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Our Health...Our Choice!

Surabhi Gautam and Rima Dada

Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India

Corresponding author: Surabhi Gautam

surabhi_gautam13@rediffmail.com

Laboratory for Molecular Reproduction and Genetics, Department of Anatomy, All India Institute of Medical Sciences, New Delhi, India.

Tel: +911126546716

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"It'll happen once you stop worrying about it." Females in today's world who have difficulty in conceiving children face a multitude of judgments and unsolicited advices. Every best possible way is then tried for the conception and most importantly to fight this taboo, infertility. Gone are those days when women shoulder the blame of infertility on themselves. Worldwide, more than 70 million couples suffer from infertility; the majority of them belong to developing countries [1]. In almost half of the infertile couples, the problem is with the male [2]. There may be derangement in the parameters of routine semen analysis like sperm count, motility and morphology. But the definitive diagnosis becomes deficient when all these parameters are normal in infertile men. One of the major factors beneath the surface is the quality and integrity of sperm DNA. The denatured and fragmented DNA has shown to result in implantation failure, congenital malformations, complex neuropsychiatric disorders, polygenic diseases like congenital diaphragmatic disease and childhood cancer like retinoblastoma and leukemia [3]. Not only infertility, the damaged DNA has the capacity to adversely impact embryonic viability and affect the developmental competence as sperm transcribes genes critical for early embryonic development. Hence, sperm is not mere a vector of paternal DNA, whose function just stops short at fertilization, but transmits a host of coding and non-coding RNA, oocyte-activating factor (OAF) and centrioles which are critical for optimal cleavage and embryogenesis. Sperm DNA telomeric length is chief determinant of telomere length in the offspring. Though a complex trait, it is mainly determined by telomere length in sperm. Oxidative stress (OS) and DNA damage targets telomeres in nuclear periphery and cause its accelerated attrition. This can jeopardize the genomic stability and result in mitotic errors. Sperm DNA damage may lead to increased pre and post implantation losses, increased incidence of miscarriages, high rate of congenital malformations and even childhood cancer [4, 5]. OS is one of the major contributory factors to sperm DNA damage and defective sperm function as it damages sperm nuclear and mitochondrial DNA. OS is also known to up regulate levels of DNA methyltransferases (DNMTs) and thus seminal oxidative stress may lead to epigenetic alterations and a recent study has reported that paternal sperm DNA methylation is associated with early signs of autism [6]. Many genetic and environmental factors have been identified to cause defects in sperm function resulting in OS that impairs the functional and structural integrity of the spermatozoa [7].

Reactive oxygen species (ROS) are oxidizing agents generated as a result of metabolism of oxygen and have at least one unpaired electron that makes them very reactive species. Small amounts of ROS are produced by spermatozoa under normal physiological conditions, which are required for the maintenance of sperm function and for redox sensitive signal transduction pathways [8]. Physiological levels of ROS mediate normal sperm function such as capacitation, hyperactivation, acrosomal reaction and sperm-oocyte fusion, but increased production of ROS can cause OS, induce pathophysiological changes in the spermatozoa and alter sperm methylome [9]. The ROS-mediated injury to spermatozoa includes peroxidative damage of the plasma membrane and oxidative damage to mitochondrial DNA, causing impairment of sperm motility and resulting in abortive apoptosis. There are mechanisms by which the supranormal concentrations of ROS can be scavenged by the anti-oxidants present in the seminal plasma. However, excessive production of ROS or defects in scavenging machinery lead to OS within the spermatozoa this leads to severe damage in sperm DNA, decrease in sperm motility, poor membrane integrity, apoptotic-like changes and finally, impaired fertilization. All cells are sensitive to OS and damage; however, except the male germ cell all other somatic cells and oocyte have adequate antioxidants to prevent damage by free radicals and contain adequate machinery for DNA repair. DNA damage is often induced by OS, rather than being the result of other processes such as defective apoptosis [10]. ROS causes DNA damage in

the form of modification of all bases, production of base free sites, deletions, frame shifts, DNA cross links and chromosomal rearrangements [11]. OS is also associated with high frequencies of single and double strand DNA breaks and formation of DNA adducts and malondialdehyde (MDA) dimers, both of which are mutagenic. OS also targets the telomeric DNA and causing its rapid attrition. The DNA repair mechanism is inadequate to completely remove oxidized DNA adducts or abasic sites (as only OGG1 is present, APE & XRCC1 are absent), thus are dependent on oocyte for complete removal of these lesions. However in cases with extensive damage or aging oocyte with genomic fatigue, the removal of these oxidized DNA adducts or basic sites are incomplete and aberrant. This result in persistence of these lesions posts S-phase and is thus present in each cell of body of embryo. Once they cross a critical threshold they manifest in autosomal dominant or complex polygenic disorders like multiple endocrine neoplasia (MEN), Apert syndrome, achondroplasia, schizophrenia, congenital diaphragmatic disease, cleft palate and autism. As sperm lacks an efficient repair system against oxidative DNA damage and if the oocyte fails to repair the damage post fertilization, the offspring harbor load of mutagenic bases to be at an increased risk of cancer [12]. Nearly 85% of *de novo* germ line mutations are paternal in origin and the frequency increases with oxidative DNA damage and accumulation of highly mutagenic base 8-hydroxy-2'-deoxyguanosine (8-OHdG) and with paternal age. Thus there is a need to prevent delay in the parenthood. Correlations between lifestyle, male fertility and paternal factors have been made in numerous studies over recent years [13-15]. Spermatogenesis is a highly complex process involving mitotic cell division, meiosis cell division and spermiogenesis; during this period, unique and extensive chromatin and epigenetic modifications occur to bring about specific epigenetic changes in spermatozoa. It has recently been suggested that the dysregulation of epigenetic modifications, in particular the methylation of sperm genomic DNA, may serve an important role in the development of numerous diseases including infertility, which is now classified as a complex lifestyle disease. Thus there is a need to remember that germ cell accumulate changes right from the time they are formed (even before the birth of parents) and biological parenting begins much before conception when parents themselves are conceived. Hence, the germ cell genome accumulate genetic and epigenetic changes which are dependent on our lifestyle and social habits (BMI, psychological stress, sedentary lifestyle, smoking, alcohol intake, intake of non-veg food, intake of processed food versus fruits and vegetables). Intake of meat by young men is associated with poor semen quality and lower sperm count [16]. Even consumption of beef by mother and xenobiotics in beef may adversely affect testicular development and reproductive capacity. Sperm concentration has been inversely correlated with mothers' beef meals per week [17]. The sperm genome is relatively stable as compared to the dynamic epigenome. The sperm epigenome is highly sensitive to the environmental changes like change in our life style habits like a sedentary lifestyle, intake of non-veg, fast and processed food, excessive alcohol intake, increased smoking, use of tobacco, psychological stress and use of mobile phones. The effect of these factors is dependent on dose and duration of the exposure [13, 18]. Excessive alcohol consumption causes an increase in systemic oxidative stress as ethanol stimulates the production of ROS, while many alcohol abusers have diet deficient in protective antioxidants. During alcohol metabolism, carcinogens like acetaldehyde are generated, which interferes with the replication of DNA, impairs the process of DNA repair and forms DNA adducts which trigger replication errors and/or mutations in oncogenes or in tumor suppressor genes [19]. Exposure to pesticides like organophosphates and air pollution have also been associated with increased levels of sperm DNA damage [20]. OS carries increased expression of NF-κB which is transcription factor regulating expression of several downstream genes. OS also causes dysregulation in levels of sperm transcripts and may lead to congenital malformations, implantation failure and poor pregnancy rates. Sperm DNA damage is associated with poor assisted reproductive technique (ART) outcome, birth of offspring with congenital malformations, recurrent spontaneous abortions after assisted and spontaneous conception and even childhood cancers [13, 18, 21]. Tobacco has many cancerous products but cadmium in smoking inhibits OGG1, impairs base excision repair mechanism and causes tissue inflammation and a burst of free radical production leading to OS. Fathers who are heavy smokers have shown increased levels of oxidative DNA base damage, high chromatin fragmentation and low concentrations of antioxidant vitamins in their semen ejaculates, which have fatal consequences on the ultimate health and well-being of the embryo. Thus, the children of heavy smokers are more likely to develop childhood cancer than the children of non-smoking fathers [13, 18]. A drastic reduction was found in sperm cell viability in nearly half of men tested who carry their phones in their pants pockets or near their testicles [22, 23]. Endocrine disrupting chemicals have antiandrogenic properties like BisphenolA which is the major component of the plastics and packaging materials cause OS. OS alters the redox buffering capacity which results in production of a highly mutagenic base 8-OHdG which causes GC◊TA transversions, SSBs, DSBs and hypomethylation of the DNA. In addition to this, it is known that OS causes preferential hypermethylation of the tumor suppressor genes, but also causes genome wide hypomethylation due to decreased expression of DNMTs. Recent studies have highlighted that our genes are not determinant of our health (only 5-10% highly penetrant genes result in disease, e.g. BRCA1 and BRCA2), however our behavior, thoughts, lifestyle significantly impact our health through impacting the highly dynamic epigenome.

For the reversal of OS, there are several antioxidants available which may increase sperm concentration and motility, but only few of them affect sperm DNA integrity and thus results in transmission of damaged DNA to the offspring and a heightened disease burden on next generation. Many natural products, including herbal formulations, plant extracts rich in polyphenols, constitute a rich source of anti-oxidants which may lead to OS reversal, but no single intervention is able to provide comprehensive benefits for free radical induced oxidative injury to the somatic as well as germ cells. Yoga and meditation (Y&M) is an emerging health discipline as a complementary, integrative and alternative medical therapy. Yoga is not just a form of

physical activity or relaxation practice but gaining popularity as a therapeutic intervention for various pathologies. Yoga results in positive mind-body modulation via a well-defined psycho-neuro-endocrine-immune pathway. It has shown to be having positive effects on various systemic conditions like hypertension, obesity, atherosclerosis, type II diabetes and mental disorders [24]. Meditation practice mainly targets mainly the cognitive and emotional functions. Meditation practices can be oriented towards the improvement of memory, emotions, cognition, concentration and attentional processes [25]. Y&M together becomes a complete package for mind and body which helps in promotion of physical and mental well-being through physical postures (asanas), breathing techniques (pranayama), and meditation (dhyana). Y&M affects a wide range of processes from basic metabolism, epigenetics, and DNA repair, oxidative bioprocesses to aging, blood pressure, organ system maintenance, subjective well-being, and reproductive health. Healthy lifestyle incorporating Y&M might lower the seminal oxidative stress, and improve DNA integrity in sperm [12, 15]. Microarray studies on effect of Y&M shows upregulation in expression levels of various anti-inflammatory, cell cycle controls, DNA repair genes and regulation of OS by practice of yoga and meditation. Thus while anti-oxidants may ultimately result in reductive stress and increase the percentage of sperm with poorly compacted DNA and adversely impaired numerus redox sensitive reactions, but yoga and meditation based lifestyle intervention (YMLI) regulates OS levels and aids in maintenance of genomic and epigenomic integrity. Thus in present day & age with constraint of space & time and few in developed countries who can rarely afford to eat adequate amount of fruits and vegetables, YMLI may be an answer to lower psychological and oxidative stress and improve health. Tolahunase et al. has shown that practice of YMLI can reverse aging by decreasing three cardinal markers of ageing like OS, DNA damage and decrease telomere activity [26]. Regular practice of Y&M could also be the key to healthy senescence as it could have a buffering effect on age-dependent DNA damage and repair capacity. Adopting a healthy life style by quitting smoking, minimizing excessive alcohol intake, minimizing exposure to endocrine disrupting channels (Bisphenol A, insecticides, pesticides), minimizing exposure to cell phone EMRs, increased intake of fruits and vegetables, maintaining optimal weight, increasing physical activity and integrating yoga and meditation as an integral part of our lifestyle will not only minimize or prevent OS and its associated squeal but also significantly improve quality of life and promote physical, mental and reproductive health. “And it'll happen once we start worrying about our declining health."

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