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Azoospermia - An Overview

Aashutosh Sinwal[1], Mudit Bhardwaj[1], Mohit Nair[1], Smrithimol Baby[1], Shagun Singh[2]

[1]Pharm D, School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India, 302017
[2]Department of Psychology, Kanoria P.G. Mahila Mahavidhyalaya, Jaipur, Rajasthan, India, 302004

Corresponding Author: Aashutosh Sinwal

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ABSTRACT

The lack of sperm in the ejaculate is the hallmark of azoospermia. 15% of male infertile individuals have azoospermia. Obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) are the two main types of azoospermia. Infertility is a widespread chronic condition that affects mostly people aged 25 to 44, accounting for around 15% of all couples worldwide. The specific causes of azoospermia are not often obvious, but when the pathophysiology is idiopathic, the sickness is primarily linked to difficulties with ciliary function and mucus quality. The lack of gonadotropin production or intrinsic testicular dysfunction might be the reason for the NOA analysis. Silber and Owen developed microsurgical procedures for treating obstructive azoospermia in 1977, which have since become the norm for reconstructive surgery in male reproductive tract disorders. Micro TESE, an innovative method based on microsurgical procedures, is successful for sperm retrieval in males with NOA having ICSI.

KEYWORDS: Azoospermia, Invitro fertilization (IVF), Spermatogenesis, Chromosome, Gonadotropin-releasing hormone.

INTRODUCTION

The lack of sperm in the ejaculate is the hallmark of azoospermia. 15% of male infertile individuals have azoospermia. Obstructive azoospermia (OA) and non-obstructive azoospermia (NOA) are the two main types of azoospermia. OA is brought on by blockages in the excurrent duct system. Males who are homozygous for CFTR mutations, for instance, are born without the vas deferens on both sides [1]. NOA may arise from main, secondary, or partial testicular failure men with azoospermia exhibit NOA in 40% of cases and OA in 60% of cases. Compared to OA, NOA causes more concerns about conception rates about in vitro fertilization (IVF) or intracytoplasmic sperm injection (ICSI) since it is more frequently linked to spermatogenesis failure, which results in the creation of few or no sperm.

The inability to produce the necessary amounts of testosterone for testicular growth is a result of both primary and secondary testicular failure; what distinguishes them is the reason for the failure. The pituitary/hypothalamic axis generates hormones that instruct the testis to manufacture testosterone; however, poor hormonal communication from this axis causes secondary failure. The primary failing is the testis' inability to produce testosterone. Klinefelter Syndrome (XXY karyotype) is one condition that causes primary testicular failure because the testes are underdeveloped and produce insufficient testosterone. Defective gonadotrophin-releasing hormone synthesis, which results in secondary testicular failure and is brought on by sporadic mutations in the chromatin protein

CHD7, is one sign of CHARGE Syndrome. [2]

Incomplete testicular failure shows as either a modest testis size or a testis volume that is normal and has normal hormone levels (for example, FSH). In some cases, spermatogenesis is defective, and maturation arrest occurs. Microdeletions on the Y chromosome and polysomy of the sex chromosomes (XXY, XYY, etc.), which are common causes of NOA, were the first genetic abnormalities found in azoospermia patients. Patients with azoospermia frequently lose a zone known as azoospermia factor (AZF) on the extended portion of the Y chromosome. [3,4]

EPIDEMIOLOGY

Infertility is a widespread chronic condition that affects mostly people aged 25 to 44, accounting for around 15% of all couples worldwide. Although maternal age is important, male factor infertility, notably azoospermia, appears to be a significant influence, affecting around 1% of males and 10-15% of infertile men. [5,7] The difficulty in reproducing not only creates significant psychological and social misery for those affected but also imposes an economic cost on both people and healthcare systems. [6]

In the United States, about 0.6 million males of reproductive age suffer from azoospermia, the majority of which is non-obstructive azoospermia (NOA). [5] Additionally, male infertility has been associated with a greater probability of cancer. Azoospermic people are more likely to develop cancer, accounting for 5-8% of all testicular cancer cases. [5,6] The true frequency, particularly in underdeveloped countries, is unknown due to underreporting and barriers to getting modern treatments. [5]

Furthermore, male fertility is closely tied to a variety of health issues. Notably, evidence suggests that males facing reproductive problems may experience extra health difficulties in the years after fertility treatments. Recent prospective studies in Europe and the United States show that infertile men have a higher risk of cardiovascular disease, some malignancies, autoimmune diseases, diabetes, and total hospitalizations. [6,7] Glazer et al underline a prominent enhancement in mortality risk among men with male factor infertility weigh to their fertile counterparts, including higher rates of hypogonadism, metabolic disorders, and impaired bone mineral density. The underlying relationships are unknown, with ideas positing that common variables such as hypogonadism or genetics may explain these correlations. However, existing data on death rates among infertile men are limited and do not include specifics about the dangers associated with certain forms of infertility, such as oligospermia and azoospermia. [7] According to reports, structural and chromosomal abnormalities affect 2% to 10% of infertile persons. Severe oligospermia and non-obstructive azoospermia (NOA) were associated with 8% and 20% of genetic abnormalities, respectively. [8]

ETIOLOGY

The specific causes of azoospermia are not often obvious, but when the pathophysiology is idiopathic, the sickness is primarily linked to difficulties with ciliary function and mucus quality. [5] Spermatogenesis is commonly normal in OA patients. The specific cause of NOA is typically unknown. NOA can arise from a variety of causes, including our administration of anabolic steroids, insensitivity to androgens, chemotherapy, congenital lack of germ cells (Sertoli cell-only syndrome), heavy metal exposure, hyperprolactinemia, Kallmann syndrome, Klinefelter syndrome, and Y chromosome microdeletions in subregions AZFa, AZFb, or AZFc can lead to reduced sperm production. [10] Mumps and orchitis, radiotherapy (Epsilon aminocaproic acid has been shown in trials to protect sperm DNA against radiation damage, but it has yet to be licensed for clinical usage.) [11,12] Symptoms may include spermatogenic (maturation) arrest, testicular torsion, testosterone supplementation, translocation or inversion

of azoospermia factor cryptorchidism, and varicoceles.

PATHOPHYSIOLOGY

Azoospermia can also be classified as pre- or post-testicular, depending on whether it is obstructive or not. In clinical practice, obstruction-based categorization is seen to be more beneficial.[5]

Pre-testicular, also known as a secondary testicular failure, is caused by pathological endocrine abnormalities in the hypothalamus, pituitary, and male gonads. While it is extravagant, up to three percent of men with infertility may have cardinal endocrinopathies. Meanwhile, testicular causes are spermatogenesis-related diseases. Both are in the non-obstructive category. [5,7]

Non-obstructive azoospermia (NOA) is caused by primary testicular abortiveness, which is marked by sublimate degree of LH and FSH as well as tiny testes and affects up to 10% of infertile men. Secondary testicular abortiveness can also be a reason, since congenital hypogonadotropic hypogonadism results in low amounts of LH and FSH, as well as undersized testes. Finally, incomplete/ambiguous testicular failure can manifest as a rise in FSH with a normal testis volume, a normal FSH with a small testis, or a normal testis volume. [13]

Azoospermia is caused by post-testicular obstructions in the male reproductive canal, which can develop anywhere throughout the whole duct system. This falls under the obstructive category. Obstructive azoospermia (OA) results from a physical obstruction in the male excurrent ductal framework, which can develop anyplace from the retetestis and the ejaculatory ducts. [5,13]

Pre-testicular causes of azoospermia

Azoospermia occurs before the testicular stage and can be congenital or acquired. It can be offered under the following circumstances:

1. Kallmann's syndrome is a congenital condition that causes hypogonadotropic hypogonadism (HGH) and midline cranial malformations. The underlying cause of this disease is a failure in the hypothalamic release of gonadotropin-releasing hormone (GnRH) because the neurons responsible for producing GnRH do not migrate to the olfactory lobe during development. Additional symptoms may include a decreased sense of smell, a cleft palate, and tiny testes. More severe cases may include congenital deafness, delayed puberty, unevenness in the skull and face, cerebellar difficulties, undescended testes, and renal problems. [14]
2. Hyperprolactinemia: Prolactin reduces the release of GnRH, inhibiting the production of LH and FSH. Symptoms of hypogonadism might vary depending on the degree of increase in prolactin levels in the circulation, with one such sign being sexual dysfunction, which eventually impairs fertility [15]. These patients may have decreased spermatogenesis due to anomalies in both testicles. [16]
3. Mumps orchitis is the most frequent non-salivary gland consequence of mumps, affecting one testicle in 10-20% of cases in males who have reached puberty. The mumps virus (MuV) has been found in semen and testicular tissues, indicating that epididymal inflammation, also known as epididymal-orchitis, might be caused by direct viral infection. However, an indirect immune-mediated mechanism may be at work. This inflammation affects both Leydig and germ cells, resulting in less testosterone synthesis. The germinal epithelium of the seminiferous tubules exhibits necrosis (cell death). Orchitis is usually accompanied by epididymitis and fever, which resolve within a week. Approximately half of the cases result in bilateral testicular atrophy, which can cause lower sperm count and reproductive problems (13% of cases), albeit infertility is uncommon. [17]
4. Klinefelter Syndrome: The most common genetic condition causing

nonobstructive azoospermia is Klinefelter syndrome (KS), characterized by an extra X chromosome. [18] The specific chemical pathways underlying primary testicular failure, as well as the vast spectrum of physical and neurocognitive features exhibited in KS, remain unknown. [19] Spermatozoa are found in around 69% of patients with Klinefelter syndrome after testicular sperm extraction procedures. [20]

5. Anabolic-androgenic steroids (AAS) can disturb the hypothalamus-pituitary-adrenal axis, leading to long-term impacts on male fertility. AAS has a negative feedback effect on the pituitary gland, reducing the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which decreases intratesticular testosterone levels and inhibits sperm generation. According to studies, about 98% of men with normal sperm counts who take AAS will have a short sperm figure or no sperm at all. Given enough time, sperm production will usually recover to normal after ceasing supplementation. [5,21]

Post-testicular causes of azoospermia

1. Congenital bilateral absence of vas deferens (CBAVD): Congenital bilateral privation of the vas deferens (CBAVD) contributes significantly to male infertility, accounting for 1-2% of cases. The fundamental feature of congenital bilateral absence of the vas deferens (CBAVD) is the lack of the vas deferens on both sides. This syndrome prevents sperm generated by the testes from being carried out of the body after passing through the epididymis, resulting in male aphoria. Congenital bilateral absence of the vas deferens (CBAVD) is primarily caused by genetic abnormalities that affect the creation or function of the vas deferens during fetal development. It is usually connected to mutations in cystic fibrosis-associated genes, as well as other genetic disorders affecting reproductive tract development.

   Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, such as ΔF508 IVS8-5T, the (TG)m variation, and M470V, can cause congenital bilateral privation of the vas deferens (CBAVD). These alternations decrease CFTR function, resulting in reduced chloride ion transport across epithelial cells and influencing a variety of physiological processes, including sperm transport and fertilization. Certain CFTR mutations, such as ΔF508 and IVS8-5T, have been confluent to an enhanced danger of infertility even in the absence of vas deferens obstruction, implicating CFTR dysfunction in spermatogenesis. Therefore, CFTR mutations play a valuable preface in the pathogenesis of CBAVD and may impact male fertility through mechanisms other than vas deferens abnormalities. [22]

2. Epididymis obstruction: Dr. David Young originally described Young's syndrome, which is characterized by obstructive azoospermia associated with persistent sinopulmonary infections, in 1950. Its scarcity in modern times has raised concerns regarding its existence. Mercury exposure has been postulated as a probable cause, with data pointing to a decrease in occurrence following the prohibition on mercury-containing medications. [23]

   Young syndrome's pathogenesis is unknown; however, it resembles Kartagener syndrome. It is unclear if ciliary dysfunction is the predominant defect in this condition. [13] Individuals with Young's syndrome symptoms should consider genetic testing. Surgical repair has had little success, leading to the suggestion of sperm retrieval with IVF/ICSI as the recommended therapeutic option for afflicted couples. [24]

3. Ejaculatory duct obstruction (EDO) is a very rare disorder that affects around five percent of infertile men. It can be caused by a variety of underlying conditions,

such as ejaculatory duct abnormalities, the presence of midline prostatic cysts, fibrosis caused by prostatitis or seminal vesiculitis, the presence of stones in the seminal vesicle (SV), or scarring from endoscopic treatments. As a result, semen cannot travel through the ducts, resulting in reduced fertility or infertility in afflicted individuals. [25]

DIAGNOSIS OF AZOOSPERMIA

NON-OBSTRUCTIVE AZOOSPERMIA: This most serious kind of male infertility is defined as an absence of sperm during ejaculation due to spermatogenesis failure. The lack of gonadotropin production or intrinsic testicular dysfunction might be the reason for the NOA analysis. NOA has been observed to affect one in every 100 males [27]. Approximately 10% of infertile guys acquire a diagnosis. [28]

1. Semen Samples: To make an accurate judgment, at least two semen samples must be evaluated. A semen sample should be centrifuged to reveal a lack of sperm. Approximately 35% of men acquire an initial diagnosis of NOA after carefully and appropriately examining several droplets of ejaculate sediment under a microscope for sperm observation. Cryptozoospermia refers to the presence of a tiny amount of sperm after centrifugation. If azoospermia is detected during a semen evaluation, the physician may diagnose the patient with OA or NOA. [26]
2. Confirm the patient's medication history, since certain drugs might impede spermatogenesis. These medications include 5α-reductase inhibitors and steroids used in anti-cancer therapy. [26,27]
3. Ultrasonography: Measuring testicular volume with an orchid meter or ultrasound is a key diagnostic criterion for (NOA). Testicular size reflects the degree of spermatogenesis, with smaller testes suggesting process failure. It is relevant for reasons other than testicular volume measurement. It provides valuable information about the pathophysiology of the testicles. This helps diagnose testicular microlithiasis, which is characterized as the presence of five or more microliths in each testis. It is linked to poor spermatogenesis and is most commonly seen in people with testicular dysgenesis syndrome (TDS). If the USG findings show testicular cancer, the doctor may prescribe further tests including an MRI and a tumor mass assessment. [26]
4. Varicocele is a common condition that may be diagnosed by physical examination. The patient must be investigated both supine and upright, with the scrotum investigated first and then palpated. It is usually detected in the male subpopulation with NOA. [29] It may affect spermatogenesis. As a result, varicocele existence should be evaluated while diagnosing NOA patients. [26] As a varicocele, it is critical to evaluate the spermatic core.[30]
5. Hormonal evaluation is crucial for diagnosing NOA. A high gonadotropin level implies primary testicular failure, even though NOA cannot always be eliminated when gonadotropin levels are normal. Following examinations of testicular volume, luteinizing hormone (LH), and follicle-stimulating hormone (FSH), about 90% of individuals with azoospermia are diagnosed with OA or NOA.[26]
6. Physical examination is necessary to examine males with azoospermia. The complete body is the major emphasis, with sexual features ranking second. Examining the inguinal and genital areas for scars from previous surgery is also required to detect any damage to the vas deferens and testicular blood flow. Evaluations of testicular consistency, size, and texture are also required.[29,30]
7. Genetic analysis: Additional testing, including karyotyping and genetic assessment, should be performed to diagnose NOA. According to studies, sex chromosomal and autosomal

abnormalities emerge next in individuals with azoospermia and Klinefelter syndrome who have atypical karyotypes. Genetic abnormalities such as KAL1 and FGFR1 have been discovered [26].

Obstructive azoospermia is characterized as the lack of spermatozoa in the ejaculate nevertheless ordinary spermatogenesis. This is a usual urologic disorder. Vasectomy is a common cause of OA; however, infection, damage, and genetic and congenital anomalies are also causes of OA. [23] The diagnosis mostly includes:

1. Ananesis: Obstructive azoospermia (OA) patients' medical histories should include genital trauma, drug allergies, medication history (including exposure to gonadotropins, anabolic steroids, and toxins), genitourinary infections/STDs, lifestyle factors (such as smoking), occupational hazards, and a family history of infertility.[5]
2. Physical examination identifies vasal gaps, vasectomy site prominence, granuloma presence, and epididymal abnormalities. Physical examination is commonly used to diagnose congenital bilateral vas deferens and epididymitis in males. Patients should be assessed for infertility, sexual history, previous medical history, and gonadotropic exposure. Testes in males with OA are hard.[30]
3. Hormone levels: Laboratory results show that FSH levels are normal in OA. A rise in FSH in OA suggests a higher requirement for assisted reproductive technology after vasectomy reversal. [13]
4. Semen analysis: If semen volume is regularly low (<1.5 mL), it's important to distinguish between an artifact and true low volume. Possible reasons include anomalies of the vas deferens/seminal vesicles, retrograde ejaculation, or emission failure. Testing post-ejaculate urine can help detect retrograde ejaculation, which is prevalent in diabetic males. Furthermore, alpha agonists such as pseudoephedrine may help convert retrograde to antegrade ejaculation, thereby alleviating some of the problems associated with OA. [31]

MANAGEMENT

Couples with infertility now have a variety of options for establishing biological children because of sophisticated assisted reproductive technology. [5]

Obstructive azoospermia

Obstructive azoospermia (OA) can be caused by a variety of reasons, including past vasectomy, anomalies in the epididymis, vas deferens, or ejaculatory ducts [32].

Because surgical repair is problematic for people with congenital vas deferens absence, assisted reproductive procedures are favored. [5]

Patients with ejaculatory ductal obstruction frequently receive a transurethral removal of the ejaculatory ducts (TURED) to reestablish ejaculatory duct integrity and improve the parameters of semen in within fifty percent to seventy percent of cases. However, potential side effects include failure, urinary tract infections, leakage into the seminal vesicles and ejaculatory ducts, and epididymitis. To assure patency and increase safety, intraoperative transrectal ultrasonography and methylene blue can be employed. The operation may additionally entail a transurethral laser incision of the ejaculatory duct and seminal vesiculoscopy. [5]

Epididymal obstruction is the most prevalent manifestation of OA, impacting 30-67% of men with adequate testicular sperm formation. Epididymal obstruction can result from infection, damage, or epididymal rupture after a vasectomy. There has been an increase in cases of epididymal obstruction of unclear origin. [32]

The major purpose of controlling obstructive azoospermia (OA) is to repair the location of obstruction utilizing microsurgical reconstructive surgical procedures such as vasoepididymostomy and vasovasostomy to give the most secure and cost-effective

option for therapy for OA individuals. Intraoperative vasography has better results than vasoepididymostomy. [5,32]

Microsurgical Reconstruction

Silber and Owen developed microsurgical procedures for treating obstructive azoospermia in 1977, which have since become the norm for reconstructive surgery in male reproductive tract disorders.

The primary reason for conducting a vasovasostomy or vasoepididymostomy is to restore fertility in patients with obstructive azoospermia. [33]

1. Vasovasostomy Approximately 6% of men who have vasectomy choose reversal surgery, with studies suggesting superior results with microscopic vs macroscopic vasovasostomy. [32] Scrotal or inguinal vasovasostomy is preferred for a variety of vassal obstructions caused by vasectomy, iatrogenic vassal injury from procedures such as herniorrhaphy or hydrocelectomy, or single-site vassal blockage due to infection or trauma. Still, it is not appropriate for multifocal obstructions along the vas deferens. [33] Following vasovasostomy, 70% to 95% of patients have sperm return to the ejaculate, resulting in births in 30% to 75% of couples without assisted reproductive technology (ART). The time between vasectomy and vasovasostomy has a substantial impact on sperm recovery and conception rates, with a larger probability of fertility within 5 years of blockage. Although the pregnancy rate may fall as blockage lengths increase, the patency rate stays largely consistent. Furthermore, the age of the female partner influences pregnancy success. [32]
2. Vaso-epididymostomy
   A vasoepididymostomy is used to treat several types of epididymal blockage, including idiopathic, related to long-standing vassal obstruction, and iatrogenic obstruction caused by procedures such as epididymal aspiration. Multifocal epididymal obstruction necessitates an anastomosis at all sites of blockage. [33] Patients with no other anatomical defects are good candidates for vasoepididymostomy, with microscopic surgery being the recommended method because of its effectiveness and lesser risk of hormonal treatment for the female spouse. Success rates vary, with patency restored in 70-90% of patients and fertility recovered in just 50%. Unilateral surgery has lower success rates than bilateral treatments. The luminal diameter of epididymal tubules is bigger in the caudal area than in the caput region, influencing vasoepididymostomy success rates.
   Sperm retrieval and cryopreservation during surgery are indicated to maximize reproductive choices in situations of surgical or pregnancy failure following vasoepididymostomy. [32]

POST-OPERATIVE CARE:

Following surgery, patients are usually recommended to use ice packs to relieve discomfort and swelling and to wear a scrotal supporter for 3-4 weeks. They should avoid strenuous physical activity such as weight lifting and sexual intercourse for 3-4 weeks, as well as ejaculation. Pain is often treated with oral analgesics such as NSAIDs and narcotics. [33]

Sperm retrieval techniques

If microsurgical repair fails, patients should be advised of the option of extracting sperm during cryopreservation surgery via testicular biopsy or aspiration at the site of a vaso-vasal or vaso-epididymal anastomosis. These techniques are useful in situations of post-vasectomy blockage, congenital bilateral absence of the vas deferens (CBAVD), ejaculatory duct obstruction (EDO), and irreversible causes of obstructive azoospermia. They generally do not generate enough sperm for intrauterine insemination (IUI) and, in rare cases, assisted reproductive technology (ART), such as in vitro fertilization (IVF). [33]

Individuals diagnosed with obstructive azoospermia have two treatment options: epididymal or testicular sperm extraction, with epididymal extraction being less intrusive. Microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), and reconstructive surgery are all methods for removing epididymal sperm. [34] If the impediment is within the testicles, treatments like TESE (Testicular Sperm Extraction) or TESA (Percutaneous Testicular Sperm Aspiration) would be required. [5]

Microsurgical Epididymal Sperm Aspiration (MESA)

Most andrologists consider microsurgical epididymal sperm aspiration (MESA) to be the optimal method of sperm retrieval for males with obstructive azoospermia. Individual incisions or tubule punctures are used to harvest sperm during this technique, which is conducted under general anesthesia or intravenous sedation.

Microsurgical epididymal sperm aspiration (MESA) involves using a high-powered operating microscope to collect sperm-containing fluid from particular locations of the epididymis. After extraction, the puncture sites are plugged or cauterized. The best quality sperm is often located near the testis in the proximal epididymis, with quantities of around 1 million sperm per microliter. [33,35]

Percutaneous epididymal sperm aspiration (PESA)

Percutaneous epididymal sperm aspiration (PESA) is offered as a less invasive method of sperm retrieval, which is frequently performed as an outpatient procedure under local anesthesia. In all, success rates of obtaining motile spermatozoa are roughly 62%. PESA has benefits over microsurgical epididymal sperm aspiration (MESA), such as reduced patient pain, fewer complication rates, and cheaper expenses due to the lack of microsurgical tools. Following PESA, cryopreservation of residual sperm material is possible, potentially removing the need for future retrieval procedures. However, questions remain about the possible harm to the epididymal duct system and the safety of recurrent PESA treatments. While studies indicate that PESA may be repeated without harming the epididymis, there is presently no agreement on the maximum number of repeat operations that can be safely performed. [36]

Percutaneous testicular sperm aspiration (TESA)

TESA involves stabilizing the testicle following a local cord block and inserting a needle along its long axis. The needle is then gently redirected many times using pressure and aspiration until enough sperm is retrieved by damaging the tubules. Fine-needle aspiration can also be used to diagnose and deliver sperm for assisted reproductive technology (ART). [33]

Percutaneous testicular biopsy (PercBiopsy)

PercBiopsy involves administering a local spermatic cord block and extracting a tiny cylindrical sample of testicular tissue with a 14-gauge biopsy gun. Multiple passes may be made if necessary. [29,33]

Testicular Sperm Extraction (TESE)

It is a surgical operation that removes a tiny section of testicular tissue to retrieve sperm. Microsurgical testicular sperm extraction (microTESE) is a procedure that has been perfected in recent years using optical magnification using a surgical microscope. This new method allows for the identification of sites with spermatogenesis, using a smaller tissue sample from the testicle. [37]

Technique	Advantages	Disadvantages
PESA	No specialized microsurgical skills needed Use of local anesthesia Limited instrument requirement Quick and repeatable procedure Minimal discomfort after surgery	Limited sperm retrieved Potential for hematoma Risk of damage to surrounding tissue

MESA	Highest clinical pregnancy rates Significant sperm yield Effective cryopreservation outcomes Lower risk of hematoma	Expertise in microsurgery needed Higher expenses Anesthesia needed, either general or local Surgical incision necessary Potential discomfort after surgery
TESE	No specialized microsurgical skills needed Anesthesia options include local or general Minimal instrument requirements The procedure is quick and can be repeated	Small quantity of sperm collected Low likelihood of testicular atrophy (with multiple biopsies)
PercBiopsy, TESA	No specialized microsurgical skills needed Localized anesthesia Minimal equipment required Quick and repeatable Minimal postoperative discomfort	Limited sperm yield Potential for testicular atrophy Hematoma risk

Table 1: Advantages and disadvantages of sperm-retrieval techniques [33]

Obstructive azoospermia-related infertility can be efficiently managed with surgical repair or sperm extraction from the epididymis or testis, followed by IVF/ICSI. Overall, sperm retrieval techniques are minimally invasive and have a low risk of consequences. For the majority of males with blockage, successful sperm retrieval is expected. [33]

Non-Obstructive Azoospermia

Non-obstructive azoospermia (NOA) is the most difficult kind of male infertility, and specialized therapies have previously been lacking. [32] The majority of individuals with NOA require modern assisted reproduction techniques. [5] Before the emergence of microsurgical testicular sperm extraction procedures combined with IVF/ICSI, men with non-obstructive azoospermia (NOA) had only one option: donor insemination. However, the addition of microdissection testicular sperm extraction (microTESE) to IVF/ICSI has transformed therapy for suitable azoospermic candidates, including those with hereditary problems. This treatment produces sperm retrieval in around 60% of instances, with greater success rates and less testicular tissue damage than non-microsurgical approaches. Furthermore, even hypogonadal males with NOA show no correlation with preoperative variables such as testicular volume, FSH levels, testosterone response to hormonal treatment, or TESE sperm retrieval outcomes. [13]

Micro TESE, an innovative method based on microsurgical procedures, is successful for sperm retrieval in males with NOA having ICSI. This minimally invasive method takes only a small amount of testicular tissue, minimizing the negative consequences on testicular function. Microsurgical TESE is more effective than conventional TESE in males with NOA. [32]

The treatment of non-obstructive azoospermia (NOA) sometimes entails looking into genetic variables that contribute to infertility, such as chromosomal abnormalities that impair testicular function and YCMD which causes isolated spermatogenic impairment. [33]

Chromosomal abnormalities, particularly sex chromosomal aneuploidies such as Klinefelter syndrome, are frequent in NOA patients. These genetic flaws not only affect fertility but also increase the chance of numerous health concerns. In addition, structural anomalies raise the likelihood of miscarriage and congenital problems in kids. As a result, genetic counseling is required before pursuing assisted reproductive procedures such as ICSI/IVF for NOA patients. [32,33]

Y chromosomal microdeletions (YCMD) are absolute contraindications to sperm retrieval, especially in the AZFa and AZFb subregions. Detecting these deletions, which can occur in 10%-15% of azoospermic or severely oligospermic males, is critical because they predict poor sperm retrieval results. Before trying sperm retrieval or utilizing sperm for intracytoplasmic sperm injection (ICSI), seek genetic counseling and testing, such as karyotyping and YCMD analysis. Offspring of males with YCMD inherit the risk, needing extensive genetic counseling for couples undertaking assisted reproduction.[35]

Men who acquire azoospermia as a result of testosterone supplementation therapy have a significant chance of spermatogenesis recovery merely by ceasing the hormonal medication and allowing time to pass. In most cases, over 85% of pre-treatment sperm counts are restored within a year, with virtually total recovery occurring within two years. [5]

Microsurgical varicocelectomy has shown promise in improving spermatogenesis, decreasing scrotal temperature, and reducing DNA fragmentation in the testis in males with non-obstructive azoospermia (NOA) with varicocele. This therapy causes sperm to return to the ejaculate in 22-55% of cases, with some men avoiding the need for testicular sperm extraction. However, the decision to undergo varicocelectomy in men with NOA should consider factors such as the female partner's age and the severity of the varicocele, as well as the best available clinical study data.[13]

Men with non-obstructive azoospermia (NOA) typically have bilateral testicular atrophy, which may be caused by primary or secondary testicular failure. Some patients with maturation arrest may have normal testicular size and FSH levels. Furthermore, a decrease in sperm volume may be related to lower blood testosterone levels. [38]

To increase spermatogenesis in persons with hypogonadotropic hypogonadism or pre-testicular azoospermia, HCG injections (ranging from three thousand IU to ten thousand IU, delivered 2 to 3 times per week) are usually indicated. This is frequently coupled with either anastrozole, clomiphene, FSH, or tamoxifen. [5]

For azoospermic males with hypogonadotropic hypogonadism, one therapy option is to inject GnRH (gonadotropin-releasing hormone) every 2 hours using a portable infusion pump, at dosages ranging from 5 mcg to 20 mcg. This regimen has been shown to produce sperm return in semen after 6 months of therapy, with approximately seventy-seven percent of initially azoospermic men experiencing sperm formation following between twelve and twenty-four months of treatment. Prior FSH production may improve the effectiveness of GnRH therapy. However, GnRH works exclusively in males with normal pituitary function. [5,15]

Individuals with diminished or non-existent pituitary function usually prefer gonadotropin therapy with HCG, with or without FSH. The normal dose varies from 1000 to 3000 IU, given twice to three times each week. This program often results in sperm production within 3 to 6 months. If the first therapy is unsuccessful, FSH can be added at levels ranging from 75 IU to 150 IU, twice a week. Overall, medicinal treatment successfully induces spermatogenesis in roughly 75% of instances of hypogonadotropic hypogonadism. However, if medical therapy is ineffective, assisted reproductive procedures are recommended. [5]

CONCLUSION

In conclusion, azoospermia, characterized by the absence of sperm in the ejaculate, presents a significant challenge for male fertility. Understanding the diverse etiologies, such as obstructive and non-obstructive causes, and the associated health implications is crucial for both clinical and emotional support. The epidemiological impact, coupled with the intricate pathophysiological and genetic aspects, underscores the need for comprehensive management strategies. The diagnosis and management of azoospermia require a multifaceted approach, ranging from detailed genetic and hormonal evaluations to advanced surgical and assisted reproductive techniques. Notably, innovative procedures such as microsurgical sperm extraction and the assessment of genetic abnormalities have brought hope to individuals facing this condition, fostering new possibilities for conception. Lifestyle considerations and potential treatment options, such as hormonal therapies, offer additional avenues for intervention. NNAs we delved deeper into understanding the intricacies of azoospermia, ongoing research, and clinical

advancements are vital for enhancing diagnosis, treatment, and overall patient care. This work not only impacts conclusion individuals and, azoospermia couples but also has implications for public health and societal well-being. Emphasizing the importance of azoospermia, whether obstructive or non-obstructive, poses significant challenges to male fertility and of continued research, on reproductive health. Understanding support, and awareness of the underlying causes and mechanisms, to improve from genetic factors to outcomes and hormonal factors a better understanding of this complex aspect of balances, is crucial in addressing this condition. It affects male reproductive health. a notable percentage of males globally and carries not only emotional and social implications but also significant economic costs and potential health correlations. The diagnostic process involving hormone evaluation, genetic testing, semen analysis, and physical examinations plays a vital role in identifying the specific form and cause of azoospermia. For obstructive azoospermia, microsurgical techniques and sperm retrieval methods are employed, each with its advantages and considerations, while managing non-obstructive azoospermia often involves modern assisted reproductive techniques and genetic counseling. advancements in microsurgical techniques such as micro TESE have significantly enhanced the prospects for sperm retrieval in individuals with non-obstructive azoospermia, offering new hope for many who previously had limited options. Overall, the management of azoospermia requires a multi-faceted approach, integrating surgical interventions, genetic considerations, assisted reproductive techniques, and hormone-based therapies. This holistic approach reflects the complexity of the condition and the need for personalized, comprehensive care for affected individuals. Moreover, continued research and development, along with increased awareness, are essential in addressing the challenges posed by azoospermia and improving the prospects for individuals facing fertility issues.

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