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THE IMPACT OF LIFESTYLE ON MALE FERTILITY - REVIEW

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ABSTRACT

Introduction and aim of study: The World Health Organization defines infertility as the disease of reproductive system defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse. It is estimated that 30% of infertility is due to the male factor, and 25% to the coexistence of the male and female factors. The purpose of this review study was to provide an overview of lifestyle risk factors for male infertility and their impact on the organism.

Materials and methods: The authors conducted an extensive review of articles available in PubMed, Google Scholar, UpToDate, Science Direct, and Cochrane databases. The keywords infertility, lifestyle, testosterone, men were the basis of the review.

Results: Leading an unhealthy lifestyle can significantly impact male fertility. The function of the reproductive system can be affected by inadequate body weight, as well as leading a sedentary lifestyle, using stimulants or anabolic steroids. They not only affect the endocrine system by disrupting steroidogenesis and spermatogenesis but may also directly damage

sperm. This leads to impaired semen quality and increases the risk of recurrent pregnancy loss and poor pregnancy outcomes.

Conclusion: Lifestyle significantly affects male fertility. A balanced diet, adequate physical activity and avoidance of stimulants can all have a beneficial effect.

Keywords: infertility, lifestyle, testosterone, men

BACKGROUND

The World Health Organization (WHO) defines infertility as the inability to conceive after 12 months of regular, unprotected intercourse. [1,2] Globally, this issue affects 10-15% of couples. Faraj et al. in their study estimated that 35% of infertility is due to female factors, 30% to male factors, 20% to both male and female factors, and in 15% the cause remains unknown. However, the authors presented the view that diseases affecting male fertility are underdiagnosed and undertreated and that male infertility statistics are underestimated, particularly in patriarchal regions and societies. [3,4] Based on studies carried out over the last few decades, a downward trend or stabilization at low levels of semen parameters has been noted. [5]. The decrease in semen quality in men is thought to be linked to environmental and lifestyle causes. [6] The aim of this study is to review the available literature on the impact of lifestyle on male infertility.

MATERIALS AND METHODS

The authors searched PubMed, Google Scholar, UpToDate, Science Direct, and the Cochrane Library to review the available medical literature on the impact of lifestyle on male infertility. The following keywords: *infertility, lifestyle, testosterone, men* were used to search for papers. The scientific papers found were published between 2000 and 2024. After analyzing the abstracts, 68 scientific papers were selected and read.

DIAGNOSTIC METHODS

In the diagnostic process of male infertility, it is important to take a medical history, conduct a physical examination and perform laboratory tests including semen analysis. [7]

Taking a medical history should focus on identifying potential causes of infertility. Puberty, past paternity, familiarity with infertility and miscarriage, recent genitourinary infections, libido disorders, and erectile dysfunction should be specified. Patients should be also asked about chronic diseases, past surgeries and taken medications that may affect fertility. A summary of lifestyle including physical activity, intake of anabolic steroids, diet, smoking, excess alcohol, or drug use is equally important. [8,9]

The physical examination should include an assessment of hair distribution, body proportions, voice, and gynecomastia. The most important element is the testicular examination. It should include an evaluation of the location of urethral meatus, measurement of testicular volume by Prader orchidometer, palpation of the testes, epididymides and scrotum. A digital rectal exam is also relevant. [9]

The leading diagnostic test for male infertility is semen analysis. The WHO, in order to standardize testing procedures, published the 1st edition of the Laboratory Manual for the Examination and Processing of Human Semen in 1980. Over time, the standards for semen analysis have changed and required revisions, resulting in the release of new editions of the manual. The Table 1 compares the reference ranges for semen analysis contained in the 5th (from 2010) and 6th (from 2021) edition of the manual. The 6th edition is the latest and currently in effect. [8,10,11,12]

REFERENCE RANGE FOR SEMEN ANALYSIS

PARAMETER	REFERENCE RANGE (2010)	REFERENCE RANGE (2021)
SEMEN VOLUME	≥1,5 ml	≥1,4 ml
SPERM CONCENTRATION	≥15 milion sperm/ml	≥16 milion sperm/ml
TOTAL SPERM COUNT	≥39 million sperm/ ejaculate	≥39 million sperm/ ejaculate
TOTAL SPERM MOTILITY	≥40% motile sperm	≥42% motile sperm
PROGRESSIVE SPERM MOTILITY	≥32% progressively motile sperm	≥30 % progressively motile sperm
SPERM MORPHOLOGY	≥4% morphologycally normal sperm	≥4% morphologycally normal sperm
SPERM VITALITY	≥58%	≥54%

Table 1. Comparison of reference range for semen analysis from 2010 and 2021. [8,10,11,12]

During the basic examination, semen is evaluated macroscopically and microscopically. At first, the ejaculate volume is assessed. This is followed by a macroscopic evaluation of color, liquefaction, viscosity, presence of odor, and pH. Later, semen is examined under a microscope. It is possible to extend semen analysis with a number of advanced procedures depending on the circumstances. [10] The examination reflects the production of spermatozoa in the testes, the patency of the duct system and the glandular secretory activity.[13] Semen is evaluated by qualified laboratory technicians. There have been ongoing efforts to improve computer-assisted semen analysis programs and home testing kits. [14]

Genetic testing is also used in diagnostics. It allows to diagnose of infertility caused by Y chromosome microdeletions and cystic fibrosis, among others. [8,15]

OBESITY

Overweight and obesity are classified as civilization diseases. It is estimated that more than 2 billion people worldwide have a BMI>25kg/m^2 and about 671 million >30kg/m^2. [16] The impact of obesity on male reproductive health is a complex issue. It may result in endocrine and inflammatory disorders, among others.

One of the enzymes produced by adipocytes is aromatase, which induces the peripheral conversion of testosterone to estradiol. [17,18,19] Its overexpression results in an increase in estrogen concentrations relative to testosterone, and consequently causes down-regulation of KISS1 neurons. Under physiological conditions, they release kisspeptin, which is responsible for stimulating the pulsatile release of gonadotropin-releasing hormone (GnRH). [20] Consequently, reduced levels of kisspeptin result in decreased concentration of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Their deficiency leads to limited spermatogenesis and steroidogenesis. [17]

Adipose tissue is also a source of leptin, a hormone that plays a significant role in satiety regulation. Under physiological conditions, it can act via receptors on KISS1 neurons to stimulate GnRH release from the hypothalamus. In obese individuals, its levels are chronically elevated, resulting in leptin-resistance. This leads to suppression of KISS1 neurons, thereby inhibiting GnRH release. [17,21] The impact of aromatase and leptin

hyperactivity on the hypothalamic-pituitary-gonadal axis is presented in Figure 1. [17,19,20,21]

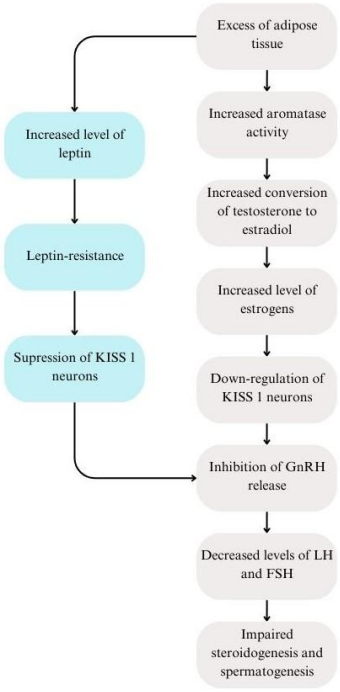

Figure 1. Aromatase and leptin mechanisms of action on the hypothalamic-pituitary-gonadal axis [17,19,20,21]

Obesity is often accompanied by insulin resistance and hyperinsulinemia causing a decrease in blood levels of sex hormone binding globulin (SHBG). This is a protein responsible for the bioavailability of sex steroids and its decreased concentration impairs normal spermatogenesis. [17,22]

An important mechanism contributing to male infertility is oxidative stress, which can result from increased fatty acid oxidation or chronic inflammation. [17,23] Spermatozoa are vulnerable to oxidative stress, and oxidative DNA damage due to their limited repair capacity and antioxidant defence. The sperm membrane may be damaged leading to reduced motility and impaired fusion with the oocyte. Mitochondrial DNA, nuclear DNA and the epigenome may also be affected. [24,25] These damages lead to an increased risk of infertility, recurrent

pregnancy loss, and poor pregnancy outcomes. The risk of congenital malformations, neuropsychiatric disorders, and childhood cancers in the offspring is also elevated. [24]

A significant aspect in obese patients is sexual dysfunction, which is thought to be the result of coexisting inflammation and reduced testosterone levels. Pro-inflammatory factors cause vascular endothelial dysfunction, resulting in erectile dysfunction. [19]

The influence of adipose tissue accumulated in areas of the scrotum, thighs and lower abdomen cannot be overlooked either. It causes elevated testicular temperature negatively affecting testosterone production and spermatogenesis. [17,19,23]

The variety of alterations in the bodies of obese men is reflected in the quality of semen. Seminological examination of this group of patients shows a higher incidence of oligozoospermia and azoospermia, decreased total sperm count, impaired sperm motility and morphology. Reduced ejaculate volume is also a significant abnormality. [17,26]

UNDERWEIGHT

Underweight is defined as having a body mass index (BMI) less than 18.5 kg/m2, according to the criteria. In developed countries, being underweight is usually related to an individual's decision on food restriction, while in developing countries it is the result of poverty and limited nutritional resources. As a result, in some countries such as Gambia, Nigeria, and Ethiopia, the infertility problem is greater and affects up to 20% of couples. [27] Many studies investigating the relationship between underweight and female fertility have been designed and conducted in the available literature. In contrast, comparatively, few studies are focusing on the effect of low body weight on fertility in men. Eating disorders (ED) are a relatively common cause of infertility in women. In general, EDs more often affect the female gender, but it should not be forgotten that male patients are also affected. Most eating disorders instruments have been researched and developed for women, which means that EDs may be underdiagnosed and under-treated in men. [28] According to statistics, over a lifetime according to DSM-5 criteria, anorexia is diagnosed in 0.1-0.3% of men, bulimia in 0.1-0.2% of men, binge eating disorder in 0.3-0.7%, other specified feeding or eating disorders by 0.2-0.3% of men, and unspecified feeding or eating disorders 0-1.6% of men.[29]

A meta-analysis of 13 studies by Dan Guo et al. proved the existence of an effect of underweight on semen quality. Low BMI was associated with reduced total sperm count and reduced semen volume. However, the relationship between insufficient body weight and sperm concentration and motility has not been proven. [30,31,32] The mechanism of this phenomenon remains unclear. According to some hypotheses, malnutrition may disrupt hormonal balance impairing reproductive capacity. [30]

On the other hand, there are also studies with different conclusions. A meta-analysis by A.A MacDonald et al. of 31 studies from 2010 showed no correlation between body mass index and total sperm count and sperm concetration, while a meta-analysis of 21 studies by N.Sermondade from 2013 found that sperm concetration does not depend on the patient's BMI. [33,34] This highlights the fact that further studies with large numbers of patients are needed to determine a more precise relationship between underweight and male infertility.

PHYSICAL ACTIVITY

Many factors affecting male fertility have been identified. Undoubtedly, a sedentary lifestyle harms men's reproductive capacity. It has been shown that the spermatozoa of men who do not participate in sports have lower motility compared to the spermatozoa of physically active patients. The differences in hormone levels were also statistically significant - LH, FSH, and testosterone levels were lower in patients with a sedentary lifestyle. [35] However, different studies seemed to give mutually exclusive conclusions. In general, some types of exercise positively correlate with an increase in pregnancy rates, but on the other hand, too much exercise may worsen fertility in men. [36]

It is believed that acute submaximal and maximal exercise probably causes a rapid increase in testosterone concentration, which adaptively increases physical performance. However, in patients undergoing chronic exercise (especially endurance training), the function of the hypothalamic-pituitary-gonadal (HPG) axis may be impaired, resulting in significant reductions in free and total testosterone concentrations. Hackney et al. have termed this phenomenon " The exercise-hypogonadal male condition’’. In response to the mechanisms mentioned, some authors suggest monitoring androgen levels in some athletes.[37,38]

Potentially, daily activities and popular forms of active leisure can negatively affect male fertility. Several studies have shown the negative impact of cycling. Male cyclists who cycled

for more than 1.5 hours a week had 34% lower sperm concentrations. In addition, cycling forces excessive pressure on the perineal region, which can cause pressure on the pudendal nerve and internal pudendal artery, resulting in nerve compression and transient oxygen deficiency in the penile tissues. [39] The mechanisms described may lead to erectile dysfunction. Nevertheless, a large study on almost 6,000 patients did not confirm the association between cycling and erectile dysfunction. [40]

In addition, it has been reported that men who play basketball, handball, volleyball, and soccer are more likely to be diagnosed with varicoceles, which are an important cause of male infertility. A potential mechanism is that these sports cause the body to move against gravity, which promotes the development of varicoceles. Furthermore, Radojevic et al. proved that six months' abstinence from all sporting activity, results in a significantly statistical improvement in semen parameters such as sperm concentration and sperm motility. [41,42]

In the available literature, randomized controlled trials have been conducted which have proven the positive effect of combined aerobic and resistance training (CET), resistance training (RT), moderate-intensity continuous training (MICT), high-intensity interval training (HIIT) and high-intensity continuous training (HICT) on men's reproductive health, including semen parameters, pregnancy rates, and live births. [43] A systematic review by B.H.Maleki et al. showed that among these forms of exercise, combined aerobic and resistance training (CET) has the most beneficial effect on male fertility. Unfortunately, most studies were conducted on small groups, so the authors agree that further research is necessary.[44] Zujie Xu et al. in their study demonstrated that 8 weeks of moderate-intensity continuous training MICT and high-intensity interval training HIIT protects against apoptotic changes, oxidative changes induced by a high-fat diet, leading to improving testicular function on obese mice.[45]

Physical activity is a pillar of a healthy lifestyle - an economical, highly effective method of prevention and treatment of many diseases (cardiovascular, metabolic, neurological), while however, too much physical exertion can impair reproductive function in men. [46]

ANABOLIC STEROIDS

Androgenic anabolic steroids (AAS) are mainly used to increase muscle mass in individuals who are undergoing training. Testosterone, with its anabolic effects, promotes protein synthesis and inhibits protein breakdown. The estimated prevalence of AAS use throughout

life is 3-4.2%, but it increases to 15-30% among gym-goers. [47] The AAS group includes numerous substances that mainly replicate the effects of testosterone, such as testosterone esters, synthetic androgens, as well as other groups of drugs with diverse mechanisms of action.[48] Using anabolic-androgenic steroids (AASs) has serious health consequences, including cardiovascular, metabolic, hematologic, and endocrine issues. It's important to note that AAS therapy is associated with increased hospitalization rates and threefold higher mortality compared to the control group. [49]

In the context of reproduction, AAS cause suppression of the HPG axis through inhibition of the pulasatile release of gonadoliberins, followed by a decrease in LH and FSH. The changes described lead to a reduction in intratesticular testosterone and hypogonadotropic hypogonadism, with consequent infertility. [50,51] In their meta-analysis, P.M.Mulawakar et al. reported that the problem of infertility among men using AAS affects 11-18% of patients. In addition, erectile dysfunction occurs in more than 10% of patients taking AAS. Patients use various methods, such as washout periods and pharmaceuticals - such as anti-estrogens - to prevent negative effects on fertility. [48] Adequate intratesticular testosterone concentrations are essential for proper spermatogenesis. in addition, FSH and testosterone have a significant effect on sperm morphology and sperm concentration. [52] The use of anabolic steroids results in reduced testicular volume, sperm concentration, and motility. The effect of ASS may vary depending on individual predispositions - in younger patients, the axis usually tends to return to normal functioning more quickly after discontinuing AAS. [53] In the case of spermatogenesis, this period is usually around 6-12 months, while there are also reports in the available literature of prolonged recovery times of up to 3 years. [54]

CIGARETTE SMOKING

It is estimated that in 2020, 36.7% of men worldwide used tobacco products. [55] This puts male fertility at real risk, as cigarette smoking contributes to its disruption by affecting the organism through multiple mechanisms.

Heavy metals contained in cigarettes, such as arsenic, cadmium, and lead are found to have mutagenic properties. They do not significantly affect sperm volume, concentration and motility. However, they can lead to sperm aneuploidies and consequently to habitual abortion and fetal developmental disorders. [56,57]

Nicotine disturbs the function of prostate, seminal vesicle, and urethral glands. In addition, it adversely affects oxygen utilization by the mitochondria, impairs spermatogenesis and causes ultrastructural abnormalities of the tail region. [58]

The mechanism resulting in changes in sperm quality is still not entirely understood. It is suspected that increased oxidative stress may be responsible. It damages the genome as well as the epigenome. [59] In addition, defects in microtubule structure and tail alterations have been observed in heavy smokers. Acrosomal reaction and capacitation, which are important processes for fertilization, are also impaired. [56]

In smokers, seminological examination may show a reduction in semen quality, including a decrease in total sperm count, density, motility, sperm morphology, and viability as well as semen volume. [57,58]

Moreover, smoking increases the risk of erectile dysfunction. It causes an elevation of blood pressure which can lead to a reduction in the elasticity of arteries. Furthermore, smoking contributes to the formation of atherosclerotic plaques that can result in arterial stenosis and vascular injury. [60] Superoxide anions produced from cigarette smoke metabolites are also important. They cause a decrease in the level of free nitric oxide, which is responsible for vasodilation in the corpora cavernosa. It is necessary for the occurrence of an erection.[61]

ALCOHOL

According to recent statistics, 2 out of 3 adults in European countries consume alcohol, 11% have alcohol use disorder and 5,9% live with alcohol dependence. [62] This stimulant not only increases the risk of cancers, liver diseases, or neurological disorders, but also male infertility. [63,64,65]

E. Ricci et al. conducted a meta-analysis and systematic review investigating the relationship between alcohol consumption and semen quality. The study found that occasional alcohol intake had no significant effect on semen quality, in contrast to daily alcohol consumption negatively affecting semen morphology and volume. [66] In addition, other studies have found increased mucus and leukocytes in semen. [67]

Alcohol can affect the testes as well as the pituitary gland or hypothalamus. [68] Some studies have shown elevated estradiol levels and reduced serum testosterone concentration. The simultaneous increase in gonadotropin levels suggests a primary testiculopathy. [67] Alcohol can also inhibit 3β-hydroxysteroid dehydrogenase and 17-ketosteroid reductase activity. These are enzymes necessary for testosterone production. In addition, alcohol induces the activity of aromatase, which is responsible for the conversion of testosterone to estradiol and androstendione to estrone. All these mechanisms lead to a decrease in serum testosterone levels. What is more, the alcohol-damaged liver is unable to properly metabolize estrogens. Their elevated serum levels inhibit the release of gonadotropins leading to a further reduction in testosterone levels. [68]

CONCLUSIONS

Infertility is an important issue affecting people of reproductive age. Diagnosis of male infertility is possible, primarily with the help of semen analysis. However, statistics seem to underestimate the prevalence of this problem. The causes of infertility are based on environmental and behavioral factors, which are strongly determined by lifestyle. Obesity, which has grown to a pandemic scale, is a complex mechanism affecting the male reproductive system. Paradoxically, being underweight can also impair male fertility. Due to contradictory results, this issue requires further research. A sedentary lifestyle has a negative effect on fertility, but physical activity does not always have a positive effect. This depends on both the intensity of training and the type of exercise. In men who want to quickly increase muscle mass, anabolic steroids are often used. They not only cause hypogonadotropic hypogonadism, but also increase the risk of cardiovascular, metabolic, haematological, or endocrine diseases. Widespread use of alcohol or cigarettes also significantly contributes to disruption of semen parameters. Studies have described many factors affecting male fertility. However, it is important to conduct further research in this field.

DISCLOSURE

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