Invited Review / Davetli Derleme
doi: 10.18678/dtfd.1181407

Duzce Med J, 2022;24(S1):1-6
Düzce Tıp Fak Derg, 2022;24(S1):1-6

Evaluation of Male Infertility

Erkek İnfertilitesinin Değerlendirilmesi

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Received / Geliş Tarihi : 15.05.2022
Accepted / Kabul Tarihi : 28.05.2022
Available Online /
Çevrimiçi Yayın Tarihi : 28.09.2022

ABSTRACT

Infertility is a condition that has psychological and social effects on couples. Around 50% of fertility problems originate in males. The causes of male infertility are highly variable, and many health conditions, congenital or acquired diseases can affect male fertility. While some causes are reversible, some of the causes are curable but not reversible. The main purpose of a male assessment is to identify correctable causes that may affect the fertility or health status of the patient. Correction of curable or reversible factors can improve both couples to have children and improve the general health of the man. Despite several research in this field, in many cases, the underlying causes are unknown. A proper infertility evaluation is essential to prevent complications associated with assisted reproductive techniques and testicular sperm extraction (TESE), and psychological problems that may result from failure, and to provide accurate preoperative information to patients. Initial evaluation for fertility should include a detailed physical examination along with his medical and reproductive history. Although sperm analysis is still a critical assessment in evaluating male infertility, the introduction of advanced diagnostic tests facilitates the determination of the etiology. This paper discusses the evaluation of male infertility in light of current guidelines.
Keywords: Genetic evaluation; hormonal evaluation; male infertility; semen analysis.

ÖZ

İnfertilite çiftler üzerinde psikolojik ve sosyal olarak etkileri olan bir durumdur. Fertilite problemlerinin yaklaşık %50'si erkeklerden kaynaklanmaktadır. Erkek infertilitesinin nedenleri oldukça değişkendir ve birçok genel sağlık durumu, doğuştan gelen veya sonradan kazanılan hastalıklar erkek fertilitesini etkileyebilir. Bazı nedenler geri döndürülebilir iken, bazı nedenler tedavi edilebilirdir ancak geri döndürülebilir değildir. Erkek değerlendirmesinin temel amacı, hastanın fertilitesini veya sağlık durumunu etkileyebilecek düzeltilebilir nedenleri belirlemektir. Tedavi edilebilir veya geri döndürülebilir faktörlerin düzeltilmesi, hem çiftin çocuk sahibi olmasını sağlayabilir hem de erkeğin genel sağlık durumunu iyileştirebilir. Bu alandaki birçok araştırmaya rağmen, çoğu durumda altta yatan etiyoloji bilinmemektedir. Doğru bir infertilite değerlendirmesi, yardımcı üreme tekniklerine ve testiküler sperm ekstraksiyonuna (TESE) bağlı komplikasyonları ve başarısızlıktan kaynaklanabilecek psikolojik sorunları önlemek ve hastalara işlem öncesi doğru bilgi vermek için gereklidir. Fertilite için ilk değerlendirme, tıbbi ve reprodüktif öykü ile ayrıntılı bir fizik muayeneyi içermelidir. Sperm analizi erkek infertilitesinin değerlendirilmesinde halen önemli bir araç olmakla birlikte, ileri tanısal testlerin kullanılmaya başlanması etiyolojinin belirlenmesini kolaylaştırmaktadır. Bu makale, mevcut kılavuzlar ışığında erkek infertilitesinin değerlendirilmesini tartışmaktadır.
Anahtar kelimeler: Genetik değerlendirme; hormonal değerlendirme; erkek infertilitesi; semen analizi.

INTRODUCTION

Infertility is defined as the inability of a couple to conceive despite having frequent, unprotected sex for at least a year for couples (1). About 85% of couples achieve pregnancy within one year of trying. At the end of one year, 15% of couples trying to conceive are diagnosed with infertility. Around 50% of fertility problems originate in males.

Male infertility can occur due to congenital or acquired diseases, as well as in completely healthy men. Routine physical examination findings and normal hormone parameters are found in healthy men, but decreased spermatozoa count (oligospermia), decreased motility (asthenospermia), and multiple abnormal forms (teratozoospermia) in the morphological inspection can be detected. There are many causes of male infertility. Some causes, such as hypogonadotropic hypogonadism and ejaculatory duct obstruction are reversible. Other causes, such as testicular torsion, trauma, or infection-related testicular atrophy are curable but not reversible. Although there is an unexplained decrease in semen quality in 25-30% of men, the etiology of male infertility cannot be determined, and it is called idiopathic male infertility. Unexplained infertility, found in approximately 25% of couples, is a condition in which semen analyses are within normal values and endocrine abnormalities are excluded (2). The etiology of male infertility is summarized in Table 1 in the European Association of Urology (EAU) guidelines (3).

The main purpose of a male assessment is to identify correctable causes that may affect the fertility or health status of the patient. Diagnosing and treating curable conditions can improve a man's fertility and allow the partner to have children through intercourse or assisted reproductive techniques. The testis is a heterogeneous organ. Spermatogenesis can occur in any part of the testis. Therefore, in azoospermic patients, there may be sperm production in the testicles, even in small quantities. Identifying incurable conditions frees couples from unnecessary interventions and allows them to consider options such as adoption or donor insemination. Male infertility may be related to other systemic comorbidities and may sometimes be an emerging symptom of an underlying severe condition (4). Failure to identify disorders such as pituitary tumors or testicular cancer can lead to severe consequences. Identifying genetic etiologies of male infertility permits couples to receive genetic counseling about genetic abnormalities that may affect their children's health. An appropriate male assessment is necessary for the couple to better understand the main cause and consequences of the problem.

EVALUATION

Couples who do not conceive after at least one year of regular, unprotected sexual intercourse should be evaluated for male infertility. Since pregnancy rates can drop severely in women older than 35, male infertility evaluation is recommended six months later for couples with a female partner older than 35. However, for men with concerns about their future fertility, evaluation before one year may be considered (2). Screening initiates with a medical and reproductive history, physical examination, and two semen samples at least one month apart. Depending on the history, physical examination, and semen analysis results, further andrological assessments such as hormonal and genetic evaluation may be recommended.

Medical and Sexual History

A history covering all etiologies affecting male fertility should be taken. The following areas should be considered in order.

Reproductive and Sexual History

The couple's sexual practices, including frequency of unprotected intercourse and duration, the timing of coitus, miscarriages, fertility treatments, prior conception and use of contraception, and ejaculatory and erectile function, should be assessed. For women with a regular cycle, ovulation typically will occur 14 days before the start of their next period. It is recommended to have intercourse every 48 hours leading up to ovulation to optimize the chances of pregnancy (5). Sexual dysfunctions can be a cause or result of infertility. The absence of sexual satisfaction, hypoactive sexual desire, erectile dysfunction, and premature ejaculation are common sexual disorders in infertile men (6). Therefore, the patient should be questioned about intercourse frequency, libido, quality of erection, possible sexual distress, and ejaculation. A solution should be offered to couples undergoing infertility treatment as soon as a diagnosis of sexual dysfunction is made. In addition, treating male infertility might reverse infertility-related sexual dysfunction (6).

Table 1. Male infertility causes and associated factors and percentage of distribution (EAU, 2021)

Diagnosis	Patients (%)
All	100
Infertility of known (possible) cause	42.6
Maldescended testes	8.4
Varicocele	14.8
Sperm auto-antibodies	3.9
Testicular tumor	1.2
Others	5.0
Idiopathic infertility	30.0
Hypogonadism	10.1
Klinefelter syndrome (47,XXY)	2.6
XX male	0.1
Primary hypogonadism of unknown cause	2.3
Secondary (hypogonadotropic) hypogonadism	1.6
Kallmann syndrome	0.3
Idiopathic hypogonadotropic hypogonadism	0.4
Residual after pituitary surgery	<0.1
Late-onset hypogonadism	2.2
Constitutional delay of puberty	1.4
Others	0.8
General/systemic disease	2.2
Cryopreservation due to malignant disease	7.8
Testicular tumor	5
Lymphoma	1.5
Leukemia	0.7
Sarcoma	0.6
Disturbance of erection/ejaculation	2.4
Obstruction	2.2
Vasectomy	0.9
Cystic fibrosis (CBAVD)	0.5
Others	0.8

EAU: European Association of Urology, CBAVD: congenital bilateral absence of the vas deferens

Medical and Surgical History

It is necessary to question the medical drugs used by the patients and their previous surgeries. Medications may disrupt male fertility by adversely affecting libido, impaired ejaculation and erectile function, damage to the hypothalamic-pituitary-gonadal axis, and direct gonadotoxic effects. The patient's medications that affect testicular function, such as alpha-blockers, immune modulators, chemotherapeutic agents, antiandrogens, testosterone preparations, and antipsychotics, should be questioned. Because of their treatments, testicular germ cell tumors, Hodgkin lymphoma, and leukemia are cancers linked with male infertility during the reproductive period. It is suggested that cancer patients should be informed about the harmful effects of chemotherapy agents on spermatogenesis (2). Scrotal surgeries such as orchiopexy, trauma or torsion, hernia repair, vasectomy, and pelvic surgeries that will affect the male's fertility should be questioned. Sperm cryopreservation should be offered to essential patients before procedures that may affect fertility.

Undescended Testis and Varicocele

Cryptorchidism can be a potential cause of subfertility by impairing spermatogenesis. In addition, it is known that the incidence of testicular germ cell tumors is increased in men with cryptorchidism. Performing undescended testis surgery between 6 and 18 months may preserve spermatogenesis and decrease the risk of testicular tumors (7). Clinic varicoceles may cause secondary infertility by mechanisms including increased intratesticular reactive oxygen species (ROS), hypoxia, sperm DNA damage, and compromised testicular cooling. A recent meta-analysis has recommended surgical varicocelectomy in men with clinically significant varicoceles with affected semen analysis (8).

Childhood

The patient’s degree of virilization should be evaluated by inquiring about the age at puberty and sexual development.

Lifestyle Factors

Male infertility is closely related to lifestyle factors. The most important of these are smoking, excessive alcohol consumption, recreational drug use, and obesity (9). These habits are associated with increased sperm morphological defects, lower sperm motility, and lower sperm concentration. Obesity-induced endocrine changes resulting in the peripheral conversion of testosterone to estrogen are associated with impaired spermatogenesis (10). Obesity has been linked with low total testosterone and serum sex hormone binding globulin (SHBG), with normal serum follicle stimulating hormone (FSH) and luteinizing hormone (LH).

Toxic Testicular Exposure

Conditions such as sexually transmitted diseases, epididymo-orchitis, and mumps orchitis can significantly impair testicular function. Chlamydia trachomatis and Neisseria gonorrhea may cause urethritis, prostatitis, and epididymo-orchitis. Epididymis inflammation can provoke male infertility through sperm tract obstruction (11). Tuberculosis, Mycoplasma genitalium, and Ureaplasma urealitycum may cause male subfertility. Epidemiological studies have reported that exposure to endocrine-disrupting chemicals such as pesticides, phthalates, and bisphenol A may impair testicular development during the intrauterine period and lead to testicular dysgenesis syndrome (12).

Family History

Genetic diseases such as immotile cilia syndrome, cystic fibrosis, deletions in the Y chromosome, and chromosomal abnormalities are hereditary causes of male infertility. Obtaining information about the reproductive history of the biological parents may help determine the etiology. Pre-pregnancy genetic counseling and preimplantation genetic diagnosis should be offered to these patients.

Physical Examination

One of the indispensable steps of male infertility evaluation is physical examination. Genitalia, body habitus, and secondary sexual characteristics such as pelvic build, hair distribution, facial and chest hair, and upper body muscular build should be evaluated. A eunuchoid body habitus, tall stature, gynecomastia, decreased body hair, or obesity might be seen in patients with Klinefelter syndrome. Because it can reflect prenatal androgen insufficiency, the location of the urethral meatus should be evaluated. Testes should be examined for bilateral presence, size, consistency, and presence of mass. Detailed evaluation should be made for plaques, penile curvature, hypospadias, or epispadias that may impair the semen deposition in the vaginal vault. Epididymides examination can reveal induration or fullness indicative of infections or obstruction. The standard diagnostic method for varicocele is still physical examination. The diagnosis is made by palpating the scrotum during a thorough physical examination. The patient is examined in the standing and supine position, and the scrotum is inspected for distended veins. Varicocele grade 1 is palpable only by the Valsalva maneuver, grade 2 is not visible but palpable without the Valsalva maneuver, and grade 3 is visible through scrotal skin. The vas deferens are palpated during the examination of the scrotum. The absence of the vasa deferentia may indicate the congenital bilateral absence of the vas deferens (CBAVD). Because the rectal examination is essential in identifying large midline cysts or dilated seminal vesicles, men with a low ejaculate volume should have a digital rectal examination. It might indicate ejaculatory duct obstruction.

Semen Analysis

World Health Organization (WHO) and recent guidelines recommend semen analysis as the first laboratory test for evaluating male fertility. The WHO Laboratory Manual for the Examination and Processing of Human Semen and Sperm-Cervical Mucus Interaction was first published in 1980. The most recent manual was published as the sixth edition in 2021. The threshold reference values for semen characteristics as published in WHO guidelines are summarized in Table 2.

Conventional semen analysis provides information about the patency of the duct system, the production of spermatozoa in the testes, and glandular secretory activity with a typical abstinence period of 2-7 days, two semen samples should be requested from all patients in general, 2-3 weeks apart.

The seminal vesicles provide 70% of the ejaculate volume. The etiology of the absence of seminal fluid after orgasm (aspermia) is variable and includes pelvic trauma, surgery or radiation, spinal cord injury, ejaculatory duct obstruction, and neurologic causes. Especially after pelvic surgery, there may be retrograde ejaculation into the bladder. In this case, a post-ejaculatory urine examination

Table 2. Cut-off reference values for semen characteristics as published in World Health Organization manuals

	1st ed. (1980)	2nd ed. (1987)	3rd ed. (1992)	4th ed. (1999)	5th ed. (2010)	6th ed. (2021)
Volume	—	≥2.0 mL	≥2.0 mL	≥2.0 mL	≥1.5 mL	≥1.4 mL
Sperm concentration	20-200x10^6 / mL	≥20x10^6 / mL	≥20x10^6 / mL	≥20x10^6 / mL	≥15x10^6 / mL	≥16x10^6 / mL
Total sperm count	≥40x10^6 / mL	≥40x10^6 / mL	≥40x10^6 / mL	≥40x10^6 / mL	≥39x10^6 / mL	≥39x10^6 / mL
Sperm motility (% progressive)	≥60%	≥50%	≥50%	≥50%	≥32%	≥30%
Sperm vitality (%)	—	≥50%	≥75%	≥75%	≥58%	≥54%
Sperm morphology (% normal)	≥80.5%	≥50%	≥30%	≥15%	≥4%	≥4%

should be performed after ejaculation. Ejaculate volume <1.4 mL is most likely due to incomplete orgasm, incomplete collection, or incorrect abstinence. However, it may also be observed in males with the absence of vas deferens, sympathetic dysfunction, retrograde ejaculation, ejaculatory duct obstruction, and hypogonadism.

Measuring pH in the ejaculate is a part of the basic semen analysis. Prostate secretion is acidic and seminal vesicle secretion is also alkaline. An acidic seminal pH in patients with azoospermia may specify obstruction. A basic seminal pH (pH is >8.0) may point out inflammation or accessory gland impairment.

The semen liquefies within a certain period with the effect of prostate enzymes. Hyperviscosity is characterized by a thick and coagulated appearance of seminal fluid. It can be caused by dysfunction or infection of the male accessory glands. Insufficient secretion of prostate proteolytic enzymes results in failure of liquefaction.

Accurate measurement of sperm concentration in ejaculates is important diagnostically. Oligospermia, also known as oligozoospermia, is considered cases under 14 million sperm per milliliter of semen. The complete absence of sperm in the ejaculate is called azoospermia. To confirm azoospermia, on two separate occasions, semen should be centrifuged and evaluated for the presence of sperm under a light microscope.

The motility of each spermatozoon is graded as progressive motility, nonprogressive, and immotility. Progressive motility is defined as sperm that move actively, regardless of speed, either linearly or in a large circle. Nonprogressive indicates movement in place or in small circles. Immotility is defined as no movement. It is known that the percentage of progressively motile sperm is associated with pregnancy rates (13). A decrease in total motility or progressive motility is defined as asthenospermia.

Sperm morphology is routinely examined with Papanicolaou, Diff-Quik, or Shorr smears on an air-dried, fixed, and stained semen smear. After examination, smears are scored according to Kruger's strict criteria classification (14). Papanicolaou, Diff-Quik, or Shorr smears can both stain spermatozoa and allow the differentiation of "round" cells. Anormal morphology is decided based on head, midpiece, and tail abnormalities. There are some criteria for the definition of normal spermatozoa: 1) the head should be smooth oval-shaped, 4-5 µm long, and 2.5-3 µm wide. It should also have a visible acrosome covering 40-70% of the sperm head. 2) The midpiece should be approximately one and a half times the length of the head and slender. 3) The tail should be uniform, straight, uncoiled, and not curled. Teratozoospermia is a condition in which less than 4% of sperm have normal morphology.

Head defects: small, large, tapering pyriform, amorphous, and vacuolated heads, double heads, small acrosomal area, or any combination of these.

Mid-piece defects: thin, thick, or irregular mid-piece, a 'bent' neck, asymmetrical insertion between the mid-piece-the head, thin, thick, or irregular mid-piece, or any combination of these.

Tail defects: short, hairpin, multiple, broken or bent, irregular width, or any combination of these.

Hormonal Assessment

The hypothalamic-pituitary-gonadal axis is the key regulator of sex development and reproduction. Gonadotropin-releasing hormone (GnRH) is a very important hormone in the hypothalamic-pituitary-gonadal axis in males and its pulsatile secretion defines the pattern of secretion of the FSH and LH, which then regulate both the spermatogenesis in the testis and the endocrine function.

FSH affects the Sertoli cells, which accelerate spermatogonial maturation. The number of spermatogonia negatively correlates with the levels of FSH (15). In Leydig cells, LH effects cause the synthesis and release of testosterone. Hypergonadotropic hypogonadism, also called primary hypogonadism, is characterized by elevated FSH and LH, as well as low or normal testosterone. A state of reduced testosterone production caused by low levels of FSH and LH is known as hypogonadotropic hypogonadism. In addition, prolonged prolactin excess affects gonadic function, reducing testosterone levels and impairing spermatogenesis.

Endocrine evaluation is not recommended as an initial evaluation in infertility evaluation. It is suitable to perform an endocrine evaluation whenever clinical findings or accompanying sexual dysfunction suggest a defined endocrinopathy and in the presence of oligospermia. In general, endocrine testing is suggested for men with sperm concentrations below 10 million/mL. Hormone analysis is critical, especially in patients with suspected nonobstructive azoospermia. Even though the initial hormonal assessment consists of total serum testosterone and FSH, the accompanying assessment of prolactin, estradiol, and LH lets for a more comprehensive analysis of the patient's endocrine status.

Genetic Evaluation

Genetic abnormalities associated with male infertility are found in approximately 15% of infertile men (16). Patients with genetic abnormalities are frequently related to impaired spermatogenesis and increased aneuploidy. While the most common type of genetic disorder is karyotype anomalies, Klinefelter syndrome is the most common karyotype anomaly. Karyotype anomalies are seen in 12-15% in azoospermia, 5% in severe oligozoospermia,

and less than 1% in normal semen (17). While the American Society for Reproductive Medicine (ASRM) recommends karyotype analysis for patients with sperm count <5 x 10^6/mL, EAU recommends for patients with sperm count <10 x 10^6/mL (2,3). Y chromosome microdeletions identified within the azoospermia factor (*AZF*) gene region are highly associated with severe oligozoospermia or azoospermia and male infertility. These microdeletions are referred to as *AZFa*, *AZFb*, or *AZFc*, based on the genomic region deleted. Both ASRM and EAU point out that Y chromosome microdeletion analysis is indicated in patients with a sperm count less than 5 x 10^6/mL (2,3). In addition, EAU guidelines recommend that Y chromosome microdeletion testing be made mandatory for patients with sperm concentration <1 x 10^6/mL. Although sperm may be found through testicular sperm extraction (TESE) in approximately 50% of men with an *AZFc* deletion, spermatozoa cannot be retrieved by TESE in men with *AZFa* or *AZFb* microdeletions. Because of *AZFc* microdeletions can be transmitted to male offspring, counseling couples is recommended before assisted reproductive techniques.

Cystic fibrosis, manifested by multisystem organ dysfunction, is a rare autosomal-recessive disease. Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene are a cause of male infertility although spermatogenesis is mostly normal, nearly all men with cystic fibrosis have abnormalities of the mesonephric duct, including atrophic seminal vesicles and vas deferens, and the absence of ejaculatory ducts. Current guidelines recommend CFTR screening in all men with clinical cystic fibrosis or CBAVD. The CFTR test is not recommended as a routine screening for men for whom obstruction is not considered for the etiology of infertility.

Specialized Sperm Evaluations

Since semen analysis does not define defects associated with the functional aspects of spermatozoa, sperm function tests were needed. Although defective sperm-zona interaction is the main cause of fertilization failure, with the widespread use of intracytoplasmic sperm injection, sperm DNA fragmentation tests have now been instead of hemizona or acrosome function assays in clinical practice. Currently, the sperm chromatin structure assay, terminal deoxynucleotidyl transferase-mediated dUTP nick-end labeling, and sperm chromatin dispersion are commonly used sperm DNA fragmentation tests. Due to the absence of strict standardization and clear cutoff values, ASRM does not recommend routine use of sperm DNA fragmentation testing. Sperm DNA fragmentation testing is recommended by the EAU only in couples with recurrent pregnancy loss or in men with unexplained infertility.

Another way to evaluate sperm function is to measure seminal oxidative stress. Excessive amounts of ROS cause oxidative stress and cause DNA, lipid, and protein damage (18). However, the EAU has recommended that these tests remain experimental until the tests used to measure ROS are validated in randomized controlled trials.

Imaging

Scrotal ultrasound (US) is an available imaging method in evaluating infertile men in some cases due to its safety, noninvasive nature, and low cost. The US provides information about testicular size, volume, and echogenicity, blood flow, epididymal structure, and the presence of varicocele. Current guidelines do not recommend scrotal color Doppler for subclinical varicocele screening. The EAU suggests performing the scrotal US in men with infertility, as they have a higher risk of testicular cancer. The transrectal US is required to evaluate seminal vesicle and ejaculatory duct dilation and midline prostate cysts in patients with suspected genital tract obstruction. If more detailed imaging is needed, a pelvic magnetic resonance imaging (MRI) can be performed. In men with hyperprolactinemia, cranial MRI can diagnose pituitary pathology. Today, vasography is used intraoperatively during reconstructive microsurgery.

CONCLUSION

Initial evaluation of the male for fertility should include a detailed physical examination along with his medical and reproductive history. Both male and female partners should be evaluated concurrent and hormonal or genetic evaluation should be done after detailed history, physical examination, and sperm analysis results. Proper evaluation of male infertility will not only reveal the etiology of infertility but also provide the emergence of pathologies that threaten male general health, such as testicular tumors and endocrinopathies.

Ethics Committee Approval: Since our study was a review, ethics committee approval was not required.

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: MAİ, ÖY; Design: MAİ, ÖY; Data Collection/Processing: MAİ, ÖY; Analysis/Interpretation: MAİ, ÖY; Literature Review: MAİ, ÖY; Drafting/Writing: MAİ, ÖY; Critical Review: MAİ, ÖY.

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