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REVIEW PAPER

Structure and function of mitochondria and its role in male infertility

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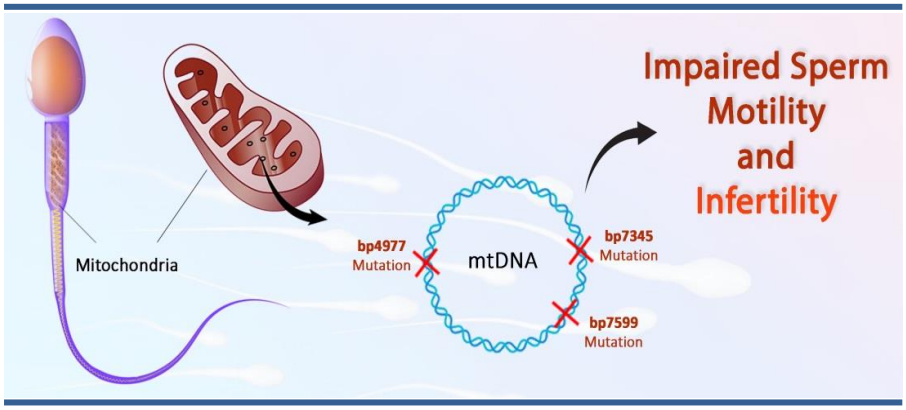
Highlights

- Mitochondria function as an organelle in various cellular processes.
- ATP production for sperm motility is provided by mitochondria.
- Mitochondrial mutations and deletions cause impaired sperm motility and infertility.

Graphical Abstract



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Abstract

Infertility refers to the inability to conceive after at least 12 months of intercourse without prevention. About half of all infertility factors are due to male factors. Genetic factors are the important factors that contributed to the infertility of men. Genetic factors influencing male infertility can be intra-nuclear or extra-nuclear. A large number of nuclear genes such as protamine genes, aryl hydrocarbon receptors, etc. are involved in male infertility. Deletions and mutations in the genome of mitochondria are one of the most important extra-nuclear factors affecting male infertility. One of the chief features of spermatozoa is its motility, which is essential for the fertilization process. Due to the supply of energy to the sperm by the mitochondria, any defect in it can impair sperm motility and asthenospermia. Mitochondrial genome disorders such as point mutations and genomic deletions, especially the three deletions bp4977, bp7345, and bp7599 may be the main cause of asthenospermia. Identification of mitochondrial molecular defects can be helpful in diagnosing infertility factors, especially asthenospermia. This study aimed to describe the structure and function of mitochondria and its role in the pathophysiology of male infertility.

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Introduction

Infertility in men is a major global problem. Immunological, anatomical, physical, or obstructive disorders, hormonal disorders, and environmental factors are significant causes of male infertility. In addition to these factors, there are other factors whose effects on normal sperm function and male fertility are not yet well known. These factors are called idiopathic or unknown factors, which account for about 25 to 30% of the causes of male infertility (1, 2). Approximately 60% of infertility cases are in idiopathic men, about 30% of which are caused by genetic factors, and it is not possible to identify genetic causes by testing for sperm parameters. In men, according to semen quality assessment, infertility is divided into three groups: oligospermia (sperm number< 15 million per milliliter), asthenospermia (progressive sperm motility< 32%), and teratospermia (sperm morphology< 4% normal). Approximately 30% of male infertility cases with chromosomal abnormalities or mutations in functional genes occur in germ cells (3).

Sperm dysfunction is one of the most usual reasons for infertility in men, which has always been difficult to evaluate and treat. Sperm motility can be affected by a wide range of conditions, including flagellar movement disorders. Mitochondria as a source of cell energy supply can play an essential role in sperm motility, spermatogenesis, maturation of sperm, and so on. Significant amounts of energy are required for sperm to swim rapidly to reach the fallopian tube during fertilization. In general, there are about seventy to eighty mitochondria in the middle part of sperm in mammalian. Motility of sperm is extremely dependent on the produced ATP by oxidative phosphorylation in the sheath of mitochondrial (4). Mitochondrial DNA (mtDNA) is produced during meiosis and spermiogenesis and always remains active in the sperm mitochondria and is also exist in ejaculate sperm. The human mitochondrial genome encodes thirteen proteins that are vital subunits of electron transport chain complexes in the inner membrane of mitochondria. It also encodes 2 rRNAs and 22 tRNAs, which are essential for the synthesis of these proteins (5).

Because the mitochondrial bioenergetic activity is required for motility of sperm, any qualitative or quantitative changes in mtDNA might influence sperm function. Several point mutations and deletions have been reported in mtDNA correlated with infertility of men, and some studies have shown that these deletions can reduce sperm motility and subsequently reduce fertility. Among the mitochondrial deletions observed in the mitochondrial genome is the deletion of 4977 bp (4977-bp), which is the most common and numerous kind of deletion (6). It is characterized by a number of pathological phenotypes, and this deletion is often seen in old age. During this deletion, a large length of mitochondrial DNA is lost, leading to the fusion of the genes of ATPase 8 and ND5, resulting in impaired respiratory function of mitochondria and a decrease in ATP synthesis. Other large deletions in the genome, such as 7491-bp, 7599-bp, and 7345-bp, may also be associated with poor sperm motility (7). In addition to deletions, point mutations are also found in the mitochondrial genome. These point mutations include C11994T, T8821C, A3243G, and A73G. A3243G point mutation of mitochondrial leu tRNA gene is correlated with many diseases such as insulin-dependent diabetes, renal failure, cardiomyopathy, decreased sperm motility, etc. Sperm mitochondria have a main role in sperm function, so genetic changes in mtDNA have serious consequences for fertility and normal spermatogenesis (8, 9). Given all of the above-mentioned contents and the importance of molecular pathology of male infertility, this study aimed to describe the role of mitochondria in male infertility.

Structure and function of human mitochondria

Mitochondria are semi-independent organs found in the cytoplasm of all eukaryotic cells except adult red blood cells and some protozoa. Mitochondria originated millions of years ago in eukaryotic cells through the symbiosis of free-living bacteria capable of metabolizing oxygen, so there are several common features between mitochondria and bacteria that support the theory of endosymbiotic. These include two-layer structures, shape and size, cyclic double-stranded DNA, specific transcription and translation systems, and similar binary fission power (10, 11). Structurally, the mitochondria have an outer and inner membrane. The outer membrane, about 6 nm thick, surrounds the organ. Inside this membrane, there is an intermembrane space (about 6 to 8 nm). Then

there is the inner membrane, which has cristas into the inner mitochondrial cavity (12). Two mitochondrial membranes regulate the transport of molecules. Large molecules are transported through the outer membrane via nonspecific purine channels. The ratio of lipids to proteins in the outer membrane is approximately 50:50, so they are permeable to molecules with a molecular weight of more than 10,000 daltons. The inner membrane of the mitochondria is relatively impermeable, consisting of approximately 80% protein (13).

Mitochondria are an energy-producing intracellular organ that is vital for aerobic metabolism in eukaryotic cells, especially those with high oxidative capacity, such as liver, heart, muscle, and nerve tissue cells. They are the site of most of the chemical reactions that convert chemical energy in food into adenosine triphosphate (ATP). The number of mitochondria per cell is dependent on the energy required and varies from tens to thousands of mitochondria per cell (14). Human cells for growth, differentiation, response to physiological stimuli, and challenging environmental conditions require ATP. ATP production is a key function of any mitochondria. The pervasive presence of ATP molecules supports cell homeostasis and also controls cellular survival and dynamics in cell division and cell mobility. Krebs cycle and beta-oxidation are two important pathways of cellular ATP production that precede oxidative phosphorylation, the main producer of ATP via the electron transport chain. During cellular respiration, the chemical energy of sugars and fatty acids is released and stored as ATP (15, 16). In addition to their bioenergetic role, mitochondria provide several basic metabolic pathways in the cell, including the breakdown of fatty acids, the modulation of intracellular calcium homeostasis, and the biosynthesis of metabolites, such as nucleotides, amino acids, folic acid, pyrimidines, and phospholipids and breakdown of metabolites such as uric acid (17). The essential role of mitochondria is also now well established in a range of physiological procedures including embryonic development, apoptosis, and the aging process (18, 19).

Mitochondrial genetics and replication and transcription of its genome

The presence of mitochondrial DNA was determined in 1963 using electron microscopy. A human cell included numerous copies of mitochondrial DNA, and each mitochondrion includes between 2-10 copies of DNA, but the total mitochondrial DNA in a cell contains only about one percent of the total DNA of a cell (20). Mitochondria have independent genomes that are organized separately from nuclear genome. The human mitochondrial genome (mtDNA) is very dense and circular and contains two strands. The two strands of the mitochondrial genome differ in buoyant density, the heavy (H-strand) purine-rich strand (A+G) while the light (L-strand) is symmetrically rich in pyrimidine (C+T). The naming of these two strands is based on their separation in the concentration gradient of cesium chloride. Transcription occurs simultaneously and in opposite directions, and many genes overlap (21, 22). In general, the genome of mitochondria encodes 37 genes, 28 of which are located on the heavy DNA strand and 9 of which are on the light strand. Of these 37 genes, 2 genes encode rRNA (16S and 12S, which are essential for expression of mRNA, 22 genes encode tRNA, and 13 genes encode respiratory chain polypeptides (the ATP production pathway). Thus, the genome of mitochondria encodes only a small fraction of the peptids required for its specific function, and most mitochondrial polypeptides are encoded by the nucleus genome and are produced on ribosomes in cytoplasm before they enter the mitochondria. The complete sequence of 16569 pairs of the genome of human mitochondria was described in 1981 by Anderson et al., (23-27).

Each electron transport chain (ETC) complex, except complex II, contains genes encoded by the genome of mitochondria. If the rest of the ETC subunits are encoded with the nuclear genome. Unlike DNA of nucleus, genes of mitochondria lack or have a small number of uncoded nucleotide sequences between their genes, in other words, they lack introns. 93% of it is coding and, in some regions, even overlapping genes can be seen. The nucleotide sequences encoding most genes are continuous and separated by only one or two bases (28). There are just 2 non-coding areas in the mitochondrial genome that are functionally important, one region is very variable and slightly unstable called D-Loop, which is about one Kbp long and covering the origin of heavy-strand (OH) and transcription promoters of light and heavy strands. This structure is created by a short

newly synthesized H strand that stays precisely in contact with the pattern molecule so that the ternary structure of DNA is formed at the origin site of the H strand during activity. Another chief non-coding sequence is a thirty-nucleotides area located at 2/3 mtDNA length from the origin of the heavy chain. This area surrounded by a cluster of 5 tRNAs genes, can create a firm hairpin structure and acts as the origin of the light strand (OL) (29-31).

Although the topology and major events of mitochondrial replication and transcription are well established, little is known about mitochondrial genetic control. Transcription in mtDNA is two-directions and begins with cis-acting elements from the light and heavy chain promoter regions. Each strand of mtDNA is transcribed as a single polycistronic transcript under the control of special light or heavy strand promoter (PH, PL), transcription factors, and specific regulatory proteins, all encoded by the nucleus genome, which eventually form an adult RNA (32, 33). Although there is an interaction between the nucleus genome and mitochondria DNA. The replication of mtDNA happens independently of the cell cycle in the mitochondrial matrix. The synthesis of each mtDNA strand takes place at two different time intervals from two origins of replication. The two mtDNA strands have 2 separate origins for replication. The origin of the H strand replication is in the D-Loop region, while the L strand replication origin is located in approximately 1/3 of the mitochondrial genome circumference. The synthesis of the heavy strand, called the leader strand, begins at the origin of the replication in the D-Loop region (24, 34-36).

Disturbance and mutations in the genome of mitochondria

Mitochondrial disorders involve a group of heterogeneous clinical phenotypes that lead to mutations in the genome of mitochondria and the genome of nucleus, or both. Electron transport chain abnormalities and the system of oxidative phosphorylation are probably the most common mitochondrial disorders. The function of respiratory chain is dependent on the coordinated expression of the nuclear and mitochondrial genomes. One mutation in each genome might result in mitochondrial respiratory chain dysfunction. The first reports of oxidative phosphorylation disorders were published in 1962 by Luft et al., and the first mutation in mtDNA was reported in 1988 by Holt et al., Mitochondrial disorders are generally caused by a variety of mutations or by the abnormal mitochondrial function (37-41). In addition, mitochondrial disorders not only indicate respiratory chain disorders but are also associated with pyruvate dehydrogenase deficiency, carnitine deficiency, deficiency of carnitine palmitoyltransferase, disorders of fatty acid beta-oxidation, and citric acid cycle disorders. Mitochondrial genome deletion has also been observed in some patients with congenital lethal myopathy, spinal muscular atrophy, and fatal hepatic impairment (42, 43). Mitochondrial disorders might happen at any time in life, from childhood to adulthood, these disorders may affect one or more tissues that require high energy and are highly dependent on oxidative metabolisms, such as peripheral and central neurons, heart, skeletal muscle, beta pancreas cells, endocrine organs, hepatocytes, and gastrointestinal tract are usually more affected. Mitochondrial disorders are generally caused by a variety of mutations or by abnormal mitochondrial function. The main and most important cause of mitochondrial disorders is mutations in genes in mitochondrial DNA. The frequency of mutations in mitochondria is about 10 to 100 times higher than in nuclear genes. The reason for this seems to be the high rate of replication, lack of nucleosome structure or histones, lack of efficient repair system, and unique inheritance model of mitochondria (37).

Mitochondrial mutations have been observed in a variety of human disorders from aging to infertility. Many mtDNA mutations are harmful and fatal and rapidly they disappear by natural selection. These mutations can be the substituted bases, recombination, and rearrangement, and can occur in female germ cells or at the beginning of the embryonic developmental stage, leading to disease. Mutations can also occur throughout life and accumulate heterogeneously in tissues resulting from mitotic division. In addition to the above, another factor can have a role in causing mitochondrial mutations, which is the storage of 90% of cell oxygen in the mitochondria. In this case, the oxidative damage to mtDNA is significant. In the mitochondrial genome of patients with oxidative phosphorylation, till now, more than fifty point mutations and numerous complicated

rearrangements, including duplications and deletions were detected (44-46). Point mutations and very large-scale deletions in mtDNA have been found in patients with mitochondrial myopathies and encephalopathies, diabetes mellitus, and multisystem diseases. In addition, abnormalities of mtDNA have been correlated with common disorders including Alzheimer's and Parkinson's diseases, and the prevalence of these disorders in the elderly has increased significantly (44, 46, 47).

Mitochondria and infertility in men

Dysfunction of mitochondria is considered a possible factor in male infertility. Because sperm need a lot of energy to move rapidly after ejaculation, oxidative damage and mutations in the mtDNA molecules that encode a large portion of the respiratory chain polypeptide subunits have a main role in male infertility. The lack of the gamma DNA polymerase gene, which synthesizes mtDNA, is also associated with poor sperm quality. Many studies have revealed that mutations in multiple points and deletions in mtDNA are directly related to abnormal sperm structure and function, especially its low motility. Studies have also shown that there is a robust association between sperm quality and respiratory chain activity in sperm mitochondria so that if extracellular ATP is added to sperm, there is a significant increase in sperm fertility potential, which indicates the importance of mitochondrial activity in male fertility. Studies have shown that there is an association between mtDNA haplotype and respiratory chain function in mitochondria and sperm motility (48, 49).

Adult mammalian sperm contain about 22-75 mitochondria that form a strong helix around the base of the flagellum in the middle part of the sperm and provide the ATP needed to move the flagellum and sperm motility. Human sperm naturally use glycolysis-derived ATP for survival, but the mitochondrial respiratory chain has main role in preparing the sperm ATP required for motility after ejaculation or certain physiological conditions. The position and structure of mitochondria in the middle area of adult spermatozoa is a chief factor in sperm motility. The position of mitochondria in the upper part of the sperm flagella is unique (50, 51). During spermatogenesis, mitochondria undergo severe morphological changes and subcellular reorganization. The organization, number, and location of mitochondria in germ cells change in the procedure of the production of adult sperm (maturation of spermatogonia to fertilizable spermatozoa). On average, about 1000-1500 copies of mtDNA are reported in the sperm cells of fertile men, while a 7-fold increase per mm^3 of cells occurs during spermatozoa maturation, indicating a higher ATP requirement and the importance of mtDNA for sperm function. In order to maintain an adequate number of mitochondria in adult spermatozoa, replication and organization of mtDNA and should be strictly regulated in the spermatogenesis procedure. Because the mitochondrial bioenergetic function is critical for spermatozoa mobility, any qualitative or quantitative abnormalities in mtDNA might adversely influence spermatozoa cell function (52, 53). The location of mitochondria and the mtDNA structure is illustrated in Figure 1.

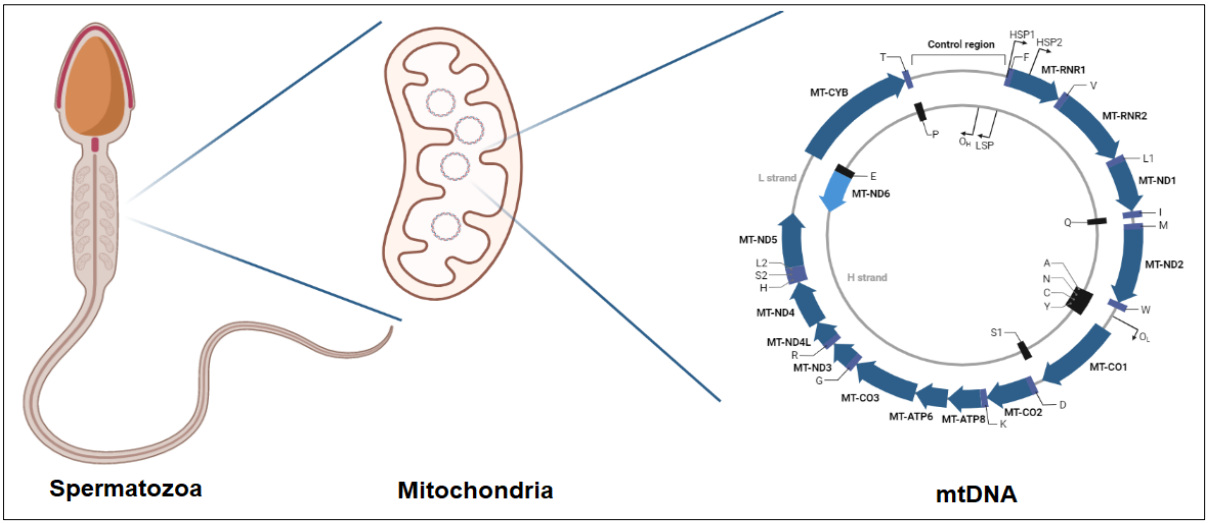

Figure 1. Mitochondria in spermatozoa.

Mitochondria are positioned in the midpiece of spermatozoa and produce essential energy for sperm. Mitochondria contain several circular genomes that encode some essential mitochondrial protein.

Mitochondrial genome mutations and sperm motility

Decreased sperm motility is most likely caused by a disorder in each of the 200-300 individual genes that are essential for the suitable accumulation and the axon and tail function of the spermatozoa. Defects in spermatozoon tail formation can be due to the absence of one of the inner or outer arms of the dynein, the absence of radial spokes, or the removal of peripheral or central double microtubules (a group of partial and complete microtubules in the structure of a cylindrical wall). Studies have shown that there is a close relation between mitochondrial volume and spermatozoa length and flagellar movement. Studies have shown that asthenospermic men have shorter midpieces of sperm and fewer mitochondria than controls. About 72 to 80 mitochondria in the middle part of the sperm are energy producers and have been described as the spermatozoa fuel machine. Deficiency in the inside structure and organization of mitochondria in the middle part of the sperm were observed in some patients with asthenozoospermia with low sperm mobility (54, 55).

Asthenospermia in men can be caused, in particular, by deficiency in the formation of tail in sperm or by deficiencies in the energy-producing machine is essential for effective motility. Mutations in mtDNA could result in this abnormality (Figure 2). The researchers observed that these mutations were strongly corelated with low sperm motility. The mtDNA analysis in asthenospermic men also showed a high and significant frequency of nucleotide alterations in ND and ATPase genes *vs*. the control group. On the other, deletion of dinucleotides in COII genes was seen in sperm with low motility. Numerous studies in recent years have shown that large mtDNA deletions are associated with sperm dysfunction and infertility in men (4, 56, 57). Among mtDNA deletions, the usual deletion of 4977-bp is common. In addition to it, the 7345 and 7599-kb deletions were identified in mtDNA of low-motility spermatozoa. Since spermatozoa require adequate numbers of functional mitochondria to store energy for motility and fertilization capacity, reducing the number of mtDNA copies can be related to reduced motility and fertility of human sperm. Because there is an interaction between the genome of nucleus and the genome of mitochondria, mtDNA fragmentation, and mitochondrial swelling have also been suggested as an important parameter in low sperm motility. In its function, one of the reasons for sperm immobility may be due to the inability to produce ATP for the flagellum (58, 59).

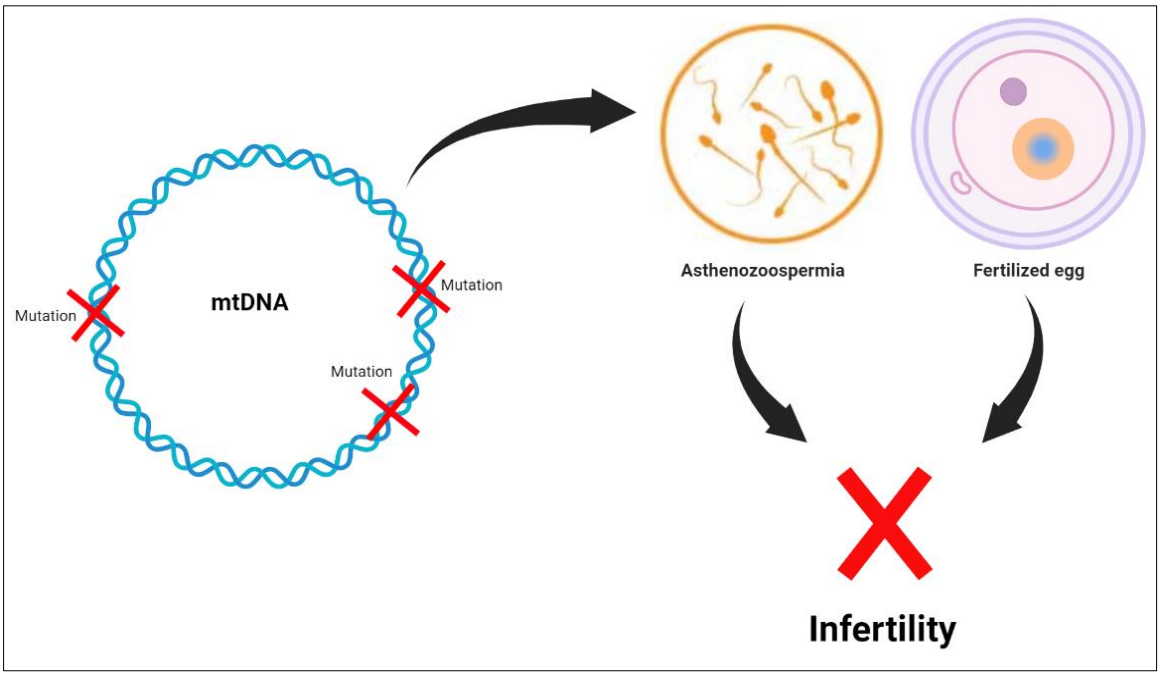

Figure 2. mtDNA mutations and male infertility. Some point mutations and mtDNA deletions could lead to in asthenospermia and subsequently male infertility.

Conclusion

In recent years, male infertility in industrialized countries has increased due to reduced sperm number, decreased motility of sperm, impaired morphology of sperm, and increased testicular and sperm damage. Sperm dysfunction is one of the chief contributors to male infertility. Sperm motility disorder is one of the major indicators of infertility in men so infertility due to inactivity or poor quality of spermatozoa motility is the key problem of patients referred to medical centers. There are several factors that can affect sperm motility that in many cases are not yet well known. One of the most important factors in dysfunction and reduced sperm motility, which has attracted the attention of many researchers today, is a condition called oxidative stress, this adverse condition is caused by an increase in reactive oxygen metabolites. Defects in sperm mitochondria can be the source of such disorders. Defects in the genome of mitochondria could influence the function of mitochondria. These mitochondrial defects include point mutations and large dilations. In general, recognizing mitochondrial molecular defects could be helpful in diagnosing the causes of male infertility, especially in asthenospermia.

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