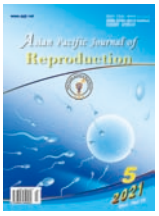

Review Article

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Male infertility: A scoping review of prevalence, causes and treatments

Kirati M. Shah, Kanan G. Gamit, Manan A. Raval, Niraj Y. Vyas✉

Ramanbhai Patel College of Pharmacy, Charotar University of Science and Technology (CHARUSAT), CHARUSAT Campus, Off. Nadiad-Petlad Highway, PIN 388421, Dist. Anand, Gujarat, India

ABSTRACT

Male factor infertility has now become a major health disorder, affecting human reproduction and developing worldwide as a serious medical and social issue. It causes trauma, emotional instability, and mental stress in the affected couples. In nearly half of the analyzed cases, male-associated factors are the major contributors. The present review outlines a wide range of factors responsible for male infertility. We performed an in-depth literature review of the global index of infertility by using data from World Health Organization's website, Elsevier's, PubMed and Scopus databases as well as journals. The quality and quantity of semen, male hormonal imbalance, genetic deterioration, and reactive oxygen species are the fundamental causes of male factor infertility. In addition, air quality, water quality, noise pollution, lifestyle changes, improper diet consumption, malnutrition, exposure to chemicals and toxins, smoking habits, drug abuses, major diseases, and medications are also contributors to infertility issues that can temporarily or permanently influence male reproductive system. We also reviewed the prevalence of male infertility in different countries.

KEYWORDS: Male infertility; Aphrodisiac; Spermatogenesis; Male sexual disorder; Erectile dysfunction; Libido; Sexual desire; Prevalence

1. Introduction

As per the report of World Health Organization (WHO) constituted International Committee for Monitoring Assisted Reproductive Technology, infertility is a disease of the reproductive system defined by an inability to accomplish the clinical pregnancy after 12 months or more of standard unprotected sexual intercourse by a couple[1]. It is a physiological condition affecting nearly about 70 million people worldwide. The WHO has estimated that around 9% of partners are suffering from fertility concerns, out of which male factor contributes to nearly 50%[2]. At the point when a man has a few ordinary boundaries for semen and sperms, even though sexual dysfunction may prompt the condition of infertility.

Male infertility is defined as the inability of a male partner to accomplish a pregnancy in a fertile female partner[3]. The male factor infertility might be a direct result of abnormalities in seminal fluid or sperm. At the point when the concentration of sperms comes under 20 million per mL of in seminal fluid, the male is considered infertile[4]. Sperm abnormalities and male sexual disorders are two major reasons for male factor infertility. Sperm motility is the prime functional parameter that decides the fertilizing capacity of spermatozoa. A fundamental loss of sperm motility might be attributed to either hormonal, biochemical, immunological, or infection reasons[5-7]. Male sexual disorders are classified as disorders of desire, erectile dysfunction, disorders of ejaculation, and failure of detumescence[8]. It can happen either as an isolated disorder or together with other complex disorders or syndromes[9].

This review article includes reports and published studies from 1985 to 2020. This scoping review was prepared by searching Elsevier's, PubMed, and Scopus databases as well as various reputed journals of subjects covering areas of fertility, reproduction, reproductive biology, sexual desire and libido. Some of the names of journals from where the data are collected include *Fertility and Sterility*, *Journal of Human Reproduction Sciences*, *Human Reproduction*, *American Journal of Medicine*, *Fertility Research and Practice*, *Asian Journal of Andrology*, *etc*. Keywords were selected based on medical subject heading terms and included (but not

✉To whom correspondance may be addressed. E-mail: nirajvyas.ph@charusat.ac.in

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limited to): "Reproduction OR fertility OR infertility OR male infertility OR sperm count OR sperm debility OR sperm motility OR libido OR sexual desire OR erectile dysfunction OR erection OR ejaculation OR sperm morphology OR azoospermia OR aspermia OR teratozoospermia OR asthenozoospermia OR sexual behaviour. Databases were searched and articles were screened for the availability and authenticity of data. Then duplicate articles and reports were screened and a total of 79 reports and articles were used to gather and compile the reports. Data pertaining to the causes and treatment of male infertility are fetched from review articles published in international journals. Data on the prevalence of male infertility in specific countries were taken from research carried out on male infertility in specific regions. Those findings were published as either research or review articles in various national and international journals.

2. Causes of infertility

2.1. Quality and quantity of semen

Male infertility is directly connected to the quality and quantity of spermatozoa present in seminal fluid. The accomplishment of mating depends on the characters and numbers of sperms conveyed to a lady and the ability of a sperm to reach the site of fertilization or the capacity of fertilizing sperm to complete the fertilization cycle. Sperm issues vary from the abnormalities in sperm numbers and characters delivered to sperm discharge. Over 90% of cases reported are the direct output of less than the required sperm numbers and/or poor sperm attributes[10].

Sperm abnormalities can be brought about by various elements, starting from intrinsic birth defects and genetic disorders to way of life propensities and natural presentations. In many instances, the reasons behind sperm abnormalities are unknown; however, quality of sperm can be examined by various parameters like sperm motility, sperm viability, developmental stage, sperm gross morphology, and sperm tail membrane integrity[11].

2.2. Hormonal imbalance

Gonadotropins and related sex hormones exhibit a significant and focal role in growth, improvement, digestion, and proliferation. The hypothalamus and the pituitary gland present in the human brain panels, the major two functions of testes: production of spermatozoa (spermatogenesis) and synthesis of testosterone (steroidogenesis). A negative mechanism on hormone synthesis is controlled by hypothalamic gonadotropin-releasing hormone (GnRH) and pituitary gonadotropin discharge[12].

2.3. Genetic causes

The genetic cause of infertility has received increasing attention nowadays. A few sorts of chromosomal defects are directly related to infertility. Out of some of the processes in genetic transformations, translocation is the most common type of chromosomal irregularity[13]. An investigation demonstrated that the recurrence of chromosomal translocation was 2.1% in infertile men[14]. Chromosomal translocation can be of numerous kinds: Robertsonian translocation, reciprocal translocation, and these records for 10% of the reasons for male infertile[15]. Genetic damage in sperm can happen at a few levels, all of which can cause infertility in men[16]. Sperm DNA is responsible for the make-up of half the portion of the genomic material to offspring. Thus, regular sperm genetic make-up is essential for fertilization, embryo and fetus development, and subsequent child wellbeing after birth[17].

2.4. Oxidative stress

Reactive oxygen species (ROS) are exceptionally super active oxidizing operators that have a place with the class of free radicals. ROS-created inside semen plays sperm pathological and physiological functions in male fertility. Oxidative stress is considered as one of the major causative factors for ROS-initiated male infertility. It happens because of awkwardness among ROS and total antioxidant capacity inside the body and prompts sperm harm, deformation and in the end male infertility[18].

2.5. Lifestyle factors

Tobacco chewing and smoking are responsible for DNA damage and lead to a generation of ROS. An interesting investigation demonstrated that teratozoospermia was found in 63% of males who drink alcohol moderately while the percentage was found 72% in males who drink alcohol heavily. None of the males who consume heavy alcohol was having normal sperm parameters. In fact, 64% of them were oligozoospermic *i.e.* having less sperm count than the normal count. Hence, it was suggested that incremental testicular damage is directly increasing with day-by-day alcohol consumption[19].

Hallucinogenic drugs like cannabis, cocaine, anabolic steroids, opiates, and amphetamines have a deteriorating effect on male fertility through impairment of the hypothalamic-pituitary-gonadal (HPG) axis, testicular histology, sperm parameters, and sperm functions[20].

Studies have also indicated that around three forth of caffeine consumers were observed with a slight increased in semen volume as compared to non caffeine consumers. In other sides, studies also confirmed that sperm motility was significantly improved in males who consumed 6 cups of coffee[21].

Obesity is also a major contributory factor indicated with the prevalence of low seminal discharge volume, low sperm concentration, and low total sperm count very commonly found in overweight and obese men[22]. The presence of ample white adipose tissue in obese people makes prolonged conversion of testosterone and influences the HPG axis, leading to a decrease in gonadotropin release and diminished spermatogenesis[23].

Diet also plays a pivotal role in male infertility. Studies indicated that regular overconsumption of prepared meat, fatty dairy products, alcoholic beverages, coffee and aerated and non-aerated sweet drinks are prone to produce sperms with poor semen quality[24].

Men under serious mental stress levels had diminished levels of testosterone and more levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) than men with normal levels. Consequently, decreased sperm counts, sperm morphology, and motility were found. Further, disturbance in sleep patterns may possibly produce adverse effects on male fertility as evident by a decrease in semen volume[25].

2.6. Environmental factors

The evidence is enough to show the deteriorating effects of poisons such as glues, volatile organic solvents, silicones, chemical dust, and pesticides on male fertility. Radiations and exorbitant warmth to the genital organs have a damaging impact on the testicles. Consequently, people exposed to such synthetic compounds have high chances of having primary or secondary infertility[26].

2.7. Systemic and iatrogenic causes

Many general clinical issues are related to male infertility, either directly or indirectly as an outcome of systemic disturbance, or as a result of clinical intervention on account of the primary disease. This contains anti-androgens, steroids, radiotherapy, and chemotherapy, particularly alkylating agents for hematological disease[27].

3. Prevalence of male infertility and disorders

The WHO estimates that around 9% of couples on the globe are affected by fertility problems, out of which almost half of the cases are due to male factor infertility. It also estimates that the general prevalence of primary infertility ranges between 3.9% and 16.8%[28]. The present review summarizes the prevalence of male factor infertility in different countries. Male infertility affects couples worldwide and India is not an exception. Studies carried out in the Indian population indicated that infertility is broadly found among Indian states, ranging from 3.7% in Uttar Pradesh, Himachal Pradesh, and Maharashtra, to 5.0% in Andhra Pradesh, and 15.0% in Kashmir[29,30]. The results of ongoing studies on the status of infertility in India express that almost 40% of infertility cases are attributed to male factor infertility[31]. The cross-sectional study carried out in Pakistan showed that infertility is a typical issue influencing about 21.9% of the Pakistani population with 3.5% primary and 18.5% secondary infertility. The two accomplices are discovered to be infertile in 30% of the cases, while the male factor is responsible for infertility in 20% to 25% of the couples[32].

In Nepali males, the prevalence of male infertility is around 45% in men aged 31-35 years. In males, the indications of infertility are oligozoospermia (17.5%), azoospermia (5.5%), and hydrocele (7.0%), and mumps orchids (6.0%). The prevalence of male infertility differed markedly by age, ranging from 27.28% in men aged 36-40 years to 9.09% in men aged 41-45 years[33]. Studies carried out in Bangladesh indicate that out of 60% of cases of infertility, males are found responsible fully or partially as a major contributory factor for infertility. Studies also demonstrated that out of the infertile male, the percentage of prevalence of azoospermia, oligosparmia, asthenospermia, and teratospermia was found 40%, 34%, 5%, and 1%, respectively, and the rest of the cases were designated as unexplained infertility[34]. The overall occurrence of sexual dysfunction was found at 5.5% in Afghanistan as evident by a clinical study. The study also categorized infertility by age group and indicated that 3.6% cases were in males aged 18–40 years and 15.7% cases were in males aged > 40 years[35]. A similar kind of study was also performed on 327 patients in Sri Lanka. Results found that 153 patients (73.9%) were having zero sperm count while 54 patients (26.1%) were suffering from severe oligozoospermia and 120 were healthy males designated as the controls. All 153 azoospermic patients had a nonobstructive etiology as evident by a standard clinical evaluation process. The age group of infertility was ranging from 25 to 35 years with a mean age of 34.8 years having a standard deviation of 5.34. Further studies also demonstrated the direct impact of a history of family members with infertility, medical history of varicocele and cryptorchidism, and habit of smoking and alcohol consumption on infertility[36].

A few investigations have investigated the study of the epidemiology of erectile dysfunction by thinking about various settings and populaces in Europe. It was found that erectile dysfunction was a very common condition in older men. The study indicated a prevalence of 52% cases of mild to moderate erectile dysfunction in men between the age group of 40 to 70 years. Furthermore, it was also found that erectile dysfunction was clearly related to age, health status, and emotional function of men too[37]. Interestingly, other studies conducted on men aged 40 to 79 years found the prevalence of 6% to 64% of erectile dysfunction which has a direct relation with increment in age[38]. The general commonness of erectile dysfunction in the overall US male populace aged 20 years and older was 18.4%. Applying this incentive to the 2 000 census gauges for men aged 20 and older recommends that there are 18 million men in the US with erectile dysfunction. The commonness of erectile dysfunction varied especially by age, ranging from 5.1% in men aged 20-39 years to 70.2% in men aged 70 years and older[39]. Data

on infertility in Australia are not very clear but as per the reports available, male factor infertility in Australia contributes to 40% of total infertility. Statistics data showed that among the males aged 40 years and more, 8% of whom have been reported to try to have children with failure and 9% are reported with infertility when tested clinically[40]. In Africa, 35.5% of couples had male infertility as per reports. In males, the male infertility was mostly due to azoospermia (26.41%), oligozoospermia (15.85%), asthenozoospermia (17.96%), and teratospermia (5.28%)[41].

4. Treatment

Wellbeing advancement and disease counteraction measures can potentially prevent male infertility. These measures include physical exercise and sports, safety precautions to protect genital organs and appropriate vaccinations in childhood. Male infertility treatment is resolved by the causative elements.

4.1. Assisted reproductive technology

In vitro fertilization (IVF) is considered as one of the most promising options for fertilization techniques available. It is mostly applied in cases where the sperm counts are less than 20 million with reasonable motile sperms. The process of IVF involves five steps starting from the collection of eggs, collection of sperms, observing and assisting the growth of healthy eggs in ovaries, a fusion of nurtured egg and healthy motile sperms in the laboratory by providing the appropriate condition. It also extends to early embryo organism development followed by transplanting the undeveloped organisms into the female uterus[42].

This therapy begins with the allocation of medicines to control egg development and to enhance the chance of collection of numbers of eggs during the female menstrual cycle. This step is followed by acquiring sperms by ejaculation. Subsequently, sperms and eggs are arranged in close contact in incubators in an artificial environment in the laboratory to enable ensured fertilization. In some circumstances where fertilization does not occur spontaneously, a newer technique called intracytoplasmic sperm infusion (ICSI) may be helpful. The eggs are observed closely to ensure that fertilization has taken place and cells are being divided. They are considered as embryos after effective fertilization. Once developed, these embryos are normally transplanted into a women's uterus where embryos are grown into various phases of pregnancy[43,44].

4.2. Hormonal treatment

4.2.1. Gonadotropin releasing hormone (GnRH)

The pulsatile delivery of GnRH in the nerve hypothalamus stimulates the delivery of FSH and LH from the anterior pituitary. In men, normal levels of FSH and LH are liable for the enlistment of spermatogenesis and keeping up elevated levels of testicular testis[45]. Pulsatile administration of GnRH is a successful treatment to supplant GnRH inadequacy in infertile men with hypogonadotropic hypogonadism because of lack of secretion from the hypothalamus. The objective of GnRH treatment is to invigorate the arrival of gonadotropins from the anterior pituitary and resulting pathways in the HPG[46]. The most effective dose for pulsatile GnRH is a dose between 5-20 μg each one to two hours conveyed by a subcutaneous pump or needle[47].

4.2.2. Pulsatile gonadotrophin delivering hormone (GnRH)

Pulsatile GnRH treatment is an elective treatment of hypothalamic-induced gonadotrophin deficiency[48]. GnRH is regularly regulated in dosages extending from 5 to 20 mg/120 min subcutaneously. Intranasal or parental GnRH organization can keep up a previously prompted spermatogenesis and lead to natural pregnancy[49]. Even though pulsatile GnRH treatment offers want to patients with gonadotrophin deficiency caused by loss of hypothalamic function, the inconvenience of its administration makes this method clinically impracticable[50].

4.2.3. Androgen therapy

Endogenous testosterone has major effects on spermatogenesis regulation. Nonetheless, external testosterone can induce a negative feedback mechanism promoting inhibition of the pituitary gland secretion and thereby inhibit spermatogenesis. It is given in injection form either as testosterone phenyl propionate or enanthate or a blend of their esters[51,52].

4.3. Dopamine agonist

Dopamine receptor agonists re-establish reproductive functions in many cases. The initial dose of bromocriptine ranges from 0.625 to 1.250 mg daily, with a standard range for a maintenance dose of 2.5–10.0 mg daily. For cabergoline, the initial dose ranges from 0.25 to 0.50 mg week after week, with a maintenance dose at 0.25–3.00 mg week by week[53,54].

4.4. Herbal treatment

Herbal medicines play a significant role in the management of male infertility. The studies have reported that the aqueous extract of *Cardiospermum helicacabum* improved numbers of sperm, motility of sperm, implantations frequencies, and viable embryos at 100 and 200 mg/kg dose levels in a dose-dependent manner[55]. Likewise, another study carried out on Chinese plant, Ginseng root (*Panax quinquefolius*) improves overall fertility. While Indian medicines, Chhota gokhru (*Tribulus terrestris*) through studies indicated that the aqueous extract could enhance sperm count, sperm morphology, and sperm motility[56]. In 2020, some Indian scientists worked on an Ayurvedic formulation "Ashwagandhadi Lehya" investigating

for its aphrodisiac and spermatogenic potential and found that this formulation had a significant effect on rat Leydig cells for the production of testosterone through *in vitro* studies, containing *Withania somnifera* as one of the major constituents[57]. In 2020, studies also planned and investigated quantitative estimation of scopoletin, a major bioactive constituent, from *Argyreia speciosa* (L. f.) sweet by a validated high performance thin-layer chromatographic method. It also showed that methanolic extracts of the roots were capable enough of promoting serum testosterone content *in vitro* and *in vivo* in rats *via* upregulation of testosterone synthesis in experimental animals[58]. In 2019, Niraj *et al*[59] investigated aphrodisiac and spermatogenic potential of unsaponifiable fraction from seeds of *Hygrophila spinosa* T. Ander in rats and found that the fraction could be able to increase the testosterone levels locally as experimented using the isolated rat Leydig cells *in vitro*. In another study, Manan *et al*[60] worked up on estimation of Withaferin-A, a biomarker of Aswagandha plant, from Ashwagandhadi Lehya formulation, highly reputed ayurvedic formulation traditionally acclaimed marketed product, by using high performance liquid chromatography (HPLC). One of the major components of Ashwagandhadi Lehya is *Withania somnifera* (Ashwagandha) which contains Withaferin-A, and it can be used in the treatment of sexual dysfunction[60]. In 2019, researchers also worked on isolation and chemical characterization of a bioactive alkaloid from one of the Ayurvedic plant, *Argyreia speciosa* Linn. which exhibited positive action on isolated rat Leydig cells. Results showed 22-fold increase in testosterone level in the treatment group and isolated compound had the ability to stimulate Leydig cells to secrete testosterone. Later on, through spectroscopic studies, it was found that the isolated compound was characterized as N-methylergometrine[61]. In 2016, another study focused on aphrodisiac and spermatogenic potential of alkaloidal fraction of *Hygrophila spinosa* T. Ander in rats, and the alkaloid enriched fraction was assessed for spermatogenic activity by using isolated rat Leydig cells and showed an increased amount of testosterone[63]. In 2018, Gamit *et al*[62] developed reversed-phase HPLC method for the estimation of guggulsterone-Z in *Gokshuradi guggulu*. The later is a formulation used in the treatment of dysuria, urinary obstruction, excessive vaginal discharge, gout, as spermatogenic, and vitiation of semen. In 2016, Vyas *et al*[64] worked on assessment of effect of unsaponifiable fraction prepared from seeds of *Hygrophila spinosa* T. Ander on testosterone production of rat Leydig cells *in vitro*, and results showed that isolated rat Leydig cells treated with the test fraction showed increased amount of testosterone level. In 2015, quantification of two marker compounds, β-sitosterol and lupeol, from unsaponifiable matter of *Hygrophila spinosa* seeds was taken up using validated TLC-densitometric method and those two compounds were reported for the activity of male infertility[65] as evident from biological studies *in vitro* and *in vivo*. These are some of the recent reports showing studies carried out on traditional plants for aphrodisiac and spermatogenic activity.

4.5. Anti–oxidant food supplements

The reason behind the utilization of antioxidant supplements in the treatment of male infertility lies in the way that sperm are a lot vulnerable to oxidative stress-induced damage. It has been recently detailed that men with significant degrees of ROS may very well suffer from low fertility compared to men with lower ROS levels[66,67]. Various antioxidants are prescribed by clinicians to their patients with low cost and relatively low risk of toxicity.

1) Carnitines: Carnitine is a water-soluble antioxidant agent mostly derived from the human eating routine that may assume a function in sperm energy metabolism and give the essential fuel to sperm motility. Carnitines improve the cell energetics in mitochondria by encouraging the passage and use of free unsaturated fats inside the mitochondria and furthermore reestablish the phospholipid creation of mitochondrial membranes by decreasing fatty acid oxidation[68,69].

2) Vitamin E: The daily necessity of vitamin E (a-tocopherol) fluctuates from 50 to 800 mg, depending upon the admission of natural products, vegetables, tea, or wine. Vitamin E is a significant lipid-soluble antioxidant agent particle in the cell membrane. It is thought to intrude on lipid peroxidation and upgrade the movement of different antioxidant agents that scavenge free radicals produced during the univalent decrease of molecular oxygen and during the normal activity of oxidative catalysts[70,71].

3) Vitamin C: Vitamin C (ascorbic acid) is a water-soluble vitamin that scavenges ROS. It is found 10 times in higher concentrations in seminal fluid than serum, thus protecting human sperms against endogenous oxidative harm by neutralizing hydroxyl, superoxide, and hydrogen peroxide radicals and preventing sperm agglutination[72,73].

4) Selenium (Se): Se may protect against oxidative sperm DNA damage and is required for normal testicular development, spermatogenesis, motility, and capacity[74].

5) Carotenoids: Carotenoids work synergistically with Se and vitamin E and have a suggested dietary recompense estimation of 1 000 mg for every day[75].

6) Glutathione: Glutathione is the most versatile reducing agent found in the body, which protects lipids, proteins and nucleic acids being getting oxidized from various ROS. It combines with vitamin E and significantly improves sperm movement[76].

7) N-acetyl cysteine: N-acetyl cysteine replenishes glutathione while scavenging free radicals and reducing ROS production in human discharge[77].

8) Pentoxifylline: Pentoxifylline is a potent phosphodiesterase inhibitor drug that increases intracellular cyclic adenosine monophosphate, hence acting as an erectile stimulating drug. Pentoxifylline also decreases ROS reactivity and protects sperms from losing motility and improves various sperm parameters[78].

9) Trace metals: Zinc and copper are the two most important metals which are needed to regularize functioning of various antioxidant enzymes superoxide dismutase to counteract the ROS produced in the body which are likely to damage sperms and other organs[79].

5. Conclusions

Male infertility is a slowly developing health condition in the 21st century with changes in lifestyle, food habits, and developing stress in busy work schedules. It is an abnormal condition generally characterized by loss of sperms, low sperms count, decreased sperm motility and viability, sperm physical defects, and sometimes the absence of sperms in the seminal fluid as well. The results of the above condition lead to infertility and non-fertilization of female eggs, which ultimately leads the couple to devoid of their offspring. A healthy lifestyle is a key to healthy sperm and subsequent fertility. The abnormal condition can be corrected by a healthy lifestyle, healthy food, and regular exercise, or by medications. The present review comprehends all factors responsible for male factor infertility, with a special focus on the prevalence of male infertility in different regions of the world like South East Asia, Europe, USA, Australia, and Africa. In totality, the quality and quantity of semen, sperm count, imbalanced hormonal levels, inherent genetic damages, oxidative stress and ROS are the basic causes of male infertility as major contributors. Other than these factors, some minor reasons also include pollution, changed lifestyle, improper diet and malnutrition, exposure to chemicals and toxins, smoking habits and drugs' addictions, diseases, and medications may also contribute to infertility issues.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Author's contributions

Collection of data related to male infertility and its prevalence worldwide was carried out by Kirati M. Shah while Kanan G. Gamit worked on data validation of herbal medicines in male infertility. Data pertaining to treatment, and etiology of male infertility were carried out and enhanced by Manan A. Raval while overall organization of article, proof check, grammar check, and revisions part were carried out by Niraj Y. Vyas.

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