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Review Article

Lifestyle factors in deteriorating male reproductive health

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Many health problems are related to lifestyle and dietary factors. Increasing trend in reproductive disorders observed in recent years may be associated at least in part with these factors, which are compounded by some of the new emergent life styles. The data available suggests that lifestyle factors such as obesity, tobacco smoking or chewing, alcohol and some of the illicit drugs like cocaine, cannabis etc and exposure to extreme heat, have adverse effects on male reproduction. The data on other factors such as use of mobile phone and stress on reproductive health are inadequate and need detailed study. Lifestyle related diseases could be lowered with modification in diet, living and working environment etc. Sub-fertile and/or normal subjects have some control over their reproductive function by adopting healthy lifestyles to avoid additional complications.

Keywords: Illicit drugs, Lifestyle factors, Obesity, Reproductive impairment, Semen quality, Stress, Tobacco smoking and chewing

Introduction

There are sufficient evidences of increasing trends in a number of human health problems like cancers, reproductive and developmental defects, cardio-vascular problem etc. Environmental, lifestyle, dietary or occupational factors may play an important role behind these trends. Over the last few decades, there have been progressive changes in many aspects of our diet, lifestyle as well as environment. Among lifestyle, factors such as tobacco smoking or chewing, alcohol, caffeine, use of illicit drugs etc. have a profound negative impact on general health. Various health problems like hypertension, diabetes mellitus, high blood cholesterol, obesity, cardiovascular disease and even some types of cancer are related to nutritional as well as lifestyle factors to some extent. These factors may also be responsible to enhance the reproductive disorders in both sexes.

Approximately 15% of the sexually active population is affected by clinical infertility and in 50% cases a male factor is involved, either as a primary problem or in combination with a problem in the female partner[1]. The cause of deterioration in reproductive health may be attributed to direct or indirect exposure to some of the environmental persistent chemicals, solvents, metals etc. The association of lifestyle factors on deterioration of reproductive health is receiving attention i.e., tobacco smoking and chewing, alcohol, caffeine, high temperature, some dietary components, stress, and some modern electronic gadget have shown to adversely affect reproduction. These factors may impair male fertility by interfering with spermatogenesis, spermiogenesis, motility, sperm DNA and chromatin integrity, hormonal regulation or by reducing the fertilising capacity of spermatozoa. The earlier review published on this aspect are based mainly on single/few life style factors[2-5]. An attempt has been made to compile the recent data pertaining to male reproductive health with reference to the different lifestyle factors except the data on occupational exposure to chemicals and ionising radiations. The data are summarized in (Table 1).

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Obesity and nutritional factors

High caloric foods, sedentary work, no exercise, easy transportation along with increase use of modern technologies that reduce the need for physical activity can explain the increasing prevalence of obesity around the world. Obesity is a condition in which excess body fat gets accumulated and has been associated with an increased risk of many serious illnesses such as cardiovascular diseases, diabetes mellitus and some types of cancer[6]. It is gradually recognizing that obesity is one of the causes of sub fertility.

Table 1— Lifestyle factors and reproductive impairments in male

Factor	Major effects
Obesity	• Reduction in semen quality[9,10] , serum testosterone, SHBG, and inhibin B while elevation in free androgen index and E 2[13-15]
Tobacco smoking and chewing	• Alter spermatogenesis[29] • Lower sperm penetration assay scores and greater numbers of leukocytes in the seminal fluid[30, 31] • Significantly lower zinc levels[45] • Decrease results of hypoosmotic swelling test[32] • Decrease in anti-oxidant defenses components of the sperm[34-37] • Raised serum E 2 and P[48], decrease FSH [49]
Alcohol	• Increase leukocytes in the seminal fluid[30] • Reduction in seminal quality[58] • Significantly high FSH, LH, and E2 and low testosterone and P [61]
Stress	• Decrease sperm count, motility and morphology[64] • Involuntary childlessness - higher frequency of male sexual disturbances[65] • Physical stress - lowers T levels, reduction in LH pulse frequency[67]
Heat	• Deteriorated sperm morphology, motility and concentration[72] • Increase risk of apoptosis in spermatogenic cells[82]
Drugs	• Narcotic drugs decrease gonadotropin and stimulate P secretion[87] • Marijuana - gonadal toxin; increase leukocytes in the seminal fluid[30,88] • Cannabis - reduce progressive sperm motility, acrosome reactions, LH, FSH, T, P, thyroid gland function, and growth hormone while elevate adrenal cortical steroids[89,90] • Khat - semen quality deteriorated, cytoplasmic droplets present[91] • Cocaine decrease in sperm count and motion kinematics (straight line velocity and linearity), linked to abnormal development of their offspring[92-95] • Heroin impaired semen quality, increase circulating total thyroxine, triiodothyronine and decrease P, T, FSH and cortisol[96-99]
Radiation-Electromagnetic Radiation	• Cell phones - decreases semen quality[103,104] • May increase ROS level and decrease in ROS-TAC score leading to oxidative stress[105]

Obesity has been associated with reproductive disorders in women, including menstrual abnormality, infertility, miscarriage, and reduced success of assisted reproduction[7,8]. Its role in male reproduction has also been documented in recent years. A significant reduction in sperm concentration, and motility was observed in the obese group than in males with BMI < 30 kg/m^2. Further, in the obese group, sperm count continuously decreased with aging. In addition, men presenting with a BMI > 25 kg/m^2 have fewer chromatin-intact, normal-motile sperm cells per ejaculate[9-10]. Most of the available data suggest negative association between semen quality and obesity. Obesity was also linked with disturbances of penile hemodynamics and found to be an independent clinical factor for vasculogenic erectile dysfunction[11]. But in another study the incidence of erectile dysfunction did not vary across BMI categories when corrected for potential contributing factors[12], indicating need for further study.

The exact mechanism of obesity-mediated effect on reproduction is not fully understood. However, overweight and obese men were found to have a markedly changed sex hormone profile along with reduced semen quality. Serum testosterone, sex hormone-binding globulin (SHBG), and inhibin B decreased while free androgen index and estradiol (E2) increased with increasing BMI[13-15]. Earlier Strain *et al*[16]., and Haffner *et al*[17]., also observed that the plasma levels of SHBG, total testosterone, free testosterone and follicle stimulating hormone (FSH) were lowered in obese men compared to non-obese men. Based on experimental and clinical studies. decline in androgen levels[14,15,18,19], increased estrogen levels[20] and suppression of the hypothalamic-pituitary-testicular axis[21] have been suggested as potential aetiologies of altered spermatogenesis in obese males[4].

In addition to obesity, some dietary habits of people from different ethnic background may

have some effect on reproductive health[22]. Chavarro *et al.*[22] suggested that higher intake of soy foods and soy isoflavones is associated with lower sperm concentration. Kumar *et al*., observed that smoke dried meat which is consumed commonly in Nagaland, India, an area prone to higher incidence of nasophyrangeal cancer, could induce sperm head shape abnormalities in mouse[23] and had mutagenic potential in bacterial system[24]. Sivaswamy *et al*[25]. detected polycyclic aromatic hydrocarbons (PAHs) in some of the salted, sun dried and oil fried vegetables and fishes. Xia *et al.*[26] studied four urinary metabolite of PAHs in relation to idiopathic male infertility and found increased urinary concentrations of 1-hydroxy pyrene,2-hydroxypyrene and some PAH metabolites were associated with increased male idiopathic infertility risk. Thus, consumption of certain food items may have some risk associated with reproductive dysfunction. However, more studies are needed on this aspect.

Tobacco smoking and chewing

Tobacco is one of the most addictive substances. Early initiation of tobacco use by adolescents is a major public health concern. Globally, nearly 5 million persons die every year from tobacco-related illnesses, with disproportionately higher mortality occurring in developing countries[27]. It is estimated that by 2030 10 million people will die every year from tobacco use, with 70% of those deaths occurring in developing countries alone[28].

Several studies suggested role of tobacco smoking in deterioration of seminal quality. Reina Bouvet *et al.*[29], in men with idiopathic infertility having habit of tobacco smoking[29] demonstrated an alterations in sperm concentration and morphology with an elevation of immature forms. Lower sperm penetration assay scores and greater numbers of leukocytes in the seminal fluid were also noticed in smokers[30,31]. Smokers had decreased results of hypoosmotic swelling test and increased concentration of leukocytes than non-smokers among infertile subjects whereas no differences were found in sperm concentration, percentage normal forms, different sperm defects, induced acrosomal reaction and aniline blue staining test between these two groups. Hence, it was suggested that cigarette smoking deteriorates semen quality, which could worsen fertilizing capability in infertile men[32]. Shen *et al.*[33], suggested that cigarette smoking enhance the extent of DNA damage in sperm. The extent of oxidative damage among smokers was associated with decrease in the anti-oxidant defences in the sperm of infertile males[34-36]. Smokers can suffer from some degree of impotence or reduction in their sexual frequency[37]. Cigarette smoking may also increase the risk of aneuploidy for certain chromosomes and those men may have different susceptibilities to aneuploidy in germ cells[38].

Study on male subjects undergoing infertility evaluations, showed a positive association of tobacco chewing and decrease in sperm quality. Tobacco chewing is more widespread in south east Asian region as compared to western countries. Among oligospermics it was observed that men with habit of tobacco chewing had reduced sperm count and motility (non- significant) than non-chewers[39]. The percentage of men with azoospermia and oligo-asthenoteratozoospermia rose with the level of addiction[40]. Further, experimental studies also revealed a significant increase in sperm head shape abnormality[41] and reduction in sperm and spermatid count as well as daily sperm production after exposure to panmasala gutkha in mouse[42]. As a consequence of panmasala treatment to both male and female mice, decline in reproductive performance and pregnancy outcome was observed[43]. To elucidate the mechanism behind this, role of oxidative stress, sperm DNA damage was studied and the results suggested that they might play a role in panmasala-induced spermatotoxicity (unpublished).

Poor semen quality was also observed in men with a prenatal exposure to tobacco smoke[44]. Further, tobacco smoking significantly lowered zinc levels, necessary for the stability of the sperm chromatin, in the ejaculates of smokers than in non-smokers[45]. Zinc has a positive role in male reproduction in the form of positive correlation between seminal plasma zinc level with sperm count and α-glucosidase activity[46]. Later Doshi *et al.*[47], also showed that the mean zinc levels were lower among azoospermic as compared to oligospermic and normozoospermic subjects.

Tobacco smoking is found to alter various sex hormones. Serum E2 and prolactin (P) were increased in smokers as compared to non-smokers[48]. In a recent study, serum levels of FSH were higher among non-smokers as compared to smokers whereas no significant differences were found for inhibin B, testosterone, SHBG, luteinizing hormone (LH) and oestradiol[49]. However, earlier a positive dose–response relationship between smoking and

testosterone, LH and the LH/free testosterone ratios was observed[50]. Various studies reported incompatible findings on the effects of smoking on serum hormones. There may be some effect of tobacco smoking on testosterone level as Kapoor and Jones[51] hypothesized that the effects of smoking on testosterone levels are due to changes in plasma-binding capacity rather than a direct effect of nicotine on androgens. Smoking in patients undergoing IVF (*in vitro* fertilization) and GIFT (gamete intra-fallopian transfer) can have negative impact on treatment outcome[52]. The data suggest the role of tobacco smoking and chewing in deteriorating semen quality or even might have effect in IVF outcome.

Alcohol

Humans have consumed alcoholic beverages since pre-historic times, for a variety of reasons. Alcohol is the second most addictive substance after nicotine. Alcohol is reported as direct testicular and Leydig cell toxin[53,54]. It has been observed that chronic alcohol use was common among infertile men[55]. Excessive alcohol consumption had the potential to decrease an already low percentage of sperm with normal morphology[56,57]. Martini *et al.*[58], also found significant reduction in seminal volume, sperm concentration, percentage of motile spermatozoa, and a significant increase of the non motile viable gametes among men with habits of alcohol and smoking. Greater numbers of leukocytes in the seminal fluid were found in alcohol users than in nonusers[30]. But studies among healthy male volunteers with habituation of alcohol showed no significant effect on sperm nuclear size, shape, or chromatin texture and sperm concentration, motility, viability, and normal morphology[59,60]. However, majority of studies reported adverse effects of alcohol on semen quality.

Alcohol use affects the hypothalamic-pituitary-gonadal (HPG) axis, a system of endocrine glands and hormones. Alcohol use is associated with low testosterone and altered levels of FSH and LH and can hence interfere with hormone production[2]. In alcoholics, FSH, LH, and E2 levels were significantly increased, and testosterone, semen volume, sperm count, motility, and number of morphologically normal sperm were significantly decreased whereas no significant change was noted in P levels[61]. It can be inferred that chronic alcohol consumption has a detrimental effect on male reproductive system and affect reproductive organs directly or indirectly via hormonal production and regulation.

Stress

Emotional and physical changes and environmental components may lead to stress. Infertility itself is the most stressful event in the lives of the person diagnosed with this condition. In general, stress affects biological systems leading to various impairments and may affect reproductive health. In many instances, stress has a subtle and less influence. Psychological job strain does not seem to affect male reproductive function[62,63]. A prospective study showed small or nonexistent effect of a man's daily life psychological stress on his semen quality. Moreover, no consistent association between stress and serum concentration of LH, FSH, inhibin B, testosterone, or estradiol was found[63]. Earlier Negro-Vilar[64] in an overview mentioned that chronic or severe stress in animals or humans was associated with decrease sperm count, motility and morphology

In couples suffering from involuntary childlessness, a higher frequency of male sexual disturbances expressed as erectile dysfunction, ejaculatory disorders, loss of libido and a decrease in the frequency of intercourse was observed[65]. Fecundity of men, experiencing the stress of a family member's death was found to be temporarily diminished[62]. Mental stress caused by final exams negatively affected semen quality during stress period compared to the non-stress period[66]. Physical stress leads to low testosterone levels due to a reduction in LH pulse frequency[67]. The data point some adverse effect of stress on male reproductive function or as an additional risk factor for subfertility and this depend upon the types of stress.

Heat

Temperature influences the development of germ cells as well as reproductive cycle of living beings. Nature has kept the scrotum outside the body cavity so that the temperature of the testes remains lower than that of the body temperature. Even moderate or physiological elevation in scrotal skin temperature is associated with a substantially reduced sperm concentration, which results in a poor semen quality[68]. Lahdetie[69] reported that active sperm production is dependent on an environment that is 4^{o}C lower than the normal body temperature. Wang *et al.*[70], reported that elevation of testicular temperature by 1^{o}C above the base line depresses spermatogenesis by 14% and thereby decreases sperm output. They also mentioned that exposure to high temperature results in modification of sperm morphology. The mean value of

sperms with abnormal morphology rises from 30 to 60% within 6-8 months of exposure to high temperature. They explained that elevated testiculoepididymal temperature decreases the synthesis of sperm membrane coating protein, which in turn results in the elevation of morphologically abnormal sperms in the ejaculate[70].

Recently, Dada *et al.*[71,72], suggested that exposure to high temperature causes deterioration in sperm morphology and impairs motility as well as sperm production that has resulted into a deleterious effect on male fertility. Heat, either due to endogenous (such as high fevers) or exogenous stimuli, decreases sperm concentration, impairs motility, and reduces the number of morphologically normal sperm[73,74]. The data on occupational health exposure and male fertility was reviewed by Thonneau *et al*[75], They mentioned that the rise of testicular temperature induced by cryptorchidism**,** extreme heat in summer, body fever, tight clothing, sauna or exposure to high temperature during occupational exposure can cause impairments in spermatogenesis[75]. The toxic effect of wet hyperthermia on semen quality may be reversible in some infertile men as observed by Shefi *et al,*[76]. Further, Zorgniotti and Mac Leod[77] have reported an improvement of sperm alterations in men wearing a cooling device inducing a chronic hypothermia of the testis[7]. A weak association of heat with male fertility (OR=0.85)[78] has also been reported.

There are few reports on reproductive health of workers occupationally exposed to high temperature. Figa-Talmanca *et al.*[79], mentioned a higher prevalence of pathologic sperm profile among the exposed subjects of ceramic industry compared to control. Bonde[80] who studied metal arc alloyed steel welders with a moderate exposure to radiant heat but without substantial exposure to welding fumes toxicants, experienced a reversible decrease in semen quality. Sperm morphology also deteriorated during six weeks of exposure and increased after a break in the exposure[80]. As per Kumar *et al.*[81,] welding may have had some adverse effects on sperm motility, morphology and physiologic function even though sperm concentration was in the normal range.

Kong *et al*[82], studied the expression of cdc2 and cyclin B1 (key components of cell cycle controlling machine which are believed to play a fundamental role in gametogenesis) in normal and cryptorchid testis and observed that the abdominal temperature had no significant influence on the transcription of cdc2 and cyclin B1 in the spermatogonia and pachytene/diplotene primary spermatocytes, but it blocked the translation of them. They suggested to study the role of cold-shock proteins of spermatogenic cells at the scrotal low temperature to uncover the functions of cold shock proteins in relation to spermatogenesis, including the control mechanism of gene transcription and translation in heat induced spermatogenetic block[82]. Based on experimental studies, it was reported that elevation in abdominal temperature increases the risk of apoptosis in spermatogenic cells, but its mechanism is not clear[83,84]. These data suggest the possible role of temperature on male reproductive function.

Drugs

Chronic medication can play a significant role in the pathogenesis of male reproductive health. It is known that some of the drugs/compounds may reach to the seminal plasma. There are evidence that many drugs enter the male genitourinary tract by an ion-trapping process. Lipid solubility and the degree of ionisation of the drug, which depend on the *p*H of plasma and seminal fluid, are important factors in this process[85]. Major groups of drugs that may affect male sexual function include drugs of abuse, central nervous system depressants, antihypertensives, and anticholinergics, and psychotherapeutics agents[86]. In this review, psychoactive and narcotic drugs are considered which can produce psychological dependence. Narcotic drugs exert their primary effect on the hypothalamic-pituitary axis and their secondary effects are on the gonads and sex accessory organs. Narcotics decrease gonadotropin secretion and stimulate P secretion, both of which are inhibitory to male sexual function[87].

The primary effect of marijuana, the most widely used psychoactive cannabis drug, is at the level of the hypothalamus, with subsequent effects on gonadotropins and testosterone[87] and at is reported as a gonadal toxin[88]. Infertile couples with habituation of marijuana showed greater numbers of leukocytes in the seminal fluid without any effect on sperm count, motility or percentage of oval sperm[31]. Further, delta-9-tetrahydrocannabinol (THC) a recreational cannabis drug reduced the percentage of progressive sperm motility and acrosome reactions *in vitro*[89]. In addition, the THC-induces block of Gonadotropin releasing hormone (GnRH) release resulting in lowered LH and FSH and subsequently reduced testosterone production. THC appears to depress P, thyroid gland

function, and growth hormone while elevating adrenal cortical steroids[90]. These data suggest that THC adversely affect male reproduction both at hormonal and spermatogenesis level.

A significant negative correlation was also found between the duration of khat consumption, another drug of abuse, and semen parameters. The total mean percentage of deformed spermatozoa at ultrastructure level was approximately 65%. Deformed heads showed aberrated nuclei with immature nuclear chromatin and polymorphic intranuclear inclusions; these were associated with acrosomal defects. Persistent cytoplasmic droplets were also observed frequently[91]. It is known that cocaine, stimulant of the central nervous system, can result in hyperactivity, restlessness, increased blood pressure, increased heart rate, euphoria etc. Bracken *et al.*[92] . mentioned that male population with the high prevalence of cocaine use were sub fertile with a decrease in sperm count and motility. Yelian *et al*[93] demonstrated that human spermatozoa, acutely exposed to high concentrations of cocaine decreased two motion kinematics of sperm, straight line velocity and linearity but had no significant effects on sperm motility and fertilizing capability. In another study, exposure of males to cocaine did not decrease viability and motility but has been linked to abnormal development of their offspring as the sperm may act as a vector to transport cocaine into an ovum[94,95].

Among heroin addicts, an elevation in circulating total thyroxine, triiodothyronine and P level[96] while depletion in serum concentrations of testosterone, FSH and cortisol were observed[97,98]. Semen analyses of heroin addicts and from the dual heroin-methadone users were abnormal, whereas 45% of the methadone takers were pathological. In all cases asthenospermia was one of the abnormalities whereas 24% cases showed teratospermia and hypospermia and 17% showed oligozoospermia. Such seminal pathology, especially of forward motility, even in combination with normal hormone levels, may be an early indication of heroin toxicity to the male reproductive tract[99]. The information available on various drugs of abuse especially cannabis or cocaine suggests that they have adverse effect on semen quality.

Radiation-electromagnetic radiation

Radiation can be classified as ionizing or non-ionizing radiation. It is known that ionising radiation affects both male as well as female reproduction. Non-ionizing radiation refers to any type of electromagnetic radiation i.e., near ultraviolet, visible light, infrared, microwave, radio waves, low frequency (radio-frequency) and static fields. There has been growing public concern on the effects of electromagnetic radiation (EMR) on human health including possible association with increased risk of cancer and effects on cellular DNA. A number of animal studies showed that electromagnetic waves have a wide range of damaging effects on the male reproductive system and sperm parameters. However, similar studies are limited in humans[100]. EMR emitted by cellular phone significantly reduces human sperm motility[101,102]. Use of cell phones is reported to be associated with deterioration in semen quality by decreasing the sperm count, motility, viability, and normal morphology as the duration of daily exposure to cell phones increases[103,104]. Agarwal *et al*[105] concluded that radiofrequency electromagnetic waves emitted from cell phone may lead to oxidative stress in human semen based on *in vitro* study. Long-term EMR exposure may lead to behavioural or structural changes of the male germ cell that may be observed later in life[102]. Still more work is needed on the use of cell phone and fertility with better study design by incorporating confounding factors associated with fertility.

Military personnels exposed to high frequency EMR through aerial and communication equipment had significant linear trends with lower ratio of boys to girls at birth and higher prevalence of involuntary childlessness[106]. Susa *et al*[107]., reported that radio-frequency fields could interact with charged intracellular macromolecular structures and could affect the mammalian reproductive system and sperm cells. In population-based studies a wide range of RF frequencies from occupational or residential exposures, no strong associations on birth defects, fertility, neuroblastoma in offspring, and reproductive hormones were found[108].

Lifestyle factor and IVF

Lifestyle factors may also affect the IVF outcome. Recently Klonoff-Cohen[109] reviewed the data on the role of female and male lifestyle habits (specifically smoking, alcohol and caffeine use, and psychological stress) on the reproductive endpoints of IVF. He mentioned that there is compelling evidence that smoking has a negative influence on IVF outcomes, whereas for stress, the evidence is suggestive but insufficient due to the heterogeneity of studies. The evidence for the effects of alcohol and caffeine on IVF

outcome is inadequate. Bellver[110] also reported that psychological stress, consumption of caffeine, alcohol and illicit drug have been implicated in a poorer IVF outcome, but evidence is inconclusive due to the scarcity and inadequate methodology.

Conclusion

Some "negative" lifestyle factors may be contributing to the increasing trends in male infertility problem in various parts of the world. There may not be conclusive evidence for the entire lifestyle factor discussed, but adopting healthy lifestyle may be useful at least in part in prevention of reproductive problem. The people should adopt healthy way of living in order to reduce or control the infertility problem.

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