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Chapter
Smoking and Its Consequences on Male and Female Reproductive Health

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Abstract

Smoking contributes to the death of around one in 10 adults worldwide. Specifically, cigarettes are known to contain around 4000 toxins and chemicals that are hazardous in nature. The negative effects of smoking on human health and interest in smoking-related diseases have a long history. Among these concerns are the harmful effects of smoking on reproductive health. Thirteen percent of female infertility is due to smoking. Female smoking can lead to gamete mutagenesis, early loss of reproductive function, and thus advance the time to menopause. It has been also associated with ectopic pregnancy and spontaneous abortion. Even when it comes to assisted reproductive technologies cycles, smokers require more cycles, almost double the number of cycles needed to conceive as non-smokers. Male smoking is shown to be correlated with poorer semen parameters and sperm DNA fragmentation. Not only active smokers but also passive smokers, when excessively exposed to smoking, can have reproductive problems comparable to those seen in smokers. In this book chapter, we will approach the effect of tobacco, especially tobacco smoking, on male and female reproductive health. This aims to take a preventive approach to infertility by discouraging smoking and helping to eliminate exposure to tobacco smoke in both women and men.

Keywords: tobacco, reproductive health, infertility, cessation therapies

1. Introduction

The higher predominance of smoking is seen among youthful men during their fertility period. It is estimated that almost half of smokers, in the world, are aged between 20 and 39 years old [1, 2].

Infertility is a complicated condition in which contribute environmental lifestyle, genetic, and epigenetic factors [3, 4].

Different studies showed that semen parameters may be affected by various lifestyles, advancement in technologies, environmental pollution [5], alcohol intake [6], smoking [7–9].
Smoking and chewing tobacco are the harmful addictions [10] that include a variety of toxic, mutagenic, and carcinogens substances, together with nicotine reported for adversely affecting semen quality and consequently male infertility [11, 12].

1.1 Hormone regulation disruption

The most toxic compound in tobacco products is nicotine. It is a psychoactive drug and an oxidizing substance, which is addictive. The nicotine in any tobacco product readily absorbs into the blood when a person uses it. Nicotine may change the hypothalamic–pituitary axis (HPG) by enhancing the release of cortisol, growth hormone, oxytocin, and vasopressin, which in turn inhibit the prolactin and the luteinizing hormone (LH) [13].

Heavy smokers are the most facing fertility problems than nonsmokers [14]. Studies showed that in smokers, the mean levels of prolactin (PRL), follicle-stimulating hormone (FSH), mean levels of LH were lower, and the mean estradiol (E2) levels were higher in comparison to nonsmokers [15]. The same is observed in another study where testosterone, E2, LH, and FSH levels are lower in smokers [16].

In contradiction, no differences in serum total testosterone, LH, and FSH levels were demonstrated among fertile male patients divided into heavy, moderate, and mild smokers [17]. Moreover, substances in tobacco smoke affect pituitary, thyroid, adrenal, and testicular functions and consequently alter semen quality of both infertile and fertile men [18], leading to a change in testosterone, E2, PRL, LH, and FSH levels, which may cause Leydig and Sertoli cell failure in smokers [19–22].

1.2 Erectile dysfunction

Smoking have been demonstrated to be a hazard factor for erectile dysfunction, a condition in which man is incapable to induce or keep an erection firm sufficient for satisfactory sexual intercourse [23].

In Korea, after a survey among 600 men aged between 40 and 80, they found that ejaculatory and erectile functions malfunction was associated with previous and current smoking habit [24].

In Australia, a second study found that ED was associated with cigarette smoking, and even this association became stronger in heavier smokers [25].

Shiri and colleagues demonstrated that the risk for ED from smoking was generally little, and the smokers had decreased chances of recuperating from ED compared with nonsmokers [26].

A group of researchers showed an association between smoking more than 20 cigarettes daily and nearly 50% high risk of erectile dysfunction [27].

He et al. concluded a relationship between nearly 12 million cases of ED in Chinese men and smoking and reported a significant dose–response association between smoking and the risk of ED [28].

Cao et al. confirmed a significant association between smoking and the high risk of ED. Besides, quitting smoking significantly improved both physiological and sexual wellbeing in male smokers, notwithstanding the level of erectile dysfunction [29].

1.3 Smoking and oxidative stress

The compounds of a cigarette enhance superoxide generation by both endothelial and smooth muscle cells from NADPH oxidase (NOXs) and uncoupled endothelial
nitric oxide synthase (eNOS) and upregulate proinflammatory cytokines and the Ras homolog gene family, member A (RhoA), and its downstream effector Rho-associated protein kinase (ROCK) (RhoA/ROCK) contractile pathway. This process leads to reduction of nitric oxide (NO) bioavailability, endothelial dysfunction, and increase of vasoconstriction [30].

Reactive oxygen species (ROS) also affect hypothalamic–pituitary-thyroid axis and reduce triiodothyronine (T3) and thyroxine (T4) secretion. Low levels of T3 reduce the levels of the protein in Leydig cells and the steroidogenic acute regulatory (StAR) mRNA, along with testosterone production [31]. ROS production interferes oxygen delivery to the testis, which is crucial for spermatogenesis [32, 33].

A possible cause of the harmful effects of nicotine and other compounds of tobacco, on the male genital tract, is the release of mediators of inflammation, such as interleukin-8 and interleukin-6, which may enroll and actuate leucocytes [34, 35]. Successively, activated leukocytes lead to excessive ROS production in semen. Studies reported high levels of oxidative stress markers such as ROS malondialdehyde (MDA) and smoking markers such as cotinine in seminal plasma of smokers [9, 36]. Even expression of antioxidant enzymes and seminal vitamin C was insufficient to provide full protection of spermatozoa [37]. Furthermore, the high levels of ROS and cotinine in seminal plasma were associated with the number of daily cigarettes. The higher consumption means a severe damage in the sperm membrane because of its polyunsaturated fatty acids composition [38].

1.4 Smoking and sperm parameters: Concentration, motility, and morphology

As mentioned before, tobacco and its compounds lead to an excessive production of ROS. The key mechanism responsible for sperm damage is the lipid peroxidation of spermatozoa membrane caused by ROS. As a result, sperm concentration, viability, mobility, and normal morphology decrease [39, 40]. It alters the fertilizing capacity of the sperm [41] and reduces antioxidant activity, which has possible adverse effect on sperm density, motility, and morphology [9, 42]. Calogero et al. demonstrated that Cigarettes Smoke Extract (CSE) in healthy nonsmokers men could suppress sperm motility and alters chromatin condensation. Besides, in a concentration- and time-dependent manner, CSE induces early apoptotic sign and a late apoptotic sign: fragmented sperm DNA [43]. In comparison to mainstream smoke, sidestream smoke contains several toxicants at higher levels including ROS such as superoxide and hydrogen peroxide [34, 40], as well as cadmium [34, 44]. They have also shown to affect semen quality and cause disturbance in sperm acrosome function [39]. Therefore, passive smokers are concerned with this problem. They are 2.5 times more exposed to cancerous substances in tobacco than active smokers [45, 46].

1.5 Smoking and sperm DNA fragmentation in sperm

The most frequent DNA anomaly is DNA fragmentation, which is associated with poor spermatozoa quality, low fertilization rates, and bad embryo quality [47]. Sperm DNA fragmentation is generally induced by oxidative stress and/or apoptosis [48, 49]. Oxidative stress (OS) caused by smoking induces oxidative DNA damage of the spermatozoa [50] and mutagenic adducts [51]. Thus, it leads to alteration of sperm quality and may cause male infertility [52].
Different techniques were used to measure the spermatozoa DNA damage. The latter showed an association with various assisted reproductive technology (ART) outcomes such as fertilization rate, embryo quality, implantation rate, pregnancy, and spontaneous abortion [53]. So, an elevated DNA damage is associated with low implantation and consequently, low pregnancy rate [54].

In men with idiopathic infertility, associated with cigarette smoking, an increase in sperm DNA stainability, sperm DNA fragmentation index, and spermatozoa with round head were noticed [55].

In addition, it has been suggested that DNA damage is the main cause of implantation failure in embryos derived from healthy eggs fertilized by sperm with chromatin defects [56, 57]. These negative effects of smoking on spermatozoa and the damage to the DNA may be due to excessive ROS production [58] and decrease the antioxidant levels in seminal plasma [42].

Dai et al. also reported that tobacco smoking negatively affects sperm parameters, such as volume, concentration, motility, morphology, and viability, leading to male infertility [59].

Moreover, an excessive production of ROS leads to oxidative stress; in turn it affects not only sperm nuclear DNA but also sperm mitochondrial respiratory activity [60] and the endocrine function resulting in several pathologies of the male reproductive system and may be leading to male infertility [61, 62].

1.6 Smoking and molecular alteration: epigenetics, miRNA/noncoding RNA of spermatozoa

Different lifestyles and environmental factors alter epigenetic profiles: chromatin modifications, DNA methylation, and noncoding RNAs, thereby altering chromatin structure and changing gene expression [63].

The protamines are fundamental in the sperm chromatin condensation and the protection of the paternal genomic DNA from alterations [56, 64, 65]. It has also been proposed that the deficiency in protamine may lead to the accumulation of lesions at the level of the spermatic DNA [66], morphological abnormalities, and the triggering of apoptotic pathways, the inactivation of mitochondria, and consequently, the decrease in the sperm motility [67].

The alterations of protamine ratio (P1/P2) at the level of the interval (0.8–1.2) in the semen have been clearly associated with the male infertility [68].

Hammadeh et al. also investigated the association between smoking and protamine deficiency of sperm chromatin and demonstrated that the high P1/P2 ratios in smoker are due to an underrepresentation of P2. This suggests that ROS production in smokers deteriorates chromatin condensation and change protamine 1 to protamine 2 ratio of spermatozoa [9].

Smoking is probably behind the underexpression of protamine ending with high levels of histone to protamines ratios [69]. Overall, the alteration from the normal P1/P2 ratio seems to be important in male fertility, although the precise manner by which this happens can differ from person to person.

Abnormalities during the arrangement of chromatin may also cause infertility [70, 71], affecting embryo development [72, 73].

Epigenetic modifications change the gene expression without altering the DNA sequence and can be transferred to next generation through both meiotic and mitotic cell divisions [74].
Different studies have investigated the relationship between the effects of smoking on epigenetic profiles such as chromatin modifications and DNA methylation and genes transcription [75, 76]. Cigarette smoking adversely affects DNA methylation patterns [77–79]. A previous study from our laboratory showed that smoking may lead to biochemical changes in many regions of the sperm DNA that are related to MAPK8IP and TKR gene. And that has negative effects on semen parameters [80].

Moreover, benzo[a]pyrene and nicotine induce alterations in sperm chromatin during histone-protamine transition, which may alter the methylation pattern of CpG in the promoter regions of DNA in the offspring of heavy smokers [81].

Furthermore, many studies took into consideration the interaction between the gene and the environment. They studied the association between tobacco smoking and genetic polymorphisms, involving DNA repair genes and genes involved in carcinogen metabolism [82, 83].

Over 100 miRNAs were found in spermatozoa. Twenty-eight of them were differentially expressed between nonsmokers and smokers. In infertile men, the expression of has-miR-146b-5p, has-miR-509-5p, has-miR-146d, and has-miR-652 was altered [83]. These four miRNAs are involved in different pathways such as cell proliferation, differentiation, and apoptosis in spermatozoa as well as early embryogenesis [83]. Altered spermatozoal mRNA profiles and miRNA changes have been shown in smokers [84, 85].

An increased risk of idiopathic male infertility was reported in male smokers, while nonsmokers did not show an increased risk of infertility. These men carried 462Ile/Val genotype of the CYP1A1 gene [86].

Moreover, a significant relationship was observed between smoking and the GSTM1+/GSTT1 del genotypes and the GST gene GSTP1 105IV/GSTT1 polymorphisms in infertile men. The GSTP1, GSTM1, and GSTT1 genes are engaged in the development of idiopathic male infertility [87].

Amor et al. demonstrated that H2BFWT, TNP1, TNP2, PRM1, and PRM2 genes were differentially expressed (p < 0.01), and these genes were downregulated in the spermatozoa of heavy smokers [7].

1.7 Male smoking and assisted reproductive treatment (ART)

Almost 50 million couples worldwide are facing infertility issue [88, 89]. Infertility is described as a disease characterized by a failure to conceive after regular unprotected intercourse of 1 year and is used interchangeably with the term “subfertility” [90].

ART technique was the solution for such couples to solve their infertility issues and to achieve pregnancy. Different lifestyles and environmental factors showed to have an adverse effect on a male and female fertility and consequently conceiving. Tobacco smoking is one of the lifestyle factors that was associated with infertility.

A smoking habit in males also has an adverse effect on pregnancy outcomes among in vitro fertilization (IVF) intracytoplasmic sperm injection (ICSI) patients [8, 91]. An association between cigarette smoking and altered ICSI and IVF outcomes was reported [41]. In a study by Klonoff-Cohen et al., the number of retrieved oocytes decreased by almost 46% in smokers. The males were active smokers, and the females were passive smokers [92]. In addition, a decrease in live birth rates was noticed in 166 couples seeking pregnancy using ART [93].
Although spermatozoa with damaged DNA is still capable of fertilization, but its effect is prominent in the later stages such as apoptosis, poor fertilization rate, high frequency of miscarriage, and morbidity of off springs [94, 95]. Because of the faulty transition histones-protamines, sperm DNA breaks increased, and this may cause poor embryo morphology at early cleavage stages. An abnormal protamine ratio was associated with poor preimplantation [56]. However, other studies have reported that there is no significant relationship between smoking and fertility outcomes in humans [96].

2. Effect of tobacco on female infertility and reproductive health

2.1 Smoking and conception delay

Smoking women experience almost 50% conception delay for over 1 year than nonsmokers women. Besides, active and/or passive tobacco smoking by either partner had adverse effects on conception [97]. Smoking couples, with a conception of over 15 cigarettes daily, demonstrated low fecundity and an increased time to achieve pregnancy [98]. The majority of studies support the negative effects of smoking on fecundity, regardless of other factors [98, 99]. Several reviews have accumulated data on female fecundity and cigarette smoking. All of them concluded that smoking adversely affects female fertility [100].

2.2 Smoking and ovarian function

Compounds of tobacco smoke seem to accelerate the loss of reproductive function and follicular depletion [101]. Women who were exposed to tobacco during the fetal period showed an increase in ovarian dysgenesis [102]. A relation was found between smoking and short menstrual cycle length, that could lead to low fecundity [103]. Moreover, smoking women have their menopause 1–4 years in comparison to nonsmokers women [104].

Women consuming tobacco have high levels of nicotine, which can induce ovarian dysgenesis, resulting in increased infertility [102, 105]. On the other hand, other chemicals in cigarettes can affect the anatomy and function of the uterine tubes [106]. Another study reported that tobacco exposure during pregnancy can cause long-lasting effects in the reproductive system [52].

2.3 Smoking and early pregnancy loss

Tobacco smoke showed an association with bacterial vaginosis, which in turn is associated with second-trimester miscarriage and with preterm labor [107]. A case–control study demonstrated that smoking women (>20 cigarettes/day) had an increased risk of ectopic pregnancy in comparison to nonsmokers women [108]. An increase in spontaneous miscarriage is associated with tobacco smoke in both natural and ART cycles [109].

Moreover, 24% of women with experience of abortion and 19% of women without experience of abortion were passives smokers [110]. Passive smoker women
had low fertility rate and a risk of abortion four times higher in comparison to
nonsmokers [111].

A dose–response relationship has been found between miscarriage and smok-
ing. One percent increase in relative risk of miscarriage per cigarette smoked daily.

Besides, the risk of miscarriage increased by 11% among pregnant women exposed to
secondhand smoke [112].

Pineles et al. demonstrated also that the amount of cigarette smoked by the preg-
nant woman increases the risks of stillbirth, neonatal death, and perinatal death [112].

In a large cohort study, parental smoking during pregnancy was found to increase
the risk of stillbirth, and paternal smoking was an independent risk factor for still-
birth despite maternal passive smoking status [113].

2.4 Female smoking and assisted reproductive treatment (ART)

A smoking woman seems to have reduced fertility and difficulty in conceiving.

Different studies showed that tobacco may affect hormone production, which makes
it difficult for a woman to become pregnant [114].

Studies have also reported that smoking woman, during fertility treatment, had
higher numbers of canceled cycles, lower peak estradiol levels, an elevated gonadotro-
pin injection for ovarian stimulation, increased testosterone, fewer oocytes retrieved,

thicker zona pellucida, and more cycles with failed fertilization and implantation
compared with nonsmokers [92, 115, 116]. Besides, the success rates of IVF were
lower in smoking woman compared with nonsmokers one [117].

Some have also shown that female smoking is associated with reduced numbers of
oocytes [118], lower fertilization [115, 119] and pregnancy [119], and higher miscar-
riages rate [120]. In contrast, other studies have reported that smoking has no adverse
effects on fertilization [3] and pregnancy outcomes [121].

Freour demonstrated that active smoking women presented poor ovarian response
and lower clinical pregnancy rate [122]. Moreover, an association has been described
between current smoking woman, undergoing IVF, and lower concentrations of
anti-mullerian hormone (AMH) [122, 123]. In addition, AMH levels were 44% higher
in nonsmokers compared with current smokers [124] and declined 21% faster yearly
in smokers compared with nonsmokers [125].

Ozbakir and Tulay investigated the association between cigarette smoking and
oocyte quality. They concluded that cigarette smoking did not affect the number of oocytes retrieved. However, a significant difference
was detected in the morphological assessment of oocyte including cytoplasmic
anomalies [126].

3. Effects of tobacco smoking on progeny

The birth defects among the offspring of smoking parents are high [127]. During
their pregnancy, smoking woman showed an increased risk of trisomy 21 in the
offspring, which results from maternal meiotic nondisjunction [128].

Maternal smoking increased the risk of spontaneous abortion, fetal growth
restriction, preterm birth, stillbirth, and low birth weight [129]. A dose–response
relationship was found between the risk of low-birth weight and the number of
cigarettes smoked daily during pregnancy [129].
Maternal smoking was suggested to have even negative effects on the sperm count of men, whose mothers had smoked more than 10 cigarettes daily, in comparison to men having nonsmoker mothers.

Benzo[a]pyrene and nicotine in cigarette smoke have recently been shown to induce harmful alterations of sperm DNA that can be transmitted through the germ line to future generations [130, 131].

It has also been reported that preconception paternal tobacco smoking increases the chances and risk of multiple forms of morbidities in the fetus and offspring, which could be mediated through epigenetic modifications [132].

Kataoka et al. showed that the high number of daily cigarettes can be the reason behind the low weight at birth. Smoking mothers, who smoked 11–40 cigarettes/day, had infants with 435 g lower weight in comparison with infants born to nonsmoking women. The same was observed for infants whose mothers smoked 6–10 cigarettes/day. Their birth weight was 320 g lower than infants of nonsmoking mothers [133].

Liu et al. concluded also that low number of cigarettes smoked during either the first or second trimester of pregnancy, even as low as 1–2 cigarettes per day, showed an association with a high risk of preterm birth. This proves that during pregnancy, there is no safe level or safe trimester for maternal smoking [134].

4. Smoking cessation

4.1 Nicotine replacement therapies

Nicotine replacement therapies (NRTs) were the first smoking cessation medications the FDA approved for use in smoking cessation therapy. NRT is an effective and safe strategy for quit smoking. They diminished withdrawal sentiments by giving you a low, controlled amount of nicotine but none of the other dangerous compounds found in cigarettes. A low amount of nicotine makes a difference by fulfilling your need for nicotine and diminishes your smoking addiction [135, 136].

There are different varieties of NRTs, which are used in different ways. Each person can choose which variety that suits him. From person to person, the results of NRT are different. Current NRT products include transdermal patch, chewing gum, nasal sprays, lozenges, and inhalers. A combination of short- and long-acting forms of NRT is more effective for smoking cessation in comparison to the use of single forms of NRT [136, 137].

There are non-nicotine medications such as bupropion and varenicline, which are approved from FDA. Their targets are the nicotine receptors in the brain. That helps with withdrawal feelings and blocks the effects of nicotine [135, 136].

4.2 Smoking cessation, reproductive health outcomes, and ART treatment

Santos et al. evaluated sperm quality after a 3-month smoking cessation. They observed a remarkable improvement of different sperm parameters: sperm concentration, sperm vitality, motility, and percentage of spermatozoa recuperated after an enrichment technique [138].

Smoking is associated with oxidative stress. Therefore, antioxidants can be recommended in treatment of infertile smoking women [139]. In addition, patients should adopt lifestyle modifications and quitting smoking [3, 140], losing weight through
different methods, such as diet, education, and exercise [141], and decreasing exposure to harmful toxins, such as phthalate [142].

Fecundity associated with smoking may be improved within 1 year of smoking cessation [143]. The physiological and sexual health in male smokers was improved after they quit smoking, regardless of their baseline level of erectile dysfunction [144].

If behavioral approaches did not work, the use of bupropion and/or varinecline have helped non-pregnant women to quit smoking [145]. Besides, the use of combined NRT was superior to any single NRT in treatment of individuals [146].

5. Conclusion

In the light of the present review, tobacco smoking has deleterious effects on reproductive health including gametes from both parents. Active or passive smoking negatively affects not only the parents but also the offspring. Therefore, the lifestyle factors are very important factors for pregnancy and delivering healthy children. Smoking women and men reproductive age should be strongly encouraged to quit smoking before trying to conceive. Besides, research is still needed to understand how and why smoking causes adverse outcomes in these patients.

Conflict of interest

The authors declare no conflict of interest.

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