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Role of Markers in Male Infertility: A Review

Rajkumar Saket[1], Alibha Rawat[2], N. Ganesh[3]

[1, 2, 3]Department of Research, Jawaharlal Nehru Cancer Hospital and Research Centre, Idgah Hills, Bhopal (M.P.), India

[2, 3]Corresponding Author

Abstract: ***Infertility is a disease of the genital system defined by the failure to realize a clinical pregnancy after 12 months or more of normal unprotected sexual activity. The causes of male infertility ranges from hormonal imbalances to physical problems to psychological and/ or behavioral problems and ill habits (Manish et al., 2015). As per guidelines of World Health Organization (WHO), the inability of couples to conceive after 2 years of regular unprotected intercourse clinically defines infertility. As per guidelines, male factor infertility can be a health problem for males and is primarily responsible for inability to conceive a child after 1 year of regular, unprotected intercourse (Amena Khatun, et al., 2018). The investigation in male infertility is assuming greater importance because approximately half of all infertility cases are caused by male factors. In wake of this fact, it is of utmost importance to look for specific and sensitive markers to identify infertility in males early on so that it can be cured or rectified before it is too late. The current review explores such studies that were devoted to the identification of such markers that ranges from chromosomal to hormonal to anatomical but each separately or in combination can help the medical fraternity and fertility experts in helping their patients and could be prove to be a boon to the infertile couple.***

Keywords: Anatomical, clinical pregnancy, chromosomal, genetic, hormonal imbalance, infertility

1. Introduction

Male infertility has been on the rise since the last one or two decades due to changing lifestyle and probably changing environmental condition. Overall, infertility is on the rise with 1 in 6 couples wishing to conceive being diagnosed as infertile. A number of potential causes can be attributed to this rising trend of male fertility including exposure to environmental endocrine disrupting chemicals (e.g., plasticizers, bisphenol A, and phthalates), rising rates of obesity, and the trend of delayed parenthood (Ravitsky *et al.*, 2019). Although previous studies suggest that a lot of cases with male infertility have a genetic and environmental etiology to the condition, and therefore, the majority of cases are idiopathic. About 10-20% of azo-ospermia patients show micro deletion in Y-chromosome. Recent works have shown that male infertility is caused by not only Y chromosome, but X chromosome and some autosomal genes also. Another causative factor has been found to be mitochondrial genome damage leading to oxidative stress that might lead to male infertility. Advanced molecular techniques have improved our understanding of genetics of infertility but still a number of questions remain unanswered (Shalaka *et al.*, 2015).

Male factor infertility is often reflected on semen analysis such as low or absent sperm counts and low motility. While interpreting semen analysis, men should be questioned thoroughly regarding possible confounding factors such as abstinence, length, recent illnesses, or testicular heat exposure. Unfortunately, seminal analysis provides limited information and cannot discriminate fertile from infertile men on an individual basis. A review done by Jared M. Bieniek, *et al.*, (2016) focused specifically on available seminal testing and advancements in biomarker research in the areas of natural male fertility with special focus on all the "omic" studies.

The population explosion and infertility are the two major problems of human reproduction. There has been a huge increase in population in countries like India, China, Bangladesh, etc., and for this the per capital income along with agriculture production has come down from what is required, especially in India where religious and socioeconomic traditions have made it mandatory for everyone to have a child. (Asha Sharma. 2017).

The sex-chromosomes are critical players in determining the sex of almost all of the multi cellular organisms. The Y-chromosome is one of the two sex-chromosomes in mammals and is usually the smallest chromosome in the karyotype. Y-chromosome is suitable for studying the evolutionary relics, speciation, and male infertility and/or sub fertility thanks to its unique features like long non-recombining region and holandric inheritance pattern, (Jasdeep Kaur Dhanoa, *et al.*, 2016).

Some advanced techniques like introduction of intracytoplasmic sperm injection (ICSI), intracytoplasmic morphological sperm injection (IMSI), and physiological intracytoplasmic sperm injection (PICSI) for successful reproductive outcome encouraged to go for newer tests which should expect the successful fertilization *in vitro* and *in vivo* (Amena Khatun, *et al.*,2018)

Genetic association of male infertility can be seen in around (10-20%) of male infertility can be new genetic marker which physicians should know about it is important to identified to genetic marker Abnormal sperm function or specific molecular defects can be hypothesized in these cases, the diagnosis in made in male infertility. they are reported as idiopathic (Alberto Ferlin and Carlo Foresta 2014).

Epigenetic mechanisms of DNA methylation has been implicated in numerous biological functions such as the development of spermatozoa and early embryos. A study was done to assess the role of DNA methylation in spermatogenesis and male infertility. The study provided strong basis for the evaluation of epigenetic quality of sperm by assisted reproductive technology (ART), (Xiangrong Cui,

et al., 2016) that can prove to be the treatment of choice for many infertile couples in future.

Another important study involved the evaluation of oxidative stress in seminal plasma by measuring SOD, catalyses and GPx where enzyme antioxidants such as tocopherol, urate, naphthoquinone and HCO3- were previously known to have oxidative protection. Their levels can have detrimental effect in the quality of sperm (Victor Duniya Sheneni. *et al.*, 2018).

Infertility may be a condition with psychological, economic, medical implications leading to trauma, stress, particularly during a social set-up like ours, with a robust emphasis on child-bearing according to the International Committee for Monitoring Assisted Reproductive Technology, (Kumar and Singh, 2015).

The last few years have seen a decline in sperm quality and more and more percent of males are being reported to be infertile in the last decade. Couples with primary infertility have never been able to conceive, while on the other hand, secondary infertility does have difficulty in conceiving after being conceived once. Technically secondary infertility will not be presentable if there is a change of partner. An anthropometric parameter, Anogenital Distance (AGD) that involves physical examination, in which the distance between anus and genital origin is measured is found to be a very good biomarker for infertility with males having less than 2 cm AGD are found to be at higher risk of infertility (Gresh Chander, *et al.*,2017).

This nucleus acts as a genome bridge from one generation to next generation. Any deterioration or alteration of the sperm chromo team can have serious consequences for the Infertility danger, it was recently confirmed that the Asian male population followed the same global trend over the amount of past 50 years. (D. M. I. H. Dissanayake, *et al.*, 2019).

The prevalence of infertility varies widely, being less in developed countries and more in developing available Infertility is an important medical and social problem in the world as regards 15% of couples are infertile and 40% are infertile because of male factor infertility and 40% are because of female factor infertility and in the remainder both factors are associated. Infertility may be a worldwide problem and approximately 8-10% of couples within reproductive age bracket are infertile. It is estimated that globally 60-80 million couples suffer from infertility per annum of which probably between 15-20 millions are in India alone. Infertility is a common gynecological problem affecting 15% of couples attempting their first pregnancy, in which cases it is called primary infertility; while those with secondary infertility are about 10% of the population. Secondary infertility could be as high as 52% in some Sub-Sahara African countries and as low as 23% in some Asian countries. (Roshan Kumar Mahat, *et al.*, 2016)

Following lifestyle factors are associated with male infertility; cigarette, alcohol, drug, use obesity, psychological, stress, consumption, of coffee other causes such; as testis stress, of addiction are past cycling, training, due to lack of sleep and also the use of mobile phones, (Durairajanayagam *et al.*, 2018).

As World Health Organization (WHO) guidelines, infertility is the couple's inability to conceive after 2 years of normal unprotected intercourse. The investigation in male infertility is assuming greater importance because approximately half will infertility cases caused by male factors. Although previous studies suggest that many cases with male infertility have a genetic and environmental etiology to the condition, and the majority of cases are idiopathic (Shalaka *et al., 2015).*

In one of the study done using traditional system of medicine which includes Ayurvedic Pharmaco therapeutics have an altogether different approach towards management of Male Infertility (Manish *et al.*, 2011).

Another review explained the fact that diagnostic tools for male infertility are limited and often consists of a standard semen analysis. Some molecular tests can serve as an additional and effective assessment of male infertility like a panel consisting of DNA RNA protein identified by metabolites, fragmentation index, sperm fluorescence in situ hybridization, and other historical sperm functional tests (Bieniek, 2016).

Studies have postulated that male infertility can be influenced by several factors such as exposure to pesticides, industrial chemicals, heavy metals, obesity, alcoholism, tobacco smoking, sedentary lifestyles, poor nutrient intake, oxidative stress, physiological factors, genetic factors Routine semen analysis and assays for sperm chromatin are all factors that are involved in male infertility. (D. M. I. H. Dissanayake, *et al.*, 2019)

Male infertility can also occurs due to associative factors like, mobile phone, lack of sleep, and such lifestyle choices (Damayanthi Durairajanayagam, 2018).

2. Conclusion

The review article extensively explores the various studies that threw light into the causes, risk factors and diagnostic tool for male infertility. It describes the fact that there are various medical reasons that make male infertile such as varicocele, testicular failure, endocrine dysfunction, genital tract infection, testicular disturbances, testicular cancer, hormonal disturbances, retrograde ejaculation, prolonged exposure to heat, obesity, older age, etc. Diagnosis of male infertility usually involves physical examination, semen analysis, hormone test, biopsy, urine test (MamunaNaz. & Mehnaz Kamal, 2017). The sperm function test is the most important of these tests as this determines the fertilization of ova and eventually conception of a fetus. Research into the genetics of male infertility is very rich and rapidly evolving field and identifies chromosome aberration assay as a very important diagnostic tool for male infertility (Alberto Ferlin and Carlo Foresta, 2014)

The zest of the review suggests that the cause of male infertility is multifactorial and various factors including genetic, anatomical and environmental determinants are

responsible for it. Various lifestyle choices and changing environment have caused serious hormonal imbalances in males making them infertile and this needs to be addressed. The medical fraternity, genetic experts, IVF experts all need to work in collaboration to treat this serious condition.

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