

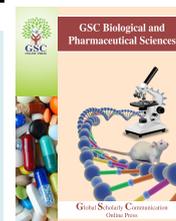


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(REVIEW ARTICLE)



## New perspectives in male infertility

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### Abstract

Male infertility refers to inability of the male partner to make a fertile female to get pregnant. In humans, it represents about 40–50% of cases of infertility. It occurs most frequently due to either decrease in the quantity of living spermatozoa or defects in semen quality. Causes of male infertility are variable, including pre-testicular, testicular and post-testicular factors. Diagnosis usually needs taking full medical history together with performing thorough physical examination and laboratory and radiological investigations. Management of male infertility is individualized according to the incriminated cause of infertility and the available methods of intervention. Recently, prognosis of cases of male infertility had significantly improved with the advancement in the methods of laboratory and radiological diagnosis together with the improvement in the assisted reproductive techniques. Further studies are needed to develop new techniques for management of resistant cases of male infertility.

**Keywords:** Infertility; Male; Diagnosis; Management; Perspectives

### 1. Introduction

Infertility is a distracting major health problem that affects the human beings especially when the cause of infertility is the male partner [1]. It is defined as inability of a sexually active couple not using contraception, to achieve pregnancy within one year of regular intercourse. Male infertility is usually attributed to deficiencies in the semen quality [2]. It accounts for about 30-40 % of overall cases of infertility and it affects approximately 7% of all males worldwide [3].

Normally, the hypothalamus secretes gonadotropin releasing hormone (GnRH) in a pulsatile manner to reach the pituitary gland which in turn secretes gonadotropins including follicle stimulating hormone (FSH) and luteinizing hormone (LH), which are targeting the testes [4]. FSH goes to the sertoli cells where it stimulates primary spermatocytes to undergo Meiosis I to secondary spermatocytes and then mature sperms [5]. Also, FSH stimulates the Sertoli cells to release androgen binding protein (ABP) which binds to testosterone that is released from Leydig cells preventing its metabolism to estradiol and also facilitates testosterone transport inside the seminiferous tubules. Moreover, FSH promotes the release of inhibin hormone which exerts a negative feedback regulatory effect at the pituitary level to decrease FSH release [6]. LH reaches the Leydig cells in the interstitial tissues between the seminiferous tubules where it stimulates the release of androgens (mainly testosterone). Any disturbance of the above regulatory mechanisms could lead to subfertility or even infertility in males [7]. This review sheds light on the novel perspective in male infertility regarding its etiology, methods of diagnosis, prognosis and possible lines of management.

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## 2. Etiology

### 2.1. Testicular factors

Testicular factors include conditions in which the testes produce sperms of low quantity and/or quality despite adequate hormonal support. They include varicocele which represents up to 35% of cases of primary infertility and 69-81% of cases of secondary infertility [8]. Other factors include age, genetic defects on the Y chromosome, Klinefelter syndrome, tumors such as seminoma, cryptorchidism, testicular trauma, mumps, hydrocele, infection with malaria, acrosomal defects affecting egg penetration and exposure of the testes to radiation therapy [9].

### 2.2. Pre-testicular factors

Pre-testicular factors include those which interfere with adequate support of the testes and include hypogonadotropic hypogonadism due to various causes such as obesity. Experimental models in animals indicated that the most common cause of leptin insensitivity in the hypothalamus is obesity, which responsible for decreased Kiss1 expression, which consecutively changes the release of gonadotropin-releasing hormone (GnRH) [10]. Also, undiagnosed and untreated coeliac disease can decrease semen quality and cause immature secondary sex characters, hypogonadism and hyperprolactinaemia which may lead to impotence and loss of libido. It is recommended that an effective evaluation for infertility must include assessment for underlying coeliac disease, both in males and females [11].

Medications such as anabolic steroids, chemotherapeutic agents, cimetidine, phenytoin, spironolactone and sulfasalazine may affect the spermatogenesis process, reduce FSH levels or markedly decrease sperm motility [12]. In addition to this, genetic abnormalities such as a Robertsonian translocation may be an important cause of male infertility [13]. Moreover, the harmful products of tobacco smoking may damage the testicles and kill sperms. Tobacco smoking was proven to increase the daily intake of cadmium, which may replace zinc in the DNA polymerase enzyme, which affects the process of spermatogenesis leading to serious damage to the testes [14].

Another pre-testicular factors that may be involved in the pathogenesis of male infertility are the common inherited variants in genes that encode enzymes involved in DNA mismatch repair leading to increased risk of sperm DNA damage and male infertility [15]. Recent studies revealed increasing amount of documented abnormal sperm DNA methylation in association with abnormal semen parameters and male infertility [16].

### 2.3. Post-testicular factors

Post-testicular factors may cause male infertility by affecting the male genital system after sperm production. They include defects of the genital tract as well as ejaculation dysfunction such as vas deferens obstruction, congenital absence of vas deferens, prostatitis, ejaculatory duct obstruction, retrograde ejaculation, hypospadias and impotence [10].

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## 3. Diagnosis

Diagnosis of male infertility necessitates taking full medical history and performing thorough physical examination by the physician in addition to laboratory and radiological investigations. Typically, two separate semen analyses will be needed in addition to blood tests to exclude hormonal imbalance, medical conditions or genetic defects [17].

### 3.1. Medical history

The history taken by the physician should include history of previous testicular or penile insults such as testicular trauma, torsion or cryptorchidism, infections such as mumps, orchitis or epididymitis, environmental factors, exposure to excessive heat or radiation, and intake of drugs that may affect spermatogenesis such as anabolic steroids, cimetidine, spironolactone or alcohol [18]. Similarly, asking the patient about his sexual habits, frequency and duration of the intercourse, use of lubricants during the sexual act and each partner's previous fertility experiences are extremely important for diagnosis of the precipitating factors for male infertility [9]. History of visual disturbances, headache or decreased libido may be strong indicative factors for diagnosis of a pituitary tumor. Previous history of thyroid or liver disease, diabetic neuropathy, hernia repair, radical pelvic or retroperitoneal surgery may be important to reveal any medical or surgical predisposing factors to male infertility. Also, family history may reveal possible genetic problems that may affect spermatogenesis [17].

### 3.2. Physical examination

The physician should perform a thorough examination of the external genitalia, urethra, urinary bladder, rectum and anus. Physical examination of the scrotum may reveal the presence of varicocele, tumors or abnormal cysts [19].

### 3.3. Laboratory and radiological investigations

Semen analysis is the golden laboratory investigation for diagnosis of male infertility. Volume of semen, total number of spermatozoa, sperm motility and the percent of abnormal forms of sperms are measured. This test may detect oligospermia, azoospermia, hypospermia, aspermia, teratospermia or asthenozoospermia. Low sperm counts are often associated with decreased sperm motility and increased abnormal morphology of the sperms [20]. Also, blood tests for determination of FSH, LH and testosterone levels may detect hormonal causes of male infertility. Genetic defects such as Klinefelter syndrome, Y chromosome microdeletion or cystic fibrosis may be revealed by examination of blood samples [21].

Scrotal ultrasonography may detect signs of testicular dysgenesis or testicular tumors. Also, decreased testicular vascularization detected by ultrasonography is characteristic of testicular torsion, while hyperemia is observed in epididymo-orchitis or in some malignant conditions such as lymphoma and leukemia [22]. Doppler ultrasonography useful in assessment of venous reflux in cases of varicocele. Ultrasonography can also detect dilation of the head or tail of the epididymis which is suggestive of obstruction or inflammation of the male reproductive tract. Scrotal and transrectal ultrasonography may detect congenital absence of the vas deferens which may be associated with abnormalities of the epididymis, seminal vesicles or the kidney [23].

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## 4. Prevention

Preventive measures are indicated for patients at risk of developing infertility such as heavy smokers and some industrial workers [24]. Some strategies were proposed to avoid male infertility including avoidance of smoking, avoidance of heavy marijuana and alcohol use, avoidance of exposure of the testes to excessive heat and maintaining optimal frequency of coital activity. Also, wearing a protective cup and jockstrap to protect the testicles is recommended in any sport in which the testes may be exposed to external trauma [25].

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## 5. Treatment

Lines of treatments vary widely according to the underlying disease and the degree of the impairment of the male fertility. Also, in any male infertility situation, the fertility of the female partner should be considered. Pre-testicular conditions can often be managed by medical treatment (Table 1) or surgical interventions [19]. Cases of male infertility in which testicular factors are the incriminated causes tend to be resistant to medical treatment. Management of these cases usually includes using the sperms for intrauterine insemination, in vitro fertilization (IVF) or IVF with intracytoplasmic sperm injection [26]. Obstructive causes of post-testicular male infertility can be managed with either surgery or IVF with intracytoplasmic sperm injection. Ejaculatory dysfunctions may be treated by either medical therapy, intrauterine insemination or IVF [27].

Antioxidants such as vitamin C, vitamin E, selenium, coenzyme Q10, L-carnitine and omega 3 fatty acids may help to relieve oxidative stress, which is considered as the main causative factor for DNA damage and decreased motility of the spermatozoa [28]. A combination of antioxidants with hormonal therapy may improve sperm count and motility and decrease abnormal sperm morphology [29]. Administration of LH or human chorionic gonadotropin and FSH is very effective in treatment of male infertility due to hypogonadotropic hypogonadism [30]. Although controversial, antiestrogens such as clomiphene citrate may be effective in management of male infertility by elevating gonadotropin levels [31]. Also, aromatase inhibitors such as anastrozole or testolactone may be effective for improvement of spermatogenesis [32]. Low-dose estrogen and testosterone combination therapy may improve sperm count and motility in some men, including those with severe oligospermia [33].

Recent studies had developed *in vitro* culture conditions using a three-dimensional agar culture system which induces mouse testicular germ cells to reach the final stages of spermatogenesis, including generation of spermatozoa [34]. If reproduced in humans, this might enable infertile men to father children with their own sperm [35]. Also, precursors of sperms from skin cells of infertile men were developed and might be a promising hope for management of male infertility [36].

**Table 1** Medical treatment of male infertility

Treatment option	Mechanism	Advantages	Disadvantages
Pulsatile gonadotropin-releasing hormone (GnRH)	Stimulate gonadotropin release from the pituitary gland	specific treatment option for male infertility due to hypogonadotropic hypogonadism (e.g., Kallmann's syndrome)	Failed as empirical therapy for idiopathic male infertility, expensive, invasive, require frequent change of needles, formation of anti-GnRH antibodies
Human chorionic gonadotropin (hCG)	Closely related to LH properties		Aromatase inhibitors may be added
Human menopausal gonadotropins (hMG)	Closely related to FSH properties		
Recombinant FSH and LH	Stimulate spermatogenesis		
Anti-Estrogens: Clomiphene citrate, Tamoxifene	Normal/high FSH and low or normal testosterone level	Inhibit negative feedback of estrogen on pituitary and hypothalamus, increases release of GnRh, FSH and LH which in turn stimulate spermatogenesis and steroidogenesis.	Elevate the T level as well as E2 which may decrease the extent of elevated T level so aromatase inhibitors may be added to clomiphene therapy
Aromatase inhibitors (2 types): Steroidal (testolactone) or Non-steroidal (Anastrozol, Letrozole)	Low testosterone and high aromatase enzyme activity converting T to E2	Used in infertility associated with obesity, hyperestrogeneamia and empirical in idiopathic infertility	Osteoporosis, Joint pain
Dopamine agonist (cabergolide, bromocryptine)	If high prolactin and low testosterone and gonadotropins	Used to treat cases of male infertility due to hyperprolactineamia	Failed to be used as an empirical treatment for idiopathic cases, headache, postural hypotension, nausea, and sleepiness
L-carnitines	Generating cellular energy via beta-oxidation by transporting fatty acyl groups across the inner mitochondrial membrane and inhibit lipid peroxidation.	In human, the concentration of free L-carnitine is highest in epididymal plasma and spermatozoa where it concentrated in both the free and acetylated forms and responsible mainly for sperm motility	
Coenzyme Q10 (ubiquinone)	A component of the electron transport chain, participating in aerobic respiration and the generation of energy.	It has direct anti-oxidant activity,	

Selenium	Selenium is a non-metal element that is an essential part of important anti-oxidant enzymes such as glutathione peroxidase.	Increases the levels of glutathione peroxidase and reductase in sperms.	
Bisolvon	Used in case of high viscosity impairing sperm movement for only 3 days no more		
Vitamin C (ascorbic acid)	natural antioxidant present in seminal fluid at concentrations 10 - 60 times the concentration in serum	Improve the DNA damage and breaks, decrease the abnormal forms of sperms.	
Zinc	cofactor for nearly 100 enzymes required for biologic processes such as DNA transcription and protein synthesis	Has membrane stabilizing effects, anti-apoptotic properties and acts as direct antioxidant	
N-acetyl cysteine (NAC)	precursor for reduced glutathione (GSH)	antioxidant	
Omega-3 fatty acids	Prevent lipid peroxidation		
Corticosteroids	20 mg of prednisolone twice daily for the first 10 days of their partner's menstrual cycle and then received 5 mg daily for days 11 and 12. The treatment period was 9 months	Useful in cases of Anti-sperm antibodies (ASA) interfere with sperm motility and sperm function	weight gain, generalized infections
NSAIDS	25 mg of COX-2 inhibitors (rofecoxib) daily for 30 days	Empirical therapy for infertile males with abacterial leukocytospermia.	
Phosphodiesterase-5 inhibitors (sildenafil, tadalafil, vardenafil)	Prevent the hydrolysis of cGMP, so increasing intracellular levels of cGMP this improves the sperm parameters especially the acrosome reaction	Male infertility due to erectile dysfunction, idiopathic male infertility	
Mast-cell stabilizers/ blockers (tranilast, ketotifen)	High levels of mast cells are present in semen fluid of infertile men	Improve sperm parameters, decrease semen WBCS count	
Parasympathomimetics (neostigmine, physostigmine)	Treatment of anejaculation	significantly more successful than alpha-agonists in treatment of anejaculation or infertility due to spinal cord injury	Neostigmine has been stopped due to invasive intrathecal delivery and side-effects as autonomic dysreflexia and cerebral hemorrhage. Physostigmine has less severe side-effects.

## 6. Prognosis

Prognosis of male infertility is variable depending on the underlying cause of infertility. The appropriate evaluation of the patients must be performed to determine the appropriate intervention needed for management of infertility. Prognosis is individualized depending on the results of evaluation and intervention [37]. In the last decades, the significant advancement in the methods of laboratory and radiological diagnosis together with the improvement in the assisted reproductive technologies had significantly improved the prognosis of cases with male infertility [38].

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## 7. Conclusion

Male infertility is an important medical condition that significantly affects the quality of life. Diagnosis of male infertility requires full medical history together with performing thorough physical examination. The possible lines of treatment mainly depend on the cause of infertility. Further studies are needed to develop new techniques for management of resistant cases of male infertility.

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## Compliance with ethical standards

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### *Disclosure of conflict of interest*

The authors have no conflict of interest to declare.

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