Invited Review / Davetli Derleme
doi: 10.18678/dtfd.1192672

Duzce Med J, 2022;24(S1):36-43
Düzce Tıp Fak Derg, 2022;24(S1):36-43

Management of the Infertile Male with Azoospermia

Azospermisi olan İnfertil Erkeğe Yaklaşım

Mesut TEK
0000-0002-5769-0730
Erdem AKBAY
0000-0001-7669-414X

Department of Urology, Mersin University School of Medicine, Mersin, Türkiye

Corresponding Author
Sorumlu Yazar
Erdem AKBAY
erdemakbay1959@gmail.com

Received / Geliş Tarihi : 15.09.2022
Accepted / Kabul Tarihi : 28.09.2022
Available Online /
Çevrimiçi Yayın Tarihi : 21.10.2022

ABSTRACT

Azoospermia means the complete absence of spermatozoa upon examination of the semen. Azoospermia may result from a lack of spermatozoa production in the testicles, or from an inability of produced spermatozoa to reach the emitted semen. Azoospermia is generally examined in two groups as obstructive and non-obstructive. Pretesticular causes usually include endocrine disorders that affect spermatogenesis, testicular causes include primary testicular pathologies, and posttesticular causes include obstructive pathologies. In order to make the exact diagnosis, a good urological, hormonal and genetic evaluation is required. The underlying etiologic cause determines the treatment strategy in azoospermic cases. If it is possible to see sperm in the ejaculate, pregnancy is tried to be achieved with ejaculate sperm, if not, with the spermatozoa obtained by interventional methods, by using assisted reproductive techniques. As the etiology of azoospermia is understood and treatment methods are improved, it is thought the rate of obtaining sperm both in the ejaculate and with interventional methods will increase, and as a result, higher pregnancy rates should be achieved. It is thought that there will be important developments in the treatment of azoospermia in the near future, as there have been significant advances in gene therapies and mesenchymal stem cell studies started on humans.
Keywords: Azoospermia; infertility; diagnosis; treatment.

ÖZ

Azospermi ejakülat incelemesinde sperm bulunmaması hali olarak tanımlanmaktadır. Azospermi testiste spermatozoa üretiminin olmamasından ya da üretilen spermatozoaların emisyon ile dışarı atılan ejakülata ulaşamamalarından kaynaklanabilir. Azospermi genel olarak obstrüktif ve non-obstrüktif olmak üzere iki grupta değerlendirilmektedir. Pretestiküler nedenler genellikle spermatogenezi etkileyen endokrin bozuklukları içerir, testiküler nedenler primer testis patolojilerini içerir ve posttestiküler nedenler ise obstrüktif patolojileri içerir. Doğru ve kesin bir tanıya ulaşabilmek için, iyi bir ürolojik, hormonal ve genetik değerlendirme yapılmalıdır. Azospermik olgularda tedavi stratejisini altta yatan etiyolojik neden belirler. Eğer ejakülatta sperm görülmesi mümkün ise bu spermlerle, ya da ejakülatta sperm görülmeyen olgularda girişimsel sperm elde etme teknikleri ile elde edilen spermlerle, yardımcı üreme teknikleri kullanılarak gebelik elde edilmesi amaçlanmaktadır. Azospermi etiyolojisi iyi anlaşılıp, tedavi yöntemleri geliştikçe, hem ejakülatta sperm görülme oranları hem de girişimsel metotlarla sperm elde edilme oranları artacak, bu sayede gebelik elde edebilme olasılığının da daha yüksek olacağı düşünülmektedir. İnsan üzerinde başlayan gen terapilerinde ve mezenkimal kök hücre çalışmalarında önemli gelişmeler kaydedilmesi nedeniyle yakın gelecekte azospermi tedavisinde de önemli gelişmelerin olabileceği düşünülmektedir.
Anahtar kelimeler: Azospermi; infertilite; tanı; tedavi.

INTRODUCTION

Azoospermia is defined as the absence of spermatozoa in the ejaculate. For the diagnosis of azoospermia, no spermatozoa should be seen at least in two microscopic seminal examinations. In order to make the differential diagnosis of azoospermia and severe oligospermia, semen analysis must also include pellet analysis in which the ejaculate fluid is evaluated after at least at a speed of 3000 G centrifugation. While the incidence of azoospermia is 1% in the normal population, this rate is reported to be 15% in men presenting with infertility (1). Azoospermia occurs as a result of the lack of adequate hormonal stimulation, spermatogenesis disorders, or obstructive pathologies. Differential diagnosis is very important in the treatment of men represented with azoospermia. In order to make the differential diagnosis in etiology, a good detailed physical examination and some basic laboratory tests are needed.

MEDICAL HISTORY

It is very important to know the medical and surgical history of the patient well, before the initial evaluation of the azoospermic patient. The story of the patient should include past fertility status, the frequency and timing of the sexual intercourse, duration of infertility, viral orchitis in childhood, and history of cryptorchidism. Also, the presence of genital trauma or pelvic surgery, history of testis torsion, epididymitis or urethritis-like infections, presence of gonadotoxic radiotherapy or chemotherapy, and family history of infertility should be questioned (2).

PHYSICAL EXAMINATION

Before proceeding to genital examination a well-detailed systemic examination may give some clues about the etiology of azoospermia. Thyroid examination, and lung, heart, and abdominal examination should be performed. For example; the detection of gynecomastia on examination may be a sign of an estrogen-secreting adrenal or testicular tumor. The patient should be evaluated for signs of Kallman and Klinefelter syndromes. A patient with Klinefelter syndrome presents with many phenotypes from complete hypogonadism to normal virilized type. It should also be kept in mind that short stature may be observed in some severe Y chromosome anomalies. After systemic evaluation, palpation of testicles and evaluation of their volumes should be performed. The expected testis volume in a normal fertile male is about 18-20 ml and the volume is directly related to spermatogenesis. Seminiferous tubules constitute a significant part of the testicular volume. When spermatogenesis is disrupted or reduced, a decrease in testis size is observed due to the loss of seminiferous tubules. In patients with non-obstructive azoospermia (NOA), testicular volume is often less than 15 ml and the diameter of the epididymis is thin (3). Epididymis and vas deferens should be palpated and the continuity should be checked. Also, the presence of varicocele should be carefully evaluated.

DIAGNOSTIC METHODS

Semen Analyses

Semen analysis should be evaluated in accordance with World Health Organization (WHO) 2010 guidelines. In an azoospermic patient at least two semen analyses should be performed, and also a two-week interval should be given between the first and the second test. Ejaculate volume takes an important place in the evaluation of the azoospermic patient. Secretion of the seminal vesicle accounts for most of the ejaculate volume. In cases with normal testicular volume and low semen volume (<1.5 ml), ejaculation disorder or ejaculatory duct obstruction should be considered. Retrograde ejaculation should be evaluated in a patient with unejaculation, or low ejaculation volume. Therefore in these cases, it is necessary to look for sperm in the urine sample after ejaculation. When azoospermia is detected in a patient, the semen sample should be centrifuged at 3000 G for 15 minutes, and then examined under the microscope at 400x magnification. In a study, the sperm detection rate was reported 35%, after centrifugation of the semen samples of the men with NOA (4).

Seminal plasma is a good source of markers that can detect many disorders in the male reproductive system. In the future, more information about the causes of azoospermia should be obtained by measuring and evaluating the different proteins in seminal plasma.

Endocrinological Evaluation

Hormonal tests have an important role in the evaluation of azoospermic cases, especially helpful in the differential diagnosis of primary and secondary testicular failure. Assessment of follicle stimulating hormone (FSH) and testosterone levels is sufficient to reveal most of the endocrine pathologies. FSH levels are regulated by inhibin B secreted by Sertoli cells (5). Inhibin B levels decrease and FSH level increase in cases where spermatogenesis is damaged such as Sertoli cell only (SCO) or testicular irradiation. The diagnostic accuracy of FSH is limited, and FSH level rises only in the final stage of the absence of spermatogenesis. FSH level may be normal in focal SCO or hypospermatogenesis (6). Serum FSH level is associated with the total spermatogonium count, not with the number of mature spermatids and the number of spermatozoa in the ejaculate. FSH levels have no clinical value in the selection of patients who are candidates for testicular sperm extraction (TESE) (7). Serum testosterone and luteinizing hormone (LH) levels may also aid in diagnosis. Low testosterone levels accompanying high LH levels may indicate hypergonadotropic hypogonadism (8).

Diagnostic Testicular Biopsy

Testicular biopsy is the definitive diagnostic test in the diagnosis of azoospermia. In selected patients with normal testicular volume, palpable vas deferens, and normal serum FSH levels, a testicular biopsy should be performed in order to differentiate obstructive azoospermia (OA) and spermatogenesis disorders. Detection of normal spermatogenesis in such a patient suggests an obstructive pathology. Testicular biopsy can be done open or percutaneously and should be done bilaterally. For an adequate assessment, each cross-sectional area should contain at least 20 seminiferous tubules. In the evaluation of the biopsy, the number of spermatids per tubule can be used to predict the expected number of spermatozoa in the ejaculate (9). These values are helpful in the differential diagnosis of obstructive and NOA.

ETIOLOGY OF AZOOSPERMIA

In order to understand the etiology of azoospermia easily, it is useful to make 3 classifications as pretesticular, testicular, and posttesticular azoospermia. Pretesticular

causes usually include endocrine disorders that affect spermatogenesis, testicular causes include primary testicular pathologies, and posttesticular causes include obstructive pathologies. While pretesticular and posttesticular causes are usually treatable, treatment success is very low in testicular azoospermia. In clinical practice, azoospermia is classified into two groups as OA and NOA. While pretesticular and testicular causes are evaluated in the NOA group, posttesticular causes are classified in the OA group.

NON-OBSTRUCTIVE AZOOSPERMIA

Pretesticular Causes

It is a condition encountered in 3% of infertile men and is due to endocrine-related problems.

Hypogonadotropic Hypogonadism (HH)

Hypogonadotropic hypogonadism (HH) is a rare and correctable cause of male infertility and it can occur from congenital or acquired causes. The most common cause include Kallmann syndrome, pituitary trauma or tumor, and the use of anabolic steroids. Kallman syndrome is a congenital malformation resulting from midline cranial structures. It is the most common cause of congenital HH (10). The pathophysiology of this syndrome is the absence of gonadotrophin releasing hormone (GnRH) release due to the non-migrating of GnRH-secreting neurons to the olfactory lobe during embryological development. The most common findings are the absence of a sense of smell, cleft palate, small testis, and in severe cases congenital deafness, skull and facial asymmetry, and cryptorchidism. Clinical findings in Kallmann syndrome depend on the degree of hypogonadism and the majority of patients represent with delayed puberty. Patients with a milder defect may have a moderate spermatogenesis disorder with an abnormal phenotype.

The use of exogenous testosterone may cause hypogonadism and azoospermia by suppressing the hypothalamohypophysial axis. Exogenous androgens impair spermatogenesis by suppressing FSH levels and cause a decrease in testicular testosterone levels (11).

When HH is detected in an azoospermic case the first step is imaging the pituitary gland with magnetic resonance imaging (MRI). Serum prolactin levels should be measured and hyperprolactinemia should be treated before GnRH replacement therapy in a case with elevated prolactin level. Because excessive prolactin secretion suppresses GnRH secretion from the hypothalamus with negative feedback. The use of some antihypertensive drugs and tricyclic antidepressants, stress, and pituitary adenomas may cause hyperprolactinemia or the cause may be idiopathic. Normal prolactin level is under 25 ng/dl and especially over 100 ng/dl suggests pituitary adenomas (12).

Androgen Resistance

The androgen receptor gene is located on the X chromosome and androgen resistance is seen at a ratio of 1:60000. There are more than 300 mutations in the androgen receptor gene and can be found in different forms, ranging from a female phenotype to an azoospermic man with normal virilization. The androgen receptor gene has 8 exons and the critical region is the region of CAG nucleotide repeats. It has been reported that men with normal virilized idiopathic azoospermia have more frequent CAG repeats than normal fertile men (13).

Testicular Causes

Also known as primer testicular failure, this deficiency of spermatogenesis includes testicular damage due to varicocele, undescended testis, testicular torsion, mumps orchitis, gonadotoxic effects of the drugs, genetic disorders, and idiopathic causes. Microsurgical testicular sperm extraction (micro-TESE) is applied to obtain sperm in this patient group which is clinically called NOA. NOA is divided into three histopathologic groups; hypospermatogenesis, maturation arrest, and SCO. In hypospermatogenesis, all stages of spermatogenesis are observed in the testis but the amount is low (14). In maturation arrest, germ cells cannot complete their maturation and remain in a certain phase. While spermatogonia and spermatocyte are seen in early-stage maturation arrest, spermatids are found in late-stage maturation arrest, but no mature spermatozoa cells are found in any stage (15). In SCO there are no germ cells (14). According to histological diagnosis, the rate of sperm finding in micro-TESE has been reported 73-100% in hypospermatogenesis, 27-86% in the maturation arrest group, and 22-41% in the group thought to have SCO, respectively (16).

Varicocele

Varicocele is detected in 4.3-13.3% of azoospermic men. For the first time, Tulloch reported in 1955 that spermatogenesis resumed and pregnancy was achieved after varicocelectomy in men with azoospermia. Spermatozoa are found in the ejaculate at a rate of 21-55% when varicocelectomy is performed in an azoospermic patient. Although spontaneous pregnancy rates are low in these cases, obtaining sperm from the ejaculate eliminates the need for an invasive procedure such as TESE (17).

While recommending varicocelectomy to the azoospermic patient, it should be informed that TESE and intracytoplasmic sperm injection (ICSI) may be required later on. Especially in patients with SCO or early-stage maturation arrest, spermatogenesis may not start after varicocelectomy. Therefore these patients should be aware of this possibility and should consider a direct alternative to micro-TESE instead of varicocelectomy (18). In addition, before deciding on varicocelectomy in an azoospermic patient with varicocele, genetic disorders such as Y chromosome microdeletions should be investigated. Varicocelectomy may contribute to healthier sperm being obtained by interventional methods, even if there is no sperm in the ejaculate after the surgery.

Undescended Testis

Undescended testis is the most common (2.7%) genital malformation in newborn boys and it decreases to 0.8% by the age of one year (19). There are 4 different theories about how cryptorchidism causes infertility; testicular dysgenesis, endocrine axis disorder, endocrinological damage, and obstruction. If the testicles have not descended spontaneously within the first year, genetic research is recommended for Klinefelter syndrome (20). Early treatment of undescended testis reduces the risk of infertility. Fertility is usually normal in unilateral undescended testicles, the age at the surgery and the testicular volume are the most important factors determining fertility. Azoospermia is found at a rate of 13% in unilateral patients and 31% in bilateral patients who have undergone undescended testis surgery (21).

Testicular Torsion

Testicular torsion is detected at a rate of 1:4000 in men under the age of 25. If surgery is not performed within the first 6 hours, the most important complication is testicular loss which can negatively affect fertility. It has been reported that spermatogenesis is impaired in both testicles after torsion. Although the reason is not certain, it is thought that anti-sperm antibodies appearing secondary to the deterioration of the blood-testicular barrier may be the cause (22).

Mumps Orchitis

The incidence of mumps orchitis decreased considerably with vaccination, 67% of the cases are unilateral and 33% are bilateral. The main cause of the pathology is thought to be necrosis developing in the seminiferous tubules due to congestion, edema, and increased pressure. The probability of infertility in mumps orchitis developing before puberty is very low (23).

Gonadotoxins and Drugs

In a patient presenting with infertility, it should be questioned whether he use any drugs or food supplement. Exposure to exogenous androgens, antiandrogens, chemotherapy drugs, radiotherapy, or toxins such as pesticides and insecticides may adversely affect spermatogenesis. Drugs and toxins may affect spermatogenesis with 4 mechanisms; direct gonadotoxic effect, by affecting the hypothalamo-pituitary axis, ejaculation disorder, and decrease in libido.

The testis consists of two parts: the germ cells, the seminiferous tubules containing Sertoli cells, and the interstitial area where the Leydig cells responsible for testosterone production are located. A continuous cell division takes place and about 100 million spermatozoa are produced daily in seminiferous tubules, therefore drug use mostly affects this region. Since the production of mature spermatozoa takes an average of 74 days, the effect of a drug on spermatogenesis occurs 3 months later (24). Cyclophosphamide, which is used for autoimmune diseases, may cause permanent azoospermia, especially when used at doses exceeding 7.5 mg/m^2 (25). Sulfasalazine also causes transient azoospermia, and spermatogenesis is expected to return to normal 3 months after the drug is discontinued.

Genetic Causes

Genetic anomalies are found in 15% of azoospermic patients and 5% of oligospermic men (26). The 2 most common genetic tests used in the diagnosis of NOA are; the analysis of microdeletions on the long arm (Yq) of the Y chromosome and the karyotype.

Klinefelter Syndrome

The most common karyotype anomaly in infertile men is Klinefelter syndrome (47,XXY), and 90% of patients have non-mosaic X chromosome polysomy. Advanced maternal and paternal ages increased the risk of Klinefelter syndrome (27). The phenotypic characteristics of Klinefelter syndrome are; tall, euicoid structure, micropenis, small and hard testicles, decreased facial hair, and female-type genital hair. Patients are often azoospermic but in a recent study, it is reported that spermatozoa could be found in 69% of cases with micro-TESE. These patients are more likely to have sperm in the ejaculate or by the micro-TESE method just after puberty. In advancing ages testicles become fibrotic and germ cells may disappear, so it is very important to diagnose at an early age and to obtain and freeze spermatozoa (20).

47,XYY Syndrome

This syndrome occurs as a result of a problem in the separation of the Y chromosome during the meiosis stage of the formation of the spermatozoa. These patients are tall, and have low intelligence and antisocial personality disorder characteristics. SCO or maturation arrest is detected in testicular biopsies of these cases (28).

Mixt Gonadal Dysgenesis

They have 45,XO and 46,XY mixed genotypes and anatomically they have a gonad with testis on one side and a line on the other side. The testis is usually undescended and does not contain germ cells. Since the risk of developing gonadoblastoma and seminoma is high in the streak-shaped gonad, this gonad should be surgically removed (29). These patients also have various degrees of ambiguous genitalia.

Y chromosome Microdeletions

Y chromosome microdeletion analysis should be performed in patients with severe oligoasthenospermia or azoospermia. It was determined that microdeletions from proximal to distal in the azoospermia factor (*AZF*) region on the q arm of the Y chromosome (Yq, *AZFa*, *AZFb*, *AZFc*) cause azoospermia (30). The frequency of Y microdeletion was reported as 7.3% in the infertile population and this rate was reported as 9.7% in men with azoospermia. Microdeletions on Y chromosome composed of 60% *AZFc*, 16% *AZFb*, 8% *AZFb+c*, 5% *AZFa*, 4% *AZFa+b+c*, and 6% non *AZF* deletions. *AZFc* is the most common Y chromosome microdeletion and is seen at a ratio of 1:4000. Its incidence in azoospermic patients has been reported as 13%.

AZF deletion determination in male infertility has prognostic importance for couples who want ICSI treatment. Depending on the complete or partial deletion of Y chromosomes, severe sperm disorders may be seen in men, ranging from mild sperm disorders to azoospermia. *AZFa* microdeletion is detected in 1% of NOA patients. It has been reported that complete *AZFa* deletion is associated with type 1 SCO syndrome and azoospermia (30). The American Society of Reproductive Medicine (ASRM) reported that sperm cannot be found with micro-TESE in those with *AZFa*, *AZFb*, and *AZFb+c* microdeletions.

Relationship between Azoospermia and microRNA

MicroRNAs (miRNA) are regulatory molecules that participate in important processes such as embryological development, cell differentiation, and apoptosis in the cell (31). In a study, it was shown that four different miRNA types (hsa-miR-34b, hsa-miR-34c, hsa-miR34c-5p, and hsa-miR-122) decreased while one miRNA (hsa-miR-429) increased in men with NOA. In another study, it was reported that before TESE is performed, it can be predicted whether there will be spermatozoa in the testis by measuring two different miRNA types (miR-539-5p and miR-941) (32). In spermatogonia, pachytene spermatocytes, and round spermatids, miRNA levels were found to be different between patients with NOA and OA. Therefore, it has been claimed that spermatogenesis can be initiated in azoospermic patients by using miRNA inhibitors and miRNA copies (33). If this theory is realized, it will be an important milestone in the treatment of azoospermia.

TREATMENT OF NON-OBSTRUCTIVE AZOOSPERMIA

In the treatment of NOA cause-oriented treatment modality should be preferred. Especially with the advances in assisted reproductive techniques and obtaining spermatozoa from the testis is used as an effective method in solving this problem. For this purpose, empirical treatment and interventional procedures are used in the treatment of NOA.

Empirical Hormonal Treatments

One of the most commonly used agents in the treatment of NOA is clomiphene citrate. In a study patients diagnosed with NOA and having no SCO were given 50 mg clomiphene citrate every other day, with a testosterone level of 600-800 ng/dl. At the end of the 9th month, 64% of patients have spermatozoa in their ejaculate while spermatozoa were found in testicular biopsy in 36% of the patients (34). In another study involving 1054 patients, clomiphene citrate, human chorionic gonadotropin (hCG), and aromatase inhibitors were given and it was reported that these treatments did not contribute to either spermatozoa findings or pregnancy and birth rates (35).

Methods for Finding Spermatozoa in Non-Obstructive Azoospermia

Methods for spermatozoa finding in NOA include testicular sperm aspiration (TESA), TESE, and micro-TESE. Percutaneous epididymal sperm aspiration (PESA), which is used in OA, is not preferred in NOA because of the lower success rates.

Testicular Sperm Aspiration (TESA)

It is a method of aspirating spermatozoa percutaneously by a needle through the skin of the scrotum. Although it is not the preferred method for NOA patients due to the low success rates, it is the cheapest method if success can be achieved. Another disadvantage of this method is that hematoma may develop due to vascular injuries (36).

Testicular Sperm Extraction (TESE)

First, the testis is exposed by the incision into the scrotum, and then an incision is made into the tunica albuginea. Since more tissue is removed from the testis in large pieces, this method may cause a problem, especially in patients with a small testicular volume. The rate of obtaining spermatozoa with TESE is reported to be two times higher than with TESA (36).

Microsurgical Testicular Sperm Extraction (micro-TESE)

Unlike TESE, in micro-TESE, after the testis is exposed, the entire testicular tissue is reviewed under the microscope at 15-20 magnification, and samples are taken from the most opaque and plump tubules. It is the most effective method to obtain spermatozoa from the testis. Predictive factors for finding spermatozoa in micro-TESE are; serum FSH and testosterone level, testicular volume, age, and obesity. For men with low testosterone levels, it is recommended that testosterone levels should be increased to normal levels before micro-TESE is performed (35). Although some studies have reported that high FSH levels decrease the rate of finding spermatozoa, it has been reported that the predictive value of FSH is very low, in a meta-analysis (37). In a meta-analysis evaluating 1764 patients, it is reported that there was no correlation between testis volume and spermatozoa finding rates (38). If testicular volumes are normal in an azoospermic patient, obstructive pathologies are more likely to be considered. NOA is more common in obese patients and the rate of finding spermatozoa is below the average (39).

OBSTRUCTIVE AZOOSPERMIA

After the testis the reproductive tract continues to the ductuli efferentes, then the epididymis, vas deferens, vesicula seminalis, and opens into the verumontanum through to the ejaculatory canal. The embryological origin of the posttesticular duct is the wolf duct (mesonephric duct).

Posttesticular Cause

Posttesticular azoospermia is seen due to obstruction or ejaculation disorders. Causes of OA are; the absence of vas deferens, vasal obstruction, and epididymal or ejaculatory duct obstruction. Among the findings to support OA; are the inability to palpate vas deferens, testicular volumes of 16 ml or more, presence of dilated caput epididymis, and normal serum FSH levels. Detection of quantitatively normal spermatogenesis in testicular biopsy performed for diagnostic purposes is also in favor of OA. Finding the etiology of azoospermia is very important in the selection of the sperm retrieval technique and in determining the probability of detecting spermatozoa. In cases without obstruction, sperm motility increases as you move away from the testis and caput epididymis. On the other hand, if there is an obstruction at the level of vas deferens, degenerated spermatozoa and macrophages increase in the most distal level of the epididymis while the best motility can be achieved in the caput epididymis or efferent channels (40).

Congenital Agenesis of Vas Deferens

This pathology is seen in 1% of the infertile population and 6% of those with azoospermia (41). There are two causes; cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation and the anomalies in the development of mesonephric duct. Cystic fibrosis (CF) is the most common autosomal recessive disease in Caucasians. CFTR gene mutation is found in 80% of those with bilateral vas deferens agenesis and 43% of those with unilateral agenesis (42). Testicular volumes and spermatogenesis are normal in patients with congenital absence of vas deferens but their ejaculates are acidic and their volumes are 1 ml or less. If the development of the wolf channel is affected before the 7th day of the gestational period, the development of the reproductive system is also affected and epididymal agenesis, seminal vesicle agenesis, or hypoplasia may occur resulting in low ejaculate volume (43). In this patient group, spermatozoa can be obtained from the head of the epididymis by microsurgical or percutaneous methods for assisted reproductive techniques.

Vasal Obstruction

The most common cause is cord injuries during the inguinal hernia repair. It can be caused by direct injury or developed due to the inflammation caused by the mesh placed during surgery. It should be considered when normal testicular volumes and full epididymis are palpated on physical examination. Another common cause in the USA is a vasectomy performed for contraceptive purposes. If fertility is desired again in these patients vasovasostomy can be performed. Vasectomy reversal which is the microsurgical method, first described by Siber and Owen is accepted as a gold standard treatment method today (44). In a study examining the long-term result of 1303 patients, the incidence of finding spermatozoa was 89% and the rate of spontaneous pregnancy was reported as 59% (45).

During the vasovasostomy operation, when the proximal vas incision is made the fluid coming from the lumen is thick and there are no spermatozoa in the microscopic

examination, and also there is no other stenosis at the distal part, epididymovasostomi technique is performed. Many studies have reported that, even in cases where the epididymis was too short after epididymovasostomi, the intact epididymis can allow some spermatozoa to gain motility and fertilization ability (46,47).

Epididymal Obstruction

Epididymal obstruction is the most common cause seen in 30-67% of patients with OA (48). Previous epididymal surgeries and infections may cause epididymal obstruction. Although its pathology is not known exactly, chronic sinusitis and respiratory dysfunctions are seen together with OA, in Young's syndrome which is characterized by a defect in ciliary activity and mucus structure. Since spermatogenesis is normal in these patients, it is possible to have children with assisted reproductive methods.

Ejaculatory Duct Obstruction

Ejaculatory duct obstruction in the literature; is defined by different names such as Mullerian duct cyst, urogenital sinus cyst, or midline cyst (48,49). It is detected in 1-3% of azoospermic patients and is characterized by acquired or congenital unilateral or bilateral ejaculatory duct obstruction. The most common congenital causes are ejaculatory duct atresia or stenosis and midline cysts. Among the acquired reasons; are previous trauma and pelvic interventions, genitourinary infections, inflammatory process, vesicoseminal dysfunction, and prostate cancer (50).

A gel-like fructose-rich secretion secreted by seminal vesicles constitutes 80% of the ejaculate volume. Other 5-10% of the ejaculate volume is composed of fluid from the testicles and epididymis that contains spermatozoa. Therefore vas deferens obstruction does not affect semen volume. If low ejaculate volume, low seminal fructose level, and acidic pH are detected in semen analysis, pathologies that may cause distal ejaculatory duct obstruction should be considered. Despite normal testis volume and hormone profile, azoospermia with low ejaculate volume and the detection of dilated seminal vesicles in transrectal ultrasound (TRUS), indicate ejaculatory duct obstruction (51).

If ejaculatory duct obstruction is caused by a midline cyst, transurethral resection of the ejaculatory duct (TURED) is performed with the aim of decorticating the cyst wall. This treatment is firstly described by Farley and Barnes in 1973. Ejaculate volume usually returns to normal after TURED, and the probability of spontaneous pregnancy is reported to be 13-30% (52,53).

Ejaculation Disorder

Ejaculation disorder should be considered in patients with low (<1 ml) ejaculate volume. Retrograde ejaculation is the most common ejaculation disorder and is characterized by the flow of seminal fluid back to the bladder. Causes include anatomical, neurogenic, pharmacological (alpha-blockers, neuroleptics, tricyclic antidepressants), or idiopathic reasons (54). The diagnosis is achieved by showing spermatozoa in a urine sample taken after ejaculation. The presence of more than 10-15 spermatozoa in each high magnification field in the urine sample is considered to be diagnostic. Conversely, in patients with emission disorders, no spermatozoa are detected in the urine sample.

CONCLUSION

There are many different causes in the etiology of azoospermia. Diagnostic and treatment approaches for these different etiologies are quite diverse. In recent years, especially with the development of technology and understanding of the subgroups of azoospermia, the rate of obtaining pregnancy get increased. Recent studies involving miRNAs that play a regulatory role in embryological development, emphasize that miRNA inhibitors and miRNA transcripts can initiate spermatogenesis in azoospermic patients. If this theory is realized, it would be an important milestone in the treatment of azoospermia. In order to achieve promising developments in the azoospermic patients to have children, more studies are needed.

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

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

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

REFERENCES

1. Jarow JP, Espeland MA, Lipshultz LI. Evaluation of the azoospermic patient. J Urol. 1989;142(1):62-5.
2. Honig SC, Lipshults LI, Jarow J. Significant medical pathology uncovered by a comprehensive male infertility evaluation. Fertil Steril. 1994;62(5):1028-34.
3. Schoor RA, Elhanbly S, Niederberger CS, Ross LS. The role of testicular biopsyin the modern management of male infertility. J Urol. 2002;167(1):197-200.
4. Ron-El R, Strassburger D, Friedler S, Komarowski D, Bern O, Soffer Y, et al. Extended sperm preparation: an alternative to testicular sperm extraction in non-obstructive azoospermia. Hum Reprod. 1997;12(6):1222-6.
5. Chillón M, Casals T, Mercier B, Bassas L, Lissens W, Silber S, et al. Mutations in the cystic fibrosis gene in patients with congenital absence of the vas deferens. New Engl J Med. 1995;332(22):1475-80.
6. Pierik FH, Vreeburg JT, Stijnen T, De Jong FH, Weber RF. Serum inhibin B as a marker of spermatogenesis. J Clin Endocrinol Metab. 1998;83(9):3110-4.
7. Bergmann M, Behre HM, Nieschlag E. Serum FSH and testicular morphology in male infertility. Clin Endocrinol (Oxf). 1994;40(1):133-6.
8. Chen CS, Chu SH, Lai YM, Wang ML, Chan PR. Reconsideration of testicular biopsy and follicle-stimulating hormone measurement in the era of inracytoplasmic sperm injection for non-obstructive azoospermia. Hum Reprod. 1996;11(10):2176-9.

9. Aydos K. Erkek infertilitesi. In: Anafarta K, Arıkan N, Bedük Y, editors. Temel üroloji. 4th ed. Ankara: Güneş Tıp Kitabevleri; 2011. p.1037-90. Turkish.
10. Thakker S, Persily J, Najari B. Kalmann syndrome and central non-obstructive azospermia. Best Pract Res Clin Endocrinol Metab. 2020;34(6):101475.
11. McLachlan RI, O'Donnell L, Meachem SJ, Stanton PG, de K, Pratis K, et al. Hormonal regulation of spermatogenesis in primates and man: insights for development of the male hormonal contraceptive. J Androl. 2002;23(2):149-62.
12. Eggert-Kruse W, Schwalbach B, Gerhard I, Tilgen W, Runnebaum B. Influence of serum prolactin on semen characteristics and sperm function. Int J Fertil. 1991;36(4):243-51.
13. Casella R, Maduro MR, Misfud A, Lipshultz LI, Yong EL, Lamb DJ. Androgen receptor gene polyglutamine length is associated with testicular histology in infertile patients. J Urol. 2003;169(1):224-7.
14. Chehrazi M, Rahimiforoushani A, Sabbaghian M, Nourijelyani K, Sadighi Gilani MA, Hoseini M, et al. Sperm retrieval in patients with Klinefelter syndrome: a skewed regression model analysis. Int J Fertil Steril. 2017;11(2):117-22.
15. Weedin JW, Khera M, Lipshultz LI. Varicocele repair in patients with non-obstructive azoospermia: a meta-analysis. J. Urol. 2010;183(6):2309-15.
16. Flannigan R, Bach PV, Schlegel PN. Microdisection testicular sperm extraction. Transl Androl Urol. 2017;6)4):745-52.
17. Cocuzza M, Pagani R, Lopes RI, Athayde KS, Lucon AM, Srougi M, et al. Use of subinguinal incision for microsurgical testicular biopsy during varicocelectomy in men with nonobstructive azoospermia. Fertil Steril. 2009:91(3):925-8.
18. Lee JS, Park HJ, Seo JT. What is the indication of varicocelectomy in men with nonobstructive azoospermia? Urology. 2007 69(2):352-5.
19. Mathers MJ, Sperlin H, Rubben H, Roth S. The undescended testis: diagnosis, treatment and long-term consequences. Dtsch Arztebl Int. 2009;106(33):527-32.
20. Zitzmann M, Aksglaede L, Corona G, Isidori AM, Juul A, T'Sjoen G, et al. European academy of andrology guidelines on Klinefelter Syndrome Endorsing Organization: European Society of Endocrinology. Andrology. 2021;9(1):145-67.
21. Grasso M, Bounaguidi A, Lania C, Bergamaschi F, Castelli M, Rigatti P. Postpubertal cryptoorchidism: review and evaluation of the fertility. Eur Urol. 1991;20(2):126-8.
22. Arap MA, Vicentini FC, Cocuzza M, Hallak J, Athayde K, Lucon AM, et al. Late hormonal levels, semen parameters, and presence of antisperm antibodies in patients treated for testicular torsion. J Androl. 2007:28(4):528-32.
23. Cırakoğlu A, Benli E. Azospermik hastanın değerlendirilmesi. In: Gül Ü, Turunç T, editors. Erkek cinsel sağlığı ve fertilitesi. İstnabul: Galenos Yayınevi; 2021. p.139-52. Turkish.
24. Neto FT, Bach PV, Najari BB, Li PS, Goldstein M. Spermatogenesis in humans and its affecting factors. Semin Cell Dev Biol. 2016;59:10-26.
25. Weber-Schoendorfer C, Chambers C, Wacker E, Beghin D, Bernard N, Network of French Pharmacovigilance Centers, et al. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. Arthritis Rheumato. 2014;66(5):1101-10.
26. Bonomi M, Libri DV, Guizzardi F, Guarducci E, Maiolo E, Pignatti E, et al. New understandings of the genetic basis of isolated idiopathic central hypogonadism. Asian J Androl. 2012;14(1):49-56.
27. Los E, Ford GA. Klinefelter syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021.
28. Wong EC, Ferguson KA, Chow V, Ma S. Sperm aneuploidy and meiotic sex chromosome configurations in an infertile men XYY male. Hum Reprod. 2008;23(2):374-8.
29. Dénes FT, Cocuzza MA, Schneider-Monteiro ED, Silva FA, Costa EM, Mendonca BB, et al. The laparoscopic management of intersex patients: the preferred approach. BJU Int. 2005;95(6):863-7.
30. Hopps CV, Mielnik A, Goldstein M, Palermo GD, Rosenwaks Z, Schlegel PN. Detection of sperm in men with Y chromosome microdeletions of the AZFa, AZFb and AZFc regions. Hum Reprod. 2003;18(8):1660-5.
31. Le Bot N. miRNAs and cell-cycle control in ESCs. Nat Cell Biol. 2012;14(7):658.
32. Barceló M, Mata A, Bassas L, Larriba S. Exosomal microRNAs in seminal plasma are markers of the origin of azoospermia and can predict the presence of sperm in testicular tissue. Hum Reprod. 2018;33(6):1087-98.
33. Yao C, Yuan Q, Niu M, Fu H, Zhou F, Zhang W, et al. Distinct expression profiles and novel targets of microRNAs in human spermatogonia, pachytene spermatocytes, and round spermatids between OA patients and NOA patients. Mol Ther Nucleic Acids. 2017;9:182-94.
34. Hussein A, Ozgok Y, Ross L, Rao P, Niederberger C. Optimization of spermatogenesis-regulating hormones in patients with non-obstructive azoospermia and its impact on sperm retrieval: a multicentre study. BJU Int. 2013;111(3 Pt B):E110-4.
35. Reifsnyder JE, Ramasamy R, Husseini J, Schlegel PN. Role of optimizing testosterone before microdissection testicular sperm extraction in men with nonobstructive azoospermia. J Urol. 2012;188(2):532-6.
36. Mangum CL, Patel DP, Jafek AR, Samuel R, Jenkins TG, Aston KI, et al. Towards a better testicular sperm extraction: novel sperm sorting technologies for non-motile sperm extracted by microdissection TESE. Transl Androl Urol. 2020;9(Suppl 2):S206-14.
37. Li H, Chen LP, Yang J, Li MC, Chen RB, Lan RZ, et al. Predictive value of FSH, testicular volume, and histopathological findings for the sperm retrieval rate of microdissection TESE in nonobstructive azoospermia: a meta-analysis. Asian J Androl. 2018;20(1):30-6.
38. Ramasamy R, Trivedi NN, Reifsnyder JE, Palermo GD, Rosenwaks Z, Schlegel PN. Age does not adversely affect sperm retrieval in men undergoing

microdissection testicular sperm extraction. Fertil Steril. 2014;101(3):653-5.
39. Berookhim BM, Palermo GD, Zaninovic N, Rosenwaks Z, Schlegel PN. Microdissection testicular sperm extraction in men with Sertoli cell-only testicular histology. Fertil Steril. 2014;102(5):1282-6.
40. Schlegel PN, Berkeley AS, Goldstein M, Cohen J, Alikani M, Adler A, et al. Epididymal micropuncture with in vitro fertilization and oocyte micromanipulation for the treatment of unreconstructable obstructive azoospermia. Fertil Steril. 1994;61(5):895-901.
41. Ferlin A, Raicu F, Gatta V, Zuccarello D, Palka G, Foresta C. Male infertility: role of genetic background. Reprod Biomed Online. 2007;14(6):734-45.
42. Claustres M. Molecular pathology of the CFTR locus in male infertility. Reprod Biomed Online. 2005;10(1):14-41.
43. McCallum T, Milunsky J, Munarriz R, Carson R, Sadeghi-Nejad H, Oates R. Unilateral renal agenesis associated with congenital bilateral absence of the vas deferens: phenotypic findings and genetic considerations. Hum Reprod. 2001;16(2):282-8.
44. Baker K, Sabanegh E Jr. Obstructive azoospermia: reconstructive techniques and results. Clinics (Sao Paulo). 2013;68 Suppl 1(Suppl 1):61-73.
45. Schwarzer JU. Vasectomy reversal using a microsurgical three-layer technique: one surgeon's experience over 18 years with 1300 patients. Int J Androl. 2012;35(5):706-13.
46. Jow WW, Steckel J, Schlegel PN, Magid MS, Goldstein M. Motile sperm in human testis biopsy specimens. J Androl. 1993;14(3):194-8.
47. Practice Committee of the American Society for Reproductive Medicine. Vasectomy reversal. Fertil Steril. 2004;82(Suppl 1):S194-8.
48. Silber SJ. Microsurgery for vasectomy reversal and vasoepididymostomy. Urology. 1984;23(5):505-24.
49. Takihara H. The treatment of obstructive azoospermia in male infertility--past, present, and future. Urology. 1998;51(5A Suppl):150-5.
50. Kadioglu A, Cayan S, Tefekli A, Orhan I, Engin G, Turek PJ. Does response to treatment of ejaculatory duct obstruction in infertile men vary with pathology? Fertil Steril. 2001;76(1):138-42.
51. Orhan I, Onur R, Cayan S, Koksal IT, Kadioglu A. Seminal vesicle sperm aspiration in the diagnosis of ejaculatory duct obstruction. BJU Int. 1999;84(9):1050-3.
52. El-Assmy A, El-Tholoth H, Abouelkheir RT, Abou-El-Ghar ME. Transurethral resection of ejaculatory duct in infertile men: outcome and predictors of success. Int Urol Nephrol. 2012;44(6):1623-30.
53. Özkaya M, Gültekin MH, Özkara H. Obstrüktif azoospermi tedavisi. In: Gül Ü, Turunç T, editors. Erkek cinsel sağlığı ve fertilitesi. İstnabul: Galenos Yayıncılık; 2021. p.152-60. Turkish.
54. Schuster TG, Ohl DA. Diagnosis and treatment of ejaculatory dysfunction. Urol Clin North Am. 2002;29(4):939-48.