Review Article

The Aging Sperm: Is the Male Reproductive Capacity Ticking to Biological Extinction?

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A B S T R A C T

In other to provide some insight into the issue of male fertility with aging, several experimental, clinical and cross-sectional epidemiological studies have been undertaken to characterize the relationship between paternal ages as a marker of the semen quality and male fertility status. The present review summarizes, comprehensively, the mechanisms that tend to relate male aging and semen quality with their consequences on semen parameters. Review of English language-published research articles from 1980, through 2013 was executed using Medline and Medscape databases. It was found that the semen volume, concentration and vitality of spermatozoa declined significantly with age. Deoxyribonucleic acid (DNA) fragmentations, as well as abnormalities of sex chromosomes, were also reported as having a significant association with men's age which may be one of the reasons for failure in some traditional *in vitro* fertilization (IVF) cycles.

KEY WORDS: Deoxyribonucleic acid fragmentation, male infertility, paternal age, semen quality, sperm count

INTRODUCTION

Aging process in the male reproductive system may include changes in testicular tissue, sperm production, and erectile function. Unlike women, men do not experience a substantial, rapid (which occurs over several months) change in fertility as they age, like menopause, instead; changes occur gradually (andropause).[1] Understanding the impact of male age on fertility has become increasingly salient in public health. This is because a growing number of men are choosing to have offsprings at older ages.[2] In the context of male fertility; semen quality is considered to be a proxy measure, and changes in semen quality can occur after exposure to toxic agents or from host factor effects such as age. The weight of evidence primarily from clinical studies suggests that age is associated with diminished semen volume, sperm motility and/or sperm morphology[1,2] however; sperm concentration is minimally affected.[3] It is unclear whether these observations are applicable to the general population of healthy men. Also, men at older ages (e.g. >50 years) were under-represented in many of these clinical studies,[4] that limited statistical power and prevented the establishment of the degree of the relationship between age and semen quality. In addition, potential confounders that might explain changes with age, such as smoking history or duration of abstinence were seldom controlled.[5] In addition, increase in paternal age may be associated with the increased exposure to some environmental, physical and chemical substances which can adversely affect sperm quality.

The purpose of the current review was to examine the possible relationships between age on semen volume, sperm concentration, morphology and motility in subclinical and nonclinical groups of men between 20 and 80 years. These studies provided extensive information on the effect of medications, lifestyle and occupational exposure on semen quality.

MATERIALS AND METHODS

The materials for this review were obtained from an extensive search using Medical Subject Headings (MeSH) of electronic databases which included Medline, Elsevier,

Access this article online	
Quick Response Code	**Website:** www.jbcrs.org
	DOI: 10.4103/2278-960X.129271

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Medscape, and PubMed. Relevant literature on the effect of paternal age on the amount and quality of spermatozoa and its impact on future natural and assisted conception cycles was retrieved. Data of the subjects with normal semen analysis or clinical problems have been excluded. We also included papers on subjects exposed to environmental and occupational chemicals, with the habits of smoking and alcohol consumption, with anomalous dietary practices and life-styles, and results reported in terms of fertility rate. The keywords used for the literature search included, aging male and fertility, paternal age and fertility, aging sperm, sperm quality and quantity, conception and infertility. Search criteria were limited to study published in English. The following reproductive outcomes were evaluated: Semen volume, sperm concentration, sperm motility, sperm morphology and androgen levels.

POSSIBLE MECHANISMS IMPAIRING REPRODUCTIVE CAPACITY WITH AGE

Several factors like, occupational and environmental exposure of metals, smoking, alcohol consumption, lifestyle, diet and oxidative stress, may be responsible for the suboptimal quality of the aging spermatozoa.[5] Apart from the well-recognized apoptosis associated with aging, adverse environmental conditions, occupation and socio-cultural lifestyle may modify the pattern of presentation or accelerate the journey towards a possible male reproductive extinction.[1,5] The final pathway may be unrelated to DNA fragmentation and damage.

Oxidative stress

Oxidative stress is defined by excessive production of reactive oxidative species (ROS) such as the hydroxide (OH) and superoxide (O_2) free radicals. Several studies have suggested that there is a correlation between increased ROS production and aging in a range of cell and animal models.[6-8] A number of factors can lead to increased production of ROS. These include compromised function and integrity of mitochondria over time causing them to "leak" ROS into the cell,[9] waning of the cell's antioxidant abilities with age,[10] and increased steroidogenic activity.[11] Although many studies exist on the effect of aging on antioxidant enzymes such as catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase, the results of these studies are controversial, and a consensus has not yet been established in this field. ROS cause damage to the cell's DNA, proteins, and lipids, thus endangering normal function. Spermatozoa are subjected to relatively high levels of oxidative stress because they generate ROS to control capacitation by redox regulation of tyrosine phosphorylation.[12] In addition, the presence of leukocytes in human semen results in an increased ROS load since these cells have a high rate of spontaneous

production of ROS. Thus, accumulation of ROS over time is likely to render spermatozoa of older men vulnerable to extremely elevated levels of oxidative stress. Indeed, previous report by the authors have found that the motility of spermatozoa in older rats becomes significantly more compromised after oxidative challenge when compared to that of young rats.[13] ROS decrease spermatozoa quality through various mechanisms including damaging lipids, DNA, and proteins. The lipid membrane, which is rich in unsaturated fatty acids, is particularly susceptible to oxidative damage. The consequences of membrane perturbation include changes in transport processes, ion channels, metabolite gradients, and receptor mediated signal transduction, which can reduce the sperm's motility, viability, and ability to undergo capacitation and the acrosome reaction.[14] Furthermore, oxidative stress can induce DNA damage in spermatozoa, which can affect fertility of the male and jeopardize optimal reproductive outcome.[12] Although spermatozoa with severely damaged DNA will not be able to fertilize an egg, sperm with less-extensive damage can still successfully fertilize, thus endangering the outcome of pregnancy and leading to recurrent miscarriages.[15] Polyspermy may indeed become more prevalent with associated gestational trophoblastic disease, and its dire consequences on maternal morbidity.[9] This precarious situation may be exacerbated in the presences of concomitant age related poor quality oocyte. Oxidative stress might also increase with age due to the compounding effect of a poor lifestyle, where diet and other factors such as smoking and alcohol consumption may play a particularly crucial role.[6,9,11]

Lifestyle

Several aspects of man's lifestyle can play a role in the quality of germ cells and are likely to be cumulative with advancing age. Although poor diet, smoking, and excessive drinking can occur in men of all ages, the adverse effects become more pronounced with increased duration of exposure.[9,11]

Diet

It has been well documented that diets rich in antioxidants such as vitamins A, E, C, selenium, and flavonoids, provide the body with a stronger antioxidant defence mechanism.[16] Moreover, a strong correlation between vitamin C levels in semen and the quality of DNA in spermatozoa has been observed.[17] In some cases of male factor infertility, glutathione supplementation has been shown to significantly protect spermatozoa from lipid peroxidation and increase motility.[18]

Smoking

It is well established that cigarette smoke contains chemicals with mutagenic and carcinogenic properties, such as polycyclic aromatic hydrocarbons and nicotine-derived nitrosamines.[19] These chemicals act as oxidants, causing a

variety of toxic effects including DNA damage in the form of breaks and bulky adducts. Although some DNA repair occurs in spermatocytes and early spermatids, it is not possible once spermatozoa mature.[20-22] Thus, smokers have been shown to have a decreased quality of spermatozoa DNA,[23] which has been correlated with adverse effects on the wellbeing of their offspring.[24] In addition to DNA damage, smoking has been associated with reduced semen quality, characterized by significant decreases in sperm density, count, number of motile sperm, and percent morphologically normal sperm,[25] most probably due to its effect on depleting tissue antioxidants and increasing semen leukocytes.[26] The adverse impact is, however, apparently reversible, and significant improvements in antioxidant status are observed after discontinuation of smoking.[27] Interestingly, smoking by males has been demonstrated to decrease the success rates of assisted reproduction procedures, such as in-vitro fertilization and intra-cytoplasmic sperm injection.[28]

Alcohol

Alcohol consumption is common in most populations, and moderate consumption has not been linked to decreased semen parameters.[29] Continuous excessive alcohol intake, however, can cause decreased free androgens to the point of inducing complete spermatogenic arrest and hypogonadism.[30] Similar to cessation of smoking, the cessation of alcohol consumption has been shown to ameliorate reproductive parameters in a murine model[31] as well as in humans.[32]

Exposure to environmental chemicals

It has been proposed that extensive exposure to industrial chemicals may contribute to declining sperm quality in the industrial world.[33,34] These reports are mainly based on publications of human data, some that have in the interim been invalidated for methodological reasons. Nevertheless, toxic substances may have a direct influence on cells involved in spermatogenesis or germ cell-DNA, whereby male age can play a role in different ways. Early short-term exposures to certain disruptive chemicals may have occurred only in certain age groups, whereas chronic exposure or accumulation of toxins over years may become relevant only in older men. Persistent effects of short-term exposures (e.g. early programming) are difficult to evaluate, whereas toxicity studies can reveal direct effects on spermatogenesis. In most cases, exposure levels are low and do not adversely affect health, but situations can occur when individuals come in contact with threatening amounts. Although this happens rarely in the general population, it is more common in people working in chemical plants, farmers, and those living in proximity to landfills. An overview of the effect of some environmental chemicals on sperm quality is provided in the following.

Polychlorinated biphenyls

Polychlorinated biphenyls (PCBs) were once widely used as coolants and lubricants, but the production and use of PCBs became restricted in the late 1970s due to their extreme stability in the environment, their accumulation in fat tissue, and toxicity to the liver, skin, and the nervous system. PCBs continue to be released into the environment, however, from hazardous waste sites, improper disposal, and leaks from old PCB containing equipment.[35] Hauser et al.[36] have shown a clear link between PCBs and semen quality. They found decreased spermatozoa concentration, decreased motility, and more cases of abnormal morphology in men with high blood levels of PCBs compared to men with lower PCB blood levels. Polychlorinated biphenyls are known to accumulate over time in men and were correlated with decreased sperm quality, especially reduced motility, whereas data about the relationship between pesticides or phthalates and human semen quality do not yet allow a definitive conclusion as highlighted in a recent review and the summary of an expert meeting about environmental challenges to reproductive health.[35]

Phthalates

Since being banned, PCBs have largely been replaced by other industrial chemicals such as phthalates. The phthalate ester class of chemicals had recently received considerable attention due to its widespread use and reported endocrine disruption activities. Early work on the endocrine disrupting activities of phthalates by the National Toxicology Program in 1991 demonstrated alterations to reproductive tract structure, seminiferous tubule degeneration, and lowered sperm counts in male. Phthalate esters are high production volume chemicals used as plasticizers in polyvinyl chloride (PVC) plastics to impart flexibility. They are also used as emulsifying agents, surfactants, and lubricants in numerous industrial, medical, and cosmetic products. As these compounds are not covalently bound to the PVC polymer, they can leach with age, use and ultraviolet light exposure, making them available for biological exposure. Although less toxic than PCBs, phthalates have been demonstrated to have antiandrogenic activity. In a recent study, it was shown that high levels of urinary phthalates are associated with decreased fertility, the main correlations being with sperm concentration, motility, and poor morphology in humans.[37] Phthalates have been suggested to be associated with the development of 'Testicular Dysgenesis Syndrome' (TDS) due to the potential for significant exposure during development and the induction of reproductive tract defects. Increased DNA damage in the sperm of the subjects was reported by the same group using the comet assay.[38]

Farmers

Farmers constitute a community that is at risk for

reproductive problems, due to their involvement with pesticides and herbicides.[39] Some reports described[40] reversible impotence in farm workers who applied pesticides. Subsequent studies showed that synthetic organochlorine pesticides such as dichlorodiphenyltrichloroethane (DDT) act as endocrine disruptors.[41] Some of these chemicals can act as antiandrogens,[42] thus causing impotence and decreased sperm count and sperm concentration in farmers. DDT is no longer registered for use in the United States, though it is still used in other countries like Nigeria and India. Another chemical that is a threat to spermatozoa quality is the phenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D). This chemical is widely used throughout the world and has been shown to be associated with increased asthenozoospermia, necrozoospermia, and teratozoospermia.[43] Therefore, it is alarming that up to 50% of Ontario farmers were found to have detectable levels of 2,4-D in their semen.[44]

Traffic pollutants

Another potential threat to the male reproductive system is pollution. As pollution with environmental chemical, increases, studies addressing its impact on health become crucial,. It was found, for example, that men continuously exposed to high levels of traffic pollution had high blood lead levels, high methemoglobin (a marker of nitric oxide exposure), and significant adverse effects on all sperm parameters except for sperm count and semen volume.[45] Sperm motility, viability, membrane function, nuclear DNA integrity, and TTP were all dramatically decreased.[46] These effects could have been mediated in part by the nitric oxide and lead found in traffic pollution. Controlled amounts of nitric oxide play an important role in spermatozoa capacitation, but this free radical has been shown to inhibit motility when present in large quantities.[47] Lead accumulates in male reproductive organs where it can replace zinc in human protamines, causing a conformational change in protein, and thus, adversely affecting sperm chromatin condensation. Zinc supplementation can help ameliorate these problems.[48]

AGING EFFECTS ON ANDROGENS

Serum levels of total testosterone and bioavailable testosterone (testosterone that is not bound to sex hormone-binding globulin) decrease in men with age.[9] Increasing male age also has an impact on every level of the hypothalamo-pituitary-testicular axis, leading to decreased circulating androgen levels and ultimately to reduced androgenic effects at target organs. Although this reduction is gradual, it can result in decreased muscle mass, osteoporosis, decreased sexual activity, and changes in cognition.[8] Secondarily, hypogonadal

subjects can suffer from different, mostly unspecific symptoms, including erectile dysfunction. Of infertile men, 20-30% has low testosterone levels but no positive effect of testosterone substitution on sperm production was shown in these subjects. Androgen replacement therapy in normal older men has demonstrated benefits on bone mass, muscle strength, and sexual functioning. These benefits, however, may result from direct effects of testosterone or from increased estradiol levels following aromatization of testosterone.[6] Recent evidence from the case of a patient with genetic aromatase deficiency suggests that bone mass changes and other physiological effects in men may in fact be attributable to changes in estradiol levels, rather than to direct testosterone effects.[14] In addition to peripheral physiological effects, age-related declines in testosterone levels may affect cognitive abilities. In a more recent study using sensitive neuropsychological measures that assess specific areas of cognitive functioning rather than global measures, high levels of free testosterone were associated with better performance on visual memory, verbal memory, divided attention, and visuospatial rotation.[18] Further, when this large cohort of elderly men was divided according to eugonadal and hypogonadal status, hypogonadal men evidenced significantly poorer performance for visual memory, verbal memory, divided attention, and visuo-spatial rotation compared to eugonadal men. The men were reassessed every two years for up to 30 years in a combination cross-sectional/longitudinal study, and declining testosterone levels over time were significantly associated with declines in visual memory.[9,18] Although it has been suggested that declines in testosterone levels may be coincident with disease or health decline, these findings remained significant after controlling for variables known to affect cognitive status, such as age, education, and health status. Not all studies, however, have found a positive relationship between cognitive abilities and endogenous testosterone levels.[18]

AGING EFFECTS ON SEMEN PARAMETERS

Studies that examined the relationship between male age and semen parameters are represented in Table 1. Most of the studies are based on infertility clinic or assisted conception populations, while the others used volunteers recruited from sperm banks. These studies showed a deterioration of semen parameters with age (volume, sperm, motility, concentration and morphology).[49-64] Although previous studies were based on small groups of older men, some large analyses of 1174, 3729, 3437 and 20411 men >45 years confirmed previous findings with a slow decrease in sperm counts.[54,55,61,64] Computer-assisted semen analysis of semen samples from older men

Table 1: Semen parameters with male aging

Reference	Year	Country	Sample size	Age	Semen volume (mL)	Sperm concentration (%)	Sperm morphology (%)	Sperm motility (%)
Nieschlag et al.[49]	1982	Germany	43	A. 29 (3.2); B. 67 (7.8)	↓ (NS)	↑ (P<0.05)	↔	↓ (P<0.0005)
Homonnai et al.[50]	1982	Israel	555	A. 31 (0.2); B. 54 (4.2)	30% ↓	↔	↔	↓
Dondero et al.[51]	1985	Italy	445	A.<40; B. 40-60; C. >60	↓ after age 40 (NS)	↓ after age 40 (NS)	↓ (NS)	↓ after age 40 (NS)
Haidl et al.[52]	1996	Germany	64	A. 32.2; B. 50.3	↔ (NS)	↓ (P=0.01)	↓ (NS)	↓ (P=0.04)
Spandorfer et al.[53]	1998	U.S.A.	821	A. ≤39; B. 40-49; C. ≥50	↓ (P<0.05)	↔	↔	↓
Andolz et al.[54]	1999	Spain	20,411	31.9 (5.4); 15-74	0.5% ↓ per year of age	0.7% ↓ per year of age	0.2% ↓ per year of age	0.3% ↓ per year of age
Rolf et al.[55]	2002	Germany	3,437	19-63	↓ (P<0.0001)	↔	nd	↔
Eskenazi et al.[56]	2003	U.S.A.	97	22-80	0.03mL decrease per year of age	r = −2.5% per year	nd	0.7% ↓ per year of age
Ng et al.[57]	2004	Australia	567	52-79	Age-dependent ↓ (P<0.001)	nd	25% ↓ per year (P<0.001)	nd
Hellstrom et al.[64]	2006	U.S.A.	1174	>45	Age-dependent ↓	Age-dependent ↓	Age-dependent ↓	Age-dependent ↓
Meeker et al.[58]	2007	U.S.A.	388	>45	Age-dependent ↓	Age-dependent ↓	Age-dependent ↓	Age-dependent ↓
Stewart et al.[59]	2009	Australia	225	>30	↓ with low sperm count	Age-dependent ↓	Age-dependent ↓	↓
Tang et al.[60]	2012	China	104	A.<35; B. 35-39; C. ≥40	↔ (NS)	↔ (NS)	nd	↓
Mukhopadhyay et al.[61]	2013	India	3,729	33-35	↓ (P<0.05)	nd	nd	↓ (P<0.05)

Data are represented as mean (SD); ↓ – Decrease; ↑ – Increase; ↔ – No change; NS – Not significant at P<0.05, no P value indicates that no statistical testing was done

objectively confirmed the decrease in sperm motility.[65] The pathophysiological basis of effects of age on semen parameters may be due to the specific effects of age alone, but can also be based on factors associated with age, as, for example, vascular diseases, obesity, infections of the accessory reproductive glands or an accumulation of toxic substances. However, elucidating the causative chain between such factors is extremely difficult, as confounding factors are almost impossible to differentiate. Obesity, for example, is associated with increased incidence of oligozoospermia and asthenozoospermia,[66] but whether life-style factors, the age-dependent increase in body fat or other obesity-associated metabolic factors cause the link remains unexplored. Semen volume and seminal fructose concentration decrease with age, possibly due to a seminal vesicle insufficiency, since the seminal vesicle contributes most to ejaculate volume.[67] Factors leading to decreased sperm motility could be found in altered functions of post-testicular glands such as the prostate and, more probable, the epididymis, as the swimming ability of spermatozoa is acquired during epididymal transit and motility is dependent on dilution into seminal plasma.[68] Prostate-specific-antigen (PSA) and α-glucosidase, markers secreted by the prostate and the epididymis, respectively, decrease with age and are positively correlated to sperm motility.[69] Age-dependent alterations of the epididymis might lead to disturbed mitochondrial functioning, as an important part of epididymal sperm maturation is the activation of sperm mitochondria,[70-75] which could by itself already be altered via several mechanisms.

The existence of a paternal age effect on semen parameters, fertility, and congenital anomalies in children demonstrates that the genetic integrity of otherwise healthy sperm is not immune to the effects of time. Genetic diseases that demonstrate a paternal age effect and are of known etiology are frequently the result of single-base substitutions. In the absence of much needed experimental data, this implies that these are the most common type of age-dependent genetic alteration found in aging sperm. The cause of increased mutation frequency in sperm from aged males is most likely a combination of an accumulation of replication errors, epigenetic mechanisms, alterations in apoptotic events, and compromised genetic defence. These changes are aggravated by occupational, environmental and lifestyle changes. In addition to well-designed epidemiological studies, the extensive use of animal models is expected to help resolve the nature and range of effects that paternal age can cause in altered progeny outcome. The particular mechanisms, of DNA damage and their environmental modifying factors during aging, is a matter of paramount concern as our population ages.

CONCLUSION

In summary, this review suggests that the trend toward later paternal parenting appears to come with risks for diminished semen quality and fertility. Future research works examining the relationship between male age and semen quality and fertility could improve on the methodological quality of the existing studies by enrolling adequate samples throughout the age spectrum, controlling for the effects of potential confounding factors, and selecting appropriate comparison groups. With the development of better biomarkers, used in epidemiological study designs, more knowledge may be gained regarding age and associations with semen quality and fertility, as well as abnormalities in offspring. In certain cultures, the paternal age at marriage and conception has been delayed due to adverse socioeconomic conditions and

the general belief that reproductive biological clock only ticks for the female. As the oocyte atresia increases with age, so also is the spermatozoa, though not at the same magnitude. Life of all living things is like a clock, so also are all the parameters that comprise the living thing. The earlier we procreate, the less chance we have to flood the universe with genetically improvised off springs.

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