumors, Klinefelter syndrome, or medications can affect hormone balance necessary for sperm production (Nieschlag et al., 2013). Anabolic steroid abuse can lower sperm count and motility, while sulfasalazine transiently lowers sperm count, with improvements usually occurring with drug cessation (Kumar & Singh, 2015). Sperm DNA damage, often attributed to reactive oxygen species-induced oxidative stress, environmental toxins, dietary factors, smoking, and alcohol intake, is another major cause of infertility (Agarwal et al., 2021). Chemotherapy, along with radiation therapy to the lower abdomen, pelvis, spine, and sex organs, and stem cell transplant, can damage sperm-producing units and lower levels of testosterone, potentially resulting in transient or permanent infertility (Meistrich & Shetty, 2018). Systemic conditions such as sickle cell anemia, renal disease, metabolic disorders, or protracted fever can detract from spermatogenesis and sperm quality (Berthaut et al., 2008).

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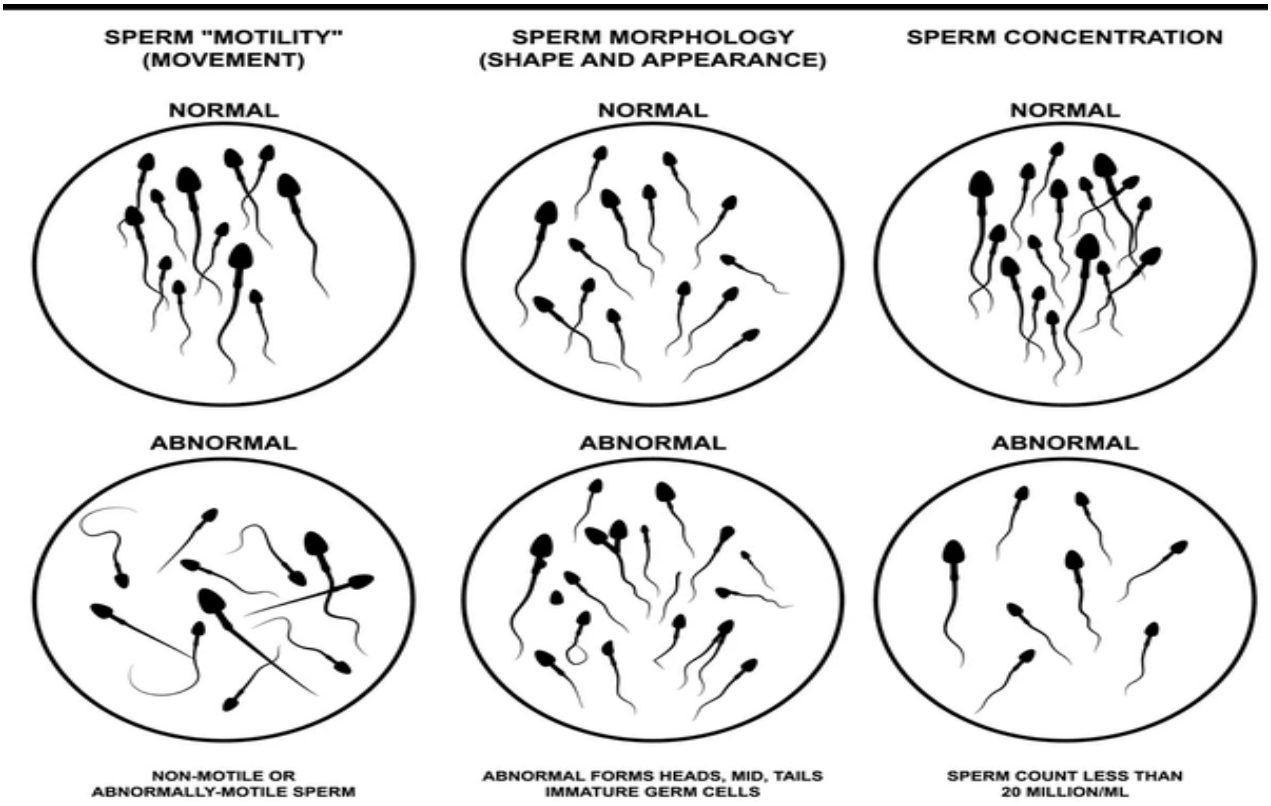

Figure 2: Terminologies in male infertility (Anastasia, 2015)

Relationship between Obesogens and Male Infertility (Adipogenesis)

Adipogenesis, or the formation of fat tissue, is the process by which preadipocytes develop into mature fat cells (Jakab et al., 2007). This transformation involves the progression of early fat cell precursors into preadipocytes, which then fully differentiate into adipocytes. The obesogen hypothesis suggests that exposure to certain environmental chemicals can promote obesity by increasing white adipose tissue. A central regulator in this process is PPARγ (peroxisome proliferator-activated receptor gamma), which plays a vital role in the development and function of white fat tissue (Tontonoz et al., 2008).

PPARγ acts as a ligand-activated transcription factor, meaning it helps control gene expression by turning specific genes on or off in response to molecular signals. Inside the cell nucleus, PPARs form a complex with the 9-cis retinoic acid receptor. This complex binds to peroxisome proliferator response elements on DNA to regulate the expression of certain genes. When a ligand binds to PPARγ, it changes shape and recruits co-transcription factors that enhance the production of messenger RNA (mRNA) from these genes (Tontonoz et al., 2008).

Endocrine-disrupting chemicals (EDCs) that act as obesogens can imitate the body's natural ligands and bind to PPARγ, affecting how fat cells form, how fat and sugar are processed, and how sensitive cells are to insulin. These chemicals can drive stem cells to become fat cells, leading to an increase in fat tissue and possible weight gain—especially if exposure occurs during early development. Because these chemicals are lipophilic (fat-loving), they tend to build up in adipose tissue over time (Tontonoz et al., 2008).

First introduced in 2006, the obesogen hypothesis proposes that environmental chemicals can not only encourage fat tissue development but also disrupt appetite regulation and hormonal balance, promoting excessive energy storage

(Grun & Blumberg, 2006). Since then, more than 50 chemicals have been identified as potential obesogens (Trasande, 2018).

Hypogonadotropic Hypogonadism and Obesity

Hypogonadotropic hypogonadism occurs due to structural, functional, or genetic issues that disrupt the hypothalamic-pituitary-gonadal (HPG) axis. A deviation in the proliferation and maturation of spermatogonial stem cells have been linked with hypogonadism and hyperestrogenism (Rocco et al., 2025). In obesity, levels of leptin, insulin, proinflammatory cytokines, and estrogen increase, while the expression of kisspeptin receptors decreases. Kisspeptin, a neuropeptide produced in the hypothalamus, plays a crucial role in triggering the release of gonadotropins, but its effectiveness is reduced under these conditions. In obese men, excess body fat leads to more testosterone being converted into estradiol (Leisegang et al., 2021). This elevated estradiol suppresses the production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), impairing testicular function and lowering testosterone levels.

Estrogen also sends negative feedback to the hypothalamus, further reducing kisspeptin production and limiting the release of gonadotropin-releasing hormone, which in turn lowers FSH and LH production (Harter et al., 2018). The higher activity of the aromatase enzyme in obese men accelerates the conversion of testosterone to estrogen, contributing to the development of hypogonadism and initially raising estrogen levels in both men and women. In some obese men, this can lead to aromatase excess syndrome, which may result in gynecomastia—a condition also associated with male infertility.

The HPG axis regulates testosterone production, influenced by testosterone's negative feedback. In response to GnRH release, LH and FSH are secreted; LH stimulates testosterone secretion by Leydig cells, while FSH induces sperm production by Sertoli cells in the testes. Hypogonadism-induced obesity disrupts the HPG axis, decreasing GnRH release from the hypothalamus, subsequently lowering FSH and LH levels and reducing testosterone levels, which in turn increases adiposity due to increased lipogenesis (Genchi et al., 2022). Researchers have reported hormonal differences between obese and normal men, indicating that obese men often have reduced levels of sex hormone-binding globulin (SHBG) and testosterone. The decrease in SHBG is a primary cause of reduced testosterone levels (Salas-Huetos et al., 2021).

Obesity can impair sperm formation and sperm parameters due to increased gonadal heat from scrotal adiposity. Elevated testicular temperature is linked to reduced motile sperm, increased DNA damage, and oxidative stress in sperm (Shiraishi et al., 2010). Studies have shown that obese men are more likely to have lower semen volume and abnormal spermatozoa compared to men with a normal body mass index (Shayeb et al., 2011). Additionally, a study by Anderson et al. (2015) found a negative association between body mass index and sperm concentration, sperm motility, count, and normal sperm morphology in severely obese men. Levels of SHBG, testosterone, and inhibin B were also negatively associated with BMI (Anderson et al., 2015). A schematic diagram illustrating the possible mechanism of action of obesogen-induced male infertility is shown in Fig 3.

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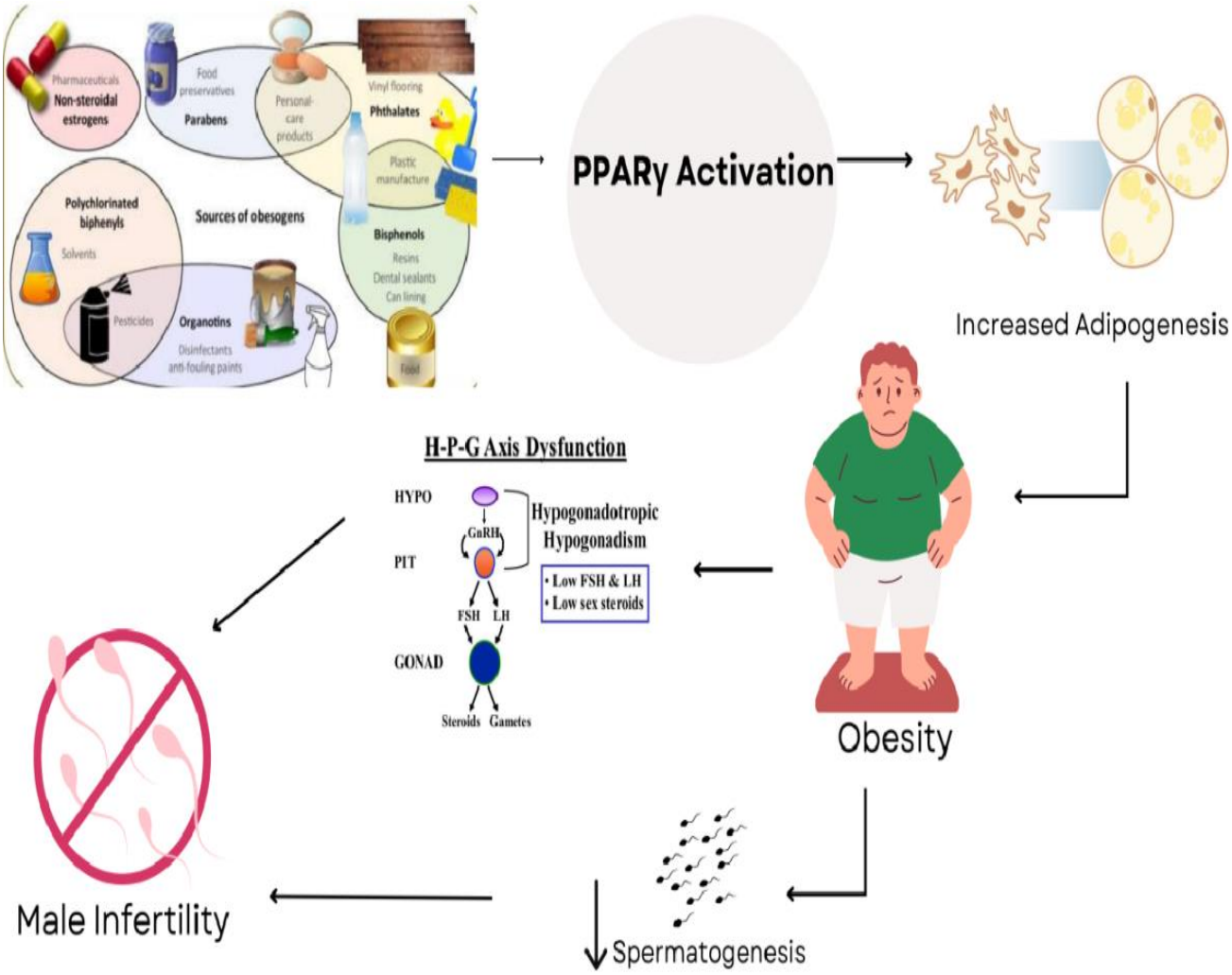

Figure 3: A schematic diagram illustrating the mechanism of action of obesogen-induced male infertility (Tontonoz et al., 2008)

Direct Relationship between Environmental Obesogen and Male Infertility

Environmental obesogens such as pesticides, mainly used in agricultural practice or used in home gardens or to eradicate pests. Exposure to pesticides in humans can occur while dealing with production or circulation of these chemicals in the food chain (Mostafalou et al., 2017). By acting as an endocrine disruptor chemical, pesticides damage the male reproductive system, a large number of pesticides are considered ECDs (Roy et al., 2017). They act as obesogens and 30 to 40% of all male infertility cases are closely associated with obesity (Darbre, 2017). Obesogens can negatively impact the male reproductive system through multiple pathways, including direct cellular damage that results in reproductive disorders. Sertoli cells play a vital role in supporting developing germ cells and preserving the integrity of the blood-testis barrier, both of which are essential for normal germ cell maturation. As shown by de Carvalho et al. (2020), when this protective barrier is disrupted, germ cell development can come to a halt.

Exposure to obesogens such as pesticides can lead to an overproduction of reactive oxygen species, which in turn damage mitochondria and trigger the apoptosis (programmed death) of Sertoli cells. When these supportive cells die,

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the blood-testis barrier—crucial for shielding maturing sperm cells—becomes compromised, ultimately leading to the death of germ cells. Pesticides can cross this barrier due to their chemical properties, directly harming the cells.

For example, de Carvalho et al. (2020) found that methamidophos, an organophosphate pesticide, caused a significant decline in Sertoli cell numbers due to its toxicity. This effect is likely related to the pesticide's unique combination of hydrophilic and hydrophobic traits, which enable it to breach the blood-testis barrier. Similarly, Elsharkawy et al. (2014) reported that rats exposed to another organophosphate, chlorpyrifos, exhibited a marked drop in spermatogenic cells, along with tissue damage that included necrosis and swelling in the testicular interstitial space. The seminiferous tubules—structures in the testes responsible for producing sperm—appear especially vulnerable to the harmful effects of pesticide exposure. Schematic diagram showing the direct effect of environmental obesogen on male infertility is presented in Fig. 4 below:

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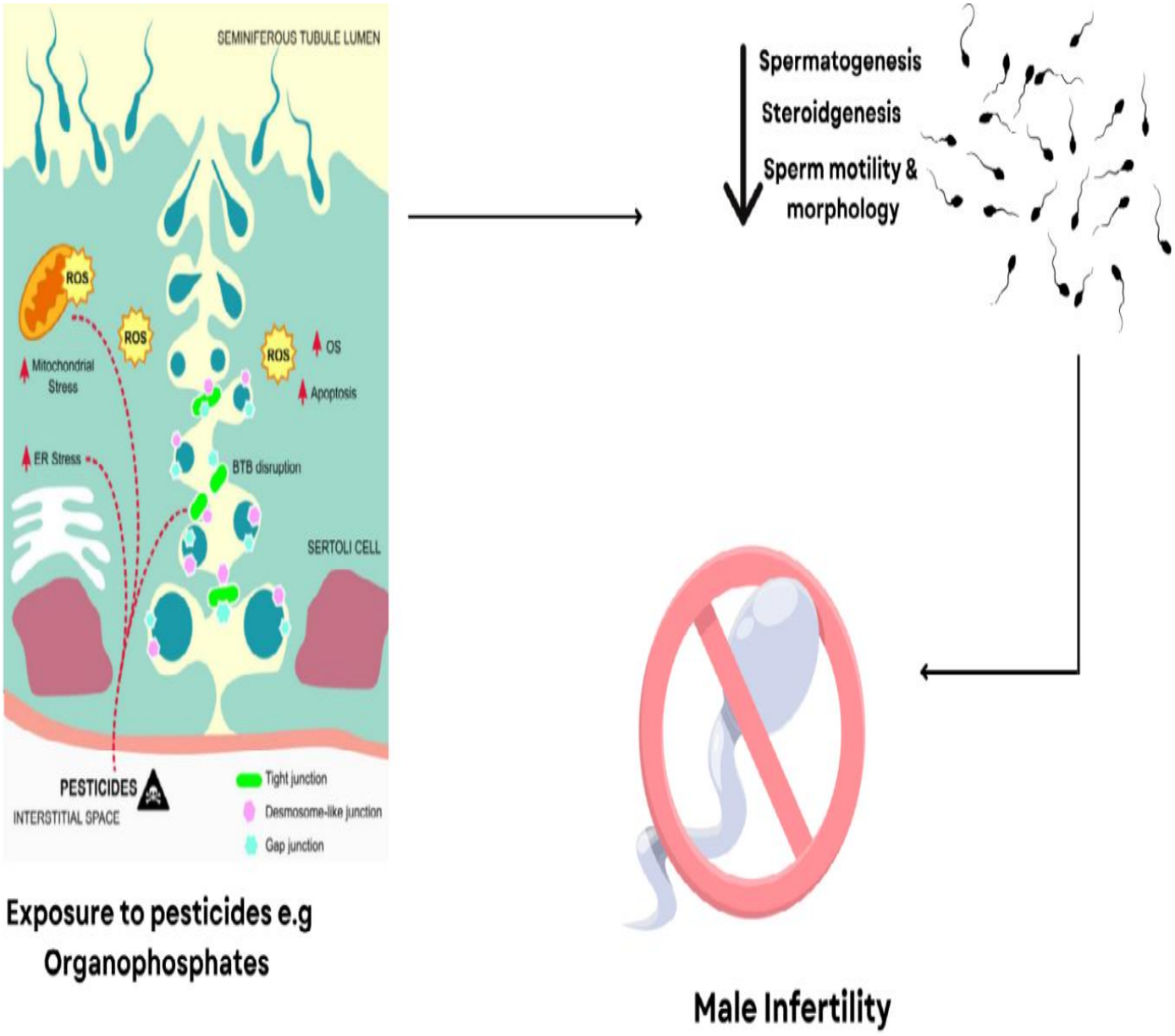

Figure 4: Schematic diagram showing the direct effect of environmental obesogen on male infertility (Moreira et al., 2021)

Obesity-linked Infertility

Obesity, often described as an "enemy of infertility" in men (Salma, 2018), is associated with alterations in semen parameters, leading to reduced testicular volume, diminished semen quality, and impaired sperm formation (Macdonald et al., 2009). The hypothalamic-pituitary-gonadal axis regulates testosterone production through a negative feedback loop involving testosterone itself. Gonadotropin-releasing hormone (GnRH) stimulates the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH acts on Leydig cells in the testes to promote testosterone release, while FSH acts on Sertoli cells, stimulating sperm production (Xu et al., 2017).

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Compared to men of normal weight, obese men exhibit abnormal levels of reproductive hormones. Excess fat reduces levels of sex hormone-binding globulin (SHBG), testosterone, and inhibin B, while increasing the conversion of testosterone to 17ß-estradiol due to heightened aromatase activity (Chavarro et al., 2010). Elevated estrogen levels, being more biologically active than testosterone, can inhibit the hypothalamic-pituitary-gonadal axis by interfering with kisspeptin signaling, ultimately reducing testosterone production. An illustration showing the possible mechanisms involved obesity-linked male infertility is presented in Fig. 5.

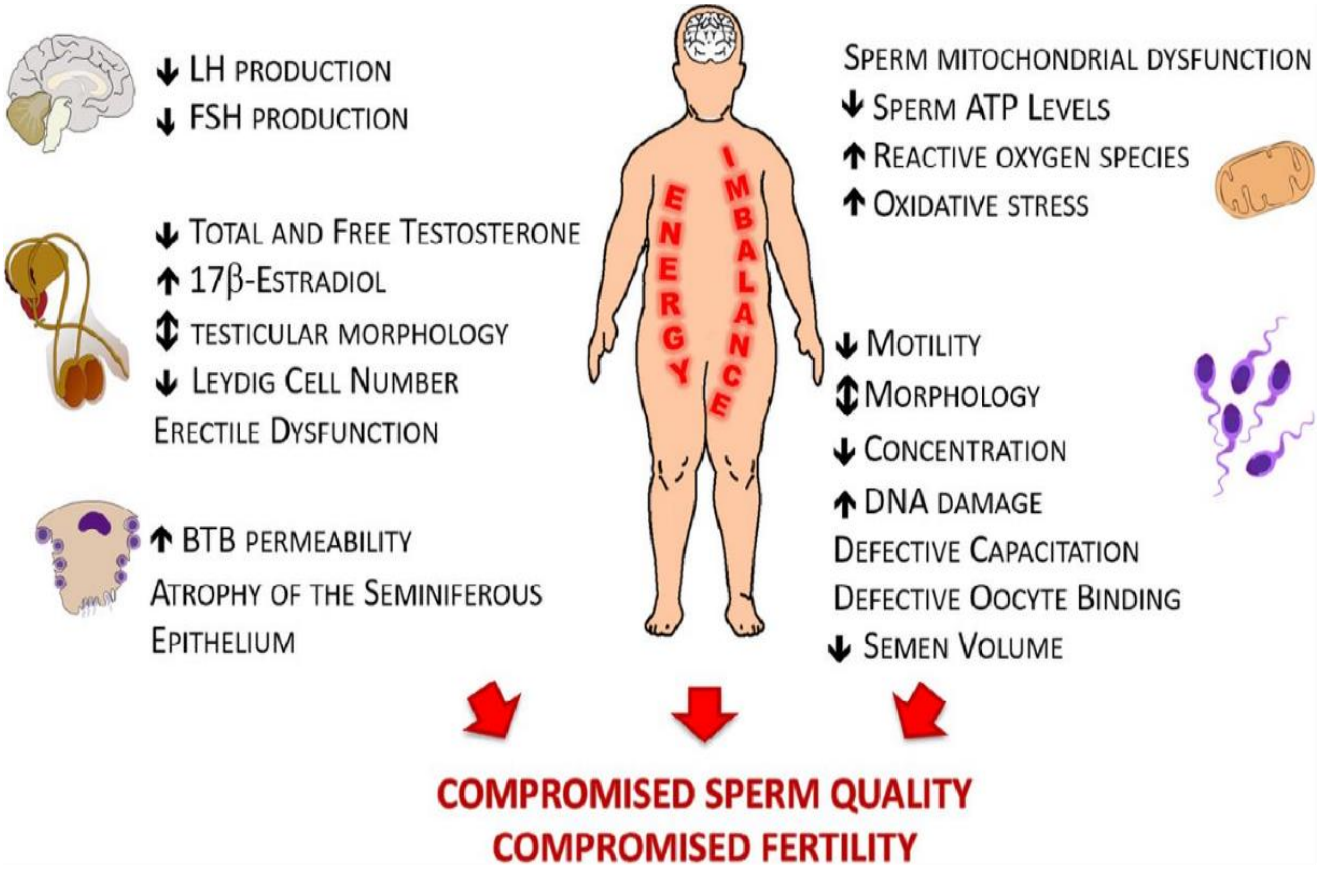

Figure 5: Possible Mechanism of Obesity-linked Male Infertility (Oliveira, 2017)

Obesity is also associated with impaired sperm quality, specifically in terms of count, motility, and morphology (Salma, 2018), due to these disrupted hormonal levels. Overweight and obese men tend to exhibit abnormal sperm parameters (Salma, 2018). A body mass index exceeding 25 kg/m^2 has been correlated with a lower total sperm count (Chavarro et al., 2010). Furthermore, obese men experience increased thermal stress in the testes due to fat accumulation around the pampiniform plexus and suprapubic region. This leads to elevated scrotal temperature, decreasing sperm motility and increasing sperm DNA fragmentation and oxidative stress (Lui et al., 2017). A summary of selected studies on environmental obesogens and male infertility is shown in Table 1 below:

Table 1: Selected Studies on Environmental Obesogens and Male Infertility

	Reference	Animal Model	Keypoints
1)	Johnson et al. (2015)	Mice	The study demonstrated that developmental exposure to bisphenol-A

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		during gestation and pregnancy resulted in reduced physical activity and energy expenditure in adult offspring, despite the absence of data on body weight and fat content.
2) Rubin et al. (2019)	Mice	This study reported that exposure to bisphenol-A enhanced fat mass and body weight more in perinatally male than in female.
3) Hassan et al. (2022)	Albino rats	This study shows that 7.5mg/kg-BW chlorpyrifos given to albino rats reduced testicular weights and induce testicular tissue damage.
4) Zhu et al. (2021)	Sprague Dawley	This study shows that 120mg/kg-BW of Atrazine reduced sperm motility and testosterone levels.
5) Erthal et al. (2020)	Wistar rats	Study shows that 10/15mg/kg-BW of Malathion reduced spermatogenesis and increased number of abnormal sperm.
6) Li et al. (2022)	Sprague Dawley rats	Study shows Cypermethrin, 50 mg/kg-BW/day and 200 μM decreased sperm count, testosterone and inhibited leydig cells development in late puberty.
7) Saleh et al. (2020)	Albino rats	Study shows that 5 mg/kg-BW of fipronil decreased number of semen in tubule lumens and led to edema around the seminiferous tubule.
8) Bagherpour et al. (2019)	Mice	Study shows that Deltamethrin, 0.6 mg/kg-BW decreased testosterone levels.
9) Sardar et al .(2023)	Sprague Dawley rats	Study shows that Imidacloprid, 5 and 10 mg/kg resulted in generation of free radicals in testicular tissues, leading to oxidative stress.
10) Hassan et al. (2021)	Albino rats	Study showed that Iprodione, 200 mg/kg-BW caused vacoular degenerative changes in sertoli and leydig cells.

Conclusion

Environmental obesogens which are seen everywhere and easily exposed to humans result in obesity and this comes with serious illnesses, both physical and physiological. Studies have clearly shown that obesity leads to infertility or subfertility in males and they are due to various mechanisms that ultimately lead to abnormal sperm parameters. New studies state that many causes of this abnormality include excess adipose-derived hormone, lipogenesis and adipokine release and as well as oxidative stress. This results in suppression and alteration of normal spermatogenesis and sperm quality.

Suggestions

A reduction in the use or contact with various environmental obesogens can serve as a preventative measure and decrease the chances of infertility or obesity-linked infertility in male. Additionally, natural weight loss

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accompanied with regular exercise could be used to treat obesity-linked infertility. Treatment with nutritional supplements rich in antioxidants or specific vitamins might also increase fertility by improving sperm motility.

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