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An Overview on the Impact of Smoking Tobacco on Male Infertility

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ABSTRACT

Numerous studies have revealed that sperm parameters, seminal plasma, and a number of other fertility factors are all adversely impacted by cigarette smoke. However, it is unclear how smoking actually affects male fertility. The relationship between smoking and the parameters of semen is based on the biological fact that smoking increases the presence of reactive oxygen species, leading to oxidative stress (OS). Male fertility is decreased as a result of OS's devastating effects on sperm parameters like viability and morphology as well as its impairment of sperm function. Not all studies, though, have reached the same conclusions. The debated relationship between smoking and male fertility is clarified by this review, which also examines the effect of different smoking methods on male infertility. Additionally, this review highlights the mechanism how tobacco smoking disrupts the entire male reproductive system.

KEYWORDS: *Infertility, Male; Smoking; Spermatogenesis; Spermatozoa; Seminal parameters; Tobacco smoke*

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INTRODUCTION

Despite the well-known negative effects of smoking on health in general and the male reproductive system in particular *(Zhang ZH, et. al, 2013)*, smoking continues to be a global phenomenon. According to the World Health Organization (WHO), 30% of all men aged 15 and up smoke *(Saleh RA, et. al, 2002)*. Men of reproductive age (20–39 years old) account for roughly 46% of smokers *(Trummer H, et. al, 2002)*. Although the prevalence of male smokers dropped from 41.2% in 1980 to 31.1% in 2012, based on nationally representative sources from 187 countries, the actual number of daily smokers increased. There were 967 million smokers in 2012, up from 721 million in 1980 *(Ng M, et. al, 2014)*. According to World Health Organization 2019, with an estimated 19% of adults using tobacco products worldwide, including 33% of men and 6% of women, tobacco use is still very common. These figures are alarming because tobacco use has long been linked to a number of chronic illnesses and negative health outcomes, including potential mutagenic effects (World Health Organization 2020). According to the WHO, male factor infertility affects 30% to 35% of all cases of infertility, with 10% to 15% of couples in industrialized countries experiencing it *(Odisho AY, et. al, 2010)*. Numerous studies have been conducted to try and find any links between smoking and male infertility, some of which have produced contradictory results. While many studies have shown that smoking has a negative effect on the metrics used for semen analysis and male infertility (*Zinaman MJ, et. al, 2000) (Lewin A, et. al, 1991) (Chia SE, et. al, 2000) (Künzle R, et. al, 2003)*. Others have found no such effects and, in some cases, even beneficial effects on the sperm's ability *(Adelusi B, et. al, 1998)* to move around and the degree of nuclear DNA damage *(Sergerie M, et. al, 2000)*. There have been reported additional inconsistent and conflicting findings regarding the impact of smoking on male infertility *(Hoidas S, et. al, 1985 (Vogt HJ, et. al, 1986)*.Furthermore, studies claiming that smoking has an impact on semen parameters have not conclusively shown that smoking has an impact on male fertility *(Brugo-Olmedo S, et. al, 2001) (Marinelli D, et. al, 2004) (ASRM, Smoking and infertility. Fertil Steril 2008)*.

These contradictory and ambiguous results are not shocking. There are three hypotheses that could account for the emergence of contradictory results. First, a variety of metrics, including semen

parameters, spermatozoa function, histologic alterations, and others are used to evaluate the impact of smoking on male fertility. The use of various assessments could lead to discrepancies in study findings. Second, the mechanisms by which smoking might affect male fertility are not well understood. Thirdly, because it is difficult to account for confounders like exposure to alcohol use, medical conditions, toxins, and socioeconomic status, it is difficult to compare data between studies directly.

In this review we discuss about the content of cigarettes, global incidence of infertility and highlight the various effects of tobacco exposure on male fertility. The effects of smoking on various components of the male reproductive system are then described, focusing on both the physiological and pathological effects of smoking. This study then summarizes the potential mechanisms by which smoking results in genetic and epigenetic changes to male reproductive function.

Content of cigarette smoke:

The components of cigarette smoke are gases, vaporized liquid, and particles. The chemical reactions of hydrogenation, pyrolysis, oxidation, decarboxylation, and dehydration result in the release of nearly 4,000 compounds. There is a biphasic smoke release (gaseous and particulate). Carbon monoxide is released during the gaseous phase, and nicotine and tar are released during the particulate phase *(Hammond D, et. al, 2006)*. Nicotine and its metabolites, cotinine, radioactive polonium, benzopyrene, dimethylbenzanthracene, naphthalene, methylnaphthalene, polycyclic aromatic hydrocarbons (PAHs), and cadmium are among the toxic chemicals, mutagenic agents, and carcinogens found in cigarette smoke *(Colagar AH, et. al, 2007) (J, Elzanaty S, et. al, 2008)*.

Nicotine is tobacco's main psychoactive substance. The substance that causes addiction to tobacco is nicotine. Humans metabolize the majority of nicotine into cotinine, which is then converted into trans-3'-hydroxycotinine (3HC) *(Zhu AZ, et. al, 2013)*. Cotinine and 3HC levels in the seminal fluid and serum appear to be similar in cigarette smokers, while nicotine levels in the seminal fluid are typically higher. Forward sperm motility is correlated with seminal cotinine levels, but total sperm motility is negatively correlated with seminal cotinine and 3HC levels *(Pacifici R, et. al, 1993)*.

The heavy metals cadmium and lead are the main active components of smoke that affect semen parameters. Cadmium has been shown to negatively affect sperm parameters in previous animal studies *(Oliveira H, et. al, 2009)*. Smokers who smoke more than 20 cigarettes per day have been found to have elevated seminal cadmium levels, and blood cadmium levels have been found to have a statistically significant positive correlation with cigarette-years and a statistically significant negative correlation with sperm density *(Oldereid NB, et. al, 1994)*. Furthermore, compared to fertile men and infertile non-smokers, infertile smokers have higher lead levels in seminal plasma *(Chia SE, et. al, 1994)*. Negative correlations between sperm concentration, motility, and morphological abnormalities in abnormal spermatozoa and seminal lead and cadmium concentrations have also been noted *(Pant N, et. al, 2015)*.

Researchers studying male reproduction are interested in tobacco use because it contains over 7000 compounds, of which about 70 have been linked to cancer *(Hecht 2003) (IARC 2012)*. By Shihadeh et al., various toxins found in tobacco smoke are reviewed in detail. Through the processes of hydrogenation, pyrolysis, oxidation, decarboxylation, and dehydration, combustible tobacco products emit gases, vaporized liquids, and particles that result in exposure *(du Plessis et al. 2014)*. Smoke from cigarettes is released in two phases: particulate phase, which contains nicotine and tar, and gaseous phase, which contains carbon monoxide *(Hammond et al. 2006)*. Cigarette smoke contains a variety of carcinogens and mutagens, including radioactive polonium, benzopyrene, dimethylbenzanthracene, naphthalene, and methylnaphthalene. It also contains heavy metals like cadmium *(Hosseinzadeh Colagar et al. 2007) (Richthoff et al. 2008) (Dai et al. 2015*).

Effect of smoking on semen parameters:

It has been demonstrated that smoking has a negative impact on a number of semen analysis parameters. According to a cross-sectional analysis of 2542 healthy men conducted by Ramlau-Hansen et al. between 1987 and 2004, smokers had lower sperm counts, sperm volumes, and sperm percentages when compared to non-smokers. Furthermore, it was hypothesized that the dose-dependent association between smoking and sperm concentration existed. Indeed, even after adjusting for age, recent fevers, length of abstinence, and diseases in the reproductive organs, men who smoked more than 20 cigarettes per day had a 19% lower sperm concentration than nonsmokers. It was determined that adult smoking had a mildly negative impact on semen quality.

Kunzle et al. found that smoking was linked to lower sperm density (15.3%), total sperm counts (17.5%), and total motile sperm (16.6%) compared with non-smokers in a different sizable cohort of 1786 men undergoing infertility workup (655 smokers and 1131

nonsmokers). Furthermore, smoking had a minor but non-significant impact on morphology (percent of normal forms) and ejaculate volume. In a study by Saaranen et al., it was discovered that smoking had an impact on ejaculate volume. They discovered that smokers had lower semen volumes per ejaculate than non-smokers, with a more specific inhibition occurring in men who smoked more than 16 cigarettes per day. The results mentioned above have been supported by a number of smaller studies. In their study of 362 Chinese men visiting an infertility clinic, Zhang et al. discovered that smoking was associated with lower semen volumes, sperm concentrations, and rates of forward progression. The enzyme superoxide dismutase, which is involved in the oxidative stress pathway and has previously been shown to be lower in the seminal plasma of infertile men, was tested in the seminal plasma of the authors in order to further investigate the physiological basis for these changes. Superoxide dismutase levels were discovered by Zhang et al to be inversely correlated with the quantity and frequency of cigarette smoking, suggesting a connection between smoking, oxidative stress, and infertility. Another study involving 200 infertile men discovered that smokers had higher rates of decreased sperm motility and abnormal sperm morphology. Similar outcomes were reported by Chia et al. in 618 Chinese men. The lower sperm counts and higher prevalence of abnormal sperm morphology observed in smokers within the cohort examined by Chia et al. were also discovered to be dose-dependent.

This kind of dose dependency was also confirmed by Merino and colleagues, who looked at 358 Mexican men who were divided into 3 groups based on how many cigarettes they smoked each day. The authors extended their findings to note that men who smoked 10 cigarettes per day experienced significant changes in their semen analysis parameters, which confirmed the effects of smoking on reduced sperm density and abnormal morphology. As a result, adverse effects on fertility appeared to be a possibility for even "light" smokers.

It's interesting that some studies have been unable to prove a connection between smoking cigarettes and undesirable effects on semen parameters. The largest of these involved a case-control study involving more than 2000 British men receiving infertility treatment. The study's findings suggested that smoking was not a separate risk factor for lower levels of motile sperm. However, other sperm characteristics, such as sperm morphology, were not evaluated. Dikshit et al. discovered that among 626 men visiting infertility clinics, neither chewing tobacco nor cigarette smoking were significant risk factors for decreased semen quality. Similar outcomes were observed in a cohort of 223 Turkish men by Hassa and colleagues. Furthermore, no discernible differences in sperm density or motility between smoking and non-smoking men were found when 889 men who were scheduled for vasectomy were examined. It's important to note that, in contrast to many of the studies mentioned above, the population for this particular study was not chosen from patients who had come in for a male infertility evaluation. Indeed, it can be assumed that men seeking vasectomy are fertile, suggesting that smoking has different effects on men who are infertile and those who are not. These studies do suggest that men who have trouble conceiving should be counseled to stop smoking in order to maximize their fertility outcomes, even though they emphasize the significance of patient selection when examining the effects of smoking on fertility.

A small number of meta-analyses have also been carried out to investigate the relationships between cigarette smoking and semen parameters in addition to the observational studies mentioned above. Over 29000 men from 57 observational studies were included in one meta-analysis by Li et al. Smoking had negative effects on all sperm parameters, including semen volume, sperm density, total sperm counts, and percentage of sperm with progressive motility. These findings were applied to both fertile and infertile men. Smokers had sperm density that was between 13% and 17% lower than non-smokers, according to an earlier, second meta-analysis by Vine et al. In conclusion, smoking has an impact on the results of semen analysis in infertile men. For this reason, it is important to advise men who are having trouble getting pregnant to give up smoking as soon as possible.

Mechanisms through which tobacco smoke affects male fertility:

Numerous reproductive abnormalities in men who smoke tobacco include impaired spermatogenesis, decreased semen quality, and altered sperm function, according to the majority of studies *(Martini et al. 2004) (La Maestra et al. 2015)*. The increased production of reactive oxygen species (ROS), which causes oxidative stress (OS), DNA damage, and apoptosis in germ cells, is one factor contributing to these results. While ROS are necessary for physiological processes *(Haque et al. 2014)*, their abnormal buildup can result in DNA strand breaks, peroxidation of unsaturated lipids, disruption of mitochondrial function, and oxidative DNA damage *(Fullston et al. 2017) (Roychoudhury et al. 2017)*.

Spermatozoa have few cytoplasmic antioxidants and few repair mechanisms *(Attia et al. 2014*), making them susceptible to ROS. The DNA damage carried in sperm DNA persists because DNA is inert to translation and transcription *(Attia et al. 2014).*

In the semen samples collected from smoking men, *Kumar et al. (2015*) found elevated levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), spermDNA fragmentation index, and seminal ROS. Another study found that smoking men's spermatozoa had lower levels of glutathione reductase mRNA expression and sperm glutathione peroxidase activity (GPx-1, 4) *(Viloria et al. 2010*). Other authors have noted decreased levels of glutathione-S-transferase and glutathione as well as elevated levels of protein carbonyls and malondialdehyde in smokers' semen *(Haque et al. 2014) (Dai et al. 2015).* Numerous studies have shown that nicotine, one of the components of tobacco smoke, can cross the blood-testis barrier and influence spermatogenesis by either altering genetic integrity or hormone production *(Toppari et al. 1996) (Kumar et al. 2015) (Aprioku and Ugwu 2016).* Since DNA is loosely bound to histones in the nucleohistone compartment of the sperm nucleus, environmental factors like exposure to endocrine disruptors may affect the integrity of the sperm genome *(Jeng 2014*). The plasma membrane of the sperm is subsequently impacted by nicotine's role as an oxidizing agent.

Polyunsaturated fatty acids (PUFA) are abundant in the sperm plasma membrane and are highly susceptible to reactive oxygen species (ROS); their invasion causes lipid peroxidation *(Haque et al. 2014) (Harlev et al. 2015).* Initiation, propagation, and termination are the three stages of lipid peroxidation. The lipid peroxyl radical is created during the initiation process when free radicals interact with fatty acid chains. Free radicals are created when fatty acids and peroxyl radicals combine, continuing the chain reaction. Finally, the two radicals react with one another and cause the breakdown of lipids *(Omolaoye and Du Plessis 2018).* The breakdown of sperm plasma membrane PUFA, the onset of oxidative stress, the development of sperm DNA damage, the impairment of spermatogenesis, the reduction in sperm production, the impairment of chromatin remodeling, and the decrease in nuclear protamination are all caused by an increase in an oxidizing agent *(Aitken et al. 2014).* Looking at how smoking affects sperm DNA, it can be hypothesized that tobacco smoke is not only bad for those who actively smoke but can also cause damage to the paternal genome even before fertilization *(Kumar et al. 2015).*

Conclusion:

The potential effects of smoking on male fertility were discussed in this review. Despite the fact that no precise, unambiguous conclusions can be drawn, some inferences can be made. First, smoking affects semen quality and function more significantly in fertile men than in subfertile men. This may be a result of the primary level impairment of spermatozoa function and semen parameters in the infertile population. The current data on smoking's impact on semen parameters have not been thoroughly analyzed, but fertility can still be impacted even when semen parameters are normal. Second, oxidizing species and the subsequent genetic and epigenetic alterations brought on by smoking may directly correlate with decreased sperm function and decreased fertility, offering a potential mechanism for how smoking affects male fertility. There should be more research done on this correlation. Third, smoking affects sperm quality and function in a dose-dependent manner. Any male smoker should be encouraged to quit, especially if he is trying to get pregnant with his partner. By educating patients, keeping track of them, and offering ongoing support, healthcare professionals should help people stop smoking. The research on the relationship between smoking and male fertility supports the preferred preventive strategy of discouraging smoking and preventing exposure to tobacco smoke in general among males and females, and in particular when trying to conceive.

References:

[1] Zhang ZH, Zhu HB, Li LL, Yu Y, Zhang HG, Liu RZ. Decline of semen quality and increase of leukocytes with cigarette smoking in infertile men. Iran J Reprod Med 2013; 11:589-96.

[2] Saleh RA, Agarwal A, Sharma RK, Nelson DR, Thomas AJ Jr. Effect of cigarette smoking on levels of seminal oxidative stress in infertile men: a prospective study. Fertil Steril 2002; 78:491-9.

[3] Trummer H, Habermann H, Haas J, Pummer K. The impact of cigarette smoking on human semen parameters and hormones. Hum Reprod 2002; 17:1554-9.

[4] Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer- Lindgren L, Thomson B, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. JAMA 2014; 311:183-92.

[5] World Health Organization. Infections, pregnancies, and infertility: perspectives on prevention. Fertil Steril 1987; 47:964-8.

[6] Odisho AY, Nangia AK, Katz PP, Smith JF. Temporal and geospatial trends in male factor infertility with assisted reproductive technology in the United States from 1999- 2010. Fertil Steril 2014; 102:469-75.

[7] Zinaman MJ, Brown CC, Selevan SG, Clegg ED. Semen quality and human fertility: a prospective study with healthy couples. J Androl 2000; 21:145-53.

[8] Lewin A, Gonen O, Orvieto R, Schenker JG. Effect of smoking on concentration, motility and zona-free hamster test on human sperm. Arch Androl 1991; 27:51-4.

[9] Chia SE, Lim ST, Tay SK, Lim ST. Factors associated with male infertility: a case-control study of 218 infertile and 240 fertile men. BJOG 2000; 107:55-61.

[10] Künzle R, Mueller MD, Hänggi W, Birkhäuser MH, Drescher H, Bersinger NA. Semen quality of male smokers and nonsmokers in infertile couples. Fertil Steril 2003; 79:287-91.

[11] Adelusi B, al-Twaijiri MH, al-Meshari A, Kangave D, al- Nuaim LA, Younnus B. Correlation of smoking and coffee drinking with sperm progressive motility in infertile males. Afr J Med Med Sci 1998; 27:47-50.

[12] Sergerie M, Ouhilal S, Bissonnette F, Brodeur J, Bleau G. Lack of association between smoking and DNA fragmentation in the spermatozoa of normal men. Hum Reprod 2000; 15:1314-21.

[13] Hoidas S, Williams AE, Tocher JL, Hargreave TB. Scoring sperm morphology from fertile and infertile cigarette smokers using the scanning electron microscope and image analysis. Fertil Steril 1985; 43:595-8.

[14] Vogt HJ, Heller WD, Borelli S. Sperm quality of healthy smokers, ex-smokers, and never-smokers. Fertil Steril 1986; 45:106-10.

[15] Brugo-Olmedo S, Chillik C, Kopelman S. Definition and causes of infertility. Reprod Biomed Online 2001; 2:41-53.

[16] Marinelli D, Gaspari L, Pedotti P, Taioli E. Mini-review of studies on the effect of smoking and drinking habits on semen parameters. Int J Hyg Environ Health 2004; 207:185- 92.

[17] Practice Committee of American Society for Reproductive Medicine. Smoking and infertility. Fertil Steril 2008; 90: S254-9.

[18] Hammond D, Fong GT, Cummings KM, O'Connor RJ, Giovino GA, McNeill A. Cigarette yields and human exposure: a comparison of alternative testing regimens. Cancer Epidemiol Biomarkers Prev 2006; 15:1495-501.

[19] Colagar AH, Jorsaraee GA, Marzony ET. Cigarette smoking and the risk of male infertility. Pak J Biol Sci 2007; 10: 3870-4.

[20] J, Elzanaty S, Rylander L, Hagmar L, Giwercman A. Association between tobacco exposure and reproductive parameters in adolescent males. Int J Androl 2008; 31:31-9.

[21] Zhu AZ, Zhou Q, Cox LS, Ahluwalia JS, Benowitz NL, Tyndale RF. Variation in trans-3'-hydroxycotinine glucuronidation does not alter the nicotine metabolite ratio or nicotine intake. PLoS One 2013; 8:e70938

[22] Pacifici R, Altieri I, Gandini L, Lenzi A, Pichini S, Rosa M, et al. Nicotine, cotinine, and trans-3-hydroxycotinine levels in seminal plasma of smokers: effects on sperm parameters. Ther Drug Monit 1993; 15:358-63.

[23] Oliveira H, Spanò M, Santos C, Pereira Mde L. Adverse effects of cadmium exposure on mouse sperm. Reprod Toxicol 2009; 28:550-5.

[24] Oldereid NB, Thomassen Y, Purvis K. Seminal plasma lead, cadmium and zinc in relation to tobacco consumption. Int J Androl 1994; 17:24-8.

[25] Chia SE, Xu B, Ong CN, Tsakok FM, Lee ST. Effect of cadmium and cigarette smoking on human semen quality. Int J Fertil Menopausal Stud 1994; 39:292-8.

[26] Pant N, Kumar G, Upadhyay AD, Gupta YK, Chaturvedi PK. Correlation between lead and cadmium concentration and semen quality. Andrologia 2015; 47:887-91.

[27] Saaranen M, Suonio S, Kauhanen O, Saarikoski S. Cigarette smoking and semen quality in men of reproductive age. Andrologia. 1987; 19(6):670–670. [PubMed: 3434857]

[28] Ramlau-Hansen CH, Thulstrup AM, Aggerholm AS, Jensen MS, Toft G, Bonde JP. Is smoking a risk factor for decreased semen quality? A cross-sectional analysis. Hum Reprod. 2007; 22(1):188–188. [PubMed: 16966350]

[29] Zhang JP, Meng QY, Wang Q, Zhang LJ, Mao YL, Sun ZX. Effect of smoking on semen

quality of infertile men in Shandong, China. Asian J Androl. 2000; 2(2):143–143. [PubMed: 11232793]

[30] Murawski M, Saczko J, Marcinkowska A, Chwilkowska A, Grybos M, Banas T. Evaluation of superoxide dismutase activity and its impact on semen quality parameters of infertile men. Folia Histochem Cytobiol. 2007; 45(Suppl 1):S123–126. [PubMed: 18292819]

[31] Sanocka D, Miesel R, Jedrzejczak P, Kurpisz MK. Oxidative stress and male infertility. J Androl. 1996; 17(4):449–449. [PubMed: 8889709]

[32] Gaur DS, Talekar M, Pathak VP. Effect of cigarette smoking on semen quality of infertile men. Singapore Med J. 2007; 48(2):119–119. [PubMed: 17304390]

[33] Chia SE, Ong CN, Tsakok FM. Effects of cigarette smoking on human semen quality. Arch Androl. 1994; 33(3):163–163. [PubMed: 7857167]

[34] Merino G, Lira SC, Martinez-Chequer JC. Effects of cigarette smoking on semen characteristics of a population in Mexico. Arch Androl. 1998; 41(1):11–11. [PubMed: 9642454]

[35] Povey AC, Clyma JA, McNamee R, et al. Modifiable and non-modifiable risk factors for poor semen quality: a case-referent study. Hum Reprod. 2012; 27(9):2799–2799. [PubMed: 22695289]

[36] Dikshit RK, Buch JG, Mansuri SM. Effect of tobacco consumption on semen quality of a population of hypofertile males. Fertil Steril. 1987; 48(2):334–334. [PubMed: 3609347]

[37] Hassa H, Yildirim A, Can C, et al. Effect of smoking on semen parameters of men attending an infertility clinic. Clin Exp Obstet Gynecol. 2006; 33(1):19–19. [PubMed: 16761532]

[38] Pasqualotto FF, Sobreiro BP, Hallak J, Pasqualotto EB, Lucon AM. Cigarette smoking is related to a decrease in semen volume in a population of fertile men. BJU Int. 2006; 97(2):324–324. [PubMed: 16430638]

[39] Vine MF, Margolin BH, Morrison HI, Hulka BS. Cigarette smoking and sperm density: a meta-analysis. Fertil Steril. 1994; 61(1):35–35. [PubMed: 8293842]

[40] Li Y, Lin H, Li Y, Cao J. Association between socio-psycho-behavioral factors and male semen quality: systematic review and meta-analyses. Fertil Steril. 2011; 95(1):116–116. [PubMed: 20674912]

[41] Harlev, A., Agarwal, A., Gunes, S. O., Shetty, A., & du Plessis, S. S. (2015). Smoking and male infertility: an evidence-based review. The world journal of men's health, 33(3), 143-160.

[42] Kovac, J. R., Khanna, A., & Lipshultz, L. I. (2015). The effects of cigarette smoking on male fertility. Postgraduate medicine, 127(3), 338-341.

[43] Omolaoye, T. S., El Shahawy, O., Skosana, B. T., Boillat, T., Loney, T., & du Plessis, S. S. (2022). The mutagenic effect of tobacco smoke on male fertility. Environmental Science and Pollution Research, 29(41), 62055-62066.

[44] Dai JB, Wang ZX, Qiao ZD (2015) The hazardous effects of tobacco smoking on male fertility. Asian J Androl 17:954–960. https://doi. org/10.4103/1008-682X.150847

[45] Hammond D, Fong GT, Cummings KM et al (2006) Cigarette yields and human exposure: a comparison of alternative testing regimens. Cancer Epidemiol Biomark Prev 15. https://doi.org/10.1158/1055-9965.EPI-06-0047

[46] Hosseinzadeh Colagar A, JorsaraeeGA, Tahmasbpour Marzony E (2007) Cigarette smoking and the risk ofmale infertility. Pakistan J Biol Sci 10. https://doi.org/10.3923/pjbs.2007.3870.3874

[47] du Plessis S, Agarwal A, Sabanegh-jr E (2014) Editors (2014) maleinfertility: a complete guide to lifestyle and environmental factors. Springer, Sci. Media New York

[48] Richthoff J, Elzanaty S, Rylander L et al (2008) Association between tobacco exposure and reproductive parameters in adolescent males. Int J Androl 31. https://doi.org/10.1111/j.1365-2605.2007.00752.x

[49] Shihadeh A, Schubert J, Klaiany J et al (2015) Toxicant content, physical properties and biological activity ofwaterpipe tobacco smoke and its tobacco-free alternatives. Tob Control 24:i22–i30. https://doi.org/10.1136/tobaccocontrol-2014-051907

[50] Hecht SS (2003) Tobacco carcinogens, their biomarkers and tobaccoinduced cancer. Nat. Rev. Cancer 3

[51] IARC (2012) A Review of Human Carcinogens. E. Personal habits and indoor combustions. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. IARC Monogr Eval Carcinog Risks to Humans Volume 100:

[52] Martini AC, Molina RI, Estofán D et al (2004) Effects of alcohol and cigarette consumption on human seminal quality. Fertil Steril 82: 374–377. https://doi.org/10.1016/j.fertnstert.2004.03.022

[53] La Maestra S, De Flora S, Micale RT (2015) Effect of cigarette smoke on DNA damage, oxidative stress, and morphological alterations in mouse testis and spermatozoa. Int J Hyg Environ Health 218:117– 122. https://doi.org/10.1016/j.ijheh.2014.08.006

[54] Haque O, Vitale JA, Agarwal A, Plessis SS du (2014) the effect of smoking on male infertility. Springer Sci 1–12

[55] Fullston T, McPherson NO, Zander-Fox D, Lane M (2017) The most common vices ofmen can damage fertility and the health of the next generation. J Endocrinol 234:F1–F6. https://doi.org/10.1530/JOE- 16-0382

[56] Roychoudhury S, Agarwal A, Virk G, Cho CL (2017) Potential role of green tea catechins in themanagement of oxidative stress-associated infertility. Reprod BioMed Online 34:487–498. https://doi.org/10.1016/j.rbmo.2017.02.006

[57] Attia SM, Ahmad SF, Okash RM, Bakheet SA (2014) Aroclor 1254- induced genotoxicity in male gonads through oxidatively damaged DNA and inhibition of DNA repair gene expression. Mutagenesis 29:. https://doi.org/10.1093/mutage/geu029

[58] Kumar SB, Chawla B, Bisht S et al (2015) Tobacco use increases oxidativeDNA damage in sperm- possible eti1ology of childhood cancer. Asian Pacific J Cancer Prev 16:6967–6972. https://doi.org/10.7314/APJCP.2015.16.16.6967

[59] Viloria T, Meseguer M, Martínez-Conejero JA et al (2010) Cigarette smoking affects specific sperm oxidative defenses but does not cause oxidative DNA damage in infertile men. Fertil Steril 94: 631–637. https://doi.org/10.1016/j.fertnstert.2009.03.024

[60] Toppari J, Larsen JC, Christiansen P, et al (1996) Male reproductive health and environmental xenoestrogens. Environ. Health Perspect. 104

[61] Aprioku JS, Ugwu TC (2016) Tobacco smoke exposure induces irreversible alteration of testicular function in prepubertal rats. J Basic Clin Physiol Pharmacol 27:577–584. https://doi.org/10.1515/jbcpp- 2015-0153

[62] Jeng HA (2014) Exposure to endocrine disrupting chemicals and male reproductive health. Front. Public Heal. 2

[63] Harlev A, Agarwal A, Gunes SO et al (2015) Smoking and male infertility: an evidence-based review. World J Mens Health 33:143. https://doi.org/10.5534/wjmh.2015.33.3.143

[64] Omolaoye TS, Du Plessis SS (2018) Diabetes mellitus and male infertility. Asian Pacific J Reprod 7:6–14. https://doi.org/10.4103/2305-0500.220978