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# PHARMACOLOGICAL THERAPIES FOR MALE INFERTILITY

**Makke Pavan*, M.Chaitanya Ch Babu Rao, Budagala Gayatri**

*Priyadarshini Institute of Pharmaceutical Education and Research, 5th mile, Pulladigunta, Guntur-522017, Andhra Pradesh, India*

***Corresponding Author**

Makke Pavan

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**Abstract**

Male infertility is a significant reproductive health issue, defined as the inability to conceive after one year of regular, unprotected intercourse. It accounts for approximately 50% of infertility cases in couples and is a primary indication for assisted reproductive techniques (ART). Among the various causes of male infertility, testicular failure is the most common but remains the least studied. Recent advancements in diagnostics and treatment approaches have provided new insights into its etiology and management. This review aims to provide a comprehensive, evidence-based summary of male infertility due to testicular failure, focusing on its causes, clinical assessment, and current therapeutic strategies for study examined various diagnostic and therapeutic approaches, including molecular diagnostics, genetic studies, hormonal treatments, and surgical interventions Male infertility is a multifactorial condition with diverse underlying causes, including genetic, environmental, anatomical, hormonal, and lifestyle factors. Testicular failure, characterized by impaired spermatogenesis, is a predominant cause, yet nearly 40% of cases remain idiopathic. Advances in molecular diagnostic tools, such as reactive oxidative species (ROS) analysis and DNA fragmentation assays, have improved the ability to assess sperm function, although these remain largely in the research phase. Diagnosis involves a combination of physical examination, semen analysis, hormonal profiling, testicular biopsy, and genetic screening to identify underlying abnormalities.

***Keywords***: Male infertility, testicular failure, spermatogenesis, assisted reproductive techniques, micro-TESE, hormonal therapy, DNA fragmentation, genetic factors, reproductive health.



## INTRODUCTION

Male factor infertility contributes to nearly 50% of all infertility cases and impacts approximately 15% of couples. Idiopathic infertility refers to infertility with no obvious or identifiable cause despite comprehensive assessment once the root cause is determined, medicinal treatments can be used to manage the European Association of Urology (EAU)'s guidelines on Male Sexual and Reproductive Health strongly advocate for medication to manage the pathophysiology of hypogonadotropic hypogonadism. However, the effectiveness of drug therapy for idiopathic male infertility is still uncertain [1].

Testicular endocrine and exocrine functions, such as testosterone production and sperm formation, are strictly controlled by the hypothalamic–pituitary–gonadal (HPG) axis. Elevated testosterone levels within the testes and the activation of Sterol cells by follicle-stimulating hormone (FSH) are essential for sperm development [2]. Male infertility results from irregular sperm characteristics in the male partner and accounts for 50% of all infertility cases. A recent systematic review indicated a 59.3% decline in total sperm counts since the 1970s across North America, Europe, and Australasia. Infertility is characterized by the failure to achieve natural conception after one year of consistent unprotected intercourse [3]. Globally, approximately 15% of couple's experience infertility, with 40-50% of cases linked to male factors. Male infertility is primarily categorized into azoospermia (AS) and coital infertility (CI) it is further divided into obstructive infertility (OI) and non-obstructive infertility (NOI) Sub-fertility refers to a delay in conception for a couple with no prior pregnancies, while secondary sub-fertility describes a delay in conceiving for a couple who have previously achieved pregnancy, even if it was unsuccessful, such as in cases of miscarriage or ectopic pregnancy approximately 30-67% of azoospermia (AS) cases are associated with epididymis blockage, often resulting from infections in the epididymis. Epididymis procedures, such as cyst excision, may lead to azoospermia, while

cryptorchidism refers to the failure of the testes to descend into the scrotum. This condition is observed in approximately 2-6% of newborns, and nearly 10% of infertile individuals are affected by cryptorchidism [4].

## ETIOLOGY OF MALE INFERTILITY

Genetic: Chromosomal irregularities impact both sex and autosomal chromosomes, leading to numerical or structural defects. Klinefelter's syndrome (KS) It primarily exists in two forms: non- mosaic 47XXY (80–90%) or mosaic 47XXY/46XY (5–10%) Semen analysis typically indicates azoospermia and may serve as the only observable phenotypic characteristic [11]. In a recent meta- analysis, one-fourth of adult men with KS who tested negative for mature sperm cells in testicular biopsy were found to have spermatogonia, suggesting a halt in sperm development Additionally, individuals with KS have been identified as having a higher likelihood of developing cardiovascular conditions, metabolic syndrome, diabetes mellitus, autoimmune disorders, and venous thromboembolis. These can be further categorized as balanced or unbalanced structural abnormalities. Balanced abnormalities are defined by alterations in chromosome structure without an overall loss or gain of genetic material [5]. Similar to other genetic factors contributing to male infertility, men with structural chromosomal anomalies should be provided with preconception genetic counseling and the opportunity for preimplantation genetic testing before utilizing ejaculated or testicular sperm in assisted reproductive technology (ART) .Y- chromosome microdeletions refer to the loss of specific genetic segments on the Y chromosome that contain essential genes for sperm production. These deletions are detected in men with severe oligozoospermia (sperm count below 5 million/ml) (3–7%) and azoospermia that leads to severe testicular tissue abnormalities, including Sterol cell-only (SCO) syndrome or complete spermatogonia arrest, where no sperm is identified during TESE in individuals with 46XXsyndrome [6].

## LIFESTYLE FACTORS OF MALE INFERTILITY

Smoking: Cross-sectional research indicates that unhealthy habits, including excessive alcohol consumption, smoking, and the use of recreational drugs, are linked to decreased fertility in men. Conversely a substantial portion of existing data originates from men seeking treatment at infertility clinics, which may not accurately reflect the impact of lifestyle factors on male fertility in the general population a meta-analysis involving 5,865 patients revealed a negative correlation between smoking and semen quality, with a significantly adverse impact on moderate and heavy smokers. Smoking is linked to reduced sperm motility and a higher incidence of sperm morphological abnormalities [7].

**Alcohol**: A meta-analysis of 16,395 men across 15 cross-sectional studies found that alcohol consumption was negatively linked to semen volume and sperm morphology, with a significant disparity between daily drinkers and occasional consumers. Recreational drug use, including
cannabis, anabolic steroids, and opioid misuse, is associated with impaired sperm quality, increased DNA fragmentation in sperm, and decreased male fertility [8].

**Caffeine**: The evidence regarding caffeine consumption and testicular dysfunction remains variable and uncertain. In in vitro studies using cultured human Sterol cells, excessive caffeine intake was found to diminish the antioxidant capacity of Sterol cells, leading to oxidative stress and damage [9].

**Physical activity**: Men who engage in regular physical activity have shown enhancements in semen quality. Therefore, structured and monitored exercise may boost reproductive health, particularly in individuals with coexisting conditions such as diabetes and obesity. Additionally, some research suggests that prolonged high-intensity strenuous exercise may negatively impact semen parameters compared to moderate-intensity work outs .

- Therapies to Enhance Spermatogenesis OF MALE INFERTILITY

**Hypothalamic Pituitary Testicular (HPT) Axis and the Role of Intra testicular**: Testosterone in Spermatogenesis

Gonadotropin-releasing hormone (Genre) is regulated by neuropeptides originating at the central level, which control its pulsatile secretion from the hypothalamus (Acevedo-Rodriguez et al., 2018). In response to this rhythmic release of Garth, the anterior pituitary gland secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Additionally, FSH, in conjunction with testosterone (T), acts on sterol cells to promote and enhance the production of sperm cells by germ cells within the seminiferous tubules (Miller et al., 2011). This process is illustrated in Figure 1, depicting the Hypothalamic-Pituitary-Testicular (HPT) Axis and the Role of Intra testicular Testosterone in Spermatogenesis [10].

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syndrome, diabetes mellitus, autoimmune disorders, and venous thromboembolism . These can be further categorized as balanced or unbalanced structural abnormalities. Balanced abnormalities are defined by alterations in chromosome illustrated in Figure 1, depicting the Hypothalamic-Pituitary-Testicular (HPT) Axis and the Role of Intra testicular Testosterone in Spermatogenesis [11].

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**Assessment of Male Infertility Due to Testicular Failure**

Testicular dysfunction is often identified incidentally during fertility assessments. A comprehensive medical history and physical examination, particularly of the testes, are essential for evaluating and addressing male infertility (Fig. 1). Identifying potentially reversible factors can offer therapeutic benefits to the couple (Table 5 and Fig. 1). Medical History: Assess the frequency of sexual activity and the duration of infertility It is important to review puberty development, previous fatherhood, and any history of undescended testes or recent infections affecting the genitourinary system.

Physical examination

Evaluate secondary sexual traits and signs of Klinefelter syndrome (KS), such as increased height, gynecomastia, and cognitive or learning difficulties. Confirm the urethral meatus position, as it indicates prenatal androgen deficiency. Testicular size should be measured using a Prade Figure 3. Treatment of choice for idiopathic male infertility Assessment of Male Infertility Due to Testicular Failure

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orchidometer, where a volume below 15 ml suggests hypogonadism or testicular dysfunction. Some men may have uncorrected cryptorchidism or a history of orchidopexy; a small, previously undescended testis is indicative of testicular failure [16]

Testicular Histology. A testicular biopsy is typically conducted alongside surgical sperm retrieval (refer to the section on 'Surgical Sperm Retrieval Techniques'). Histologically, spermatogenesis is categorized into four primary patterns: complete spermatogenesis, observed in normal testes and obstructive azoospermia; hypo spermatogenesis, where all cell types are present but in reduced numbers; maturation arrest, where sperm development halts at a specific stage; and Sertoli cell-only (SCO) syndrome, characterized by the absence of germ cells..

**Conclusion**

Infertility is influenced by both male and female factors, requiring thorough counseling and investigation of both partners. The rising prevalence of male infertility calls for urgent attention to its underlying causes. Male infertility has significant social and psychological impacts on couples, making it essential to focus on restoring reproductive health .Various medical, social, genetic, and environmental factors contribute to male infertility. Pharmacological treatments are effective only when the underlying etiology is known. Literature suggests that hormonal therapies are not widely used for idiopathic infertility due to inconsistent efficacy. In cases of treatment failure and idiopathy, assisted reproductive technologies (ART) are recommended, though they remain inaccessible to many due to high costs. Research has explored the potential of medicinal plants in treating male infertility, but they are not widely recommended due to a lack of clinical data on safety, efficacy, and adverse effects. Therefore, enhanced national and international collaboration is necessary to advance research in male reproductive health. Male infertility remains a complex issue with significant implications for affected couples. Despite advancements in ART, viable sperm remain essential for successful conception. Pharmacological therapies play a crucial role in managing male infertility, demonstrating varying levels of success in improving spermatogenesis. Hormonal treatments, such as gonadotropins, SERMs, and aromatase inhibitors, help restore hormonal balance in conditions like hypogonadotropic hypogonadism Non-hormonal treatments, including antibiotics and anti-inflammatory medications, target infections and inflammation, which negatively impact fertility. Antioxidant-based empirical therapies aim to reduce oxidative stress in semen. Emerging research highlights the role of intestinal microbiota in male reproductive health, showing its influence on systemic hormone regulation and spermatogenesis. Preliminary studies suggest that probiotics may enhance sperm quality and hormonal profiles, but further research is needed to confirm these findings .Despite the promise of pharmacological interventions, their effectiveness remains inconsistent due to the heterogeneous nature of male infertility and individual variability in treatment response. Future research should focus on identifying reliable biomarkers for diagnosing infertility, optimizing patient selection for targeted therapies, and developing personalized treatment protocols.

## AUTHOR CONTRIBUTIONS
All authors are contributed equally

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## DECLARATION OF COMPETING INTEREST
The Authors have no Conflicts of Interest to Declare.

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