Smoking Effects on Male Fertility

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Key Points

- There is no consensus across the literature regarding just how smoking contributes to male infertility.
- Smoking has detrimental impacts across nearly all organ systems, impairing hormonal signaling in the hypothalamic pituitary axis, disrupting spermatogenesis, and directly damaging sperm morphology and genetic contents.
- Some studies have shown various sperm parameters to be influenced by cigarette by-product exposure such as impaired sperm morphology, decreased sperm motility, and decreased sperm volume.
- More research is needed to determine just exactly how smoke impairs normal male reproductive processes at the molecular level.
- Treatment of male infertility in smokers depends on reversing or managing the damage caused by the toxins and chemical assailants of cigarette smoke.

40.1 Introduction

The association between smoking and male fertility has not been fully established. Conflicting studies reporting the effects of smoking and nicotine on male reproductive physiology make it difficult to conclude how exactly male fertility is affected by this habit (Table 40.1). Lifestyle modifications have become the focus of many topics in modern medicine as achievable solutions to a wide variety of health concerns and disorders. The goal of this chapter is to provide a thorough review of the literature describing how smoking may impact male fertility.

40.2 Overview of Smoking

Tobacco use, specifically cigarette smoking, is the most common culprit behind preventable causes of mortality across the world. Diseases beyond obvious lung involvement have become increasingly connected to a current or even past medical history of smoking, in addition to worsening prognoses. There are over 7000 ingredients in cigarettes including carbon monoxide, toluene, cadmium, methane, and polycyclic aromatic hydrocarbons (PAHs), each of which has adverse effects on normal physiologic function at the microscopic and macroscopic levels [13, 22]. There are two parts to smoke discharge, the first of which releases carbon monoxide gas; the second particulate phase contains nicotine and tar [6]. The addictive nature of cigarettes is due to the nicotine component. This is then metabolized into cotinine and then continued to be processed into trans-2′-hydroxycotinine [6]. The initial ingredients in addition to the metabolized end products have devastating effects on male reproductive physiology [15].

Though the prevalence of male daily smokers has decreased from 28.4% to 25.0%, it still proves to be an important contributor to adverse health effects across all body systems [28]. Consistently, smoking has been linked to cancers of the oropharynx, larynx, esophagus, trachea, bronchus, lung, stomach, liver, pancreas, cervix, and bladder. Smoking has also been shown to cause stroke, blindness, coronary heart disease, pneumonia, COPD, diabetes, ectopic pregnancy, rheumatoid arthritis, and immune disorders.

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Table 40.1 Overview of published literature findings on the effects of smoking on sperm analysis parameters

Author	Smoking effects on semen parameters			
	Concentration	Motility	Morphology	Other findings
Stillman et al. [1]	↓	↓	↓	
Dikshit et al. [2]	–	–	–	
Klaiber et al. [3]	↓			
Osser et al. [4]	–	–	–	
Dunphy et al. [5]	–	–	–	
Pacifici et al. [6]				
Sofikitis et al. [7]			↓	
Vine et al. [8]	↓	↓	↓	
Chia et al. [9]	↓	↓	↓	
Horak et al. [10]	↓	↓		Increased bulky DNA adducts in smoker sperm
Künzle et al. [11]	↓	↓	↓	
Pasqualotto et al. [12]	–	–	–	
Colagar et al. [13]	↓			
Tremellen et al. [14]		↓	↓	Increased DNA damage, membrane damage
Calogero et al. [15]		↓	↓	Increased DNA damage
Oyeyipo et al. [16]	↓		↓	
Taha et al. [17]	↓	↓	↓	
Sharma et al. [18]	↓	↓	↓	
Zhang et al. [19]	↓	↓	↓	
Kumar et al. [20]	↓	↓	↓	
Dai et al. [21]		↑		
Harlev et al. [22]	↓	↓	↓	
Cui et al. [23]	↓	↓	↓/–	Significance of sperm damage differs based on smoking amount
Esakky et al. [24]	↓			Increased DNA damage
Jenkins et al. [25]	–	–	–	
Sharma et al. [26]	–	↓		Decreased sperm count
Al Khaled et al. [27]	–	–	–	No significant difference in sperm DNA

↓ decreased from normal parameter; – no effect; ↑ increased from normal parameter

Smoking as a burden to public health has been extensively analyzed across a wide array of domains. Consumption has dramatically contributed to global burden of health in over 195 countries [29]. While the dispersal of this is weighed heavily toward low socioeconomic areas and in populations with lower education levels, smoking is a universal public health risk and does not discriminate in its ability to devastate the human body [28]. Economically, the costs associated with smoking are staggering, amounting to 8.7% of annual healthcare costs [30]. In the United States, smoking-related illnesses have cost over 300 million dollars in healthcare spending [30]. This includes 176 billion dollars in medical expenditures due to associated morbidities, as well as over 156 million dollars lost in expected productivity due to exposure to secondhand smoke [31]. Since the iconic Surgeon General's report on the economic effects of smoking, various energies have been made to stall tobacco sales, and 8 million deaths and 175 million years of life have been saved due to this emphasis [31]. Yet, the tobacco industry continues to flourish, and still smoking remains the principal source of preventable mortality across both the developing and developed worlds.

The impact of smoking on the reproductive system is not fully established. In males, smoking has been shown to contribute to impaired sperm motility and quantity, in addition to reduced ability to produce and maintain an erection (Fig. 40.1). In women, cigarette usage is complicit in increased rates of ectopic pregnancy and developmental disabilities in the growing fetus.

40.3 Overview of Male Reproductive Physiology

40.3.1 Hormonal Axis

The male hormonal axis is but another feedback loop of the hypothalamic pituitary axis. The pathway begins by the pulsatile secretion of gonadotropin-releasing hormone (GnRH) by the hypothalamus which stimulates the anterior pituitary to release luteinizing hormone (LH) and follicular stimulating hormones (FSH) that are secreted into systemic circulation [32]. Upon reaching the testes, LH induces Leydig cells to produce 5–7 grams of testosterone daily. The active metabolite 5-alpha-dihydrotestosterone (DHT) is crucial for regular male genital tract development. FSH works upon Sertoli cells, stimulating their production of proteins that support spermatogenesis as well as inhibin B [32].

The production and secretions of the hormones in this axis are highly dependent upon and regulated by negative feedback

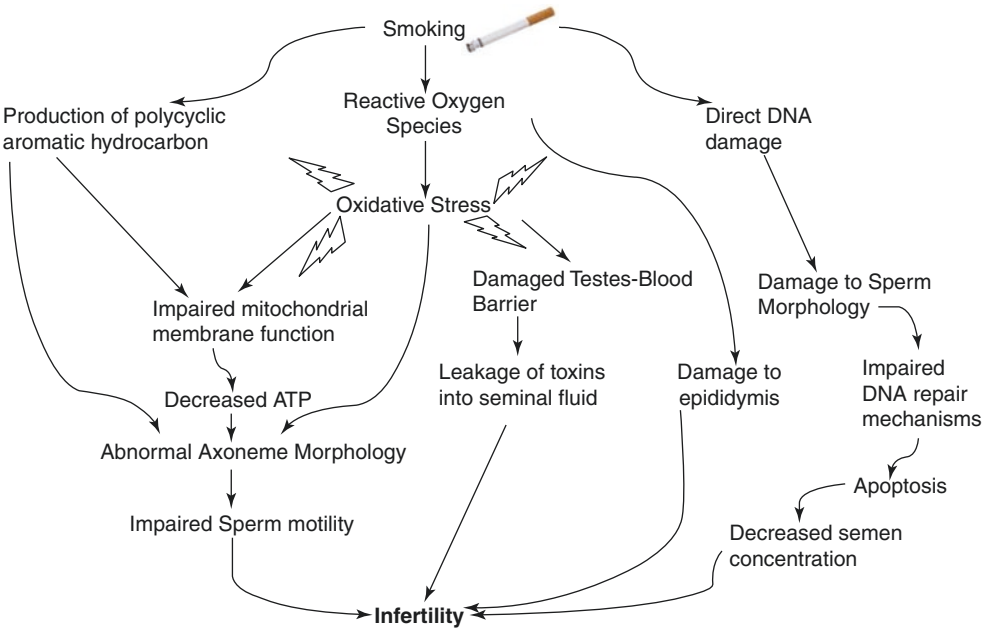

Fig. 40.1 Suggested mechanisms for how smoking impairs sperm physiology and function

principles. Increased circulating levels of testosterone and DHT inhibit the production of GnRH and LH levels by the hypothalamus and anterior pituitary, respectively. This then downregulates the testis production of hormones and proteins. FSH secretion is blocked by inhibin B from Sertoli cells. This pathway is extremely sensitive to stress, both endogenous and environmental. Smoking directly impacts the normal functioning of this exquisitely designed hormonal relay.

40.3.2 Normal Reproductive Pathway

The normal reproductive pathway of males cannot be addressed without introduction of relevant anatomical structures. The testes, as aforementioned, are a principal reproductive organ responsible for male fertility. They are divided into two anatomical compartments separated by the blood-testis barrier. The interstitial compartment contains the Leydig cells that are responsible for producing testosterone as discussed. The seminiferous tubule compartment is significantly larger, composing the majority of the testis organ. Sertoli cells reside here that secrete proteins and nutritional components required for regulating spermatogenesis. Undifferentiated spermatogonia are also occupants of the seminiferous tubule system. The damage caused by smoking to these components of male reproductive anatomy and their associated physiological processes has deleterious effects on male fecundity.

40.3.3 Spermatogenesis

The process of spermatogenesis begins with puberty, as GnRH pulsations reach the levels necessary to stimulate LH and FSH secretion, and is divided into three stages [33]. The first is the mitotic or proliferative stage where undifferentiated immature stem cells go through mitosis. Part of this group is destined to fill the stem cell reserve; the others will continue to complete spermatogenesis and become mature spermatocytes [34]. The second phase is where these spermatogonia push through blood-testis barrier and undergo meiosis to become two distinct primary spermatocytes. These then complete two further rounds of meiosis, resulting in two secondary spermatocytes and then finally four spermatids. The third and final phase of spermatogenesis is when these four spermatids differentiate into mature spermatozoa [33, 34]. This entire process yields around 100 million mature sperm products per day [35]. This process has been evolutionarily tailored to progress very specifically and can be interrupted by the toxins introduced into the body by smoking, thereby contributing to male infertility (Fig. 40.1).

40.3.4 Erectile Physiology

An erection is achieved by arteriolar dilation of vessels in the corpus cavernosum. When a man is sexually aroused, neurotransmitters are released from nerve terminals that then causes blood flow into the penis to increase. This results in compression of subtunical venous outflow, trapping blood within the penile vessels, thus causing in an erection.

The innervation of the penis is complex and is dependent upon sympathetic, parasympathetic, sensory, and motor synapsing. This combination of excitatory and inhibitory neuronal signaling pathways is crucial for obtaining and maintaining an erection. Sympathetic signaling originates through the sacral and caudal sympathetic chain ganglia before projecting to the penis and is responsible for ejaculation [36]. Parasympathetic innervation to the penis stems

from the pelvic plexus; its projections are responsible for erection [36].

Somatic and motor innervations begin at sensory receptors located in the skin of the penis, glans penis, and urethra within the corpus cavernosum. These small free nerve endings join to form the dorsal nerve of the penis, which projects medially to form the pudendal nerve with other nerve fibers. Motor innervation is crucial for ejaculation. Fibers projecting to the bulbocavernosus muscle are responsible for the rhythmic contraction necessary for expelling sperm products through the urethra [36].

40.4 Male Infertility

Each component contributing to normal, healthy male reproductive anatomy and physiology can be damaged by the toxins in smoke products. When a couple experiences difficulty in conception, both partners must be evaluated. Approximately 30% of infertility can be credited exclusively to male issues [37].

Evaluation of male infertility begins during the history taking and physical exam. Timing of intercourse, use of lubricants, or childhood illnesses such as mumps orchitis, undescended testes, or testicular torsion have all been shown to contribute to infertility in adult life [37]. Exposures to environmental toxins have become prominent in modern research into this subject.

40.4.1 Factors Affecting Male Fertility

In humans, male infertility accounts for 40–50% of all cases [38] and affects approximately 7% of all males in reproductive age. In 2010, the WHO reassessed their sperm study standards and made changes to the requirements for assessment of volume, motility, and morphology [26]. Since these changes, volume is measured by weight; motility is divided into two categories, progressive and nonprogressive; and morphology is evaluated using the Tygerberg criteria [26]. The consequences of these changes include disqualifying males once deemed infertile, thus calling for a re-examination of sperm parameters among males struggling with fertility issues.

40.4.2 Testicular Factors

Varicocele is the circumstance of swollen testicular veins prevalent in 40% of men, 15% of which have been deemed infertile [39]. Left-sided varicoceles are ten times more likely to occur because the left spermatic vein empties at a right angle into the left renal vein, whereas the right spermatic vein empties directly into the inferior vena cava. Men with varicocele are more likely to have abnormal semen quality and quantity as compared to men without. While it is well documented that varicocele is more prevalent in infertile men, the pathophysiology behind this etiology is not well understood. However, as blood pools in the pampiniform plexus, this causes relative hyperthermia of the groin, which is well known to be harmful to developing spermatozoa [40].

Comparison of smokers and nonsmokers with varicocele showed that there was a ten times greater risk of oligozoospermia in the smoking men, suggesting potentially a compounded effect of smoking and varicocele on male fecundity [3]. A study conducted by Agarwal et al. showed that men with varicocele had reduced sperm count and motility [41]. Furthermore, it seems that there is an inverse association between varicocele grade and measured sperm motility and concentration [42].

40.4.3 Genetic Contribution

Genetic abnormalities affecting hormones and receptors of the hypothalamic pituitary gonadal axis can cause infertility [37]. Kallmann syndrome is an X-linked disorder that causes idiopathic hypogonadotropic hypogonadism (IHH). A mutation in the Ka1 gene results in reduced GnRH secretion by the hypothalamus. This lack of GnRH leads to reduced FSH and LH production and secretion by the pituitary, thereby leading to decreased stimulation of the testes. Low testosterone and spermatoprotective growth factors are produced as a result [43]. Congenital adrenal hyperplasia has also been shown to cause IHH due to a mutation in the Dax1 gene associated with maintenance of testis epithelium and spermatogenesis [43]. The Prader-Willi syndrome is a congenital disorder of maternal imprinting of chromosome 15, or deletion of the short arm of paternal chromosome 15, that causes obesity, cryptorchidism, and IHH [37]. Klinefelter's syndrome is the most common genetic cause of male infertility. This sex chromosome disorder has a range of karyotype abnormalities, the most common of which is 46XXY. Yet despite this heterogeneity in chromosomal count and components, all clinically present with some variation of compromised male fertility [43]. In adolescence and adulthood, men diagnosed with Klinefelter's syndrome present with small, firm testes and some amount of androgen deficiency [43]. Others will have one testis, which may be cryptorchid or descended, and one streak gonad [37]. If the testis completed its descent into the scrotal sac, normal concentrations of Leydig and Sertoli cells are usually present. However, lost are the germ cells within the seminiferous tubules. In one study, 70% of men above the age of 25 complained of decreased libido [43].

In 46,XX men, there is a deletion of the sex-determining region (SRY) on the short arm of the Y chromosome [37]. On the long arm of the Y chromosome is the azoospermia factor region (AZF), which is integral in normal spermatogenesis.

Any disruption in hormonal signaling facilitating sexual maturity, sex hormone release, or sex hormone biosynthesis is the etiology behind male infertility. Mutations affecting the hormone, or its receptor, impede regular signaling and secondary messenger activation, leading to adverse effects ranging from moderate hypogonadism to complete failure of virilization and impaired male sexual function [37].

Other mutations that impair correct maintenance and utility of male reproductive organs include mutations of the steroidogenic acute regulatory protein (StAR) [44]. This protein serves as the rate-limiting step in steroid hormone biosynthesis by regulating transport of cholesterol into the mitochondria [44]. Mutations in enzymes responsible for conversion of cholesterol into androgens can fully halt normal male sexual development and obviously thereby male fertility. For example, 5α-reductase is essential for the complete development of external male genitalia by converting testosterone to its active metabolite DHT [37]. This results in impaired sperm delivery upon entrance into the female reproductive tract and thereby compromised fertilization.

At the DNA level, mutations in androgen nuclear receptors result in androgen insensitivity syndromes that also clinically manifest as various levels of male infertility [37].

40.4.4 Immune

Antisperm antibodies (ASAs) have been implicated as causing infertility in approximately 10–30% of infertile couples [45]. Abnormally elevated amounts have been found in men suffering from testicular torsion, orchitis, and testicular cancer [45]. These antibodies target antigens on the sperm surface and can be IgG, IgA, and IgM in nature [45]. Studies have shown that these different kinds of ASAs bind to specific regions on the sperm, be it acrosomal binding, on the sperm body, or in the tail region. This hinders the sperm's ability to navigate through the female reproductive tract and successfully penetrate the zona pellucida of the ovum. ASAs have also been documented to cause a release of spermatocytic cytokines, in addition to increasing sperm phagocytosis [45]. Yet other studies have shown healthy, fertile men to have marked levels of ASA, so it is difficult to definitely associate these antibodies with infertility [45].

The testicular blood barrier also has an immunoregulatory role in protecting sperm from immune cell destruction. This barrier develops throughout puberty as the cell-cell junctions between neighboring Sertoli cells, thus preventing passage of large immunoglobulins and lymphocytes into the tubular lumen.

Further defensive measures are found in the seminal plasma. Components of this impede the lymphocyte-antigen interaction, thereby preventing antigenic activation of the immune system's NK cells and T-lymphocytes. Prostaglandin H2 synthase, also found in seminal plasma in the rete testis and epididymis, prohibits prostaglandin synthesis and thus impairs lymphocyte extravasation through the tubular epithelium.

Sertoli and Leydig cells also have a direct protective effect on paracrine secretion or spermatoprotective substances that facilitate healthy normal spermatogenesis. Anti-inflammatory cytokines including IL-10, IL-13, IL-14, and TGF-β are immunosuppressive and prevent the antagonistic response of the immune system against sperm.

40.5 Effects of Smoking on Male Fertility

As aforementioned, the extensive toxic components of cigarettes make it difficult to assess their individual effects on the body. Regardless, there is indubitable evidence that marks cigarettes' implicit negative effects on human health.

40.5.1 Adverse Effects on General Homeostasis

The 2014 Surgeon General's report on cigarette smoking was paradigm in changing the approach to cigarette consumption and anti-smoking measures. It concluded that if smoking rates continued as projected, 5.6 million young adults under the age of 18 would prematurely die secondary to cigarette effects [46]. Many included in this estimate were subject to environmental secondhand smoke, bringing to light a public health burden that extends beyond the direct cigarette consumer. This report continued to break down causes of death due to cigarettes. Popularly known is cigarette's link to cancer. Between 1965 and 2014, smoking-related cancers claimed 6,587,000 lives, trumped only by 7,787,000 deaths due to cardiovascular and metabolic disorders. Pulmonary diseases, diseases related to birth and pregnancy, lung cancer, and coronary heart disease are all documented morbidities due to cigarette smoking.

Chronic diseases have also been attributed to cigarette smoking. Diabetes mellitus, rheumatoid arthritis, general immune impairment, as well as peripheral vascular disease have all been studied as linked to smoking [46, 47].

40.5.2 Adverse Effects on Male Reproductive System as a Whole

Cigarette smoking introduces harmful free radicals into a homeostatic system [20]. Cigarette usage consistently bar-

rages this delicate balance, resulting in a cascade of stressors that dramatically affects normal reproductive physiology at the molecular and macroscopic levels [48, 49] (Table 40.1). Reduced semen quality, compromised auxiliary gland functions, tubular obstruction, and dysfunctional spermatogenesis all result from the increased oxidative stress introduced by cigarette smoking [50, 51]. The main product of all these male reproductive processes is sperm, which under these great oxidative stressors can be fatally damaged.

Such oxidative stress also leads to increased inflammatory reactions in the male genitourinary tract [51]. This damages the local tissues, further escalating the inflammatory response [51]. Reactive oxygen species are released spurring immune system defenses. Local release of provocative inflammatory mediators, such as proteases and proinflammatory cytokines, further incites the local immune reactions [49].

40.5.3 Mechanism of Smoking Effects on Male Fertility

Depending on the mode of smoke exposure, different effects on male fertility can be found. Firsthand smoke exposure through personal cigarette usage, inhalation, and exhalation of cigarette by-products has been shown to impact sperm motility, morphology, and overall sperm quantity [1]. Active cigarette smoking is called mainstream smoking and also yields sidestream smoke, the smoke that is produced by the burning end of the cigarette. A study conducted by Polyzos et al. compared the effects of sidestream and mainstream smoke sources on murine germ cell cultures. Mainstream smoke increased sperm DNA fragmentation, while sidestream smoke impaired normal sperm motility mechanisms [52].

Secondhand smoke has been a popular topic of discussion in advocating for smoking law reformation. This refers to the passive inhalation of cigarette by-products by nonsmokers that are released into the environment by smokers [53]. This mechanism of cigarette smoke consumption has also been shown to have adverse effects on reproductive health parameters [53]. However, this is more difficult to study due the variety in secondhand smoke exposure, as well as various other confounding variables. Regardless, secondhand smoke has higher levels of reactant oxygen species as compared to the smoke actively inhaled that has been documented to impair sperm motility [14].

Evermore common, especially in younger populations, are electronic nicotine delivery systems such as electronic cigarettes [54, 55]. Though the user is inhaling vapor and not smoke, this vapor includes many chemicals such as propylene glycol, glycerol, and concentrated flavorings and is available containing a variety of nicotine concentrations [54]. Due to their relatively recent debut into the commercial marketplace, their exact effects on human biology have not yet been established [54]. Specific research focusing on their effects on reproductive physiology is required.

40.5.4 Risks to Spermatogenesis and Sperm Function

Smoking has adverse effects on spermatogenic processes and mature sperm function. Introducing a toxic environment at any point along this pathway results in abnormal spermatozoa and mature sperm production [26]. Paternal subjection to cigarette chemicals like polyaromatic hydrocarbons increases the rate of sperm death throughout spermatogenesis [24]. Aryl hydrocarbon receptor, a cytoplasmic transcription factor, has an important regulatory factor across the entire spermatogenic timeline [24]. When activated by polyaromatic hydrocarbons, this receptor was shown to impede antioxidant protective processes. Furthermore, this transcription factor was implicated in increased spermatic apoptosis [24].

40.5.5 Sperm Morphology

Well documented is how sperm morphology was impaired in smokers. Active firsthand smoking directly affects sperm morphology, but surprisingly secondhand smoke exposure has also been shown to lead to impaired sperm morphology [7, 52]. Animal studies attempted to further elucidate to what extent sperm quality was affected by smoke exposure, regardless of route [52]. However, further research is needed to completely clarify these conclusions (Table 40.1). Ultrasound evaluation of the microtubule axoneme array showed 99% of smokers to have aberrant construction of this apparatus, while 24% of nonsmokers showed altered microtubule organization [22].

40.5.6 Motility

Sharma et al. found sperm motility to be dramatically impaired in moderate and severe smokers as compared to mild and nonsmokers [18]. Sperm gain motility through the microtubules of the axoneme that compose the cytoskeleton of its tail. They are connected by the protein dynein. Much like skeletal muscle contraction, mitochondrial ATP hydrolysis generates the energy necessary for sperm motility. Any malfunctioning of this, be in protein insufficiency or defective ATPase activity, can render sperm immotile [18].

Additionally, insufficient anti-oxidative measures lead to the peroxidation of sperm membrane components and faulty

membrane stability and reliability [56]. Increased amount of lipid peroxidation results in conceded ability of sperm to maintain mobility, as compared to sperm with lower measured levels of peroxidative by-products [56].

Spermatozoa obtained from healthy males and exposed to cigarette smoke extract were shown to have reduced motility, and increased the number of spermatozoa with lower mitochondrial membrane potential [15]. Remember, this is where the sperm obtains most of its energy utilized for motility. As such, these sperm with lower potentials across the mitochondrial membrane therefore had less energy to dedicate to motility [15]. Vine et al. described a negative correlation between the number of cigarettes smoked per day, pack-years, and sperm motility [8]. Here, it is well documented this parameter of sperm quality is clearly and diversely impacted by the contents of cigarette smoke.

Another study conducted by Taha et al. explored the effects of smoking on sperm parameters in addition to the zinc concentration in seminal fluid. Zinc has proven antioxidant and antibacterial roles making it integral to the development of mature sperm [17]. When looking at both fertile and infertile males, this research showed there to be decreased sperm motility, decreased sperm concentration, decreased sperm viability, and decreased semen concentration. Seminal zinc concentration was also decreased in both fertile and infertile smokers, thus suggesting these sperm samples to be more susceptible to bacterial infection, as well as ROS damage.

Yet not all studies corroborate these findings. Work performed by Dai et al. used gel electrophoresis to isolate various proteins in the testes of mice that had daily exposure to nicotine [21]. Fifteen proteins found to be directly involved in the tricarboxylic acid cycle and cytoskeleton regulation, both integral in maintaining sperm motility, were uniquely expressed in these smoking mice. Additionally, profilin 1, a protein with critical value in cytoskeleton management, was found to be overexpressed in the nicotine-exposed cohort and revealed increased sperm motility [21].

The variation in results calls for increased research efforts to elucidate the effects of smoking on sperm at the molecular level.

40.5.7 Sperm Concentration and Volume

Sperm count was significantly reduced in smokers as compared to their nonsmoker counterparts [1, 18, 23, 57]. A meta-analysis conducted by Vine et al. measured that the sperm density in smokers was on average 13–17% lower than the sperm density of the nonsmoker cohort [57]. A separate study showed that smoking greater than or equal to ten cigarettes each day led to a dramatic decrease in sperm concentration [1]. Ramlau-Hansen et al. reported that the sperm concentration in heavy smokers was 19% reduced from healthy males.

While it seems that there is a consensus on smoking and sperm fluid concentration, Sharma et al. did not find a significant difference in seminal fluid volume between cigarette smokers and nonsmokers [18]. Again, further research is needed to untangle just how smoking disturbs seminal fluid balance and what measures can be taken to reverse this.

40.6 Impairment of Genetic Environment

40.6.1 Gene Methylation

Tobacco- and cigarette-specific carcinogens have also been linked to increased gene methylation. This process typically suppresses gene transcription. More research has been dedicated to elucidating the epigenetic causes of male factor infertility. However, studies have been inconclusive and contradictory. Work performed by Jenkins et al. found regions with increased methylation and other foci with decreased methylation in the infertile cohort as compared to the DNA methylation sites in healthy couples [25].

Santi et al. evaluated specific sites along the genome where aberrant methylation was suspected to impact sperm quality. They concluded that anomalous methylation levels of the cell cycle-associated genes of H19, MEST, and SNRPN resulted in impaired male fecundity [58].

An opposing study conducted by Al Khaled et al. also compared CpG alterations between smoker and nonsmoker sperm samples. Yet, out of 485,000 CpG sites analyzed, only seven sites were shown to have significant differences between the smokers and nonsmokers [27]. Yet six of these were found in single-nucleotide polymorphism regions, where variation is already increased across the population. The last site was found in an intron region. Their work could not determine any causative negative effects on biologically active regions of DNA between smoker and nonsmoker spermatocytes.

40.6.2 DNA Damage

While it is well documented that aging leads to DNA breakage, and therefore impaired sperm quality, smoking has also been linked to DNA damage [23]. Heavy smoking has been linked to abnormal spermatozoa and therefore male infertility [23]. In the cell cycle, there are various checkpoints at which DNA quality is assessed. If the DNA is damaged, by mutation, incorrect base pairing, the cell cycle is halted. Specifically, the checkpoint kinase 1 (Chk1) is activated, which then prevents the cell cycle from continuing through the S phase, where DNA is replicated, in addition to halting

progression past G2, thus stalling cell growth [23]. A study conducted by Cui et al. showed spermatocytes in smoking males to have markedly decreased expression of Chk1 as compared to nonsmoking men [23]. Reduced checkpoint proteins thus allow sperm with damaged DNA to continue through the cell cycle. As such, these sperm undergo less repair of impaired DNA and consequently increased amounts of apoptosis, thereby reducing sperm quality.

Sperm isolated from healthy males and exposed to cigarette smoke extract were shown to have faulty chromatin condensation as well as more early signs of apoptosis [15]. Phosphatidylserine externalization, marking the beginning of an apoptotic cell, was increased, alongside DNA fragmentation, another late presenting sign of apoptosis [15].

DNA repair mechanisms have also been reported as effected by smoking. Mismatch repair pathways are integral in maintaining DNA integrity [59]. Polymorphisms in genes involved in mismatch repair have been linked to male factor infertility [59].

Another study conducted by Horak et al. showed there to be a statistically significant increase bulky DNA accumulations in smokers, as compared to their nonsmoking counterparts [10].

40.7 Male Fertility Rescue

40.7.1 Does Cessation of Smoking Increase Male Fecundity?

The difficult and intricate nature of smoking's effects of various parameters contributing to male fertility makes it even more difficult to assess whether cessation of smoking can allow sperm and male physiology to return to a healthy state. Work performed by Oyeyipo et al. in animal models documented, as concluded previously, that nicotine and smoke contents negatively affect semen quality by all the parameters aforementioned [16]. Yet when rats were removed from the smoking environment, there was a marked increase in normal spermatozoa and male reproductive processes [16]. Thus, perhaps semen could recover from the toxins and deleterious effects of smoke exposure, essentially curing these causes of male infertility [16]. However, further research is needed in both animal and human subjects to conclude whether sperm quality and male reproductive physiology can be rejuvenated after exposure to cigarette smoke.

Further confounding any conclusions is the variety in smoke exposure. However, studies have shown a dose-dependent relationship between the level of cigarette by-product consumption and the degree of negative effects that were documented in the sperm. Ramlau-Hansen et al. exhibited an inverse relationship between the amount of smoke exposure and sperm volume, sperm quantity, and sperm quality [60]. Those with high cigarette consumption were shown to have 19% lower sperm concentration as compared to the nonsmoker cohort [60]. As such, decreasing cigarette usage and smoke exposure may reduce these adverse effects.

40.8 Conclusions

There is no question that cigarettes and their smoke contents are destructive to normal human anatomy physiology across all body systems. While the effects of smoking on female reproductive processes have been well documented, evidence has been inconclusive regarding the effects of smoking on male reproductive physiology. Environmental factors become difficult to untangle from a wide variety of confounding factors; however, it is important to provide conclusive evidence regarding just how normal male fertility can be impaired. This chapter aimed to provide an array of information regarding the multitude of avenues through which reproductive anatomy, male reproductive physiology, as well as spermatozoa end products can be impaired by cigarette smoke. Research into these subjects is also complicated by the immense difficulty in the methodology required to accurately assess spermatic fluid contents and quality. New WHO guidelines with specific protocols on how exactly to navigate this have not been globally implicated. As such, some studies may not have complied with the most recent standards and therefore may have reached conclusions that are no longer applicable. Regardless, further research is needed to better elucidate just how male fertility is impacted by cigarette smoke and whether male infertility secondary to these toxins can be cured by smoking cessation.

40.9 Review Criteria

An extensive search was conducted using the PubMed search engine to examine the effects of smoking and cigarette by-products on male infertility and sperm parameters. The search began in October 2018 and continued through January 2019. Keywords of "male infertility," "cigarette smoking," "spermatogenesis," "sperm quality," "male germ cell DNA methylation," "infertility," "semen parameters," "sperm motility," "sperm morphology," and "WHO guidelines," as well as the names of specific enzymes, were used to help formulate our conclusions. Published peer-reviewed articles were the mainstay of our information, supplemented by book chapters and some online bulletins specifying WHO parameters.

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