

# Genetic Factors and Environmental Factors Affecting Male Infertility

Shoemun Park

BA Biochemistry, University of Washington, Seattle, WA, USA

Email address: syknano1010@gmail.com

**Abstract**—Infertility has traditionally been thought of as a woman's problem. But, about one out of every three cases of infertility is due to the man alone. A diagnosis of male infertility can be one of the hardest challenges a man can face. Sperm are made in the testicles. They're then stored inside yards of "plumbing" called the epididymis, which lies on top of each testicle. Sperm are nourished by semen, which is made by glands along the way. Nanorobot give sperm an artificial boost to get into an sperm.

**Keywords**— Sperm, egg, infertility, pregnancy.

## I. INTRODUCTION

In 1950s many couples married at the age of early 20s and the fertility rate was high. This is highly related to female's age and ovum quality. At puberty the number oocytes decrease from 1-2 million to 300,000 to 500,000 million. The decrease in oocytes happen until the female is in menopause [1]. However, in the mist of oocyte decrease, the healthiest oocytes are produced during the age of 20s. Recently, due to social factors, women started to have child after the age of 30s and this is the age when women fertility rate decrease. Kimberly Liu et al. stated that the decline in birth rate started when women reach the age of 35 [1]. It seemed like women was the major cause of having no child. This was not even surprising due to the fact that male infertility measure techniques were not detailed [2]. The lack technique to find men's infertility was not well researched and women had to hold the blame [6]. However, recent researches emphasize that female is not the only cause of having no child but male has equal responsibility. It has not been so long of researchers looking for the cause of male fertility. In 2002, Donald P. Evenson et al was surprised that there was no reference containing the influence of defective sperm that is the possible cause of unsuccessful pregnancy outcome [2]. This indicates that researches on male fertility were not considered to be important ten years ago and most of the female had to hold the blame. However, as many semen analysis developed, male infertility was well exposed and researchers started to find factors that cause male infertility. From this essay I would like to review the factors that are related to male infertility. In male infertility, the major two factors that influence is the sperm problem and environmental factors. When we say sperm and environmental it is referring all possible and detailed factors that influence male infertility.

## II. GENETIC FACTOR

The major cause of male infertility comes from the problem of sperm DNA. Patients that have no visible sperm in

semen analysis are diagnosed with Azoospermia. There are several genes that encode spermatogenesis and when these genes have mutations, this leads to defective spermatogenesis [10]. The AZF region in Y chromosome is specifically related to spermatogenesis and have three sub regions (AZFa, AZFb and AZFc) containing specific genes [11]. In 2012, Toshinobo Miyamoto et al have asserted that in AZFa region USP9y gene, AZFb region RBMY gene, and AZFc region DAZ gene was assumed critical in spermatogenesis. However, in 2015 Xiao-Wei Yu et al. found that in AZFa DBY gene was critical in spermatogenesis and in AZFb additional gene called PRY gene was considered critical. In AZFc, all of the genes in this region were specifically for spermatogenesis [12]. The progress of finding the correct genes for spermatogenesis provides the key to prevent male infertility. Also, further findings show that DNA damage due to mutation can cause sperm azoospermia. The study conducted by Marcos Meseguer et al. concluded that sperm DNA damage in azoospermic males were higher than normoozpermic males [8]. In addition, 15% of azoospermic patients or oligozoospermic patients were observed AZF micro deletion. Once again, the mutation in AZF region was the caused a defect in sperms. This led to further study on what induced the mutation in AZF region and Faizan Khan et al point out environmental pollutant. In 2010, Faizan Khan et al. tried to find whether the environmental pollutant, which is hexachloro-cyclohexane (HCH) isomer, induces Y chromosome micro-deletion [13]. They have discovered that azoospermic males have high HCH level in their semen samples and they assumed that this was due to continuous exposure to HCH. However, researchers could not find the specific mechanism of HCH inducing micro-deletion [13]. Further research should conduct the AZF region and environmental pollutant correlation and moreover, find the influence in spermatogenesis for male infertility.

The formation of Chromatin structure can cause male infertility. Sperm chromatin structure is compact and well organized due to the nature of safely transporting the genome to embryo. However, when there is an abnormality in sperm chromatin structure, the male is potentially infertile. Protamine is arginine rich nuclear protein that is essential for sperm head formation and sperm DNA structure stabilization. During the phase of transition from diploid to haploid in spermatogenesis, protamine are known to replace the histones in sperm DNA. When protamine replaces histone the positive charge arginine in protamine relieves the negative charge of the phosphate in DNA and increase the stability of DNA structure [3]. There

are two types of protamine which are P1 and P2 and these proteins are produced by interaction between *prml* gene and *prm2* gene [3]. When these two genes do not interact well, they cannot produce protamine the sperm DNA will have less stable due to less arginine and will have loose chromatin.

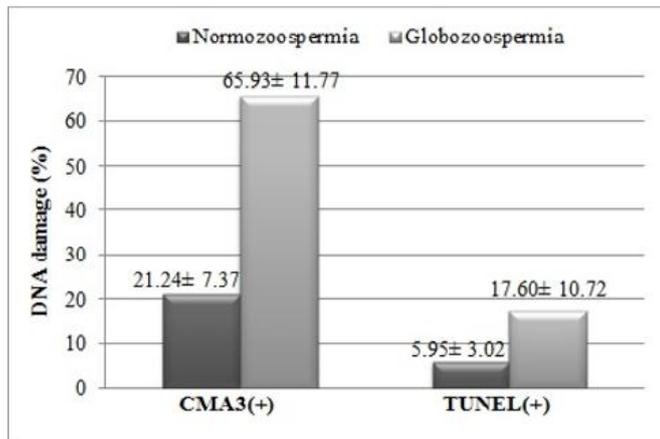


Fig. 1. DNA damage comparison to CMA3 and TUNEL tests in case and control group (by sperm protamine deficiency).

Jatal Ghasemzadeh et al. looked for deficit protamine by chromomycin A3 and apoptosis detection by TUNEL assay to find DNA damage in Normozoospermia and globozoospermia [4]. The result showed that males who had high deficit in protamine had high percent of DNA damage than the normozoospermia. Also, the apoptosis detection was high in male who had globozoospermia than normozoospermia, but it did not show significant DNA damage percent than protamine detection (Figure 1). An interesting point was chromomycin A3 had higher DNA damage detection than apoptosis. This is because protamine deficiency induces sperm chromatin abnormality but apoptosis happen after sperm chromatin abnormality. The importance of the graph (Figure 2) consent to the findings that PRM 1 was reduced in PRM-2 deficit sperm and inactivation of either of two gene caused protein deficit in all genes leading to DNA damage and possible male infertility [3]. Furthermore PRM-2 deficient sperm, which produced less protamine, had less compact chromatin than healthy sperms. The importance of protamine genes affects of sperm chromatin structure and this highly correlates with a normal sperm DNA production and moreover, the development of an embryo.

However, a sperm chromatin with abnormal structure has a chance to repair its problem depending on the oocyte's capacity to repair the preexisting damage [2]. Alba Fernandez-Encinas et al. also confirmed that if oocytes do not process DNA repair during the first stage of embryo development for sperm DNA then the damage result in decreased pregnancy rate [5]. Another possible cause of male infertility is the nuclease activity in sperm DNA. Nuclease is an enzyme that is capable of cleaving phosphodiester bonds between nucleic acids and nucleotide subunits. It is involved in the processes of DNA repair, apoptosis, and DNA cleavage [5]. In human, nuclease activities are very active in ejaculate body fluid which is semen. Especially in epididymal and vas deferens

spermatozoa, the DNA cleavage (topoisomerase 2) degrades sperm DNA in to loop-sized fragment. The nuclease activity is reversible in epididymal but not in vas deferens because of the nuclease activity that degrades the DNA in irreversible manner [7]. Alba Fernandez-Encinas et al. tried to find out the relation between nuclease activity and sperm DNA fragmentation to find how this affects male infertility [4]. They used Single Radial Enzyme Diffusion (SRED) method to find nuclease activity in fertile male and infertile male.

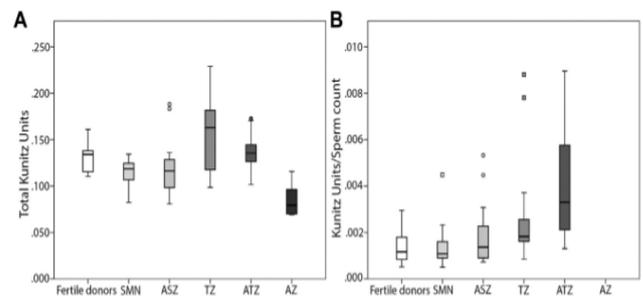


Fig. 2. Total nuclease activity and nuclease activity corrected by sperm count measured by SRED.

From the test, they have found the relationship between semen parameters and nuclease activity. When the sperm count was corrected, the graph showed that patients with sperm motility and morphology problem had high nuclease activity. Especially patients who were diagnosed with astheno-tetrazoospermia had high nuclease activity. Due to sperm DNA problem mitochondria produces ROS (Reactive Oxygen Species) and this initiate apoptotic cascade resulting in abnormal motility. In the apoptotic cascade endo-nuclease fragments chromatin structure and this is the reason why astheno-tetrazoospermia patients have high nuclease activity.

### III. ENVIRONMENTAL FACTORS

In 1970s, the issue of chemicals affecting male's reproductive system was exposed due to pesticide manufacturers and agricultural workers. The manufacturers and workers suffered with this issue due to the nematocide and researchers have started to look for chemicals that were hazardous to human reproductive system [21]. Alejandro Olive et al studied Litoral Sur region in Argentina because the region was heavily agricultural base environment [21]. The result showed that males who worked in heavily chemical used agriculture had high semen volumes but low sperm concentrations and motility compared to those who did not work in farms. Also males who were exposed in heavy metals and multiple chemical agents increased abnormality of semen. Another recent study support that pesticide induces toxicological substance that disrupts the function of the reproductive system. Especially, pesticides alter hormones that are crucial for the formation of Testosterone in male body [22]. From the studies, male infertility is affected by their career.

Smoking is one of the environmental factor that is considered to affect male infertility [20]. M. F. Hamad et al. have done a research on cigarette smoking and histone to

protamine ratio in spermatozoa [14]. The team found out that patients who smoke had higher histone [H2B] and protamine ratio compared to nonsmokers in their semen analysis. The high rate of H2B in sperm DNA breaks the balance of histone [H2B] and protamine ratio. When this balance breaks, the sperm DNA could not have compact packaging and will increase the vulnerability from oxidative stress leading to sperm DNA damage. Cotinine, which is the metabolite of nicotine, is detected in seminal plasma and smokers who had high cotinine also had high H2B [14]. This is the evidence that the cotinine is affecting the protamine ratio and histone level in the DNA. Furthermore, cigarette smoking increased leucocyte and ROS level in semen due to oxidative stress [19]. From male infertility and genetics part, increased ROS level triggered high nuclease activity causing abnormal sperm motility. With the information of cigarette affecting ROS level, it agrees to the fact that smoking can cause high nuclease activity potentially obstruct the development of an embryo.

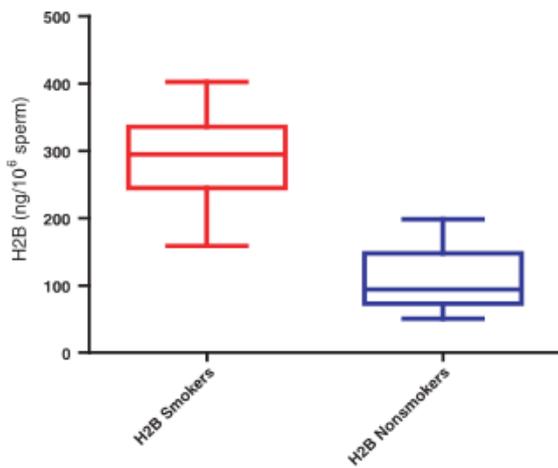


Fig. 3. Histone level in Smokers and nonsmokers.

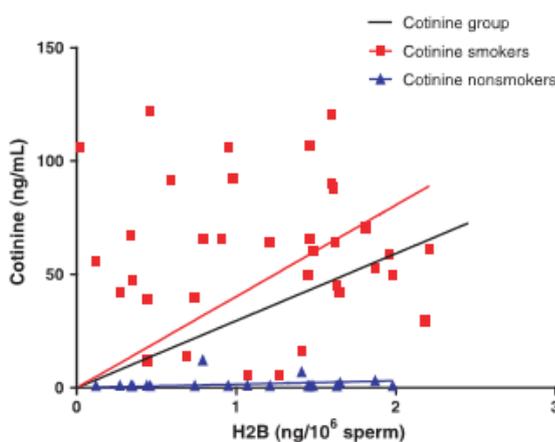


Fig. 4. Cotinine and histone correlation.

Furthermore Sebastiano La Maestra et al., used mouse testis and spermatozoa to find the DNA damage and oxidative stress resulting in morphological changes [16]. It is well

known that smoking increases seminal oxidative stress, increasing ROS (reactive oxygen species) level. The increase of ROS in male reproductive organs degrades chromatin structure and further more affecting sperm DNA [2]. In addition, study from Sebastian La Maestra et al. used mouse to see the cigarette and DNA damage. The DNA damage was high in mouse that was in Cigarette smoking condition and this definitely showed the possible relation in Cigarette and sperm DNA damage [16], [18]. Recently, David F Yao and Jesse N Mills have stated that benzo(a)pyrene can causing damage by binding to sperm DNA, disrupting DNA structure[17]. All of these data complements to the idea of smoking affect sperm motility and morphology.

However, there are conflicting views on smoking and male infertility. Avi Harlev et al. stated that the oxidative stress affect sperm parameters but they emphasized that not all studies agreed to this statement [15]. This is because they could not find the direct mechanisms of smoking and spermatozoa DNA and the biases on selecting candidates for the study were not consistent [15]. Further researches should be conducted on the specific mechanism to relate behavior of smoking cigarette to male infertility.

Another environmental factor that affects male infertility is cell phones. Cell phones have been an important part of our lives until now and it is always close to our body. However, the convenience of having cell phone also gives negative impact to sperms. One study showed that participants who had their cell phone within 50 cm from their genitals had higher rate of abnormal sperm concentration [25]. Cell phones emit radiofrequency electromagnetic waves (EMW) between 400MHz- 2000MHz, and the phones we are more familiar (Smart Phones) emit above 2000MHz. The problem is that the hormones related to producing testosterone [28] and inhibin in male rats elevated after emitting 900MHz for 30 days [26]. Moreover, Leydig cells, which produce testosterone, were more vulnerable to EMW. Leydig cells produce testosterone by the signal of LH hormone. When leydig cells are impaired due to EMW, then spermatogenesis cannot occur [24] and this leads to male infertility. Researchers tried to find the mechanism that relies on the damage by EMW and Joan Raymond stated that “high EMW frequency can lead to higher free radicals in sperm samples [23]. Free radical such as H<sub>2</sub>O<sub>2</sub> is related to apoptosis and necrosis in germ cell death [2]. When there are low amount of free radical this regulates the germ cell to proliferate by controlling the level of apoptosis. However, excessive free radical triggers unregulated apoptosis and this kind of oxidative stress further damage sperm DNA [2]. Cell phone usage and especially when using internet through mobile have more EMW emission. To protect the reproductive system from free radical reactions, it is important to put cell phones away from the reproductive system.

#### IV. TREATMENTS IN FUTURE

Male fertility issues contribute to about half of the cases of infertility. One in five men have slow swimmers, properly known in the medical community as low sperm motility. It's one of the leading causes of infertility, One major cause is low sperm motility, or the sperm's inability to swim to the egg.

Reduced fertility is a sensitive and common problem globally, with a vast spectrum causes, ranging from Klinefelter's syndrome to a low sperm count. Nanotechnology could be appeared as an innovative solution to problems of male infertility, Nanorobot Could Help Slower Sperm Swim to Egg.

V. CONCLUSION

There are so many factors that can relate to male infertility. The knowledge of knowing several factors of male infertility with genetic factor can help people who do not know about male infertility. On top of genetic factors as being the core reason of male infertility, environmental factors are the major cause of genetic issues. There should be more researches on the relationship between specific environmental factors and spermatogenesis. Women is important when having a baby but men also take the same responsibility for providing a good sperm that would eventually become the child.

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