EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 10
364-374
Year: 2022

UPDATE ON POTENTIAL CAUSES OF AZOOSPERMIA: A SYSTEMATIC REVIEW

Renu Jaiswal, Ishwerpreet Kaur Jawanda, Thomson Soni, Harkeerat Kaur, Divya and Vijay Prabha*

Department of Microbiology, Panjab University, Chandigarh-160014, India.

***Corresponding Author: Vijay Prabha**
Department of Microbiology, Panjab University, Chandigarh-160014, India.

Article Received on 20/08/2022 **Article Revised on 10/09/2022** **Article Accepted on 30/09/2022**

ABSTRACT
Utter devoid of spermatozoa in the ejaculate is known as azoospermia. It is one of the most substantial and serious consequences of male infertility. Azoospermia precise pathogenesis is often not understood. About 1% of males in the overall population and 10%-15% of infertile men have azoospermia. This may be attributed to pre-testicular, testicular, and post-testicular causes. It is also categorized as obstructive or non-obstructive azoospermia (NOA). Obstructive azoospermia is a potent source of male infertility and may be caused by inflammation, genetic malformations, or iatrogenic harm. Across many instances of obstructive azoospermia, microsurgical vasal restoration is an effective therapy; nonetheless, some couples may need sperm extraction and in vitro fertilisation. On the other hand, non-obstructive azoospermia (NOA) is the most serious consequence of male infertility and is characterised by the apparent lack of sperm in the discharge owing to malfunction of spermatogenesis. NOA is caused by either intrinsic testicular dysfunction or insufficient gonadotropin synthesis. There is a somewhat high occurrence of chromosomal or genetic anomalies compared to the general population, thus they should be examined. NOA owing to insufficient gonadotropin production is a disorder that may be treated medically to enhance fertility. This significant study gives an up-to-date account of the most current evidence regarding azoospermia's aetiology.

INTRODUCTION
Azoospermia is a medical ailment in which the ejaculate of male is entirely devoid of spermatozoa that accounts for approximately 15% - 20% of infertile men associated with poor reproductive chances (Kang *et al*., 2021). No spermatozoa is discovered in the bottom of a centrifuged specimen, according to the definition of azoospermia given in the World Health Organization (WHO) manual, 5th edition (World Health Organization, 2010). Azoospermia differs from aspermia, as aspermia is actually the complete lack of seminal fluid at the time of ejaculation. But, in case of azoospermic patient spermatozoa cannot be seen under a microscope when a concentrated semen sample is observed (Aziz, 2013). Azoospermia may result from a wide range of illnesses or conditions. Azoospermia is becoming a health burden across the globe, as it is increasing rapidly. It shows a negative impact on the male reproductive potential, since males with azoospermic condition are infertile. It is estimated that 5,000 to 7,500 males out of a total of 50,000 will be infertile, with 500 of those men being azoospermic. If the female is unsuccessful in getting pregnant despite of unprotected intercourse, azoospermia is considered as one of the reasons (Matschinske *et al.*, 2021). Even though azoospermia has a wide range of etiologies, but still the causes of this disorder fall under three wide-range of categories: pretesticular, testicular and post-testicular.

Pretesticular endocrine disorders are the primary causes of azoospermia. It is extremely rare and affects 3% of infertile men, according to statistics (Sigman and Jarow, 1997). Congenital or acquired hypogonadotropic hypogonadism also comes under the etiologies. A deficiency in gonadotropin-releasing hormone release from the hypothalamus is involved in the pathogenesis (GnRH). Pituitary tumours, trauma, and steroid use are all examples of acquired causes. Other pre-testicular reasons include androgen resistance brought on by mutations in the androgen receptor gene (Mak and Jarvi 1996) and hyperprolactinemia (Burrows *et al.*, 2002), which inhibits GnRH secretion.

Spermatogenesis abnormalities are inherent to testicular etiologies. Direct testicular pathology might result from the genetic defects, undescended testes, testicular torsion, mumps orchitis, gonadotoxic drug side effects, varicocele-induced testicular injury and some idiopathic causes. One of the most prevalent genetic problems in infertile males is chromosomal abnormalities that affect spermatogenesis, which seem to be present in 15% of azoospermic and 5% of oligospermic men (Pandiyan and Jequier 1996; Peschka *et al.*, 1999).

Both sperm delivery blockage and ejaculatory dysfunction are post testicular origins of azoospermia. According to the prevalence of pathological

abnormalities, such as the absence of the vas deferens and ejaculatory duct disorders, the obstruction may occur at several locations, including the vas deferens, epididymis, or ejaculatory duct. The clinical treatment of obstructive azoospermia varies depending on the underlying reason and may include surgical removal of the obstruction, which may result in natural conception, or direct sperm harvesting from the testis or epididymis, followed by the use of Assisted Reproductive Technology (ART) (Practice Committee of American Society for Reproductive Medicine, 2008).

Together, pre-testicular and testicular azoospermia constitute the category of non obstructive azoospermia. Whereas, the post-testicular azoospermia is referred to as the obstructive azoospermia, wherein the spermatozoa are produced by normal testicles but is not ejaculated because of an obstruction present inside the genital tract. So, this disorder can be categorized into two major categories: obstructive azoospermia (OA) and non-obstructive azoospermia (NOA). The former refers to a blockage in the sperm pathway by an obstruction in the seminal tract and normal spermatogenesis, whilst the latter refers to the failure in spermatogenesis (Wosnitzer *et al*., 2014). Although the identification of the aetiology of azoospermia depends on the history and physical examination, but laboratory and genetic testing could also be used for such a purpose.

1. Obstructive Azoospermia

The absence of spermatozoa in the ejaculate despite adequate spermatogenesis is known as obstructive azoospermia (OA). OA is a prevalent urologic problem that affects 6.1% to 13.6 % (Jequier 1985; Aziz *et al*., 2006) of people seeking reproductive treatment. Although vasectomy is a common cause of OA, other etiologies account for 19% to 69 % (Kim *et al.,* 1998; Chan *et al.,* 2005) undergoing surgical investigation for OA. It may also be affected by a multitude of factors, including iatrogenic damage, genetic abnormalities that are present from birth and microbial infections (Baker and Sabanegh, 2013). Genetic disorders and anomalies that cause post-testicular azoospermia (obstructive azoospermia) are Ejaculatory duct obstruction, Phimosis and Midline Congenital Cysts. Ejaculatory duct obstruction is a pathological condition in which one or both ejaculatory ducts are obstructed (Farah *et al.*, 2019).

1.1. Etiologies of OA

1.1.1. Ejaculatory duct obstruction (EDO): About 1% of patients presenting with male infertility have EDO, a very rare cause of OA. Ejaculatory duct blockage is a pathological disease in which one or both ejaculatory ducts are blocked. It can be congenital or acquired (Goldwasser *et al.,* 1985; Pryor *et al.,* 1991). When a patient with semen that has low volume, acidic pH, no spermatozoa, the diagnosis of total EDO must be examined. Fructose is present in the secretions from the seminal vesicles, hence the lack of fructose in the semen confirms the diagnosis. Ejaculatory duct blockage accounts for 1 to 5% of male infertility cases and this problem was first identified by Farley and Barnes (Farley *et al*., 1973; Porch *et al.,* 1978). Although azoospermic males with total blockage were the first to be documented, it is now obvious that obstruction can appear in a variety of forms, including azoospermia and oligoasthenospermia (Smith *et al*., 2008). Extrinsic constriction of the ejaculatory ducts by Mullerian (utricular) or Wolffian (diverticular) cysts is a congenital cause. Iatrogenic trauma (postsurgical), prostatic calcification, seminal vesicle calculi and infection-related scar tissue are all examples of acquired causes. Although there are no pathognomonic signs or symptoms of ejaculatory duct blockage, there are a number of clinical signs and symptoms that are strongly indicative of the disorder. Low-volume azoospermia, dilated seminal vesicles and normal secondary sex characteristics, testes size, and hormonal profiles are all present in men with this disorder. EDO was first identified in males with azoospermia and total ductal blockage, but the condition is now more commonly associated with oligoasthenospermia, which is a symptom of partial EDO. Functional EDO is a type of ejaculatory dysfunction that presents in the same way as physical EDO but without the actual obstruction (Walsh and Turek, 2006).

1.1.2. Congenital bilateral absence of the vas deferens (CBAVD): It affects 1% of infertile males and up to 6% of those suffering from obstructive azoospermia. This problem can be caused by two different mechanisms: 1) mutations in the cystic fibrosis transmembrane regulator (CFTR) gene and 2) anomalies in the mesonephric duct differentiation (McCallum *et al.,* 2001; Ferlin *et al*., 2007). CBAVD is a genital tract disease that is genetically similar to Cystic Fibrosis (CF) but has a different clinical presentation. A small %age of individuals have chronic sinusitis, non progressive bronchitis and pneumonia in children but their primary complaint as adults is infertility (Augarten *et al*., 1994; Casals *et al.,* 1995). The semen parameters are comparable to those found in men with CF (Oates and Amos, 1994). With a prevalence of 1:2500 births and a carrier frequency of 1:20, cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasians (Welsh *et al*., 1995). The CFTR gene is 250 base pairs long and has 27 exons. The most prevalent mutation in the Caucasian population is a three-base-pair deletion in exon 10 (delta F508), however there are over 800 variants known (Uzun *et al.,* 2005). CFTR gene mutations can be found in 80% of men with CBAVD and 43% of males with a congenital unilateral absence of the vas deferens. Normal testis size and spermatogenesis are some of the clinical findings of CBAVD. Although the caput epididymis is usually present, the corpus and cauda are only observed in exceptional cases. Seminal vesicles can be lacking or atrophic, enlarged or cystic, as well as the ejaculate is acidic and less in volume (less than 1 mL) (Clausters *et al.,* 2005; Lebo *et al*., 2007).

1.1.3. Wolffian duct abnormalities: Adults with anomalies of the Wolffian duct frequently exhibit symptoms of pelvic and ejaculatory discomfort, bladder dysfunction, and UTIs. Ectopic ureters with ureterovasal fusion are rare and frequently accompanied by anorectal anomalies and ipsilateral renal agenesis. Any type of damage to wolffian duct results in the emergence of congenital absence of the vas deferens (CAVD). A variation in the CFTR gene, that controls the function of the membrane conductance regulator in cystic fibrosis, frequently results in congenital bilateral absence of the vas deferens (CBAVD). The absence of a palpable vas deferens at the time of the physical examination raises suspicions about this condition. The testicles should be normal in size, consistency and the caput of the epididymis is visible; however, most individuals lack or have hypoplastic seminal vesicles. In a small %age of patients, unilateral renal agenesis can also be linked to CBAVD.

1.1.4. Epididymal obstruction (EO): According to WHO (2010), about 30–67% of azoospermia patients suffer from epididymal obstruction. Sometimes, the surgery of epididymis for cyst removal may also result in azoospermia (Dohle *et al.*, 2005). Infection, iatrogenic therapy, trauma, vasectomy and some of the idiopathic reasons are all possible causes of EO (Chan *et al.*, 2002). Patients may experience sino-bronchial symptoms as early as childhood, and bronchiectasis can develop over time. Chronic sinusitis, bronchiectasis, and obstructive azoospermia are the three conditions that make up Young's syndrome. This syndrome is a pathophysiology characterised by obstructive azoospermia, bronchiectasis, and persistent sinopulmonary infections. Mercury exposure is also one of the leading causes for Young's syndrome, and in an elegant argument supporting this theory, Hendry *et al*. 1993 demonstrated the decreasing incidence of Young's syndrome in men born after mercury-containing teething powder and worm medications were banned in the United Kingdom. Young's syndrome might be caused by genetic variants of Kartagener syndrome (Ichioka *et al*., 2006) or mutations in the CFTR gene (Goeminne and Dupont, 2010). In these cases, genetic testing is essential. This condition can result in azoospermia due to a bilateral epididymal blockage. The presence of an amorphous substance within the epididymal lumen causes the blockage (Handelsman *et al.*, 1984). Abnormal mucus quality or ciliary function might be part of the pathogenesis. Although surgical repair is theoretically possible but the results are dismal (Hendry *et al*., 1993). People with this syndrome exhibit normal spermatozoa, and paternity has been established in these patients (Handlesman *et al*., 1984).

1.1.5. Infection: Infections also contribute in the emergence of azoospermia. Under this category, Epididymitis is a common genitourinary condition and also it is an infectious etiology that should always be considered in men with this diagnosis. *Gonorrhea*, *Chlamydia*, *Trichomonas*, brucellosis, BCG, *ureaplasma*, *mycoplasma*, coliforms bacteria, adenovirus, and enterovirus have all been reported as cause of epididymitis. Regardless of the etiology, epididymitis can lead to a strong inflammatory reaction further causing secondary scarring and obstruction of the epididymis. Physical examination may reveal enlarged or indurated epididymis and a transition point suggesting the site of obstruction.

1.1.5.1. Epididymitis: Whenever the epididymis, a long, twisted tube at the end of each of a man's both testicles turns inflamed it is known as epididymitis. The epididymis is a 20-foot-long coil that wraps around the rear of a man's testicle. Some of the symptoms of epididymitis are similar to those of a relatively threatening condition known as testicular torsion (whenever a testicle is twisted around the cord that connects it to the body). Symptoms of testicular torsion, on the other hand, frequently appear considerably sooner. Torsion is a medical issue that can result in the loss of a testicle if not treated promptly. One of the most prevalent reasons of epididymitis are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, both of which are sexually transmitted infections (STIs). In most cases, *Chlamydia trachomatis* or *Neisseria gonorrhoeae* cause the inflammation in young, sexually active males, although *E. coli* is more commonly identified in elderly men (Weidner *et al.*, 1999; Ludwig, 2008). An increased incidence of urethral restrictions, bladder neck obstruction, or benign prostatic hyperplasia (BPH) has been observed in the latter group of patients (Chan & Schlegel, 2002). Inflammation of the epididymal duct has been proposed as a causative agent of prolonged azoospermia or oligozoospermia (Schuppe & Bergmann, 2013). Extensive neutrophil infiltration in the interstitial section, loss of the adluminal chamber, and thicker lamina propria in the seminiferous tubules are histopathological features of epididymitis (Schuppe & Bergmann, 2013). The swelling, known as 'epididymo-orchitis,' can migrate towards the adjacent testes and has been linked to high rates of infertility in numerous clinical investigations. Many males with unilateral epididymo-orchitis had contralateral biopsies demonstrating bilateral gonadal destruction and also, they experienced azoospermia, according to a publication by Osegbe (Osegbe, 1991). In 60 % of instances, a testicular infection with disruption in the process of spermatogenesis occurs as a result of the bacterial infection mounting towards the testis (Ludwig, 2008). A systematic findings of all instances of epididymitis identified in three sexual health clinics during the time period of January to December 2018 was undertaken, with demographics, findings, management, and symptom resolution for two weeks follow up were collected. There were 127 cases of epididymitis in all (mean age 32 years, heterosexual 97, MSM 30). Seven cases of chlamydia, six cases of gonorrhoea, one case of syphilis, and one case of *Trichomonas vaginalis* were found among the 14 cases (around 11 %) caused by sexually transmitted

infections (<35 years n=9; >35years n=5), Three cases of urinary tract infection were also discovered (Shivaraj *et al.*, 2021). Every year, around 600,000 instances of epididymitis are recorded in the United States, with the majority of cases occurring in men aged 18 to 35. Epididymitis is most commonly caused by a bladder or urinary tract infection in males over the age of 35. In rare cases, *E. coli* and *Mycobacterium tuberculosis* can also cause epididymitis. Concomitant infections, such as *Cytomegalovirus*, *Salmonella*, *toxoplasmosis*, *Ureaplasma urealyticum*, *Corynebacterium*, *Mycoplasma*, and mycobacteria, could indeed induce epididymitis in individuals affected with human immunodeficiency virus (HIV). Epididymitis has been frequently associated with orchitis (testicular inflammation) a condition known as epididymo-orchitis. Pain and scrotal swelling last fewer than six weeks in the case of acute epididymitis. Chronic epididymitis is defined by discomfort as in lack of scrotal enlargement and lasts longer than three months.

1.1.6.Vasectomy: Vasectomy is a surgical procedure mainly used for the purpose of male sterilization or permanent contraception. During the procedure, the male vas deferens is cut and tied or sealed so as to prevent sperm from entering into the urethra and thereby prevent fertilization of a female through sexual intercourse. Vasectomy is a procedure that is usually performed in a physician's office, medical clinic. Hospitalization is not normally required as the procedure is not complicated, the incisions are small, and the necessary equipment routine.

1.1.7.Vasal obstruction: Inadvertent damage during the conduct of a hernia repair is the most common cause of unintended vasal blockage. This complication is more common in childhood, but it can happen after any inguinal operation that involves the manipulation of the vas and cord (Matsuda *et al*., 1992). Unilateral Vas Deferens obstruction is compatible with natural fertility. Therefore, Congenital Unilateral Absence of VD (CUAVD) is believed to remain in the most cases undiagnosed. CUAVD is attributable to defective organogenesis of the Wolffian duct system. Renal agenesis is a common clinical feature as well. Also, bilateral or unilateral vasal hypoplasia or unilateral absence of the VD may cause obstructive azoospermia. It was found that a high %age of men with CUAVD demonstrated abnormalities in the contralateral ejaculatory ducts or seminal vesicles as well (Raviv *et al*., 2006). CUAVD is also associated with CFTR mutations (Mickle *et al*., 1995).

1.1.8.Disorders of Ejaculation: Ejaculatory dysfunction encompasses a wide range of disorders, each with its own set of therapeutic options. Ejaculatory dysfunction, as opposed to anorgasmia, should be considered in any patient with a low volume (less than 1.0 ml) or nonexistent ejaculate. The aberrant backward flow of semen into the bladder with ejaculation is known as retrograde ejaculation, and the cause might be anatomic, neurogenic, pharmacologic and idiopathic. Neuroleptics, tricyclic antidepressants, alpha-blockers used to treat prostatism, and some antihypertensives have all been linked to retrograde ejaculation (Hendry *et al.*, 1998; Debruyne *et al.*, 2000; Schuster *et al.*, 2002). The presence of sperm in the post-ejaculate urine is used to diagnose retrograde ejaculation. Although exact criteria for a positive post-ejaculate urinalysis have not been defined, the presence of more than 10 to 15 sperm per high-power field verifies the existence of retrograde ejaculation. A patient with failure of emission, on the other hand, will not have sperm in their urine, which must be evaluated properly on the clinical basis.

2. Non Obstructive Azoospermia

One of the most dreadful types of male infertility is non-obstructive azoospermia (NOA) and it is defined as no spermatozoa in the ejaculate owing to spermatogenesis failure. NOA (type of azoospermia that includes testicular and pre testicular disorders) is found in approximately 60% of azoospermic men (Jarow *etal.*, 1989) is differentiated from OA on the basis of many reasons. NOA is caused by either intrinsic testicular dysfunction or insufficient gonadotropin production. NOA can be caused by various reasons and in this there is observed insufficient gonadotropin production that can be treated medically to increase fertility (Chiba *et al.*, 2016).

2.1. Etiologies of NOA

2.1.1 Hypogonadotropic hypogonadism: Hypogonadotropic hypogonadism is characterised by a lack of gonadotropin secretion (FSH and LH). In the absence of LH and FSH stimulation, testicular Leydig cells secrete less testosterone, and spermatogenesis suffers (Dimitriadis *et al.*, 2017). Kallmann's syndrome, pituitary trauma, pituitary tumours, and anabolic steroid usage are common causes of hypogonadotropic hypogonadism (HGH). HGH is an uncommon cause that give rise to male infertility which can be hereditary or acquired (Liu *et al.*, 2003). Kallmann's syndrome, a congenital source of HGH is linked to a midline cerebral abnormality, mainly with a malformation of the midline cranial structures (Cunningham *et al.*, 1986). The aetiology of this condition is a deficiency in gonadotropin-releasing hormone (GnRH) secretion at the hypothalamus level caused by the inability of GnRH-releasing neurons to move towards the olfactory lobe during the development. In a limited %age of the patients (less than 30%), mutations in any of the five known disorder genes (KAL1, FGFR1, FGF8, PROKR2, PROK2) were discovered. It's possible that up to 30% of the mutations detected in FGFR1 are de novo mutations, which should be considered when determining the probability of this genetic type recurrence in a family. The genetic testing technique is determined by the patient's gender, familial history (if any), and hypothesised mechanism of illness inheritance, as well as the existence of other clinical abnormalities that may

lead the geneticist to a specific disease gene and in rare cases, a contiguous gene syndrome (Dodé *et al.,* 2009). Pituitary tumours, damage to the pituitary, panhypopituitarism, and anabolic steroid usage are some of the acquired causes of HGH. Exogenous testosterone suppresses the hypothalamic-pituitary gonadal (HPG) axis and causes azoospermia by suppressing gonadotropins through the HPG axis' feedback loop, leading to hypogonadism (Kim *et al.,* 2008). Excess exogenous androgens from anabolic steroid usage reduce FSH levels and lower intratesticular testosterone levels, which impede spermatogenesis (McLachlan *et al.,* 2002). A pituitary MRI may be used to rule out a pituitary tumour as part of the first screening of individuals with suspected HGH (Cocuzza *et al.,* 2007). The anterior pituitary can be destroyed by pituitary tumours.

2.1.2 Hyperprolactinemia: It is a form of HGH caused due to excessive prolactin secretion (Burrows *et al.,* 2002). Hyperprolactinemia has not been demonstrated to be beneficial (Eggert-Kruse *et al.,* 1991). Prolactin is generated in the anterior pituitary and has no physiological consequences in males. Medication, concomitant medical diseases, tricyclic antidepressants, certain antihypertensives, stress, pituitary tumours (macroadenoma or microadenoma) and some idiopathic cause (Siddiq *et al.,* 2002) can induce hyperprolactinemia, which suppresses both FSH and LH. Phenothiazines, imipramine, methyldopa, and reserpine are the most prevalent drugs that cause hyperprolactinemia (Sussman *et al.,* 1997). Prolactin-secreting microadenomas and prolactin-secreting macroadenomas are the most prevalent causes of hyperprolactinemia (Jane *et al.,* 2001). Infertility, reduced libido, galactorrhea, headache, lethargy, and erectile dysfunction are the symptoms of prolactinomas. Gonadotropin and testosterone levels are usually repressed in individuals with prolactin-secreting pituitary adenomas, although prolactin levels are raised. The degree of prolactin rise can reveal the type of pathology (Burrows *et al.,* 2002).

2.1.3 Genetic reasons: One of the most prevalent genetic disorders in infertile males, these chromosomal alterations may now be detected in 15% of men with azoospermia and 5% of men with oligospermia (Tournaye *et al.,* 1996; Pandiyan *et al.,* 1996; Peschka *et al.,* 1999). Azoospermia attacks 1% of men and could be caused by a variety of factors, including hypothalamic-pituitary dysfunction, quantitative spermatogenic abnormalities and urogenital duct blockage. Each of these groups have known genetic components and genetic analysis is part of the usual diagnosis for azoospermic males (Cioppi *et al.,* 2021). A genetic defect affects around 29% of males with azoospermia. Chromosome or genetic disorders (nuclear or mitochondrial) and epigenetic alterations are among the most common genetic disorders (Dohle *et al.,* 2002).

2.1.4 Androgen Resistance: It affects around 1 in every 60,000 births. The androgen receptor gene (Xq11-q12) present on the X chromosome has been reported to consist over 300 mutations (Bhasin *et al.,* 1998). Mutations present in the gene promoter region have also been documented, in addition to well-known mutations in its 8 exons. The disease is clinically heterogeneous, ranging from phenotypic females (total androgen insensitivity) to typically virilized yet sterile men, due to the many variants that occur (partial and minimal androgen insensitivity). Serum testosterone levels might be low, normal, or high depending on the severity of the abnormality. It has been suggested that minor androgen receptor deficiencies may be the major cause of poor or no sperm counts in 40% of males (Aiman *et al.,* 1979). Modern genetic research on the androgen receptor gene has shown some of the intriguing new clinical associations with the male infertility. Exon 1 of the androgen receptor gene contains a crucial area of CAG nucleotide repeats, which are generally 15-30 in number (Küpker *et al.,* 1999). When this repeat area is extended, it causes spinal and bulbar muscular atrophy (Kennedy disease), a neurological condition that starts around the age of 30 and causes muscle cramping and atrophy as well as sterility due to testicular shrinkage. There is now enough data to suggest that minor changes in the CAG repeat area might possibly be the cause of certain cases of idiopathic azoospermia. In typically virilized males with idiopathic azoospermia, Yoshida *et al.* detected longer than usual CAG nucleotide repeats (Yoshida *et al.,* 1999). Casella *et al.* also located that the polyglutamine length of the androgen receptor gene is linked to testicular histology in azoospermic individuals (Casella *et al.,* 2003).

2.1.5 Gonadotoxins and medications: Direct gonadotoxic effects, altered hypothalamic-pituitary-gonad axis (HPG), ejaculation dysfunction, and reduced libido are four methods by which drugs and pharmaceuticals can damage male fertility. Human testis consists of various types of cell. Sertoli and Leydig cells are the two cell types necessary for spermatogenesis development. The former is a crucial assisting cell for germ cell development in the testis, whereas the latter generates testosterone, a crucial hormone in maintenance of the spermatogenesis process. Apoptosis of germ cells and aberrant spermatogenesis are favoured by conditions such as advanced age and gonadotoxin contact (Alkandari *et al*., 2021). Gonadal toxins, on the other hand, may directly harm testicular germ cells or impair spermatogenesis through Sertoli cell malfunction (Nudell *et al.,* 2002). As a result, complete drug histories, including prescriptions, over-the-counter medicines, illicit narcotics, and health functional foods, are required. Although the majority of these drugs do not cause azoospermia, patients who are using or taking exogenous androgens, antiandrogens, chemotherapeutic agents, or radiation therapy, as well as patients who have been exposed to environmental toxins such as pesticides, fumigants, solvents, should exercise special caution.

2.1.6 Congenital Adrenal Hyperplasia- Congenital Adrenal Hyperplasia (CAH) refers to a group of autosomal recessive diseases caused by mutations in genes that code for enzymes involved in the biochemical processes of steroidogenesis (Warrell, 2005). Any change in sex steroid production might have a negative impact on primary or secondary male sex characteristics (Milunsky, 2010). CAH can cause infertility, reduced testes volume, decreased sperm counts up to azoospermia, and decreased gonadotropic levels if not treated properly (Winters, 1999). Normalizing spermatogenesis requires adequate restoration of glucocorticoids and mineralocorticoids levels (Winters, 1999).

2.1.7 Undescended testes: Undescended testes are the most frequent genital abnormality in males, affecting up to 0.8% of one-year-olds (Mathers *et al.,* 2009). Cryptorchid testes must be distinguished from retractile testes, which are caused by hyperactive cremasteric muscles causing the testes to dwell in the inguinal canal or the elevated scrotum on a regular basis.

Testicular dysgenesis, an altered endocrine axis, immunologic damage, and blockage are all suggested reasons for cryptorchidism-induced subfertility (Grasso *et al.,* 1991). Despite the fact that the majority of individuals with a history of unilateral undescended testes are paternal, testicular volume and age at orchiopexy are independent indicators of reproductive potential and sperm retrieval in men with a history of cryptorchidism (Grasso *et al.,* 1991; Raman *et al.,* 2003). In unilateral and bilateral cryptorchidism, the incidence of azoospermia after therapy for undescended testes is between 13 and 34 %, respectively. Untreated unilateral and bilateral undescended testes, on the other hand, cause azoospermia in 30 and 80 % of cases, respectively (Grasso *et al.,* 1991).

2.1.8 Varicocele: A vascular malformation of the testes' venous drainage system is known as varicocele. The pampiniform or cremasterium plexus may be affected by abnormally dilated veins. Varicocele has been identified as a cause of infertility in 35 % of men with primary infertility issues and 81% of men with secondary infertility, respectively (Clarke 1966; Gorelick *et al.,* 1993). There is substantial evidence that varicoceles have a progressive and severe impact on the testis, and that varicocelectomy can prevent and repair this damage (Cocuzza *et al.,* 2008). Varicoceles repair has also been demonstrated to improve pregnancy rates and ART outcomes (Agarwal *et al.,* 2007; Marmar *et al.,* 2007; Esteves *et al.,* 2010 Identifying people with varicocele who will benefit from varicocele therapy remains a challenge for andrologists. Between 5% and 10% of males have azoospermia in conjunction with a varicocele (Czaplicki *et al.,* 1979; Kim *et al.,* 1999). Tulloch was the first to observe the return of sperm in the ejaculate and subsequent pregnancy mainly in azoospermic patient following varicocelectomy in 1955 (Tulloch *et al.,* 1955). These findings sparked increased interest in varicocele therapy at the time. However, it is still unclear why varicocele may have such a severe effect in certain individuals, resulting in azoospermia, despite the fact that 75 % of men with varicocele have normal semen results (Kadioğl *et al.,* 2001). Because of the wide variety of effects that varicocele has on testicular function, there is presently no effective diagnostic approach for evaluating males who present with clinical varicocele. Although sperm can be discovered in azoospermic men's ejaculate after varicocele treatment in 21 to 55 % of instances, spontaneous births are exceedingly rare (Kim *et al.,* 1999; Kadioğl *et al.,* 2001; Cocuzza *et al.,* 2009). In this group, however, varicocelectomy may eliminate the need for more invasive treatments like TESE by giving sperm via ejaculation for ICSI (Schlegel *et al.,* 2011). To avoid TESE, men with clinical varicoceles linked with non obstructive azoospermia will seldom have enough sperm in the ejaculate following varicocele repair (Schlegel *et al.,* 2004).

2.1.9 Mumps orchitis: The risk and complications of mumps have decreased since the mumps vaccine was introduced. On the other hand, in the case of scrotal edema, orchitis caused by mumps should be suspected (Davis *et al.,* 2010). This is because mumps orchitis is increasing among men after puberty in recent years. Puberty parotid orchitis is unilateral in 67% of patients and bilateral in 33% (Werner *et al.,* 1950). Testicular atrophy occurs in 36% of patients with bilateral lesions, whereas infertility occurs in only 13%. However, mumps orchitis before puberty has little effect on fertility (Werner *et al.,* 1950).

2.1.10 Chromosomal Disorders: Approximately 4% of males who get ICSI have a chromosomal defect, with 80% of them being sex chromosome related. The most prevalent chromosomal abnormalities are Robertson translocation and Klinefelter syndrome (KFS), which affect 10-20% of males with azoospermia (Chandley *et al.,* 1979). Sex chromosomes and autosomal chromosomes are examples of chromosomal abnormalities. Men with azoospermia are more likely to have numerical sex chromosomal aneuploidies. Polysomy of the sex chromosomes (XXY, XYY, etc) and microdeletions on the Y chromosome are the common etiologies of NOA and were the first genetic abnormalities found in azoospermic patients (Miyamoto *et al.,* 2015).

2.1.11 X Chromosome–Linked Abnormalities: The significance of X chromosome genes in male infertility is poorly understood, in part because researchers have relied on rodent studies that may not adequately represent human expression patterns. As a result, only around ten genes have clinical significance such as the androgen receptor (AR) gene, which is found in both humans and mice. Although research on these genes has been indefinite, the hemizygous nature of the X

chromosome in males implies that unique X chromosome mutations may have an effect. Segregation abnormalities and azoospermia are caused by disruption of these genes (Stouffs *et al*., 2009).

2.1.12 Y Chromosome Microdeletion: The most prevalent cause of azoospermia is microdeletions on the Y chromosome, which are identified in 5-15 % of infertile males with azoospermia. Regions on the long arm of the Y chromosome that were commonly deleted in patients with azoospermia, are called azoospermia factor (AZF). Within this region, a testes specific RNA binding protein termed as Deleted in Azoospermia (*DAZ*) was identified as the first gene linked to patients with azoospermia. The amorphous factor (AZF) region on the long arm of the Y chromosome is critical for the formation and differentiation of germ cells (Chandley *et al.*, 1979; Poongothai *et al*., 2009). AZFa, AZFb, and AZFc are only a few of the gene families found in the AZF area. AZFc is the most prevalent deletion (60%) compared to AZFa (5%), AZFb (16%), or a mix of the three (14%). This is due to the fact that AZFc is four times longer than AZFa (Ferlin *et al*., 2007; Walsh *et al.*, 2009). Men with deletions spanning more than one AZF locus, as well as those with AZFa and AZFb deletions, frequently develop azoospermia (Hopps *et al.*, 2003). Due to the availability of autosomal homologues and numerous copies, AZFc deletion is generally linked with a varied phenotype. According to Luddi *et al.* (2009), deletion of the USP9Y gene in AZFc resulted in azoospermia and severe process autism. Men with an AZFc deletion suffer a continuous reduction in sperm count and develop azoospermia over time, according to studies (Dada *et al*., 2003; Luddi *et al*., 2009).

2.1.13 Aneuploidy: NOA (Non Obstructive Azoospermia) is caused by Klinefelter Syndrome (KFS) the most prevalent etiology of sex chromosomal aneuploidies. KFS affects about 14% of males who have azoospermia. Reduced testicle size, elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), and reduced testosterone levels are all symptoms of KFS in men. The 46, XX male condition is a rare aneuploidy that affects around one out of every 20,000 live births. The sex determination region on the Y chromosome (SRY) has been translocated to the X chromosome or an autosome in around 90% of these males. Although 46, XX males possess normal internal and external male genitalia, they are azoospermic since they lack the AZF region (Oates *et al*., 2008).

2.1.14 Testicular cancer: Testicular cancer is a condition that manifests as a painless protuberance on the external surface of one or both testes when testicular cells turn out to be abnormal (malignant) and exhibit irregular testicular growth. It is also known as malignant testicular neoplasm. Almost all testicular tumours have a germ cell origin. Because testicular cancer damages germ cells, that further reduces male fertility, it seems to have a severe impact on spermatogenesis (Hamano *etal*., 2017). Young males are more likely to develop testicular cancer than other males, which has a lifetime risk of 1 in 250. The optimal age for men looking to start a family is between 25 and 29 years old, which is also the peak presentation age. Currently, there are about 250,000 testicular cancer survivors living in the US (DeSantis *etal.*, 2014). Reproductive health in males with many different cancer types is now well-documented to suffer from a variety of pre-treatment impairments. Pre-treatment studies have indicated that testicular cancer has the greatest negative impact on sperm concentration and total sperm count of any prevalent malignancy (Dohle *etal.*, 2010). It has been found that the testicular cancer is associated with the non obstructive azoospermia (NOA) (Parekh *et al.*, 2019).

2.1.15 Testicular torsion: It is a significant andrological and urological emergency condition marked by strenuous twisting of the spermatic cords, excruciating pain, testicular infarction/ischemia, which may ultimately lead to diminished or obstructed blood flow and testicular loss (Singh *et al.*, 2012). Torsion of the testis is a serious medical disease that put the testis viability in danger. Although a prompt surgical procedure may be able to save the torn testis, infertility is still a major risk (Bartsch *et al.*, 1980). Histologic changes can also be found in the "normal" non-torsed contralateral testis (Turek 2008). Before the age of 25, testicular torsion affects about 1 in every 4,000 males. (Williamson *et al.*, 1976). The most serious side effect of testicular torsion is the loss of the testis, which can result in fertility problems (Chen *et al.*, 2001). After unilateral testicular torsion, severe oligospermia or azoospermia is rare; nevertheless, these disorders can occur if the contralateral testis has any prior abnormalities, such as orchiopexy for an undescended testis (Daehlin *et al.*, 1996). The endocrine trait of the testicles should be regular with loss of the gonads. In contrast, the characteristics of the exocrine testis (spermatogenesis) are often affected. (Cosentino *et al.*, 1985; Lievano *et al.*, 1999). Patients with bilateral abnormalities provided with testicular volvulus resulted in the condition of decreased spermatogenesis (Krarup *et al.*, 1978). It is unknown whether this anomaly is due to an autoimmune procedure that occurs after the barrier. Testicular hematopoiesis is impeded primarily by the formation of antibodies to sperm or damage by testicular reperfusion (Becker *et al.*, 1997; Lievano *et al.*, 1999; Arap *et al.*, 2007). One-sided testicular biopsy was strange in 88% of cases at the time of twisting. Therefore, it is widely believed that some anomalies were present even before the twist began (Chen *et al.*, 2001).

2.1.16 Toxins: Toxins such as some industrial chemicals are toxic to the testes or gonads. Long-term azoospermia can be caused by radiation, various alkylating chemotherapy drugs (such as procarbazine, busulfan, cyclophosphamide, chlorambucil, melphalan) and cisplatin as these create DNA adducts and cross-links like the alkylating drugs (Felice *et al*., 2018).

2.1.17 Chemotherapy: Chemotherapy is the term used to describe the use of pharmaceuticals or medications to treat malignant growths. Chemotherapy's primary goal is to kill the body's rapidly dividing cells. Sperm cells are an easy target for chemotherapy harm because they divide quickly. The length of time it takes for germ cells to recover from chemotherapy treatment increases with the chemotherapy dose. Sometimes, the males become permanently infertile when the spermatogenesis stops (Hamano *et al*., 2017).

2.1.18 Radiotherapy: Radiotherapy is used in order to treat reproductive organs in cancer patients without surgery. But, it may have adevastating extended eternal effect on male reproductive function. The plan of the delivered irradiation (total dose, number of fractions, and duration) is an imperative andduration) is an imperative determinant of the radiobiological effect on the tissues involved. The exposure to radiation undoubtedly can result in the reduction of spermatozoa production which may often return to normal. Radiations such as X- rays and gamma rays can have more devastating effect on germ cells, Leydig cells etc. and hence, disrupt the process of spermatogenesis, which consequently may lead to permanent sterility (Meirow and Nugent, 2001). Ogilvy-Stuart and Shalet (1993) reported that the doses in excess of 2 Gray (Gy) to pelvis results in azoospermia which may be permanent.

REFERENCES

1. AgarwalA, Deepinder F, CocuzzaM, AgarwalR, ShortRA, Sabanegh E, Marmar JL. Efficacy of varicocelectomy in improving semen parameters: newmeta-analyticalapproach. Urology, 2007; 70(3): 532-538.
2. Aiman J, Griffin JE, Gazak JM, Wilson JD, MacDonald PC. Androgen insensitivity as a cause of infertility in otherwise normal men. New England Journal of Medicine, 1979; 300(5): 223-227.
3. Alkandari MH, ZiniA. Medical management of non-obstructive azoospermia: A systematic review. Arab Journalof Urology, 2021; 19(3): 215-220.
4. Arap MA, Vicentini FC, Cocuzza M., Hallak J, Athayde K, Lucon AM, SrougiM. Late hormonal levels, semen parameters, and presence of antisperm antibodies in patients treated for testicular torsion. Journal of Andrology, 2007; 28(4): 528-532.
5. Augarten A, Yahav Y, Laufer J, Szeinberg A, Dor J, Mashiach S, Kerem BS. Congenital bilateral absence of vas deferens in the absence of cystic fibrosis. The Lancet, 1994; 344(8935): 1473-1474.
6. Aziz, N. The importance of semen analysis in the context of azoospermia. Clinics, 2013; 68: 35-38.
7. AzizN, Agarwal A, NallellaKP, ThomasJrAJ. Relationship between epidemiological features and aetiology of male infertility asdiagnosed by a comprehensive infertility service provider. Reproductive Bio Medicine Online, 2006; 12(2): 209-214.
8. Baker, K., & Sabanegh Jr, E. Obstructive azoospermia: reconstructive techniques and results. Clinics, 2013; 68: 61-73.
9. Bartsch G, Marberger H, Mikuz G. Testicular torsion: late results with special regard to fertility and endocrine function. The Journal of urology, 1980; 124(3): 375-378.
10. Becker EJ, Prillaman HM, Turner TT. Microvascular blood flow isalteredafterrepair oftesticulartorsionintherat. TheJournalofUrology, 1997; 157(4): 1493-1498.
11. BhasinS,Ma K,SinhaI,Limbo M,Taylor WE,Salehian B.Thegenetic basis of male infertility. Endocrinology and Metabolism Clinics of NorthAmerica, 1998; 27(4): 783-805.
12. Burrows PJ, Schrepferman CG, Lipshultz LI. Comprehensive officeevaluation inthenewmill ennium. Urologic Clinics, 2002; 29(4): 873-894.
13. Casals T, Bassas L, Ruiz-Romero J, Chillon M, Gimenez J, Ramos MD, Estivill X. Extensive analysis of 40 infertile patients with congenital absence of the vas deferens: in 50% of cases only one CFTR allele could be detected. Human Genetics, 1995; 95(2): 205-211.
14. Casella R, Leibundgut B, Lehmann K, Gasser TC. Mumps orchitis:reportofamini-epidemic.The Journal of Urology, 1997; 158(6): 2158-2161.
15. Casella R, Maduro MR, MisfudA, Lipshultz LI, Yong EL, Lamb DJ.Androgen receptor gene polyglutamine length is associated with testicularhistologyininfertile patients.TheJournalof Urology, 2003; 169(1): 224-227.
16. Chandley AC. The chromosomal basis of human infertility. British MedicalBulletin, 1979; 35(2): 181-186.
17. Chan, P. T., & Schlegel, P. N. Epididymitis and other inflammatory conditions of the male excurrent ductal system. In The Epididymis: From Molecules to ClinicalPractice (pp. 533-553). Springer, Boston, MA., 2002.
18. Chen WC, Wu HC, Lin WC, Wu MC, Hsu CD, Tsai FJ. Theassociation of androgen-and oestrogen-receptor gene polymorphisms with urolithiasisinmen. BJUInternational, 2001; 88(4): 432-436.
19. ChibaK, EnatsuN, FujisawaM.Managementofnon-obstructiveazoospermia. ReproductiveMedicineandBiology, 2016; 15(3): 165-173.
20. Cioppi F, Rosta V, Krausz C. Genetics of Azoospermia. International Journal of Molecular Sciences, 2021; 22(6): 3264.
21. Clarke BG. Incidence of varicocele in normal men and among men of different ages. Jama, 1966; 198(10): 1121-1122.
22. ClaustresM.MolecularpathologyoftheCFTRlocusinm aleinfertility. ReproductiveBiomedicine Online, 2005; 10(1): 14-41.
23. Cocuzza M, Athayde KS, Agarwal A, Pagani R, Sikka SC, Lucon AM, Hallak J. Impact of clinical varicocele and testis size on seminal reactiveoxygen

species levels in a fertile population: a prospective controlled study. FertilityandSterility, 2008; 90(4): 1103-1108.
24. CocuzzaM, CocuzzaMA, Bragais FMP,AgarwalA. Theroleofvaricocele repair in the new era of assisted reproductive technology. Clinics, 2008; 63(3): 395-404.
25. Cocuzza M, Pagani R, Lopes RI, Athayde KS, Lucon AM, Srougi M,HallakJ. Useofsubinguinalincision formicrosurgical testicularbiopsyduringvaricocelectomyinmenwithno nobstructiveazoospermia.FertilityandSterility, 2009; 91(3): 925-928.
26. Cosentino MJ, Nishida M, Rabinowitz R, Cockett AT. Histologicalchanges occurring in the contralateral testes of prepubertal rats subjected to variousdurations of unilateral spermatic cord torsion. The Journal of Urology, 1985; 133(5): 906-911.
27. Cunningham GR, Lipshultz LI. Diseases of the testes and male sexorgans. Basicclinicalend ocrinology. NewYork: JohnWileyand Sons, 1986; 263-78.
28. Czaplicki M, Bablok L, Janczewski Z. Varicocelectomy in patients withazoospermia. Archives ofAndrology, 1979; 3(1): 51-55.
29. Dada, R., Gupta, N.P., & Kucheria,K. Semencryoconserva tioninmenwith AZ Fcmicrodeletion. ClinicalGenetics, 2003; 64(1): 74-75.
30. Daehlin, L., Ulstein, M., Thorsen, T., & Høisaeter, P. A. Follow-up aftertorsion of the spermatic cord. Scandinavian journal of urology and nephrology. Supplementum, 1996; 179: 139-142.
31. Davis NF, McGuire BB, Mahon JA, Smyth AE, O'MalleyKJ, FitzpatrickJM. Theincreasingincidence ofmumpsorchitis: acomprehensivereview.BJUInternational, 2010; 105(8): 1060-1065.
32. DebruyneFM.Alphablockers:areallcreatedequal.Urol ogy, 2000; 56(5): 20-22.
33. De Felice F, Marchetti C, Marampon F, Cascialli G, Muzii L, Tombolini V. Radiation effects on male fertility. Andrology, 2019; 7(1): 2-7.
34. DeSantis CE, Lin CC, Mariotto AB, Siegel RL, Stein KD, Kramer, JL, Jemal A. Cancer treatment and survivorship statistics, 20140. CA: ACancer Journal for Clinicians, 2014; 64(4): 252-271.
35. DimitriadisF,AdonakisG,KaponisA,MamoulakisC,T akenakaA,Sofikitis N. Pre-testicular, testicular, and post-testicular causes of maleinfertility. EndocrinologyoftheTestisandMaleReproduction. Cham: Springer, 2017; 1-47.
36. Dodé C,HardelinJP. Kallmannsyndrome. European Journal ofHumanGenetics, 2009; 17(2): 139-146.
37. Dohle GR, Colpi GM, Hargreave TB, Papp GK, Jungwirth, A, Weidner WEAU, EAU Working Group on Male Infertility. EAU guidelines on male infertility. European urology, 2005; 48(5): 703-711.
38. DohleGR,HalleyDJJ,VanHemelJO,VanDenOuwelA MW, Pieters MHEC, Weber RFA, Govaerts LCP. Genetic risk factors ininfertile men with severe oligozoospermia and azoospermia. Human Reproduction, 2002; 17(1): 13-16.
39. Dohle GR. Male infertility in cancer patients: review of the literature. International journal of urology, 2010; 17(4): 327-331.
40. Eggert-Kruse W, Schwalbach B, Gerhard I, Tilgen W, Runnebaum B. Influenceofserumprolactinon semencharacteristicsandspermfunction.International JournalofFertility, 1991; 36(4): 243-251.
41. Farah Dayana, R.Ameliorative potential of thymoquinone in nicotine-treated rats: Sperm characteristics and expression level of PRM1 and TNP2 genes/Farah Dayana Rosli (Doctoral dissertation, Universiti Malaya), 2019.
42. Farley S, Barnes R. Stenosis of ejaculatory ducts treated by endoscopicresection. TheJournalof Urology, 1973; 109(4): 664-666.
43. Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C. Maleinfertility: role of genetic background. Reproductive Biomedicine Online, 2007; 14(6): 734-745.
44. Goeminne PC, Dupont LJ. The sinusitis-infertility syndrome: Young's saint, old devil. European Respiratory Journal, 2010; 35(3): 698-698.
45. GoldwasserBZ,WeinerthJL,CarsonCC.Ejaculatoryd uctobstruction: the case for aggressive diagnosis and treatment. The Journal of Urology, 1985; 134(5): 964-966.
46. Gorelick JI, Goldstein M. Loss of fertility in men with varicocele. Fertility and sterility, 1993; 59(3): 613-616.
47. Grasso M, Buonaguidi A, Lania C, Bergamaschi F, Castelli M, Rigatti P.Postpubertal cryptorchidism: review and evaluation of the fertility. EuropeanUrology, 1991; 20: 126-128.
48. Hamano I, Hatakeyama S, Ohyama C. Fertility preservation of patients with testicular cancer. Reproductive Medicine and Biology, 2017; 16(3): 240-251.
49. Hamosh A, Cutting GR, Oates R, Amos J. Correlation of the level of full-length CFTR transcript with pulmonary phenotype in patients carrying R117H and 1342-1,-2delAG mutations. American Journal of Human Genetics, 55(CONF-941009-). 1994.
50. Handelsman DJ, Conway AJ, Boylan LM, Turtle JR. Young'ssyndrome:obstructiveazoos permia and chronicsinopulmonaryinfections. NewEnglandJournalof Medicine, 1984; 310(1): 3-9.
51. Hendry WF, A'hern RP, Cole PJ. Was Young's syndrome caused by exposure to mercury in childhood. British Medical Journal, 1993; 307(6919): 1579-1582.
52. HendryWF.Disordersofejaculation:congenital,acquir edandfunctional. BritishJournalofUrology, 1998; 82(3): 331-341.
53. HoppsCV,MielnikA,GoldsteinM,PalermoGD,Rosen waksZ,Schlegel PN. Detection of sperm in men with Y chromosome microdeletions of theAZFa,AZ

FbandAZFc regions.HumanReproduction, 2003; 18(8): 1660-1665.
54. Ichioka K, Kohei N, Okubo K, Nishiyama H, Terai A. Obstructive azoospermia associated with chronic sinopulmonary infection and situs inversus totalis. Urology, 2006; 68(1): 204-e5.
55. JaneJA,LawsER.Thesurgicalmanagementofpituitary adenomasinaseries of 3,093 patients. Journal of the American College of Surgeons, 2001; 193(6): 650-659.
56. Jarow JP, Espeland, MA, Lipshultz LI. Evaluation of the azoospermic patient. The Journal of urology, 1989; 142(1): 62-65.
57. Jequier AM. Obstructive azoospermia: a study of 102 patients.ClinicalReproductionandFertility, 1985; 3(1): 21-36.
58. Kadioğlu A, Tefekli A, Cayan S, Kandirali E, Erdemir F, Tellaloğlu S.Microsurgical inguinal varicocele repair in azoospermic men. Urology, 2001; 57(2): 328-333.
59. KimED,WinkelE,OrejuelaF,LipshultzLI.Pathologica lepididymalobstructionunrelatedtovasectomy:results withmicrosurgicalreconstruction.The JournalofUrology, 1998; 160(6): 2078-2080.
60. Kim HG, Kurth I, Lan F, Meliciani I, Wenzel W, Eom SH, Layman LC. Mutations in CHD7, encoding a chromatin-remodeling protein, cause idiopathic hypogonadotropic hypogonadism and Kallmann syndrome. The American Journal of Human Genetics, 2008; 83(4): 511-519.
61. Kang C, Punjani N, Schlegel PN. Reproductive chances of men with azoospermia due to spermatogenic dysfunction. Journal of Clinical Medicine, 2021; 10(7): 1400.
62. Kim ED, Leibman BB, Grinblat DM, Lipshultz LI. Varicocelerepairimprovessemenpara metersinazoospermicmenwithspermatogenicfailure. The JournalofUrology, 1999; 162(3): 737-740.
63. KrarupT.Thetestesaftertorsion. BritishJournalofUrology, 1978; 50(1): 43-46.
64. Kupker W, Schwinger E, Hiort O, Ludwig M, Nikolettos N, Schlegel PN, Diedrich K. Genetics of male subfertility: consequences for the clinical work-up.HumanReproduction, 1991; 14(1): 24-37.
65. Lebo RV, Grody WW. Variable penetrance and expressivity of the splice altering 5T sequence in the cystic fibrosis gene. Genetic Testing, 2007; 11(1): 32-44.
66. LievanoG,NguyenL,RadhakrishnanJ, Fornell,L,JohnE.Newanimalmodel to evaluate testicular blood flow during testicular torsion. Journal of PediatricSurgery, 1999; 34(6): 1004-1006.
67. Liu PY, Handelsman DJ. The present and future state of hormonaltreatmentformaleinfertility.Human ReproductionUpdate, 2003; 9(1): 9-23.
68. Luddi A, Margollicci M, Gambera L, Serafini F, Cioni M, De Leo V, PiomboniP. Spermatogenesisinamanwithcompletedeletion of USP9Y. NewEnglandJournalofMedicine, 2009; 360(9): 881-885.
69. LudwigM.Diagnosisandtherapy ofacuteprostatitis,epididymitisandorchitis.Andrologi a, 2008; 40(2): 76-80.
70. Marmar JL, Agarwal A, Prabakaran S, Agarwal R, Short RA, Benoff S, Thomas Jr A J. Reassessing the value of varicocelectomy as a treatment formalesubfertilitywithanewmeta-analysis.FertilityandSterility, 2007; 88(3): 639-648.
71. Mathers MJ, Sperling H, Rubben H, Roth S. The undescended testis:diagnosis, treatment and long-term consequences. Deutsches Arzteblatt International, 2009; 06(33): 527.
72. MatschinskeJ,AlcarazN,BenisA,GolebiewskiM,Gri mmDG,HeumosL, BlumenthalDB. TheAI Meregistry forartificialint elligencein biomedicalresearch. NatureMethods, 2021; 18(10): 1128-1131.
73. Matsuda T, Horii Y,Yoshida O. Unilateral obstruction of the vasdeferenscausedbychildhooding uinalherniorrhaphyinmaleinfertilitypatients. Fertility andSterility,1992; 58(3): 609-613.
74. Mak V, Jarvi KA. The genetics of male infertility. The Journal of Urology, 1996; 156(4): 1245-1257.
75. McCallum TJ, Milunsky JM, Munarriz R, Carson R, Sadeghi-Nejad H, Oates RD. Unilateral renal agenesis associated with congenital bilateralabsence of the vas deferens: phenotypic findings and genetic considerations. HumanReproduction, 2001; 16(2): 282-288.
76. McLachlanRI,O'DonnellLIZA,MeachemSJ,StantonP G,deKretser DM, Pratis K, Robertson DM. Hormonal regulation ofspermatogenesi sinprimatesand man:insightsfordevelopment ofthemale hormonalcontraceptive. Journalof Andrology, 2002; 23(2): 149-162.
77. Mickle J, Milunsky A, Amos JA, Oates RD. Immunology: Congenital unilateral absence of the vas deferens: A heterogeneous disorder with two distinct subpopulations based upon aetiology and mutational status of the cystic fibrosis gene. Human Reproduction, 1995; 10(7): 1728-1735.
78. Milunsky JM. Prenatal diagnosis of sex chromosome abnormalities. Genetic disorders andthe fetus: diagnosis, prevention and treatment, 2010; 273-312.
79. Miyamoto T, Minase G, Okabe K, Ueda H, Sengoku K. Male infertility and its genetic causes. Journal of Obstetrics and Gynaecology Research, 2015; 41(10): 1501-1505.
80. Nudell DM, Monoski MM, Lipshultz LI. Common medications anddrugs: howtheyaffectmalefertility. Urologic Clinics, 2002; 29(4): 965-973.
81. Oates RD. The genetic basis of male reproductive failure. Urologic Clinics of NorthAmerica, 2008; 35(2): 257-270.
82. Ogilvy-Stuart AL,Shalet SM. Effect of radiation on the human reproductive system. Environmental health perspectives, 1993; 101(2): 109-116.

83. PandiyanN,JequierAM.Genetics:mitoticchromosomal anomaliesamong 1210infertilemen.Human Reproduction, 1996; 11(12): 2604-2608.
84. Peschka B, Leygraaf J, Van der Ven K, Montag M, Schartmann B, Schubert R, Schwanitz G. Type and frequency of chromosome aberrations in 781 couples undergoing intracytoplasmic sperm injection. Human Reproduction, 1999; 14(9): 2257-2263.
85. PilatzA,FijakM,WagenlehnerF,SchuppeHC.Orchitis. DerUrologe. Ausg. A, 2019; 58(6): 697-710.
86. PilatzA,KilbJ,KaplanH,FietzD,HossainH,SchuttlerCG,Schuppe HC.Highprevalenceofurogenitalinfection/inflammationinpatientswith azoospermiadoesnotimpedesurgicalspermretrieval.Andrologia, 2019; 51(10): 13401.
87. Poongothai J,GopenathTS,Manonayaki, S.Genetics of humanmaleinfertility. Singapore MedicalJournal, 2009; 50(4): 336-47.
88. Porch PP. Aspermia owing to obstruction of distal ejaculatory duct andtreatmentbytransurethralresection. The Journal ofUrology, 1978; 119(1): 141-142.
89. PryorJP, HendryWF. Ejaculatoryductob structionin sub fertilemales: analysisof 87patients.Fertility andSterility, 1991; 56(4): 725-730.
90. RamanJD, SchlegelPN.Testicularspermextraction withintracytoplasmic sperm injection is successful for the treatmentof nonobstructiveazoospermia associated with cryptorchidism. The Journal of Urology, 2003; 170(4): 1287-1290.
91. Schuppe, H. C., & Bergmann, M. Inflammatory conditions of the testis. In Atlas on theHuman Testis (pp. 113-121). Springer, London, 2013.
92. Schuster TG, Ohl DA. Diagnosis and treatment of ejaculatory dysfunction. UrologicClinics, 2002; l29(4): 939-948.
93. SchlegelPN, KaufmannJ.Roleofvaricocelectomyinmenwithnonobstructive azoospermia.Fertility andSterility, 2004; 81(6): 1585-1588.
94. Schlegel PN, Goldstein M. Alternate indications for varicocele repair:non-obstructive azoospermia, pain, androgen deficiency and progressive testiculardysfunction.Fertility andSterility, 2011; 96(6): 1288-1293
95. Siddiq FM, Sigman M. A new look at the medical management ofinfertility.UrologicClinics, 2002; 29(4): 949-963.
96. Singh R, Hamada AJ, Bukavina L, Agarwal A. Physical deformities relevant to male infertility. Nature Reviews Urology, 2012; 9(3): 156-174.
97. Sigman M, Jarow JP. Endocrine evaluation of infertile men. Urology, 1997; 50(5): 659-664.
98. Smith L, Ciarrochi J, Heaven PC. The stability and change of trait emotional intelligence, conflict communication patterns, and relationship satisfaction: A one-year longitudinal study. Personality and Individual Differences, 2008; 45(8): 738-743.
99. StouffsK,TournayeH,LiebaersI,LissensW.Male infertilityandtheinvolvementofthe Xchromosome. Human Reproduction Update, 2009; 15(6): 623-637.
100. Sussman EM, Chudnovsky A, Niederberger CS. Hormonal evaluationof the infertile male: has it evolved. Urologic Clinics of North America, 2008; 35(2): 147-155.
101. Tournaye H, Staessen C, Liebaers I, Van Assche E, Devroey P, Bonduelle M, Van Steirteghem A. Genetics: Testicular sperm recovery in nine 47, XXYKlinefelterpatients.HumanReproduction, 1996; 11(8): 1644-1649.
102. TullochWS.Varicoceleinsubfertility.Britishmedicaljournal, 1955; 2(4935): 356.
103. Turek PJ. The Hypothalamic Pituitary Gonadal Axis. General Urology, 2008; 684.
104. UzunS,GokçeS, WagnerK.Cysticfibrosistransmembraneconductancerегulator gene mutations in infertile males with congenital bilateral absence of the vasdeferens.The TohokuJournalofExperimentalMedicine, 2005; 207(4): 279-285.
105. Walsh TJ, Turek PJ. Ejaculatory duct obstruction: new approaches to diagnosis and treatment. Contemporaray Urology, 2006; 18(9): 48.
106. Walsh,T.J.,Pera,R.R.,&Turek,P.J., March.Thegeneticsofmaleinfertility.In Seminarsin Reproductive Medicine, 2009; 27(2): 124-136.
107. WeidnerW,LudwigM,BrahlerE, SchieferHG. Outcomeof antibiotictherapy withciprofloxacininchro nicbacterial prostatitis.Drugs, 1999; 58(2): 103-106.
108. Welsh DK, Logothetis, DE, Meister M, Reppert SM. Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. Neuron, 1995; 14(4): 697-706.
109. Werner CA. Mumps orchitis and testicular atrophy. II. A factor in malesterility.Annals ofInternal Medicine, 1950; 32(6): 1075-1086.
110. Winters SJ. Male hypogonadism. In Male Reproductive Function (pp. 119-138). Springer, Boston, MA., 1999.
111. WilliamsonRCN. Torsion of the testis and allied conditions. Journal ofBritishSurgery, 1976; 63(6): 465-476.
112. WosnitzerM, Goldstein M, Hardy MP. Review of azoospermia. Spermatogenesis, 2014; 4(1): e28218.
113. Yoshida KI, Yano M, Chiba K, Honda M, Kitahara S. CAG repeatlengthintheandrogenreceptorgeneisenhancedinpatientswithidiopathicazoospermia).Urology, 1999; 54(6): 1078-10.