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Modulation of Genetics and Epigenetics Factors in Male Infertility through Yoga-Based Lifestyle Intervention

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Abstract

Male infertility, a complex condition affecting a significant proportion of couples worldwide, often involves genetic factors such as Y chromosome microdeletion, mutations in Azoospermia factor (AZF) genes, SRY gene, and Androgen receptor (AR) gene. These genetic abnormalities can lead to impaired spermatogenesis and resultant azoospermia or oligospermia. Understanding these genetic factors is crucial for diagnosis and management of male infertility.

Yoga-based alternative therapies have gained attention for their potential in improving overall health and well-being, including reproductive health. Studies have suggested that yoga practices, encompassing physical postures (asanas), breathing techniques (pranayama), and meditation, can reduce stress, enhance hormonal balance, improve blood circulation, and modulate immune function. These benefits may contribute to ameliorating underlying causes of male infertility associated with genetic mutations.

This review explores the role of Y chromosome microdeletion, AZF gene mutation, SRY gene mutation, and AR gene mutation in male infertility and reviews the potential of yoga-based alternative therapies in mitigating these genetic factors. Further research and clinical trials are warranted to validate the efficacy of yoga as a complementary approach to conventional treatments for male infertility.

Keywords: Azoospermia factor; AZF mutation; cytogenetic; Male infertility; Y chromosome microdeletion; SRY gene mutation; Yoga.

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INTRODUCTION

Several genes are involved in male fertility, including those involved in spermatogenesis as well as in DNA recombination, repair, and replication. The genomic stability and integrity are critical for germ cells (Eddy, 2002). Using modern genomics and proteomics methodologies, as well as advanced gene expression tools such as RNA sequencing and microarray could aid in deciphering the causes of infertility (Shamsi *et al.*, 2011). This would not only reduce the threats of Assisted Reproductive Technology (ART) but

would also bring insight into previously unknown sides of infertility. As a result, not only is it necessary to comprehend the role of fertility-related genes, but also to have a better understanding of the role of promoters, regulators, and non-coding RNA like microRNA (Yoshida *et al.*, 1997). Even though much has been explored about the different molecular aspects associated with fertility, there are still gaps in our knowledge that need to be filled and explored so that a potential diagnosis mechanism can be made. This manuscript would also assist ART clinicians in treating and managing fertility disorders in males. Assisted Reproductive Technologies (ART) and yoga represent two distinct approaches that can complement each other in supporting fertility treatment, though their direct interaction or combination is not widely studied or standardized.

Definition

The inability to become pregnant following a year of unprotected sexual activity is known as infertility. Approximately 10% to 15% of married couples worldwide struggle with this issue, with male infertility accounting for 50% of cases (Kumar and Singh, 2015).

An estimated 15% to 30% of male infertility cases are caused by genetic causes. The mitotic, meiotic, and post-meiotic differentiation phases of spermatozoa creation happen in sequence and are all governed by complex genetic programs. Numerous physiological functions, including the growth and differentiation of germ cells and the hypothalamus-pituitary-gonadal axis, are regulated by genes. Understanding the genetic causes of infertility is crucial in the age of assisted reproduction technology to give the couple the most appropriate therapies and counseling (Dada *et al.*, 2007).

Role of genetics and epigenetics in Male Infertility

Numerous candidate genes have been identified as responsible for the pathogenesis of male infertility, the consequences and their correlation along with a role in diagnosis are discussed.

Role of Y Chromosome

The Y chromosome plays a crucial role in male infertility primarily because it contains genes that are essential for the development and function of male reproductive organs, sperm production (spermatogenesis), and overall fertility.

Genes on the Y chromosome, particularly in the AZF (Azoospermia Factor) region, are crucial for spermatogenesis. Deletions or mutations in these genes can lead to impaired sperm production or complete absence of sperm (azoospermia). For example, deletions in the AZF region can disrupt the process of sperm maturation in the testes. The Y chromosome is involved in the final stages of sperm development (spermiogenesis), which includes the formation of the sperm tail and other structural components necessary for motility and fertilization. Mutations or deletions affecting these genes can lead to sperm with abnormal morphology or impaired motility, reducing fertility. Aneuploidies involving the Y chromosome (*e.g.*, XYY syndrome, YY syndrome) can affect male fertility. These conditions can lead to abnormal spermatogenesis, reduced sperm production, and sometimes complete infertility. The gene for the androgen receptor (AR), which is located on the X chromosome but has implications for male fertility, interacts with genes on the Y chromosome.

Testing for Y Microdeletions

Testing for Y chromosome microdeletions is an important diagnostic tool in the evaluation of male infertility, especially when there is a suspicion of azoospermia (no sperm) or severe oligospermia (very low sperm count). Y chromosome microdeletion testing is usually recommended for men who have severely impaired sperm production (azoospermia or severe oligospermia), particularly in cases where there is no clear anatomical obstruction (obstructive azoospermia). It helps to determine if the cause of infertility is due to genetic factors affecting spermatogenesis. Before testing, genetic counseling is often recommended to discuss the implications of the test results, potential inheritance patterns, and available reproductive options.Y chromosome microdeletion testing involves analyzing specific regions on the Y chromosome known as the Azoospermia Factor (AZF) regions. These regions (AZFa, AZFb, AZFc, and sometimes AZFb+c) contain genes critical for spermatogenesis (Bor et al., 2001). The testing typically uses PCR (Polymerase Chain Reaction) or other molecular techniques to detect deletions within these regions. The test results will indicate whether there are deletions in one or more of the AZF regions. Different types of deletions can have varying impacts on sperm production:

AZFa Deletion: Associated with the most severe form of spermatogenic failure, leading to the complete absence of sperm.

AZFb Deletion: Associated with a less severe form of spermatogenic failure.

AZFc Deletion: Usually associated with a milder form of spermatogenic impairment, where some sperm production may still occur.

A positive result (Deletion Detected) indicates a higher likelihood of severe spermatogenic impairment or absence of sperm, which may affect fertility. Negative Result (No Deletion Detected): Suggests that the infertility may be due to other causes, and further evaluation may be needed. Y chromosome microdeletion testing helps in providing a more accurate prognosis for male infertility and guides appropriate management strategies, including assisted reproductive techniques (ART) such as Intracytoplasmic Sperm Injection (ICSI) in cases where viable sperm can still be retrieved. It's important to note that while Y chromosome microdeletion testing is valuable, not all cases of male infertility are due to Y chromosome abnormalities. Other genetic factors, hormonal imbalances, environmental factors, and anatomical issues can also contribute to male infertility. In summary, Y chromosome microdeletion testing is a specialized genetic test that plays a crucial role in diagnosing genetic causes of male infertility. It provides valuable information for both prognosis and management of infertility in affected individuals (Henegariu *et al.*, 1994; Qureshi *et al.*, 1996).

Clinical implications of Y Chromosome microdeletions

Y chromosome microdeletions have significant clinical implications for male infertility. Y chromosome microdeletion testing provides prognostic information regarding the severity of spermatogenic impairment. The presence and type of microdeletion (AZFa, AZFb, AZFc, or combinations thereof) can help predict the likelihood of successful sperm retrieval and the potential for natural conception. Knowing the presence of Y chromosome microdeletions guides fertility specialists in determining appropriate management strategies. In cases where sperm can be retrieved despite microdeletions (*e.g.*, in AZFc deletions), techniques like Intracytoplasmic Sperm Injection (ICSI) can be employed to achieve fertilization. In cases of severe microdeletions (*e.g.*, AZFa deletions), where sperm production is completely impaired, the use of donor sperm may be recommended as a viable alternative for achieving pregnancy. Results of Y chromosome microdeletion testing inform genetic counseling sessions. This includes discussions about the inheritance pattern of the microdeletion and its implications for future generations. It helps couples understand the risks of passing on infertility-related genetic abnormalities to their offspring. Identifying Y chromosome microdeletions prompts screening of other male family members who may also be at risk of inheriting the same genetic condition (Sen *et al.*, 2013). This proactive approach can aid in the early diagnosis and management of male infertility within families. For couples undergoing ART, pre-implantation genetic testing (PGT) may be considered to screen embryos for the presence of Y chromosome microdeletions before embryo transfer. This can help ensure that only embryos without the genetic abnormality are selected for transfer, thereby increasing the chances of a successful pregnancy. Understanding the genetic basis of male infertility through Y chromosome microdeletion testing can have significant psychosocial implications for individuals and couples. It may provide clarity on the cause of infertility, reduce uncertainty, and facilitate informed decision-making regarding treatment options and family planning (Choi *et al.*, 2013).

In conclusion, Y chromosome microdeletions play a crucial role in the clinical management of male infertility by providing valuable diagnostic, prognostic, and genetic counseling information. They guide fertility treatment decisions, optimize reproductive outcomes, and support comprehensive care for affected individuals and couples.

Y genes and male infertility

In 1992, we reported three men with severe damage to spermatogenesis and normal chromosome analysis, but where molecular probes revealed microdeletions on the long arm of the Y chromosome (Sakthivel and Swaminathan, 2008; Colaco and Modi, 2018). Recent investigations have suggested stimulation to probe the long arm of the Y chromosome because of men with azoospermia and deletions of the long arm of the Y chromosome transecting interval 6 with the loss of all distal genetic material and an infertile man with a short arm and a dicentric Y, there have been a large number of publications of case series and it is clear that, while microdeletions may occur in the fertile population they are more prevalent in the infertile populations. It has been reported that the microdeletion detected might be large, but there are preliminary reports of much smaller deletions within genes (Girardi *et al.*, 1997). Microdeletions have been found in three non-overlapping regions of the Y chromosome AZF a-b-c (Ma *et al.*, 1993). Several genes have been described and these include RBM, DAZ, DFFRY40, DBY, and CDY (Yu *et al.*, 2015). The abnormality most commonly reported in the literature is a microdeletion in the AZFc region encompassing the

DAZ gene. However, there is no exact correlation between DAZ deletion and the presence or absence of spermatogenesis, but this may be because for the DAZ gene, there is also an autosomal copy.

Azoospermia

It is estimated that up to 1% of males suffer from azoospermia, which is characterised by the absence of sperm in the ejaculate. The use of healthy spermatozoa from testicular or epididymal biopsies has allowed some azoospermic men (those with a post-meiotic abnormality) to conceive after assisted reproductive technologies have revolutionised the treatment of infertility. While there are many contributing causes to male infertility, genetic factors are thought to have a major role in the development of severe oligozoospermia and azoospermia (Cocuzza *et al.*, 2013). Not with standing this assumption, which is supported by the large number of infertile knockout (KO) mice and the even higher number of genes expressed primarily in the testis, little is understood about the pathophysiology of decreased sperm production, its underlying causes, the genetic and epigenetic implications for the gamete, and the implications for future research (Mitchell *et al.*, 2017). Therefore, it is critical to identify genetic anomalies in order to comprehend spermatogenesis, choose the best course of action for the patient, and deliver appropriate genetic counselling. With an emphasis on genetic abnormalities that directly affect sperm production, the author attempted to evaluate the most recent research on the genetics of azoospermia and oligozoospermia. Recent advances in sequencing technologies have accelerated the rapid evolution of infertility genetics.

Azoospermia is characterized as the absence of sperm in two different ejaculates (Organization, 2010). In the scientific community, azoospermia may not be considered as the condition of prime importance in male infertility. But its molecular characterization needs to be answered which can improve patient care. The alternative and complementary therapy like Ayurveda described various herbal formulations that are scientifically provent heir efficacy on Azoospermia (Pandey *et al.*, 2012b) and other sperm dysfunctions (Pandey *et al.*, 2012a).

The etiology of azoospermia (Nailwal and Chauhan, 2017) can be broadly divided into three main categories: pre-testicular, testicular, and post-testicular. (i) Pre-testicular azoospermia has been associated with low levels of gonadotropins. (ii) Post-testicular include ejaculatory disorders that obstruct the transport of sperm from the testis. Azoospermia may be testicular that include trauma, torsion, infections (*e.g.* mumps and orchitis). It may also be associated with genetic abnormalities (Y chromosome deletions), or in the genes regulating spermatogenesis. Even though multiple genes have been known that are important for spermatogenesis still chromosomal aberrations like Y microdeletions and chromosomal abnormalities such as Klinefelter syndrome have long remained the only known genetic cause of non-obstructive azoospermia (Cerván-Martín *et al.*, 2020).

Genetic and the epigenetic factors play an important role in male infertility (Dai *et al.*, 2012). The major genetic factors in male infertility include chromosomal abnormalities and Y chromosomal microdeletions (Edwards and Bishop, 1997). Y chromosomal deletions contribute 10-15% of total cases related to azoospermia.

Molecular investigations show AZF regions AZFa, AZFb, and AZFc (Yu *et al.*, 2015) that are the hotspots of microdeletions (Kent-First *et al.*, 1999). Spermatogenesis is hampered by microdeletions in these areas. But questions regarding the manifestation of the AZF gene function and its relationship to microdeletions and infertility still need to be addressed. AZF deletion was diagnosed worldwide using the Sequence-tagged site polymerase chain reaction (STS-PCR) and the multi-analyte suspension array (MASA) technique (Bonduelle *et al.*, 1999), (Cram *et al.*, 2000).

The rapid development of assisted reproductive technologies (ART) increases the chances of having biological children for millions of infertile couples. However, these techniques may increase the risk of vertical transmission of Y chromosome-related deletion to their male progenies (Evenson *et al.*, 2002). Therefore, it is the need of the hour to screen AZF related microdeletion before ART treatment. In this review, we will discuss the recent trends related to screening and diagnosis of AZF microdeletion and elucidate their different molecular attributes related to male infertility.

mRNA and Infertility

Male infertility has been linked to dynamic cellular variation, which has been demonstrated by RNA profiling of fertile and infertile males. Many different types of transcripts coding for sperm-specific proteins are generated by the haploid genome during early spermatogenesis or during spermiogenesis in round spermatids. The transcripts are stored in the spermatid cytoplasm before the related proteins are expressed (Evenson

et al., 2002). In mid-spermiogenesis, chromatin remodelling leads to the transcriptional inactivation of the genome (Agarwal and Allamaneni, 2004) Thus the highly condensed sperm nucleus is transcriptionally inert and contains diverse RNA populations, mRNA, antisense, and miRNAs that have been transcribed before inactivation (Suganthi *et al.*, 2014). The presence of transcripts in human spermatozoa has been established using reverse transcription-polymerase chain reaction (PCR) and real-time PCR.

Role of AZF Gene

Spermatogenesis is a crucial reproductive process that is controlled by numerous genes unique to the Y chromosome. The majority of these genes are found in the long arm of the human Y chromosome, specifically in an area referred to as the azoospermia factor region (AZF). The most common structural chromosomal abnormalities, known as AZF microdeletions, are the main cause of infertility in men. Natural fertilisation barriers can be overcome by assisted reproductive techniques (ART), such as intracytoplasmic sperm injection (ICSI) and testicular sperm extraction (TESE), which can help some infertile couples become pregnant. However, the risk of genetic defects being passed on to offspring is increased with these techniques. Many AZF microdeletion types have been identified by sequence-tagged site polymerase chain reaction (STS-PCR), suspension array technology (SAT), and array comparative genomic hybridization (aCGH); however, there are still obstacles to be addressed with each of these methods. AZF microdeletions and their associated phenotypes in infertile males have been studied in great detail. Arguments explaining the occurrence of de novo deletions and expansion and linking ART to the incidence of AZF microdeletions remain unresolved, despite the fact that the transmission of AZF microdeletions has been reported globally. This review provides a thorough update on the state of knowledge on AZF microdeletions and their phenotypes, AZF areas and the genes that are related with them, and new methods for screening AZF microdeletions using the most recent research in the field. Additionally, the field's future research orientation and the transmission features of AZF microdeletions will be extensively examined. Disorders of sex development, formerly known as intersex conditions, are caused by deletions or translocations of the Y chromosome's SRY sex-determining gene, which results in dysgenic gonads. Infertility and a higher incidence of germ cell tumours (GCTs), including gonadoblastoma and several forms of testicular GCT, are the outcomes of gonadal failure (Suganthi *et al.*, 2014; Yu *et al.*, 2015)

The AZFa region

The proximal region of deletion interval 5 contains the 400–600 kb long AZFa region of DNA. Two protein-encoding genes, USP9Y and DBY (recently renamed DDX3Y), are located in the AZFa region. Sertoli-cell-only syndrome, type I, is characterised by deletions in the AZFa locus.(Vog *et al.*, 1996).

The AZFb region

Located on the distal end of deletion interval 5 to the proximal end of deletion interval 6 (subinterval 5O–6B), the AZFb spans approximately 1-3 Mb of DNA. The X-degenerate euchromatin contains the protein-encoding genes EIF1AY, RPS4Y2, and SMCY, while the ampliconic area contains the genes HSFY, XKRY, PRY, and RBMY. (Vog *et al.*, 1996).

The AZFc region

Located in the distal portion of deletion interval 6 (subinterval 6C-6E) on the Y chromosome, AZFc covers 3.5 Mb of euchromatin. The majority of men with idiopathic oligozoospermia or azoospermia had deletions in the AZFc region. Eight spermatogenesis-related gene families are included in the AZFc region: BPY2, CDY, DAZ, CSPG4LY, GOLGAZLY, TTY3.1, TTY4.1, and TTY7 (Dada *et al.*, 2003)

Prevalence of AZF microdeletion transmission

AZF microdeletions are inherited through the paternal germline or occur as de novo events. It has been reported by many studies that more than 80% of AZF microdeletions are of de novo origin (Dada *et al.*, 2003). While some deletions happen after fertilisation, the majority happen before fertilisation. A male offspring will inherit the YCMs if an egg is fertilised by a sperm carrying the mutation. Conversely, if the deletion happens after fertilisation, it could result in mosaicism, which is characterised by Y chromosomes that are normal in leukocytes and Y chromosomes that have the post-fertilization deletion in sperm or testicular DNA (Liu *et al.*, 2014). It has rarely been documented that AZF microdeletions naturally transmit because infertility is the predominant characteristic of men with these mutations. According to Dai *et al.*, 7 out of 10 infertile men had YCMs that were passed on organically from father to son. Samli *et al.*, also

noted that a father's three sons naturally inherited an AZFb microdeletion (Cram *et al.*, 2000). On the other hand, it has been well documented that AZF microdeletions can be vertically transmitted from father to son by ICSI. Studies conducted in the past detailed the sons born to a group of 32 couples who were assisted in becoming pregnant by ICSI and also discovered that the ICSI population's incidence of microdeletions was approximately 9.4%, which was comparable to the incidence of AZF microdeletions in men who were infertile. ART has been linked to higher rates of sperm aneuploidy, de novo chromosomal abnormalities, and sexual chromosomal aberrations. Therefore, whether ART causes AZF microdeletions is one of the main questions surrounding ART. The YCM prevalence in 19 candidate, genes from 199 fathers and their 228 sons (of Chinese and Han ethnicity) who were born naturally (70 boys), through IVF (85 sons), or by ICSI (73 sons) was compared in a recent study by Liu *et al.* They found that the fathers' YCM rates for spontaneously conceived sons, IVF sons, and ICSI sons were 10.7%, 3.2%, and 8.2%, respectively (Ambulkar *et al.*, 2014). Of the 70 naturally conceived offspring, they discovered one de novo YCM, but none of the 158 ART created offspring. The incidence of de novo YCMs in the normally conceived boys and the sons conceived through assisted reproduction did not differ statistically significantly among the three groups. They ultimately came to the conclusion that there is no discernible increase in the risk of YCM in male offspring due to ART. This finding, however, is still debatable; further research is required to confirm if AZF microdeletions and ART are correlated in a sizable, geographically and ethnically diverse cohort of infertile men and their children.

Expansion of AZF microdeletions in the offspring

Recent years have seen a substantial amount of study devoted to examining genetic alterations in babies generated by in vitro fertilisation. According to some research, ICSI can only transmit YCMs vertically; it cannot expand YCMs' de novo occurrence. A case of what was likely an identical partial deletion occurring over three generations in the distal part of the AZFb region was reported by Rolf *et al.* (Vog *et al.*, 1996).

Role of SRY Gene

The DNA-binding protein known as testis-determining factor (TDF), also called sex-determining region Y (SRY) protein, is encoded by the SRY gene and is responsible for initiating male sex determination in therian mammals (placental mammals and marsupials). On the Y chromosome, the sex-determining gene SRY is intronless. A variety of disorders of sex development (DSD) are caused by mutations in this gene, and their impact on an individual's phenotype and genotype vary (Mittwoch, 1988).

TDF is a DNA-binding protein that belongs to the SOX (SRY-like box) gene family. TDF functions as a transcription factor that upregulates other transcription factors, most notably SOX9, when it forms a complex with the SF-1 protein. Primary sex cords, which eventually give rise to seminiferous tubules, are caused to form as a result of its expression. The core region of the undifferentiated gonad becomes a testis when these cords form there (Kashimada and Koopman, 2010). The testis's now-induced Leydig cells subsequently begin to secrete testosterone, and the Sertoli cells create anti-Müllerian hormone concurrently.The effects of the SRY gene generally occur 6–8 weeks after foetus development and prevent males from developing feminine anatomical structures. Additionally, it aims to develop the traits of the dominant man. (Veyrunes *et al.*, 2008; Marshall Graves, 2015)

Regulation

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Further sex-determining systems that depend on SRY/TDF outside of XY are the mechanisms that occur later in an embryo's development, depending on whether SRY is present or absent. In a typical scenario, the TDF will cause the medulla to grow the gonads into testes if SRY is present for XY. The next step is the production of testosterone, which starts the development of additional male sexual traits. In contrast, since XX lacks a Y chromosome, there won't be a TDF if SRY is absent. In the absence of TDF, the cortex of developing gonads will mature into ovaries, which will generate oestrogen and give rise to further female sexual traits.

Role in other diseases

Individuals with an XY karyotype and a functional SRY gene may exhibit an overtly female phenotype because of an underlying androgen insensitivity syndrome (AIS). SRY has been demonstrated to

interact with the androgen receptor. A mutation in the androgen receptor gene causes people with AIS to react to androgens improperly. Affected individuals may have partial or total AIS. Males are more likely than females to acquire dopamine-related disorders like schizophrenia and Parkinson's disease, which has also been connected to SRY. Dopamine is a neurotransmitter that delivers messages from the brain to coordinate movement and coordination. SRY encodes a protein that regulates the amount of this neurotransmitter (Bondurand and Southard-Smith, 2016; Gottlieb and Trifiro, 2017)

AR (androgen receptor) Gene

It has been shown that 'idiopathic' male infertility and reduced spermatogenesis are strongly correlated with mutations and polymorphisms of the androgen receptor (AR) gene and its expressed protein.

Molecular biology of the AR

The cellular processes that react to androgens are crucial for the development of the male phenotype and the start of spermatogenesis, which produces male gametes. Of the physiological androgens, testosterone and 5a-dihydrotestosterone (DHT) are the two most significant. AR is a mediator between androgens and their effects. Only one AR has been found and cloned, despite the fact that there are two distinct types of androgens. The Wolfian duct requires testosterone to survive, and only then can it differentiate into the epididymis, ductus deferens, and seminal vesicles. The growth of the penis and scrotum is influenced by DHT, a byproduct of testosterone. During adolescence, androgens stimulate the growth of the prostate and other accessory sex organs as well as the start of spermatogenesis. All these androgen-dependent developmental processes culminate in successful spermatogenesis; thus, perturbation to any of these steps can result in spermatogenic failure (Handelsman, 2020).

The AR is encoded by a single-copy gene in the X-chromosome. The eight exons that make up the AR gene encode an intracellular transcription factor that is a member of the steroid/nuclear receptor superfamily, which also includes receptors for vitamin D, progesterone, oestrogen, adrenal hormones, thyroid hormones, and retinoid acid.

Consistent with other steroid receptors, the ARD when activated by androgens translocates to the nucleus and binds to specific chromosomal DNA sequences (androgen response elements) in the regulatory regions (promoters/enhancers) of AR-regulated genes. The binding of the androgen±AR complex activates or represses, the expression of androgen-regulated proteins. Furthermore, the androgen±AR complex operates in conjunction with co-regulatory proteins. Pre-initiation complexes made up of several coactivator proteins on promoters are formed by the liganded AR, which activates protein synthesis and gene transcription.

The AR contains four main functional domains: the amino-terminal transactivation domain (TAD); the centrally positioned DNA-binding domain (DBD); the hinge region; and the carboxyl-terminal ligand-binding domain (LBD) (Tan *et al*., 2015). Two portions (encoded by GGN and CAG, respectively) of the TAD are made up of repeats of the amino acids glutamine and glycine. These repeat tracts are polymorphic, in that their size varies among individuals in a normal population. While each domain has specific functions, intramolecular interactions between domains and intermolecular interactions with coactivator proteins have also become major themes in understanding the structure/function properties of the AR and are critical for understanding the molecular basis of male infertility caused by AR malfunction. The well-known complete AIS (testicular feminising syndrome) is caused by AR mutations that severely impair the quantity, structure, or function of the AR. This is demonstrated by the complete feminization of 46 XY persons at birth. Partial AIS (PAIS) is caused by mutations that partially impair AR function. This condition results in varying degrees of ambiguous genitalia, such as partial labial-scrotal fusion, hypospadias, inflated scrotum, and gynecomastia. The most intriguing finding is that mild mutations causing limited AR malfunction also cause minimal AIS, which results in decreased spermatogenesis without causing any abnormalities in secondary male sexual traits (Wang *et al*., 2009).

Molecular Signatures of male Infertility and Yoga-based lifestyle Intervention

The role of yoga-based lifestyle interventions in improving male infertility is an emerging area of interest, primarily focusing on holistic approaches to enhance reproductive health. Here, we discuss the potential mechanisms and evidence supporting the benefits of yoga in this context.

One of the key mechanisms through which yoga may improve male infertility is by reducing stress levels (Yadav *et al*., 2012). Chronic stress can adversely affect reproductive health by disrupting hormonal balance, particularly the hypothalamic-

pituitary-gonadal (HPG) axis, which regulates testosterone production and spermatogenesis (Sengupta *et al.*, 2013). Yoga practices such as asanas (postures), pranayama (breathing exercises), and meditation have been shown to reduce stress hormones like cortisol and increase parasympathetic activity, promoting relaxation and hormonal equilibrium. This, in turn, may positively impact sperm quality and quantity (Hagen and Hagen, 2024).

Yoga involves stretching, twisting, and deep breathing exercises that improve blood circulation throughout the body, including the pelvic region. Enhanced blood flow to the testes can provide better oxygenation and nutrient delivery, crucial for supporting healthy sperm production. Improved circulation may also help in reducing oxidative stress, a common factor contributing to sperm DNA damage and male infertility (Bisht and Dada, 2019).

Yoga practices are known to modulate immune function by reducing inflammation and enhancing immune responsiveness (Sharma *et al.*, 2023). In conditions where male infertility is associated with immune system dysregulation (*e.g.*, autoimmune conditions affecting sperm), yoga may help restore immune balance, potentially alleviating barriers to fertility.

Yoga is linked to alterations in the DNA methylation of around 400 genes, 229 of which were hypomethylated and 147 of which were hypermethylated. Among them were promoters for multiple genes associated with maintaining both genomic integrity and fertility. This innovative work establishes a clear connection between healthy lifestyle choices and the reproductive health of men (Bisht *et al.*, 2020).

Beyond physiological mechanisms, yoga offers significant psychological benefits that can indirectly influence male fertility. Many men facing infertility experience psychological stress, anxiety, and depression, which can further exacerbate reproductive health issues. Yoga-based interventions promote mental well-being through mindfulness practices and relaxation techniques, improving mood and emotional resilience.

In clinical settings, yoga is increasingly being integrated into conventional infertility treatments as a complementary therapy. It is often used alongside medical interventions such as assisted reproductive technologies (ART) to enhance treatment outcomes. Yoga's holistic approach addresses multiple aspects of health simultaneously, potentially optimizing the overall effectiveness of infertility treatments.

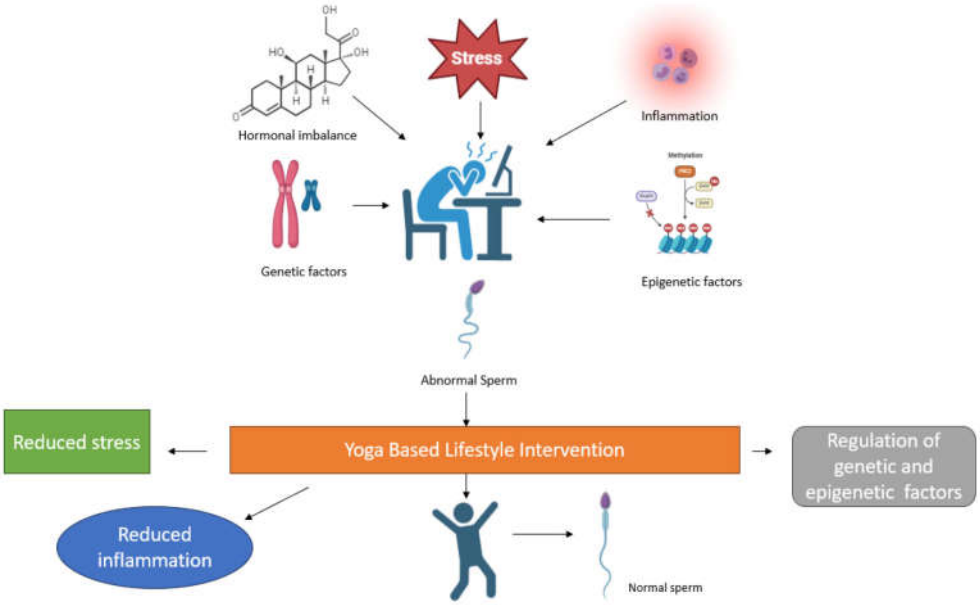

Fig 1: Role of Yoga-Based Lifestyle Intervetion In Male Infertility

While the evidence base is growing, research supporting the direct impact of yoga on male infertility remains limited but promising. Several studies have demonstrated beneficial effects of yoga on sperm parameters such as sperm count, motility, and morphology in men with infertility. (Bisht and Dada, 2019) reported significant improvements in sperm quality and DNA integrity after a 3-month yoga intervention in infertile men.

Some studies have revealed that yoga-based lifestyle intervention significantly declines oxidative DNA damage and normalization of sperm transcript levels (Dhawan *et al.*, 2018).

While these potential benefits are promising, it's essential to note that more high-quality, randomized controlled trials are needed to establish a clear causal relationship between yoga practice and improved male fertility outcomes. Additionally, individual responses to yoga may vary, and it may not be a standalone solution for addressing male infertility.

Around 70 million people are globally affected by infertility disorder. Since diagnostic techniques are not able to detect the condition hence 40% of the cases remain unknown.

Therefore it is very important to develop a novel diagnostic method that can help in better diagnosis, prevention, and management of the disease. Clinicians may be able to create new treatment methods if they have a better understanding of the molecular and genetic mechanisms behind the pathophysiology of male infertility and how lifestyle variables affect the expression of genes that control male fertility. In adjunct to the conventional therapeutic approach Yoga yoga-based alternative therapy might prove useful in management of the male infertility at the genetic level. Earlier studies also show the beneficial effects of yoga-based lifestyle intervention at the molecular and genetic levels (Sharma *et al.*, 2022b; a).

CONCLUSION

Yoga-based lifestyle interventions show promising results in improving male infertility through mechanisms such as stress reduction, hormonal balance, enhanced blood flow, immune modulation, and overall well-being (Fig. 1).

Integrating yoga into the management of male infertility offers a holistic approach that addresses both physical and psychological aspects of reproductive health. Further research is warranted to elucidate the specific mechanisms and optimal protocols for using yoga as a supportive therapy in the treatment of male infertility.

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Conflict of Interest

Authors disclose there are no conflicts of interest.

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