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The Impact of Cosmetics on Male Fertility

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Infertility is defined clinically in women and men who cannot achieve pregnancy after 1 year of having intercourse without using birth control, and in women who have two or more failed pregnancies. Studies suggest that after 1 year of having unprotected sex, 15% of couples are unable to conceive, and after 2 years, 10% of couples still have not had a successful pregnancy **[1,2].**In couples younger than age 30 who are generally healthy, 20% to 37% are able to conceive in the first 3 months **[3].**Many different medical conditions and other factors can contribute to fertility problems, and an individual case may have a single cause, several causes, or—in some cases—no identifiable cause. Overall, one-third of infertility cases are caused by male reproductive issues, one-third by female reproductive issues, and one-third by both male and female reproductive issues or by unknown factors**[4].**To conceive a child, a man's sperm must combine with a woman's egg. The testicles make and store sperm, which are ejaculated by the penis to deliver sperm to the female reproductive tract during sexual intercourse. The most common issues that lead to infertility in men are problems that affect how the testicles work. Other problems are hormone imbalances or blockages in the male reproductive organs. In about 50% of cases, the cause of male infertility cannot be determined **[5].**

A complete lack of sperm occurs in about 10% to 15% of men who are infertile **[6].**A hormone imbalance or blockage of sperm movement can cause a lack of sperm. In some cases of infertility, a man produces less sperm than normal. The most common cause of this condition is varicocele, an enlarged vein in the testicle. Varicocele is present in about 40% of men with infertility problems **[7].**

In the United States, among heterosexual women aged 15 to 49 years with no prior births, about 1 in 5 (19%) are unable to get pregnant after one year of trying (infertility). Also, about 1 in 4 (26%) women in this group have difficulty getting pregnant or carrying a pregnancy to term (impaired fecundity).Infertility and impaired fecundity are less common among women with one or more prior births. In this group, about 6% of married women aged 15 to 49 years are unable to get pregnant after oneyear of trying and 14% have difficulty getting pregnant or carrying a pregnancy to term **[4].**

Infertility in men can be caused by different factors and is typically evaluated by a semen analysis. When a semen analysis is performed, the number of sperm (concentration), motility (movement), and morphology (shape) are assessed by a specialist. A slightly abnormal semen analysis does not mean that a man is necessarily infertile. Instead, a semen analysis helps determine if and how male factors are contributing to infertility.Varicocele, a condition in which the veins within a man's testicle are enlarged. Although there are often no symptoms, varicoceles may affect the number or shape of the sperm.Trauma to the testes may affect sperm production and result in lower number of sperm.Heavy alcohol use, smoking, anabolic steroid use, and illicit drug use.Cancer treatment involving certain types of chemotherapy, radiation, or surgery to remove one or both testicles.Medical conditions such as diabetes, cystic fibrosis, certain types of autoimmune disorders, and certain types of infections may cause testicular failure.Improper function of the hypothalamus or pituitary glands. The hypothalamus and pituitary glands in the brain produce hormones that maintain normal testicular function. Production of too much prolactin, a hormone made by the pituitary gland (often due to the presence of a benign pituitary gland tumor), or other

conditions that damage or impair the function of the hypothalamus or the pituitary gland may result in low or no sperm production.These conditions may include benign and malignant (cancerous) pituitary tumors, congenital adrenal hyperplasia, and exposure to too much estrogen, exposure to too much testosterone, Cushing's syndrome, and chronic use of medications called glucocorticoids.Genetic conditions such as a Klinefelter's syndrome, Y-chromosome microdeletion, myotonic dystrophy, and other, less common genetic disorders may cause no sperm or low numbers of sperm to be produced **[4].**The observed prevalence of infertility will evidently depend on the definition used. Whilst common clinical practice, and many studies, are based on a definition of failure to conceive after 12 months of unprotected intercourse, many authorities, based upon the distribution of fecundity observed in a 'normal' population, have defined infertility as the failure of a couple to conceive after 2 years of unprotected regular coital exposure.As was suggested above, a major obstacle to meaningful study of the epidemiology of maleinfertility is the difficulty in accurate diagnosis of the presence or absence of a problem. Traditionally, the diagnosis of male infertility is based upon the conventional semen profile, constructed according to recognized guidelines. This profile incorporates information on the volume of the ejaculate, the concentration of spermatozoa, their motility and their morphological appearance. Unfortunately, a number of significant shortcomings limit the diagnostic value of this assessment. Marked inter-ejaculate variability is a major problem in the assessment of human semen**[8].**Recent discovery of declining trend of semen quality overpast decades became a major concern. Retrospective evaluations of laboratory semen records are plentiful and have indicated a decrease in semen quality as reported from Belgium,Finland,France, Scotland, Norway, the United Kingdom,Greece, Canada, and the United States.In

contrast, novariations have been reported from regions such as Denmark,Israel,Australia,and AfricaBut, the data reporting novariation in semen quality is still unconvincing considering theglobal trends. For example, it was recently confirmed thatthe Asian male population followed the same global trend overthe period of past 50 years**[9].**Despite years of intensive research, educational efforts, Male infertility remain major social and medical problem globally, which affects people both medically and psychosocially,directly responsible for 60% of cases involving reproductive age couples with fertility issues. Although the actual fertility of a semen sample cannot be completely determined until it is known to achieve fertilization, careful and thorough analysis of all the semen‘s parameters by a specialised laboratory can allow treatment options to be appropriately considered.Before puberty, humans are naturally infertile; their gonads have not yet developed the gametes required to reproduce: boys' testicles have not developed the sperm cells required to impregnate a female; girls have not begun the process of ovulation which activates the fertility of their egg cells (ovulation is confirmed by the first menstrual cycle, known as menarche, which signals the biological possibility of pregnancy). Infertility in children is commonly referred to as prepubescence (or being prepubescent, an adjective used to also refer to humans without secondary sex characteristics).The absence of fertility in children is considered a natural part of human growth and child development, as the hypothalamus in their brain is still underdeveloped and cannot release the hormones required to activate the gonads' gametes. Fertility in children before the ages of eight or nine is considered a disease known as precocious puberty. This disease is usually triggered by a brain tumor or other related injury.

In some cases, both the man and woman may be infertile or sub-fertile, and the couple's infertility arises from the combination of these conditions. In other cases, the cause is suspected to be immunological or genetic; it may be that each partner is independently fertile but the couple cannot conceive together without assistance. In the US, up to 20% of infertile couples have unexplained infertility. In these cases, abnormalities are likely to be present but not detected by current methods. Possible problems could be that the egg is not released at the optimum time for fertilization that it may not enter the fallopian tube, sperm may not be able to reach the egg, fertilization may fail to occur, transport of the zygote may be disturbed, or implantation fails. It is increasingly recognized that egg quality is of critical importance and women of advanced maternal age have eggs of reduced capacity for normal and successful fertilization. Also, polymorphisms in folate pathway genes could be one reason for fertility complications in some women with unexplained infertility. However, a growing body of evidence suggests that epigenetic modifications in sperm may be partially responsible.

Male fertility cycle

Men do not have a 'fertile window because sperm is continually formed and stored in the testicles, ready to be used at any time.There are several theories of why men are more fertile during cooler months. Men used to be the main workers in the family. Much of how the human body functions is based on primal need and genetic programming. Just a few decades ago, men worked extremely hard in the fields, chopping trees, clearing lands, tending animals, and building during the summer months. Sex was the last thing on their minds unless that sex occurred during the morning hours when they were well-rested and, according to science, when sperm levels were highest. There may also be a connection between conception dates and birth dates based on season. For instance, children conceived during early spring would be born during the harsh winter months when food is scarce, but children conceived during the winter months would be born during the harvest months when food is plentiful.

There are few medical professionals that take male fertility cycles into consideration, but science cannot impact genetic programming. Sometimes, at the root of all problems is a simple answer that dates back a millennium. Male fertility generally starts to reduce around age 40 to 45 years when sperm quality decreases. Increasing male age reduces the overall chances of pregnancy and increases time to pregnancy (the number of menstrual cycles it takes to become pregnant) and the risk of miscarriage and fetal death. Children of older fathers also have an increased risk of mental health problems (although this is still rare). Children of fathers aged 40 or over are 5 times more likely to develop an autism spectrum disorder than children of fathers aged 30 or less. They also have a slightly increased risk of developing schizophrenia and other mental health disorders later in life.Usually, the patient disrobes

completely and puts on a gown. The physician, physician assistant, or nurse practitioner will perform a thorough examination of the penis, scrotum, testicles, I vas deferens, spermatic cords, ejaculatory ducts, urethra, urinary bladder, anus and rectum. An orchidometer can measure testicular volume, which in turn is tightly associated with both sperm and hormonal parameters. A physical exam of the scrotum can reveal a varicocele, but the impact of detecting and surgically correct a varicocele on sperm parameters or overall male fertility is debated **[10].**The main cause of male infertility is low semen quality. In men who have the necessary reproductive organs to procreate, infertility can be caused by low sperm count due to endocrine problems, drugs, radiation, or infection. There may be testicular malformations, hormone imbalance, or blockage of the man's duct system. Although many of these can be treated through surgery or hormonal substitutions, some may be indefinite.Infertility associated with viable, but immotile sperm may be caused by primary ciliary dyskinesia. The sperm must provide the zygote with DNA, centrioles, and activation factor for the embryo to develop. A defect in any of these sperm structures may result in infertility that will not be detected by semen analysis.Antisperm antibodies cause immune infertility. Cystic fibrosis can lead to infertility in men.

Male infertility problems

Infertility is a common problem, affecting perhaps one couple in six, the majority of whom now seek medical care. Although diagnostic problems make it difficult to establish the extent of the male partner's contribution with certainty, a number of studies suggest that male problems represent the commonest single defined cause of infertility. The World Health Organization has proposed a scheme for the diagnostic classification of male infertility, based upon a standardized approach to clinical assessment and to the assessment of semen quality. Some of these classifications are now controversial, and many are descriptive, rather than aetiological. Increasingly, the importance of occupation, environmental and particularly genetic factors in the causation of male infertility is being recognized **[11].**

Notwithstanding the difficulties in diagnosis outlined above, the WHO has proposed a scheme for the diagnostic classification of the male partner of the infertile couple. This approach is of enormous value as a basis for standardization, and for comparative multi-centre studies. However, many of the male diagnostic categories are of a descriptive nature (e.g. idiopathic oligozoospermia) or of controversial clinicalrelevance (e.g. male accessory gland infection) **[12].**

Environmental, occupational, and modifiable lifestyle factors may contribute to this decline of male fertility. Lifestyle factors associated with male infertility include smoking cigarettes, alcohol intake, and use of illicit drugs, obesity, psychological stress, advanced paternal age, diet composition, and coffee consumption. Among other factors are testicular heat stress, intense cycling training, lack of sleep, and exposure to electromagnetic radiation from mobile phones **[13].**

Tobacco smoking is responsible for DNA damage and the formation of reactive oxygen species. A study on the male partners of couples facing primary infertility found that teratozoospermia (abnormal morphology) was present in 63% and 72% of males who drank alcohol moderately (40-80 g/d) and heavily (>80 g/d), respectively. None of the heavy alcohol drinkers were normozoospermic (normal sperm) and most (64%) were oligozoospermic (low sperm count), which is suggestive of progressive testicular damage in relation to increasing daily alcohol intake **[14].** Recreational drugs such as marijuana, cocaine, anabolic–androgenic steroids, opiates (narcotics), and methamphetamines are examples of illicit drugs that exert a negative impact on male fertility. The adverse effects of these drugs could impair the hypothalamic–pituitary– gonadal (HPG) axis, testicular architecture, and sperm function **[15].**

More than 76% of caffeine consumers (3.0 + 1.8 cups of coffee/d) had a slight increase in semen volume, whereas fertile vasectomy patients who drank 6 cups of coffee/d presented with higher sperm motility. A recent systematic review involving 19 967 men found that in most of the studies, semen parameters were affected by cola-containing beverages and caffeine-containing soft drinks, but not by caffeine intake from coffee, tea, and cocoa drinks. Caffeine intake may impair male reproductive function possibly through sperm DNA damage **[16].**

A study involving 13 077 men reported that obese men were more likely to be oligozoospermic or azoospermic compared to men within a normal weight range. A population-based study found that as body mass index and waist circumference increased, the prevalence of low ejaculate volume, sperm concentration, and total sperm count were also greater in overweight and obese men of unknown fertility **[17].** The presence of excess white adipose tissue in obese individuals causes increased

conversion of testosterone to estrogen, and affects the HPG axis leading to a reduction in gonadotrophin release, and impaired spermatogenesis and increased oxidative stress **[18].**Antisperm antibodies (ASA) have been considered as infertility cause in around 10–30% of infertile couples. In both men and women, ASA production are directed against surface antigens on sperm, which can interfere with sperm motility and transport through the female reproductive tract, inhibiting capacitation and acrosome reaction, impaired fertilization, influence on the implantation process, and impaired growth and development of the embryo. The antibodies are classified into different groups: There are IgA, IgG and IgM antibodies. They also differ in the location of the spermatozoon they bind on (head, mid piece, tail). Factors contributing to the formation of antisperm antibodies in women are disturbance of normal immunoregulatory mechanisms, infection, and violation of the integrity of the mucous membranes, rape and unprotected oral or anal sex. Risk factors for the formation of antisperm antibodies in men include the breakdown of the blood-testis barrier, trauma and surgery, orchitis, varicocele, infections, prostatitis, testicular cancer, failure of immunosuppression and unprotected receptive anal or oral sex with men.Similarly, diet such as vegetables and fruits, fish and poultry, cereals, and low-fat dairy products were among the foods positively associated with sperm quality. However, diets consisting of processed meat, full-fat dairy products, alcohol, coffee, and sugar-sweetened beverages were associated with poor semen quality and lower fecundity rates **[19].**Industrial chemicals such as Metadinitrobenzene and methoxyacetic acid, which are plasticizers, can impair sperm fertilizingability and sperm motility (measured using computer-assistedsemen analysis) at both acute and chronic dose levels.Exposure to industrial chemicals not only degrades male infertility but also can result

in DNA fragmentation. Stress, in its many forms, may be detrimental to male reproductive potential. The classical stress response activates the sympathetic nervous system and involves the hypothalamus– pituitary–adrenal (HPA) axis. Both the HPA axis and gonadotrophin-inhibitory hormone exert an inhibitory effect on the HPG axis and testicular Leydig cells. Men who were significantly stressed had lower levels of testosterone andhigher levels of FSH and LH than men with normal well-being thus reducing sperm counts and sperm morphology and motility **[20].**Further, sleep disturbances may possibly have adverse effects on male fertility, as semen volume was lower in patients with difficulty in initiating sleep, including those who smoked or were overweight **[21].**

Infections with the following sexually transmitted pathogens have a negative effect on fertility: *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. There is a consistent association between *Mycoplasma genitalium* infection and female reproductive tract syndromes. *M. genitalium* infection is associated with an increased risk of infertility. Mutations to the NR5A1 gene encoding steroidogenic factor 1 (SF-1) have been found in a small subset of men with non-obstructive male factor infertility where the cause is unknown. Results of one study investigating a cohort of 315 men revealed changes within the hinge region of SF-1 and no rare allelic variants in fertile control men. Affected individuals displayed more severe forms of infertility such as azoospermia and severe oligozoospermia. Small supernumerary marker chromosomes are abnormal extra chromosomes; they are three times more likely to occur in infertile individuals and account for 0.125% of all infertility cases. See Infertility associated with small supernumerary marker chromosomes and Genetics of infertility Small supernumerary marker chromosomes and infertility.

Cosmetics and male infertility

Men burdened by infertility is a global health concern **[22].**The psychological, social and economic consequences of a diminished capacity to father children are often severe and range beyond individuals to whole families and society at large. While considerable differences in male reproductive health exist within and between developed countries, a negative trend of low semen quality and high incidence of cryptorchidism, hypospadias and testicular cancer has been observed in many areas **[23,24].**Thus, 35% of young men in Denmark have low semen quality **[25].**Both genetic and environmental factors may contribute to this deficit in reproductive health **[24].**At present, several common consumer products invented to ease our everyday lives are suspected of impairing key reproductive functions **[26].**

Personal care products (PCPs) include all non-pharmaceutical items consumed or applied to enhance personal health, hygiene or appearance **[27].**While these products typically contain a multitude of chemicals, common ingredients include phthalate esters, parabens, ultraviolet (UV) filters, polycyclic musks, antimicrobials, formaldehyde and formaldehyde-releasers **[26,28].**In addition, non-intentional, technically unavoidable contamination with metals such as lead, cadmium, antimony, arsenic, mercury and aluminum is still detectable in many PCPs **[29].**Following dermal uptake, inhalation or ingestion, compounds may reduce reproductive function through either direct damage to testicular tissue or via endocrine disruption **[26,30,31].**The mechanisms for disruption include weak agonism or antagonism to estrogen or androgen receptor activity evident through in vitro and in vivo testing **[26].**Though extensive animal studies warn of potential toxicity, knowledge of adverse reproductive effects of PCPs in humans is lacking **[26].**

Current PCP regulations are widely based on assessment of single product exposures **[32].**In reality, consumers often co-use multiple products. Hence, their aggregated exposure may exceed the intended margins of safety for numerous chemicals in the products **[33].**Adding to this complexity, consumer habits vary according to age, sex, ethnicity, educational level, skin type, geographical and cultural settings**[34,35,36].**As the boundaries of beauty and gender are constantly challenged by modern society, male acceptance of and adaptation to routines previously practiced exclusively by women are rising **[26].**Refining our knowledge of the actual use of PCPs in young men may, therefore, improve our options for qualified risk assessment and protection through regulation. Our aims in this study were, therefore, to assess the extent of use and co-use of PCPs and examine potential associations between aggregated exposure and semen quality in a population of young Danish men. Fragrance and flavor components are often protected trade secrets and, therefore, not declared individually for PCPs **[37].** As fragranced PCPs may contain higher levels of especially endocrine disrupting chemicals (EDCs), we specifically assessed associations for the use of fragranced PCPs **[38,39].**

Cosmetic and marriage age

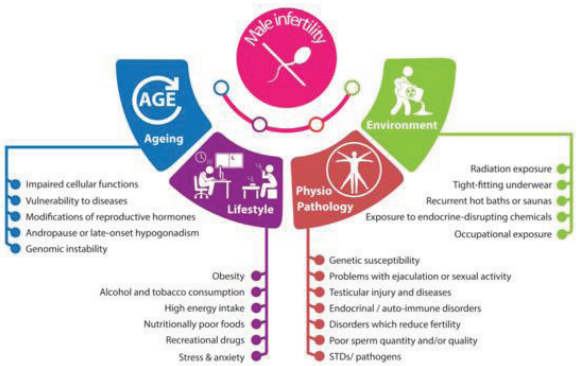
Aging, a complex multifactorial process, progressively impairs cellular function and promotes vulnerability to diseases. It is associated with disturbances in reproductive endocrinology that potentially causes andropause or late-onset hypogonadism in males. However, the molecular underlying mechanisms impacting semen quality and common test parameters are poorly understood. Although the global mean paternal age is 21 years, the most widely referenced cutoff age for advanced paternal aging or andropause is 40 years. Andropause increases infertility risk and affects semen volume and both sperm morphology and motility. However, the effects of aging on sperm concentration remain unclear.

The multiple facets affecting male infertility (**Figure1**), deeply embedded in genome–lifestyle–environment crosstalk, complicate accurate diagnostics development and effective therapeutics. The increasing rates of male infertility highlight the need for integrative approaches that address its complex etiology.

People these days give prime importance in improving their health and appearance. They areconscious of health on one side and on the other side their life style has been changed. Theycan't resist themselves from this behaviour and then opt for aerobics and health clubs. In additionto this they use cosmetics to increase acceptance in the society by presenting themselves well,which in turn adds to their self-esteem and satisfaction. Advertising and technology creates incredible impact on public in portraying the so called standards of beauty. Increasing acceptancefor cosmetics and its usage in the society can be the outcome of the perfect blend between the demographic variables such as age, gender, and marital status of individuals. Men who have been exposed to common chemicals known as parabens have lower testosterone levels and more sperm that

are abnormally shaped and slow moving, according to a study that suggests these ingredients may contribute to infertility. In men, we have data to show that bisphenol-A (BPA) likely diminishes sperm quality. You've heard of BPA by now, it's a compound in plastics – we're exposed through contact with food and beverages. The most conclusive data is still in animals models, where they're able to establish that BPA causes these negative effects, it's not just a hypothesis. Studies in rat models show that exposure to BPA decreases sperm count and motility, increases DNA fragmentation, and lowers testosterone, FSH, LH, GnRH in males **[40].**In a study on humans, 218 men "exposed to BPA in the workplace have an increased risk for compromised semen quality compared to men not exposed to BPA. In particular, an increasing urinary BPA level was significantly associated with the decrease of sperm concentration, total sperm count, sperm vitality and motility." **[41].**

A meta-analysis of 14 human studies showed an association between reduced sperm concentration and exposure to phthalates (also found in plastics. We are exposed to phthalates through food, water, and fragrances, primarily) **[42].**



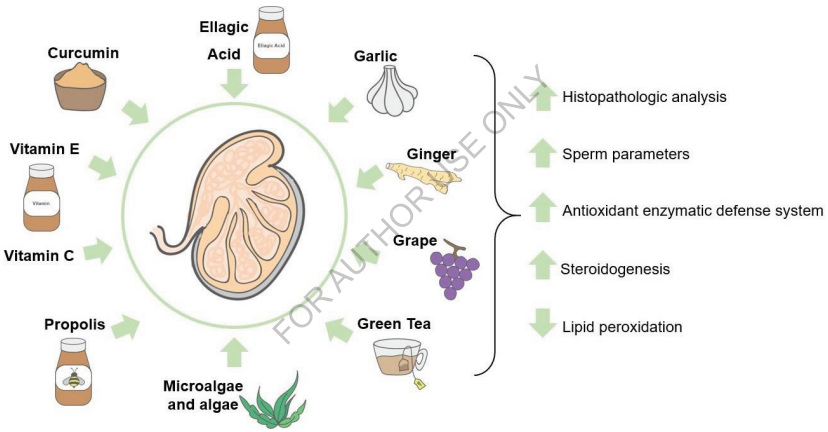
(Figure 1). Multifactorial etiology of male infertility

Random use of medical drugs as cosmetics

The male reproductive system is highly susceptible to noxious influences, such as oxidative stress, inflammation, drugs, and even diseases that can induce germ cell damage and alterations in spermatogenesis. All of these factors, which are caused by actions at the testicular level and/or at the excurrent ducts and accessory glands, significantly affect sperm parameters and male fertility. For this reason, it is of major importance to investigate possible ways to protect the male reproductive system since males are exposed to these toxic factors constantly. For centuries, natural products have been used by humans in folk medicine as therapeutic agents, and because of their beneficial properties for human health, plenty of them have been introduced to the pharmaceutical market as supplementary therapies. The present review aims to compile available information regarding different natural exogenous factors that demonstrate potential useful activity in the male reproductive system **[42].**Exposure to non-persistent chemicals in consumer products is ubiquitous and associated with endocrine-disrupting effects. These effects have been linked to infertility and adverse pregnancy outcomes in some studies and could affect couple fecundability, i.e. the capacity to conceive a pregnancy, quantified as time to pregnancy (TTP).Male infertility is an increasing and serious medical concern, though the mechanism remains poorly understood. Impaired male reproductive function affects approximately half of infertile couples worldwide. Multiple factors related to the environment, genetics, age, and comorbidities have been associated with impaired sperm function. Present-day clinicians rely primarily on standard semen analysis to diagnose male reproductive potential and develop treatment strategies. To address sperm quality assessment bias and enhance analysis accuracy, the World Health

Organization (WHO) has recommended standardized sperm testing; however, conventional diagnostic and therapeutic options for male infertility, including physical examination and semen standard analysis, remain ineffective in relieving the associated social burden. Instead, assisted reproductive techniques are becoming the primary therapeutic approach. In the post-genomic era, multiomics technologies that deeply interrogate the genome, transcriptome, proteome, and/or the epigenome, even at single-cell level, besides the breakthroughs in robotic surgery, stem cell therapy, and big data, offer promises towards solving semen quality deterioration and male factor infertility. This review highlights the complex etiology of male infertility, especially the roles of lifestyle and environmental factors, and discusses advanced technologies/methodologiesused in characterizing its pathophysiology **[43].**Obesity can have a significant impact on male and female fertility. BMI (body mass index) may be a significant factor in fertility, as an increase in BMI in the male by as little as three units can be associated with infertility. Several studies have demonstrated that an increase in BMI is correlated with a decrease in sperm concentration, a decrease in motility and an increase in DNA damage in sperm. A relationship also exists between obesity and erectile dysfunction (ED). ED may be the consequence of the conversion of androgens to estradiol. The enzyme aromatase is responsible for this conversion and is found primarily in adipose tissue. As the number of adipose tissue increases, there is more aromatase available to convert androgens, and serum estradiol levels increase. Other hormones including inhibin B and leptin, may also be affected by obesity. Inhibin B levels have been reported to decrease with increasing weight, which results in decreased Sertoli cells and sperm production. Leptin is a hormone associated with numerous effects including appetite control, inflammation, and decreased insulin secretion,

according to many studies. Obese women have a higher rate of recurrent, early miscarriage compared to non-obese women.Low weight: Obesity is not the only way in which weight can impact fertility. Men who are underweight tend to have lower sperm concentrations than those who are at a normal BMI. For women, being underweight and having extremely low amounts of body fat are associated with ovarian dysfunction and infertility and they have a higher risk for preterm birth. Eating disorders such as anorexia nervosa are also associated with extremely low BMI. Although relatively uncommon, eating disorders can negatively affect menstruation, fertility, and maternal and fetal well-being.



Semen quality, especially sperm concentration and motility, is the most widely accepted diagnostic marker of male infertility. The WHO has stipulated standard operating procedures (SOPs) for sperm parameters' analysis to prevent assessment bias and enhance analysis accuracy. However, certain limitations, including ambiguous threshold values, affect the reliability of semen analysis. Irrespective of the ongoing effort to refine these reference values into more relevant subcategories, such as

subfertile, indeterminate, and fertile groups, the standard approaches still lack accuracy, reproducibility, and therapeutic efficacy. Semen analysis and assays for sperm chromatin integrity are the most widely utilized and best studied adjunctive diagnosticsin male infertility. Sperm DNA fragmentation detects a highlevel of defective spermatozoa. DNA damage is more common in infertile men than fertile men. If sperm count is lessthan 40 million, artificial insemination can be recommended **[44].**In traditional medicine, various herbal plants are used to treatmale infertility. Cardiospermumhelicacabum or "Welpenala"is one such example.The aqueous extract improved spermcount, sperm motility, number of implantations, and viableembryos at 100 and 200 mg/kg dose levels. Similarly, Chineseherbal medicine such as Ginseng roots (Panaxquinquefolius)improves overall fertility; Tribulus fruit (Tribulusterrestris)improves sperm count, morphology, and motility; Maca root(Lepidiummeyenii) improves hormonal balance **[45].**

Endocrine disruptors

Endocrine disrupting chemicals (EDCs) have been known to adversely affect the endocrine system leading to compromised functions of hormones. The presence of these compounds in everyday products such as canned food, water bottles, plastics, cosmetics, fertilizers, kid's toys and many others goods is a greater concern for general population. The persistent and long-term use of EDCs has deleterious effects on human reproductive health by interfering with the synthesis and mechanism of action of sex hormones. Any change during the synthesis or action of the sex hormones may result in abnormal reproductive functions which includes developmental anomalies in the reproductive tract and decline in semen quality. The present paper provides an overview of the EDCs and their possible impact on male reproductive health with major focus on semen quality which leads to male infertility **[46].**

The endocrine system maintains homeostasis of the bodily systems through hormones that can travel long distances in the body and often have amplified effects. Endocrine disrupting chemicals (EDCs) are the substances which change the course of endocrine systems in a way that adversely affects the organism itself or its progeny **[47].**These chemicals can be found in a variety of everyday products and goods, such as in foods, water, plastics, shampoos, clothes, toothpastes, soaps, fertilizers, paper, textiles, carpets, utensils, bedding, toy, cosmetics, deodorant, etc. **[48-49].**Because of the use of EDCs in several consumer goods and personal care products, humans are exposed to the harmful effects of these substances in a variety of ways which include ingestion, germination, inhalation, and dermal contact. Hence, EDCs call for greater attention because of their increasing utility in daily products and possible correlation with compromised male reproductive health. The endocrine

system is particularly important for male reproductive development because androgens (such as testosterone) promote the maturation of male secondary characteristics as well as the process of spermatogenesis. Male reproductive health- specifically sperm count and testosterone-have been declining **[50,51].**, which is correlated with an increase in a variety of EDCs, such as perfluoroalkyl compounds **[48].**Regional differences have also been reported in urban versus rural areas showing a statistical correlation between poor semen quality and higher levels of EDCs found in pesticides, such as alachlor, diazinon, atrazine, metolachlor, and 2,4-dichlorophenoxyacetic acid **[52].**Such evidence linking the increasing prevalence of EDCs to declining semen quality and male reproductive health calls attention to the detrimental effects of EDCs.

We present a schema of the effects of EDCs on couple fecundability in **(Figure2**). Specifically, consumption, inhalation and/or absorption of these environmental chemicals may directly affect the functioning of the ovaries and testes by disrupting ovulation and oocyte quality as well as spermatogenesis and sperm quality. Endocrine disruption can also occur at the brain level, affecting the hypothalamus–pituitary (HP)–gonadal, HP–adrenal and/or HP–thyroid axes, resulting in immune–endocrine–metabolome–microbiome–epigenome interactions that may impact not only gonadal function and gametes but also endometrial receptivity and other aspects of biological aging, thereby reducing fecundability and increasing TTP.

Phthalates' interference with cholesterol in Leydig cells poses a major issue. StAR helps in the transport of cholesterol to Leydig cell mitochondria. High levels of MEHP decrease the production of StAR and reduce cholesterol transport to mitochondria, which is a necessary step for testosterone production. MEHP also decreases the production of

p450scc, which converts cholesterol into pregnenolone, an essential step in testosterone synthesis. Furthermore, DBP, another phthalate, decreases fetal plasma cholesterol levels, consequently leading to low fetal testosterone synthesis, which can impair testicular descendance and secondary sexual characters**.**The most likely effect of endocrine disruption in men may be a reduction in sperm production and also in the sperm's ability to fertilise an egg. In normal human males, the number of sperm produced per ejaculate is normally close to the level required for fertility. Thus, even a small reduction in daily sperm production can lead to infertility. Sperm production by the average man in western countries, including the U.S., today is reported by some to be half of what it was in 1940. One report indicates that average sperm count has declined 42% and average volume of semen diminished by 20%. Another report showed an increase in infertility in the last twenty years concluding that one in twenty men are either subfertile or infertile. However, these may be an over simplification and later reports have questioned these kind of conclusions**[53].**

In recent years, a growing incidence of EDs has led the scientific community to show how these substances may affect the male reproductive system. The in vitro evaluation of steroidogenesis and spermatogenesis are necessary for the screening potential of reproductive toxicants such as alkylphenols, bisphenols, phthalates, and many others. The mechanism of their negative effect is diverse but one important endpoint is reduced processes, essential for normal reproductive functions. This review has demonstrated that certain groups of EDs may directly or indirectly interfere with the biosynthesis of steroid hormones and spermatogenesis via different mechanisms of action. Dysfunction of these processes may cause incomplete masculinization, suppressed libido,

reduced steroidogenic capacity, develop various malformations in spermatozoa, and subsequently totally inhibit the reproductive potential of humans and animals. It must be noted that further studies are required to understand the effects of EDs on male reproductive functions and their contributions to male sub- or infertility **[54].**

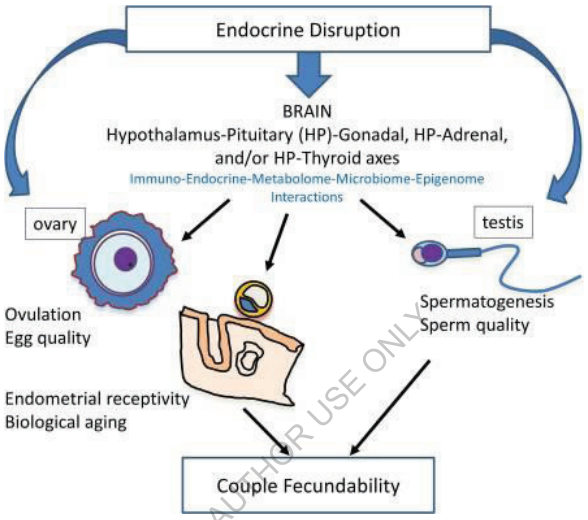


Figure 2: The effects of endocrine-disrupting chemicals (EDCs) on couple fecundability.

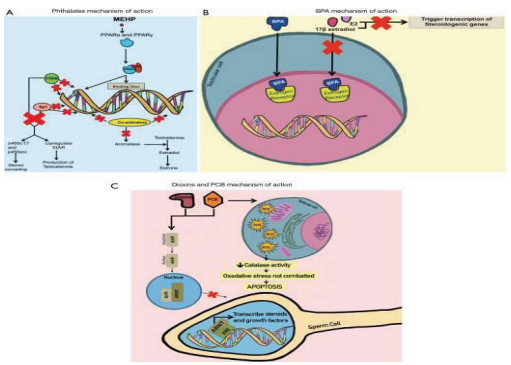


Figure 3: EDCs' mechanisms of action during leading to decrease semen quality.

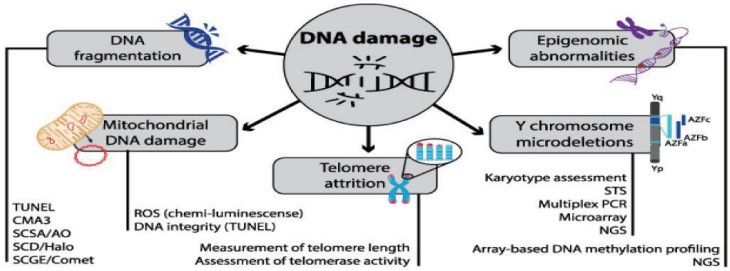


Figure 4. Different types of DNA damage and their possible methods of assessment.

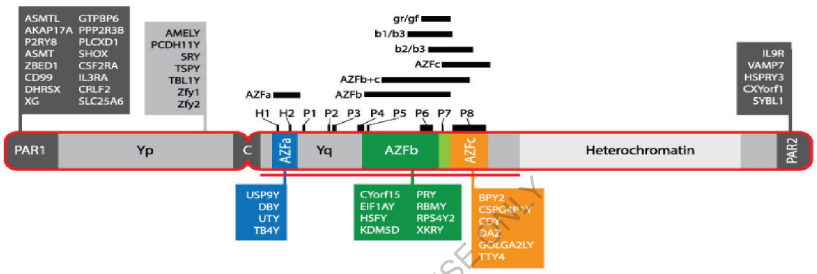


Figure 5. Structure and genes of the Y chromosome. Genes of each region are listed in a color-coded box with corresponding segments.

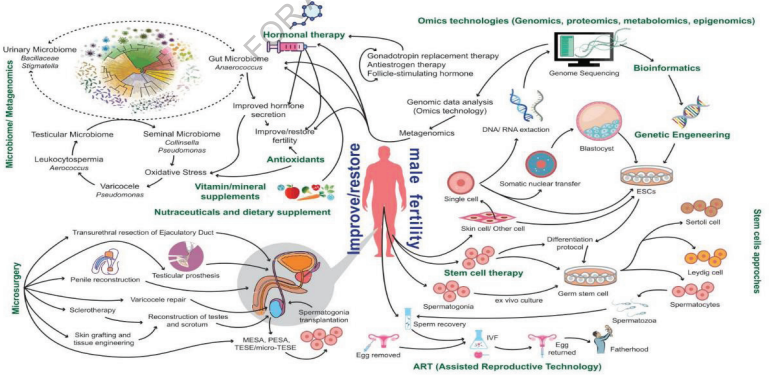


Figure 6. An overview of current advanced approaches to assess and restore male fertility.

Male infertility in Africa

Infertility is a worldwide public health agenda affecting the personal, social, and economic life of an individual and the family as a whole. The difference in terms of definition, diagnostic cut points, study design, and source population make performing a meta-analysis on infertility difficult. The prevalence, classification, and causes of infertility are reported in population-based studies, demographic and health survey report or institution-based studies. Each method has its own advantages and disadvantages.The etiologic sources of infertility can be of either the man or the woman or both. In developing countries, most of the causes are attributed to infection. The majority of African women infertility is due to infectious causes and about 46% of Sub-Sahara African men have infertility related to sexually transmitted diseases.In many African countries, the success of marriage overlies on the ability of a woman to bear children. Being infertile results in a serious psychological trauma and social stigma. In some cases, it may end up with social disgrace and exclusion, verbal and physical abuse, and marriage violence and breakup. Especially for women, infertility significantly reduces their quality of life, expose for multiple sexual partners, sexually transmitted diseases, increased sexual dysfunction, and poor kinship. Therefore, it is a real personal, social, and public health issue, mainly in developing countries **[55].**Although infertility is a global issue, the majority of its causes are reported from the third world nations. It is a practical concern for Africans due to the high social stigma. The magnitude of infertility is reported worldwide differently. The infertility rate ranges from 5–30% as reported for different countries **[56].**

Infertility in the male, therefore, refers to the inability of a man to impregnate a woman after 12 months of regular and unprotected sexual

intercourse. That is if the woman has no gynecological problems. The World Health Organization in 1991 estimated that, 8–12% of couples worldwide experienced some forms of infertility during their reproductive lives, thus affecting 50–80 million couples with 20–35 million in Africa **[57].**Infertility is a worldwide problem, and according to Sharlip et al, it affects 15% of couples that have unprotected intercourse **[58].**Although this statistic is commonly cited, it is an amalgamation of numbers taken from around the world and thus does not reflect rates in specific countries and regions. On a global scale, accurate information regarding rates of male infertility is acutely lacking, and has not been accurately reported.Calculating regionally based male infertility rates is challenging for a number of reasons. First, population surveys generally interview couples or female partners of a couple who have unprotected intercourse and wish to have children. This is a very specific population. As such, data from a significant number of infertile individuals is never included, which may bias the data.Second, unlike female infertility, male infertility is not well reported in general but especially in countries where cultural differences and patriarchal societies may prevent accurate statistics from being collected and compiled. For example, in Northern Africa and Middle East, the female partner is often blamed for infertility. Men, therefore, do not usually agree to undergo fertility evaluation, resulting in underreporting of male infertility. Furthermore, polygamy is a common practice in many cultures **[59].**One of the reasons for polygamy is to overcome infertility and increase the probability of having children. Additionally, in some African countries, the tradition of "Chiramu" allows an infertile male to bring in a brother or a relative to impregnate his wife **[59].**In this way, the man retains his masculine identity and status in his community's eyes.A third challenge stems from the fact that male infertility has never been defined as a disease, which has resulted in

sparse statistics. Additionally, demographic and clinical studies vary in epidemiological definition of infertility. While many clinical studies have examined infertility over the course of a year, several demographic studies examine infertility over a five-year projection **[60].**Finally, while some studies only examine females, others only examine the men presenting to infertility clinics, which are generally small groups who are not representative of the larger population of infertile men.Without accurate, region-specific data, it is not possible to identify and comprehensively treat infertile men. Therefore, to bridge this gap in knowledge, we have consolidated current data and, where recent information is lacking, estimated rates of male infertility using pre-existing data on female infertility in areas around the world. We focused especially on North America, Latin America and the Caribbean, North Africa and the Middle East, Sub-Saharan Africa, Europe, Eastern Europe, Central Asia, Eastern Asia, the Pacific, and Australia. The developing world has much less data available, which is why the above regions were selected.

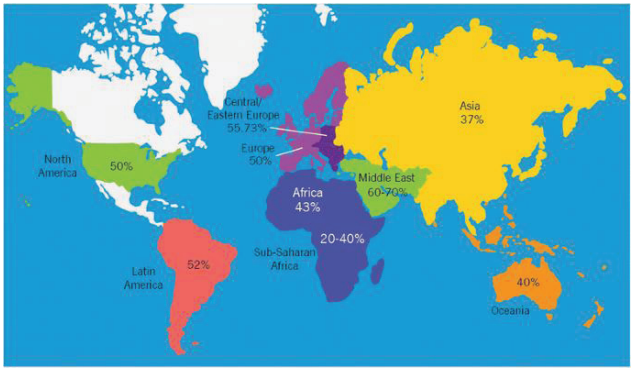


Figure 7. demonstrates rates of infertility cases in each region studied (North America, Latin America, Africa, Europe, Central/Eastern Europe, Middle East, Asia, and Oceania) due to male factor involvement.

The rates in North Africa, Sub-Saharan Africa, and Eastern Europe are close to some of the higher percentages of male infertility estimated worldwide **[61].**With the discovery that male infertility is most prevalent throughout this region, this may be where marketing for assisted reproductive therapy, treatment for infection, and efforts for WHO research can be concentrated. The highest numbers relate to a region known as the "African Infertility Belt," which stretches east to west across central Africa from Gabon to the United Republic of Tanzania **[62].**This region of the world has very high rates of infertility in women, and as men are involved in up to 43% of the problem, the argument follows that male infertility is also high in this region. Male factor contribution to infertility is also extremely high in the close geographical region of the Middle East **[63].**We also noticed that primary infertility rates were much lower than secondary infertility. This may result from the high amount of child marriage and young pregnancy occurring in developing countries, and the later development of sexually transmitted diseases (STDs) and pelvic infections **[64].**However, these numbers are of questionable significance due to the scant nature of their collection. Additionally, the population of sub-saharan Africa grows yearly. This does not imply that the rates of male infertility may not be high, but rather that the population may be growing in other ways. Typically, in regions of Africa and other societies, the male is seen as the dominant individual in both the community and the family structure. Therefore, men, especially in Africa and the Middle East do not report their infertility, as they believe it is emasculating to be unable to impregnate a woman. As a result of this, the men in these societies especially tend to blame females for the lack of child and do not get help.The "African Infertility Belt" also has high rates of STDs such as *N. gonnorrhoeae* and *C. trachomatis,* which may have some correlation and relationship with

the high rates of infertility in this region of the world. Collet and co-workers discovered that a tubal factor was present in 82.8% of females presenting to infertility clinics and frequently positive endocervical cultures for N. gonorrhoeae and C. trachomatis **[65].**Additional limitations of any epidemiological study regarding infertility and sexual activity include that the quality of data varies from very poor to very good. Reproductive information is private and couples may not be inclined to be truthful in surveys **[66].** Many men may not be willing to participate in semen studies **[66].** Another limitation included the difference between one-year infertility rates and the five-year infertility rates reported by Mascarenhas et al. This difference in rates over a five-year projection may be due to the fact that over five years, the cases of infertility may either resolve, these couples may have found an alternative to the traditional conception or the study could have suffered from attrition. A major limitation of this study is that much of our data are based on WHO studies from the 1900s and that the definition of a malefactor in these studies was not well defined. Male factor infertility was based on both abnormal semen analyses and on associated factors like varicoceles and urogenital infections, and STDs in men with normal semen analyses. In countries with an accurate registration of diseases, the prevalence of both male infertility and male factor leading to couples' infertility is lower than that in developing countries. Rates from developing countries are more likely due to a problem with the definition of male infertility and a lack of accurate reporting rather than a true reflection of male infertility in those regions. There is a decrease in sperm concentration as men age: 90% of seminiferous tubules in men in their 20s and 30s contain spermatids, whereas men in their 40s and 50s have spermatids in 50% of their seminiferous tubules, and only 10% of seminiferous tubules from men aged > 80 years contain spermatids. In a

random international sample of 11,548 men confirmed to be biological fathers by DNA paternity testing, the oldest father was found to be 66 years old at the birth of his child; the ratio of DNA-confirmed versus DNA-rejected paternity tests around that age is in agreement with the notion of general male infertility above age 65–66 [67].Globally, infertility affects 15% of couples at reproductive age, with male infertility accounting for up to half of all cases. The age-standardized prevalence of male infertility reportedly increases by 0.3% annually. However, the increased male factor infertility rate was geographically inconsistent and ranged from 20–70%. Male infertility rates may be underestimated because of cultural differences, social dilemmas, and patriarchy preventing accurate sampling and analysis. In men, it can also trigger anxiety about the stigma of hegemonic masculinity.It is particularly challenging in pronatalist societies, where both virility and fertility are considered hallmarks of manhood, but also in Western societies, where male infertility and impotence are conflated. Paradoxically, assisted reproduction technologies (ARTs) can create additional layers of stigma and secrecy. Moreover, male infertility is associated with significant psychosocial and marital stress, increased cancer risk, poorer overall health, and decreased life expectancy.Semen quality, especially sperm concentration, and motility, is the most widely accepted diagnostic marker of male infertility. The WHO has stipulated standard operating procedures (SOPs) for sperm parameters analysis. To prevent assessment bias and enhance analysis accuracy. However, certain limitations, including ambiguous threshold values, affect the reliability of semen analysis.

Summary

Semen quality plays a pivotal role in maintaining healthy fertilizing ability of spermatozoa. Male infertility is a rising global problem with an increasing declining in male semen quality among men living in Africa, Europe, North American, and Asia. Though the sperm acquire proactive mechanisms during spermatogenesis and their epididymalmaturation, they still remain viable for toxic insult. Declining semen quality is a major contributor to infertility. Studies have postulated that different factors, such as exposureto pesticides, industrial chemicals, heavy metals, obesity, alcoholism, tobacco smoking, sedentary lifestyles, poor nutrient intake,oxidative stress, physiological factors, and geneticfactors can influence male fertility. Routine semen analysis and assays for spermchromatin integrity are the most widely utilized and best studied adjunctive diagnostics in male infertility. Over the years, scientists have developed different treatment options for male infertility. Male infertility with known etiology can be treated successfully, but other causes like genetic factors require pragmatic approaches. Industrial chemicals such as Meta dinitrobenzene and methoxyacetic acid, which are plasticizers, can impair sperm fertilizingability and sperm motility (measured usingcomputer-assistedsemen analysis) at both acute and chronic dose levels.Exposure to industrial chemicals not only degrades male infertility but also can result in DNA fragmentation. To combat infertility, it is essential to optimize lifestyle factorsin order to maximize fertility. Sedentary lifestyle, obesity,smoking, heat exposure, stress, poor nutrition, and harmfulenvironmental toxicants may all adversely affect sperm countand quality. Hence, it is important to be aware of harmfulchemicals, to be more active, and finally, to live a healthylifestyle. Simply put, just simple lifestyle changes can

improvemale fertility. However, in other cases, if natural conception isimpossible, assisted reproduction techniques can overcome theproblem and advanced techniques such as ICSI treatment canbe used. Identifying risk factors to improve the management ofhuman wellness and health throughout standardized analysis,which correlates the accumulation of biotoxins in the seminalfluid with semen quality can be considered in the agenda ofpublic prevention policies. Overall, infertility is not only a personal issue rather a matter of generation. Therefore, health policymakers and the governments should focus on the provision and advancement of infertility clinics and prevention and management of reproductive tract infection and abortion. Unexplained causes of infertility were also reported, this signals to advance our diagnostic modalities.North Africa and East Africa had more primary and secondary infertility respectively. Older and recent studies respectively reported a higher pooled proportion of secondary and primary infertility.While age may not be the most important factor when it comes to male fertility decline, there are other important effects of male age on the health of the pregnancy and the child. There's evidence that the chance of miscarriage increases with paternal age, potentially due to genetic abnormalities in the sperm.Additionally, the child's chances of birth defects, schizophrenia, and autism all increase with their father's age. In one report, offspring of men over 50 were shown to be 2.2 times more likely to have autism than offspring of men under 29. In another, the risk of schizophrenia increased with paternal age, and men over 45 were 2 times more likely to father children with schizophrenia.The mechanism for this affect is not fully understood yet by researchers. It's possible that these increased rates of illness are caused by what experts call "de novo mutations," or a genetic alteration appearing for the first time. However, a 2016 study concluded that de novo mutations are probably a small part of the cause; researchers

posited, instead, that men who are genetically predisposed to psychiatric illnesses may also be more likely to delay fatherhood. An additional high-priority area for research is to examine the long-term health outcomes of the children born from men with compromised fertility whatever the nature of the compromising event(s) such as genetics, environmental, iatrogenic, and/or occupational. It is important to identify the most effective educational initiatives that will improve our understanding of male infertility. Finally, it is now high time for the World Health Organization to produce a 6th version of the semen assessment manual. The evidence base for the current (5th version) manual is at least 10 years out of date and a lot has changed since then. It is vital to encompass educating future learners by integrating reproductive health into the school education system. In addition to the prevailing evaluation criteria of infertile males, country-specific or region-specific counselling and treatment modalities should be established.

Treatment depends on the cause of infertility but may include counseling, and fertility treatments, which include in vitro fertilization. According to ESHRE recommendations, couples with an estimated live birth rate of 40% or higher per year are encouraged to continue aiming for a spontaneous pregnancy. Treatment methods for infertility may be grouped as medical or complementary and alternative treatments. Some methods may be used in concert with other methods. Drugs used for both women and men include clomiphene citrate, human menopausal gonadotropin (hMG), follicle-stimulating hormone (FSH), human chorionic gonadotropin (hCG), gonadotropin-releasing hormone (GnRH) analogs, aromatase inhibitors, and metformin. Medical treatment of infertility generally involves the use of fertility medication, medical devices, surgery, or a combination of the following. If the sperm is of

good quality and the mechanics of the woman's reproductive structures are good (patent fallopian tubes, no adhesions or scarring), a course of ovulation induction may be used. The physician or WHNP may also suggest using a conception cap cervical cap, which the patient uses at home by placing the sperm inside the cap and putting the conception device on the cervix, or intrauterine insemination (IUI), in which the doctor or WHNP introduces sperm into the uterus during ovulation, via a catheter. In these methods, fertilization occurs inside the body. If conservative medical treatments fail to achieve a full-term pregnancy, the physician or WHNP may suggest the patient undergo in vitro fertilization (IVF). IVF and related techniques (ICSI, ZIFT, GIFT) are called assisted reproductive technology (ART) techniques. ART techniques generally start with stimulating the ovaries to increase egg production. After stimulation, the physician surgically extracts one or more eggs from the ovary, and unites them with sperm in a laboratory setting, with the intent of producing one or more embryos. Fertilization takes place outside the body, and the fertilized egg is reinserted into the woman's reproductive tract, in a procedure called embryo transfer. Other medical techniques are e.g. tuboplasty, assisted hatching, and preimplantation genetic diagnosis.

Lifestyle encompasses all behavioral factors affecting health, including diet, exercise, and the consumption of harmful substances (e.g., tobacco and alcohol). Diet-induced obesity, for example, can affect male fertility by altering sleep and sexual behavior, hormonal profiles, scrotal temperatures, and semen parameters; the risk of a non-viable pregnancy is high for obese men. Moreover, the risk of azoospermia sperm is high in both underweight and overweight men compared to normal-weight counterparts. Decreased sex-hormone-binding globulin levels have been reported in obese men, resulting in hyperinsulinemia and elevated total

estradiol levels; contrastingly, weight-loss programs have been associated with reduced cellular DNA damage, increased total motile sperm count, and improved semen morphology. Nutritional habits, alcohol and tobacco consumption, recreational drug usage, and psychological stress affect fertility. Through gut microbiota composition alteration, a high-fat diet can induce intestinal dysbiosis and impede fertility through elevated blood endotoxin levels, inflammation, epididymitis, and dysregulated gene expression in the testes. High-energy and nutritionally poor processed foods have been associated with asthenozoospermia risk, whereas a balanced diet (e.g., Mediterranean diet) is associated with better sperm quality. Lifestyle modifications, particularly in the quality of food consumed, are recommended besides common prescriptions to treat poor semen quality.

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