



## MALE INFERTILITY: A REVIEW OF MEDICAL AND SURGICAL APPROACHES

Aiysha Gul<sup>1\*</sup>, Rizwanullah<sup>2</sup>, Isameldin Elamin Medani<sup>3</sup>, Fath Elrahman Elrasheed<sup>4</sup>, Selim Maan Alameddine<sup>5</sup>, Einas Mustafa Mudawi Ahmed<sup>6</sup>, John David Ruffier<sup>7</sup>, Mahdi Ibrahim elnaim Ibrahim<sup>8</sup>, Ayman Mohamed Elamain Jomma Alsafi<sup>9</sup>, Saeed Ismail Saeed Ahmed<sup>10</sup>

<sup>1\*</sup>Department of Obstetrics and Gynaecology, Mardan Medical Complex, Mardan, Pakistan, Email address: [ayeshag0342@gmail.com](mailto:ayeshag0342@gmail.com)

<sup>2</sup>Department of Medicine, Hayatabad Medical Complex, Peshawar, Pakistan, [urizwan600@gmail.com](mailto:urizwan600@gmail.com)

<sup>3</sup>Department of Obstetrics and Gynaecology, Jazan university hospital, Jazan, Saudi Arabia, [isameldin2015@gmail.com](mailto:isameldin2015@gmail.com)

<sup>4</sup>Department of Obstetrics and Gynaecology, Najran University, Najran, Saudi Arabia, [fathsaed@yahoo.com](mailto:fathsaed@yahoo.com)

<sup>5</sup>Department of Medicine, Beirut Arab University, Lebanon, Beirut, [selimalamedine@gmail.com](mailto:selimalamedine@gmail.com)

<sup>6</sup>Department of Obstetrics and Gynecology, Najran University, Najran, Saudi Arabia, [wanosa@hotmail.com](mailto:wanosa@hotmail.com)

<sup>7</sup>Department of Medicine, American University of Antigua, Antigua and Barbuda, USA, [Jdruffier@gmail.com](mailto:Jdruffier@gmail.com)

<sup>8</sup>Department of Obstetrics and Gynecology, Maternity and Children Hospital, Najran, Saudi Arabia, [Medohima551@gmail.com](mailto:Medohima551@gmail.com)

<sup>9</sup>Department of Obstetrics and Gynecology, Maternity and Children hospital, Najran Saudi Arabia, [Dr.ayman\\_89@hotmail.com](mailto:Dr.ayman_89@hotmail.com)

<sup>10</sup>Department of Obstetrics and Gynecology, Maternity and Children hospital, Najran Saudi Arabia, [soos-77@hotmail.com](mailto:soos-77@hotmail.com)

**\*Corresponding Author:** Aiysha Gul

\*Email address: [ayeshag0342@gmail.com](mailto:ayeshag0342@gmail.com)

**Abstract:** Male infertility is a complex condition with multifactorial causes, impacting a significant proportion of couples seeking to conceive. This review provides a comprehensive overview of both medical and surgical approaches to managing male infertility. It examines medical interventions including hormonal treatments, lifestyle modifications, and advanced diagnostic techniques such as sperm DNA fragmentation and oxidative stress assessments. The review also explores surgical options, including varicocelectomy and procedures addressing anatomical abnormalities. Additionally, emerging treatments such as gene therapy, stem cell therapy, and advancements in assisted reproductive technologies (ART) are discussed, highlighting their potential to enhance treatment efficacy. Personalized medicine's role in tailoring interventions based on individual genetic and hormonal profiles is also considered. The review underscores the importance of integrating these approaches to offer effective, individualized care and improve fertility outcomes. Future research and clinical advancements are essential to further refine these strategies and provide new solutions for male infertility.

**Key words:** Male infertility, Assisted Reproductive Technologies, Surgical Approaches

### **Overview of Male Infertility:**

Infertility is a widespread issue, effects a number of couples in the reproductive age group.(1) Infertility is defined by the inability to conceive after a year of regular, unprotected intercourse. Male infertility specifically refers to a reduced ability to father a child, which can result from problems with sperm production, sperm function, or sperm delivery. Globally, over 186 million people experience infertility, with the majority residing in developing countries.(2) A Global Burden of Disease survey found that from 1990 to 2017, the age-standardized prevalence of infertility rose annually by 0.370% in women and by 0.291% in men.(3) Incidence rates of infertility can differ by region, influenced by factors such as environmental exposures, lifestyle choices, and genetic predispositions. For instance, industrialized countries often report higher rates, which may be linked to environmental pollutants and lifestyle factors. Globally, the prevalence of infertility is between 10-15%, whereas in Pakistan, the infertility rate is 21.9%.(4) Globally, approximately 15% of couples experience infertility, with 40-50% of these cases being attributed to male factors.(5) Infertility issues are attributed to females in about 50% of cases, males in about 40%, and both partners in about 10%.(6) Additionally, roughly 15% to 20% of couples are diagnosed with unexplained infertility after thorough diagnostic evaluations.(7)

Infertility impacts couples significantly, causing emotional and psychological stress, including frustration, sadness, and anxiety, which can lead to depression and a decreased quality of life. It can also strain relationships, leading to conflicts or feelings of isolation and affecting communication and intimacy. Social stigma associated with infertility may result in societal pressure and judgment, with couples facing intrusive questions or a lack of understanding from others. Additionally, the financial burden of fertility treatments and procedures can add to the emotional strain and affect family finances.

On a public health level, infertility places a strain on healthcare systems due to the need for specialized care and advanced medical interventions. The economic impact includes the costs of treatments, loss of productivity, and potential long-term financial effects on families. Increased public awareness and education about reproductive health are essential for earlier diagnosis and better management of infertility, as well as for reducing stigma. High infertility rates can also influence population growth and demographic changes, affecting long-term community planning and resource allocation. Overall, infertility has broad implications for both individual well-being and public health systems, requiring comprehensive support and management strategies.

### **Etiology of Male Infertility:**

Male infertility can result from a variety of factors that affect sperm production, function, or delivery. Understanding the etiology of male infertility is crucial for diagnosis and treatment. Male infertility with a known cause often has a significant treatment success rate. However, in cases of genetic or idiopathic male infertility, treatment approaches tend to be more empirical and optimized. Male infertility is primarily categorized into azoospermia (AS) and coital infertility (CI).(8) Azoospermia (AS) refers to the complete absence of sperm in the ejaculate and affects about 15% of infertile men. It is categorized into obstructive infertility (OI) and non-obstructive infertility (NOI).(9) In obstructive infertility, sperm are absent in the ejaculate despite normal endocrine and exocrine functions and normal spermatogenesis, due to a blockage in the genital tract, which can occur anywhere from the ejaculatory ducts to the rete testes. Non-obstructive infertility, on the other hand, is characterized by abnormal spermatogenesis resulting from primary or secondary testicular failure. Coital infertility is marked by normal sperm production and a healthy genital tract but is secondary to sexual dysfunction affecting ejaculation.(10) Sub-fertility can be primary, where there is a delay in conceiving for a couple with no prior pregnancies, or secondary, where a couple experiences a delay in conceiving after a previous pregnancy, regardless of its outcome, such as miscarriage or ectopic pregnancy.(11)

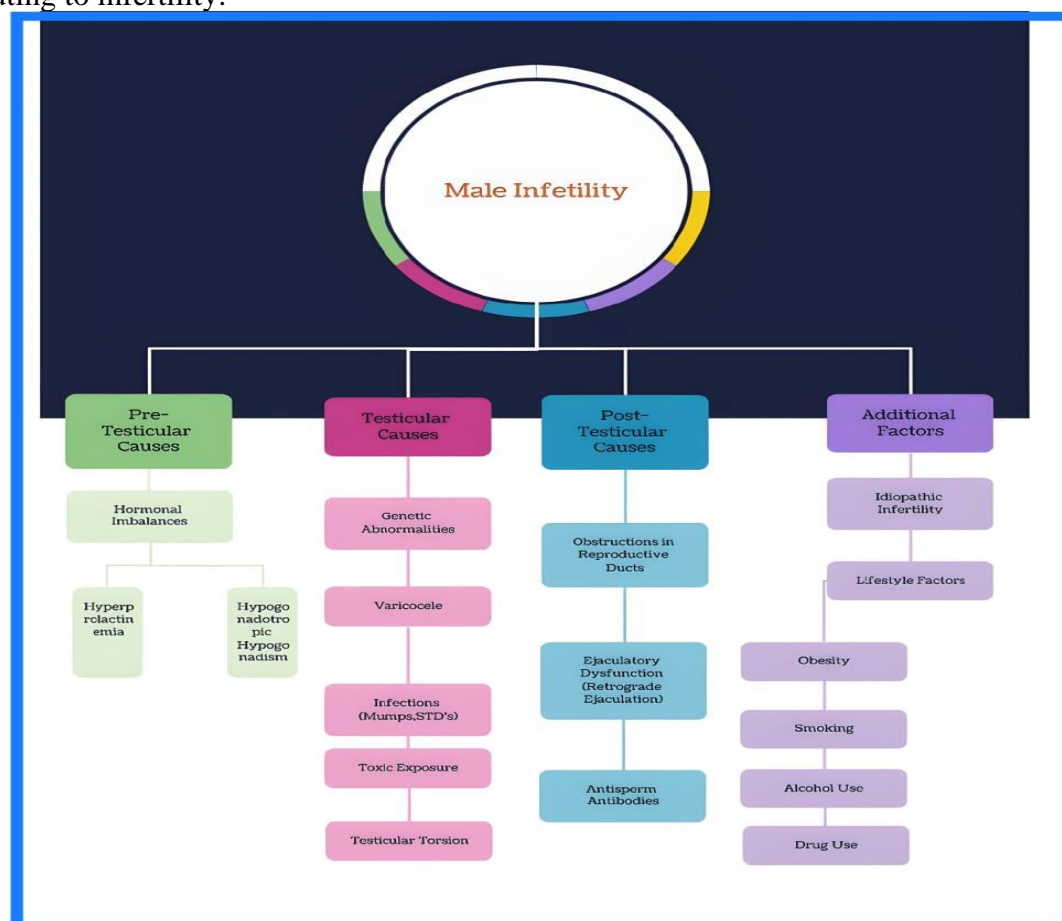
Spermatogenesis is a complex process involving the division and differentiation of germ cells,

which requires intricate communication between these developing germ cells and the somatic cells within the testes. Disruptions in hormonal signaling or inherent defects within the testes can negatively impact the progression of spermatogenesis, resulting in subfertility or infertility. In recent years, male infertility has gained attention as a global public health issue, and extensive research has shed light on its multifaceted causes. These include congenital reproductive abnormalities, genetic mutations, and disorders in endocrine or metabolic function, all of which have been linked to male infertility and subfertility.

Male infertility is a multifaceted condition with various causes, including genetic, environmental, hormonal, and lifestyle factors (Figure 1). It can be classified into different categories:

- Pre-testicular,
- Testicular, and
- Post-testicular.

Pre-testicular issues involve hormonal imbalances originating from the hypothalamus or pituitary gland, such as hypogonadotropic hypogonadism (where insufficient gonadotropin production impairs sperm stimulation) and hyperprolactinemia (where high prolactin levels interfere with gonadotropin release). Testicular causes include genetic abnormalities (like Klinefelter syndrome or Y chromosome microdeletions), varicocele (enlarged scrotal veins leading to increased temperature and oxidative stress), infections (which cause testicular inflammation and scarring), toxic exposure (to substances like pesticides or heavy metals), and testicular torsion (a twist in the spermatic cord cutting off blood supply). Post-testicular factors affect sperm transport and ejaculation, including obstructions in the reproductive ducts, ejaculatory dysfunction (such as retrograde ejaculation), and antisperm antibodies (which can cause sperm clumping or decreased motility). In some cases, the cause of infertility is unknown, termed idiopathic infertility. Lifestyle factors, such as obesity, smoking, alcohol use, and drug use, can also impact sperm production and quality. Additionally, age-related declines in sperm quality and quantity become more pronounced after age 40, contributing to infertility.



**Figure 1: Causes of male infertility**

**Diagnosis and Assessment:**

The diagnosis and assessment of male infertility involve a comprehensive evaluation to identify underlying causes and determine the most appropriate treatment strategies. The process typically includes the following steps:

**1. Medical History and Physical Examination**

- **Medical History:** Detailed history is obtained, including information about the patient's general health, sexual history, previous illnesses, surgeries, lifestyle habits (e.g., smoking, alcohol use), and exposure to environmental toxins.
- **Physical Examination:** A physical exam focuses on the reproductive system, assessing testicular size, consistency, and presence of abnormalities such as varicocele. Evaluation of the penis and scrotum is also conducted to check for signs of infection, trauma, or structural abnormalities. It includes patient interviews and a physical examination of the genital area, which encompasses assessing the prostate, anal sphincter tone, and bulbocavernosus reflex.

**2. Laboratory Tests**

- **Semen Analysis:** Semen analysis is a fundamental diagnostic procedure used to evaluate male fertility. This test assesses several critical parameters of the semen, including its volume, sperm concentration, motility, morphology, and overall quality.(12, 13) These factors provide insight into the functional capacity of the sperm to fertilize an egg. Typically, semen samples are collected after a period of 2-5 days of sexual abstinence to ensure the accuracy and consistency of the results.(14) The analysis can reveal potential issues such as low sperm count, poor motility, or abnormal morphology, all of which can contribute to infertility.
- **Hormonal Assessment:** Hormonal evaluation is another essential component of diagnosing male infertility. Blood tests are conducted to measure the levels of key hormones that regulate spermatogenesis, the process of sperm production. These hormones include testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin. Each of these hormones plays a critical role in maintaining the health and functionality of the testes and the overall reproductive system. Distinguishing between obstructive and non-obstructive infertility is crucial in assessing male infertility. In cases of obstruction, FSH levels are usually normal, and testicular volume is standard on both sides. However, it's important to note that 29% of individuals with normal FSH levels may still experience impaired spermatogenesis or spermatogenic arrest.(15) Abnormal levels can indicate underlying issues such as hypogonadism, pituitary disorders, or disruptions in the hormonal axis that may impair sperm production and function.
- **Genetic Testing:** Genetic testing is often recommended when infertility is suspected to have a hereditary component. This testing can identify chromosomal abnormalities that might be responsible for impaired fertility. Karyotyping is conducted for men exhibiting signs of primary testicular failure and small testes to confirm a clinical diagnosis of Klinefelter's syndrome. Klinefelter syndrome (47, XXY) is a chromosomal disorder that can significantly impact sperm production.(16) Additionally, testing for Y chromosome microdeletions is important, as these deletions can disrupt genes crucial for spermatogenesis.(17) Specific gene mutations, such as those associated with cystic fibrosis, may also be examined, as they can lead to congenital absence of the vas deferens or other reproductive anomalies that affect fertility.

A higher incidence of autosomal abnormalities, particularly balanced autosomal translocations, is associated with defective spermatogenesis. These translocations may be passed on to offspring in an unbalanced form.(18) Microdeletions in the AZF regions on the long arm of the Y chromosome have been identified in 3-15% of men with severe primary spermatogenic disorders.(19)

- **Antisperm Antibody Testing:** Antisperm antibody testing is used to detect the presence of antibodies in the blood or semen that target sperm cells.(20) Antisperm antibodies (ASA) were first identified as a cause of male infertility in 1954, and since then, several factors contributing to their production have been recognized.(21) These antibodies are generated when mature germ cells are abnormally exposed to the immune system. The WHO manual first described ASA testing methods, such as the mixed anti-globulin reaction and the immunobead binding test, in its 5th edition, and

these tests are now included among the extended semen tests in the 6th edition.(21) The link between ASA and infertility is complex. While sperm agglutination can suggest the presence of ASA, it is not definitive for diagnosing immunological infertility, as ASA can exist without visible agglutination. The management of ASA in male infertility is tailored to the underlying cause and varies based on individual clinical practices. In some cases, the immune system may mistakenly recognize sperm as foreign invaders and produce antibodies against them. These antibodies can impair sperm motility, hinder their ability to penetrate the cervical mucus, or cause them to clump together, thereby reducing their effectiveness in fertilizing an egg. Identifying the presence of these antibodies can help in diagnosing immunological infertility and guide appropriate treatment strategies.

- **Sperm functional tests:** Sperm functional tests are specialized evaluations that go beyond standard semen analysis to assess the ability of sperm to fertilize an egg. These tests provide critical insights into various aspects of sperm function, including penetration ability, acrosome reaction, DNA integrity, membrane functionality, and oxidative stress levels. Key tests include the Sperm Penetration Assay, Acrosome Reaction Test, Sperm DNA Fragmentation Test, Hypo-Osmotic Swelling Test, Reactive Oxygen Species Test, Zona Binding Assay, and Sperm Chromatin Structure Assay, all of which help diagnose potential issues affecting male fertility. The hypo-osmotic swelling (HOS) test assesses the integrity of the sperm membrane and its viability, while the acrosomal intactness (AI) test evaluates the acrosome's functionality and its capacity to penetrate the oocyte. The nuclear chromatin decondensation (NCD) test examines the sperm chromatin's ability to decondense after fertilization, and the sperm mitochondrial activity index (SMAI) test detects motility issues and defects in the flagella and mitochondria. Capacitation and sperm penetration assays are performed when sperm abnormalities are suspected. Inhibin B levels can provide insights into acrosomal activity, with elevated levels potentially indicating seminiferous tubule disorders or ductal obstructions that may lead to sperm self-destruction.(22)

### 3. Imaging and Other Diagnostic Modalities:

Imaging and other diagnostic techniques are crucial in assessing male infertility, offering detailed insights into the structural and functional aspects of the male reproductive system.(23) These methods help identify abnormalities or conditions that may contribute to infertility. Commonly used imaging techniques include scrotal ultrasound, which evaluates the testes and surrounding structures for issues such as varicoceles or testicular masses, and transrectal ultrasound (TRUS), which assesses the prostate and seminal vesicles for obstructions or abnormalities.(24, 25) Ultrasonography is valuable for detecting testicular tumors, especially in cases where the testes are challenging to palpate due to a tense hydrocele. In more complex cases, magnetic resonance imaging (MRI) provides detailed images of the reproductive organs. Additionally, testicular biopsy is employed to examine sperm production on a microscopic level, and vasography assesses the vas deferens for potential blockages. When combined with clinical evaluations and laboratory tests, these diagnostic tools offer a comprehensive approach to diagnosing and treating male infertility.

### The Role of Advanced Techniques in Male Infertility Evaluation:

Advanced techniques such as sperm DNA fragmentation and oxidative stress assessment play a pivotal role in the comprehensive evaluation of male fertility. Sperm DNA fragmentation tests are designed to measure the degree of DNA damage within sperm cells, a critical factor that can influence fertilization outcomes, embryo development, and the success rates of pregnancy.(26) High levels of DNA fragmentation are often linked to recurrent miscarriages and failed IVF cycles, making this assessment vital in identifying underlying issues that may not be apparent in standard semen analysis.

In addition to DNA fragmentation, oxidative stress assessment is another crucial advanced technique. This involves quantifying the levels of reactive oxygen species (ROS) within semen, as excessive ROS can lead to oxidative damage in sperm cells.(27) Such damage can negatively affect sperm motility, morphology, and overall viability, contributing to male infertility. Elevated

oxidative stress is recognized as a significant factor in male reproductive dysfunction, and its evaluation is essential for diagnosing and managing fertility issues that might otherwise go undetected.

### **Medical Approaches:**

#### **Pharmacological Treatments in Male Infertility:**

Hormonal therapy is a key pharmacological treatment for male infertility, especially when hormonal imbalances are present. Medications such as Clomiphene citrate, human chorionic gonadotropin (hCG), and follicle-stimulating hormone (FSH) are commonly used to address these imbalances. Clomiphene citrate, an oral drug, boosts gonadotropin production, increasing testosterone levels and supporting sperm production. hCG and FSH are administered via injections to directly stimulate sperm and testosterone production in the testes, particularly in cases of hypogonadotropic hypogonadism. Additionally, antioxidants and nutraceuticals play a role in mitigating oxidative stress, which can damage sperm DNA and reduce sperm quality. Supplements such as vitamins C and E, coenzyme Q10, selenium, and zinc protect sperm from oxidative damage, making them a vital component of strategies to improve sperm health. Combined, these treatments enhance sperm production and quality, significantly improving male fertility outcomes. To lower oxidative stress in infertile men, a variety of enzymatic and non-enzymatic antioxidants are employed to reduce reactive oxygen species (ROS) production. Glutathione peroxidase (GP) is a key component in the seminal enzymatic antioxidant system, working to reduce hydroperoxides through glutathione. This enzyme helps defend against oxidative damage; however, inhibiting it with mercaptosuccinate increases sperm lipid peroxidation, highlighting its critical role in protecting sperm.

Vitamin E, a lipid-soluble vitamin, enhances sperm motility by reducing malondialdehyde levels.(28) Carnitine supports sperm energy and motility by aiding fatty acid transport and reducing oxidation in mitochondria. Selenium is crucial for spermatogenesis, testicular development, and sperm motility while protecting sperm DNA from oxidative damage.(29) Low levels of CoQ-10 and ubiquinol in sperm and seminal plasma are linked to infertility; CoQ-10 supplements can improve sperm motility by reducing hydrogen peroxide.(30) Zinc is essential for sperm motility and semen concentration, stabilizing sperm cell membranes and chromatin.(31)

#### **Role of Assisted Reproductive Technologies (ART):**

Male infertility can be addressed through assisted reproductive technologies (ART) such as Intracytoplasmic Sperm Injection (ICSI), In Vitro Fertilization (IVF), and Intrauterine Insemination (IUI). Among these, ICSI is often the preferred method at most ART centers. In ICSI, oocytes at the metaphase-II stage are prepared by removing the corona radiata and cumulus cells with hyaluronidase. A single sperm, collected from the epididymis, ejaculate, or testis, is then injected into the oocyte's cytoplasm using a micropipette, while the oocyte is immobilized under oil. This injection process activates the oocyte and enhances fertilization, with sperm tail immobilization facilitated by positioning the micropipette and petri dish to prevent tail movement.(32) IUI involves depositing sperm directly into the uterus during ovulation to enhance fertilization chances, particularly helpful for issues like low sperm motility, low sperm count, unexplained infertility, or cervical factors. IUI is a relatively simple and minimally invasive procedure that can be combined with ovarian stimulation to boost success rates.

In vitro fertilization (IVF) involves retrieving multiple mature eggs from a woman, fertilizing them with a man's sperm in a laboratory, and then implanting the resulting embryos into the uterus after three to five days.(33) In zygote intra-fallopian transfer (ZIFT), the fertilized egg is placed directly into the fallopian tube, while in gamete intra-fallopian transfer (GIFT), sperm and eggs are mixed and introduced into the fallopian tube for fertilization. Intracytoplasmic sperm injection (ICSI), an advanced ART technique, involves injecting a single sperm directly into an egg using a microscope and micropipette, with the fertilized eggs then implanted into the uterus. IVF with ICSI has been shown to improve fertility outcomes, though further research is needed to assess potential risks to

offspring.(32)

### **Surgical Approaches:**

Varicocele repair addresses varicoceles, which can affect sperm production and lead to infertility.(34) It involves techniques such as microsurgical varicocelectomy, which uses high magnification to carefully ligate affected veins, and laparoscopic surgery, which offers a minimally invasive approach through smaller incisions.(35) Both methods aim to alleviate scrotal vein pressure and improve sperm quality, with high success rates and notable improvements in semen parameters. Sperm retrieval techniques are used when sperm is absent from the ejaculate but can be extracted directly from the reproductive tract. Methods include percutaneous epididymal sperm aspiration (PESA), which uses a needle to extract sperm from the epididymis, and testicular sperm extraction (TESE), which involves surgically removing testicular tissue.(36-38) Micro-TESE, a more advanced technique, utilizes microscopic methods to locate and extract sperm from testicular tissue.(39) Vasectomy reversal aims to restore fertility in men who have undergone vasectomy by reconnecting the severed vas deferens (vasovasostomy) or addressing blockages at the epididymal end (vasoepididymostomy).(40) Management of obstructive azoospermia involves surgical correction of ductal obstructions, such as transurethral resection of the ejaculatory ducts (TURED), to restore sperm flow and enhance the chances of natural conception or successful sperm retrieval for ART.

### **Comparative Analysis of Medical vs. Surgical Approaches**

**Indications for Each Approach:** Medical approaches are typically indicated for cases where infertility is due to hormonal imbalances or oxidative stress. Hormonal therapies are used when deficiencies or imbalances in reproductive hormones are identified, while antioxidants address oxidative damage to sperm.(41) Surgical approaches, on the other hand, are generally indicated for structural issues or blockages, such as varicoceles, obstructive azoospermia, or complications following vasectomy.(42, 43) Procedures like varicocele repair or sperm retrieval techniques are performed when physical abnormalities impact fertility.

**Success Rates and Outcomes:** The effectiveness of medical and surgical approaches can vary in the short-term and long-term. Medical treatments like hormonal therapy and antioxidant supplements may show improvements in semen parameters and fertility potential relatively quickly, but long-term success often depends on continuous management and addressing underlying causes. Surgical interventions, such as varicocele repair or sperm retrieval techniques, often provide more immediate results with significant improvements in fertility outcomes. However, the long-term effectiveness of surgery can be influenced by factors such as the underlying condition, the success of the procedure, and post-operative recovery. Both approaches have their roles, and their success rates can be complementary depending on the specific infertility issues being addressed.

**Risks and Complications:** Medical treatments may lead to side effects like hormonal imbalances, mood swings, or gastrointestinal problems due to medications. While antioxidant supplements are usually well-tolerated, they can occasionally trigger allergic reactions or interact with other drugs. Surgical options, although often effective, come with risks such as infection, bleeding, or anesthesia-related complications. Recovery periods can differ, with some procedures needing extended post-operative care and lifestyle changes. Assessing these risks and side effects is essential for choosing the most suitable method for addressing male infertility.

### **Emerging Treatments and Future Directions**

Gene therapy targets genetic causes of male infertility by correcting defective genes, using methods like CRISPR-Cas9 to potentially restore sperm production. Stem cell therapy seeks to regenerate sperm-producing tissues, using testicular or pluripotent stem cells to create sperm, though it remains experimental. Innovations in ART improve success rates with better sperm selection and enhanced

IVF/ICSI techniques, such as microfluidic sorting and advanced embryo monitoring. Personalized medicine customizes treatments based on genetic profiles, hormones, and lifestyle factors, aiming to enhance treatment effectiveness and outcomes in male infertility.

**Conclusion:** This review of medical and surgical approaches to male infertility highlights the multifaceted nature of the condition and the diverse strategies available for its management. Medical treatments, including hormonal therapies, lifestyle modifications, and advanced techniques like sperm DNA fragmentation analysis and oxidative stress assessment, have shown promising results in addressing various causes of male infertility. Similarly, surgical interventions, such as varicocelelectomy and corrective procedures for anatomical abnormalities, offer significant benefits for improving fertility outcomes in specific cases.

The integration of emerging treatments, such as gene therapy and stem cell therapy, alongside innovations in assisted reproductive technologies (ART) and personalized medicine, represents a forward-looking approach in managing male infertility. These advancements hold the potential to offer more targeted and effective solutions, tailored to individual patient profiles.

Overall, while significant progress has been made, continued research and clinical trials are essential to refine these approaches and improve their efficacy. By combining established treatments with emerging technologies and personalized care, the field of male infertility stands poised to offer new hope and enhanced outcomes for affected individuals and couples.

#### References:

1. Agarwal A, Baskaran S, Parekh N, Cho C-L, Henkel R, Vij S, et al. Male infertility. *The Lancet*. 2021;397(10271):319-33.
2. Vander Borgh M, Wyns C. Fertility and infertility: Definition and epidemiology. *Clinical biochemistry*. 2018;62:2-10.
3. Wu AK, Elliott P, Katz PP, Smith JF. Time costs of fertility care: the hidden hardship of building a family. *Fertility and sterility*. 2013;99(7):2025-30.
4. Boivin J, Bunting L, Collins JA, Nygren KG. International estimates of infertility prevalence and treatment-seeking: potential need and demand for infertility medical care. *Human reproduction*. 2007;22(6):1506-12.
5. Babakhanzadeh E, Nazari M, Ghasemifar S, Khodadadian A. Some of the factors involved in male infertility: a prospective review. *International journal of general medicine*. 2020:29-41.
6. Direkvand-Moghadam A, Delpisheh A, Khosravi A. Epidemiology of female infertility; a review of literature. *Biosci Biotechnol Res Asia*. 2013;10(2):559-67.
7. Quaas A, Dokras A. Diagnosis and treatment of unexplained infertility. *Reviews in obstetrics and gynecology*. 2008;1(2):69.
8. Naz M, Kamal M. Classification, causes, diagnosis and treatment of male infertility: a review. *Oriental pharmacy and experimental medicine*. 2017;17:89-109.
9. Cocuzza M, Alvarenga C, Pagani R. The epidemiology and etiology of azoospermia. *Clinics*. 2013;68:15-26.
10. Anwar S, Anwar A. Infertility: A review on causes, treatment and management. *Womens Health Gynecol*. 2016;5:2-5.
11. Velasquez M, Tanrikut C. Surgical management of male infertility: an update. *Translational andrology and urology*. 2014;3(1):64.
12. Vasan S. Semen analysis and sperm function tests: How much to test? *Indian journal of urology*. 2011;27(1):41-8.
13. Geneva S, Press W. WHO laboratory manual for the examination and processing of human semen. Cambridge: Behalf of the World Health Organization; 2010.
14. Alipour H, Van Der Horst G, Christiansen O, Dardmeh F, Jørgensen N, Nielsen H, et al. Improved sperm kinematics in semen samples collected after 2 h versus 4–7 days of ejaculation abstinence. *Human Reproduction*. 2017;32(7):1364-72.
15. Weber R, Dohle G, Romijn J. Clinical laboratory evaluation of male subfertility. *Advances in*



- clinical chemistry. 2005;40:318-64.
16. Staessen C, Tournaye H, Van Assche E, Michiels A, Van Landuyt L, Devroey P, et al. PGD in 47, XXY Klinefelter's syndrome patients. *Human reproduction update*. 2003;9(4):319-30.
  17. Chandley AC. Chromosome anomalies and Y chromosome microdeletions as causal factors in male infertility. *Human Reproduction*. 1998;13(suppl\_1):45-50.
  18. Martin R. Cytogenetic determinants of male fertility. *Human reproduction update*. 2008;14(4):379-90.
  19. Deng C-Y, Zhang Z, Tang W-H, Jiang H. Microdeletions and vertical transmission of the Y-chromosome azoospermia factor region. *Asian Journal of Andrology*. 2023;25(1):5-12.
  20. Silva AF, Ramalho-Santos J, Amaral S. The impact of antisperm antibodies on human male reproductive function: an update. *Reproduction*. 2021;162(4):R55-R71.
  21. Gupta S, Sharma R, Agarwal A, Boitrelle F, Finelli R, Farkouh Aa, et al. Antisperm antibody testing: a comprehensive review of its role in the management of immunological male infertility and results of a global survey of clinical practices. *The world journal of men's health*. 2022;40(3):380.
  22. Barak S, Baker HG. *Clinical management of male infertility*. 2015.
  23. Ammar T, Sidhu P, Wilkins C. Male infertility: the role of imaging in diagnosis and management. *The British journal of radiology*. 2012;85(special\_issue\_1):S59-S68.
  24. Freeman SJ, Parker PC. *Ultrasound of the Testes and Male Pelvis*. Abdominal Ultrasound E-Book: Abdominal Ultrasound E-Book. 2022:229.
  25. Lam IS, Trost LW, Casalino DD, Brannigan RE. Ultrasound in male infertility. *Ultrasound Imaging in Reproductive Medicine: Advances in Infertility Work-up, Treatment and ART*. 2019:213-35.
  26. Sakkas D, Alvarez JG. Sperm DNA fragmentation: mechanisms of origin, impact on reproductive outcome, and analysis. *Fertility and sterility*. 2010;93(4):1027-36.
  27. Robert KA, Sharma R, Henkel R, Agarwal A. An update on the techniques used to measure oxidative stress in seminal plasma. *Andrologia*. 2021;53(2):e13726.
  28. Matorras R, Pérez-Sanz J, Corcóstegui B, Pérez-Ruiz I, Malaina I, Quevedo S, et al. Effect of vitamin E administered to men in infertile couples on sperm and assisted reproduction outcomes: a double-blind randomized study. *F&S Reports*. 2020;1(3):219-26.
  29. Moslemi MK, Tavanbakhsh S. Selenium–vitamin E supplementation in infertile men: effects on semen parameters and pregnancy rate. *International journal of general medicine*. 2011:99-104.
  30. Lafuente R, González-Comadrán M, Solà I, López G, Brassesco M, Carreras R, et al. Coenzyme Q10 and male infertility: a meta-analysis. *Journal of assisted reproduction and genetics*. 2013;30:1147-56.
  31. Dissanayake D, Wijesinghe P, Ratnasooriya W, Wimalasena S. Effects of zinc supplementation on sexual behavior of male rats. *Journal of human reproductive sciences*. 2009;2(2):57-61.
  32. Zarinara A, Zeraati H, Kamali K, Mohammad K, Rahmati M, Akhondi MM. The success rate and factors affecting the outcome of assisted reproductive treatment in subfertile men. *Iranian journal of public health*. 2020;49(2):332.
  33. Elder K. In vitro fertilization. *Preimplantation Genetic Diagnosis*. 2001:53-78.
  34. Jarow JP. Effects of varicocele on male fertility. *Human reproduction update*. 2001;7(1):59-64.
  35. Ding H, Tian J, Du W, Zhang L, Wang H, Wang Z. Open non-microsurgical, laparoscopic or open microsurgical varicocelectomy for male infertility: a meta-analysis of randomized controlled trials. *BJU international*. 2012;110(10).
  36. Shah R. Surgical sperm retrieval: Techniques and their indications. *Indian Journal of Urology*. 2011;27(1):102-9.
  37. Leung A, Mira J, Hsiao W. Updates on sperm retrieval techniques. *Translational Andrology and Urology*. 2014;3(1):94.
  38. Esteves SC, Agarwal A. Sperm retrieval techniques. *Human assisted reproductive technology: future trends in laboratory and clinical practice*. 2011;1:41-53.

39. Alkandari MH, Moryousef J, Phillips S, Zini A. Testicular sperm aspiration (TESA) or microdissection testicular sperm extraction (Micro-tese): which approach is better in men with cryptozoospermia and severe oligozoospermia? *Urology*. 2021;154:164-9.
40. Marks SH. *Vasectomy reversal: manual of vasovasostomy and vasoepididymostomy*: Springer; 2018.
41. Torres-Arce E, Vizmanos B, Babio N, Marquez-Sandoval F, Salas-Huetos A. Dietary antioxidants in the treatment of male infertility: counteracting oxidative stress. *Biology*. 2021;10(3):241.
42. Persily JB, Thakker S, Najari BB. *Surgical Management of Male Infertility. Men's Reproductive and Sexual Health Throughout the Lifespan: An Integrated Approach to Fertility, Sexual Function, and Vitality*. 2023:113.
43. Lopushnyan NA, Walsh TJ. Surgical techniques for the management of male infertility. *Asian journal of andrology*. 2012;14(1):94.