Synopsis of the toxicological effects of cigarette smoking on male fertility in humans-A Narrative Review

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ABSTRACT

Numerous studies have revealed that sperm parameters, seminal plasma, and a number of other reproductive markers are all adversely impacted by cigarette smoking. However, it is unclear how smoking actually affects male fertility. The relationship between smoking and the characteristics of semen is based on the biological fact that smoking increases the presence of reactive oxygen species,

leading to oxidative stress (OS). Smoking adversely affects fertility by drastically lowering sperm count and normal sperm morphology. Oxidative stress brought on by smoking has a negative impact on semen parameters. Although the majority of male smokers are still fertile, they are more likely to have infertility or subfertility due to the amount of action of reproductive hormones. Only a small number of studies found insignificant variations in semen parameters between smokers and non-smokers.In addition to analysing the effect of tobacco consumption in non-smoking modes on male infertility, this analysis clarifies the debatable link between smoking and male fertility. Additionally, it addresses the genetic and epigenetic evidence that ties smoking to male infertility and analyses its clinical ramifications. According to this analysis of published articles, males with poor semen quality can still benefit from quitting.

Key Words: Smoking, male infertility , semen parameters, spermatogenesis

INTRODUCTION

Tobacco, *Nicotiana tabacum*, is an herbaceous plant in the family Solanaceae grown for its leaves(1). Thick, hairy stem and large, simple leaves which are oval in shape are the morphological features of tobacco plant(1). It is used to manufacture cigarettes and cigars where it contains nicotine content (1). It was employed for smoking purposes about 1800 (2). Spanish sailors spread its seeds in many locations while they were travelling, giving it widespread fame (2-3).

Components of cigarette : There are approximately 600 ingredients in cigarettes. More than 7,000 chemicals are produced when a cigarette is burned (4).At least 69 of these chemicals are known to cause cancer, and are toxic (4). Few of the chemicals are tar, nicotine, carbon monoxide, nitric oxide, hydrogen cyanide, acrolein, benzo(a)pyrene, and N-nitrosamines etc (5).Studies shows that smoking behaviour is related to social factors such as influence of peer groups (5-6). Taste and smell influences the inclination to smoke (7).It has an adverse outcome on respiratory diseases , infertility conditions, cardiovascular diseases , pancreas ,stomach etc (8-10).

Infertility is a disease characterized by inability to achieve pregnancy even after unprotected sexual intercourse (11). The World Health Organization (WHO) defines a male as infertile (sterile) if his sperm parameters fall below those required by the applicable standards (12).There are several unhealthy habits such as obesity , smoking ,alcohol consumption that causes male infertility (11).These factors contribute towards deterioration of semen quality (13). Available data do not demonstrate that smoking decreases male infertility but it plays an indirect role in decreasing male fertility (2).Tobacco smoking increases DNA damage, aneuploidies and mutations in sperm (13). Increased oxidative stress, DNA damage, and cell apoptosis plays a combined role in not only the reduction in semen quality, but also impaired spermatogenesis, sperm maturation, and sperm function (14-15). Substances from tobacco smoke can interfere with the anterior pituitary's ability to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which can affect testosterone production and spermatogenesis.

The WHO adopted the "Health for All in the 21st Century" Strategy and Program Tasks in 1999, obliging all of its members to carry out a number of objectives, including those that directly or indirectly aimed to promote general, but also reproductive health. These objectives included a healthy start in life, a safe and healthy physical environment, the fight against smoking, alcohol consumption, and drug use.

MATERIAL AND METHODS

We conducted an extensive electronic search of PubMed, Scopus, and Web of Science. Up until the year 2022, appropriate MeSh keywords included "male infertility," "Smoking," "erectile dysfunction," "infertile male," and "spermatogenesis." Semen parameters (oligozoospermia, asthenozoospermia, teratozoospermia, and azoospermia), spermatozoa structural abnormalities, and reproductive hormones were all evaluated as clinical endpoints in writing this review.

I. CIGARETTE SMOKE

Composition-

Smoke from cigarettes contains a complex mixture of chemicals. Some are gases like carbon monoxide (CO) and hydrogen cyanide, while others are volatile chemicals present in the liquid-vapor component of the smoke aerosol (HCN). The term "concentrated aerosol of liquid particles suspended in an environment consisting primarily of nitrogen, oxygen, carbon monoxide, and carbon dioxide" or a "multi compositional collection of compounds arising from distillation, pyrolysis, and combustion of tobacco" has been used by researchers to describe cigarette smoke.(16)

Formation of cigarette smoke-

After lighting the cigarette and taking a puff, smoke will start to form. Mainstream smoke is discharged from the butt end of a burning cigarette when someone puffs, and sidestream smoke is released when a coal is burning and smouldering. (16) In the vicinity of an active smoker, smoke from cigarettes, smoke exhaled by smokers, and smoke that enters the air through the permeable paper covering the tobacco all mix together. (17) As a result, how a cigarette is smoked (such as the puff volume and intervals between puffs) can affect how much mainstream and sidestream smoke is present (18). Additionally, the toxicant ratio of sidestream to mainline smoke decreases with greater puffing intensity (19).

Tobacco smoke can be divided into 2 phases, Particulate phase and Gaseous phase.
As smoke dissipates, chemicals may pass between these 2 phases (20).

Table 1 (20)

About 4000 chemicals are produced by a lit cigarette as a result of several chemical processes, including hydrogenation, pyrolysis, oxidation, decarboxylation, and dehydration. Smoke can be divided into two stages: gaseous and particle. The key chemicals that have an effect on health are nicotine, particulate tar, and gaseous carbon monoxide(21).

SMOKING INDEX (SI)

Smoking index is a parameter used to quantitate cumulative smoking exposure. In this, smokers can be classified as either heavy smokers (>30 pack-years) or light smokers (<8 pack-years), where pack-year is the number of packs smoked/day × number of smoking years (20). SI is defined as the product of number of cigarettes/day × years of smoking; mild <200 SI, moderate 200–600 SI and heavy >600 SI (22).

II. SMOKING AND INFERTILITY

It is unclear how smoking actually affects male fertility. Smoking has detrimental impacts on sperm characteristics, including viability and morphology, and it inhibits sperm function, which lowers male fertility. This review emphasises the mounting genetic and epigenetic evidence that connects smoking to male infertility.

Effect of smoking on reproductive hormones

Considering nicotine and its metabolites share an androgen disposal mechanism and may therefore compete with androgen disposal, smoking may enhance testosterone.
Leydig cell function or the hypothalamic-pituitary axis may be affected by smoking , though hormone levels and the length of smoking are unrelated. A greater sex hormone binding globulin(SBHG) level is linked to smoking. About 65 to 80 percent of the testosterone circulating in the blood is inactive and closely attached to SHBG, which is the major transporter of testosterone. Furthermore, testosterone levels and SHBG levels, (but not cotinine levels which is a marker of cigarette smoking), correlated, suggesting that smoking has a bigger relative impact on SHBG levels (23,24,25)

Effect of smoking on semen

Nicotine- The semen quality is significantly affected by nicotine exposure (26). Cotinine, a metabolite of nicotine, is an alkaloid present in tobacco. The levels of trans-3'-hydroxycotinine and cotinine in the seminal fluid were found to be inversely linked with overall sperm motility in in vitro investigations. High nicotine concentrations (100 ng ml-1), decreased the proportion of viable spermatozoa, encouraged spermatozoal apoptosis with DNA fragmentation or changed the compactness of the chromatin (27). Additionally, it has been demonstrated that seminal nicotine and cotinine levels are measurably affected by environmental cigarette smoke exposure and are associated with the reported exposure amount (28).

Heavy metals- If a smoker smokes more than 20 cigarettes per day, researchers have discovered that their seminal fluid has higher levels of cadmium (Cd) (29). It has been demonstrated that seminal Cd in normozoospermics is connected with daily cigarette use and is higher in smokers than non-smokers. Additionally, smoking has been shown to increase lead levels in seminal plasma compared to non-smoking, which may possibly contribute to infertility (30).

Benzo(a)pyrene - It is a component of cigeratte smoke resulting from tobacco combustion. Adducts are created when the main diol epoxide (DE-I) binds covalently to DNA strands. It could be viewed as a significant contributor to DNA damage in smokers (31).

Effect of smoking on sperm quality and quantity

Sperm concentration - Studies have shown a marked 23% decrease in sperm concentration in men who smoke (32,33,34,35,36).

Sperm DNA- The results of some previous studies show that smokers' sperm had higher DNA breakage. Sperm with DNA damage may have problems fertilising eggs, developing embryos, implanting those embryos and may even increase the likelihood of miscarriage. Men who smoke may also have abnormal hormone levels, which may affect their ability to conceive (37). Comparing heavy smokers to non-smokers, anomalies in the number and organisation of axonemal microtubules have also been observed (38). Heavy smoking has been found to be connected with the percentage of coil sperm. Plasma membrane tail filament coiling was discovered using electron microscopy (39).

Sperm morphology- It has been suggested that sperms with unusual shapes can't swim well enough to reach the egg and are not able to fertilise it. Male smokers have fewer healthy shaped sperm than non-smokers (26).

Sperm motility- The ability of the sperm to swim is referred to as sperm motility. Sperm may have problems reaching the egg and fertilising it if they are unable to swim properly. Researchers discovered a

13% reduction in sperm motility in males smokers (26).

Effect of smoking on acrosin

In the presence of normal sperm count and motility, smokers have been observed to exhibit reduced acrosin activity (40). Semen exhibits substantially less acrosome response in the smoking men.

Smoking and accessory sex glands

Smokers had considerably reduced 1,4-glucosidase (epididymis) activity. It has been determined that tobacco usage, especially smoking, affects genitalia's ability to ejaculate. Significant reductions in vesicular and prostatic parameters were observed in smokers (41).

Other complications due to smoking

Quantitative alterations of spermatogenesis

The testis is thought to be particularly susceptible to hypoxia because of its high metabolic needs as a result of ongoing spermatogenesis and its relatively inadequate vascular supply in the spermatic cord. Smoking impedes the supply of oxygen and is thereby harmful to testicular functions.In the testis of the smoking group, it is discovered four CpGs that are close to the Pebp1 transcriptional start point are hypermethylated. This proposes a line of inquiry into how smoking affects DNA methylation patterns (42).

1.Varicocele

Male fertility gradually declines due to varicocele, an abnormal expansion of the pampiniform venous plexus in the scrotum. Men who smoke are shown to have a 10 times higher incidence of oligozoospermia than non-smokers (43-47).There are theories that link hormonal dysregulation, internal spermatic vein hypertension, reflux of toxic renal/adrenal metabolites, and venous stasis to testicular hypoxia (48).

2.Testicular failure

Nicotine (0.5 mg kg1) may affect the male reproductive system in such a way as to reduce sperm motility and count while raising the percentage of defective sperm (49). Significantly lower intratesticular and plasma testosterone concentrations, intratesticular testosterone activities, and plasma gonadotropin concentrations were seen in the testes.Smoking reduced the rate of testicular androgen-binding protein secretion and had negative effects on Sertoli cell secretory function (50).

Qualitative alterations of spermatogenesis

1.Oxidative stress

Smokers' seminal plasma has higher amounts of oxidative damage as a result of smoking. Smoking has been demonstrated to lower levels of seminal plasma antioxidants and to enhance ROS (oxidative damage) concentrations in seminal leukocytes (51). Male infertility increases as a result of increased sperm DNA damage and apoptosis caused by prolonged cigarette smoke exposure (52).

2. Erectile or ejaculatory dysfunction

After extensive research, smoking is now formally recognised as a risk factor for erectile dysfunction (53). An extensive review of observational studies revealed that middle-aged men who smoke have a much higher risk of developing erectile dysfunction than non-smokers (54), which can finally result in vasculogenic (55), and arteriogenic, impotence (56).

Table 2

III. DISCUSSION

Smoking affects the function of spermatozoa, sperm maturation, and spermatogenesis as well as causing issues with reproductive hormones. Numerous papers we've looked at claim that nicotine has an impact on the male reproductive hormone system by preventing androgen synthesis and inducing Leydig cell death. This study showed that the semen parameters were lower among infertile smokers (total count, motility, and morphology). The morphology and sperm count were different among smokers. Furthermore, it causes oxidative stress, which compromises the properties of semen.

In this review, we have discussed that the smokers had sex hormone binding globulin (SHBG) levels that were noticeably lower. One of the causes of oxidative stress (OS) is smoking, which is brought on by high levels of ROS and a lack of antioxidants. An increased incidence of abortion, birth abnormalities, and childhood malignancies is brought on by this DNA damage.

It has been observed that the normal functions of male reproductive hormones depend upon the balance between the reactive oxygen species (ROS) generation and antioxidant defense method in the reproductive system. Excessive production of ROS can affect reproductive tissues directly or may impede the hypothalamic–pituitary–gonadal (HPG) axis and its relationship with other endocrine glands, thus causing infertility. Smoking affects male fertility by affecting testosterone secretion, which could be due to OS potentiated by the smoking.There were no discernible differences in the sperm's quality between past smokers and those who had never smoked. This result revealed that smoking may have a less significant impact on the early phases of spermatogenesis than on sperm development.Sperm counts and semen volumes are much lower in smokers than in non-smokers. Smokers had significantly lower ultrasound-derived seminal quantities both before and after ejaculation (71).The key outcome measure in such investigations should be successful pregnancy rates; yet, semen analysis parameters are commonly employed as primary endpoints in the articles we examined (71).

Furthermore smoking generally has a harsher impact on health than tobacco chewing, but tobacco chewing is by no means risk-free and can potentially have an impact on male fertility. Studies show that excessive chewing might negatively impact sperm concentration, motility, morphology, and viability (72). It's not known if it's sufficient to lower fertility. Smoking is also strongly linked to a threefold greater incidence of erectile dysfunction in men, claim some research (73). The more cigarettes a man smokes, the more likely it is that he may have erectile dysfunction. Erectile dysfunction and infertility are not the same thing. However, if sexual performance is difficult, getting pregnant won't be straightforward. Knowing that stopping smoking does seem to improve performance is encouraging.A study (73) indicated that slightly more than 50% of participants reported increased sexual performance six months after quitting smoking.

There is strong evidence that smoking negatively affects several crucial semen properties. Future studies should try to shed more light on the possible mechanisms causing this connection.

IV. CONCLUDING REMARKS

There have been a number of published case-control studies on smoking and how it affects male fertility, but there hasn't been much population-wide study looking at natural conceptions and the real reasons why a couple's (male) infertility) is unfeasible. The majority of research do, however, indicate that smoking, which contains more than 4000 dangerous substances, may be detrimental to the health of the male reproductive system. Serum quality, comprising density, motility, viability, and regular morphology, is certainly decreased by smoking.The majority of male smokers are still fertile, but because of the level of action of reproductive hormones, they are more likely to have infertility or subfertility.

Smoking has the potential to seriously harm DNA, which could hinder the growth of embryos or the fertilisation of eggs. So smokers ought to give up smoking for the sake of the future generation.

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