Azoospermia – Evaluations and treatments

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Azoospermia can be caused by the obstruction of the excurrent ductal system of the male reproductive tract or by failure of spermatogenesis in the testes. Various advanced diagnostic tools are available to help clinicians determine the underlying etiologies. These include transrectal ultrasonogram, vasography and antisperm antibody assays. In addition, advanced genetic evaluations, such as karyotype analysis, Y chromosome microdeletion and cystic fibrosis transmembrane conductance regulator mutation screening are used commonly, not only to determine the etiology of azoospermia, but also to provide crucial information for counselling of couples who choose to use assisted reproductive techniques to have children. Recent advances in the management of obstructive azoospermia with microsurgical reconstruction, such as vasovasostomy and vasoepididymostomy, have significantly improved the postoperative outcomes. For patients with spermatogenic failure that requires assisted reproduction, the recent refinements in various surgical sperm retrieval techniques, including microsurgical testicular sperm extraction and epididymal sperm aspiration, have provided more optimal treatment outcomes.

Key Words: *Assisted reproduction; Azoospermia; Intracytoplasmic sperm injection; Male infertility; Microsurgery; Oligospermia*

L'azoospermie : Les évaluations et les traitements

RÉSUMÉ : L'azoospermie peut être causée par l'obstruction du système canalaire excrétoire des voies reproductrices mâles ou par l'échec de la spermatogenèse des testicules. Il existe divers outils diagnostiques avancés pour aider les cliniciens à déterminer les étiologies sous-jacentes. Ces outils incluent l'échographie transrectale, la vasographie et le dosage des anticorps immobilisants. De plus, des évaluations génétiques évoluées, telles que le caryotypage, la microdélétion du chromosome Y et le dépistage de la mutation du régulateur de la conductance membranaire de la fibrose kystique, sont souvent utilisées, non seulement pour établir l'étiologie de l'azoospermie, mais également pour fournir de l'information essentielle en vue de conseiller les couples qui choisissent de faire appel aux techniques de reproduction assistée pour avoir des enfants. Les récents progrès dans la prise en charge de l'azoospermie obstructive par la reconstruction microchirurgicale, comme la vasovasostomie et la vasoépididymostomie, ont amélioré considérablement les issues postopératoires. Dans le cas des patients présentant un échec spermatogène et qui ont besoin de reproduction assistée, les raffinements récents des diverses techniques chirurgicales d'extraction du sperme, y compris l'extraction microchirurgicale du sperme testiculaire et l'aspiration du sperme épipidymal, assurent des issues plus optimales des traitements.

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The evaluation and management strategies for infertile men have undergone tremendous changes in recent years, making the study of male infertility one of the fastest growing subspecialties in urology. In fact, just a decade ago, effective treatment options for men with azoospermia were limited. Hence, azoospermia was once considered by clinicians to be the most dismal form of male infertility. Today, with the advances in the various microsurgical and assisted reproduction techniques, such as intracytoplasmic sperm injection (ICSI), many of the men with azoospermia who were once considered to be sterile can now father biological children.

Although azoospermia is the focus of this discussion, the management strategies and considerations presented in this article apply to severe oligospermia as well. In fact, while most pathological conditions considered in this article commonly lead to the complete absence of spermatozoa in ejaculate, they may also affect the reproductive system partially (though severely) to allow some sperm to be found in the ejaculate.

The first step in managing a patient with azoospermia or severe oligospermia is to determine whether the condition involves any obstructive processes. Not uncommonly, the distinction between obstructive azoospermia and nonobstructive azoospermia may be difficult to make for an individual patient. Often, advanced and invasive investigations are required for reproductive specialists to correctly distinguish the two entities.

NONOBSTRUCTIVE AZOOSPERMIA

A wide range of etiologies can lead to nonobstructive azoospermia (Table 1). Because some of the pathological conditions that lead to nonobstructive azoospermia can be acquired or progress later in life, a history of fecundity (secondary infertility) in a man with azoospermia does not rule out nonobstructive causes.

Physical findings suggestive of nonobstructive azoospermia are summarized in Table 2. However, clinicians should be aware that many of the physical signs of nonobstructive azoospermia may be subtle. In fact, men with nonobstructive azoospermia may have a normal physical examination. Thus, prudent investigations are required to aid in making a correct diagnosis.

Endocrinological causes of nonobstructive azoospermia

Interpretation of hormonal levels for infertile patients should be cautious. The 'normal' range of values from various laboratories for hormonal profiles are generally derived from a population of subjects who are not known to have any pathological conditions that can affect the particular parameters (as opposed to being from a fertile population, as is done for semen analysis). However, most men with subfertility or infertility are asymptomatic and generally are not aware of their conditions. Hence, in subfertile and infertile men, the finding of hormonal parameters falling within the wide 'normal' range does not rule out the possibility of subtle endocrinopathies contributing to their subfertility or infertility.

Endocrinological causes of nonobstructive azoospermia include hyperprolactinemia, various forms of hypogonadism and, less frequently, congenital adrenal hyperplasia and hypothyroidism. Prolactin affects fertility by its downregulating effect on gonadotropin-releasing hormone (GnRH) and inhibitory effect on luteinizing hormone (LH) binding to Leydig cells. The causes of hyperprolactinemia include pituitary tumours (macroadenoma or microadenoma), hypothyroidism, liver disease and drugs (such as phenothiazines, tricyclic antidepressants and some antihypertensive medications). Pituitary imaging studies are required to rule out pituitary adenoma. Surgical removal of pituitary macroadenoma and medical therapy with a dopaminergic agonist may normalize prolactin levels with improvement in semen parameters.

Hypogonadotropic hypogonadism (low serum follicle-stimulating hormone [FSH] and testosterone) may be either congenital or acquired. Kallmann's syndrome is the congenital form that results from abnormal production or secretion of GnRH by the hypothalamus. It may be associated with various 'midline' anomalies such as anosmia and cleft palate, and other anomalies such as deafness and renal malformation. Acquired hypogonadotropic hypogonadism may be associated with anabolic steroid abuse, pituitary tumours, isolated gonadotropin deficiency and panhypopituitarism.

The management of hypogonadotropic hypogonadism using exogenous GnRH or gonadotropins, such as human chorionic gonadotropic, human menopausal gonadotropin, and purified and recombinant FSH, are effective in improving sperm production and pregnancy rate (1). Various treatment regimens have been described clinically, and consultations with reproductive specialists before beginning treatment should be considered.

Genetic causes of nonobstructive azoospermia

Hypergonadotropic hypogonadism (elevated FSH with low testosterone) is due to testicular failure in both the endocrinological and spermatogenic functions. Various acquired conditions listed in Table 1 are associated with hypergonadotropic hypogonadism. The most well known congenital or genetic cause of hypergonadotropic hypogonadism is Klinefelter's syndrome. Occurring in one in 500 live male births and accounting for 14% of cases of azoospermia (2), Klinefelter's syndrome is the most commonly encountered chromosomal abnormality in male infertility. The chromosomal constitution of the classic form is 47 XXY (90% of cases), whereas that of the mosaic form is 46 XY/47 XXY. The fertility prognosis is better in the mosaic form, and natural fecundity in such men has been reported.

In addition to 47 XXY in Klinefelter's syndrome, other common karyotypical abnormalities found in men with nonobstructive azoospermia include translocation of chromosomes, XX male, 45 X/46 XY (mixed gonadal dysgene-

TABLE 1
Common etiologies of nonobstructive azoospermia

Congenital or developmental
Genetic
Karyotypical abnormalities
Y chromosomal microdeletions
Testicular
Cryptorchidism
Torsion
Bilateral anorchia
Endocrinological
Gonadotropin-releasing hormone deficiencies
Luteinizing hormone and follicle-stimulating hormone deficiencies
Excess of androgen, estrogen, prolactin, glucocorticoid
Thyroid abnormalities
Receptor abnormalities
Varicocele
Acquired
Drugs or gonadotoxins
Infectious or inflammatory
Neoplastic diseases
Iatrogenic
Ischemic atrophy
Radiotherapy or chemotherapy
Systemic illness
Environmental hazards
Radiation
Heat or thermal injury

Adapted from reference 6

TABLE 2
Physical signs suggestive of nonobstructive azoospermia

General appearance
Eunuchoidal appearance
Malnourished or cachectical appearance
Stigma of genetic disorders
Head or neck 'midline' defects (cleft palate, harelip, anosmia, cranial facial asymmetry, thyroid abnormalities)
Gynecomastia
Genitalia
Varicoceles
Testicular hypotrophy/atrophy
Soft texture of testis
Cryptorchidism
Ambiguous genitalia or hypospadias

sis), 46 XY Noonan's syndrome and XYY male. Recently, different spermatogenesis loci have been mapped on the Y chromosome and named 'azoospermia factors' (AZFa, b, c and d). Deletion of a microsegment of the Y chromosome results in severe testiculopathy leading to male infertility. Y chromosome microdeletion is the most prevalent molecularly definable genetic abnormality in male infertility and is found in 5% to 21% of men with severe oligospermia or azoospermia (see "Genetic risks associated with advanced assisted reproductive technology", to appear in next issue).

Evaluations

The diagnosis of azoospermia or severe oligospermia should be made with at least two complete semen analyses (see Bénard, pages 101-104). The basic hormonal workup for nonobstructive azoospermia should include a morning total serum testosterone and FSH/LH. If abnormalities are found, the levels of serum prolactin, estradiol and thyroid function (especially if thyroid dysfunction is suspected clinically) should be evaluated as indicated.

Azoospermia in a man with significant abnormalities in the hormonal profile strongly suggests a diagnosis of nonobstructive azoospermia. In cases where the hormonal profile is normal with no clear clinical indications of the cause of azoospermia, a testicular biopsy should be considered to evaluate the presence and extent of spermatogenesis.

Additional workups to evaluate nonobstructive azoospermia include genetic evaluation with karyotype analysis. In addition, Y chromosome microdeletion analysis should be performed. Although there is no specific treatment for any of these various genetic abnormalities, the value of a genetic workup lies in the provision of proper genetic counselling for the couple, who, in most cases, with the use of advanced assisted reproductive technology, may have biological offspring (see "Genetic risks associated with advanced assisted reproductive technology", to appear in next issue). The potential risks and implications of passing genetic or congenital disorders to future generations should be addressed with these couples. In virtually all reproductive centres offering advanced assisted reproduction, genetic counselling is available or compulsory to couples diagnosed with genetic abnormalities.

TREATMENTS FOR NONOBSTRUCTIVE AZOOSPERMIA

The key to the successful management of nonobstructive azoospermia is identifying treatable causes. The use of drugs and medications that are gonadotoxic should be discontinued. Cryptorchidism, even when diagnosed in adults presenting with azoospermia, should be treated with orchiopexy, which has been reported to result in recovery of spermatogenesis (3). A thorough evaluation also allows proper identification of conditions such as testicular neoplasm, which is 16-fold more commonly diagnosed in men presenting for infertility evaluation (4) and is life threatening if diagnosis and treatment are delayed.

TABLE 3
Common causes of obstructive or secretory azoospermia

Congenital
Congenital absence of vas deferens
Ejaculatory duct obstruction or cysts
Obstruction at prostatic utricle
Malformation of excurrent ductal system
Inflammatory conditions
Epididymo-orchitis
Vasitis
Prostatitis
Neurogenic
Anejaculation or retrograde ejaculation
Iatrogenic
Vasectomy
Postradiation ductal fibrosis
Vasal or epididymal injury from surgeries
Bladder neck injury
Drugs or medical therapy
Trauma
Neurological injuries
Excurrent ductal injuries

The single most common specific cause of a decline in sperm production is varicocele (5), which is discussed further by Zini, pages 119-124).

Endocrinopathies should be identified and treated accordingly. The success of the use of exogenous GnRH and gonadotropins has been confirmed in various studies (1). However, a standard protocol has yet to be established and patient selection is the important key to effective treatment. For azoospermic and oligospermic men with hypergonadotropic hypogonadism or normogonadism, the benefit of exogenous gonadotropin is not well established. Various empirical therapies, including the use of various forms of antiestrogens, have been used clinically without consistent success.

With regard to the management of azoospermic and oligospermic men with isolated low testosterone levels, the use of exogenous testosterone should not be implemented. Exogenous testosterone will downregulate the release of gonadotropins, resulting in a further decline in testicular functions in hormone and sperm production. Although 'rebound spermatogenic recovery' has been reported when stopping the exogenous testosterone, the routine use of testosterone generally is not effective and is detrimental to spermatogenesis.

ASSISTED REPRODUCTION FOR NONOBSTRUCTIVE AZOOSPERMIA

While some of the underlying causes of nonobstructive azoospermia may be reversible to a degree, advanced assisted reproductive techniques are needed for the majority of patients with this condition. With the advent of assisted reproductive technology, particularly ICSI combined with testicular sperm extraction (TESE), many of these men are now able to father their own biological children (6).

For men with nonobstructive oligospermia or azoospermia, rare sperm can sometimes be found in the ejaculate for ICSI. More often, however, retrieval of sperm from the testis is required. Various techniques of sperm retrieval for these patients have been documented (6,7). Testicular sperm aspiration (TESA), in which a gauge 21 to 25 needle is inserted into the testis parenchyma percutaneously, has been used to aspirate sperm. The success rate of sperm retrieval in nonobstructive azoospermia has been poor, with a significant risk of vascular injury and hematoma formation postoperatively. TESE in the form of an open biopsy has been more successful for these patients. In an attempt to limit the amount of testicular tissue removed and to minimize the risk of vascular injury, a microsurgical technique has been employed in TESE. Using the microdissection technique, sperm have been identified in 50% of men explored. In those men in whom sperm are found, a pregnancy rate of 50% has been achieved using in vitro fertilization and/or ICSI. The spontaneous abortion rate is 19%. The high rate of spontaneous abortion is probably due to the increased incidence of chromosomal abnormalities and DNA damage in the sperm of men with nonobstructive azoospermia (8). Even in severe cases of congenital or acquired testicular failure, as in Sertoli-cell-only syndrome (9), postchemotherapy azoospermia (10) and nonmosaic (47 XXY) Klinefelter's syndrome (11), sperm have been found and pregnancy and live births have been achieved.

OBSTRUCTIVE AZOOSPERMIA

Before serving their role in fertilizing oocytes, spermatozoa must exit the testis and pass through a complex excurrent ductal system, which includes the efferent ductules, epididymis and vas deferens leading to the ejaculatory duct. Pathological conditions in any part of the excurrent ductal system obviously may have a significant impact on spermatozoa transport, resulting in subfertility or infertility.

Typically, azoospermia is evident when complete obstruction occurs bilaterally. It should, however, be noted that the finding of some sperm in the ejaculate does not rule out the presence of obstruction. In fact, partial obstruction of the excurrent ductal system, which is an underdiagnosed clinical entity, can occur, leading to impaired quantity as well as quality of sperm in semen. Proper diagnosis and treatment of obstruction can result in improved semen parameters.

By far the most common cause of excurrent ductal obstruction is previous vasectomy. In addition, various inflammatory conditions (12,13), particularly those involving the epididymides, are among the prevalent etiologies of excurrent ductal obstruction. Other conditions that can lead to obstructive or, as some investigators preferred, secre-

tory azoospermia (the inability to release sperm to ejaculate) are summarized in Table 3.

EVALUATION FOR OBSTRUCTIVE AZOOSPERMIA

Clinically, men with azoospermia or severe oligospermia due to obstruction generally have normal testicular volume and texture, and normal serum hormonal profiles. Additional clinical findings suggestive of obstruction include dilation of the epididymides, hydroceles and absence of vas. In addition to azoospermia, in cases of ejaculatory duct obstruction, biochemical characteristics of seminal fluid may reveal decreased volume, pH of less than 7.4 or negativity for fructose. On the other hand, azoospermia from obstruction in the vasa or epididymides generally has a normal biochemical profile in the seminal fluid. A recent study suggested that a high titre of antisperm antibodies, measured by indirect immunobead assays in seminal fluid and serum, has a clinical value in predicting the presence of obstruction of the excurrent ductal system (14).

As stated previously, testicular biopsy is indicated in azoospermic men with normal testicular examinations and hormonal profiles. However, if a congenital absence of vas deferens is diagnosed clinically, testicular biopsy is generally not necessary, because virtually all of these men have active spermatogenesis. For this latter group of patients, surgical sperm retrieval for assisted reproduction yields a high success rate (15).

In addition, unlike men with nonobstructive azoospermia, men with azoospermia due to obstruction (hence, 'normal' spermatogenesis) do not require karyotypical evaluation. However, for men with congenital absence of vas, the evaluation of cystic fibrosis transmembrane conductance regulator mutation, which is found in 50% to 80% of these men, is required for the couple because they are at a higher risk of having offspring with cystic fibrosis.

TREATMENT OF OBSTRUCTIVE AZOOSPERMIA

The principal of treating obstructive azoospermia is to bypass the obstruction with surgical reconstruction in the excurrent ductal system whenever possible. The most common surgeries for excurrent ductal reconstruction are vasovasostomy (for vasal obstruction) and vasoepididymostomy (for epididymal obstruction). In cases where reconstruction is not feasible, as in most men who have a congenital absence of vas in which the gap defects are usually too large to bridge by reconstruction, surgical retrieval of sperm for assisted reproduction is a feasible treatment option. It should be pointed out, however, that various studies have established that surgical reconstruction is a more cost effective treatment than is upfront assisted reproduction (16-18).

Significant advances in microsurgical techniques have resulted in improved success rates for both vasovasostomy and vasoepididymostomy (see Dwyer and Grantmyre, to appear in next issue).

In addition to the vasa and epididymides, another common site of obstruction in the excurrent ductal system is the ejaculatory duct. Pathological conditions such as ductal compression by congenital midline cyst of the prostate and seminal vesicle ducts, and various inflammatory conditions involving the prostatic urethra are common etiologies of ejaculatory ductal obstruction. As stated previously, semen biochemical profiles can aid in the diagnosis of ejaculatory duct obstruction. Physical examination looking for palpable midline cysts on prostate examination or dilation of seminal vesicles is generally unyielding. The use of transrectal ultrasound, on the other hand, can reveal dilation of seminal vesicles and the presence of prostatic cysts, suggesting a diagnosis of ejaculatory duct obstruction. Diagnosis can also be confirmed on vasography, which should be done only intraoperatively, in the same setting of attempted reconstruction.

Ejaculatory ductal obstruction can be treated surgically with transurethral resection of the prostatic verumontanum until patency of the ejaculatory duct openings is achieved. This should be done in conjunction with intraoperative vasography. Injection of indigo carmine intravasally facilitates determination of the adequacy of resection. Transurethral resection improves semen parameters in about 50% to 70% of cases. Complications of such treatment include urinary reflux to ejaculatory ducts, epididymitis, retrograde ejaculation and urinary incontinence.

In addition to obstruction, ejaculatory disorders may also lead to azoospermia. Anejaculatory and retrograde ejaculation are seen in men with neurological disorders or injuries to the lower urinary tract that involve the bladder neck, seminal vesicles, prostate and urethra. While medical treatment with sympathomimetics and electroejaculation may induce antegrade ejaculation in some cases to allow pregnancy through natural intercourse or intrauterine insemination, surgical sperm retrieval may be required in many of these patients seeking assisted reproduction.

ASSISTED REPRODUCTION FOR OBSTRUCTIVE AZOOSPERMIA

For patients with obstruction not amenable to surgical reconstruction or other treatments, those who elect to forego reconstruction, or for couples in whom a significant female factor (such as advanced age) requires the use of ICSI, sperm retrieval for assisted reproduction is an excellent option for the management of obstructive azoospermia. In virtually all patients with obstruction azoospermia, sperm can be obtained surgically. Using ICSI for obstructive azoospermia, pregnancy rates exceeding 60% can be obtained with motile sperm from either fresh or cryopreserved samples (19-21).

Several techniques have been employed for sperm retrieval for obstructive azoospermia. Microsurgical epididymal sperm aspiration (MESA), in which sperm is collected from a microsurgically isolated epididymal tubule, results in retrieval of greater than 100×10^6 sperm, with motility sufficient for cryopreservation of multiple aliquots (22). If the patient is opposed to an open procedure, if a microsurgeon is not available to perform MESA, or if the

couple is considering only one in vitro fertilization cycle, a percutaneous procedure may be employed. Percutaneous procedures include TESA, percutaneous epididymal aspiration of sperm and percutaneous testicular biopsy. It should, however, be emphasized that percutaneous procedures are associated with a greater risk of hematoma formation compared with open procedures.

CONCLUSIONS

There have been tremendous recent advances in management strategies for azoospermia. Nonetheless, azoospermia remains the most challenging category of male factor infertility to manage. Various diagnostic strategies, particularly those involving genetic analyses, are being introduced not only to identify the etiologies of the reproductive failure, but more importantly to allow better counselling to those couples who are at risk of transmitting significant pathology to their offspring. Microsurgical reconstruction and advanced surgical sperm extraction combined with ICSI are established standard treatments. The effectiveness and safety of these procedures are well established and are commonly performed to successfully manage many men with obstructive and nonobstructive azoospermia who were previously considered to be sterile.

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