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The impact of tobacco on spermatogenesis: Recent findings and reproductive outcomes

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Abstract

The use of tobacco is widespread among men and poses a significant concern for reproductive health. This review synthesizes recent evidence on the impact of cigarette smoking on spermatogenesis, emphasizing its effects on semen quality, reproductive hormone levels, metabolic profile, and sperm DNA fragmentation, which contribute to infertility.

Smoking is associated with increased oxidative stress and DNA fragmentation in sperm, both of which impair fertility outcomes. By examining these adverse effects, this review underscores the importance of addressing tobacco use in male populations to mitigate infertility risks. Insights into the mechanisms of action and broader public health implications are provided.

Keywords: Spermatogenesis; Psychoactive substance; Male infertility; Tobacco use; Reproduction.

1. Introduction

Tobacco use remains a major public health concern worldwide, with significant implications for male reproductive health. Cigarette smoking introduces a range of toxic substances into the body that can disrupt spermatogenesis, the complex process by which sperm cells are produced in the seminiferous tubules of the testes. This process, which relies on hormonal regulation by the hypothalamic-pituitary-gonadal axis, is crucial for male fertility and is highly sensitive to environmental toxins such as those found in tobacco smoke. Key hormones like testosterone, follicle-stimulating hormone (FSH), and luteinizing hormone (LH) support the development of sperm, a process that also depends on the optimal functioning of Sertoli and Leydig cells to nurture germ cells and maintain a stable environment for sperm maturation [1].

One primary mechanism by which tobacco affects spermatogenesis is through oxidative stress. Tobacco smoke introduces harmful reactive oxygen species (ROS) into the reproductive system, which overwhelm the body's antioxidant defenses and damage the cells involved in sperm production. This oxidative stress can lead to DNA fragmentation in sperm, a condition strongly linked to infertility in men [1,2, 3]. Additionally, the presence of mutagenic agents in tobacco smoke can impair Sertoli and Leydig cells, further disrupting the hormonal signals and cellular support essential for healthy sperm development [4].

The DNA fragmentation induced by tobacco not only reduces sperm quality but also poses risks for offspring, as genetic damage in sperm has been associated with adverse reproductive outcomes (Fig.1). This review examines the specific

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mechanisms through which tobacco use impairs spermatogenesis, focusing on the oxidative and mutagenic effects on sperm and reproductive hormones. By synthesizing recent findings, we aim to highlight the need for effective interventions to reduce tobacco consumption among men to counteract its damaging impact on fertility [5, 6].

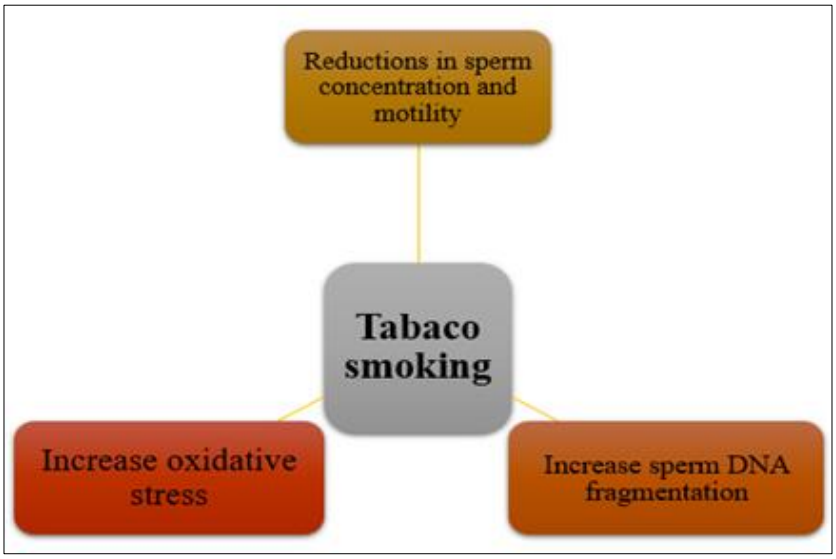

Figure 1 General effects of psychoactive substances on spermatogenesis [4; 3]

2. Current situation of smoking and male fertility

Currently, smoking has become a critical factor in male infertility, as semen quality has been considerably affected. Research highlights that in the last 40 years, semen quality in men has been decreasing by more than 50% [7]. This decline is related to the lifestyles that have been adopted in recent years and smoking is one of them. Semen quality is measured by parameters such as sperm count, motility and morphology, which are negatively affected in male smokers. Exposure to tobacco smoke causes oxidative stress, which damages the germ cells, affecting the ability of the sperm to fertilize the ovum [6].

In the context of Latin America, smoking has become a growing concern because of the socioeconomic factors associated with it, due to stigmatization and limited treatment. According to studies, smoking is not only harmful to the man who consumes it, but also to his offspring, since alterations in sperm DNA increase the probability of genetic diseases and malformations.[4]

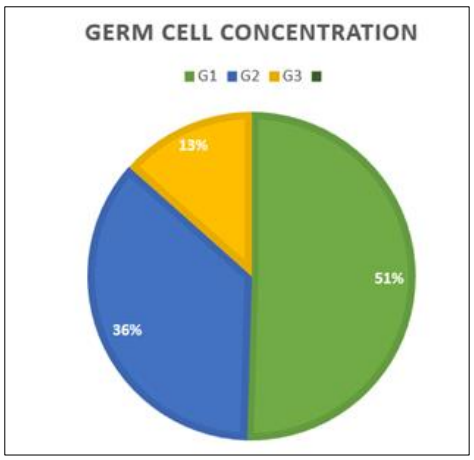

Figure 2 Average sperm concentration (10) 6/ml) in the populations: G1: smokers of more than 20 cig/day, G2: smokers of less than 20 cig/day, G3: non-smokers

Globally, tobacco use has been shown to be a public health problem, and despite growing awareness, the prevalence of male smokers remains high. Many male fertility parameters are negatively impacted by smoking, especially for heavy

smokers. Compared to moderate smokers and non-smokers, heavy smokers had a much decreased average sperm concentration [Fig. 2]. Also, smokers, particularly those who consume large amounts of tobacco, have a significantly reduced percentage of normal sperm morphology [Fig. 3]. The negative effects of tobacco on male reproductive health are confirmed by the significantly lower concentration of germ cells among those who smoke more cigarettes [Fig.4].

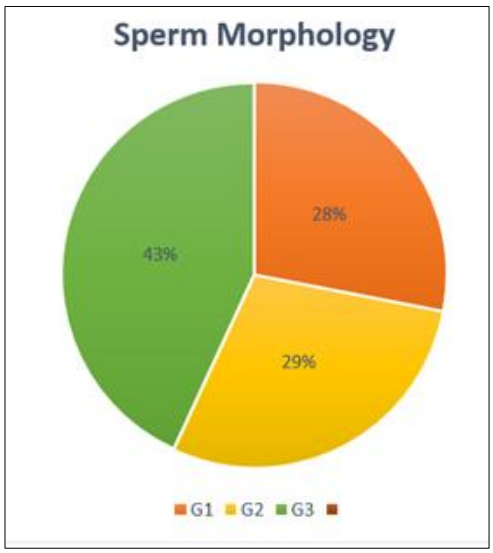

Figure 3 Average sperm morphology (% normal sperm) in G1: smokers of more than 20 cig/day, G2: smokers of less than 20 cig/day, G3 non-smokers

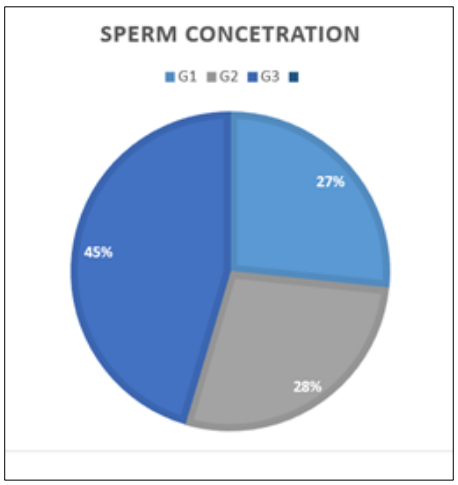

Figure 4 Average germ cell concentration(106/ml) in G1: smokers of more than 20 cig/day, G2: smokers of less than 20 cig/day and G3 non-smokers

3. Evolution of Smoking Effects on Male Fertility

Association between the use of tobacco and harmful effects on general health and male fertility has been proven, but, despite all this, smoking has remained globally prevalent. The main content of tobacco smoke, which is nicotine and other toxic substances, can cross the blood-testis barrier [8], causing harm to the germ cells, showing its effects in the decrease of sperm motility, sperm concentration, and abnormal sperm morphology.

Some of the most significant defects in the morphological structure of spermatozoa caused by tobacco smoke are shown in the head, neck and tail of the cells. Continuous observation has identified complex genetic and epigenetic alterations, with recent studies revealing that in addition to the decrease in sperm count, male smokers have a higher DNA fragmentation, which is compromising their gametes. [5]

By presenting a fragmentation in the DNA, it can be noticed an important marker for infertility since the sperm that exhibit this damage will be compromised in their ability to fertilize an ovum, increasing the risk of spontaneous abortions and congenital defects. It has been described how smoking alters patterns in sperm DNA methylation, which will modify gene expression during embryonic development, resulting in predisposition of the offspring to develop diseases such as cancer, diabetes and neurodevelopmental disorders.[7]

4. The effects of smoking on semen quality

Studies have demonstrated the effects of smoking on the antioxidant defense system due to the increase in oxidative stress, with the high concentrations of nitric oxide, peroxynitrite and free radical, that cigarette smoke contains, inducing the production of reactive oxygen species (ROS). This increased production of ROS can damage various parameters of sperm, including proteins, nucleic acids and polyunsaturated fatty acids. Zinc, which has antioxidant properties, can counteract the excessive production of ROS, but it has been noticed a depletion or deficiency of this element as a side effect of smoking, which can produce a variety of effects on the quality of semen [9, 10].

5. Detection of alterations in sperm DNA

Smoking is currently believed to cause oxidative stress in sperm due to the formation of reactive oxygen species (ROS). This phenomenon occurs because the sperm plasma membrane contains a large amount of polyunsaturated fatty acids, which are very vulnerable to ROS attack. In addition, sperm have a lower amount of antioxidant enzymes, which creates an environment conducive to oxidative stress. [11].

Due to these characteristics, sperm are particularly susceptible to oxidative stress and, consequently, to oxidative DNA damage. Their limited ability to detect and repair DNA damage increases their vulnerability compared to other cells in the body. [12].

Oxidative damage is the most common cause of DNA fragmentation in sperm, causing impairment in sperm functions, leading to a decrease in male fertility [13].

Damage to the DNA of sperm cells can occur at any stage of the spermatogenesis process, being a multifactorial phenomenon and not fully elucidated that can affect both mitochondrial and nuclear DNA.

There are some factor known for producing irreversible damage to male gametes DNA, these can appear during the production of transportation of sperm cells and included: the production of oxygen-free radicals or oxidative stress (including hydroxyl radicals and nitric oxide during transport of sperm through the seminiferous tubules and epididymis), abnormal chromatin packing (errors in the substitution of histones for protamine), deficiencies in recombination, apoptosis in the process after the movement of spermatozoon into the tubules, and external causes that can cause or enhance the effect mentioned above, with certain environmental conditions, such as pollution, smoking, elevated testicular temperature, etc., are considered: [14]

Mechanisms of sperm DNA fragmentation; These can occur during either the production or the transport of the sperm cells and include (Fig.5): 1) apoptosis during the process of spermatogenesis; 2) DNA strand breaks produced during the remodeling of sperm chromatin during the process of spermiogenesis; 3) post-testicular DNA fragmentation induced mainly by oxygen radicals, including the hydroxyl radical and nitric oxide, during sperm transport through the seminiferous tubules and the epididymis; 4) DNA fragmentation induced by endogenous caspases and endonucleases; 5) DNA damage induced by radiotherapy and chemotherapy; and 6) DNA damage induced by environmental toxicants. [15].

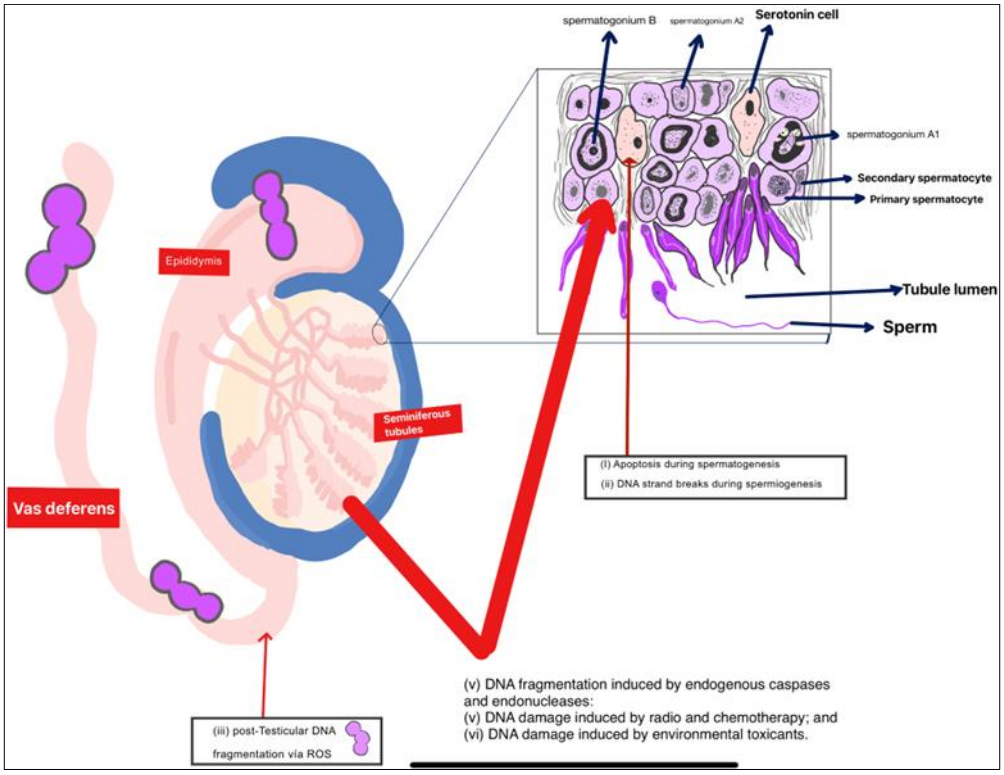

Figure 5 Main mechanisms of induction of sperm DNA damage during sperm production or transport. Inspired by the article [15]

6. Impact of Smoking on DNA and Genetic Factors.

A variety of chemical compounds released by smoking might affect the integrity of sperm DNA, the compounds include: carbon monoxide, nicotine, and cotinine (a nicotine metabolite). These are directly absorbed into the systemic circulation and accumulate in seminal plasma, inducing oxidative stress, which dramatically affects seminal parameters, including DNA fragmentation [16].

Smoking has been showed to increase genetic and epigenetic aberration in spermatozoa, including oxidative damage to DNA, abnormalities in chromatin packing, mutations, polymorphism, DNA methylation and deficiency in the regulation of mRNA expression, all of this influencing sperm functionality and fertility. [16, 17].

Recent studies suggest that genetic and epigenetic changes in spermatozoa caused by the genotoxic components of tobacco can be transmitted to the offspring [13, 17].

To counteract oxidative damage, sperm use two main enzymes: superoxide dismutase and glutathione peroxidase. Superoxide dismutase, in particular, is considered an important marker of male fertility. Its main function is to protect sperm against oxidative DNA damage, lipid peroxidation (affecting membrane lipids) and mitochondrial DNA deterioration. Studies have shown that a decrease in the levels of this enzyme may be associated with fertility problems.

Glutathione peroxidase also plays a crucial role in the normal functioning of sperm, as it helps reduce the harmful effects of oxidative stress. Both enzymes are essential for protecting male reproductive cells and maintaining fertility.

A recent study analyzed the impact of smoking on these antioxidant enzymes and hormone levels, separating subjects into smokers and non-smokers, and further classifying them as fertile or infertile. The results indicated that, although factors such as age, weight and body mass index (BMI) did not show significant variations between the groups, levels of testosterone, superoxide dismutase and glutathione peroxidase were affected. Both fertile and infertile smokers had lower levels of these enzymes compared to non-smokers, suggesting a negative impact of smoking on fertility. [17, 18].

7. Conclusions

Smoking constitutes one of the most important risk factors for male fertility, with implications that go beyond the individual affected. The toxic substances present in tobacco, such as nicotine, carbon monoxide and its combustion derivatives, generate a significant increase in the production of reactive oxygen species, which contributes to oxidative stress. This imbalance is a central mechanism in the alteration of spermatogenesis, as it damages testicular cells and compromises key parameters such as sperm motility, morphology and sperm count.

In addition, oxidative damage affects the integrity of sperm DNA, causing fragmentation and genetic alterations that not only reduce the chances of conception, but also increase the risk of transmitting mutations to offspring. These genetic abnormalities can lead to congenital malformations and hereditary disorders, underscoring the seriousness of the impact of smoking on reproductive health.

Smoking also interferes with hormonal balance, decreasing levels of testosterone, luteinizing hormone (LH) and follicle stimulating hormone (FSH). This aggravates the deterioration of spermatogenesis and increases the risk of transmitting genetic mutations to offspring, which can lead to congenital malformations and genetic disorders.

It is thus imperative to develop comprehensive strategies that combine prevention, education, treatment and awareness campaigns on the adverse effects of smoking.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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