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Causes of Male Infertility

Erkek İnfertilite Nedenleri

Münevver Serdaroğulları[1,2]

[1]Department of Embryology, British Cyprus IVF Hospital, Nicosia, Cyprus
[2]Faculty of Medicine, Cyprus International University, Nicosia, Cyprus

ORCID ID: M.S. 0000-0001-5196-297X

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ABSTRACT

Infertility is a global health problem and is defined as an inability to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse. The global incidence of infertility is approximately 8–12%, and half of these patients seek medical help for the condition. The use of assisted reproduction technology (ART) has been increasingly used worldwide, and advances in ART have enabled many couples to overcome infertility. Infertility can be related to female infertility, male infertility, a combination of the two or unexplained factors. Male infertility constitutes nearly half of all instances of infertility and affects approximately 7% of the male population. The initial evaluation of male infertility includes obtaining a detailed medical history, a physical examination, an endocrine assessment and semen analysis. Male infertility can be due to hormonal imbalances, genetic problems, physical causes, environmental lifestyle factors or psychological or behavioural factors. Also, advanced male age may affect the quality of sperm, which can lead to male infertility. In conclusion, the causes of male infertility are multifarious. The evaluation and management of male infertility during infertility treatment are of the utmost importance for couples.

Keywords: Male infertility, infertility

ÖZ

İnfertilite dünya çapında bir sağlık sorunu olup, 12 aylık düzenli korunmasız cinsel ilişkiden sonra klinik bir hamilelik elde edememe olarak tanımlanmaktadır. Dünya çapında infertilitenin insidansı yaklaşık %8-12 olarak belirtilmekle birlikte hastaların yarısı bu durum için tıbbi yardım istemektedir. Yardımcı üreme teknolojisinin (YÜT) kullanımı dünya çapında giderek artmakla birlikte, YÜT'deki gelişmeler birçok çiftin infertilite sorunun üstesinden gelmesine izin vermiştir. İnfertilite, kadın infertilitesi, erkek infertilitesi, kadın ve erkek veya açıklanamayan faktörlerin bir kombinasyonu ile ilişkili olabilmektedir. Erkek infertilitesi, tüm infertilite vakalarının neredeyse yarısını oluşturur ve erkek nüfusun yaklaşık %7'sini etkilemektedir. Erkek infertilitesinin ilk değerlendirmesi, ayrıntılı bir tıbbi öykü, fizik muayene, endokrin değerlendirme ve semen analizini içermektedir. Erkek infertilitesi hormonal dengesizlikler, genetik problemler, fiziksel nedenler, çevresel yaşam tarzı faktörleri veya psikolojik veya davranışsal faktörlerden kaynaklanabileceği raporlanmıştır. Ayrıca, ileri erkek yaşı, sperm kalitesini etkileyerek erkek infertilitesine yol açabilir. Sonuç olarak, erkek infertilitesinin nedenleri çok yönlüdür. İnfertilite tedavisi sırasında erkek infertilitesinin değerlendirilmesi ve yönetimi çiftler için son derece önemlidir.

Anahtar Kelimeler: Erkek infertilitesi, infertilite

Infertility is a global health problem and is defined as an inability to achieve a clinical pregnancy after 12 months of regular unprotected sexual intercourse (1). The global incidence of infertility is approximately 8–12%, and half of these patients seek medical help for the condition (2). Assisted reproduction technology (ART) has been increasingly used worldwide, and advances in ART have enabled many couples to overcome infertility. Infertility can be related to female infertility, male infertility, a combination of the two or unexplained factors. Male infertility constitutes nearly half of all instances of infertility and affects approximately 7% of the male population (3). The initial evaluation of male infertility includes obtaining a detailed medical history, a physical examination, an endocrine assessment and semen analysis. The parameters assessed in a semen analysis are the sperm concentration, motility and morphology, and the semen volume and pH. The sperm vitality, the presence of leukocytes, and the number of immature germ cells are also assessed and compared to reference values from the World Health Organization (WHO) (1).

It is well documented that male infertility can be due to hormonal imbalances, genetic problems, physical causes,

Corresponding Author/Sorumlu Yazar: Münevver Serdaroğulları **E-mail:** munevver.coban@gmail.com
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or psychological or behavioural factors. Malnutrition, anaemia, excessive stress and exposure to environmental hazards such as pesticides, lead paint, radioactive substances, mercury, benzene, boron and heavy metals have also been reported to cause male infertility (4-6). Furthermore, advanced male age may affect the quality of sperm, which can lead to male infertility (7).

Spermatogenesis and steroidogenesis (steroid hormone production) are the main functions of the testis. Spermatogenesis is the process by which spermatogonia transform into mature spermatozoa through mitotic and meiotic division (8). Spermatogenesis begins at puberty and occurs in the epithelium of seminiferous tubules in the testis. The induction of spermatogenesis and the persistence of sperm production are regulated through the hypothalamic-pituitary-gonadal axis. In the seminiferous tubules, Sertoli cells are the main cell type, while Leydig cells predominate in the interstitium, which is another main compartment of the testis that consists of loose connective tissue along with blood and lymph vessels (9-11). Testosterone, follicle-stimulating hormone (FSH) and luteinizing hormone (LH) participate in spermatogenesis. The synthesis of these hormones is stimulated by gonadotropin-releasing hormone (GnRH), which is secreted from the hypothalamus. Testosterone production occurs in Leydig cells and is induced by LH. FSH acts on Sertoli cells to support the synthesis of androgen-binding protein and the blood-testis barrier. GnRH secretion disorder causes testosterone deficiency and impairs sperm production (12).

Genetic factors that cause male infertility are heterogeneous. Chromosomal abnormality is defined as any alteration in one or more chromosomes and is categorised as either numerical or structural. Numerical abnormality is when a chromosome is missing or when there is an extra chromosome. For instance, Klinefelter syndrome, the presence of an extra X chromosome in men, is the most common numerical abnormality in men with impaired spermatogenesis (13-15). By contrast, the modification of chromosomal structures, such as translocations, inversions, Y chromosome microdeletions and copy number variations (CNVs), are defined as structural chromosomal abnormalities. Translocations can be Robertsonian (where a whole chromosome has joined to another at the centromere) or reciprocal (sections from two distinct chromosomes have been swapped). Translocations are 10 times more common among infertile men compared with the normal population. These translocations can lead to decreased fertility, spontaneous abortion and birth defects (16). Inversions occur when a piece of a chromosome rotates 180 degrees within the same chromosome; thus, there is no loss of genetic material (17). Like translocations, inversions may cause infertility, spontaneous abortions and birth defects (16-18). Y chromosome microdeletions may also be a cause of spermatogenetic failure. Three regions on the long arm (Yq) of the Y chromosome have been identified: the azoospermia factors (AZFs) AZFa, AZFb and AZFc. Any deletions in these regions might cause male infertility (19). CNVs are large DNA segments that repeat in the genome; the number of repeats varies among individuals (20,21). CNVs have been found to cause spermatogenetic failure by affecting genes that are essential for spermatogenesis (22,15).

Spermatogenesis is a complex process, and large numbers of genes are present during this event. Gene mutations that cause abnormal spermatogenesis without any other symptoms give rise to non-syndromic male infertility (23). Identified gene mutations have been generally grouped according to the resulting phenotype, such as spermatogenic failure, teratozoospermia and asthenozoospermia (13). Technological advances have enabled researchers to analyse the whole genome to identify various specific gene mutations that lead to male infertility (24). However, no single gene is known to cause male infertility (25). Some genes are notable owing to their prevalence in specific groups. *AURKC* and *DPY19L2* mutations have been related to teratozoospermia (26, 27). Two recurrent mutations have been identified for *AURKC*: one in the North African population and one in the European population. A carrier frequency of 1/50 was established in North African patients who had macrocephaly (large head and multi-tailed spermatozoa) (26). Later, it was demonstrated that the majority of macrocephalic spermatozoa are tetraploid, meaning that they have no chance of intracytoplasmic sperm injection (ICSI) (28). Mutations in the *DPY19L2* gene have been correlated with globozoospermia (round-headed spermatozoa); this mutation is found in 60% of globozoospermic patients (27). It has been demonstrated that assisted oocyte activation enables better fertilization rates (29). Although there is no dominant gene yet to be the reason for spermatogenic failure, it has been reported that *TEX11* mutation can cause meiotic arrest and azoospermia with a frequency of 2-15% in azoospermic men (8,13,30). Furthermore, although there is limited evidence, mutations in *TEX15* are thought to cause spermatogenic failure and a decreased sperm count over time. Patients with this mutation could be advised to undergo sperm cryopreservation at an early age with the aim of protecting future fertility potential (31). According to a recent study, it has been demonstrated that *M1AP* mutation can cause severe spermatogenic failure leading to male infertility. In the study, they were able to trace *M1AP* mutation in different independent patients in different countries and concluded that *M1AP* should be included in the growing list of validated non-obstructive azoospermia (NOA) genes (32). In recent years, due to the discovery and presence of various specific gene mutations, there are few custom gene panels for infertility that are available as a diagnostic tool. Genes included in each custom panel are different but in general, gene panels would provide a definitive causal diagnosis and more accurate treatment in ART (33-36).

Physical problems can decrease the sperm count and/or sperm morphology. Varicocele is a congenital vascular anomaly that causes impaired sperm motility, decreased sperm count, and impaired sperm structure (37). Moreover, in some infertile men, sperm cannot travel from the testicles to the penis because of sperm duct obstruction. The blockage or deficiency of one or both tubes can be caused by genetic or developmental factors.

Torsion occurs when the testicle is bent in the scrotum and is characterized by excessive swelling. This leads to testicular damage because the blood vessels that feed the testicle are compressed. Furthermore, infections and diseases such as tuberculosis, brucellosis, gonorrhoea, typhoid, flu, chickenpox, rubella and syphilis can cause obstructions and testicular atrophy (38). These conditions can lead to changes in sperm quality by decreasing the sperm count and motility. Retrograde ejaculation (where the semen does exit the body at the time of ejaculation but instead transfers to the bladder), premature ejaculation or anejaculation (the lack of ejaculation) can also be reasons for male infertility (39).

In conclusion, the causes of male infertility are multifarious. Along with the assistance of emerging technology, the identification of genes for diagnostic purposes would provide better guidance to clinicians. The evaluation and management of male infertility during infertility treatment are of the utmost importance for couples.

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