An update on non-obstructive azoospermia; a narrative review

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Abstract:

Azoospermia could be either non-obstructive azoospermia (NOA) or obstructive azoospermia (OA). Clinical assessment (testis consistency & volume), laboratory testing (FSH), and genetic testing (karyotype, Y chromosome microdeletion, or specific genetic testing for hypogonadotropic hypogonadism) are used to distinguish NOA (which includes primary and secondary testicular failure) from OA. The treatment of NOA is still empirical. For hypogonadotropic hypogonadism, gonadotropin therapy is the only particular indication that consistently improves semen analysis and rates of conception. The typical treatment consists of gonadotropins (hCG and rFSH) combined, with GnRH therapy maintained for non-responders. Although there is a paucity of level I clinical data, drug therapy combining aromatase inhibitors and gonadotropins may be able to improve outcomes for men who need surgical sperm retrieval. This review offers a current overview of the causes, treatments, and management of non-obstructive azoospermia.

Keywords: non-obstructive azoospermia; treatment; fertility.

Introduction:

Azoospermia (a-, without + –zoo– » Greek zôion, animal + –spermia– » Greek sperma, sperm/seed) is identified by at least two different ejaculate samples that don't contain any sperm (which incorporates the centrifuged sample) *(Aziz, 2013)*.

Epidemiology

Nearly 15% of all couples experience infertility. Male factors are responsible for 50% of all cases of infertility *(Rowe et al., 2000)*. Around 10% to 15% of infertile men have azoospermia and it affects nearly 1% of all males *(Cocuzza et al., 2013)*. Around 600,000 males of reproductive age are azoospermic

in the United States at any given moment, with NOA being the most common condition *(Cocuzza et al., 2013)*. One in seven heterosexual couples in the United Kingdom suffers from infertility. Male factor infertility is the single most common reason for infertility in the United Kingdom as it is responsible for 30% of cases *(Pillai et al., 2021)*.

Clinically, azoospermia can be divided into obstructive (post-testicular) and non-obstructive types (pretesticular or testicular). Obstructive azoospermia (OA) affects 15-20% of men with azoospermia and is less common than non-obstructive azoospermia (NOA) *(Stephen and Chandra, 2006)*.

Functional (non-obstructive) azoospermia:

Male infertility due to NOA is typically regarded as an incurable condition. These patients, who make up to 10% of all infertile males, have azoospermia due to defective spermatogenesis. In the context of azoospermia, adequate confirmation of a non-obstructive etiology is regarded as the absence of normal spermatogenesis by testicular histology with increased follicle-stimulating hormone (FSH) level. Causes of NOA are shown in Figure (1) *(Kumar, 2013)*.

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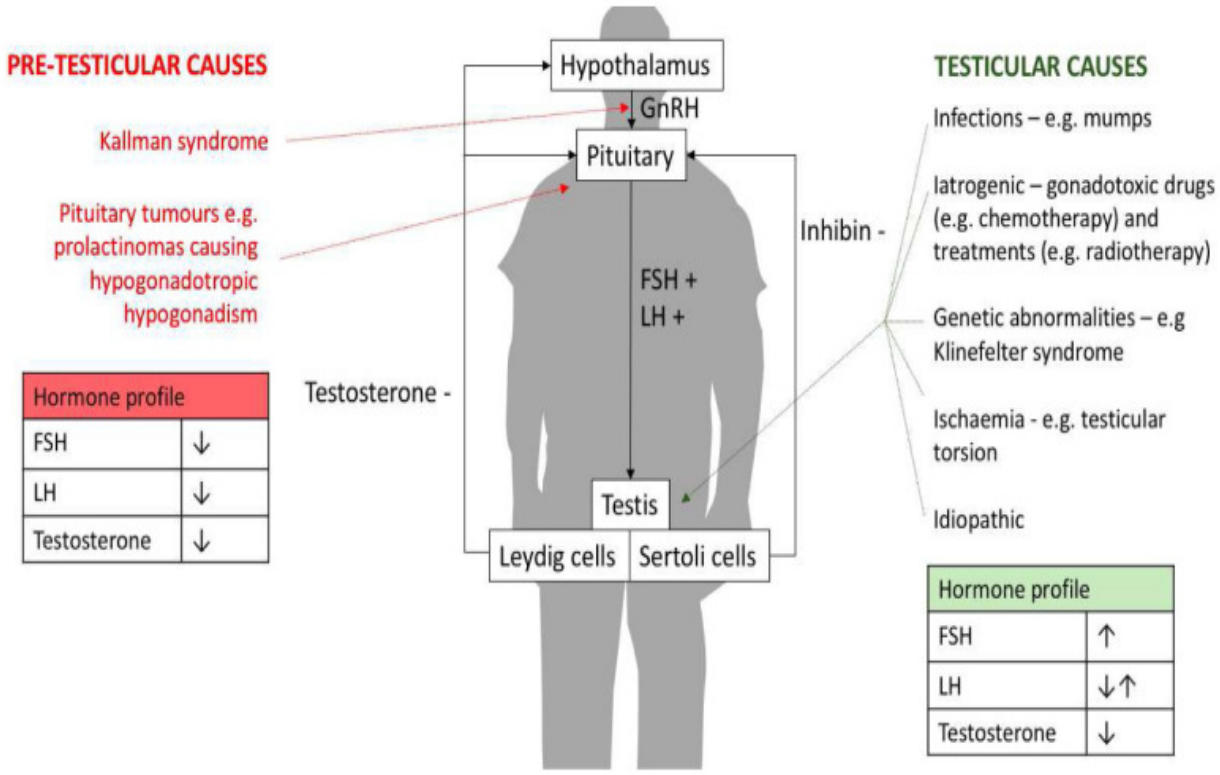

A- Hypogonadotropic hypogonadism:

Low serum testosterone is a symptom of hypogonadotropic hypogonadism (HH), which is brought on by a decrease in the pituitary gland's release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). HH can be idiopathic, acquired, or congenital *(Kumar, 2013)*.

I. Congenital Hypogonadotropic Hypogonadism

It is an uncommon hereditary condition. Congenital hypogonadotropic hypogonadism (CHH) is caused by lack of GnRH. It is characterized by infertility and absent or delayed puberty *(Boehm et al., 2015)*. Congenital types such as Prader-Willi syndrome, Kallmann syndrome and Laurence-Moon syndrome are typically syndromic *(Kumar, 2013)*.

1. Kallmann syndrome:

It is considered a congenital form of HH that causes hypo- or anosmia. It is due to the inability of gonadotropin-releasing hormone (GnRH) neurons that originate embryologically in the olfactory mucosa to migrate to and establish residence in the hypothalamus that causes this drop-in gonadal activity. Low levels of sex steroids induced by a GnRH hormone shortage induce a lack of sexual growth and secondary sexual characteristics *(Laitinen et al., 2011)*.

These symptoms include lack of testicular growth as measured by testicular volume, infantile voice, and lack of pubic hair growth. Micropenis, as well as cryptorchidism or undescended testicles, may be present in a tiny number of male cases. Low levels of FSH and LH, which result in low testosterone in males, are related to these characteristics *(Boehm et al., 2015)*.

2. Prader-Willi syndrome:

The rare and difficult hereditary disorder known as Prader-Willi syndrome (PWS) affects several neurological, endocrine, metabolic systems and impairs behavior and cognition *(Butler et al., 2016; Heksch et al., 2017)*. Most cases of PWS are sporadic, while familial occurrences can happen when the father's genes have a microdeletion in the imprinting region inherited from his mother *(Butler et al., 2016)*.

Early infancy PWS is characterized by severe hypotonia, poor appetite, and feeding difficulties. These symptoms are followed by early childhood

overeating and the gradual evolution of morbid obesity (unless food intake is strictly controlled). Motor milestones, language and cognitive development are not progressing as expected. Hypogonadism, insufficient pubertal development, and usually, infertility which can affect both men and women. A common trait is short height. Temper outbursts, obstinacy, manipulative conduct, and obsessive-compulsive behaviors are examples of typical behavioral traits. Scoliosis/kyphosis, osteoporosis, hypopigmentation, viscous, thick saliva, high pain sensitivity, decreased vomiting, and temperature instability are further symptoms. Typical face traits including strabismus, scoliosis, and strabismus are usually present *(Cassidy et al., 2012)*.

3. Laurence-Moon syndrome:

An uncommon ciliopathic, pleiotropic autosomal recessive disorder called Laurence-Moon-Bardet-Biedl syndrome (LMBBS) mostly impacts consanguineous couples' offspring. The initial symptom is typically poor night vision manifests in the first ten years of life *(Khan et al., 2017)*. There must be four primary features or three major characteristics with two additional features for a diagnosis to be made clinically. Speech difficulties, polyuria/polydipsia, ataxia, lack of coordination/clumsiness, diabetes mellitus, developmental delay, left ventricular hypertrophy, brachydactyly, hepatic fibrosis, spasticity, and hearing loss are categorized as secondary features. Cone-rod dystrophy, polydactyly, obesity, learning difficulties, renal anomalies, and polydactyly are considered the primary features. Along with these traits, it is also known that individuals with short height, crowded teeth, hypermobile or loose joints, and early osteoarthritis *(Abbasi et al., 2009)*.

II. Acquired Hypogonadotropic Hypogonadism:

Drugs (such as analogs of gonadotropin-releasing hormones and sex steroids), pituitary & brain radiation, hyperprolactinemia, exhausting exercise, infiltrative or infectious pituitary lesions, encephalic trauma and abusing alcohol or illicit drug use are all potential causes of acquired HH *(Darby and Anawalt, 2005)*. HH is also linked to systemic conditions such as hemochromatosis, sarcoidosis, and histiocytosis X *(Hayes et al., 1998)*.

B- Hypergonadotropic Hypogonadism/ Eugonadism

Hypergonadotropic hypogonadism in men results from insufficient testosterone production by the testes. Luteinizing hormone (LH) and follicle-stimulating hormone (FSH) are secreted, at increased rates, by the pituitary as part of the feedback response. Three varieties of causes of HH are available; genetic disorders that lead to primary testicular failure; are under the first group. Hypergonadotropic hypogonadism-causing developmental disorders consist the second group. The third group details the acquired causes of primary testicular failure *(Sobel and Imperato-Mcginley, 2004)*.

I. Genetic causes

1) Klinefelter's Syndrome:

A phenotypical man with two or more extra X chromosomes will have Klinefelter syndrome (KS). Gynecomastia in males, tiny testes, tall stature and azoospermia were the first to be identified as the clinical presentation of KS, and the genetic cause of extra X chromosomes was discovered in 1959 *(Forti et al., 2010)*. Genital diseases, most often hypogonadism and infertility, are brought on by the hyalinization, fibrosis, and hypofunction of the testicles caused by excess X chromosomes. In the mid and latter decades of the twentieth century, understanding of neurocognitive impairments associated with KS began to develop. The use of testosterone replacement therapy, cognitive therapies, and adaptable therapies in the treatment of KS is typically beneficial *(Davis et al., 2016; Ross et al., 2017; Piot et al., 2022)*.

The most common KS karyotype is 47 XXY (greater than 90 percent). Mosaic karyotypes like 46 XY/47 XXY and diverse aneuploidies like 48 XXXY and 49 XXXXY have both been described. The extra X chromosome is acquired at random and is frequently the outcome of post-zygotic or meiotic nondisjunction. The extra X chromosomal material that exists present appears to be related to how severe the illness is overall *(Davis et al., 2016; Bonomi et al., 2017)*.

A low upper/lower segment ratio will be seen in most KS patients due to their tall height and long limbs. Weight and head circumference are in the 50th percentile while mean height is in the 75th percentile. In childhood, the phallus and testicles may be relatively small. Although the growth of pubic and phallic hair is common during adolescence, testes are seldom more than 4 mL in size and are normally hard due to

hyalinization and fibrosis. Testosterone levels often low with gynecomastia which is rather common *(Davis et al., 2016; Bonomi et al., 2017)*.

2) XX males:

The XX male syndrome, which affects 1 in 20 000 live births, is caused by crossover between the X and Y chromosomes outside of the pseudo autosomal region during Meiosis I. This crossover transfers the Y chromosomes SRY (sex-determining region) to the X chromosome, causing testicular development to occur instead of ovarian development. These guys have low to normal testosterone levels, high amounts of FSH and LH, and normal external and internal genitalia. They are infertile because they lack the Y chromosome's azoospermia factor (AZF) region, which is necessary for spermatogenesis and prevents them from generating sperm *(Dominguez and Reijo Pera, 2013)*.

3) Myotonic Dystrophy (DM):

Myotonic dystrophy, an autosomal dominant multisystem condition, comes in two primary forms: type 1 (DM1), also known as Steinert disease, and type 2, also known as proximal myotonic myopathy *(Hahn and Salajegheh, 2016)*. The central nervous system, heart, eyes, skeletal/smooth muscles, and endocrine system are all impacted by DM1. There are three categories of phenotypes: congenital, classic, and mild. The most prevalent symptoms of DM2 are myotonia (90%) and muscular dysfunction (82%) as well as cataracts (36%) and cardiac conduction abnormalities (19 %) *(Dimitriadis et al., 2017)*.

In all forms, abnormalities in reproduction are a well-known finding. A major hallmark of DM1 and DM2 is progressive testicular atrophy, which can occur in up to 60%-80% of cases, respectively. Seminiferous tubule fibrosis, hyalinization, and atrophy are examples of histological abnormalities *(Sarkar et al., 2004)*. About 73 percent of patients with DM1 report having oligospermia or azoospermia *(Klesert et al., 1997)*. Small testes are the most obvious physical sign of gonadal failure. Patients typically have high FSH, LH, and low testosterone levels *(Sobel and Imperato-Mcginley, 2004)*.

4) Inherited disorders of LH and FSH:

Mutations in the gonadotropin α-chain are unknown in humans. Mutations in the LH and FSH chains have been reported. In diseases

caused by these mutations, low levels of testosterone are commonly accompanied by high levels of one or both gonadotropins, which may be a sign of hypergonadotropic hypogonadism. The afflicted man exhibited slowed spermatogenesis, low testosterone, and delayed puberty; one LH mutation has been found. This patient has a missense mutation in the LH beta gene. Although the hormone was no longer able to bind to its receptor, the mutation nonetheless permitted hormone production and immunoreactivity *(Sobel and Imperato-Mcginley, 2004)*.

The patient's LH level was therefore elevated but his FSH level was normal, according to radioimmunoassay results. The patient's infertility remained despite the HCG therapy's effects on the patient's testosterone levels, testicular size, virilization, and sperm count. At age 44, all of his gonadotropin levels were elevated *(Sobel and Imperato-Mcginley, 2004)*.

5) LH and FSH resistance:

The LH and FSH receptors belong to the seven transmembrane domains G protein-coupled family of receptors. The failure of the cyclic AMP-regulated receptor activation cascade or the receptor's inability to bind ligands is two potential effects of mutations in the LH and FSH receptors (cAMP). LH resistance, which is caused by LH receptor-inactivating mutations, is a relatively unusual form of hypergonadotropic hypogonadism. *(Sobel and Imperato-Mcginley, 2004)*.

The syndrome's most severe symptoms include male pseudo-hermaphroditism, feminine or ambiguous genitalia, low testosterone levels, high LH levels, the absence of male secondary sexual characteristics, and a lack of response to HCG or LH challenge *(Sobel and Imperato-Mcginley, 2004)*.

II. Developmental causes:

The absence of one or both testicles from the scrotum is known as cryptorchidism. It is the most typical male genitalia congenital abnormality. In around 3% of full-term and 30% of preterm male babies, one or both testicles may not descend. By the seventh month of gestation, the testes typically descend. By the third month following birth, the testes of about 80% of cryptorchids should descend. As a result, the actual incidence is only about 1% *(Khatwa and Menon, 2000)*. It is improbable that the testis would naturally descend if it

has not done so by the age of six months, hence surgical correction should be taken into consideration *(Shin and Jeon, 2020)*.

The most frequent cause of NOA is cryptorchidism *(Docampo and Hadziselimovic, 2015)*. Azoospermia is present in 13% of people with unilateral cryptorchidism and rises to 89% in patients with bilateral cryptorchidism who are untreated *(Urry et al., 1994)*.

III- Acquired causes:

A. Chemotherapy:

Compared to the ovaries, the testes are more vulnerable to radiation or chemotherapy-induced damage. Leydig cells are less susceptible than germinal epithelium to the negative effects of chemotherapy *(Santaballa et al., 2022)*. The effects of chemotherapy on the gonadal system can vary. Azoospermia with increased LH and FSH levels and signs of testicular injury on pathology specimens may all be present in patients. The normal range of testosterone is often present. Chemotherapeutic agent-induced testicular damage is often dose-dependent *(Sobel and Imperato-Mcginley, 2004)*.

B. Radiotherapy:

One of the most radiosensitive tissues is the testis, and even very low radiation doses can have a big impact on its function. Direct radiation to the testis or, more frequently, dispersed radiation during therapy to nearby tissues might harm it. Although effective cancer therapy is of the utmost importance, potential gonadal damage may cause patients great distress, particularly in those who are of reproductive age *(Dillon and Gracia, 2012)*. The younger the testicular cell is, the more vulnerable to radiation damage. There are limits for how much radiation will specifically harm testicular cells, and these limits have been defined. For spermatogenesis to recover, type A spermatogonia must be in good condition and, accordingly, the radiation dosage must have been absorbed. Leydig cells are more radiation resistant than the germinal epithelium, despite the fact that damage from high radiation doses, which are infrequently used to treat testicular cancer, can still occur *(Nistal et al., 2017; De Felice et al., 2019)*.

C. Infections:

Viral orchitis is typically brought on by lymphocytic choriomeningitis virus, echovirus,

mumps, and group B arbovirus *(Riggs and Sanford, 1962)*. Since the mumps vaccine was introduced, mumps orchitis incidence has significantly decreased *(Wu et al., 2021)*. More than 50% of patients, with mumps after puberty, have risk becoming infertile since the disease is linked to clinical orchitis. Acute orchitis causes the testes to become inflamed, uncomfortable, and swollen and might cause them to shrink in size. They have two options: atrophy or restore to their original size and capacity *(Sobel and Imperato-Mcginley, 2004; Nistal et al., 2017)*. Additionally, orchitis and gonadal insufficiency can result from leprosy *(Achdiat et al., 2018)*.

D. Trauma/Torsion:

When the testis ruptures or develops an intratesticular hematoma as a result of blunt trauma to the scrotum, the testicular tissue is damaged, and anti-sperm antibodies are produced due to the blood-germinal epithelial barrier being broken *(Raheem et al., 2012)*. Testicular torsion affects one in every 4000 males younger than 25. If the condition isn't addressed within six hours, ischemic necrosis results in long-term harm and testicular atrophy *(Ringdahl and Teague, 2006)*. Additionally, following this might be the development of sperm antibodies that harm the testes *(Raheem et al., 2012)*.

E. Varicocele:

A varicocele is an enlargement of the testis' pampiniform or cremasteric plexus. Palpable varicoceles in NOA-men make up between 4 and 14 percent of the whole NOA-men population *(Schlegel, 2004; Lee et al., 2007)*. Varicoceles are known to have a detrimental effect on both the steroidogenic and spermatogenic functions of the testis, making them the commonest treated male factor cause of infertility *(Neto et al., 2016)*. The temperature of the testicles rises in persons with left varicocele *(Goldstein and Eid, 1989)*. The Leydig cellular secretory function in humans is known to be negatively impacted by an increase in testicular temperature *(Khera and Lipshultz, 2008)*.

Low peripheral serum testosterone levels have been found in a subset of males with left varicocele *(Sofikitis et al., 2014)*. It is understood that androgens have a significant role in (a) controlling the Sertoli cell secretory activity, which is essential for the triggering of male meiosis *(Russell and Brinster, 1996)*, and (b) finishing the spermiogenesis process *(Sofikitis et*

al., 1999). The end outcome may be the male gamete's failure to go through meiosis or the early haploid male gamete's inability to go through elongation for the subgroup of guys who suffer a severe negative impact from varicocele on the secretory function of Leydig cell secretory function. *(Cozzolino and Lipshultz, 2001)*.

Additionally, The elevation in testicular temperature may have an immediate unfavorable influence on the function and structure of Sertoli cells *(Namiki et al., 1987)*. Also, it's been proposed that men with varicoceles may experience testicular hypoxia due to a problem with the male genital system's venous drainage *(Gat et al., 2005)*.

Diagnosis:

A. History and clinical examination:

Two semen assays showing absence of spermatozoa in the centrifuged samples support the azoospermia diagnosis. Differentiating between obstructive and non-obstructive etiologies is the primary objective while examining patients with azoospermia. The preservation of the testis' natural processes, including spermatogenesis and testosterone production, is a core concept of OA. A detailed medical history and physical examination provide the clinician with information regarding the state of testicular function. The patient interview should include covering the patient's reproductive history, risk factors for blockage, and any female-specific concerns. The state of the HPT axis should be checked further by analyzing the symptoms. Hypogonadism is frequently incompatible with OA, according to the evidence *(Hayden and Tanrikut, 2015)*.

It is important to assess any past sexually transmitted infections and tuberculosis exposure. Bronchiectasis, repeated recurrent lung infections or sinus infections, may suggest an underlying ciliary deficit or inspissated secretions. Primary ciliary dysfunction and atypical cystic fibrosis presentations are two examples (formerly young syndrome). Failure of spermatogenesis is suspected when there is a history of causes like anticancer chemotherapy or undescended testicles. Knowing the medication taken by the patient is crucial since some medications, such as steroids, might affect spermatogenesis *(Ramasamy et al., 2015)* and 5a-reductase inhibitors *(Chiba et al., 2011)*.

A physical exam will assist the

doctor in identifying the etiology whether it is obstructive or not. Normal testicular volume (greater than 15 ml) is expected in a patient with OA. Examination of the scrotum and inguinal regions for surgical scars, and palpation of the spermatic cord and epididymis should be done during routine genital examination. One probable anatomical difference is the congenital absence of one or both vasa differentia, which can be seen in up to 2% of infertile males *(Patrizio et al., 1993)*. Any missing excurrent duct segment should prompt further testing for CFTR gene variations. Finally, a digital rectal examination may be useful in detecting midline cysts or SV fullness, both of which can be associated with EDO *(Mcquaid and Tanrikut, 2013)*.

According to the Tanner phases, secondary sexual traits' development is assessed *(Marshall and Tanner, 1970)*. Poor pubic hair development or genital developments are indicators of hypogonadism. Physical examination can reveal the common disorder known as varicocele. Examination of the patient should be done while lying down and while standing, with the scrotum being checked out visually and then felt. Even though only 20 percent of patients with confirmed varicocele experience issues with conception *(Robinson et al., 2010; Diamond et al., 2011)*, this syndrome may result in spermatogenesis dysfunction or perhaps azoospermia. Therefore, it is important to check for varicocele while diagnosing NOA patients *(Chiba et al., 2016)*.

B. Laboratory and genetic testing:

Azoospermia diagnosis is made when there is ejaculation without sperms. It is significant to remember that for a precise diagnosis, evaluation of at least 2 different ejaculates should be done **(Schlegel, 2004)**. Centrifugation of the semen sample should also be used to establish the lack of sperm. In as many as just 35 percent of patients who were initially labeled as NOA, sperm has been found after a detailed microscopic inspection of many droplets of debris from the ejaculate **(Ron-El et al., 1997)**.

The NOA diagnosis can also benefit from hormonal analysis. High blood gonadotropin levels often suggest primary testicular failure, however, normal gonadotropins levels can’t exclude the diagnosis of NOA (especially in those with germ cell maturational halt) *(Schoor et al., 2002)*.

Patients without visible or palpable testicles may have full anorchia or cryptorchidism. The intramuscular administration of HCG can help distinguish between the two disorders. In cryptorchid men, there should then be a spike in plasma testosterone. There won't be an increase in testosterone in anorchid guys *(Bhansali et al., 2016)*.

Additionally, anti-Mullerian factor hormone (AMH) in anorchid men is undetectable during infancy. Therefore, the existence of testicular tissue in prepubertal men is indicated by measurable levels of AMH *(Kanakatti Shankar et al., 2022)*. Radiographic Assessment:

Making a diagnosis of NOA requires testicular volume measuring using ultrasonography or an orchidometer. Small testes signify spermatogenesis failure since the testes' size indicates spermatogenesis activity. The testes in persons with NOA often have a volume of lower than 15 cc and the epididymis is flat *(Schlegel, 2004)*. Ultrasonography is helpful for evaluating testicular volume as well as for learning about the pathophysiology of the testicles. Five or more microliths per testis are considered to be testicular microlithiasis *(Bennett et al., 2001)* and can be identified via ultrasound imaging. This disease is known to be connected to spermatogenesis failure *(Xu et al., 2014)*, and people with testicular dysgenesis syndrome (TDS) can exhibit it. Skakkebaek et al. promoted the idea of TDS, which contends that hypospadias, undescended testes, low semen quality, and testicular cancer are all aspects of the same disease entity *(Skakkebaek, 2003)*.

At the end of the 1990s, it was speculated that testicular microlithiasis and testicular cancer might be related, however, subsequent research refuted this theory. Follow-up ultrasound only when the identified risk factors are present: testicular atrophy (volume of less than 12 cc), an earlier germ cell tumor, germ cell tumor history in first-degree relatives and history of an orchidopexy or cryptorchid testicles *(Richenberg et al., 2015)*. In the case of suspicious of testicular cancer by the results of examination by ultrasonography, the doctor should think about performing additional tests such as tumor marker measurements, MRIs, and surgical orchidectomies *(Chiba et al., 2016)*.

C. Biopsy:

In azoospermic men with palpable vasa differentia, normal sized testes, normal FSH levels, and

a negative serum anti-sperm antibody test, an open testicular biopsy may be recommended to differentiate OA from NOA. Formaldehyde, which alters testicular architecture, should never be used with testis biopsy specimens. Instead, collidine-buffered glutaraldehyde solutions, Zenker, or Bouin should be used *(Wosnitzer and Goldstein, 2014)*.

Even though testicular sperm has demonstrated greater rates of implantation than sperm from ejaculates, TESE may not be required to perform ICSI on these patients *(Hauser et al., 2011)*. Usually, a testicular biopsy is not necessary to diagnose NOA because according to reports, more than 90 % of individuals with azoospermia may be diagnosed accurately as OA or NOA by total measurement of testicular volume, LH, and FSH *(Schoor et al., 2002)*.

- **Additional investigations for NOA patients:**

Additional tests like Karyotyping and genetic testing need to be done when NOA is diagnosed *(Van Assche et al., 1996)*.

The most prevalent and important genomic analysis for NOA management is an assessment of each of the three sub-regions of the azoospermia factor (AZF), which is found on the long arm of the Y chromosome (Yq) (AZFa, AZFb, and AZFc). According to studies, Yq microdeletions were present in around 8% of NOA patients in Western countries *(Ferlin et al., 2007)*. A new genetic diagnostic tool has recently been created that can be used to evaluate Y-chromosome deletions in Japanese patients in a routine clinical setting *(Iijima et al., 2014)*.

Treatment:

With the advancement of assisted reproductive technologies, infertile couples now have several ways to grow their family biologically.

Non-obstructive azoospermia:

Advanced assisted reproductive techniques are required for most NOA patients. ICSI with micro-TESE may be beneficial for some patients. The underlying etiology affects the increased failure rates of sperm retrieval in NOA. The overall success rate for sperm retrieval in these individuals appears to be as high as 75%, despite an average of roughly 50%. Furthermore, the likelihood of vascular injury is significant. In addition, it has been observed that chromosomal abnormalities and

sperm damage are rather common in NOA patients, and male progeny may inherit genes associated with infertility. Micro-TESE procedures can be repeated *(Ghalayini et al., 2022)*.

Should a man become azoospermic due to testosterone supplementation medicine, there is a high likelihood that he can regain spermatogenesis by merely stopping the hormonal treatment and waiting *(Kohn et al., 2017)*. After a year, the majority of men will regain 85% of their pretreatment sperm counts, and nearly all in two years *(Ly et al., 2005; Liu et al., 2006)*.

In cases of pre-testicular azoospermia (secondary hypogonadism, testosterone therapy) or hypogonadotropic hypogonadism, gonadotropin analogs such as FSH and HCG, are administered to enhance spermatogenesis. The suggested course of treatment involves injecting HCG (3,000 IU to 10,000 IU) two to three times a week in addition to anastrozole, clomiphene citrate, FSH, or tamoxifen *(Kohn et al., 2017)*.

This medication has demonstrated success in producing at least some sperm in the ejaculate of 75% to 77% of men with NOA due to hypogonadotropic hypogonadism, despite the fact that treatment may take up to six months *(Rastrelli et al., 2014)*. While it is an option, pulsed GnRH is typically more costly and does not significantly improve upon normal care. In particular, testosterone therapy is not advised.

Even though it has been shown that up to 11% of azoospermic men who underwent hormone therapy (typically clomiphene) benefit from having sperm in their ejaculate, there is no standardization of this medicine and no high-quality randomized trials. Because of this, many medical professionals including the European Association of Urology (EAU) advise against utilizing hormone therapy in males with primary hypogonadism and NOA in general *(Minhas et al., 2021)*. When possible, microscopic testicular sperm extraction and ICSI are the major treatments for these men. The overall success rate of these expensive procedures in producing a pregnancy is only 25%.

The role of gonadotropins, estrogen receptor modulators, and aromatase inhibitors in males with primary hypogonadism and NOA is even more controversial. These are frequently used to enhance sperm parameters in oligozoospermia men

who are infertile, and there is some evidence to support their effectiveness *(Selman et al., 2006; Shiraishi et al., 2012; Hussein et al., 2013)*. However, their effectiveness in improving sperm retrieval rates through TESE or TESA is somewhat uncertain and has not been definitively proven *(Minhas et al., 2021)*. Although a progressive strategy starting with clomiphene and rising to HCG has been proposed, the ideal procedure and dose schedule are still to be found *(Hussein et al., 2013)*. There can be unforeseen complications to the therapy. Nevertheless, despite these disadvantages and the lack of a better course of treatment, hormone stimulation therapy is nevertheless often utilized in clinical settings *(Tharakan et al., 2020)*.

Treatment for HH has a reasonable chance of success. Azospermic men with HH are given 5 mcg to 20 mcg of GnRH every 2 hours via a pulsatile infusion pump. After 12 to 24 months of treatment, 77% of men who were azoospermic at first were found to have spermatogenesis; the recovery of sperm in the semen was often seen after 6 months of therapy *(Pitteloud et al., 2002)*.

The FSH stimulation appears to improve the results prior to GnRH treatment. GnRH is only active in without FSH) is advised in patients with reduced or absent pituitary function. 1000 IU to 3000 IU is the recommended dosage, to be taken two or three times each week. This normally leads to sperm production after three or six months. If that doesn't work, FSH is added at a level of 75 IU to 150 IU twice a week *(Bhasin, 2007)*. Overall success rates for spermatogenesis treated medically for HH are about 75%. If medical treatment is not successful, assisted reproductive techniques are recommended *(Resorlu et al., 2009; Tharakan et al., 2020)*.

men with normal pituitary function. Gonadotropin therapy with HCG (with or

Men with NOA are three times more likely than infertile men without azoospermia to develop a malignancy in the future, and they are more likely to have pituitary prolactinomas, various neoplasms (such as Sertoli cell, Leydig cell, and germ-cell tumors), and other health-related conditions *(Eisenberg et al., 2013)*.

Conclusion:

Testis consistency/volume, laboratory testing (FSH), and genetic testing are used to distinguish patients with NOA

(which encompasses primary and secondary

testicular failure) from OA. The treatment of NOA is still empirical. For hypogonadotropic hypogonadism, gonadotropin therapy is the only particular indication that consistently improves semen analysis and rates of conception. The typical treatment consists of gonadotropins (hCG and rFSH) combined, with GnRH therapy maintained for non-responders. Although there is a paucity of level I clinical data, drug therapy combining aromatase inhibitors and gonadotropins may be able to improve outcomes for men who need surgical sperm retrieval. Varicocelectomy may be helpful when varicocele is present together with NOA.

References

1. **Abbasi A , Butt N , Sultan B and Munir SM.** Hypokalemic paralysis and megaloblastic anaemia in Laurence-Moon-Bardet-Biedl syndrome. Journal of the College of Physicians and Surgeons--Pakistan : JCPSP, 2009; 19, 186-8.
2. **Achdiat PA , Fadilla Y , Gunawan H and Suwarsa OJLR.** Testicular atrophy and its clinical manifestations in a patient released from leprosy treatment. 2018; 89, 83-6.
3. **Aziz N.** The importance of semen analysis in the context of azoospermia. Clinics (Sao Paulo, Brazil), 2013; 68 Suppl 1, 35-8.
4. **Bennett HF , Middleton WD , Bullock AD and Teefey SA.** Testicular microlithiasis: US follow-up. Radiology, 2001; 218, 359-63.
5. **Bhansali A , Aggarwal A , Parthan G , Gogate Y , Bhansali A , Aggarwal A , Parthan G and Gogate YJCRIEVI-PE.** Disorders of Sex Development. 2016, 291-334.
6. **Bhasin S.** Approach to the infertile man. The Journal of clinical endocrinology and metabolism, 2007; 92, 1995-2004.
7. **Boehm U , Bouloux PM , Dattani MT , De Roux N , Dodé C , Dunkel L , Dwyer AA , Giacobini P , Hardelin JP , Juul A , Maghnie M , Pitteloud N , Prevot V , Raivio T , Tena-Sempere M , Quinton R and Young J.** Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment. Nature reviews. Endocrinology, 2015; 11, 547-64.
8. **Bonomi M , Rochira V , Pasquali D , Balercia G , Jannini EA and Ferlin A.** Klinefelter syndrome (KS): genetics, clinical phenotype and hypogonadism. Journal of endocrinological investigation, 2017; 40, 123-34.
9. **Butler MG , Manzardo AM and Forster JL.** Prader-Willi Syndrome:

Clinical Genetics and Diagnostic Aspects with Treatment Approaches. Current pediatric reviews, 2016; 12, 136-66.

10. **Cassidy SB , Schwartz S , Miller JL and Driscoll DJ.** Prader-Willi syndrome. Genetics in medicine : official journal of the American College of Medical Genetics, 2012; 14, 10-26.
11. **Chiba K , Enatsu N and Fujisawa M.** Management of non-obstructive azoospermia. Reproductive medicine and biology, 2016; 15, 165-73.
12. **Chiba K , Yamaguchi K , Li F , Ando M and Fujisawa M.** Finasteride-associated male infertility. Fertility and sterility, 2011; 95, 1786.e9-11.
13. **Cocuzza M , Alvarenga C and Pagani R.** The epidemiology and etiology of azoospermia. Clinics (Sao Paulo, Brazil), 2013; 68 Suppl 1, 15-26.
14. **Cozzolino DJ and Lipshultz LI.** Varicocele as a progressive lesion: positive effect of varicocele repair. Human reproduction update, 2001; 7, 55-8.
15. **Darby E and Anawalt BD.** Male hypogonadism : an update on diagnosis and treatment. Treatments in endocrinology, 2005; 4, 293-309.
16. **Davis S , Howell S , Wilson R , Tanda T , Ross J , Zeitler P and Tartaglia N.** Advances in the Interdisciplinary Care of Children with Klinefelter Syndrome. Advances in pediatrics, 2016; 63, 15-46.
17. **De Felice F , Marchetti C , Marampon F , Cascialli G , Muzii L and Tombolini V.** Radiation effects on male fertility. Andrology, 2019; 7, 2-7.
18. **Diamond DA , Gargollo PC and Caldamone AA.** Current management principles for adolescent varicocele. Fertility and sterility, 2011; 96, 1294-8.
19. **Dillon KE and Gracia CR.** Pediatric and young adult patients and oncofertility. Current treatment options in oncology, 2012; 13, 161-73.
20. **Dimitriadis F , Adonakis G , Kaponis A , Mamoulakis C , Takenaka A , Sofikitis NJEOTT and Reproduction M.** Pre-testicular, testicular, and post-testicular causes of male infertility. 2017; 1, 981.
21. **Docampo MJ and Hadziselimovic F.** Molecular Pathology of Cryptorchidism-Induced Infertility. Sexual development : genetics, molecular biology, evolution, endocrinology, embryology, and pathology of sex determination and differentiation, 2015; 9, 269-78.
22. **Dominguez AA and Reijo Pera RA.** Brenner's Encyclopedia of Genetics (Second Edition) , . 2013; 4, 71-4.
23. **Eisenberg ML , Betts P , Herder D , Lamb DJ and Lipshultz LI.** Increased risk of cancer among azoospermic men. Fertility and sterility, 2013; 100, 681-5.
24. **Ferlin A , Arredi B , Speltra E , Cazzadore C , Selice R , Garolla A , Lenzi A and Foresta C.** Molecular and clinical characterization of Y chromosome microdeletions in

infertile men: a 10-year experience in Italy. The Journal of clinical endocrinology and metabolism, 2007; 92, 762-70.

25. **Forti G , Corona G , Vignozzi L , Krausz C and Maggi M.** Klinefelter's syndrome: a clinical and therapeutical update. Sexual development : genetics, molecular biology, evolution, endocrinology, embryology, and pathology of sex determination and differentiation, 2010; 4, 249-58.

26. **Gat Y , Zukerman Z , Chakraborty J and Gornish M.** Varicocele, hypoxia and male infertility. Fluid Mechanics analysis of the impaired testicular venous drainage system. Human reproduction (Oxford, England), 2005; 20, 2614-9.

27. **Ghalayini IF , Alazab R , Halalsheh O , Al-Mohtaseb AH and Al-Ghazo MA.** Repeated microdissection testicular sperm extraction in patients with non-obstructive azoospermia: Outcome and predictive factors. Arab journal of urology, 2022; 20, 137-43.

28. **Goldstein M and Eid JF.** Elevation of intratesticular and scrotal skin surface temperature in men with varicocele. The Journal of urology, 1989; 142, 743-5.

29. **Hahn C and Salajegheh MK.** Myotonic disorders: A review article. Iranian journal of neurology, 2016; 15, 46-53.

30. **Hauser R , Bibi G , Yogev L , Carmon A , Azem F , Botchan A , Yavetz H , Klieman SE , Lehavi O , Amit A and Ben-Yosef D.** Virtual azoospermia and cryptozoospermia--fresh/frozen testicular or ejaculate sperm for better IVF outcome? Journal of andrology, 2011; 32, 484-90.

31. **Hayden R and Tanrikut CJUP.** Detection and Management of Obstructive Azoospermia. 2015; 2, 33 -7.

32. **Hayes FJ , Seminara SB and Crowley WF, Jr.** Hypogonadotropic hypogonadism. Endocrinology and metabolism clinics of North America, 1998; 27, 739-63, vii.

33. **Heksch R , Kamboj M , Anglin K and Obrynba K.** Review of Prader-Willi syndrome: the endocrine approach. Translational pediatrics, 2017; 6, 274-85.

34. **Hussein A , Ozgok Y , Ross L , Rao P and Niederberger C.** Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. BJU international, 2013; 111, E110-4.

35. **Iijima M , Koh E , Izumi K , Taya M , Maeda Y , Kyono K , Yoshida A and Namiki M.** New molecular diagnostic kit to assess Y-chromosome deletions in the Japanese population. International journal of urology : official journal of the Japanese Urological Association, 2014; 21, 910-6.

36. **Kanakatti Shankar R , Dowlut-Mcelroy T , Dauber A and Gomez-Lobo V.** Clinical Utility of Anti-Mullerian Hormone in Pediatrics. The Journal of clinical endocrinology and metabolism, 2022; 107, 309-23.

37. **Khan PA , Nishaat J , Noor S and Fatima NJIJMPH.** Laurence Moon Bardet Biedl Syndrome: a rare case report in a tertiary care teaching hospital, Hyderabad, Telangana, India. 2017; 7, 68-71.

38. **Khatwa UA and Menon PS.** Management of undescended testis. Indian journal of pediatrics, 2000; 67, 449-54.

39. **Khera M and Lipshultz LI.** Evolving approach to the varicocele. The Urologic clinics of North America, 2008; 35, 183-9, viii.

40. **Klesert TR , Otten AD , Bird TD and Tapscott SJ.** Trinucleotide repeat expansion at the myotonic dystrophy locus reduces expression of DMAHP. Nature genetics, 1997; 16, 402-6.

41. **Kohn TP , Louis MR , Pickett SM , Lindgren MC , Kohn JR , Pastuszak AW and Lipshultz LI.** Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy. Fertility and sterility, 2017; 107, 351-7.e1.

42. **Kumar R.** Medical management of non-obstructive azoospermia. Clinics (Sao Paulo, Brazil), 2013; 68 Suppl 1, 75-9.

43. **Laitinen EM , Vaaralahti K , Tommiska J , Eklund E , Tervaniemi M , Valanne L and Raivio T.** Incidence, phenotypic features and molecular genetics of Kallmann syndrome in Finland. Orphanet journal of rare diseases, 2011; 6, 41.

44. **Lee JS , Park HJ and Seo JT.** What is the indication of varicocelectomy in men with nonobstructive azoospermia? Urology, 2007; 69, 352 -5.

45. **Liu PY , Swerdloff RS , Christenson PD , Handelsman DJ and Wang C.** Rate, extent, and modifiers of spermatogenic recovery after hormonal male contraception: an integrated analysis. Lancet (London, England), 2006; 367, 1412-20.

46. **Ly LP , Liu PY and Handelsman DJ.** Rates of suppression and recovery of human sperm output in testosterone-based hormonal contraceptive regimens. Human reproduction (Oxford, England), 2005; 20, 1733-40.

47. **Marshall WA and Tanner JM.** Variations in the pattern of pubertal changes in boys. Archives of disease in childhood, 1970; 45, 13-23.

48. **Mcquaid JW and Tanrikut C.** Ejaculatory duct obstruction: current diagnosis and treatment. Current urology reports, 2013; 14, 291-7.

49. **Minhas S , Bettocchi C , Boeri L , Capogrosso P , Carvalho J , Cilesiz NC , Cocci A , Corona G , Dimitropoulos K , Gül M , Hatzichristodoulou G , Jones TH , Kadioglu A , Martínez Salamanca JI , Milenkovic U , Modgil V , Russo GI , Serefoglu EC , Tharakan T , Verze P and Salonia A.** European Association of Urology Guidelines on Male Sexual and Reproductive Health: 2021 Update on Male Infertility. European urology, 2021; 80, 603-20.

50. **Namiki M , Nakamura M , Okuyama A , Sonoda T , Nishimune Y , Takatsuka D and Matsumoto K.** Influence of temperature on the function of Sertoli and Leydig cells of human testes. Fertility and sterility, 1987; 47, 475-80.

51. **Neto FT , Bach PV , Najari BB , Li PS and Goldstein M.** Spermatogenesis in humans and its affecting factors. Seminars in cell & developmental biology, 2016; 59, 10-26.

52. **Nistal M , González-Peramato P , Serrano Á , Nistal M , González-Peramato P and Serrano ÁJCITDON -TTP.** Treatment-Related Testicular Changes. 2017, 363-76.

53. **Patrizio P , Asch RH , Handelin B and Silber SJ.** Aetiology of congenital absence of vas deferens: genetic study of three generations. Human reproduction (Oxford, England), 1993; 8, 215-20.

54. **Pillai RN , Mceleny KJO, Gynaecology and Medicine R.** Management of male infertility. 2021; 31, 192-8.

55. **Piot A , Plotton I , Boutroy S , Bacchetta J , Ailloud S , Lejeune H , Chapurlat RD , Szulc P and Confavreux CB.** Klinefelter Bone Microarchitecture Evolution with Testosterone Replacement Therapy. Calcified tissue international, 2022; 111, 35-46.

56. **Pitteloud N , Hayes FJ , Dwyer A , Boepple PA , Lee H and Crowley WF, Jr.** Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. The Journal of clinical endocrinology and metabolism, 2002; 87, 4128-36.

57. **Raheem AA , Ralph D , Minhas SJBJOM and Urology S.** Male infertility. 2012; 5, 254-68.

58. **Ramasamy R , Armstrong JM and Lipshultz LI.** Preserving fertility in the hypogonadal patient: an update. Asian journal of andrology, 2015; 17, 197-200.

59. **Rastrelli G , Corona G , Mannucci E and Maggi M.** Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. Andrology, 2014; 2, 794-808.

60. **Resorlu B , Abdulmajed MI , Kara C , Unsal A and Aydos K.** Is intracytoplasmic sperm injection essential for the treatment of hypogonadotrophic hypogonadism? A comparison between idiopathic and secondary hypogonadotrophic hypogonadism. Human fertility (Cambridge, England), 2009; 12, 204-8.

61. **Richenberg J , Belfield J , Ramchandani P , Rocher L , Freeman S , Tsili AC , Cuthbert F , Studniarek M , Bertolotto M , Turgut AT , Dogra V and Derchi LE.** Testicular microlithiasis imaging and follow-up: guidelines of the ESUR scrotal imaging subcommittee. European radiology, 2015; 25, 323-30.

62. **Riggs S and Sanford JP.** Viral orchitis. The New England journal of medicine, 1962; 266, 990-3.

63. **Ringdahl E and Teague L.** Testicular torsion. American family

physician, 2006; 74, 1739-43.

64. **Robinson SP , Hampton LJ and Koo HP.** Treatment strategy for the adolescent varicocele. The Urologic clinics of North America, 2010; 37, 269-78.

65. **Ross JL , Kushner H , Kowal K , Bardsley M , Davis S , Reiss AL , Tartaglia N and Roeltgen D.** Androgen Treatment Effects on Motor Function, Cognition, and Behavior in Boys with Klinefelter Syndrome. The Journal of pediatrics, 2017; 185, 193-9.e4.

66. Rowe PJ , Comhaire FH , Hargreave TB and Mahmoud AM. *WHO manual for the standardized investigation and diagnosis of the infertile male*, Cambridge university press 2000.

67. **Russell LD and Brinster RL.** Ultrastructural observations of spermatogenesis following transplantation of rat testis cells into mouse seminiferous tubules. Journal of andrology, 1996; 17, 615-27.

68. **Santaballa A , Márquez-Vega C , Rodríguez-Lescure Á , Rovirosa Á , Vázquez L , Zeberio-Etxetxipia I , Andrés M , Bassas L , Ceballos-Garcia E , Domingo J and Manau-Trullas D.** Multidisciplinary consensus on the criteria for fertility preservation in cancer patients. Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 2022; 24, 227-43.

69. **Sarkar PS , Paul S , Han J and Reddy S.** Six5 is required for spermatogenic cell survival and spermiogenesis. Human molecular genetics, 2004; 13, 1421-31.

70. **Schlegel PN.** Causes of azoospermia and their management. Reproduction, fertility, and development, 2004; 16, 561-72.

71. **Schoor RA , Elhanbly S , Niederberger CS and Ross LS.** The role of testicular biopsy in the modern management of male infertility. The Journal of urology, 2002; 167, 197-200.

72. **Selman H , De Santo M , Sterzik K , Cipollone G , Aragona C and El-Danasouri I.** Rescue of spermatogenesis arrest in azoospermic men after long-term gonadotropin treatment. Fertility and sterility, 2006; 86, 466-8.

73. **Shin J and Jeon GW.** Comparison of diagnostic and treatment guidelines for undescended testis. Clinical and experimental pediatrics, 2020; 63, 415-21.

74. **Shiraishi K , Ohmi C , Shimabukuro T and Matsuyama H.** Human chorionic gonadotrophin treatment prior to microdissection testicular sperm extraction in non-obstructive azoospermia. Human reproduction (Oxford, England), 2012; 27, 331-9.

75. **Skakkebaek NE.** Testicular dysgenesis syndrome. Hormone research, 2003; 60 Suppl 3, 49.

76. **Sobel V and Imperato-Mcginley J.** Hypergonadotropic Hypogonadism. 2004, 549-54.

77. **Sofikitis N , Ono K , Yamamoto Y , Papadopoulos H and Miyagawa I.**

Influence of the male reproductive tract on the reproductive potential of round spermatids abnormally released from the seminiferous epithelium. Human reproduction (Oxford, England), 1999; 14, 1998-2006.

78. **Sofikitis N , Stavrou S , Skouros S , Dimitriadis F , Tsounapi P and Takenaka AJEUS.** Mysteries, facts, and fiction in varicocele pathophysiology and treatment. 2014; 13, 89-99.

79. **Stephen EH and Chandra A.** Declining estimates of infertility in the United States: 1982-2002. Fertility and sterility, 2006; 86, 516-23.

80. **Tharakan T , Luo R , Jayasena CN and Minhas S.** Non-obstructive azoospermia: current and future perspectives. Faculty reviews, 2021; 10, 7.

81. **Tharakan T , Salonia A , Corona G , Dhillo W , Minhas S and Jayasena C.** The Role of Hormone Stimulation in Men With Nonobstructive Azoospermia Undergoing Surgical Sperm Retrieval. The Journal of clinical endocrinology and metabolism, 2020; 105.

82. **Urry RL , Carrell DT , Starr NT , Snow BW and Middleton RG.** The incidence of antisperm antibodies in infertility patients with a history of cryptorchidism. The Journal of urology, 1994; 151, 381-3.

83. **Van Assche E , Bonduelle M , Tournaye H , Joris H , Verheyen G , Devroey P , Van Steirteghem A and Liebaers I.** Cytogenetics of infertile men. Human reproduction (Oxford, England), 1996; 11 Suppl 4, 1-24; discussion 5-6.

84. **Wosnitzer MS and Goldstein M.** Obstructive azoospermia. The Urologic clinics of North America, 2014; 41, 83-95.

85. **Wu H , Wang F , Tang D and Han D.** Mumps Orchitis: Clinical Aspects and Mechanisms.

86. Frontiers in immunology, 2021; 12, 582946.

87. **Xu C , Liu M , Zhang FF , Liu JL , Jiang XZ , Teng JB , Xuan XJ and Ma JL.** The association between testicular microlithiasis and semen parameters in Chinese adult men with fertility intention: experience of 226 cases. Urology, 2014; 84, 815-20.