Review Article
Open Access
CrossMark

Recent advances in the diagnosis and genetic understanding of male infertility: implications for assisted reproductive technologies

Abstract

About 7% of males worldwide suffer from male infertility, a complex disorder marked by the inability to conceive with a partner after a year of unprotected sexual activity. Male infertility has a wide range of causes, such as lifestyle choices, physical barriers, hormone imbalances, and genetic abnormalities. The quality of semen is essential for preserving spermatozoa's capacity to fertilize. The quality of male semen is falling among men in Africa, Europe, North America, and Asia, contributing to the growing global issue of male infertility. Even after developing proactive defenses during spermatogenesis and epididymal maturation, the sperm are still susceptible to harmful insults. Infertility is largely caused by declining semen quality. Scientists have created a variety of treatments for male infertility over time. Male infertility that has a recognized reason can be effectively treated, but other causes, such as genetic factors, call for practical solutions. The best possible reproductive and developmental results could be achieved by combining these cutting-edge strategies in a global, multicentric context while obtaining the appropriate ethical approval. The creation of molecular stratification classes, diagnostic markers, and individualized treatment plans ought to be possible using these combinatorial methods. Because environmental factors and lifestyle choices affect male fertility, they must be incorporated into any comprehensive strategy for safe, proactive, cost-effective, and noninvasive precision male infertility theranostics that are accessible, affordable, and help couples achieve their goal of having children. Semen analysis, hormonal profiling, genetic testing, and imaging techniques are all part of the diagnostic process for male infertility to find the root causes. Management approaches include everything from medication and lifestyle changes to surgery and ART, including intracytoplasmic sperm injection (ICSI) and in vitro fertilization (IVF). The application of artificial intelligence to semen analysis and the creation of innovative sperm retrieval methods are two examples of emerging technologies that hold promise for improving treatment results and diagnostic precision. Even with great advancements, issues with expanding access to care and addressing moral dilemmas around ART usage still exist. Improving the quality of life and reproductive health of impacted individuals and couples is the ultimate objective. This review summarizes current knowledge on the causes, diagnostic methods, and management of male infertility, with an emphasis on recent advances in genetic and assisted reproductive technologies (ART).

Keywords: male infertility, sperm, etiology, aging, semen analysis, assisted reproductive technology

Volume 11 Issue 3 - 2025

Tibyan Abd Almajed Altaher,[1] Abdelwahab Abdien Saeed,[1], Ghanem Mohammed Mahjaf,[2] Dalia Elmusharaf Khalifa,[3] Fania Abdallah El Badri,[4] Mosab Nouraldein Mohammed Hamad[5]

[1]Department of Clinical Chemistry, Faculty of Medical Laboratory Sciences, Sudan
[2]Department of Medical Microbiology, Faculty of Medical Laboratory Sciences, Sudan
[3]Embryologist, Imperial College, UK
[4]Obstetrics and Gynecology Department, Faculty of Medicine, ELsheikh Abdallah Elbadri University, Sudan
[5]Microbiology Department, Faculty of Medicine, Elsheikh Abdallah Elbadri University, Sudan

Correspondence: Mosab Hamad, Assistant professor, Microbiology department, Faculty of Medicine, Elsheikh Abdallah Elbadri University, Sudan, Corresponding

Received: July 30, 2025 | **Published:** September 25, 2025

Introduction

Millions of couples throughout the world suffer from infertility, which is the inability to conceive after 12 months of consistent, unprotected sexual activity. In this regard, male infertility, either alone or in combination with female causes, accounts for almost half of all cases of infertility.[1] Despite its high frequency, male infertility is frequently overlooked in studies and public discourse in favor of female infertility, which results in a lack of knowledge and comprehension regarding its profound effects on afflicted individuals and couples.[2] Given the complexity of its origins and the multimodal methods needed for diagnosis and therapy, the research on male infertility spans a wide variety of fields, including endocrinology, genetics, urology, and reproductive medicine.[3] Though many elements of male infertility are still poorly understood, medical science advancements over the past few decades have greatly enhanced our understanding of male reproductive health, highlighting the need for ongoing research and education.[4] Numerous reasons, such as genetic abnormalities, hormone imbalances, anatomical blockages in the reproductive canal, lifestyle choices, and environmental exposures, can lead to male infertility.[5] Male fertility may suffer as a result of these factors' effects on spermatogenesis, the process by which sperm are produced, and/or the sperm's capacity to fertilize an egg.[6] Beyond the biological incapacity to conceive, infertility influences many men's and their partners' psychological health, relationships, and quality of life.[7] Male fertility is mostly determined by spermatogenesis, the process by which spermatozoa grow from spermatogonia in the testes. Both meiotic and mitotic divisions, as well as significant morphological and biochemical differentiation, are hallmarks of this painstaking developmental process, which culminates in a mature spermatozoan. Spermatogenic failure, or aberrant spermatozoa parameters, such as complete absence (azoospermia), low count (oligozoospermia), abnormal morphology (teratozoospermia), and/or abnormal motility (asthenozoospermia), is the cause of male infertility. Up to half of all cases of infertility are male, and 15% of couples worldwide who are of reproductive age have infertility.[8,9] According to reports, the age-standardized prevalence of male infertility rises by 0.3% per year. However, the rate of infertility caused by increasing male factors varied widely, ranging from 20 to 70 percent.[30] Because of cultural differences, social difficulties, and patriarchy, which hinder reliable sampling and analysis, male infertility rates may be underestimated.[10] It can also make males anxious about the stigma associated with hegemonic masculinity. It is especially difficult in Western societies where male infertility and impotence are confused, as well as in pronatalist civilizations where both virility and fertility are regarded as characteristics of manhood. Ironically, ARTs have the potential to engender secretiveness and stigma on top of existing layers. Male infertility is also linked to severe marital and psychological stress, a higher risk of cancer, worse general health, and a shorter life expectancy.[10]

Epidemiology

Male reproductive abnormalities are found in almost half of male partners in infertile unions, and a wide range of medical illnesses can negatively impact male fertility. About 7% of all men experience male factor infertility, which is indicated by abnormal semen characteristics. Its extreme form, azoospermia, is observed in 1% of the general population and in 20% of patients who visit a fertility clinic. Research indicates that the metabolic health and reproductive potential of the offspring may be impacted by the health of the male partner at the time of conception.[11]

Sperm counts have been reported to be declining globally over the past 50 years, and a comprehensive review by Levine et al. showed a reduction of 50–60% between 1973 and 2011, further highlighting the growing role of male factors in infertility.[12] The length of infertility, the age of the female spouse, problems with semen production, and the type of infertility—primary or secondary—are all prognostic factors that affect how well fertility therapy works. The treatment of male factor infertility has not advanced much, and it is frequently limited to assisted reproduction, despite improvements in male reproductive health. For male infertility to be successfully managed, early diagnosis via timely and comprehensive assessment of the male reproductive system is essential. Epidemiology indicates that the prevalence of infertility varies and that male infertility has been less commonly reported in developing countries.[13] The burden of infertility is usually higher in underdeveloped countries because of a lack of access to quality healthcare, high treatment expenses, cultural stigmas, taboos, and worries. In areas where access to basic medical care is already restricted, identifying and treating infertility is much more challenging. One in five couples do not conceive within the first year of trying, and between 13% and 15% of couples worldwide have infertility. Nearly half of young, healthy couples in the United States who failed to conceive during their first year of unprotected sexual activity will conceive within the next 12 months, even without any particular therapy. One out of every six couples has some fertility issues with their first child, and one out of every six couples still have issues with a second child. Among 20% to 30% of cases, males may be the sole cause of infertility, accounting for 50% of cases among couples.[14] The exact prevalence of male infertility is still unknown because it is not a disease that can be recorded. Furthermore, medical insurance statistics do not include male infertility treatments because they are usually paid for privately. Moreover, male infertility is often treated in outpatient settings, and this kind of information is typically absent from large clinical databases. Agarwal et al. estimate that between 2.5% and 12% of infertility may be attributable to pure male causes.[14] According to most estimates, male infertility rates range from 4.5% to 6% in North America, 9% in Australia, and maybe as high as 8% to 12% in Eastern Europe.[14] Research by Bayasgalan et al. found that male variables alone account for 25.6% of infertility cases. A parallel study by Thonneau et al. found that male variables alone accounted for 20% of all cases of infertility in the French population. Similarly, Philippov et al. used a WHO questionnaire in Western Siberia to show a rate of 6.4%, whereas Ikechebelu et al. found a male infertility incidence of 42.4% in Nigeria.[15,16] We assume that around one-sixth of couples worldwide experience infertility and that male factors account for approximately half of cases and are the only cause in approximately 20% to 30% of cases. It is alarming that sperm counts have been falling globally over the past couple of decades, as has been widely reported.[17,18] Sperm counts averaged 113 million/mL in 1940 but dropped to 66 million/mL in the 1990s. This trend has continued globally, as seen by the 51.6% decline in the mean sperm count between 1973 and 2018. The fact that the pace of decline accelerated after 2000—from 1.16% annually after 1972 to 2.64% annually after 2000—is much more worrisome.[18] Although the exact causes are uncertain, variables that are thought to be contributing include increased long-term exposure to environmental toxins and improved global medical care, which paradoxically allows more men with questionable health to participate in reproductive activities. Different counting techniques, incompatible lab standards, or advancements in laboratory technology could all be the cause of the reported drop in sperm counts. Infertility-affected males tend to have more health-related comorbidities than normally fertile men. Male infertiles with abnormal semen parameters are more prone to develop testicular cancer; those who are azoospermic are particularly vulnerable. Azoospermic men also have a greater death rate and a higher risk of cancer overall than men with normal sperm counts. Infertile men's first and second-degree relatives may also be more susceptible to cancer. However, 5–8% of testicular cancer patients have been shown to have azoospermia.[19] Due to COVID-19, some men who have recovered appear to have somewhat reduced fertility or even infertility, especially if the infection is severe. The virus appears to infect the testis directly through a cytokine storm and the negative effects of the many antiviral and immunological medications used to treat it.[20] Further study is needed to better understand the mechanisms of damage and possible therapies specific to COVID-19-induced infertility.[20]

Etiology of male infertility

The underlying complicated etiology of male infertility, which results from interactions between genetics, lifestyle choices, environmental variables, and comorbidities, is largely responsible for the lack of success in treating this condition (Figure 1). With the current trend of planning pregnancies at later ages (40 years), the impact of aging on male fertility has also increased.[21]

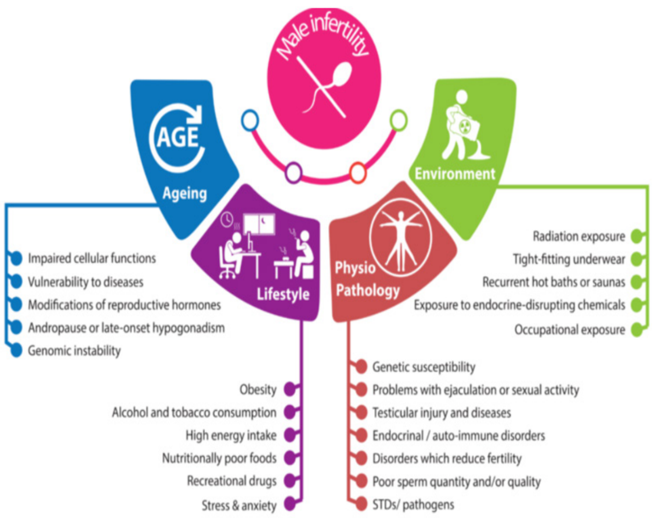

Figure 1 Multifactorial etiology of male infertility.

Citation: Altaher TAA, Saeed AA, Mahjaf GM, et al. Recent advances in the diagnosis and genetic understanding of male infertility: implications for assisted reproductive technologies. *Pregnancy & Child Birth.* 2025;11(3):66–75. DOI: 10.15406/ipcb.2025.11.00325

Anatomo-Pathophysiological Factors

Male infertility is influenced by a number of pathophysiological and anatomical variables, such as obstruction of the sperm ducts (epididymis or vas deferens), problems with ejaculation, testicular disease or injury, hormonal imbalance, genetic diseases, and other medical conditions (e.g., iatrogenic causes). About 5% of infertile men experience duct obstruction, which stops them from ejaculating and is a sign of either severe oligozoospermia or azoospermia.[22] Infertility, sexual dysfunction, and hormonal imbalance can all result from testicular injury or disease.[23] About 2% of cases of infertility are caused by retrograde ejaculation, which is a malfunction of the bladder sphincter that manifests as semen ejaculating into the bladder.[24] Sexual development and function depend on male reproductive hormones. Due to faulty sexual hormones and/or impaired sperm production, some endocrine abnormalities involving the hypothalamus, pituitary, and testicular glands can result in infertility.[25] Sperm function is also hampered by sperm antibodies generated in several autoimmune diseases. Infertility may develop from varicocele, an excessive growth of the scrotal veins that causes retrograde blood flow.[24] Infertility is caused by the Zika virus,[28] some bacteria,[27] and several sexually transmitted diseases (STDs) that affect the reproductive system.[26] Oxidative stress (OS), which is linked to male infertility, is induced by several diseases of the male reproductive system, including genitourinary tract infections.[29,30]

Environmental factors

Through epigenetic pathways, a number of environmental variables, including pollution, impact fertility.[31] The epigenome can transfer epigenetic marks from one generation to the next and connect the genome and environment.[32] The sperm-specific epigenetic signature, its transfer to oocytes, and its consequences on embryo development have been the subject of several recent research.[32] For example, a higher incidence of male infertility, poorer semen quality, and less motile sperm are linked to occupational exposure to hazardous physical and chemical agents.[33,34] Fertility can also be impacted by prolonged sitting, exposure to high temperatures (such as in bakeries and metallurgical industries), or high levels of stress. In addition to psychological, physical, and sexual problems, early andropause is positively connected with job demand or workload.[35] Additional environmental factors include exposure to endocrine-disrupting chemicals (e.g., pesticide residue, bisphenol A, phthalates, and dioxins), tight-fitting underwear, frequent hot baths or saunas, and radiation exposure from mobile phones or laptops.[36] According to recent meta-analyses, exposure to mobile phones, particularly those placed near the genitalia, is linked to decreased sperm motility and viability.[37,38] Through endocrine, circadian, and molecular connections, the human microbiome plays a role in the regulation of both health and disease. The majority of non-communicable diseases are at risk due to microbial dysbiosis. Although the exact mechanisms are still unknown, several correlations between the microbiome and male fertility have been documented.[39,40] Immune system activation brought on by the testicular and/or gut microbiota may result in inflammation of the epididymis and abnormal hormone production, including that of leptin, ghrelin, LH, FSH, and testosterone, which can impact erectile function and spermatogenesis.[41]

Lifestyle

All behavioral aspects that impact health, such as nutrition, exercise, and the use of dangerous substances (such as alcohol and tobacco), are included in the category of lifestyle. For instance, diet-induced obesity can change scrotal temperatures, hormone profiles, sleep and sexual behavior, and semen characteristics, all of which can impact male fertility; obese men are at a higher risk of having a non-viable pregnancy.[42] Furthermore, compared to their normal-weight peers, males who are underweight or overweight have a higher risk of developing azoospermia sperm. On the other hand, weight-loss programs have been linked to decreased cellular DNA damage, increased total motile sperm count, and improved semen morphology.[43] Obese men have been found to have decreased sex hormone-binding globulin levels, which leads to hyperinsulinemia and elevated total estradiol levels. Fertility is impacted by dietary practices, alcohol and tobacco use, recreational drug use, and psychological stress.[36] A high-fat diet can cause intestinal dysbiosis by altering the composition of the gut microbiota, and it can also hinder fertility by causing inflammation, epididymitis, higher blood endotoxin levels, and dysregulated gene expression in the testes.[44] Processed foods that are high in calories and low in nutrients have been linked to the risk of asthenozoospermia, while a balanced diet, such as the Mediterranean diet, is linked to higher-quality sperm. In addition to standard prescriptions for poor semen quality, lifestyle changes are advised, especially about the quality of food consumed.[45] Smoking and excessive alcohol use have negative impacts on a number of sperm parameters,[46] which lowers fertility and passes on epigenetic abnormalities to the progeny.[31] Male fertility is impacted by excessive use of caffeine and recreational drugs such as cannabis, opiates, and anabolic steroids.[41] Lack of exercise, exposure to stressful situations, and sleep deprivation are other important lifestyle factors that hinder men's ability to reproduce.[47]

Aging and male infertility

A complicated, multifaceted process, aging gradually reduces cellular function and increases susceptibility to illness. In males, it is linked to reproductive endocrinology abnormalities that may result in andropause or late-onset hypogonadism.[35,48] Nevertheless, little is known about the molecular mechanisms influencing common test parameters and semen quality. The most commonly used cutoff age for severe paternal aging or andropause is 40 years old, even though the average paternal age worldwide is 21 years old.[21] Andropause alters sperm motility and morphology, as well as semen volume, and raises the chance of infertility. It is yet unknown, nevertheless, how aging affects sperm concentration.[49] Andropause raises the incidence of spontaneous miscarriages and other problems in infancy, including autism, schizophrenia, genetic illnesses, and lower birth weights.[50,51] Cellular senescence or apoptosis can result from several cumulative molecular and/or cellular processes brought on by aging, such as DNA damage and sperm telomere shortening.[48,52] Male infertility, the buildup of de-novo mutations, and elevated genetic risk in the progeny are all linked to andropause. During senescence, telomerase malfunction appears to trigger a DNA damage response. The impact of andropause on sperm DNA damage is still debatable, albeit.[53] Additionally, andropause inhibits the DNA repair machinery and antioxidant defense system, which raises the production of reactive oxygen species (ROS) and may result in genomic instability.[54] This can cause dysregulation of gene expression and microRNA (miRNA) patterns,[53] two important regulators of normal spermatogenesis. The various factors influencing male infertility, which are intricately linked to genome-lifestyle-environment interaction, make it more difficult to create precise diagnoses and efficient treatments. The necessity for integrative strategies that address the complex etiology of male infertility is underscored by the rising incidence of this condition.

Diagnostic evaluation

Semen analysis

Semen analysis remains the cornerstone of male infertility evaluation, providing essential information on sperm count, motility, and morphology.[55] Parameters such as semen volume, sperm concentration, total sperm count, vitality, and morphology are assessed according to the World Health Organization (WHO) criteria. Abnormal results may indicate issues with spermatogenesis, obstruction, or ejaculation and require further investigation.[56] The foundation of laboratory testing for male infertility is semen analysis. At least two distinct samples ought to be taken, ideally a month apart but at least a week apart. Each specimen should be abstained for at least three days. Given the incredibly high degree of variability in semen assays, this is advised. The results of the semen analysis, the reproductive status of the female partner, and the classification of primary or secondary fertility all have a significant impact on the outcomes and prognosis of male infertility. Analyses of semen are very helpful in determining and categorizing the severity of any male variables. A comprehensive semen collection methodology has been released by the WHO. Commercial at-home sperm tests are now available, however, they are not advised because they do not assess all of the essential semen criteria and their reliability is in doubt.

Giving precise directions for the collection of semen is crucial. Masturbating or using specialized condoms that don't contain any harmful chemicals are two ways to obtain semen.[57] Although it is desirable to collect the specimen at the lab, it is possible to do it at home. The sample must be studied within an hour of collection, thus if it is taken at home, it should be stored at room temperature and sent straight to the lab. The Clinical Laboratory Improvement Amendments (CLIA) defined the standards for the semen analysis quality control program, and their website has comprehensive information. The sperm are analyzed for count, concentration, vitality, motility, advancement, debris, and morphology, while the semen is evaluated for volume, pH, leukocytes, immature germ cells, and liquefaction.[58] The Kruger-Tygerberg criteria or the WHO criteria for sperm morphology score should be applied.

The lower reference limits of a semen analysis (with 95% confidence intervals) adapted from WHO (2010)

a. Ejaculate volume: 1.5 mL (1.5–5 ml) (If low volume, possible retrograde ejaculation, anejaculation, ejaculatory duct obstruction, or hypogonadism. Check post-ejaculation urine, TRUS, and hormonal analysis. If high volume, suspect contamination)

b. pH > 7.2

c. Sperm concentration: 15 million/mL (12–16) (Usual normal value is >20 million/mL). If low, check for varicocele and consider a hormonal analysis.

d. Total sperm count: 39 million/ejaculate (33–46 million)

e. Sperm Morphology: > 4% normal forms (Usual normal value >30%)

f. Motility: 40% (38%–42%) (The usual normal value is 60%). If low, check for varicocele and consider an anti-sperm antibodies test.

g. Vitality: 58% live (55%–63%). If low, check for varicocele and consider an anti-sperm antibodies test.

h. Progressive motility: 32% (31%–34%)

i. Total motility: >40% (Usual normal value is >60%). If low, check for varicocele and consider an anti-sperm antibodies test.

j. Forward progression: >2

k. Seminal fructose: >13 micromol/ejaculate

l. Liquefaction: 20 to 30 minutes

m. Optional investigations

a. Immunobead test with <50% motile spermatozoa with bound beads

b. Mixed antiglobulin reaction test with <50% motile spermatozoa with bound particles

c. Seminal fructose≥13 micromol/ejaculate

d. Seminal neutral glucosidase ≤20 milliunits/ejaculate

e. Seminal zinc ≥2.4 micromol/ejaculate[59]

The nomenclature related to the pathological semen quality as adapted from the World Health Organization laboratory manual for the examination and processing of human semen, WHO (2010)[60]

a. Aspermia: No ejaculate at all.

b. Asthenozoospermia: <32% progressively motile spermatozoa. Absolute asthenozoospermia is when no sperm moves at all, but they are still viable and not dead.

c. Azoospermia: No spermatozoa in the ejaculate.

d. Cryptozoospermia: Spermatozoa was absent from fresh preparation but was observed in a centrifuged pellet.

e. Leukospermia: >1 million white blood cells/mL ejaculate (also called pyospermia and leukocytospermia).

f. Necrospermia or Necrozoospermia: Complete when all the sperm are dead on a fresh semen sample; incomplete if 5%-45% are still viable.

g. Normospermia: All semen parameters are within the acceptable reference limits.

h. Oligozoospermia: Sperm concentration <15 million/mL; total sperm number <39 million/mL. Severe if <5 million/mL.

i. Oligo-astheno-teratozoospermia: Disturbance of all 3 parameters.

j. Teratozoospermia: <4% morphologically normal spermatozoa.[60]

Hormonal assessment

In order to detect hypothalamic-pituitary-gonadal axis problems that may impact spermatogenesis and general reproductive health, hormonal profiling is essential. Follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone, and prolactin levels are commonly measured. Unusual values could indicate hyperprolactinemia, hypogonadism, or other endocrine conditions that need specific care.[61] Infertility Genetic Testing Genetic testing can detect chromosomal abnormalities, Y chromosome microdeletions, and gene changes that impact fertility in men with significant sperm production problems or particular clinical manifestations (such as azoospermia). These tests aid in advising couples on reproductive options, such as the use of donor sperm or the possibility of passing on genetic disorders to children.[62]

Aberrant spermatogenesis and sexual function are linked to disturbances of the hypothalamic-pituitary-gonadal axis. A hormone evaluation should be performed on males who exhibit additional clinical signs of endocrinopathy, diminished libido, or anomalies on semen tests, particularly sperm concentrations below 103 million per milliliter. Serum testosterone and FSH levels are measured as part of the initial testing. Serum LH and prolactin levels should also be assessed if anomalies are found. A particular diagnosis is characterized by the relationship between a patient's serum hormone levels (Table 1). A tiny, flat epididymis and soft testes that are less than 10 cm^3 are common in men who are azoospermic due to testicular failure. Reduced testosterone production results in less negative feedback inhibition on the pituitary, which is therefore prompted to enhance FSH secretion (hypergonadotropic hypogonadism) in the context of primary testicular failure. These men frequently have excessive aromatase activity or the conversion of testosterone to estrogen, and they respond to aromatase inhibitor therapy by normalizing their testosterone levels and producing more sperm. Because testosterone production is normal and the complete hormone profile resembles the normal state, men with obstruction-induced azoospermia have normal FSH levels. Not all men with aberrant spermatogenesis have elevated FSH, even if a markedly elevated FSH is consistent with spermatogenic failure. To determine whether azoospermia is due to blockage or testicular failure, a physical examination and hormone evaluation are a very helpful combination. It has been determined that 89% of men with nonobstructive azoospermia had FSH levels larger than 7.6 mIU/mL or testicular long axis of 4.6 cm or more, while 96% of men with obstructive azoospermia had FSH levels of 7.6 mIU/mL or less.[63] To rule out chromosomal anomalies such as Klinefelter syndrome and microdeletion of the Y chromosome, men with primary testicular failure, small, soft testes, increased FSH, and often poor ejaculate volume due to low testosterone levels may be encouraged to undergo genetic assessment.

Table 1 Correlation between serum hormone levels and diagnosis

Diagnosis	T	FSH	LH	Prolactin
Normal	Normal	Normal	Normal	Normal
Primary Testicular Failure (Hypergonadotropic hypogonadism)	Low	High	Normal→High	Normal
Hypogonadotropic hypogonadism	Low	Low	Low	Normal
Functional pituitary adenoma	Low	Low→Normal	Low	High

FSH is the follicle-stimulating hormone; LH is the luteinizing hormone, and T is testosterone.

In hypogonadotropic hypogonadism, the pituitary produces insufficient FSH, which results in inadequate testosterone production. This condition is commonly characterized by low testosterone, low FSH, and low LH. Hypogonadotropic hypogonadism can be brought on by pituitary defects, such as pituitary adenoma, or Kallman syndrome, a hypothalamic condition in which the body does not produce enough GnRH. Midline abnormalities including anosmia,[65] as well as less frequent synkinesia, unilateral renal agenesis, and a high, arched palate, are also linked to Kallman syndrome. A cranial MRI should be performed on men with this hormone profile to check for pituitary adenoma in the sella turcica. High levels of prolactin produced by pituitary functional adenomas can suppress the pituitary glands gonadotropes by negative feedback, resulting in a drop in FSH, LH, and testosterone. The development of a hypoandrogenic state that leads to insufficient virilization may be preceded by decreased libido. To evaluate the pituitary gland, a cranial MRI is recommended. Large macroadenomas that could result in serious morbidity from the mass effect should be identified for follow-up and potential neurosurgical consultation if the mass enlarges or causes other neurologic signs, even though medical therapy for microadenomas and macroadenomas is typically the same. When compared to the fertile population, recent research has revealed that many men with nonobstructive azoospermia have an elevated testosterone: estradiol (T: E2) ratio.[65] Serum testosterone levels are raised by aromatase inhibitors because they reduce the conversion of testosterone and androstenedione to estradiol and estrone, respectively. It has been discovered that giving aromatase inhibitors to oligospermic men greatly improves semen characteristics including sperm concentration and motility in addition to bringing the T: E2 back to normal.[65,66] Although these data were not available for assessment and inclusion in the current recommendations of the Male Infertility Best Practice Policy Committee, an E2 level can be obtained in oligospermia, infertile men to estimate the T: E2 ratio.

Imaging modalities (Ultrasound, magnetic resonance imaging (MRI))

The diagnosis of anatomical reasons for infertility, including congenital abnormalities, obstructive azoospermia, and varicoceles, is aided by imaging tools. The most used imaging method for assessing the testicles and associated organs is scrotal ultrasonography. When ultrasound results are unclear or require a more thorough evaluation of complicated cases, MRI may be used.[67] Semen analysis, hormonal profiling, genetic testing, and imaging are all part of the multimodal approach used in the thorough diagnostic examination of male infertility to determine the underlying causes of infertility. This makes it possible to create a customized treatment plan that targets particular problems and raises the likelihood of a successful pregnancy.

Ultrasound

To check for ejaculatory duct obstruction, transrectal ultrasonography (TRUS) is recommended for patients with palpable vasa who have an acidic, low-volume ejaculate with little to no fructose. Semen with partial or unilateral ductal blockage may include fructose and have a slightly acidic pH. The ejaculatory ducts may be seen to be blocked on ultrasonography, and the seminal vesicles may seem dilated (greater than 1.5 cm in anteroposterior diameter).[68] The seminal vesicles may be aspirated under ultrasound guidance in an azoospermic patient suspected of having ejaculatory duct obstruction,[69] and the aspirate is analyzed under a microscope after surgery. Motile sperm should be cryopreserved if they are present so they can be used in ICSI/ IVF. Transurethral resection of the ejaculatory ducts is the final treatment; in 50% to 75% of cases, sperm may be observed returning to the ejaculate, and in 25% of couples, pregnancy occurs.[70] IVF with ICSI is advised if viable but subpar sperm return to the ejaculate.

Contralateral segmental atresia of the seminal vesicle or vas deferens may be linked to unilateral vasal agenesis.[71] TRUS can be used to assess the seminal vesicle and ampullary segment of the contralateral vas. Additionally, 10% of men with CBAVD and 25% of men with congenital unilateral absence of the vas deferens have unilateral renal agenesis; abdominal ultrasonography is recommended for kidney evaluation in this population.[72] Since most scrotal pathology may be palpated during a physical examination, trans-scrotal ultrasound is rarely required. Palpation alone is most frequently used to diagnose testis cancers, congenital lack of the vas deferens, and clinically severe varicoceles. Scrotal ultrasonography is not recommended unless the results of a physical examination are unclear or cannot be completed sufficiently.

Genetic analysis

Male infertility is obviously linked to chromosome disorders. The sex chromosome anomaly Klinefelter syndrome (47, XXY), microdeletions of the Y chromosome, and mutations in the CF transmembrane conductance regulator (CFTR) gene are the best-characterized genetic abnormalities.

Mutations within the cystic fibrosis transmembrane conductance regulator gene

The range of vasal aplasia includes congenital epididymal blockage, congenital bilateral partial absence of the vas or epididymides, congenital unilateral absence of the vas deferens, and congenital CBAVD. The cystic fibrosis transmembrane conductance regulator (CFTR) gene,[73] which is placed on the short arm of the chromosome, has mutations in at least one allele in at least 80% of men with CBAVD. In addition to affecting the development of the vas deferens, seminal vesicle, ejaculatory duct, and the distal two-thirds of the epididymis, the gene encodes a protein that functions as an ion channel. The proportion of males with CBAVD who are found to have CFTR mutations rises as more mutations in the CFTR gene are identified. All men with CBAVD may have CFTR gene mutations. If these mutations are not found, it limits the testing methods available today and raises practical concerns about how many mutations should be tested in a particular patient because some mutations are uncommon. Carriers of CFTR gene mutations make up about 4% of the Caucasian population. Before trying ART, the female partner must be checked for CF gene mutations to assess the risk of passing on CF or CBAVD to the child, as men who exhibit vasal agenesis are presumed to be carriers of CF mutations. It seems that the CF carrier state has little ability to cause CBAVD.[74]

Klinefelter syndrome

Karyotypic anomalies are present in up to 10% of men with nonobstructive azoospermia. The Klinefelter syndrome (47, XXY or 46, XY;47, XXY mosaicism) is the most prevalent chromosomal abnormality. The clinical spectrum of Klinefelter syndrome includes severe oligospermia in rare instances and varying degrees of defective spermatogenesis, with a total absence of spermatogenesis at one extreme. Most males with Klinefelter syndrome can recover testicular spermatozoa with microsurgical testicular sperm extraction (TESE). All of our center's offspring born following ICSI using recovered sperm have so far had normal karyotypes. Autosomal translocations are among the other karyotypic anomalies in infertile males.[75] When using sperm from males with known chromosomal abnormalities, preimplantation diagnosis (examination of fertilized embryos by biopsy during IVF) employing fluorescence in situ hybridization for detection of normal chromosome composition may be taken into consideration.[76]

Microdeletions of the Y-chromosome

Up to 7% of infertile men have been found to have Y chromosomal microdeletions.[77] Three nonoverlapping sections of the Y chromosomes long arm, known as AZF (AZoospermic Factor) a, b, and c, may have pertinent microdeletion.[78] Deletions must be found using a polymerase chain reaction-based method that uses several sequence-tagged sites since they are too tiny to be detected by karyotype analysis alone. Phenotypes cannot predict the presence of a deletion. Different sperm retrieval rates are linked to deletions within the various areas. The majority of men with AZFc area deletions may have enough spermatogenesis to generate spermatozoa in their ejaculate,[79] but if not, sperm may be extracted via microdissection TESE. However, men who have AZFa or AZFb area deletions are less likely to have effective sperm retrieval. The clinical significance of deletions within the recently described AZFd area is yet unknown, but they are linked to proper spermatogenesis.[80] Since all male children will inherit the Y chromosome, there is a risk that all male children may have defective spermatogenesis, and it has been shown that deletions can be vertically transmitted. All azoospermic men contemplating ICSI should be examined for Y chromosome microdeletions and chromosomal abnormalities using karyotype analysis because of the predictive value and consequences for progeny. The couples should get counseling not only on the potential for infertility to be passed on to the child but also about the likelihood of genetic disorders that are not yet understood and cannot be identified by existing genetic testing methods.

Treatments

The most popular and thoroughly researched supplementary diagnostics for male infertility are semen analysis and sperm chromatin integrity assays. A substantial percentage of faulty spermatozoa are detected by sperm DNA fragmentation.[81] Compared to fertile men, infertile men are more likely to have DNA damage. It may be advised to use artificial insemination if the sperm count is less than 40 million. Nonetheless, the following therapies are advised if the sperm count is less than 20 million:

Assisted reproductive technology

In vitro fertilization (IVF) can be performed if the sperm counts are fewer than 20 million and they have a respectable level of motility. A complete change in the focus of reproductive medicine was brought about by the debut of IVF in 1978. After the first reports of successful surgical sperm retrieval, things started to change. The process of fertilizing eggs and sperm outside of the body in a lab setting is known as in vitro fertilization. After forming, the embryo or embryos are inserted into the uterus. In IVF and embryo transfer, there are five basic steps: ova and sperm collection, monitoring and promoting the development of healthy ovum/ova in the ovaries, fusing nurtured ova and desired sperm in the lab by creating the right conditions for fertilization and early embryo growth, and then transferring the embryos into the uterus.[82] First, ovulation induction, the process of controlling ova maturation and increasing the likelihood of obtaining multiple ova during the menstrual cycle, is accomplished by prescribing fertility drugs. Since some ova will not mature or fertilize after retrieval, many ova are desired. Ultrasound is used to track ovum development, and urine or blood test samples are examined to determine hormone levels. Laparoscopic or transvaginal ultrasound-guided aspiration is the method used to collect ova.[83]

A hollow needle is guided through the pelvic cavity using ultrasound imaging to extract eggs from the ovaries during a minor surgical procedure known as second follicular aspiration. Third, ejaculation is used to produce sperm, and the sperm and ova are then put in laboratory incubators to facilitate fertilization. Intracytoplasmic sperm injection (ICSI) may be used in situations where fertilization is less advanced. To ensure that fertilization and cell division are occurring, the ova are observed. Once fertilization has been successful, they are regarded as embryos. Although the transfer normally takes place between two and three days after egg retrieval, it can happen anywhere from one to six days later.[84] A hollow needle is guided through the pelvic cavity using ultrasound imaging to extract eggs from the ovaries during a minor surgical procedure known as second follicular aspiration. Third, ejaculation is used to produce sperm, and the sperm and ova are then put in laboratory incubators to facilitate fertilization. Intracytoplasmic sperm injection (ICSI) may be used in situations where fertilization is less advanced. To ensure that fertilization and cell division are occurring, the ova are observed. Once fertilization has been successful, they are regarded as embryos. Although the transfer normally takes place between two and three days after egg retrieval, it can happen anywhere from one to six days later.[84] In order to reduce the amount of time artificially fertilized embryos are exposed to environmental fluctuations like temperature, pH, or humidity, these researchers used a revolutionary static technique called time-lapse imaging (TLI). Additionally, they proposed that TLI minimizes multiple pregnancies, a significant issue encountered during the traditional morphological examination, by enabling continuous monitoring of early embryonic development by picture acquisition every 5 to 20 minutes. However, there is no way to determine which individual sperm in a given specimen has the highest reproductive competence, even in cases where males exhibit signs of spermatogenic dysfunction (found by semen analysis, DNA fragmentation assay, or sperm functional assays). There is currently little clinical evidence to support the use of the only assays that try to separate the most reproductively competent sperm following conventional washing procedures. High-powered magnification morphology examination is possible with intracytoplasmic morphologically chosen sperm injection (IMSI). Higher egg yields and more embryos transplanted were associated with the pregnancy rate in the IMSI group as opposed to the ICSI group, indicating that patients in the IMSI groups had a better prognosis.[85] Testicular sperm extraction can be performed if an injection of a single spermatozoa fails. When a man's sperm count is less than 5 million/mL, karyotyping is crucial. Autosomal anomalies are substantially more common in these individuals than in fertile populations (about 4%), with azoospermia men (mostly Klinefelter disease) having the highest frequency. The most prevalent sex chromosomal aneuploidy is Klinefelter syndrome (47, XXY including variations [48, XXXY], and XX males [SRYþ and SRY]). Knowing if there is a chromosomal anomaly helps with therapeutic planning and patient follow-up in the future. Therefore, karyotype analysis should be carried out either before surgical testis sperm extraction or before using ejaculated sperm in conjunction with ICSI.[86] The hyaluronic acid (HA) binding assay is the alternative method for selecting sperm. This is predicated on membrane changes brought on by the presence of HA binding sites during regular spermiogenesis. Embryos produced from oocytes injected with HA-bound sperm had higher ICSI improvements in implantation rates because HA-bound sperm had reduced rates of aneuploidy and apoptosis.[87]

Management

Infertility caused by male causes can occasionally be difficult to control, and concurrent female factors must be taken into account. Typically, management consists of a combination of medicinal or surgical treatment along with lifestyle changes. The use of assisted reproductive technology (ART) and, in certain cases, donor sperm may be necessary for individuals with severe male factor infertility, particularly when testicular failure is present. Counseling for lifestyle change is crucial in the early treatment of alcoholism, drug addiction, dangerous occupational exposure, and obesity. An evaluation of pharmaceuticals is crucial since spermatogenesis can be impacted by numerous medications used to treat other systemic conditions.

Medical management

Numerous hormone drugs have been used to treat male factor infertility, however, there is conflicting data regarding their effectiveness as indicated by actual pregnancy outcomes.[88] Exogenous gonadotrophin replacement is highly efficient at increasing sperm production and conception in the clinical management of gonadotrophin deficiency. Pulsatile gonadotrophin-releasing hormone (GnRH) has been proven to be helpful and has been linked to better spermatogenesis in patients with hypogonadotropic hypogonadism. Bromocriptine and cabergoline are examples of dopamine agonists that have been proven to be effective in treating hyperprolactinemia. Glucocorticoids, on the other hand, have been used to successfully treat sperm autoimmunity; nevertheless, early use of assisted reproductive techniques is recommended because of the potentially harmful risks of long-term high-dose therapy. Additionally, it has been discovered that the antioestrogen tamoxifen increases the rate of natural conception in some patients with idiopathic oligospermia.[89] Multivitamin intake with vitamins C and E may promote conception, and antioxidants have been shown to reduce DNA fragmentation brought on by oxidative stress.[90]

Surgical management

Male factor infertility has been treated with a variety of surgical approaches, with varying degrees of success. One of the most common surgical procedures is varicocelectomy, which has been shown to enhance semen quality in roughly 44% of patients.[91] Vasovasostomy and epididymovasostomy are examples of reconstructive surgical treatments that are typically carried out as microsurgical operations. Congenital or acquired blockages at the epididymis level are among the indications for epididymovasostomy. Determining testicular function with a hormone profile or testicular biopsy is a crucial precaution before beginning these treatments. Along with other prognostic factors including the female partner's age and the quality of her semen, the development of anti-sperm antibodies is a limiting factor that affects pregnancy outcomes. The transurethral incision is typically used to address obstruction of the prostatic urethra, and it has been shown to enhance semen quality and spontaneous conception.[92] When using assisted reproductive techniques for men with obstructive azoospermia, surgical sperm aspiration methods like testicular sperm aspiration (TESA), microsurgical epididymal sperm aspiration (MESA), and percutaneous epidydimal sperm aspiration (PESA) are combined with intracytoplasmic sperm injection (ICSI). During in-vitro fertilization (IVF), these techniques enable the collection of a small number of spermatozoa from the male reproductive organ and their injection into the egg (Figure 2).

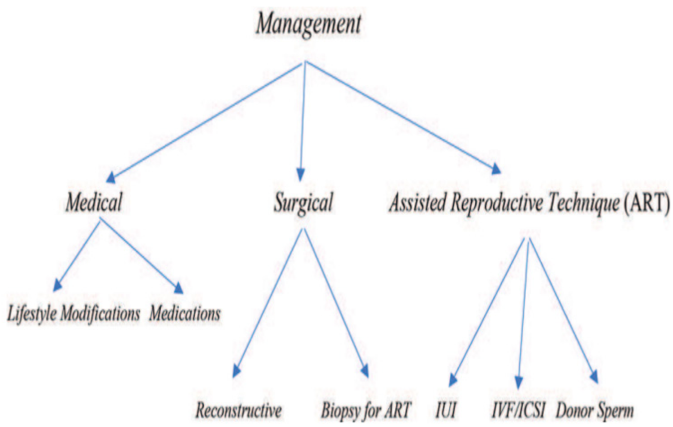

Figure 2 Schematic representation of the management of male factor infertility.

SFA, seminal fluid analysis; SDF, sperm DNA fragmentation; IUI, intrauterine insemination; IVF/ICSI, in-vitro fertilization/intracytoplasmic sperm injection

The patient's written consent has been collected.

Consent and ethical approval

It is not applicable.

Sources of funding

There was no specific grant for this research from any funding organization in the public, private, or nonprofit sectors.

Acknowledgements

None.

Conflict of interest

The authors have declared that no competing interests exist.

References

1. WHO. Infertility: A global public health issue. 2020.
2. Harlow AF, Zheng A, Nordberg J, et al. A qualitative study of factors influencing male participation in fertility research. *Reprod Health.* 2020;17(1):186.
3. Jarow JP, Sharlip ID, Belker AM, et al. Best practice policies for male infertility. *J Urol.* 2002;167(5):2138–2144.
4. Barratt CLR, Björndahl L, De Jonge CJ, et al. The diagnosis of male infertility: an analysis of the evidence to support the development of global WHO guidance challenges and future research opportunities. *Hum Reprod Update*. 2017;23(6):660–680.
5. Biggs SN, Kennedy J, Lewis SL, et al. Lifestyle and environmental risk factors for unexplained male infertility: study protocol for Australian Male Infertility Exposure (AMIE), a case–control study. *Reprod Health*. 2023;20(1):32.
6. McLachlan RI, O'Bryan MK. State of the art for genetic testing of infertile men. *J Clin Endocrinol Metab.* 2010;95(3):1013–1024.
7. Schmidt L. Psychosocial burden of infertility and assisted reproduction. *Lancet*. 2006;367(9508):379–380.
8. Agarwal A, Baskaran S, Parekh N, et al. Male infertility. *Lancet*. 2021;397:319–333.
9. Agarwal A, Mulgund A, Hamada A, et al. A unique view on male infertility around the globe. *Reprod Biol Endocrinol*. 2015;13:37.
10. Sun H, Gong TT, Jiang YT, et al. Global, regional, and national prevalence and disability–adjusted life–years for infertility in 195 countries and territories, 1990–2017: Results from a global burden of disease study, 2017. *Aging*. 2019;11:10952.
11. Craig JR, Jenkins TG, Carrell DT, et al. Obesity, male infertility, and the sperm epigenome. *Fertility and Sterility*. 2017;107(4):848–859.
12. Levine H, Jørgensen N, Martino–Andrade A, et al. Temporal trends in sperm count: A systematic review and meta–regression analysis. *Human Reproduction Update.* 2017;23(6):646–659.
13. Cates W, Farley TM, Rowe PJ. Worldwide patterns of infertility: is Africa different? *Lancet*. 1985;2(8455):596–598.
14. Agarwal A, Mulgund A, Hamada A, et al. A unique view on male infertility around the globe. *Reprod Biol Endocrinol*. 2015;13:37.
15. Philippov OS, Radionchenko AA, Bolotova VP, et al. Estimation of the prevalence and causes of infertility in western Siberia. *Bull World Health Organ*. 1998;76(2):183–187.
16. Ikechebelu JI, Adinma JI, Orie EF, et al. High prevalence of male infertility in southeastern Nigeria. *J Obstet Gynaecol*. 2003;23(6):657–659.
17. Sengupta P, Dutta S, Krajewska–Kulak E. The disappearing sperms: analysis of reports published between 1980 and 2015. *Am J Mens Health.* 2017;11(4):1279–1304.
18. Levine H, Jørgensen N, Martino–Andrade A, et al. Temporal trends in sperm count: a systematic review and meta–regression analysis of samples collected globally in the 20th and 21st centuries. *Hum Reprod Update*. 2023;29(2):157–176.
19. Petersen PM, Skakkebaek NE, Vistisen K, et al. Semen quality and reproductive hormones before orchiectomy in men with testicular cancer. *J Clin Oncol.* 1999;17(3):941–947.
20. Ardestani Zadeh A, Arab D. COVID–19 and male reproductive system: pathogenic features and possible mechanisms. *J Mol Histol.* 2021;52(5):869–878.
21. Sharma R, Agarwal A, Rohra VK, et al. et al. Effects of increased paternal age on sperm quality, reproductive outcome and associated epigenetic risks to offspring. *Reprod Biol Endocrinol*. 2015;13:35.
22. Achermann APP, Esteves SC. Diagnosis and management of infertility due to ejaculatory duct obstruction: Summary evidence. *Int Braz J Urol Off J Braz Soc Urol*. 2021;47:868–881.
23. Saab MM, Landers M, Hegarty J. Males' awareness of benign testicular disorders: An integrative review. Am J Men's Health. 2018;12:556–566.
24. Babakhanzadeh E, Nazari M, Ghasemifar S, et al. Some of the factors involved in male infertility: A prospective review. *Int J Gen Med.* 2020;13:29.
25. Lucas X. Clinical use of deslorelin (GnRH agonist) in companion animals: A review. *Reprod Domest Anim*. 2014;49:64–71.
26. Tsevat DG, Wiesenfeld HC, Parks C, et al. Sexually transmitted diseases and infertility. *Am J Obstet Gynecol*. 2017;216:1–9.
27. Farsimadan M, Motamedifar M. Bacterial infection of the male reproductive system causing infertility. *J Reprod Immunol*. 2020;142: 103183.
28. Liu W, Han R, Wu H, et al. Viral threat to male fertility. *Andrologia*. 2018;50:e13140.
29. Dutta S, Majzoub A, Agarwal A. Oxidative stress and sperm function: A systematic review on evaluation and management. *Arab J Urol*. 2019;17:87–97.
30. Bisht S, Faiq M, Tolahunase M, et al. Oxidative stress and male infertility. *Nat Rev Urol*. 2017;14:470–485.
31. Hart K, Tadros NN. The role of environmental factors and lifestyle on male reproductive health, the epigenome, and resulting offspring. *Panminerva Med*. 2019;61:187–195.
32. Cescon M, Chianese R, Tavares RS. Environmental impact on male (In) fertility via epigenetic route. *J Clin Med*. 2020;9:2520.

33. Mari´ CT, Fuˇ ci´ C, A Aghayanian. Environmental and occupational exposures associated with male infertility. *Arch Ind Hyg Toxicol.* 2021;72:101–113.

34. Giulioni C, Maurizi V, Scarcella S, et al. Do environmental and occupational exposure to pyrethroids and organophosphates affect human semen parameters? Results of a systematic review and meta—analysis. *Andrologia*. 2021;53:e14215.

35. Martelli M, Zingaretti L, Salvio G, et al. Influence of Work on Andropause and Menopause: A Systematic Review. *Int J Environ Res Public Health*. 2021;18:10074.

36. Leisegang K, Dutta S. Do lifestyle practices impede male fertility? *Andrologia*. 2021;53:e13595.

37. Yu G, Bai Z, Song C, et al. Current progress on the effect of mobile phone radiation on sperm quality: An updated systematic review and meta–analysis of human and animal studies. *Environ Pollut*. 2021;282;116952.

38. Kim S, Han D, Ryu J, et al. Effects of mobile phone usage on sperm quality–No time–dependent relationship on usage: A systematic review and updated meta–analysis. *Environ Res.* 2021;202:111784.

39. Wang H, Xu A, Gong L, et al. The microbiome, an important factor that is easily overlooked in male infertility. *Front Microbiol*. 2022;13:831272.

40. Venneri MA, Franceschini E, Sciarra F, et al. Human genital tracts microbiota: Dysbiosis crucial for infertility. *J Endocrinol Investig.* 2022;45:1151–1160.

41. Wang Y, Xie Z. Exploring the role of gut microbiome in male reproduction. *Andrology*. 2022;10:441–450.

42. Campbell JM, Lane M, Owens JA, et al. Paternal obesity negatively affects male fertility and assisted reproduction outcomes: A systematic review and meta–analysis. *Reprod Biomed Online*. 2015;31:593–604.

43. Mir J, Franken D, Andrabi S, et al. Impact of weight loss on sperm DNA integrity in obese men. *Andrologia*. 2018;50:e12957.

44. Ding N, Zhang X, Di Zhang X, et al. et al. Impairment of spermatogenesis and sperm motility by the high–fat diet–induced dysbiosis of gut microbes. *Gut*. 2020;69:1608–1619.

45. Skoracka K, Eder P, Łykowska–Szuber L, et al. Diet and nutritional factors in male (in) fertility—underestimated factors. *J Clin Med.* 2020;9:1400.

46. Ricci E, Viganò P, Cipriani S, et al. Coffee and caffeine intake and male infertility: A systematic review. *Nutr J.* 2017;16:1–14.

47. Kumar N, Singh AK. Impact of faulty lifestyle behaviors on male fertility: a narrative review. *Eurasian J Med Biol Sci.* 2021;1:70–79.

48. Gentiluomo M, Luddi A, Cingolani A, et al. Telomere length and male fertility. *Int J Mol Sci.* 2021;22:3959.

49. Mazur DJ, Lipshultz LI. Infertility in the aging male. *Curr Urol Rep*. 2018;19:1–9.

50. du Fossé NA, Van der Hoorn MLP, van Lith JM, et al. Advanced paternal age is associated with an increased risk of spontaneous miscarriage: A systematic review and meta–analysis. *Hum Reprod.* 2020;26:650–669.

51. Fang Y, Wang Y, Peng M, et al. Effect of paternal age on offspring birth defects: A systematic review and meta–analysis. *Aging*. 2020;12: 25373.

52. Shay JW, Wright WE. Telomeres and telomerase: Three decades of progress. *Nat Rev Genet*. 2019;20:299–309.

53. Brandt JS, Cruz Ithier MA, Rosen T, et al. Advanced paternal age, infertility, and reproductive risks: A review of the literature. *Prenat Diagn*. 2019;39:81–87.

54. Nguyen–Powanda P, Robaire B. Oxidative stress and reproductive function in the aging male. *Biology*. 2020;9:282.

55. Esteves SC. Novel concepts in male factor infertility: clinical and laboratory perspectives. *J Assist Reprod Genet.* 2016;33(10):1319–1335.

56. Nair S, Jadhav S, Lila A, et al. Spectrum of phenotype and genotype of congenital isolated hypogonadotropic hypogonadism in Asian Indians. *Clin Endocrinol*. 2016;85(1):100–109.

57. Jones DM, Kovacs GT, Harrison L, et al. Immobilization of sperm by condoms and their components. *Clin Reprod Fertil*. 1986;4(6):367–372.

58. Gottardo F, Kliesch S. [Semen analysis: spermiogram according to WHO 2010 criteria]. *Urologe A.* 2011;50(1):101–108.

59. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. H*um Reprod Update*. 2010;16(3):231–245.

60. Krausz C. Male infertility: pathogenesis and clinical diagnosis. *Best Pract Res Clin Endocrinol Metab.* 2011;25(2):271–285.

61. Krausz C, Riera–Escamilla A. Genetics of male infertility. *Nat Rev Urol*. 2018;15(6):369–384.

62. Lotti F, Maggi M. Ultrasound of the male genital tract about male reproductive health. *Hum Reprod Update*. 2015;21(1):56–83.

63. Schoor RA, Elhanbly S, Niederberger CS, et al. The role of testicular biopsy in the modern management of male infertility. *J Urol.* 2002;167:197.

64. Seminara SB, Hayes FJ, Crowley WF Jr. Gonadotropin–releasing hormone deficiency in the human (idiopathic hypogonadotropic hypogonadism and Kallmann's syndrome): Pathophysiological and genetic considerations. *Endocr Rev.* 1998;19:521.

65. Pavlovich CP, King P, Goldstein M, et al. Evidence of a treatable endocrinopathy in infertile men. *J Urol*. 2001;165:837.

66. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. *J Urol.* 2002;167:624.

67. Sharma R, Biedenharn KR, Fedor JM, et al. Lifestyle factors and reproductive health: taking control of your fertility. *Reprod Biol Endocrinol*. 2013;11:66.

68. Carter SS, Shinohara K, Lipshultz LI. Transrectal ultrasonography in disorders of the seminal vesicles and ejaculatory ducts. *Urol Clin North Am*. 1989;16:773.

69. Jarow JP. Seminal vesicle aspiration in the management of patients with ejaculatory duct obstruction. *J Urol.* 1994;152:899.

70. Jarow JP. Diagnosis and management of ejaculatory duct obstruction. *Tech Urol*. 1996;2:79.

71. Hall S, Oates RD. Unilateral absence of the scrotal vas deferens associated with contralateral mesonephric duct anomalies resulting in infertility: Laboratory, physical and radiographic finding, and therapeutic alternatives. *J Urol*. 1993;150:1161.

72. Schlegel PN, Shin D, Goldstein M. Urogenital anomalies in men with congenital absence of the vas deferens. *J Urol.* 1996;155:1644.

73. Oates RD, Amos JA. The genetic basis of congenital bilateral absence of the vas deferens and cystic fibrosis. *J Androl*. 1994;15:1.

74. Shin D, Gilbert F, Goldstein M, et al. Congenital absence of the vas deferens: incomplete penetrance of cystic fibrosis gene mutations. *J Urol.* 1997;158:1794.

75. Rucker B, Mielnik A, King P, et al. Preoperative screening for genetic anomalies in men with non–obstructive azoospermia before sperm extraction. *J Urol*. 1998;160:2068.

76. Tournaye H, Staessen C, Liebaers I, et al. Testicular sperm recovery in nine 47XXY Klinefelter patients. *Hum Reprod*. 1996;11:1644.

77. Pryor JL, Kent–First M, Muallem A, et al. Microdeletions in the Y chromosome of infertile men. *N Engl J Med.* 1997;336:534.

78. Vogt PH, Edelmann A, Kirsch, S, et al. Human Y–chromosome azoospermia factors (AZF) mapped to different subregions in Yq11. *Hum Mol Genet.* 1996;5:933.

79. Mulhall JP, Reijo R, Alagappan R, et al. Azoospermic men with deletion of the DAZ gene cluster are capable of completing spermatogenesis: Fertilization, normal embryonic development and pregnancy occur when retrieved testicular spermatozoa are used for intracytoplasmic sperm injection. *Hum Reprod.* 1997;12:503.

80. Kent–First M, Muallem A, Shultz J. Defining regions of the Y–chromosome responsible for male infertility and identification of a fourth AZF region (AZFd) by Y–chromosome microdeletion detection. *Mol Reprod Dev*. 1999;53:27.

81. Rebecca N Sumner, Mathew Tomlinson, Jim Craigon, et al. Independent and combined effects of diethylhexyl phthalate and polychlorinated biphenyl 153 on sperm quality in the human and dog. *Sci Rep*. 2019;9(1):3409.

82. Tournaye H. Male factor infertility and ART. *Asian J Androl.* 2012;14(1):103–108.

83. Man L, Baron J, Har–Vardi I, et al. A live birth after IVF following egg retrieval only 12 hours after hCG priming. *Case Rep Obstet Gynecol*. 2013;2013:1–3.

84. Casper R, Haas J, Hsieh TB, et al. Recent advances in in vitro fertilization. *F1000Research*. 2017;6:1616.

85. Gatimel N, Parinaud J, Leandri RD. Intracytoplasmic morphologically selected sperm injection (IMSI) does not improve outcome in patients with two successive IVF–ICSI failures. *J Assist Reprod Genet.* 2016;33(3):349–355.

86. Barratt CLR, Bjo¨rndahl L, De Jonge CJ, et al. The diagnosis of male infertility: an analysis of the evidence to support the development of global WHOguidance—challenges and future research opportunities. *Hum Reprod Update.* 2017;23(6):660–680.

87. Morin SJ, Scott RT. Knowledge gaps in male infertility: a reproductive endocrinology and infertility perspective. *Transl Androl Urol.* 2018;7(S3):S283–S291.

88. Liu PY, Handelsman DJ. The present and future state of hormonal treatment for male infertility. *Human Reproduction Update*. 2003;9(1):9–23.

89. Adamopoulos DA, Pappa A, Billa E, et al. Effectiveness of combined tamoxifen citrate and testosterone undecanoate treatment in men with idiopathic oligozoospermia. *Fertility and Sterility*. 2003;80(4):914–920.

90. Makker K, Agarwal A, Sharma R. Oxidative stress and male infertility. *The Indian Journal of Medical Research.* 2009;129(4):357–367.

91. Dohle GR, Colpi GM, Hargreave TB, et al. EAU Working Group on Male Infertility. EAU guidelines on male infertility. *European Urology*. 2005;48(5):703–711.

92. Schroeder–Printzen I, Ludwig M, Köhn F, et al. Surgical therapy in infertile men with ejaculatory duct obstruction: Technique and outcome of a standardized surgical approach. *Human Reproduction.* 2000;15(6):1364–1368.