Azoospermia - Treatable & Sometimes Curable - Case Reports and Guidelines for Management

Dr. Puvithra Thanikachalam[1], Dr. Divya Gopalakrishnan[2], Dr. Radha Pandiyan[3], Dr. Pandiyan Natarajan[4]

[1]Senior Consultant & Head of the Department,
[2]Consultant Obstetrician; MA Pregnancy and Fertility Care, Sholinganallur, Chennai,
[3]Associate Professor & Senior Consultant (Retd.),
[4]Professor, Chief Consultant & Head of the Department (Retd.).
Chettinad Fertility Services, Department of Andrology & Reproductive Medicine, Chettinad Super Speciality Hospital, Kelambakkam, Chennai.

Abstract

Azoospermia is the absence of spermatozoa in the neat semen sample and the centrifuged resuspended semen pellet on more than one occasion. Around 10-15% of infertile men are diagnosed to have azoospermia either due to obstructive or non-obstructive causes. A meticulous history and physical examination may reveal the cause for azoospermia in many men. Laboratory investigations help substantiate the findings or diagnose conditions that may not be revealed during a physical exam. Azoospermia due to hypogonadotropic hypogonadism is the only condition that is amenable to medical management. Surgical spermatozoa retrieval and assisted reproduction with intracytoplasmic spermatozoa injection have helped many couples achieve biological parenthood.

Introduction:

Azoospermia is defined as the absence of spermatozoa in the neat semen sample and the centrifuged resuspended semen pellet.[1]The incidence of azoospermia in the general population is around 1% and around 10-15% in infertile men.[2]This must be differentiated from Aspermia which is the absence of ejaculate. Cryptozoospermia is the absence of Spermatozoa in the neat semen sample, but the presence of spermatozoa in the pellet obtained from centrifugation of the semen sample.[1] Azoospermia can be either due to obstructive causes or non-obstructive causes. Advances in microsurgery have helped in the surgical correction of many of the patients with obstructive azoospermia.[3] In patients with non-obstructive Azoospermia, the advent of ART and intracytoplasmic sperm injection (ICSI) using spermatozoa retrieved from the testes helps achieve biological parenthood.[4] In patients with hypogonadotropic hypogonadism, medical management with Gonadotropins is effective in restoring fertility.[5] This article presents a few case reports with different causes of Azoospermia and highlights the diagnosis and management of this condition and the expected outcome.

Case Reports

1) A 32-year-old gentleman, married for three years with primary infertility, was diagnosed with azoospermia and was offered heterologous insemination for his wife, which the couple declined. He was referred to us, and on a detailed history, examination, and preliminary investigations, we diagnosed his condition to be due to bilateral vasal aplasia (CBAVD-congenital bilateral absence of vas deferens). The condition was obstructive azoospermia due to the non-development of the outflow tract. We, therefore, recommended epididymal sperm aspiration for him and in-vitro fertilization (IVF) and embryo transfer for his wife. The advanced assisted reproduction technique was carried out successfully and resulted in healthy offspring.

2) A 37-year-old gentleman and a 31-year-old lady were married for eight years. They were referred to us by the Family Gynaecologist for primary infertility due to Ejaculatory dysfunction. While taking a detailed history, we made out a case of ASPERMIA - No antegrade ejaculate during sexual intercourse but **RETROGRADE EJACULATION** into the bladder. Due to the acidic nature of urine, the expelled spermatozoa were non-viable or immotile and contributed to their primary infertility. The female partner did not have any gynecological or general health problems. We suggested spermatozoa retrieval from the bladder by a non-invasive method pioneered by us and assisted conception with ICSI. The same was carried out successfully, and the couple could achieve parenthood with healthy offspring.

3) A 35-year-old gentleman and his wife, a 31-year-old lady, referred themselves to us from West Bengal for primary infertility and a diagnosis of Azoospermia. Clinical and laboratory evaluations were in favor of **Obstructive Azoospermia.** He desired surgical restoration of the genital tract. Microsurgical Vaso epididymal anastomosis (VEA) was done, demonstrating motile spermatozoa from the caput Epididymis intraoperatively. He did not report for follow-up of seminogram after three months. After a year following the VEA, he reported with his wife for irregular menstrual cycles with a history of amenorrhea. His semen report revealed motile spermatozoa, and his wife was diagnosed with a single live intrauterine pregnancy of 7 weeks duration. She delivered healthy offspring. VEA and Vaso vasostomy are options in obstructive Azoospermia, the following latter vasectomy. In older couples or for those with female factors, Assisted Reproduction techniques are advised.

4) A 33-year-old gentleman and his wife, a 28-year-old lady, were referred to us by their family physician for Primary infertility due to Azoospermia. Detailed clinical and laboratory investigations led us to diagnose the condition as **Non-Obstructive Azoospermia** due to Seminiferous tubular failure. Options for fertility were discussed with the couple, and they chose Surgical spermatozoa retrieval and Assisted Reproductive techniques. Bilateral multiple site testicular biopsies were taken for spermatozoa retrieval after the wife underwent transvaginal oocyte retrieval. Few motile spermatozoa were recovered, and the technique of Intracytoplasmic sperm injection (ICSI) was done to the wife's mature oocytes. Two good embryos were transferred on Day 3 of egg collection. His wife became pregnant with twin gestation. During the 4th month of pregnancy, one twin was diagnosed with meningomyelocele and did not survive. The other normal fetus progressed to 9 months and was born as a healthy girl baby. We had the opportunity to follow up with this child during our Annual Babies' Meet up to 5 years, and she was found to be normal and healthy.

Causes of Azoospermia

Azoospermia maybe due to pre-testicular, testicular, or post-testicular causes.

1. Pre-testicular causes

Spermatogenesis requires proper functioning of the hypothalamo pituitary-gonadal axis. Absent or less than normal production of gonadotropin-releasing hormone (GnRH) or the gonadotropins, Follicle-stimulating hormone (FSH), and Luteinizing hormone (LH), can affect spermatogenesis and fertility. This condition is called 'Hypogonadotropic hypogonadism.[5] Hormone estimation reveals low FSH, low LH, low testosterone, and normal prolactin. Patients need testosterone for restoring their secondary sexual characteristics and Gonadotropins for restoring their fertility. A classic example of this condition is Kallmann Syndrome.[6] These patients, besides having hypogonadotropic hypogonadism, also have either Hyposmia or

anosmia. Patients are often hypo androgenized with poor secondary sexual characteristics with small testes. The extent of androgenization and development of secondary sexual characteristics depends on the pre-or post-pubertal onset of the pathology. [5]

2. Testicular causes

In these men, the primary pathology is in the testes, and it could be due to a genetic, inflammatory, or traumatic cause.[7,8,9] There is either no spermatozoa production or the production is so less that no spermatozoon comes out in the ejaculate. In certain instances, spermatozoa production is arrested in the various developmental stages, and thereby no mature spermatozoa are seen in the ejaculate. Genetic studies in these patients may reveal chromosomal defects as in Klinefelter's syndrome (47-XXY), or deletions of Y Chromosome.[7] Testes biopsy reveals either seminiferous tubular failure, hypospermatogenesis, or maturation arrest in men with azoospermia (Box 1). Spermatozoa Retrieval from the testes is effective in about 40-50% of these patients.[10,11]

Box 1- Johnsen score for testicular biopsy

(Score -10) Full spermatogenesis

(Score -9) Slightly impaired spermatogenesis, many late spermatids, disorganized epithelium

(Score - 8) Less than five spermatozoa per tubule, few late spermatids

(Score -7) No spermatozoa, no late spermatids, many early spermatids

(Score - 6) No spermatozoa, no late spermatids, few early spermatids

(Score - 5) No spermatozoa or spermatids, many spermatocytes

(Score - 4) No spermatozoa or spermatids, few spermatocytes

(Score - 3) Spermatogonia only

(Score - 2) No germinal cells, Sertoli cells only

(Score - 1) No seminiferous epithelium

3. Post testicular causes

Obstruction to the outflow tract of the Spermatozoa and the ejaculate may lead to obstructive Azoospermia.

1. Obstruction at the epididymis (Infective, iatrogenic, Young's Syndrome)
2. Obstruction at the vas (infective, iatrogenic, or post-vasectomy).
3. Congenital bilateral absence of the vas deferens.
4. Ejaculatory duct obstruction

Clinical Features and Diagnosis:

Azoospermia is a Spermatological diagnosis. Patients with Azoospermia should have a repeat semen sample evaluated after a few days for confirming Azoospermia.[12] Several conditions contribute to Azoospermia. The clinical features depend on the condition causing Azoospermia

1. History

It is imperative to obtain a complete medical and surgical history like the history of undescended testes (corrected or uncorrected), mumps, trauma to the scrotum, sexually transmitted diseases, hernia or hydrocele repair, and chronic medications including steroids, gonadotoxic chemotherapy, or radiation therapy. History should also be obtained about other associated conditions like anosmia or hyposmia, sexual dysfunction, chronic respiratory pathologies, head injury, or other neurological disorders. Most of the time, a detailed history and clinical examination may be sufficient to arrive at a diagnosis.

2. Clinical examination

A clinical examination will include a general systemic examination, evaluation for signs of androgenization and gynaecomastia, and a local examination of the genitalia. The position, size, and consistency of the testes should be noted, and the cord structures palpated at the base of the scrotum.In Obstructive Azoospermia, testes are normal-

sized (8 to 20 ml) andfirm. In Non-Obstructive Azoospermia, the testes are normal or small-sized.

3. Investigations

Diagnosis of Azoospermia requires reconfirmation by repeat Semen analysis on at least one or more occasions. The centrifuged pellet has to be examined to rule out cryptozoospermia. All patients with Azoospermia require Serum FSH estimation. Serum LH, Prolactin, and Testosterone estimation are required only in cases where Hypogonadotrophic Hypogonadism is suspected or when a patient has associated Sexual Dysfunction[12]. The clinical features and laboratory parameters in patients with obstructive and non-obstructive azoospermia are mentioned in Table 1 & Table 2.

Karyotype and Y chromosome deletion studies are required only in cases of Non-Obstructive Azoospermia and Severe Oligozoospermia.[8]

Table 1-Obstructive Azoospermia(Source- Handbook of Andrology, Pandiyan N, 2001)

Condition	FSH	Testes size	Semen volume	Fructose
Ejaculatory duct obstruction	Normal	Normal	Very low	Absent
Vasal aplasia	Normal	Normal	Very low	Absent
Vasal obstruction	Normal	Normal	Normal	Present
Epididymal obstruction	Normal	Normal	Normal	Present
Intratesticular obstruction	Normal	Normal	Normal	Present

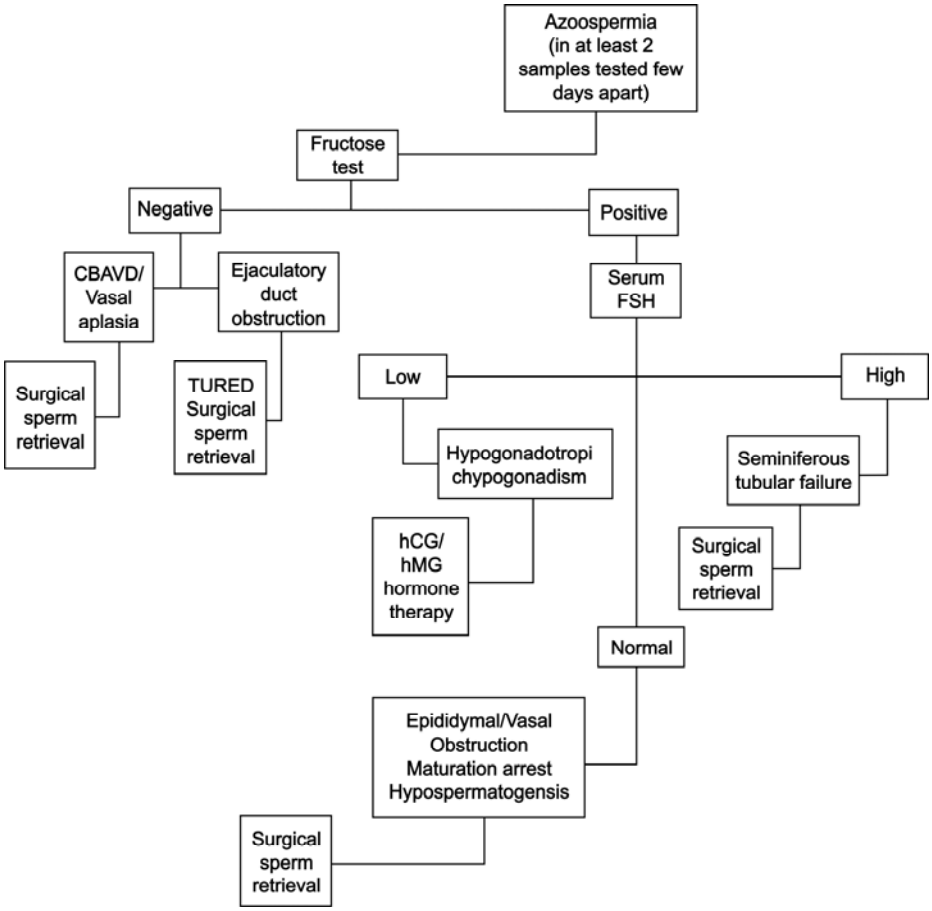

Fig 1. Diagnosis and Management - Outline:

Table 2- Non-obstructive Azoospermia(Source- Handbook of Andrology, Pandiyan N, 2001)

Condition	FSH	Testes size	Semen Volume
Hypogonadotrophic Hypogonadism	Low or undetectable	Small, soft	Normal
Seminiferous tubular failure	Elevated	Small, soft, or firm	Normal
Borderline azoospermia	Normal to mild elevation	Normal to slightly small	Normal

Management

Treatment depends on the cause and the expectations of the couple. Figure 1 shows an outline of diagnosis and management of fertility in a man with Azoospermia. Managing fertility can be discussed under the following headings:

1. Hypogonadotropic Hypogonadism.
2. Obstructive Azoospermia.
3. Non-Obstructive Azoospermia.

(CBAVD – Congenital bilateral absence of vas deferens; TURED – Transurethral resection of the ejaculatory duct; FSH – Follicle-stimulating hormone; hCG – human chorionic gonadotropin; hMG – human menopausal gonadotropin)

1. Hypogonadotropic Hypogonadism

In men with the prepubertal onset of hypogonadotropic hypogonadism, testosterone therapy will help develop secondary sexual characteristics.[13] Testosterone replacement therapy also helps in improving sexual function and can be continued until fertility is requested. If and when Fertility is desired, testosterone therapy is discontinued, and gonadotropins therapy is administered. In men with acquired hypogonadotropic hypogonadism, the cause should be identified and treated if it is a treatable condition.[14,15,16] If the patient presents to the clinic for fertility concerns, evaluation of the female partner is also necessary to determine the fertility treatment required for the couple.

The onset of spermatogenesis after commencing gonadotropin therapy is variable, ranging from 6 months to 18 months.[17] Human chorionic gonadotropin (hCG) acts as a surrogate for LH and is initiated in a dose 1000-1500 IU twice or thrice weekly and continued up to 8-12 weeks. In some patients, spermatogenesis is induced with hCG treatment alone. In those who do not have sufficient endogenous FSH, hMG or recombinant FSH can be used at a dose of 75-150 IU three times a week for a period of up to 18 months.[18] Spermatogenesis is seen in around 90% of men with hypogonadotropic hypogonadism with this treatment regimen.[19] Patients have to be counseled regarding the duration and cost of treatment, and that results will be affected if the treatment is not continued for the desired duration. Surgical sperm retrieval can be attempted in men who remain to be azoospermic after adequate gonadotropin treatment. Pulsatile Gonadotropin-releasing hormone (GnRH) therapy has been tried but not as a routine as it is quite cumbersome, expensive, and requires supervision.[20]

2. Obstructive Azoospermia

Microsurgical reconstruction techniques such as vasovasostomy or vasoepididymostomy may be attempted for certain conditions of obstructive azoospermia after counseling the patient regarding the success rates with the procedures and the option of assisted reproduction. Vasal reconstruction gives good results in men who request vasectomy reversal. Whereas the success rates are much lesser when the obstruction is due to an infective etiology.[3]Pregnancy rates also depend on other factors such as the age of the female partner

and other associated factors for male and female sub fertility.[21]

Surgical sperm retrieval and ART with ICSI are options in men with obstructive azoospermia, which is either not amenable to reconstruction or the surgical procedure has failed. Percutaneous epididymal sperm aspiration (PESA), Microepididymal sperm aspiration (MESA), and Macroepididymal sperm aspiration (MAESA) are techniques for spermatozoa retrieval in all causes of vasal obstructionwhere surgical correction is not desired or possible. When the intratesticular obstruction is suspected, testicular sperm aspiration (TESA) can be attempted. In any of these cases, if spermatozoa are not retrieved, it could be associated with hypospermatogenesis. Therefore testicular sperm extraction (TESE) will be the next resort in such men.

3. Non-Obstructive Azoospermia

Men with non-obstructive azoospermia will require either a conventional TESE (cTESE) or microdissection TESE (mTESE).[4]

A retrospective data collection was done in the Department of Andrology and Reproductive Medicine at Chettinad Super Speciality Hospital (unpublished), which included 74 men who underwent surgical spermatozoa retrieval between 2008-2017 (Divya N, Pandiyan N). Out of the 74 men, spermatozoa were retrieved in 47 men, and the outcome with surgically retrieved spermatozoa was studied. The results are given below (Tables 3-6).

Table 3: Summary of type of azoospermia and sperm collection and insemination method (N=47)

Group	**Frequency**	**Percentages**
Type of azoospermia		
Non obstructive	19	40.40%
Obstructive	28	59.60%
Source of sperm collection		
Testicular	24	51.1%
Epididymal	23	48.9%
Type of insemination		
Frozen	18	38.30%
Fresh	29	61.70%

Table 4: Descriptive analysis of Fertilization rate; Cleavage rate following ICSI in study population (N=47)

Parameter	Mean ±STD
Fertilization rate	65.36 ± 25.32
Cleavage rate	84.23 ± 32.37

Table 5: Clinical pregnancy rate in study population (N=47)

Clinical pregnancy status	Frequency	Percentage
Pregnancy	14	29.8%
No pregnancy	29	61.7%
Not transferred/loss for follow up	4	8.5%

Table 6: Descriptive analysis of Live birth in study population (N=47)

Live birth	Frequency	Percentage
No pregnancy	34	72.3%
Singleton	9	19.1%
Twin babies	2	4.30%
Miscarriage/ Ectopic	2	4.20%

There are no definitive predictors for the success of spermatozoa retrieval in any surgical method. Small-sized testes, very high FSH levels, Klinefelter's syndrome, and Y-chromosome microdeletion are associated with reduced chances of sperm retrieval. Men having microdeletions involving AZFa or AZFb regions of the Y-chromosome should not be provided the option of surgical spermatozoa retrieval.[10] In azoospermic men, varicocele

repair has not proven to be beneficial in improving spermatozoa count or pregnancy rate.[22] Except in hypogonadotropic hypogonadism, there is no role for medical management in men with Azoospermia.[22]

Conclusion

Azoospermia is not a terminal condition. Most patients with azoospermia can be treated, and some of them with obstructive Azoospermia can also be cured of the problem. Identifying the cause and following the appropriate treatment protocol for that particular individual or couple will help the couple achieve a pregnancy. In case of genetic causes of azoospermia, the couple may need to be evaluated further and require genetic counseling to understand the heritability of the condition fully. Third-party reproduction by insemination using donor spermatozoa may be offered to a couple who are not willing for surgical procedures or in those whom surgical or medical management have been unsuccessful.

References

1. Zegers-Hochschild F, Adamson GD, Dyer S, Racowsky C, de Mouzon J, Sokol R, et al. The International Glossary on Infertility and Fertility Care, 2017. Hum Reprod. 2017 Sep 1;32(9):1786–801.
2. Cocuzza M, Alvarenga C, Pagani R. The epidemiology and etiology of azoospermia. Clinics. 2013 Feb;68(Suppl 1):15–26.
3. Baker K, Sabanegh E. Obstructive azoospermia: reconstructive techniques and results. Clinics. 2013 Feb;68(Suppl 1):61–73.
4. Miyaoka R, Esteves SC. Sperm Retrieval Techniques. In: Parekattil SJ, Esteves SC, Agarwal A, editors. Male Infertility: Contemporary Clinical Approaches, Andrology, ART and Antioxidants [Internet]. Cham: Springer International Publishing; 2020 [cited 2021 Oct 19]. p. 621–35. Available from: https://doi.org/10.1007/978-3-030-32300-4_50
5. Morris GC, Lloyd-Evans E, Cahill DJ. Induction of spermatogenesis in men with hypogonadotropic hypogonadism. J Assist Reprod Genet. 2021 Apr 1;38(4):803–7.
6. Stamou MI, Georgopoulos NA. Kallmann syndrome: phenotype and genotype of hypogonadotropic hypogonadism. Metabolism. 2018 Sep 1;86:124–34.
7. Kim SY, Kim HJ, Lee BY, Park SY, Lee HS, Seo JT. Y Chromosome Microdeletions in Infertile Men with Non-obstructive Azoospermia and Severe Oligozoospermia. J Reprod Infertil. 2017;18(3):307–15.
8. Esteves SC. Clinical management of infertile men with nonobstructive azoospermia. Asian J Androl. 2015;17(3):459–70.
9. Wu H, Wang F, Tang D, Han D. Mumps Orchitis: Clinical Aspects and Mechanisms. Front Immunol. 2021;12:582946.
10. Arshad MA, Majzoub A, Esteves SC. Predictors of surgical sperm retrieval in non-obstructive azoospermia: summary of current literature. Int Urol Nephrol. 2020 Nov 1;52(11):2015–38.
11. Corona G, Minhas S, Giwercman A, Bettocchi C, Dinkelman-Smit M, Dohle G, et al. Sperm recovery and ICSI outcomes in men with non-obstructive azoospermia: a systematic review and meta-analysis. Hum Reprod Update. 2019 Nov 5;25(6):733–57.
12. Diagnostic evaluation of the infertile male: a committee opinion. Fertil Steril. 2015 Mar 1;103(3):e18–25.
13. Viswanathan V, Eugster EA. Etiology and treatment of hypogonadism in adolescents. Pediatr Clin North Am. 2011 Oct;58(5):1181–200, x.
14. Pelusi C, Gasparini DI, Bianchi N, Pasquali R. Endocrine dysfunction in hereditary hemochromatosis. J Endocrinol Invest. 2016 Aug;39(8):837–47.
15. Srisukh S, Ongphiphadhanakul B, Bunnag P. Hypogonadism in thalassemia major patients. J Clin Transl Endocrinol. 2016 Aug 16;5:42–5.
16. Kanayama G, Hudson JI, DeLuca J, Isaacs S, Baggish A, Weiner R, et al. Prolonged hypogonadism in males following withdrawal from anabolic-androgenic steroids: an under-recognized problem. Addict Abingdon Engl. 2015 May;110(5):823–31.
17. Fraietta R, Zylberstejn DS, Esteves SC. Hypogonadotropic Hypogonadism Revisited. Clinics. 2013 Feb;68(Suppl 1):81–8.

18. Zitzmann M, Nieschlag E. Hormone substitution in male hypogonadism. Mol Cell Endocrinol. 2000 Mar 30;161(1–2):73–88.

19. Han TS, Bouloux PMG. What is the optimal therapy for young males with hypogonadotropic hypogonadism? Clin Endocrinol (Oxf). 2010 Jun;72(6):731–7.

20. Hayes F, Dwyer A, Pitteloud N. Hypogonadotropic Hypogonadism (HH) and Gonadotropin Therapy. In: Feingold KR, Anawalt B, Boyce A, Chrousos G, Dungan K, Grossman A, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2019 Dec 22]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK279078/

21. Dubin JM, White J, Ory J, Ramasamy R. Vasectomy reversal vs. sperm retrieval with in vitro fertilization: a contemporary, comparative analysis. Fertil Steril. 2021 Jun 1;115(6):1377–83.

22. Schlegel PN, Sigman M, Collura B, De Jonge CJ, Eisenberg ML, Lamb DJ, et al. Diagnosis and Treatment of Infertility in Men: AUA/ASRM Guideline PART II. J Urol. 2021 Jan;205(1):44–51.