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ETIOLOGY AND DIAGNOSIS OF MALE INFERTILITY

ERKEK KISIRLIĞININ ETİYOLOJİSİ VE TANISI

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Abstract
The global incidence of infertility is increasing year by year, and infertility has become a major medical, psychological, and social problem. According to the World Health Organization's report in 2023, 17.5% of the population worldwide had fertility problems. During the last 25 years, sperm quantity and quality have shown a great diminishment. The male factor is responsible for approximately 50% of infertility cases. Several factors, such as sperm morphologic problems, genital tract structural anomalies, drugs, genetics, environmental factors, and endocrine dysregulation, have a strong bearing on reproductive health. The causes and mechanisms leading to male infertility are very important to understand in order to diagnose and conduct the treatment of the condition to help a couple conceive. This review intends to give an overview of male infertility with regard to causes and diagnostic methods.

Keywords: Diagnosis, Hypogonadism, Infertility, Male, Spermatogenesis.

Öz
İnfertilitenin küresel görülme sıklığı her geçen yıl artmaktadır ve infertilite önemli bir tıbbi, psikolojik ve sosyal sorun haline gelmiştir. Dünya Sağlık Örgütü'nün 2023 yılı raporuna göre dünya genelinde nüfusun %17,5'inde doğurganlık sorunu yaşamaktadır. Son 25 yılda sperm miktarı ve kalitesinde büyük bir azalma görülmüştür. Kısırlık vakalarının yaklaşık %50'sinden erkek faktörü sorumludur. Sperm morfolojik sorunları, genital sistem yapısal anormallikleri, ilaçlar, genetik, çevresel faktörler ve endokrin düzensizlikleri gibi çeşitli faktörlerin üreme sağlığı üzerinde güçlü bir etkisi vardır. Erkek kısırlığına yol açan nedenler ve mekanizmaların anlaşılması, bir çiftin hamile kalmasına yardımcı olmak amacıyla durumun teşhis edilmesi ve tedavisinin gerçekleştirilmesi açısından çok önemlidir. Bu derlemenin amacı, erkek kısırlığına nedenleri ve tanı metotları açısından genel bir bakış sunmaktır.

Anahtar Kelimeler: Erkek, Hipogonadizm, İnfertilite, Spermatogenez, Tanı.

1. Introduction

Infertility is defined as the failure of pregnancy despite uninterrupted and unprotected sexual intercourse for more than a year (Poulter et al., 2024). According to the World Health Organization's report in 2023, 17.5% of the population worldwide experienced fertility problems (WHO., 2023). The male factor is responsible for approximately 50% of infertility cases (Rambhatla et al., 2024). Worldwide, in the 15-49-year-old male population, infertility affects approximately 2% of the males (Liang et al., 2025). Infertility in males can be due to a number of factors ranging from hypogonadism to varicocele (Jungwirth et al., 2012; Eisenberg et al., 2023). Despite advances in diagnosis and treatment methods, 30% of cases are idiopathic (Karimian et al., 2021).

The testicles have two main functions: spermatogenesis and steroid hormone secretion (Carreau et al., 2007). Spermatogenesis: It is the process of developing spermium from spermatogonia and begins with puberty (Christin et al., 2022; Zhang et al., 2024). Spermatogenesis occurs as a result of serial mitosis and meiosis of germ cells in the seminiferous tubule epithelium. It is a sensitive and complex process controlled through hormonal feedback and genetic mechanisms (Cohen et al., 2024).

The hypothalamic-pituitary-gonadal axis plays a very important role in the hormonal regulation of spermatogenesis. Gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) are the main hormones of this control mechanism (Esteves & Humaidan, 2025). GnRH triggers the release of LH and FSH. LH induces

the release of testosterone from interstitial Leydig cells. FSH affects Sertoli cells in the seminiferous tubules. Sertoli cells produce the regulators and nutrients necessary to maintain spermatogenesis (Oduwole et al., 2018).

In men with impaired secretion of LH and FSH, the diagnosis is hypogonadotropic hypogonadism, and spermatogenesis is interrupted (Fraietta et al., 2013). There are two types of hypogonadotropic hypogonadism. It may be congenital or acquired. Congenital hypogonadotropic hypogonadism is Kallmann syndrome, and the other is idiopathic hypogonadotropic hypogonadism. Acquired hypogonadotropic hypogonadism can be caused by tumors, traumas, infections, secondary to drug therapy, radiation, alcohol, and systemic diseases (Salenave et al.,2012; Fraietta et al., 2013). The incidence of congenital hypogonadotropic hypogonadism is approximately 1-10:100,000, and approximately 60% of cases are caused by Kallmann syndrome and 40% are idiopathic hypogonadotropic hypogonadism (Bianco et al., 2009).

2. Etiology of Male Infertility

2.1. Varicocele

Varicocele is a pathologic dilatation and twisting of the pampiniform venous plexus in the scrotum caused by reflux of the veins, which is most often on the left side. It is present in 15% of all men and is a major cause of male infertility. Varicocele is a multifactorial condition due to genetic, epigenetic, and environmental causes (Naderi et al.,2024). In patients with varicocele, increased scrotal temperature, oxidative stress, and impaired sperm production are the factors that affect the fertility (Hassanin et al.,2018). Varicocele is a surgically repairable cause of male infertility (Rochdi et al., 2024). Microsurgical low ligation of varicocele is the gold standard for surgical therapy (Shiraishi, 2024). Also, varicocelectomy is another choice in the surgical treatment of varicocele, and these treatments support the spermatozoa count, motility, and morphology (Rochdi et al., 2024).

2.2. Cryptorchidism

Cryptorchidism is known as the congenital absence of one or both testicles in the scrotum. It increases the risk of infertility and testis cancer. The most successful treatments for cryptorchidism are orchidopexy and hCG therapy (Hutson, 2009). Testicular descent is the result of interactions between testosterone and its androgen receptor. Also, insulin-like factor 3 (INSL3) / relaxin family peptide 2 (RXFP2) are essential for the first phase of testicular descent. Mutations in these factors are in the etiology of cryptorchidism (Krausz, 2011).

2.3. Genetic factors

Studies on somatic chromosomes in infertile men have shown that approximately 15% of azoospermic men and 5% of oligozoospermic men have an abnormal karyotype. Also, the patient whose sperm count is less than 10 million has the risk of autosomal structural abnormalities 10 times higher than the general population (Van Assche et al., 1996; Vincent et al., 2002). The most common sex chromosome abnormality in men is Klinefelter syndrome (KS; 47XXY) (Xu et al., 2022). The incidence in male newborns is approximately 1/600 (150 per 100,000 live-born boys) (Chang et al., 2020). KS is characterized by bilateral gynecomastia, small testes, aspermatogenesis, androgen deficiency, decreased testicular volume, azoospermia, and reduced intelligence (Bojesen et al., 2007; Blackburn et al., 2025). The typical endocrine finding in KS is hypergonadotropic hypogonadism, and its treatment is testosterone replacement (Chang et al., 2020).

Another genetic disease that causes spermatogenesis disorder is Y chromosome microdeletions. On the long arm of the Y chromosome, three regions are defined: They are defined as azoospermia factors. These (AZFs) are AZFa, AZFb, and AZFc. Any deletion in the AZF region may cause male infertility (Vogt et al., 1996). The most common deletion type is the AZFc region deletion (~80%), followed by AZFa (0.5–4%), AZFb (1–5%), and AZFbc (1–3%) deletions (Krausz et al., 2014). Epithelial cell membranes have the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which encodes an anion-selective channel. Mutations in CFTR cause cystic fibrosis, an inherited disease. In cystic fibrosis, the epithelium of the genital ducts (the epididymis and vas deferens) is damaged, so nearly all patients are infertile (Coatti et al., 2024; Sapru et al., 2025). Approximately 96% of patients with CF have congenital bilateral absence of vas deferens (CBAVD) and are infertile due to azoospermia (de Souza et al., 2018). However, cystic fibrosis patients can also become fathers by using assisted reproductive technology along with surgical sperm retrieval and intracytoplasmic sperm injection (ICSI) (Sapru et al., 2025).

2.4. Environmental factors and lifestyle factors

Environmental factors such as heavy metals, chemicals, pesticides, and radiation negatively affect male fertility. They damage genital organs and disrupt the hormonal balance. Continuous intake of heavy metals (lead, cadmium, mercury, and arsenic) and metal welding fumes such as carbon disulfide and ozone has been negatively associated with sperm quality (Abilash et al., 2024; Adeogun et al., 2024; Bhardwaj et al., 2024; Dubey et al., 2024; Maher et al., 2024). Pesticides may damage fertility by triggering

congenital anomalies, fetal death, and infertility (Mahmoud et al., 2025). Various pesticides are apoptotic inducers for Sertoli cells (Mansukhani et al., 2024; Moreira et al., 2024). Radiation has two types: ionizing and non-ionizing. Exposure to ionizing radiation has been proven to cause male sterility. In males, chronic exposure to non-ionizing radiation may have a negative impact on sperm characteristics such as count, motility, morphology, and viability (Ebrahimi et al., 2024; Simson et al., 2024; Korhonen et al., 2025).

Stress, immobility, obesity, aging, alcohol, cigarettes, and cannabis are the lifestyle factors. Metabolic syndrome is characterized by hypertension, insulin resistance, increased oxidative stress, and inflammation. Its prevalence is nearly 40% of men in Europe (Salvio et al., 2022). Stress has harmful effects on spermatogenesis, sperm count, motility, and sperm quality. Also, a decrease in testosterone, FSH, and LH levels causes deterioration in testicular histopathology (Ilacqua et al., 2018; Yadav et al., 2025). Long hours of sedentary employment cause visceral obesity and chronically high scrotal temperatures; both have a negative impact on sperm production. Nowadays, it turns out that low-to-moderate intensity exercises are more beneficial for male reproductive health than high-intensity exercises, which have a negative effect on sperm (Hamim et al., 2025). Metabolic syndrome has been reported to be related to increased oxidative stress, negatively influencing the spermatogenesis process, which can lower the semen quality and quantity (Bhattacharya et al., 2024).

There is strong proof that smoking has negative effects on spermatogenesis in both infertile and fertile men, which makes it a risk factor for male reproductive health (Cargnelutti et al., 2023). Smoking has detrimental effects on main sperm parameters and male fertility rates. A man who is planning fatherhood has to quit smoking and improve his lifestyle to not face infertility (Fan et al., 2024). Tobacco smoke contains lead and cadmium, which contribute to lower male fertility via oxidative stress pathways, destroying sperm DNA and reducing sperm production (Fan et al., 2024; Marchlewicz et al., 2007). Smoking, specifically, has been closely established to have a negative impact on male reproductive health, and smokers often need more IVF attempts to achieve conception (Fan et al., 2024). Sedentary life and obesity have both been associated with decreased male fertility (Gaskins et al., 2014; Hamim et al., 2025). With advancing age, oxidative stress increases in sperm cells, and DNA repair ability decreases (Kaltsas et al., 2024).

Wi-Fi and mobile phone usage has negative effects on a male's reproductive system. Exposure to radiofrequency electromagnetic radiation, in particular, can harm the male reproductive system by affecting Leydig cell processes, including the generation of testosterone (Jangid et al., 2024). According to studies on animals, cell phone electromagnetic radiation can have a harmful effect on testicular tissue and sperm characteristics such as morphology, motility, viability, and sperm count (Assefa et al., 2025).

Psychoactive drugs could affect fertility by producing testicular oxidative stress, blocking the neuroendocrine axis, and increasing the circulating levels of proinflammatory cytokines that can trigger germ cell apoptosis and testicular degeneration, thus decreasing the quality of semen (Hamed et al., 2023). Studies have indicated that cannabis has been found to reduce sperm count and concentration, induce sperm morphological defects, reduce sperm motility and viability, and impair capacitation and fertilization (Whan et al., 2006; Banerjee et al., 2011). Methamphetamine inhibits testosterone production and increases germ cell apoptosis in rats (Yamamoto et al., 2002).

Cannabis/marijuana: In the United States in 2021, approximately 45% of young adults ages 19 to 30 report using marijuana (Lee et al., 2022). Many studies have demonstrated that tetrahydrocannabinol (THC) reduces male fertility and promotes gonadal dysfunction, particularly at the testis and sperm levels. As a result, THC affects serum testosterone levels and lowers sperm count, motility, normal morphology, and acrosome reaction (Nahas et al., 2002; Gundersen et al., 2015; Y. Li et al., 2022; Truong et al., 2023). Alcohol harms reproductive health by suppressing the hypothalamic-pituitary-gonadal axis, resulting in infertility in men (Finelli et al., 2021). Chronic alcohol consumption also decreases testosterone and LH levels (Moosazadeh et al., 2024).

2.5. Infectious factors

Genital tract infections account for approximately 15-20% of male infertility cases. Infections can affect various parts of the male reproductive tract, including the testis, epididymis, and male accessory sex glands. Urogenital infections can influence spermatozoa at various stages of development, maturation, and transport (Pellati et al., 2008; Sleha et al., 2013). Sexually transmitted infections may cause obstruction and scar tissue formation in the genital tract (Kumar, 2008; Henkel, 2021; Henkel et al., 2021). Chlamydia trachomatis, Neisseria gonorrhoeae, and Treponema pallidum are the most commonly found bacteria involved in sexually transmitted illnesses that interfere with male fertility. Male infertility is less frequently caused by non-

sexually transmitted epididymo-orchitis, which is usually caused by Escherichia coli (Sleha et al., 2013; Ruggeri et al., 2016). Enterococcus faecalis (EF) disrupts sperm concentration and morphology. The incidence of oligozoospermia and teratozoospermia is higher in EF infection (Mehta et al., 2002). Ureaplasma urealyticum is one of the most common causes of male infertility. It impairs sperm quality. It disrupts the motility, density, and morphology of sperm (Ruggeri et al., 2016). Escherichia coli is the most isolated microorganism in genitourinary infections that causes prostatitis and epididymitis. This bacteria has an agglutination effect on sperm. Also, it impairs the acrosomal function (Kaur et al., 2014., Folliero et al., 2022). Genital tract tuberculosis is characterized by granulomas. Usually, the inflammation that follows infection causes granuloma formation. This granuloma causes scarring and obstruction, which leads to infertility (Kumar, 2008). Viral infections like the human papillomavirus (HPV) cause DNA fragmentation in sperm cells, and lower sperm count, concentration, and viability. Coronavirus causes high fever, oxidative stress and sperm DNA fragmentation (Çetinavci et al., 2021). Other viruses that affect semen quality are hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) (Guo et al., 2024).

3. Diagnosis of Male Infertility

To diagnose male infertility, first, a detailed medical history must be taken to examine the risk factors. Then, a physical examination must be performed to eliminate the anatomical abnormalities. In the next step, semen analysis and imaging methods need to be applied. Anatomical causes can be detected with radiological methods (Jhaveri et al., 2010; Krausz, 2011; Jungwirth et al., 2012; Tournaye et al., 2017).

3.1. Semen analysis

Semen analysis is a simple, inexpensive method that provides valuable information for diagnosis. It provides critical information about sperm concentration, motility, and morphology. The WHO manual, 5th edition, was published in 2010 and revised as the 6th edition in 2021. For this manual, normal semen parameters are semen volume ≥1.5 mL, sperm concentration of ≥15 million/mL, total sperm count ≥39× 10^6/mL, motility of ≥32%, sperm vitality ≥58%, and normal morphology of ≥4% (WHO 2010, WHO 2021).

Table 1. Pathological Semen Quality According to (WHO, 2010; WHO, 2021).

Nomenclature	Evaluation Result
Oligozoospermia	Sperm concentration <15 x 10^6/ml; total sperm number <39 x 10^6/ml
Asthenozoospermia	<32% progressively motile spermatozoa
Teratozoospermia	<4% morphologically normal spermatozoa
Oligo-asteno-teratozoospermia	Disturbance of all three parameters
Azoospermia	No spermatozoa in the ejaculate
Cryptozoospermia	Spermatozoa absent from fresh preparation but observed in a centrifuged pellet
Leucospermia (leucocytospermia)	>1 x 10^6 ml leucocytes in the ejaculate
Aspermia	No ejaculate

Semen analysis may show a decrease in sperm count (oligozoospermia), decreased sperm motility (asthenozoospermia), and structurally abnormal sperm (teratozoospermia). Semen volume and pH may give clues about seminal vesicle pathologies (Jungwirth et al., 2012; WHO, 2021; Song et al., 2025). The diagnosis should be made based on at least 2 semen analyses. Factors that may compromise the reliability of the analysis and need to be considered are that sperm samples must be collected appropriately. It should be kept at body temperature during transportation. Sexual intercourse should be avoided for a period of 2-5 days. Before semen collection, a high fever illness should be questioned. Additionally, the antibiotics and medications used should be questioned (Krausz, 2011).

3.2. Endocrine analysis

One of the other important diagnostic methods is hormonal tests. Required to identify endocrine disorders. Testosterone, FSH, and LH levels must be examined for checking the hypothalamic-pituitary-gonadal axis (Viramgami et al., 2025). Pituitary adenomas cause hyperprolactinemia, which

suppresses gonadotropin-releasing hormone (GnRH) secretion and causes infertility (Haidenberg et al., 2024). Thyroid dysfunctions such as hyperthyroidism and hypothyroidism change semen parameters and reduce fertility (Anelli et al., 2024).

3.3. Radiologic analysis

Imaging of the male genital system plays a very important role when investigating the causes of infertility. Ultrasound is considered the gold standard method for scrotal examination. Scrotal lesions like varicoceles, testicular cancers, and epididymal obstruction may be detected by ultrasound examination (Lotti et al., 2021; Lotti et al., 2024). Color Doppler ultrasonography, contrast-enhanced ultrasonography, and sonography allow doctors to evaluate the size, vascularity, and abnormal appearance of structures within the scrotum. Scrotal ultrasonography is also used to investigate scrotal pain, masses, and trauma (Bertolotto et al., 2018; Huang et al., 2020). Transrectal ultrasound is especially used to examine the distal parts of the genital tract. Allows visualization of the vas deferens, seminal vesicles, prostate, and ejaculatory ducts (Sihag et al., 2018). MR imaging has the ability to provide high-quality and multiplanar images. In this way, it is used especially in examining the pathological conditions of the prostate, seminal vesicles, and ejaculatory ducts (Donkol, 2010).

3.4. Genetic analysis

Genetic tests are not needed to be performed on every azoospermic patient who applies for infertility. It should be evaluated according to the clinical characteristics of each patient. There is no need for genetic testing in a patient whose vasa is palpable during physical examination and also whose testicular volume, semen volume, and FSH levels are normal (Wosnitzer, 2014). In addition, genetic testing is not required for patients who have not had infertility problems in the past, patients who have received chemotherapy or radiotherapy treatment, or patients whose sperm concentration in previous tests is >5 million/mL ejaculate fluid (Meistrich, 2013). Patients who need testing are those with suspicion of congenital obstruction, primary testicular failure with low testicular volume, and high FSH. Also, genetic testing is recommended for the patients with oligospermia or azoospermia to identify chromosomal abnormalities (Wosnitzer, 2014). Karyotype analysis is generally used in Klinefelter syndrome (Wosnitzer, 2014; Hssaini et al., 2024). The Y chromosome is responsible for a wide range of processes, from the development of the testicles to spermatogenesis. There are some testis-specific gene regions on the long arm of the Y chromosome. Most of these genes are located in the "azoospermia factor" AZF region and are the most important target in the study of genetic causes of male infertility (Deng et al., 2023; Osadchuk et al., 2024). In Y chromosome microdeletions, AZFa, AZFb, and AZFc gene regions may be analyzed (Krausz et al., 2017). Also, in cystic fibrosis patients, CFTR gene mutations may be searched for diagnosis of infertility (Li et al., 2024).

4. Conclusion

Male infertility is multifactorial, due to endocrine, genetic, anatomic, infection, environmental, and lifestyle causes. Diagnosis generally requires a thorough evaluation that typically consists of a history, physical examination, and semen analysis. Genetic testing, imaging, and medications could be employed in finding underlying problems. Also, lifestyle, diet, smoking, alcohol, and drugs must be controlled. Male infertility is a global health problem that requires a multidisciplinary approach for effective diagnosis and treatment. Ongoing research, public awareness, and advances in medical technology are essential to improve outcomes for affected individuals and couples. Nowadays, there are rapid developments in medicine. The advancements in diagnostic methodologies and treatments, hormone treatment, surgical techniques, and assisted reproductive technologies have benefited many couples so far. Future research on male infertility may uncover the mechanism of idiopathic infertility, examine the prevention of underlying genetic deterioration, and develop new biomarkers and AI-based algorithms. Additionally, stem cell therapies may be tested, and assisted reproductive technologies may be optimized. Research may also focus on developing cost-effective solutions and expanding healthcare delivery to larger areas. In summary, elucidating the etiology of infertility and diagnosing it, together with therapeutic developments, can help effectively manage male infertility.

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