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REVIEW

Cigarette smoking and male infertility

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Abstract Numerous studies have identified specific body systems affected by the hazardous effects of the cigarette smoking particularly the respiratory and cardiovascular systems. The effect of smoking on male reproduction has also been studied where semen quality was investigated in different cross-sectional studies including infertile patients with conflicting results. This article aimed to assess the relationship between smoking and male infertility. A review of published articles was carried out, using PubMed, medical subject heading (MSH) databases and Scopus engine excluding the effects of smoking outside male infertility. Key words used to assess exposure, outcome, and estimates for the concerned associations were: smoking, semen, male infertility, sperm, humans, and fertility. Most of the reports showed that smoking reduces sperm production, sperm motility, sperm normal forms and sperm fertilising capacity through increased seminal oxidative stress and DNA damage. Few papers reported nonsignificant differences in semen parameters between smokers or non-smokers. It is concluded that although some smokers may not experience reduced fertility, men with marginal semen quality can benefit from quitting smoking.

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Introduction

Tobacco is a plant with green foliage and tubular flowers. Biologically titled *Nicotiana tabacum*, it derives its name from Jaen Nicot, the French ambassador to Portugal who brought it back with him as a medicine in 1560. In 1800, it was used for smoking achieving worldwide popularity as Spanish sailors carried it with them in their travels planting its seeds in a variety of places [1,2].

There are strong evidences that smoking behaviour is related to social factors, particularly the influence of parents and peer groups. Taste and smell also influence the inclination to smoke where excit-

ing sensory organs in the lips, mouth and throat provide sensations of touch, taste and irritation. Also, it has been suggested that high negative mood variability is a risk factor for future smoking escalation and that its mood-stabilising effects may reinforce and maintain daily cigarette use among youths [3].

Available data do not conclusively demonstrate that smoking decreases male fertility. However, with much debate for its impact on various semen parameters, it is regarded as an infertility risk factor [4,5]. Therefore, this review has sought to assess the relationship between smoking and male infertility.

Composition of cigarette smoke

Cigarette smoke consists of gases, vaporised liquids and particles, many of which are minute droplets. About 4000 compounds are generated by a lit cigarette through variety of processes including; hydrogenation, pyrolysis, oxidation, decarboxylation and dehydration. Smoke is separated into two phases; gaseous and particulate phases. The major constituents that affect health are: nicotine, tar in the particulate phase and carbon monoxide in the gaseous phase [6]. Main stream smoke emerges into the environment after it is

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drawn through the cigarette, filtered by the smoker's own lungs and then exhaled. Side stream smoke arises from the burning end of the cigarette and enters directly into the environment [7]. Passive smoking refers to the involuntary inhalation of tobacco smoke present in the air breathed.

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 \times number of smoking years [8]. SI is defined as the product of number of cigarettes/day \times years of smoking; mild <200 SI, moderate 200–600 SI and heavy >600 SI [9].

Smoking and fecundity

In one study, on 2607 planned pregnancies, smoking amongst men and women was observed to be associated with decreased fecundity (the monthly probability of conception) [10]. Wilks and Hay [11] evaluated the relationship between smoking and female fertility, dealing with 22 primary papers and 2 reviews. All but 3 indicated a detrimental effect of smoking on reproduction, despite varying considerably in their approach, definitions used and populations studied. The strength of association was significant and a dose response relationship suggested that smoking was a causative factor.

Smoking and infertility

Numerous studies had identified specific effects of maternal smoking during pregnancy, including foetal growth retardation, neonatal deaths, pregnancy complications, premature delivery and possible effects on lactation and long-term effects on surviving children. Further, there have been indications that smoking decreases fertility in women, increases the frequency of menstrual abnormalities and decreases the age of spontaneous menopause [12,13]. In males, it has been suggested that cigarette smoking negatively affects every system involved in the reproductive process. Spermatozoa from smokers have reduced fertilising capacity, and embryos display lower implantation rates [14,15].

Smoking and semen parameters (Tables 1–3)

Different articles have demonstrated a negative impact of smoking on human semen parameters, correlated with cigarettes smoked/day

and smoking duration. Most papers have argued that smokers demonstrate lower semen volume, sperm count, sperm motility and viability compared with non-smokers. In addition, smokers showed increased seminal leukocytes, oval sperm percentage, head-piece spermatozoa defects percentage and spermatozoa with cytoplasmic droplets [16–37].

Smoking and chromosomal damage

A number of papers related to male smoking have suggested that severe DNA damage, which might prevent oocyte fertilisation or the development of the embryo, could be a cause of infertility. Chromosome damage was observed in Golgi-phase or cap-phase spermatids, showing frequencies of 1.15% in infertile smokers and 0.82% in infertile non-smokers [38]. Diminished fertilising capacity at the chromosomal level, with a significantly higher ratio of single-stranded/double-stranded DNA spermatozoa, was found also in smokers [39].

Increased percentage of spermatozoa with fragmented DNA in male smokers compared with non-smokers has been estimated to be 4.7% vs. 1.1% in one study [40] and 32% vs. 25.9% in another one [41]. Analysis of sperm DNA fragmentation after capacitation detected a detrimental effect produced by tobacco, altering the sperm swim-up selection process in smokers [42]. On the other hand, others did not find an association between smoking and DNA fragmentation in the spermatozoa of healthy light and heavy smokers compared with non-smokers, though a clear negative trend was observed, especially in respect of disturbance of plasma membrane phospholipid asymmetry [43,44].

Smoking had been demonstrated to increase disomic spermatozoa [45] where an increased risk of aneuploidy was observed, though only for the frequency of disomy 13 [46]. In addition, Horak et al. [47] reported that a significant difference existed between current smokers and non-smokers (1.7-fold increase) with a negative correlation between DNA adduct and sperm count and sperm motility among infertile patients.

Smoking and acrosin

Smokers have been found to exhibit lower acrosin activity in the presence of normal sperm count and motility [48]. Acrosome reaction was shown to be significantly lower in semen samples from smokers than fertile groups, whereas a nonsignificant difference was demonstrated in spermatozoa from patients associated with varicocele. Both the percentages of spermato-

Table 1 Relevant studies concerning smoking effect on sperm count.

Reference	Conclusion(s)	Study type	S	NS
Close et al. [19]	Smokers had lower sperm count vs. non-smokers	Comparative		164
Ochedalski et al. [22]	Sperm count was lower in smokers vs. non-smokers	Comparative	40	30
Chia et al. [23]	Smokers had significantly poorer sperm density vs. non-smokers	Comparative		184
Chia et al. [24]	Smoking affects sperm density	Comparative		618
Vine et al. [25]	Smokers' sperm density was 13–17% lower than non-smokers	Meta-analysis		
Merino et al. [27]	Smokers had poorer sperm density, being worse in heavy smokers	Comparative	197	161
Zhang et al. [29]	Sperm density was lower in smokers vs. non-smokers	Comparative	110	191
Künzle et al. [31]	Smoking led to decreased sperm count	Comparative	655	1131
Reina Bouvet et al. [33]	Smoking alters sperm concentration	Clinical study		131
Ramlau Hansen et al. [35]	Smokers had an inverse dose-response relation and sperm count	Cross analysis		2542

S: smoking; NS: non-smokers.

Table 2 Relevant studies concerning smoking effect on sperm motility.

Reference	Conclusion(s)	Study type	S	NS
Shaarawy and Mahmoud [16]	Smokers had decreased initial sperm motility	Comparative	25	20
Rantala and Koskimies [17]	Heavy smoking may have a detrimental effect on the motility of sperm			164
Saaranen et al. [18]	Sperm motility was affected in heavy smokers vs. non-smokers	Comparative	54	110
Close et al. [19]	Smokers had lower sperm motility vs. non-smokers			164
Moskova and Popov [21]	Smokers had higher deviations from normal sperm motility vs. non-smokers	Comparative		169
Ochedalski et al. [22]	Sperm motility was lower in smokers vs. non-smokers	Comparative	40	30
Vine et al. [26]	Smoking associated with lowered semen quality	Meta-analysis		
Merino et al. [27]	Smokers had a low percent of motile sperm, being worse in heavy smokers	Comparative	197	161
Zhang et al. [29]	Sperm forward progress was lower in smokers vs. non-smokers	Comparative	110	191
Künzle et al. [31]	Smoking led to decreased motile spermatozoa	Comparative	655	1131
Hassa et al. [32]	Smoking was negatively correlated with progressive motile sperm count	Comparative	126	97
Gaur et al. [34]	Asthenozoospermia early indicated reduced semen quality in light smokers	Comparative	100	100
Ramlau Hansen et al. [35]	Smokers had inverse dose-response relation and percentage motile sperm	Cross analysis		2542
Hosseinzadeh Colagar et al. [36]	Smokers had low semen quality vs. non-smokers before and after swim-up	Comparative	48	53
Hassan et al. [37]	Seminal cotinine was negatively correlated with sperm motility	Comparative		110

S: smoking; NS: non-smokers.

zoa with halo formation and halo diameters were significantly lower in varicocele associated cases compared with fertile men [49].

Smoking and toxic materials in semen

Nicotine has a significant influence on sperm morphology and sperm count [50]. Smokers have been shown to have seminal cotinine and trans-3'-hydroxycotinine levels similar to the serum, while seminal nicotine was significantly increased compared to the serum. Total sperm motility was negatively correlated to seminal cotinine and trans-3'-hydroxycotinine levels, where forward sperm motility was correlated with seminal cotinine levels [51]. Also, passive exposure to environmental tobacco smoke has been shown to result in measur-

able seminal nicotine and cotinine levels correlated with the degree of reported exposure [52].

Elevated seminal cadmium (Cd) in smokers has been observed if >20 cigarettes/day were consumed, with a significant negative correlation between Cd in blood with cigarette-years and sperm density [23,53]. Seminal Cd in normozoospermics was shown to be higher in smokers compared with non-smokers, being correlated with number of cigarettes consumed/day [54]. Also, lead in seminal plasma has been shown to be higher in infertile smokers compared with fertile men and infertile non-smokers [55].

Zenzes et al. [56] showed that benzo(a)pyrene diol epoxide-DNA adducts in sperm cells are increased by smoking, with comparatively higher levels in smokers than in non-smokers, indicating that envi-

Table 3 Relevant studies concerning smoking effect on sperm morphology.

Reference	Conclusion(s)	Study type	S	NS
Shaarawy and Mahmoud [16]	Smokers had elevated percentage of sperm abnormal forms	Comparative	25	20
Close et al. [19]	Smokers had greater percentage of oval spermatozoa	Comparative		164
Moskova and Popov [21]	Smokers had higher changes in sperm morphology vs. non-smokers	Comparative		169
Chia et al. [23]	Smokers had high percent of head-piece sperm defects vs. non-smokers	Comparative		184
Chia et al. [24]	Smoking affects sperm morphology, especially the head-piece	Comparative		618
Merino et al. [27]	Smokers had significantly poorer normal sperm morphology	Comparative	197	161
Mak et al. [28]	Smokers had increased sperm with cytoplasmic droplets vs. non-smokers	Comparative	18	69
Reina Bouvet et al. [33]	Smoking alters sperm morphology with increased immature forms	Comparative		131
Gaur et al. [34]	Heavy smoking produces teratozoospermia	Comparative	100	100
Hosseinzadeh Colagar et al. [36]	Smokers had low semen quality vs. non-smokers before and after swim-up	Comparative	48	53

S: smoking; NS: non-smokers.

ronmental exposure is also substantial. The formation of adducts in spermatozoa is a potential source of transmissible pre-zygotic DNA damage.

Smoking and reproductive hormones

Nicotine can alter the hypothalamic-pituitary axis through stimulation of growth hormone, cortisol, and vasopressin and oxytocin release, which in turn inhibit LH and PRL release [57]. Ochedalski et al. [58] reported that the mean 17 beta-estradiol (E) level was higher and the mean levels of LH, FSH and PRL were lower in smokers compared with non-smokers, whereas the mean levels of T and dehydroepiandrosterone (DHEA) did not differ. Trummer et al. [30] found increased free and total serum T and decreased PRL in smokers.

Jurasović et al. [59] showed that smoking was significantly associated with a decrease in seminal PRL. Ramlau-Hansen et al. [35] observed a positive dose-response relation between smoking and T, LH and LH/free T ratios. However, Pasqualotto et al. [60] evaluated hormonal levels in 889 fertile men divided into mild, moderate and heavy smokers, with nonsignificant differences in levels of FSH, LH and total T.

Smoking and accessory sex glands

The function of accessory sex glands in smokers has been assessed by determining the ejaculate contents of various glandular markers: N-acetyl amino sugar, total phosphate (seminal vesicles) zinc, acid phosphatase (prostate gland), and alpha-1,4-glucosidase (epididymis). Both vesicular and prostatic parameters were reduced significantly in smokers [61].

Smoking and seminal abnormal constituents

Detached ciliary tufts (DCTs) were observed in the semen of men associated with a high incidence of smoking [62]. It has been postulated that DCTs originate from the epididymal epithelium, possibly shed as part of epididymal involvement as a result of testicular pathology caused by several agents. In addition, El-Karakasy et al. [63] showed that seminal mast cells were detected at higher frequency among smokers.

Smoking and seminal antioxidants

Ascorbic acid is one of the most essential antioxidant in semen, with human seminal plasma containing ~10 mg/dl ascorbic acid, >9 times its concentration in blood plasma [64]. Heavy smoking in men is associated with a 20%–40% decrease in serum ascorbic acid, and ascorbic acid supplement to heavy smokers lead to improved sperm quality [64,65]. Seminal Zn, Cu and superoxide dismutase (SOD) have been shown to be much lower in medium, heavy and long-term smokers than non-smokers, being negatively correlated with the amount and duration of cigarette smoking [29]. Saleh et al. [66] associated smoking with a 48% increase in seminal leukocytes, a 107% increase in ROS levels, and a 10-point decrease in ROS-TAC scores.

The active transfer of cigarette components through the blood-testis barrier has been shown to possibly induce oxidative stress-induced DNA damage, one of the causes of sperm quality alteration [41]. Mostafa et al. [67] showed that fertile subjects, smok-

ers or not, had significantly higher seminal ascorbic acid levels compared with infertile groups. Seminal ascorbic acid in smokers and non-smokers was correlated significantly with sperm count, sperm motility and sperm normal forms percentage. Kiziler et al. [55] showed that malondialdehyde (MDA), protein carbonyls, ROS levels, GSH levels and glutathione S-transferase activities were lower in infertile smokers compared with fertile men or infertile non-smokers. Pasqualotto et al. [68] and El Shal et al. [69] reported that seminal SOD levels were negatively correlated with cigarette smoking.

Smoking and varicocele

The combination of smoking and varicocele has been shown to be strongly related to the incidence of oligozoospermia. Male smokers with varicocele had an incidence of oligozoospermia 10 times greater than non-smokers with varicocele and five times greater than men who smoked but were free of varicocele [70]. The pathophysiologic basis of this interaction might be due to the increased secretion of catecholamine from the adrenal medulla, induced by cigarette smoking, reaching the testes via retrograde flow down the internal spermatic vein. An additional factor is the concomitant increase in the oxidative stress eliminated by both smoking and varicocele [68,71–73].

Smoking and sperm ultrastructure

Changes in the number and arrangement of axonemal microtubules and axonemal abnormalities had been noted in heavy smoker compared with non-smokers [74]. The percentage of coiled sperm had been observed to be correlated with heavy smoking. Electron microscopy revealed coiling of tail filaments within the plasma membrane [75].

Smoking and cystic fibrosis transmembrane conductance regulator

Because cigarette smoke is a rich source of oxidants, Cantin et al. [76] assessed the hypothesis that cystic fibrosis transmembrane conductance regulator (CFTR) may be suppressed by exposure to cigarette smoke *in vitro* and *in vivo*. They concluded that smoking decreased expression of CFTR gene, protein, and function *in vitro* and that acquired CFTR deficiency occurs in the nasal respiratory epithelium of smokers. It was suggested that acquired CFTR deficiency may contribute to the physiopathology of cigarette-induced diseases such as chronic bronchitis.

Effect on smokers' seminal plasma

It has been indicated that exposure of spermatozoa from non-smokers to the seminal plasma of smokers yields a significant reduction in the sperm motility, acrosome reaction and elevated MDA [77]. Exposure of spermatozoa from smokers to the seminal plasma of non-smokers resulted in a nonsignificant improvement in the altered sperm functional parameters. Therefore, removal of smoker's seminal plasma and subsequent reconstitution with physiological media could be of clinical significance in the various ART programs utilised for smokers [78,79].

Table 4 Relevant studies concerning nonsignificant smoking effects on male infertility.

Reference	Conclusion(s)	Study type	S	NS
Dikshit et al. [87]	Tobacco use is not associated with impaired semen quality	Comparative	219	288
De Mouzon et al. [88]	Effect of tobacco on fertility is due to behavioural factors	Prospective	1887 couples	
Oldereid et al. [89]	No differences in DNA distribution between non-smokers and smokers	Clinical study	350	
Holzki et al. [20]	No effect of smoking on semen parameters	Retrospective	50	40
Dunphy et al. [90]	No association between smoking and any semen parameter	Comparative	165	195
Oldereid et al. [91]	No association between sperm quality and smoking habits	Questionnaire	252	
Osser et al. [92]	No effect of smoking on sperm density, motility, morphology, quality	Comparative	186	164
Goverde et al. [93]	Poor semen quality did not differ between heavy smokers or non-smokers	Retrospective	47	68
Pasqualotto et al. [60]	No effect of smoking and semen parameters or gonadal hormones	Comparative	367	522

S: smoking; NS: non-smokers.

Prenatal tobacco exposure

Baird and Wilcox [80] tested the hypothesis that prenatal exposure to cigarette smoke is associated with impaired fertility in adulthood in 600 couples by counting the number of non-contraception cycles required to conceive. In contrast to data on laboratory animals, husbands and wives prenatally exposed to cigarette smoke showed no evidence of reduced fertility. Ratcliffe et al. [81] showed nonsignificant effects of early exposure to maternal smoking on semen characteristics, hormone levels (FSH, LH and T), urogenital abnormalities or perceived infertility problems.

Jensen et al. [82] found nonsignificant differences in mean sperm count among sons of non-smokers, sons of mothers who smoked 1–10 cigarettes/day, and sons of mothers who smoked >10 cigarettes/day. The former group had a higher odds ratio for oligozoospermia of 1.5, the latter group of 2.6 with a dose-dependent association between prenatal tobacco exposure, lower sperm concentration and higher risk of oligozoospermia.

Ramlau Hansen et al. [35] reported on a Danish pregnancy cohort of 347 sons selected according to their exposure to tobacco smoke in foetal life, finding an inverse association between maternal smoking during pregnancy and total sperm count. Men exposed to >19 cigarettes daily during pregnancy had 19% lower semen volume, 38% lower total sperm count and 17% lower sperm concentration compared with unexposed men.

Smoking and IVF outcome

Female cigarette smoking has been suggested as having a detrimental effect on IVF outcomes mediated through diminished ovarian reserve and elevated pregnancy loss. Joesbury et al. [83] investigated the effect of male smoking on the collective quality of embryos selected for uterine transfer, and the likelihood of achieving ongoing pregnancies at 12 weeks, of 498 consecutive IVF treatment cycles. Male smoking was shown to interact with male age, indicating a decrease of 2.4% in the likelihood of achieving a 12-week pregnancy/year. They concluded that reduced pregnancy rate was associated with male smoking possibly through pre-zygotic genetic damage.

In addition, Waylen et al. [84] provided in their meta-analysis evidences for a negative effect of smoking on clinical outcomes of intracytoplasmic sperm injection success (clinical pregnancy) in

women with smoking and non-smoking partners (22% vs. 38%). Similar results were seen also for IVF (18% vs. 32%) [85]. On the other hand, several reports denied a deleterious effect of smoking and male fertility potential and semen parameters, particularly when considering the fact that many fertile males are smokers (Table 4).

Hoidas et al. [86] applied image analysis to photographs of sperm samples obtained using an electron microscope with no association between the number of abnormal spermatozoa and cigarette smoking. Dikshit et al. [87] denied the effect of tobacco use on semen quality compared with controls, concluding that tobacco use is not associated with impaired semen quality. De Mouzon et al. [88] suggested that the effect of tobacco on fertility found in different studies is due to behavioural factors related to cigarette consumption, even if it is not possible to eliminate the possibility that the apparent association between fertility and confounding factors could be explained by an association between these factors and cigarette smoking.

Oldereid et al. [89] reported nonsignificant differences in sperm quality, including DNA distribution between non-smokers, moderate smokers and heavy smokers. Holzki et al. [20] studied the effect of smoking on semen volume, total sperm count, sperm count/ml, total sperm motility, progressive sperm motility and sperm morphology, with no affect on sperm parameters. Also, Dunphy et al. [90] supported a nonsignificant association between smoking and any semen parameter.

Oldereid et al. [91] administered a questionnaire correlated with sperm quality to 252 males, focusing on any possible association between life style factors and male fertility. No association was observed between sperm quality and smoking habits. Osser et al. [92] reported a nonsignificant effect of cigarette smoking on sperm density, motility, morphologic features of sperm or sperm quality. In addition, Goverde et al. [93] investigated smoking in a control group and in a group with defined poor semen quality (PSQ). The distribution of heavy smokers and light smokers did not differ between all groups. A higher, though nonsignificant, proportion of heavy smokers was found in the PSQ group compared with the controls (50% vs. 32.3%).

Pasqualotto et al. [60] evaluated the semen quality and hormonal levels of 889 fertile men, divided into non-smokers, mild smokers, moderate smokers and heavy smokers. There were nonsignificant differences among these groups in sperm concentration, motility, levels of serum FSH, LH, total T or sperm motion characteristics. Lately, Rybar et al. [94] failed to confirm a relationship between

smoking and sperm quality in men from any of the investigated groups.

Finally, due to the fact that cigarette smoke contains known harmful substances, there has been concern that smoking could have adverse effects on male reproduction. Despite the modest reduction in semen quality and altered hormone levels of smokers compared to non-smokers, different studies have not shown a reduction in male fertility associated with paternal smoking.

Improved studies that clarify the association between smoking and male reproductive function should include exposure information in relation to various time windows whilst controlling modifying factors. More sensitive and specific laboratory assays with increased sample sizes are also required to establish accurate results. A point of interest is the effect of passive smoking on the reproductive parameters.

In conclusion, although smokers as a group may not experience reduced fertility, males with marginal semen quality may benefit from quitting smoking. Also, smokers should quit smoking for the sense of responsibility for their future generation as tobacco smoke contains numerous mutagenic substances.

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