Role of Tradafertil in Male Reproductive System

Content

Background and Objective of the Survey

Tradafertil plays a crucial role in supporting the male reproductive system. As a dietary supplement, Tradafertil is specifically formulated to address factors that may contribute to male infertility. It contains a blend of essential nutrients, including vitamins, minerals, and antioxidants, known for their positive impact on sperm health and overall reproductive function.

The ingredients in Tradafertil work synergistically to enhance sperm quality, motility, and morphology. Substances like zinc, selenium, and vitamins C and E contribute to the protection of sperm cells from oxidative stress. Additionally, Tradafertil may support hormonal balance, crucial for optimal reproductive health in men. By addressing nutritional deficiencies and promoting a favorable environment for sperm development, Tradafertil aims to improve male fertility and increase the chances of successful conception. Regular use, combined with a healthy lifestyle, may contribute to the overall well-being of the male reproductive system.

The objective of the survey is:

To evaluate the role of Tradafertil in male reproductive system

Methodology of the Survey

A survey was conducted to evaluate the role of Tradafertil in male reproductive system. A total of 125 doctors from India participated in the survey.

Step 1: A literature search was done on the topic. Below topics were covered in the literature search

- Introduction
- Factors involved in male infertility
- Main Causes of Infertility
- Sperm Recovery in Infertile Men
- Dual Role of ROS and Antioxidant System in Male Fertility
- Genesis of Oxidative Stress, Lipid Peroxidation and DNA Damage
- Role of Inositols in Male Fertility
- MI: In Vitro Studies
- MI: In Vivo Studies
- Role of Antioxidant in Male Fertility
- Abstracts

Step 2: A survey questionnaire was prepared based on the literature search. The survey form was shared through the digital medium with physicians across India.

Step 3: Their responses were analyzed and the findings are provided in this survey analysis booklet.

Literature Review

Introduction[1]

Infertility is defined as the inability of couples to have a baby after one year of regular unprotected intercourse, affecting 10–15 percent of couples.[–] According to the latest WHO statistics, about 50–80 million people worldwide suffer from infertility.[,] Large-scale studies have shown that about half of all cases of infertility occur due to female factors, 20 to 30 percent male factors, and 20 to 30 percent due to common causes of both gender.[–] Recent meta-analysis studies by researchers show that male's factors are present in 20–70 percent of infertility cases.[,] These findings are significantly broader than previously reported. However, the wide range of male infertility in meta-analysis studies may not reflect the prevalence of this complication in all parts of the world because of reasons such as the lack of rigorous statistical methods that include bias, heterogeneity in data collection, and cultural constraints. Given the significant contribution of male factors to infertility in couples, as well as high levels of unknown factors in male infertility, a lack of understanding of the underlying mechanisms seems to be one of the most important challenges facing this problem. In this article, we have reviewed the histological studies of testicular tissue specimens, male reproductive structure, factors influencing male infertility, strategies to find genes involved in infertility, available therapeutic methods for male infertility, sperm recovery methods in infertile men, and assisting reproductive method.

Factors involved in male infertility[1]

Male's Reproductive Organ

In order to better understand the issues and problems associated with infertility, we first discuss some of the key elements involved in male fertility. Human reproductive organs include the primary and secondary organs. Primary reproductive organs include the gonads (responsible for gamete and hormone production), while the secondary organs include the ducts and glands, which play a role in the growth, maturation and transmission of gametes.[,] The testicles are the primary male reproductive organs enclosed by the tunica albuginea capsule in the testicle sack. Two morphologically and functionally separated parts are in the testis. Tubular components include seminiferous tubules and intercellular portions between seminiferous tubules. The

intertubular portions of the seminiferous tubules are involved in providing blood and immune responses.[–] Leydig cells are one of the most important cells in testis that are the source of testicular testosterone and insulin-like factor 3. In addition to Leydig cells, intercellular components include immune cells, lymphatic and blood vessels, nerves, connective tissue, and fibroblasts.[–] The seminiferous tubules are functional units in the testis, accounting for 60–80 percent of testicular volume.[–] These tubes are surround by epithelial tissue and include two types of cells: Sertoli cells and spermatogenic cells. The function of Sertoli cells is to nourish and develop sperm through the stages of spermatogenesis and their mechanical support.[–] These cells produce two types of inhibin and activin hormone that have positive and negative feedback to FSH.[–] In addition, Sertoli cells control the stages of sperm release into the lumen, phagocytosis of the degraded germ cells and additional cytoplasm resulting from sperm release. In adulthood, Sertoli cells are meiotically inactive.[–] Sertoli cell division terminates concurrently with the first meiotic division of the germ cells, giving rise to tight junctions between these cells, known as the Blood-Testis Barrier (BTB). The epithelium of seminiferous tubules is divided into two (functionally different) regions by BTB. Two important functions for BTB are: (a) the physical separation of the germ cells that protect them against the immune system; (b) providing an environment for meiosis and sperm development.[–]

Spermatogenesis

Spermatogenesis is one of the most crucial stages in male fertility.[–] The slightest deviation from the natural course of spermatogenesis can lead to infertility in men. The term spermatogenesis is a description of the development of male gametes in the seminiferous epithelial tissue from diploid spermatogonia that results in the release of differentiated haploid germ cells into the seminiferous tubules. Each cycle of spermatogenesis in humans requires 16 days and almost 4.6 cycles for development and differentiation of spermatogenic cells into adult sperm, which takes approximately 74 days in humans.[–] The regulation of spermatogenesis occurs in two main stages: a) hormonal and endocrine b) paracrine and autocrine. Many studies have shown that testosterone and FSH are required to successfully complete spermatogenesis.[,] The spermatogenesis process divided into four general phases: 1) mitotic proliferation and spermatogonial differentiation into pre-leptotene spermatocytes (spermatogoniogenesis); 2) Meiotic division of spermatocytes that leads to spermatids (meiosis); 3) Conversion of round spermatids into adult spermatids (spermogenesis); 4)

Release of elongated spermatids into the lumen (spermatogenesis). Considering the importance of spermatogenesis and since the disorder at any of its stages can have irreversible consequences, below are some of the most important features of each stage.

Spermatogoniogenesis

The germ cell lines originate from the primary germ cell (PGC). In humans, PGCs develop between endoderm cells at the end of the third week of development, and by the fifth week they migrate to the genital tract, where the presence of the Y chromosome results in the proliferation and transformation of the genital tract into primary male sexual organs.[–] PGCs are commonly called gonocytes during the first trimester of mitosis, then stop in the G3 phase of the cell cycle and remain silent until birth (i.e., when they become spermatogonia).[–] Spermatogonia remain silent until puberty. Spermatogenesis begins with the mitotic proliferation of spermatogonia after birth.[–] Spermatogenesis during puberty is probably initiated by the production of bone morphogenetic protein 8B (BMP8B). Mice with lack of Bmp8b do not initiate spermatogenesis at puberty and consequently are infertile.[–] Two distinct fates await reproductive cells: (a) self-renewal by replication; (b) becomes spermatozoa. Apoptosis in spermatogonia rarely occurs in the human seminiferous epithelial tissue, but the rate of apoptosis is increased in patients with impaired spermatogenesis, especially in spermatocytes and spermatids.[,]

Meiotic Division

Meiosis is the distinction between sexual reproduction and non-sexual reproduction.[,] Meiosis eventually results in the production of haploid gametes from diploid cells. During mammalian meiosis, nuclear division is done twice in a cycle of DNA replication. Each meiosis division is generally divided into two stages Meiosis I and Meiosis II.[–] In meiosis I, also called subtractive division, the microtubules are attached to sister chromatids via the kinetochore and transported to opposite poles.[–] This transition leads to a decrease in the number of chromosomes from diploid to haploid. Meiosis II is an equal division, in which the microtubules attach to the kinetochore of centromere and separate the sister chromatids, resulting in the formation of four daughter haploid cells. Meiosis begins with the production of two pre-leptotene spermatocytes from spermatogonia. In meiosis I, primary spermatocytes become two secondary

spermatocytes, and these cells then form spermatids in meiosis II. The result of meiosis is four different (genetically) cell types.[–]

Spermogenesis

Spermogenesis is a process that transforms the meiosis II final product (i.e., spherical spermatids) without splitting into specialized elongated spermatids. This process requires the development of the cytoplasm and nucleus regeneration, which can comprise four distinct phases: the Golgi phase, the capping phase, the acrosomal phase, and the maturation phase.[–]

Spermatogenesis

Sperm production is the final stage of spermatogenesis, which mature spermatids are released from the somatic supporting Sertoli cells into the lumen of the seminiferous tubules. At this stage, the cells are known as spermatozoa and continue their journey to epididymis. Seminiferous spermatozoa have low motility and fertility. Spermatozoa passage through the epididymal duct is crucial for final maturation and ability to move.[–] A small amount of cytoplasmic content, cytoplasmic droplets remain in the neck region and the middle segment of the spermatozoa, which facilitates the achievement of epididymis. During the transition from epididymis, which takes approximately two weeks, the cytoplasmic droplets move and exit during the spermatozoa tail, which is associated with increased spermatozoa movement. This event is associated with an increase in the movement of spermatozoa.[–]

Main Causes of Infertility[1]

As mentioned, infertility can have a feminine or masculine origin, with the male factor only present in one third of cases. The diagnosis of infertility in men is mainly based on semen analysis. Unusual parameters of semen include: sperm concentration, appearance and motility.[,] There are seven main cases of semen-related abnormalities. Infertility in men can be due to a variety of causes, however, in almost 40% of infertile men there is no clear etiology. There are various reasons for male infertility, the most important of which are: Hormonal deficits, physical causes, sexually transmitted problems, environment and lifestyle, and genetic factors.[–]

Hormonal Defects

The male reproductive hormone axis is known as the hypothalamic-pituitary-gonadal axis. It consists of 3 major components: the hypothalamic, pituitary and testicular glands. This axis works very regularly to provide the right concentration of hormones for male sexual development and function. Any abnormality in the system can lead to infertility.[8] If the brain is unable to produce gonadotropic releasing hormone (GnRH), this disorder results in a lack of testosterone and stopping sperm production.[9] Lack of GnRH causes a group of disorders known as hypogonadotropic hypogonadism.[9] One of them is known as Kallmann syndrome, which is associated with a change in sense of smell and immaturity. Treatment options for gonadotropin-releasing hormone deficiency include: Use of sex steroids, gonadotropins and injection of gonadotropin releasing hormone. Testosterone injections are mainly used to improve testicular growth, normalize testosterone concentration, and stimulate the development of secondary sexual traits.[8] Similarly, the pituitary's inability to produce sufficient amounts of luteinizing hormone and follicular stimulating hormone results in a failure to stimulate the testes and to produce testosterone and sperm.[9] Patients with pituitary deficiency require long-term hormonal therapy, which can lead to complications such as diabetes mellitus, heart disease and bone defects. Conversely, elevated concentrations of LH and FSH are associated with low concentrations of testosterone, leading to defects in spermatogenesis.[9] Therefore, using high doses of testosterone and estrogen can be a viable treatment option because it suppresses the production of LH and FSH. Increased prolactin can also lead to reduced sperm production, libido and impotence. Hyperprolactemia leads to infertility in 11% of people with oligospermia. In many cases, a dopamine agonist can be a good treatment.

Physical Reasons

Physical problems can disrupt sperm production and blockage of the ejaculatory pathway. Enlargement of the sperm vessels known as varicocele is one of the most common male infertility problems affecting about 40% of men.[9] Testicular torsion within the testicle sac can cause testicular damage due to pressure on the sperm vessels and impaired testicular circulation. Chronic and acute genital tract infections can also be common causes of infertility in men. Mumps viral infection can lead to testicular atrophy and infertility. Sexually transmitted diseases such as Gonorrhea and Chlamydia can also lead to infertility in men due

to obstruction in the epididymis. In some cases, semen is ejaculated in the bladder, known as recurrent ejaculation, and accounts for about 2% of infertility cases that can be caused by anatomical problems of the bladder sphincter.

Sexual Problems

Many sexual problems are both physical and psychological. Erectile dysfunction, known as impotence, early ejaculation and inability to ejaculate are examples of intercourse problems.

Environment and Lifestyle

Men exposed to hazardous substances in their workplace, including solvents, insecticides, adhesives, silicones and radiation, exposure to these and similar substances can lead to infertility. Exposure to radiation can lead to reduced sperm production, and exposure to high doses can lead to complete infertility. Overuse of the sun bath can also lead to a temporary decrease in sperm count. Occupations that require prolonged sitting (such as driving) or being exposed to high temperatures (such as bakeries) can have negative effects on fertility. Concerning alcohol consumption and smoking, there is no definite agreement regarding their effect on sperm parameters and fertility outcomes. However, progressive degradation in sperm quality may be associated with cigarette smoking and alcohol consumption. Poor nutrition can also play an important role in male infertility. There has been a recent report of a decrease in sperm concentration in men with an increase in saturated fat intake. Repeated use of drugs such as cocaine and cannabinoids is associated with a significant decrease in sperm concentration, and urinary testosterone in men. In addition, studies have also shown that air pollution in men reduces sperm motility, and the way to deal with and prevent this problem is to continually use antioxidants and vitamin C-containing substances. Moreover the presence of pollutants and sulfur dioxide in the air changes the natural shape of sperm and also has a detrimental effect on sperm motility.

Genetic Factors

Genetic factors are detected in 15% of male infertility cases and can be classified into two groups: chromosomal abnormalities and single-gene mutations.[7] Any lack or acquisition of unusual rearrangements in genetic material at the chromosomal level is known as chromosomal abnormalities and is one of the major genetic causes involved in male infertility. About 14% of men with azoospermia and 2% of men with oligospermia have chromosomal abnormalities, which is much higher than the general population (about 0.6%).[7] Some chromosomal abnormalities are inherited and some are acquired. The most common genetic cause of azoospermia in the aneuploid sex chromosome is Klinefelter syndrome, which accounts for about 14% of male infertility cases. 47,XYY, chromosomal defects can cause spermatogenesis malfunction due to increased FSH and Y chromosome disomy.[7] Noonan syndrome in men, such as Turner syndrome in women, which is XO/XY mosaic, can lead to cryptocidism and spermatogenesis deficiency due to increased FSH.[7] Translocations occur in 3% of patients with severe oligozoospermia, the most important is Robertsonian and bilateral translocation.[7] Inversion is called chromosomal translocation, in which a fragment of the chromosome is broken and rearrangement within itself. Autosomal inversions are eight times more frequent in infertile men, although these rearrangements are balanced, in some cases leading to severe oligoasthenoteratozoospermia or azoospermia. The role of the Y chromosome was identified by Zofardi and colleagues by karyotype analysis of deletions in the long arm of the Y chromosome in six infertile men, they termed the deletion region as azoospermic factor (AZF). This region contains three zones AZFa, AZFb, and AZFc. Micro-deletions occur following the recombination of similar fragments in palindromic sequences. Y chromosome microdeletions are present in 10% of infertile men, whereas in oligozoospermic males, the prevalence is 7%.[7] The most common microdeletion occurs in the AZFc region, accounting for 80% of cases. Deletions that encompass the entire AZFa region result in the Sertoli cell phenotype. Intra-AZFb deletion usually results in azoospermia. Deletion in the AZFc region can lead to a wide range of infertility phenotypes including azoospermia, Sertoli cell syndrome and oligozoospermia. Some gene mutations with pathological syndromes can be associated with infertility, such as congenital bilateral absence of the vas deferens (CBAVD), which cause obstructive azoospermia in 80 to 90% of cases. This defect is caused by a mutation in the Cystic fibrosis transmembrane regulator (CFTR). Primary ciliary defects are an autosomal recessive heterogeneous defect caused by a lack of normal eyelash function and present in half of men with asthenospermia. Little has been known so far about non-syndromic infertility.

Epigenetic Factor

Acetylation and methylation are two effective factors in epigenetic modifications that cause different expression of genes. Epigenetic factors act a critical role in male infertility, and numerous studies have been devoted to it. During spermatogenesis, germ cells face major epigenetic reprogramming that includes the organization of sex-specific designs in the sperm, which substitution of histone to protamine is one of them.[–] Numerous experiments have revealed altered epigenetic function in sperm from men with oligozoospermia and oligoasthenoteratozoospermia. Besides, many studies have been reported that hypermethylation in several genes, lead to deficiency in semen parameters or male infertility.[–]

Sperm Recovery in Infertile Men[1]

For infertile men, sperm must be recovered directly from the testicles or epididymis. Obstructive azoospermia (OA) and non-obstructive azoospermia are two major categories of azoospermia. Obstructive azoospermia is the result of physical obstruction of the male genital tract, which may be due to or acquired factors (i.e., infection, vasectomy or physical injury to the genital tract), congenital absence of the vas deferens (congestion of the vas deferens, which accounts for about 60% of men with azoospermia), epididymal obstruction. On the other hand, NOA is due to the lack of testicular sperm production in the ejaculate.[,] The best way to treat NOAs is to extract sperm from the testis (TESE) and done intracytoplasmic sperm injection (ICSI). However, in half of the cases of azoospermia, sperm cannot be found as a result of TESE. Unfortunately, serum hormone levels such as FSH and inhibin B and noninvasive assessments such as testicular volume cannot predict sperm recovery and to date only testicular histopathology can be used as a predictor of successful sperm recovery rate (SSR). In the conventional TESE method, spermatozoa are extracted from testicular biopsies by local or general anesthesia. On the other hand, sperm extraction is much safer and more successful by micro-TESE.

The purpose of the micro-TESE is to identify the nuclear regions of testicular sperm production based on the size and appearance seminiferous tubules with the aid of a microscope, in which spermatozoa can be recovered from open seminiferous tubules, the whole process being visible under the microscope. Micro-TESE is a better alternative to TESE because of the increased chance of sperm recovery and reduced testicular damage due to the smaller size of the harvested tissue. In general, testicular tissue resection for histopathologic evaluation can potentially

eliminate sites that still produce sperm, despite abnormalities.[1] Testis biopsy before sperm recovery is generally not recommended. Testicular biopsy is usually performed on the day of egg retrieval. Biopsy specimens are examined for the presence of sperm. A small sample is taken from an accessible area and evaluated for histopathology.[2] Due to the uncertainty of sperm retrieval and failure of sperm retrieval, egg retrieval will be unnecessary. This can cause emotional, economic, and physical stress for couples, so sperm retrieval requires the use of predictive factors, and this will not be possible unless you have in-depth knowledge of all the steps that can lead to Infertility in men.

Dual Role of ROS and Antioxidant System in Male Fertility[2]

Oxidative stress is an important cause of male infertility due to detrimental changes during spermatogenesis, epididymal maturation, and sperm capacitation, that can lead to infertility.

Spermatozoa are produced in the testes during the hormone-regulated process of spermatogenesis. The crucial step to achieve fertilization capacity, motility and complete maturation occurs into epididymis. During this phase, spermatozoa are physiologically exposed to ROS that are also involved into physiological functions such as sperm capacitation and acrosome reaction. These are necessary for efficient fertilization and require high levels of energy provided by metabolic pathways as glycolysis or oxidative phosphorylation (OXPHOS). Capacitation is a cascade of different cellular reactions that enables spermatozoa to bind the zona pellucida of oocyte. This induces the acrosome reaction, a release of proteolytic enzymes.

Another feature to consider is that the sperm membranes are made up of a high amount of polyunsaturated fatty acids (PUFA), which guarantee the fluidity necessary for fertilization. At the same time, this high amount of PUFA represents a risk for the spermatozoa, being PUFA vulnerable to lipid peroxidation (LPO). The oxidative damage that can result is associated with the loss of membrane fluidity, mitochondrial dysfunction, alteration of morphology, reduction of vitality and other alterations that lead to the failure of fertilization.

Furthermore, the structure of mature spermatozoa has no capacity to respond to stress stimuli because the haploid and highly compacted nucleus does not transcribe anymore. Indeed, during the last stages of spermatogenesis, spermatozoa has eliminated most of its cytoplasm, which is

the major source of antioxidants. So, in spermatozoa, the cytoplasm content is very small and it is mainly occupied by DNA.

While physiological levels of ROS are necessary for the regulation of spermatic functions, an excessive quantity can overwhelm the antioxidant mechanisms responsible for the protection of spermatozoa. In the seminal fluid there is an antioxidant system dedicated to maintaining normal cellular function, composed of enzymatic and non-enzymatic factors, which interact with each other to ensure optimal protection against ROS. Among these factors, important roles are covered from the enzymatic triad that includes superoxide dismutase (SOD), catalase (CT) and glutathione peroxidase (GSHPX).

SOD is a metalloenzyme that catalyzes the superoxide anion dismutation reactions and specifically, plays a leading role in the protection of PUFA, constituents of the plasma membrane, and in the fragmentation of DNA. It can perform its functions both in extra and intracellular space, even though the principal enzymatic activity is located to the cytoplasm of the cells.

Catalase (CT) is responsible for the transformation of hydrogen peroxide into molecular oxygen and water. It is characterized by the presence of the heme system, with an iron atom in the center of the group. Its activity has been found in different organelles: peroxisomes, mitochondria, endoplasmic reticulum and in the cytosol of different cell types.

Another enzyme that is part of the sperm antioxidant system is glutathione peroxidase (GSHPX), whose active site is made up of selenocysteine. Generally, this enzyme is responsible for the reduction of hydrogen peroxide and organic peroxides. There are three isoforms: cytosolic, mitochondrial and nuclear. Specifically, the mitochondrial isoform is necessary for sperm quality and motility.

When the antioxidant system fails to counteract the excessive increase in ROS, cell death occurs. Therefore, ROS have a double role: physiologically to complete the maturation of spermatozoa and/or to achieve fertilization, but in excess they are harmful to cell structures, functions and survival.

Genesis of Oxidative Stress, Lipid Peroxidation and DNA Damage[2]

When ROS production passes antioxidant defenses, dangerous effects on spermatozoa can be summarized as increased LPO and DNA damage and reduction of sperm motility, morphology and viability which are associated with lower sperm fertility. The main sources of ROS are attributable to two metabolic pathways that produce energy: glycolysis and OXPHOS.

To produce ATP molecules, the cells rely on mitochondria, which generate ROS during mitochondrial respiration.. The electron transport chain and oxidative phosphorylation generate ATP in the mitochondria, transferring electrons from the inner mitochondrial membrane complexes. Consequently, the process leads to a pumping of protons to the intermembrane space. Here, the electron chain may generate a local excess of ROS, especially by complexes I and III.

The production of ROS starts with the formation of a superoxide anion radical (O_2^-), which is physiologically recycled by SOD into hydrogen peroxide (H_2O_2). Hydrogen peroxide is very stable molecule and can cross the plasma membrane to contact all the cellular and extracellular compartments. Despite that hydrogen peroxide is one of the non-radical species, it can generate highly reactive hydroxyl radicals in the presence of metal ions. Via the Fenton and Haber–Weiss reactions, an excess of H_2O_2 leads to the generation of very aggressive radicals (hydroxyl and alkoxyl, OH and OH^-).

Furthermore, the main target of ROS is the peroxidation of unsaturated fatty acids that produces highly reactive lipid and aldehyde, which in a positive feedback react with cellular components producing increasing ROS contents.

Spermatozoa are also particularly susceptible to the damage induced by excessive ROS because their plasma membranes contain large quantities of PUFA as the decohexaenoic acid (DHA, where six double bonds between their methylene groups are not conjugated). PUFA undergo lipid peroxidation by ROS, and this reduces the integrity of the membranes

Role of Inositols in Male Fertility[2]

Inositol exists as nine stereoisomers, resulting from epimerization of the six OH- groups (cis-, epi-, allo-, myo-, neo-, scyllo-, L-chiro-, D-chiro-, and muco-inositol). The most diffused form in nature is cis-1,2,3,5-trans-4,6-cyclohexanehexol, or myo-inositol (MI), followed by D-chiro-inositol (DCI). The conversion of MI into DCI is accomplished by an enzyme with epimerase activity, which is responsible for their different tissue distribution. In fact, every organ or tissue has a specific ratio of MI:DCI, fundamental for the correct inositol-related functions. In animals, inositol is both synthesized and taken with the diet through grains, wheat germ, citrus fruits and meats, primarily as inositol-phosphates. The absorption of free inositol in the intestine is achieved with an active transporter of sodium/myo-inositol transporter (SMIT) family, temperature and pH dependent. SMIT is an active symporter which allows uptake and accumulation, dependently on both concentration of substrates and energy. Furthermore, intestinal absorption of a high amount of myo-inositol is considered safe, as highlighted by several studies that proved the absence of side effects even after ingesting large quantitie. In addition, in vitro and in vivo results support an increased MI intestinal absorption when combined with alpha-lactalbumin administration. Once absorbed, inositol-phosphates are metabolized into un-phosphate MI by inositol-phosphate-phosphatase 1 (MINPP1) and then transported to the cytosol of cells. Specifically, an integral membrane protein of the SMIT family encoded by the SLC5A3 gene and controlled by osmoregulatory elements transports one molecule of MI and two of Na^+ . In recent years, the SLC5A3 cellular transporter was found to be expressed in several tissues. Among others, testis and epididymis displayed (high/medium/low) expression, while Sertoli cells display elevated expression, as the hypertonic conditions increase MI uptake. Therefore, here the concentration of MI is 28 times higher compared to the plasma. Moreover, the presence of the blood-testicular barrier prevents the free passage of MI from the blood to the testicle and vice-versa. Owing to this mechanical barrier, MI remains strongly concentrated into seminiferous tubules. In spermatozoa, MI plays a key role as an intracellular second messenger through the regulation of Ca^{2+} levels. It also intervenes in the regulation of sperm motility, capacitation and the acrosome reaction. The activation of intracellular transmission systems necessarily leads to an increase in cytoplasmic and mitochondrial Ca^{2+} level. High Ca^{2+} levels stimulate the oxidative metabolism, inducing the production of ATP depending on the energy requirements. This system needs a good functional state of the mitochondria and consequently of high mitochondrial membrane potential (MMP). Recently, researchers proved that high MMP correlates to higher fertilizing

capacity of spermatozoa and to higher spermatic motility. Several studies highlighted an interesting role of MI, which proved able to increase MMP and sperm motilit. Finally, regulating intracellular levels of Ca^{2+}, MI is able to improve the main characteristics related to the "state of health" of spermatozoa, increasing their fertilizing capacities. The acrosome reaction is a prerequisite for fertilization in mammals. It consists of a fusion between the plasma membrane and the outer acrosome membrane above the anterior portion of the sperm head. It takes place on the surface of the zona pellucida, after specific binding with a specific glycoprotein, the ZP3. Once the acrosome reaction is completed, the sperm cell is able to penetrate the zona pellucida. A premature acrosome reaction leads to a loss of the recognition sites of the zona pellucida on the spermatozoa surface and thus it affects gamete fusio. In contrast, the inability to achieve activation, which is responsible for initiation of the acrosome reaction, prevents the oocyte penetration.

Moreover, in IP3 form, MI is involved in the activation of Akt, which is a fundamental protein involved in maturation of spermatozoa. In fact, Akt regulates a wide range of proteins by phosphorylation. Akt phosphorylating some proteins as Bcl-2 (at the level of the residue Ser70, S473, T308) negatively regulates the apoptosis process. Indeed, phosphorylation determines the passage from the mitochondria to the cytosol and making it a marker of cell survival. The MI in the IP3 form initiates a cascade of reactions which always lead to the phosphorylation of tyrosine residues and reflect the state of capacitation that makes male gamete available to fusion with the oocyte (acrosome reaction).

MI also represents the second messenger of the gonadotropin Follicle-stimulating hormone (FSH). At the testicular level, FSH plays a key role in the control of Sertoli cell number and function, promoting the differentiation of these cells essential to sustain a normal spermatogenesis. MI, acting as second messenger, regulates the activities of FSH, and thus may result useful to counteract alterations of the hormone levels. In addition, MI administration lowers LH concentration. High FSH and LH serum concentrations relate with low sperm concentration. On the other hand, MI increases the levels of Inhibin B, a glycoprotein secreted from the testis as a product of Sertoli cells that act as negative feedback to regulate FSH secretion. In men, either with normal or altered spermatogenesis, a strong inverse correlation is reported between inhibin B and FSH levels.

MI: In Vitro Studies[2]

One of the first studies evaluating the impact of MI treatment on sperm samples from OAT patients showed that 2 mg/mL MI determine the absence of amorphous material. This material is responsible for the high viscosity of the seminal fluid and consequently for the reduction of sperm motility. Furthermore, the mitochondria of the treated cells showed a morphology similar to the physiological, free from damage to the mitochondrial crests, in contrast to the untreated ones, which display altered morphology. To investigate the effects of MI on mitochondrial function, researchers incubated samples from OAT patients with 2 mg/mL and then evaluated: MMP, phosphatidylserine externalization (PS) and chromatin compactness. At the end of the treatment, although there were no appreciable results on PS and chromatin compactness, the number of spermatozoa with high MMP had increased, otherwise the number of spermatozoa with low MMP had decrease. Another similar in vitro study showed the same outcomes of higher sperm numbers with high MMP and higher progressive motility in both normospermic and OAT patients. Furthermore, motility improvement in the first group was associated with a significant increase in the percentage of spermatozoa with high MPP. As studies showed that sperm motility is directly associated to fertilization rate, even in IVF procedures, different studies evaluated the impact of MI in IVF procedures. For this reason, MI use was shown to improve the culture conditions necessary for a successful ICSI technique. This led to improvement in outcomes as the fertilization rate, the percentage of grade A embryos on day 3 and progressive motility in normospermic and OAT patients undergoing in vitro fertilization (IVF). In sperm samples from patients with hyper viscosity, MI also improved progressive motility compared to the control group. As the thawing process of sperm samples leads to a reduction in motility, sperm quality and fertilization rate, the efficacy of MI was evaluated on both fresh and thawed sperm samples. The results obtained showed an improvement in motility in both samples. Similar results were obtained when evaluating the use of MI in culture media for cryopreservation processes. Again, the results showed a significant increase in the cryo-survival rate (CSR), defined as the percentage of total motility after thawing, divided by the percentage of total pre-freezing motility and multiplied by 100. Hence, in vitro supplementation of MI has been shown to induce a significant increase in sperm motility and oxygen consumption, the main index of the efficiency of oxidative phosphorylation and ATP production. Previous studies provided only indirect results on the antioxidant power of MI. Therefore, researchers decided to evaluate 8-OHdG, one of the first products of oxidative damage to DNA. The samples treated with MI displayed reduced levels

of 8-OHdG. Therefore, MI can improve the sperm parameters related to the quality and in vitro fertilization process. In fact, the antioxidant properties of MI, although not yet fully known, can contribute to the improvement of sperm parameters to optimize the results of assisted reproduction techniques.

Table 1 Myo-inositol: in vitro studies.

Author and Publication Year	Samples	Treatments	Results
Colone et al., 2010	OAT patients	Inositol 2 mg/mL and then submitted to scansion electron microscopy (SEM) and to transmission electron microscopy (TEM)	Absence of amorphous material and reduction of mitochondrial damage to the crests
Condorelli et al., 2011	5 normozoospermic and 7 OAT patients	Incubated in-vitro with 2 mg/mL of myo-inositol or placebo (control) for 2 h	Increased the number of spermatozoa with high MMP and decreased the number of those with low MMP in OAT patients
Condorelli et al., 2012	20 normozoospermic and 20 OAT patients	Incubated in vitro with 2 mg/mL of myo-inositol or phosphate-buffered saline as a control for 2 h	Increased sperm motility and the number of spermatozoa after swim-up and in OAT patients, the improvement was associated with sperm mitochondrial function.
Rubino et al., 2015	Myo-inositol group (*n* = 262 oocytes), placebo group (*n* = 238 oocytes)	Washed and subjected to swim-up with 2 mg/mL of myo-inositol or	Improved spermatozoa motility in swim-up selected samples, fertilization rate (%),

		placebo-supplemented medium for 30–60 min. Spermatozoa recovered used for ICSI.	grade A embryos on day 3.
Artini et al., 2017	31 normospermic e 32 OAT patients	2 mg/mL MI and incubated 30 min at 37 °C	Improved total motile sperm concentration, progressive motile sperm concentration.
Scarselli et al., 2016	30 patients with grade II and III varicocele	Semen centrifuged at 1800 rpm/10 min, resuspended, and incubated with 2 mg/mL myo-inositol and 133 mg/mL myo-inositol in 9 mg/mL sodium chloride) for 15 min at 37 °C	Patients suffering from varicocele response in >60% of the samples
Palmieri et al., 2017	46 normospermic, 19 oligospermic, 15 asthenospermic patients	Semen supplemented with 15 µL/mL of myo-inositol incubated 15 min at 37 °C	Improved progressive and total motility
Mohammadi et al., 2019	40 normospermic patients	Semen divided into two aliquots ad cryopreserved: one with 2 mg/mL myo-inositol; one without myo-inositol (control)	Improved progressive and total motility, normal sperm morphology, reactive oxygen species, malondialdehyde, total antioxidant assay and DNA fragmentation

Saleh et al., 2018	41 samples: 15 normal and 26 abnormal	Semen samples supplemented with 1 mg myo-inositol to cryoprotectant	Total and progressive motility, cryo-Survival Rate
Pallotti et al., 2019	9 normokinetic semen samples with nonlinear progressive motility	Incubation with a solution of myo-inositol	Increased linear progressive motility, significant reduction in nonlinear progressive motility, increased curvilinear velocity
Governini et al., 2020	56 Caucasian males with possible causes of male infertility such as varicocele, cryptorchidism, endocrine disorders or systemic diseases	The aliquots were incubated with standard medium (untreated sample) or medium supplemented with myo-inositol at 20 mg/mL (treated sample) for 20 min.	Increase in sperm motility and in oxygen consumption, the main index of oxidative phosphorylation efficiency and ATP production, both in basal and in in vitro capacitated samples.

MI: In Vivo Studies

Several studies evaluated the improvements in sperm and metabolic parameters related to male infertility following dietary supplement based on MI. A study carried out on patients with idiopathic infertility demonstrated that MI can be useful for improving sperm parameters such as percentage of spermatozoa with acrosome reaction, spermatozoa concentration, total count and progressive motility, when compared to placebo. Furthermore, the same study evaluated hormonal parameters and highlighted a reduction in follicle-stimulating hormone and luteinizing hormone and a concomitant increase in inhibin B concentrations. In another study, samples from healthy and oligoasthenospermic (OA) patients were analyzed by light microscopy to evaluate semen volume, sperm number and motility before and after the density gradient separation method. The study considered these parameters before and after the

administration of 4000 mg/day of MI and 400 mg of folic acid for 2 months. After treatment there was a significant increase in sperm concentration in the OA patient group and a significant increase in sperm count in the healthy patient group. Furthermore, such supplementation highlighted promising results in asthenospermic patients with metabolic syndrome, showing significant improvements in sperm (concentration, motility and morphology), hormonal (testosterone, E2, LH, SHBG) and metabolic (HOMA index) parameters. In addition, 85.32% of asthenospermic patients achieved significant improvement in sperm motility. In particular, 34.86% of patients restored normal sperm motility while only 12.84% showed no beneficial effect. For the first time, researchers investigated the effect of MI on cholesterol efflux, a hallmark of capacitation. They underlined an increase in cholesterol efflux in the spermatozoa of patients with OAT treated either in vitro or in vivo with a blend of nutraceuticals, containing mainly MI. The same study also found an increase in the activity of G6PDH, associated with the increase in glucose metabolism through pentose phosphate pathway (PPP), both in normal patients and in patients with OAT.

Table 2. Myo-inositol: in vivo studies.

Author	Study Design and Patients	Treatments	Results
Calogero et al., 2015	Double-blind, randomized, place-bo-controlled; 194 men with idiopathic infertility	Group 1 (*n* = 98) received 2 g of myo-inositol and 200 mcg of folic acid twice daily. Group 2 (*n* = 96) received one placebo sachet twice day for 3 months	MI significantly increased the percentage of acrosome-reacted spermatozoa, sperm concentration, and total count and progressive motility. In addition, reduced serum luteinizing hormone, follicle-stimulating hormone, and in-creased inhibin B concentration

Gulino et al., 2013	Prospective study; 62 patients divided into three different groups: healthy fertile patients (Group A); patients with oligoasthenospermia (OA)–(Group B)–control group (CTR).	4000 mg/die of MI and 400 µg of folic acid for 2 months	Increase of basal and after density-gradient separation method spermatozoa concentration in Group B, and a significant increase of spermatozoa count after density-gradient separation method in Group A
Montanino Oliva et al., 2016	Prospective longitudinal study; 45 asthenospermic males	The patients were treated by a dietary supplement administered twice a day containing 1 g MI, 30 mg L-carnitine, L-arginine and vit-amin E, 55 µg selenium, and 200 µg folic acid	Improved spermatic, hormonal and metabolic parameters: HOMA index, SHBG, E2, LH, free and total testosterone, sperm concentration, motility and normal morphology
Dinkova et al. et al., 2017	Prospective longitudinal study; 109 patients with astheno-zoospermia	1 g myo-inositol, 30 mg of L-carnitine, L-arginine, and vitamin E, 55 mcg of selenium, and 200 mcg of folic acid twice a day for 3 months	A significant improvement in spermmotility was reported in 85.32% of the patients

Role of Antioxidant in Male Fertility

Researchers observed an enhancement in semen parameters with the use of antioxidants, suggesting that such substances minimize the toxic effects of oxidative stress in spermatozoa.

Folic Acid

One of these antioxidants is folate, a vitamin from the B group involved in many biochemical processes and several functions as: DNA synthesis, which is fundamental for the development of spermatozoa; oxidative pathway, as the synthetic form of the folate, folic acid, effectively scavenges oxidizing free radicals and inhibits LPO. Different studies evaluated the free radical scavenging properties and possible antioxidant activity of folic acid. Its constituents, pyrazine and pterin, can easily be reduced by hydrated electron to the corresponding hydroderivatives in the pyrazine ring of the molecule. Furthermore, free radical intermediates are suggested in the chemical oxidation of reduced pterins by air, H_2O_2 or iron ions. Moreover, a folate deficiency is involved into apoptosis process through p53, as it happens in case of certain types of DNA damage. As a consequence of the involvement of folate in scavenging processes, researchers found that the concentration of indexes of lipid peroxidation in folate-deficient cells are drastically increased. This folate deficiency activates a redox-sensitive transcription factor, NF-κB, which controls an apoptosis mediated by reactive oxygen species.

Different studies analyzed the supplementation of folic acid in sub-fertile male. A study reported an improvement in number and motility of spermatozoa and a decrease in the number of immature cells after 3 months of supplementation with 15 mg of folic acid (5-formyl tetrahydrofolate) in 65 men of infertile couples with cell idiopathic syndrome. A recent systematic review and meta-analysis analyzed seven randomized controlled trial (RCT) involving sub fertile men to evaluate oral folic acid supplementation alone or in combination with zinc sulfate, evaluating inhibin B, FSH, testosterone and concomitantly sperm characteristics as concentration, morphology and motility. Folic acid may also improve endocrine parameters by stimulating the Sertoli cells, the main producers of inhibin B. The serum concentration of inhibin B relates with sperm concentration, testicular volume and the state of the spermatogenetic epithelium. Intuitively, the concentration of inhibin B reflects the quality of the Sertoli cell and thus represents a marker of good spermatogenesis in humans. As a consequence, supplementation with folate significantly improve sperm concentration.

L-carnitine

L-carnitine is detectable as free or acetylated forms in epididymal tissue, seminal plasma and spermatozoa. The pivotal role of L-carnitine is to transport acetyl and acyl groups, which are essential for mitochondrial metabolism, across the mitochondrial inner membrane. L-carnitine likely accelerates the metabolism of long-chain fatty acids in mitochondria. During this process L-carnitine temporarily binds acetyl groups, producing L-acetyl-carnitine. These reactions modulate mitochondrial concentrations of acetyl coenzyme A (CoA), which is implicated in the energetic metabolism, such as the Krebs cycle, the β-oxidation of organic acids and the degradation of amino acids. L-acetyl-carnitineand L-carnitine participate in the energetic metabolism, which improves the motility and the maturation of spermatozoa. Furthermore, L-carnitine and L-acetyl-carnitine participate in protection against oxidative damages. The excess of acetyl-CoA generated allows the formation of L-acetyl-carnitine as a buffer of acetyl groups. Moreover, L-carnitine shows the activity of free radical scavenger, especially to superoxide anion. In a study involving rats, L-carnitine taken before doxorubicin, a chemotherapy drug, partially preserved the acrosome integrity of sperm. In another study on mice, L-carnitine raises Bcl-2 levels and reduces Bax expression, indicating that this compound may inhibit apoptosis. Several studies on L-carnitine involved also antimicrobials, anti-inflammatory drugs or pentoxifylline. These studies showed positive results as an increase in sperm vitality, motility and a reduction in ROS. The treatment also improved the sperm count when in combination with pentoxifylline.

L-arginine

L-arginine actively participates in the formation of sperm and prevents the peroxidation of membrane lipids. This mechanism seems to involve nitric oxide (NO), a short-lived free radical, synthesized in many mammalians cell types by a class of NADPH dependent enzymes called nitric oxide synthases (NOS). These enzymes catalyze the conversion of L-arginine to L-citrulline and NO. In vitro studies investigated the effects of exogenous NO donors on sperm function as motility and viability, with controversial results. There is evidence that low concentrations of NO increase human sperm capacitation. In addition, other studies suggest that the stimulation of NO generation relates with the enhancement of tyrosine phosphorylation in sperm proteins, which leads to sperm capacitation. Moreover, NO inactivates superoxide

anions. When NO predominates, it inactivates superoxide; when superoxide predominates, it inactivates NO.

N-acetylcystenine

Since the 1960s, N-acetyl-cysteine (NAC), has been widely described as a mucolytic agent. In particular, the mucolytic action of NAC is due to its ability to break the disulfide bonds in the high-molecular-weight glycoproteins of mucus, reducing the viscosity. For this reason, NAC is also considered as an option for the treatment of diseases involving oxidative stress. In addition, several in vitro studies reported efficient antioxidant activity of NAC using different oxidants, substrates, and methods to assess the oxidative processes.. The antioxidant activity of NAC can be related to at least three different mechanisms:

A direct antioxidant effect toward certain oxidant species including NO_2 and hypohalous acids (HOX). HOX, due to their high reactivity, are not specific oxidants and also react with many biologically important molecules, thus inducing a cytotoxic effect.

As NAC acts as a predecessor of cysteine and is part of important step to glutathione synthesis has an indirect antioxidant effect. Then GSH is engaged in different detoxification processes as elimination of by-product of lipid peroxidation and hydroperoxides.

From a chemical point of view, NAC acts as a reducing agent, and therefore exerts its activity against the disulfide groups by reducing them and generating SH group.

Further studies involved animal models to evaluate NAC efficacy. For example, a study evaluated the protective effect of NAC against the toxic effects of orally administered TiO_2 nanoparticles in 50 adult male albino rats. It is known that the TiO_2 particles trigger pathological alterations at the testicular level, which results in an increase in MDA and a corresponding reduction in GSH. The simultaneous administration of NAC restores the previously mentioned alterations by exerting a protection against DNA damage. Another study on mice evaluated the protective role of NAC against arsenic trioxide (As_2O_3), which is often used in treatment of leukemia. Following NAC administration, animals showed improved sperm parameters and seminal vesicle weight. The exposure to another substance, chlorpyrifos (CPF), may cause chronic toxicity in male genital system, and the treatment with NAC after the exposure significantly improves spermatogonia, spermatocytes, spermatid cell counts as well as sperm parameters.

Abstract

The effect of Myo-inositol on sperm parameters and pregnancy rate in oligoasthenospermic men treated with IUI: A randomized clinical trial[3]

Background

In about 40% of the couples, the cause of infertility problems is attributed to men because of low sperm production and disturbed motility of sperm. Pieces of evidence show that Myo-inositol has a potential role for the treatment of sperm morphology and male fertility.

Objective

This study aimed to determine the effect of Myo-inositol on the sperm parameters and fertility rate in patients with oligoasthenospermia treated by intrauterine insemination (IUI).

Materials and Methods

This study was a randomized clinical trial conducted on 37 patients with oligoasthenospermia treated by IUI during 2016-2017. In this study, the patients were randomly divided into two groups of oligoasthenospermia treated with (Case group) and without Myo-inositol (Control group). The case group received 0.5 ml of Myo-inositol with a concentration of 2 mg/ml and incubated at 37°C incubator for 2 hr, but the control group had no interventions.

Results

The results of this study showed that although there was no significant difference in sperm parameters including sperm motility and concentration before processing with Myo-inositol in the case group, but there was a significant increase in sperm motility during the treatment with Myo-inositol. The therapeutic effect of this method was confirmed on induction of pregnancy in 18% of the treated patients, in such a way that was about twice greater than those who did not receive the drug.

Conclusion

According to the results of this study, the use of Myo-inositol is efficient enough to change sperm parameters to increase the chance of fertility.

Effect of Myoinositol and Antioxidants on Sperm Quality in Men with Metabolic Syndrome[4]

This prospective longitudinal study investigated the effects of a dietary supplement in patients affected by reduced sperm motility (asthenospermic males) with metabolic syndrome. The product tested was Andrositol®, which contains myoinositol (MI) as principal compound, in association with other molecules, and the parameters evaluated were semen characteristics as well as hormone and metabolic profiles. The inclusion criteria were subjects aged over 18 years, with asthenospermia and metabolic syndrome. The exclusion criteria were presence of cryptorchidism, varicocele, and prostatitis. For this study, 45 males who had such features were enrolled. Their selection was made according to the 2010 World Health Organization (WHO) criteria (5th Edition) for the Evaluation of Human Semen. Hormone and metabolic profiles and semen parameters were assessed at the beginning of the study and after three months of treatment with Andrositol. The differences between the values before and after the supplementation were found statistically significant. Andrositol normalized the metabolic profile of these patients, improving their insulin sensitivity. Moreover, testosterone levels were increased and the semen characteristics, such as sperm concentration, motility, and morphology, highly improved. In conclusion, the association of MI with other molecules (micronutrients and vitamins) could be an effective therapy for metabolic disorders, as well as hormonal and spermatic changes responsible for male infertility.

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2. De Luca MN, Colone M, Gambioli R, Stringaro A, Unfer V. Oxidative Stress and Male Fertility: Role of Antioxidants and Inositols. *Antioxidants (Basel)*. 2021;10(8):1283.
3. Ghasemi A, Amjadi F, Masoumeh Ghazi Mirsaeed S, et al. The effect of Myo-inositol on sperm parameters and pregnancy rate in oligoasthenospermic men treated with IUI: A randomized clinical trial. *Int J Reprod Biomed*. 2019;17(10):749-756.
4. Montanino Oliva M, Minutolo E, Lippa A, Iaconianni P, Vaiarelli A. Effect of Myoinositol and Antioxidants on Sperm Quality in Men with Metabolic Syndrome. *Int J Endocrinol*. 2016;2016:1674950.

Survey Form

1. On average, how many male infertility patients do you see in a month?

A. Fewer than 50

B. 100

C. More than 100

2. How often do patients consult you for male infertility issues as a primary concern?

A. Rarely

B. Occasionally

C. Frequently

3. For male infertility patients in your practice, how often do you consider or recommend "Tradafertil" as part of the treatment plan?

A. Occasionally

B. Frequently

C. Rarely

4. What age range do you commonly observe in male infertility patients?

A. Under 25

B. 25 - 35

C. 36 - 45

D. 46 - 55

E. 56 and above

5. Do you typically see male patients who have already sought advice for fertility concerns elsewhere before consulting you?

A. Yes

B. No

6. What factors influence your decision to prescribe or recommend "Tradafertil" for male infertility patients?

A. Clinical evidence

B. Patient's medical history

C. Other treatment failures

D. Patient preferences

E. Other

7. In your experience, how common are psychological factors contributing to male infertility?

A. Not common

B. Somewhat common

C. Very common

8. How frequently do you encounter male infertility cases linked to chronic medical conditions?

A. Rarely

B. Occasionally

C. Frequently

9. What percentage of male infertility patients have a history of genital trauma or injury?

A. Less than 10%

B. 10-25%

C. 26-50%

D. More than 50%

10. How important do you consider the role of lifestyle factors (e.g., smoking, alcohol consumption) in male fertility?

A. Not important

B. Somewhat important

C. Very important

11. How frequently do you encounter male patients with hormonal imbalances affecting fertility?

A. Rarely

B. Occasionally

C. Frequently

12. Do you routinely check testosterone levels in male infertility patients?

A. Yes

B. No

13. How do you typically monitor the progress of male infertility patients using "Tradafertil"?

A. Regular followup appointments

B. Hormonal tests

C. Semen analysis

D. Other

14. In what scenarios do you consider "Tradafertil" to be a preferable option over other treatments for male infertility?

A. Primary infertility concerns

B. Secondary infertility concerns

C. Unexplained infertility

D. Lifestyle-related infertility

E. Other

15. In your experience, what has been the general effectiveness of "Tradafertil" in improving male fertility outcomes?

A. Excellent

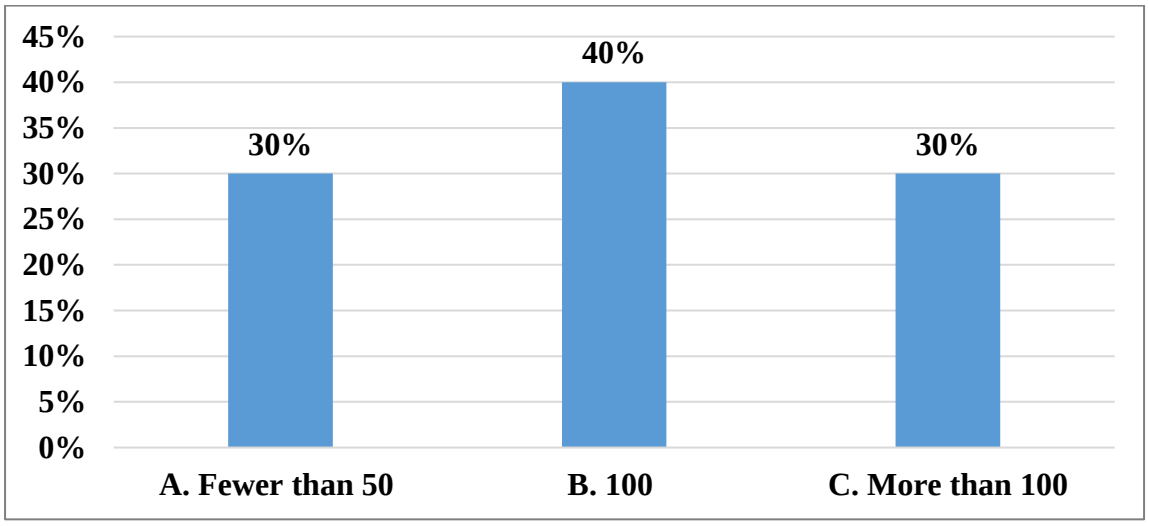
B. Good

C. Neutral

D. Poor

Survey Findings

1. **On average, how many male infertility patients do you see in a month?**
2. A. Fewer than 50
3. B. 100
4. C. More than 100



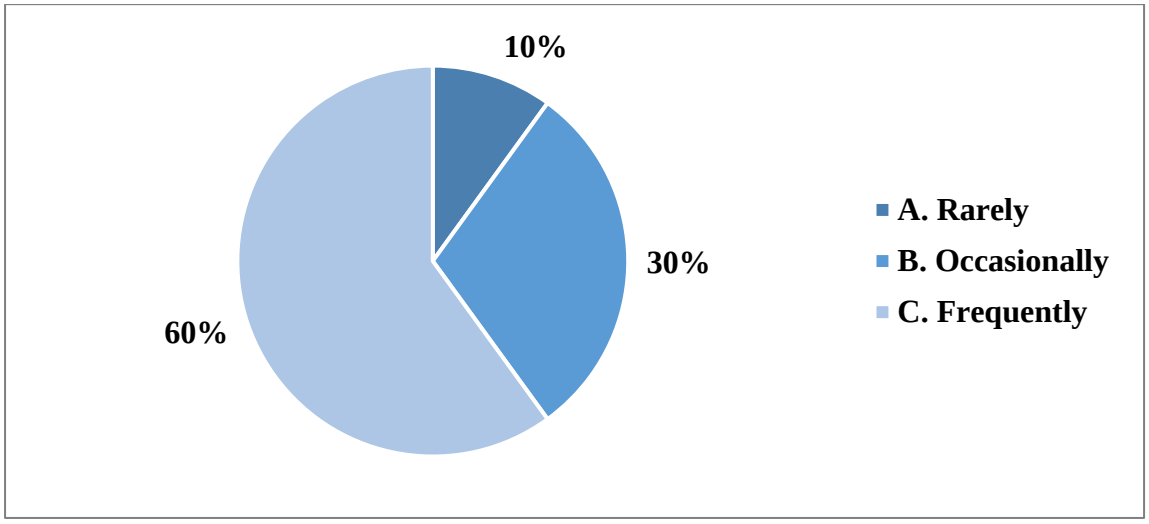
Majority of doctors, 40%, see around 100 male infertility patients on an average in a month.

2**. How often do patients consult you for male infertility issues as a primary concern?**

A. Rarely

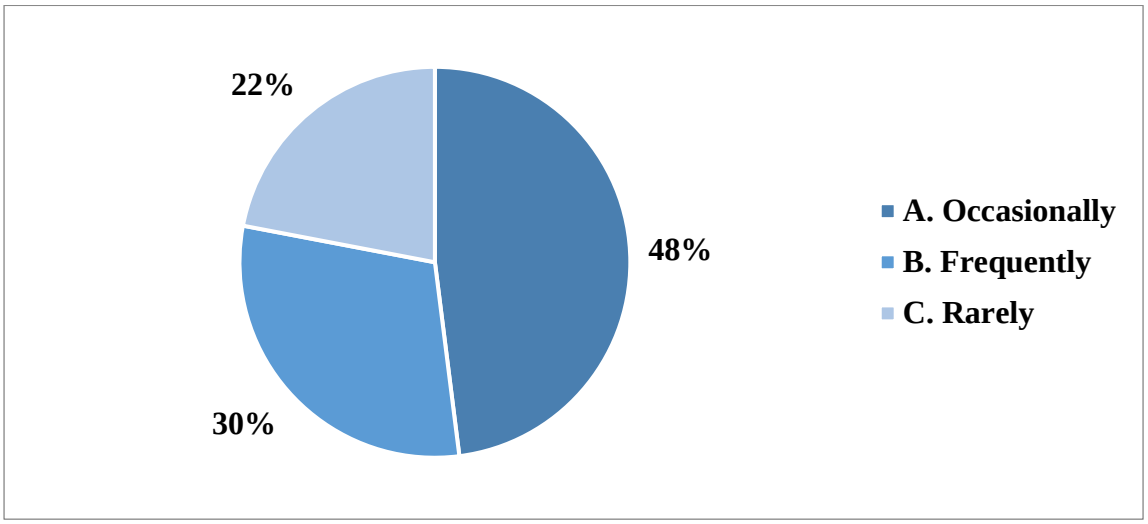
B. Occasionally

C. Frequently



As per 60% of doctors, patients consult them frequently for male infertility issues as a primary concern.

3. **For male infertility patients in your practice, how often do you consider or recommend "Tradafertil" as part of the treatment plan?**
4. A. Occasionally
5. B. Frequently
6. C. Rarely



According to 48% of doctors, for male infertility patients in their practice, they consider or recommend "Tradafertil" as part of the treatment plan occasionally.

4. What age range do you commonly observe in male infertility patients?

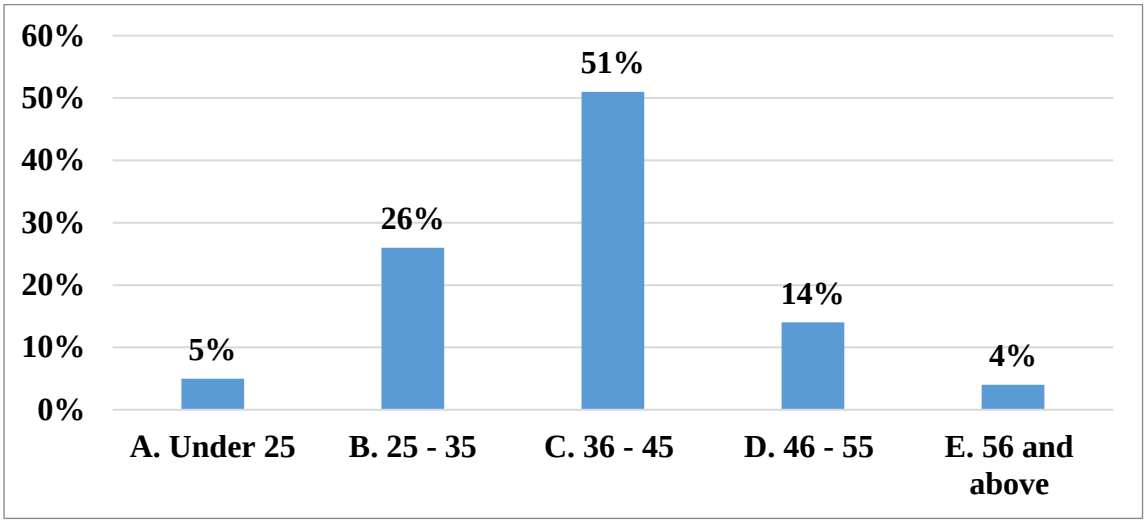
A. Under 25

B. 25 - 35

C. 36 - 45

D. 46 - 55

E. 56 and above

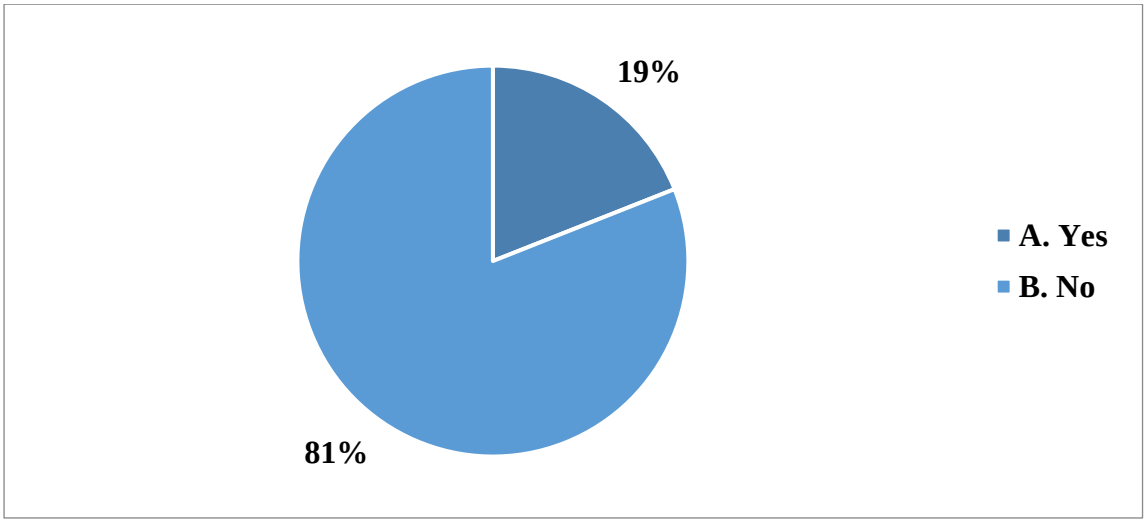


51% of doctors commonly observe male infertility patients in the age range of 36 – 45.

5. Do you typically see male patients who have already sought advice for fertility concerns elsewhere before consulting you?

A. Yes

B. No



Majority of doctors, 81%, disagree that typically they see male patients who have already sought advice for fertility concerns elsewhere before consulting them.

6. What factors influence your decision to prescribe or recommend "Tradafertil" for male infertility patients?

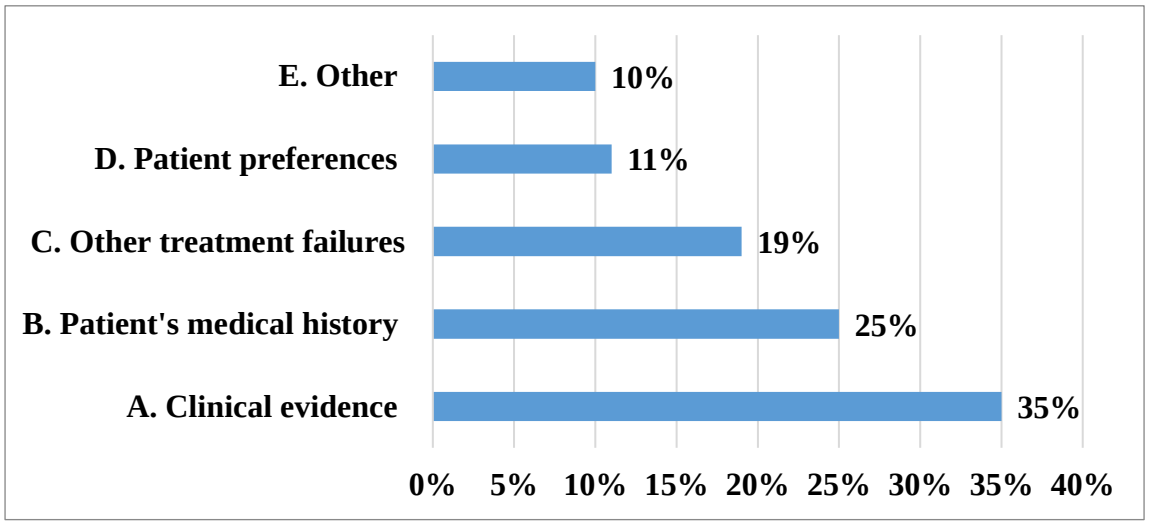
A. Clinical evidence

B. Patient's medical history

C. Other treatment failures

D. Patient preferences

E. Other



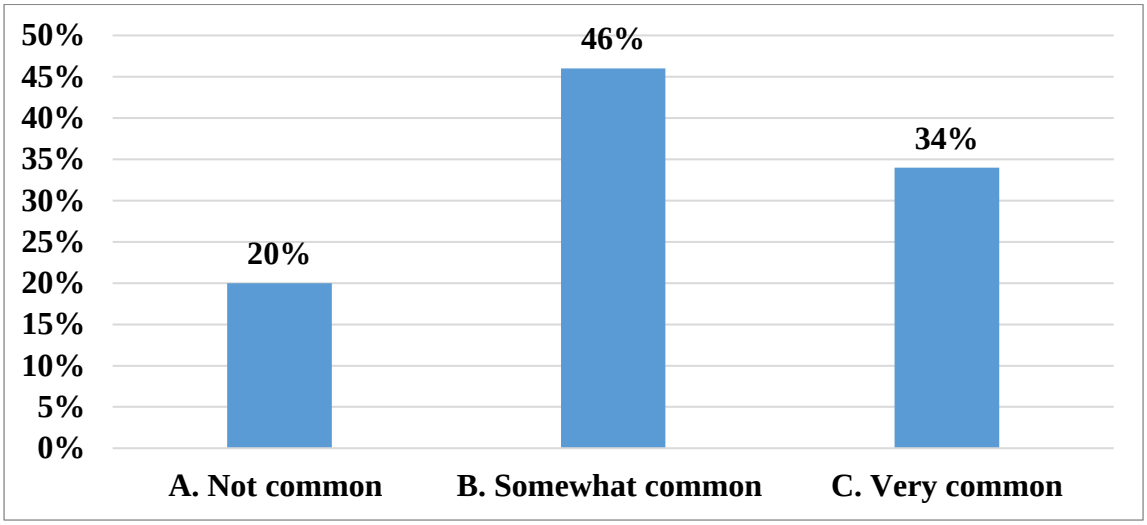
According to 35% of doctors, their decision to prescribe or recommend "Tradafertil" for male infertility patients is influenced by clinical evidence.

7. In your experience, how common are psychological factors contributing to male infertility?

A. Not common

B. Somewhat common

C. Very common



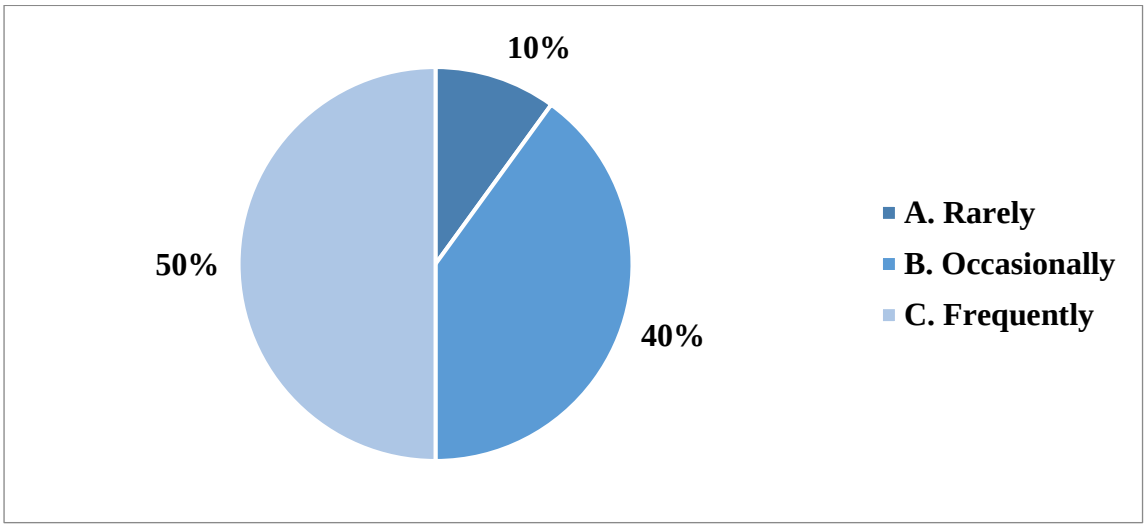
In the experience of 46% of doctors, psychological factors contributing to male infertility are somewhat common.

8. How frequently do you encounter male infertility cases linked to chronic medical conditions?

A. Rarely

B. Occasionally

C. Frequently



According to 50% of doctors, they frequently encounter male infertility cases linked to chronic medical conditions.

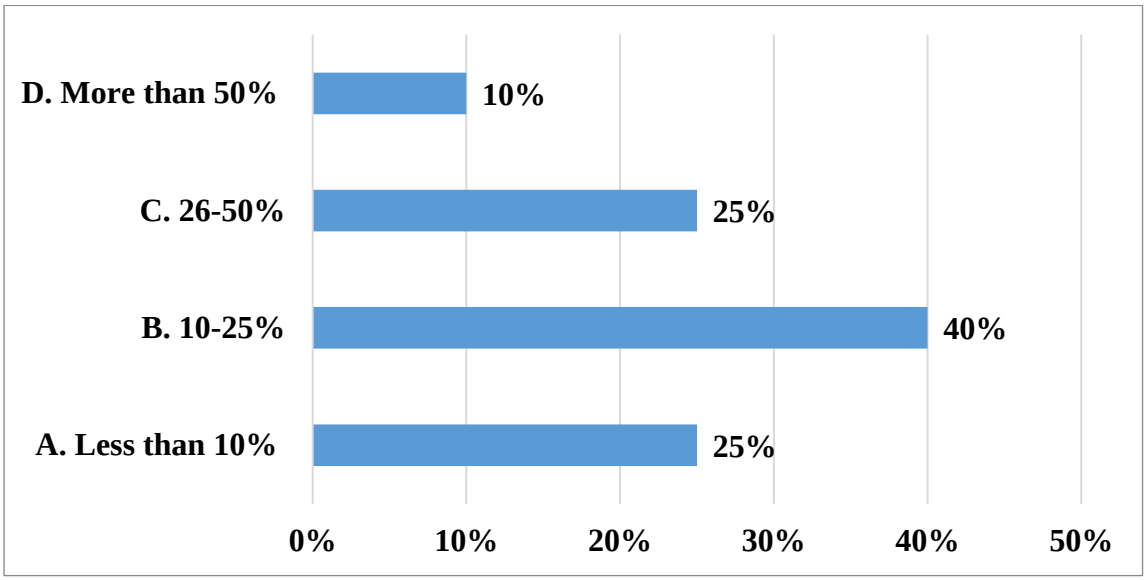
9. What percentage of male infertility patients have a history of genital trauma or injury?

A. Less than 10%

B. 10-25%

C. 26-50%

D. More than 50%



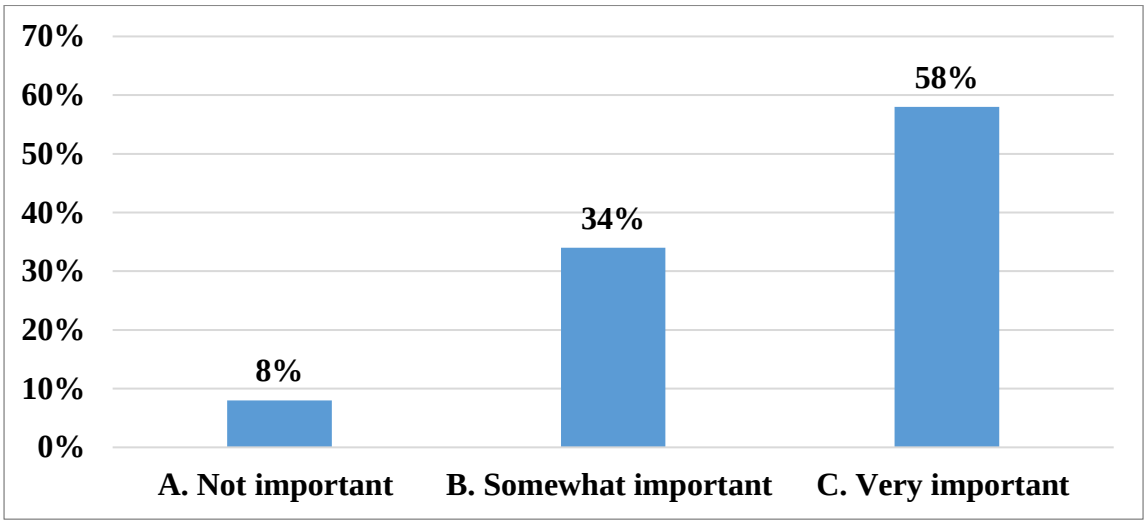
According to 40% of doctors, 10-25% of male infertility patients have a history of genital trauma or injury.

10. How important do you consider the role of lifestyle factors (e.g., smoking, alcohol consumption) in male fertility?

A. Not important

B. Somewhat important

C. Very important



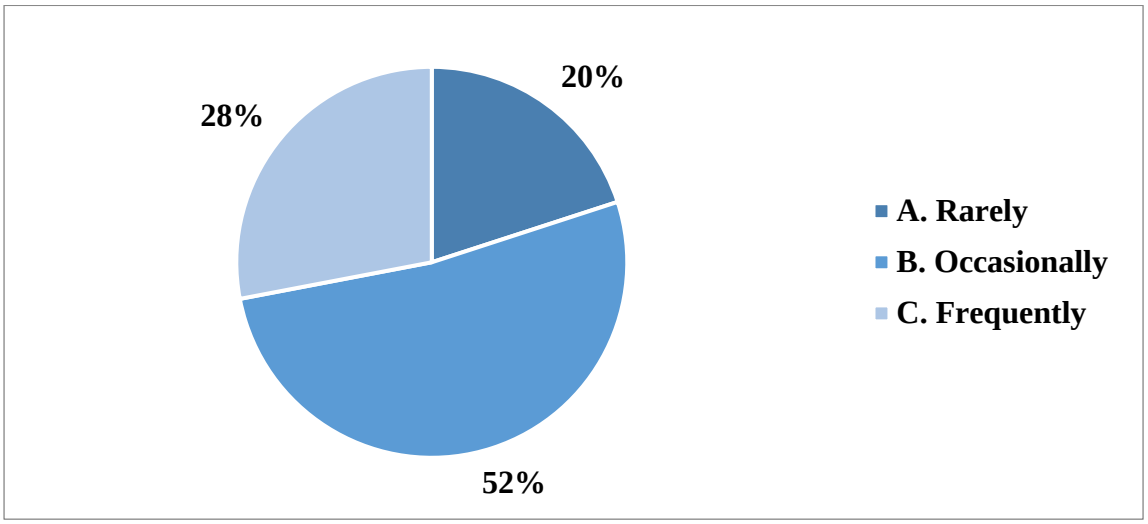
According to 58% of doctors, they consider the role of lifestyle factors (e.g., smoking, alcohol consumption) in male fertility very important.

11. How frequently do you encounter male patients with hormonal imbalances affecting fertility?

A. Rarely

B. Occasionally

C. Frequently

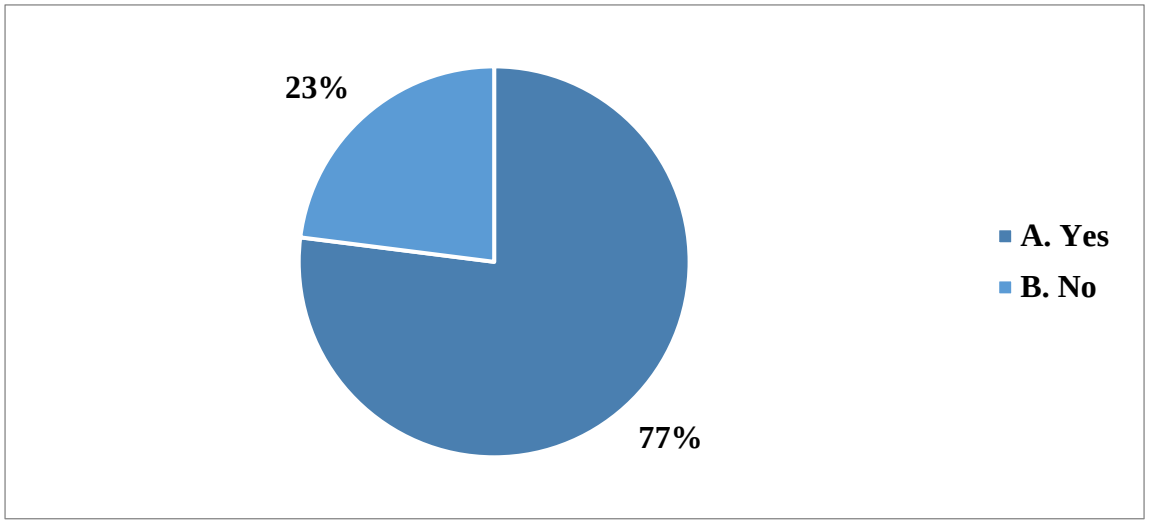


Majority of doctors, 52%, occasionally encounter male patients with hormonal imbalances affecting fertility.

12. Do you routinely check testosterone levels in male infertility patients?

A. Yes

B. No



Majority of doctors, 77%, routinely check testosterone levels in male infertility patients.

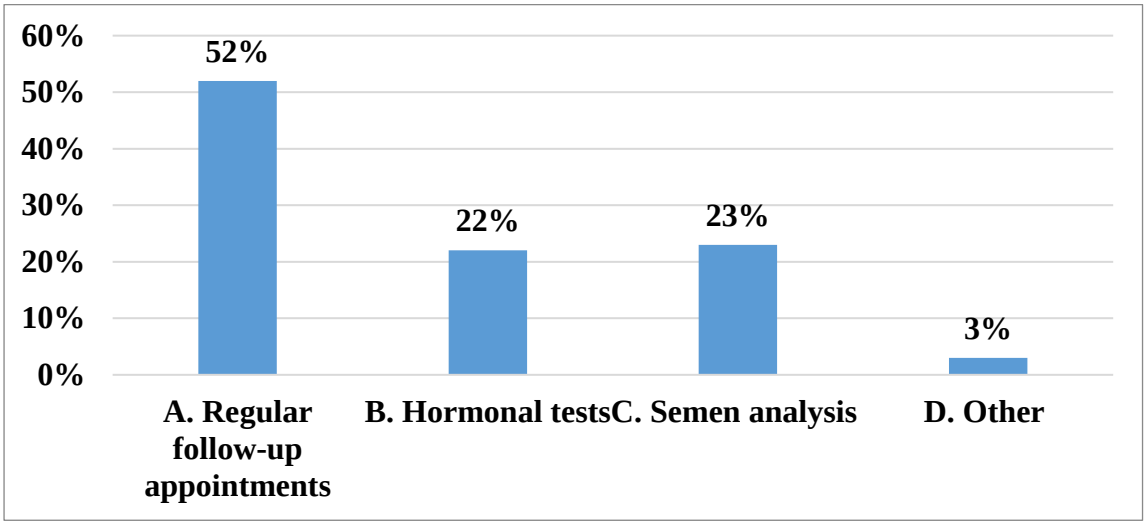
13. How do you typically monitor the progress of male infertility patients using "Tradafertil"?

A. Regular followup appointments

B. Hormonal tests

C. Semen analysis

D. Other



According to 52% of doctors, they typically monitor the progress of male infertility patients using "Tradafertil" through regular follow-up appointments.

14. In what scenarios do you consider "Tradafertil" to be a preferable option over other treatments for male infertility?

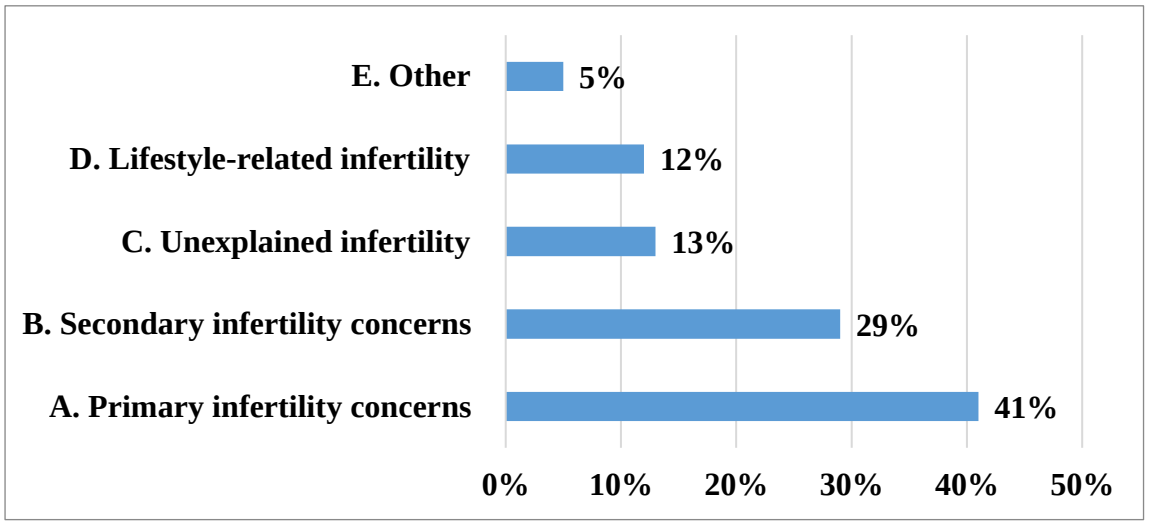
A. Primary infertility concerns

B. Secondary infertility concerns

C. Unexplained infertility

D. Lifestyle-related infertility

E. Other



According to 41% of doctors, they consider "Tradafertil" to be a preferable option over other treatments for male infertility in the scenarios of primary infertility concerns.

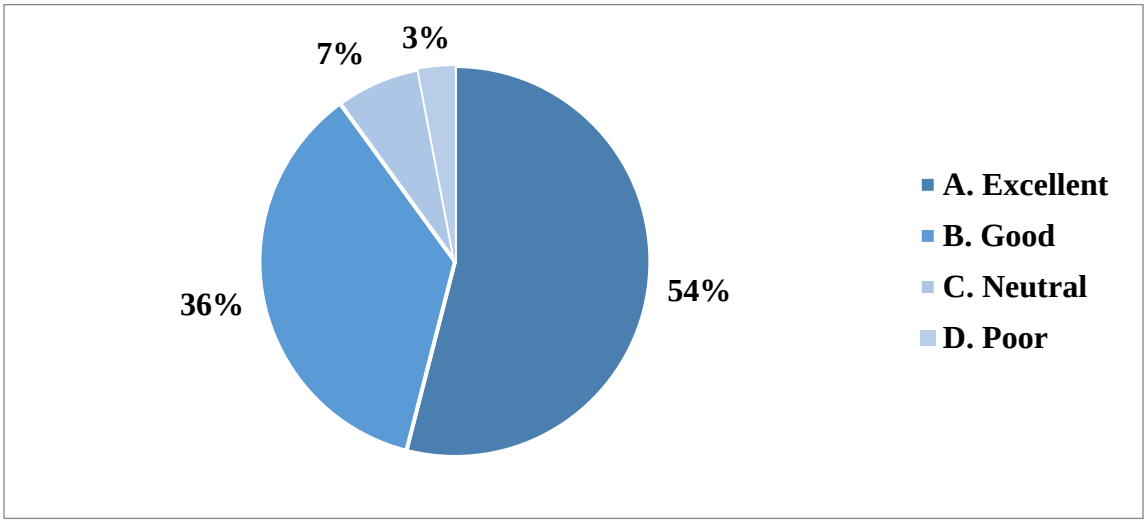
15. In your experience, what has been the general effectiveness of "Tradafertil" in improving male fertility outcomes?

A. Excellent

B. Good

C. Neutral

D. Poor



In the experience of majority of doctors, 54%, the general effectiveness of "Tradafertil" in improving male fertility outcomes is excellent.

Summary

- Majority of doctors, 40%, see around 100 male infertility patients on an average in a month.
- As per 60% of doctors, patients consult them frequently for male infertility issues as a primary concern.
- According to 48% of doctors, for male infertility patients in their practice, they consider or recommend "Tradafertil" as part of the treatment plan occasionally.
- 51% of doctors commonly observe male infertility patients in the age range of 36 – 45.
- Majority of doctors, 81%, disagree that typically they see male patients who have already sought advice for fertility concerns elsewhere before consulting them.
- According to 35% of doctors, their decision to prescribe or recommend "Tradafertil" for male infertility patients is influenced by clinical evidence.
- In the experience of 46% of doctors, psychological factors contributing to male infertility are somewhat common.
- According to 50% of doctors, they frequently encounter male infertility cases linked to chronic medical conditions.
- According to 40% of doctors, 10-25% of male infertility patients have a history of genital trauma or injury.
- According to 58% of doctors, they consider the role of lifestyle factors (e.g., smoking, alcohol consumption) in male fertility very important.
- Majority of doctors, 52%, occasionally encounter male patients with hormonal imbalances affecting fertility.
- Majority of doctors, 77%, routinely check testosterone levels in male infertility patients.
- According to 52% of doctors, they typically monitor the progress of male infertility patients using "Tradafertil" through regular follow-up appointments.
- According to 41% of doctors, they consider "Tradafertil" to be a preferable option over other treatments for male infertility in the scenarios of primary infertility concerns.
- In the experience of majority of doctors, 54%, the general effectiveness of "Tradafertil" in improving male fertility outcomes is excellent.

Consultant Opinion

Market Opportunities:

- The high number of male infertility patients seen by doctors indicates a significant market opportunity for pharmaceutical companies to develop and market products tailored for male fertility issues.

Value for Healthcare Professionals:

- Healthcare professionals frequently encounter male infertility concerns as a primary reason for patient consultation, highlighting the importance of effective treatment options in this field.

Adverse Effect Management:

- Clinical evidence plays a significant role in influencing doctors' decisions to prescribe or recommend "Tradafertil," indicating a focus on adverse effect management and evidence-based practice.

Withdrawal Management:

- Regular follow-up appointments are conducted by doctors to monitor the progress of male infertility patients using "Tradafertil," emphasizing the importance of withdrawal management and ongoing patient care.

Market Positioning:

- "Tradafertil" is perceived favorably by doctors, with a majority considering it a preferable option over other treatments for male infertility, suggesting strong positioning in the market.

Personalized Treatment Decisions:

- Doctors take into account various factors such as clinical evidence, lifestyle factors, hormonal imbalances, and medical history when making treatment decisions for male infertility patients, reflecting a personalized approach to care.

Improving Patient Outcomes:

- The general effectiveness of "Tradafertil" in improving male fertility outcomes is perceived as excellent by the majority of doctors, indicating its potential to significantly improve patient outcomes in male infertility cases.

In summary, there are significant opportunities for pharmaceutical companies to address the needs of male infertility patients by developing effective treatments like "Tradafertil." Healthcare professionals prioritize evidence-based practice, personalized treatment decisions, and ongoing patient care to improve outcomes in this field. Strong market positioning and favorable perceptions of "Tradafertil" among doctors suggest promising prospects for its success in the male infertility treatment market.

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

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