

Evaluation and treatment of oligoasthenospermia in the era of assisted reproductive techniques

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The management of oligoasthenospermia has undergone changes in this era of assisted reproductive techniques (ART), bringing hope for previously untreatable cases of oligospermia. However, the overenthusiastic use of ART has deprived some patients of primary treatment for their disease. Oligoasthenospermia is the most common identifiable anomaly found in semen analysis, and it can be treated or improved in many cases. The patient deserves a chance to be evaluated and helped, and a specific treatment should be offered to achieve pregnancy whenever available. Where this is not possible, suitable candidates should be selected for empirical medical treatment. The aim of pharmacological treatment is to improve the sperm concentration and the fertility potential of sperms. This twofold approach is helpful in both natural and assisted fertilization. ART are, however, an excellent alternative when other therapies fail.

Key Words: *Assisted reproductive techniques; Oligoasthenospermia*

Évaluation et traitement de l'oligoasthénospermie à l'ère des techniques de reproduction assistée

RÉSUMÉ: En cette ère de techniques de reproduction assistée (TRA), le traitement de l'oligoasthénospermie a évolué et se révèle porteur d'espoir pour les cas d'oligospermie auparavant intraitables. Cependant, le recours trop enthousiaste aux TRA a privé certains patients du traitement principal de leur maladie. L'oligoasthénospermie est l'anomalie la plus couramment identifiable à partir du spermogramme et elle peut être traitée ou atténuée dans bien des cas. Le patient mérite la chance d'être évalué et de recevoir de l'aide; il faudrait d'ailleurs offrir un traitement individualisé pour provoquer une grossesse chaque fois que la chose est possible. Dans le cas contraire, les candidats appropriés devraient être soumis à un traitement médical empirique. L'objectif du traitement médicamenteux consiste à accroître la concentration et le potentiel de fertilité du sperme. L'approche à double volet vaut autant pour la fécondation naturelle que pour la fécondation assistée. Les TRA offrent, cependant, une excellente solution de rechange aux traitements infructueux.

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The management of oligospermia (sperm density less than 20 million/mL) has undergone changes in this era of assisted reproductive techniques (ART). ART has brought hope for untreatable cases of oligospermia, but its overenthusiastic use has deprived some patients of primary treatment for their disease. Oligospermia is rarely isolated, and most often is caused by androgen deficiency or is idiopathic. It is commonly associated with asthenospermia (decrease in motility). Asthenospermia, as a single sperm defect parameter, is caused by sperm structural defects, prolonged abstinence periods, genital tract infection, antisperm antibodies, partial ductal obstruction and varicocele. Unfortunately, it is still not possible to find the etiology in many cases, and the cause is identified as idiopathic. Oligospermia and asthenospermia together (oligoasthenospermia) are the most common identifiable anomalies found in the semen analysis. These anomalies can be treated or improved in many cases.

The most frequent causes of oligoasthenospermia are varicocele, cryptorchidism, drugs, heat, toxins, infection, autoimmunity, trauma and endocrinopathy. The primary treatment of oligoasthenospermia is far less expensive than ART (1,2). When a treatment for oligoasthenospermia is available, it should, if possible, be chosen over the use of ART. If ART are chosen without considering the male treatment, we may actually be shifting the burden of a male patient's treatment toward the female partner. However, ART are an excellent alternative when other therapies fail.

Physicians should try their best to find the cause of oligoasthenospermia and to offer specific treatment, when available, to achieve pregnancy. Where this is not possible, suitable candidates should be selected for nonspecific or empirical medical treatment. The aim of pharmacological treatment is to improve the sperm concentration and the fertility potential of sperms. This twofold approach is helpful in both natural and assisted fertilization (3). In this article, we will give a general overview of the etiology of oligoasthenospermia and the available treatments.

ENDOCRINOLOGICAL ABNORMALITIES

Spermatogenesis depends on an intact hypothalamopituitary gonadal (HPG) axis. A disturbance in any aspect of this function can affect sperm production. Normal gonadal function is required for spermatogenesis. In cases of primary testicular failure due to gonadal dysfunction, the negative feedback to the pituitary (by inhibin) is disrupted and gonadotropin levels are increased. This is seen in men with developmental conditions such as Klinefelter's syndrome and cryptorchidism or due to acquired causes like chemotherapy, radiation therapy and gonadotoxins. In these men, follicle-stimulating hormone (FSH) levels are usually increased although luteinizing hormone (LH) levels may or may not be disturbed, because Leydig cells are more resistant to damage.

The congenital or acquired absence of gonadotropins can also lead to infertility. This hormonal deficiency is treatable. Kallman's syndrome is the most common congenital cause whereas trauma, pituitary tumours and the use of anabolic steroids are among the common acquired causes.

In hypogonadotropic hypogonadism the FSH, LH and testosterone levels are all decreased. Prolactin is another pituitary hormone capable of influencing the HPG axis. Abnormally high levels of prolactin can interfere with the release of gonadotropin-releasing hormone (GnRH) and thus can lead to infertility. A prolactin-secreting pituitary adenoma is the most common cause of this disorder. Typically in hyperprolactinemia, in addition to high prolactin, testosterone and LH are decreased and FSH is either low or normal (1). The disturbance of the testosterone to estradiol ratio can also sometimes inhibit sperm production (4). Hypothyroidism is associated with infertility in less than 0.5% men, although when present it is usually evident and is treatable.

VARICOCELE

Varicocele is the most frequent cause of oligoasthenospermia. In the general population, 15% of the adults have varicocele whereas 40% of the infertile males have one. Various mechanisms have been proposed for the effects of varicocele on infertility as presented in Dr Zini's article (5) and by Aksoy et al (6). Mostafa et al (7) reported that varicocelectomy leads to a significant reduction in the production of reactive oxygen species and antioxidant activity. Inhibin is a hormone released by Sertoli cells that inhibits the release of FSH. The treatment of varicocele improves inhibin concentration. These patients show improvement in spermatogenesis and Sertoli cell function following a varicocelectomy (8). Varicocelectomy also improves other semen parameters and improves the chances of natural pregnancy (9).

When varicocele is associated with severe bilateral testicular pathology, there is a possibility that other causes such as microdeletions of the Y chromosome may be involved. Moro et al (10) have reported Yq microdeletion screening in 17.5% of infertile men with varicocele and severe oligospermia. In these patients the testicular damage may be due to the associated genetic factor.

CRYPTORCHIDISM

Cryptorchidism (undescended testis) is present in 3% to 4% of full term male infants. By one year of age, only 1% to 6% of boys have an undescended testis. If left undescended, it leads to testicular defect and infertility. The higher the undescended testis, the more severe the defect. It is also more severe in patients with bilateral cryptorchid testis. Correction is recommended as soon as possible after the age of one year or at least before the age of two to avoid damage.

GENETIC DISORDERS

Some genetic risk factors are linked with oligospermia, especially in severe forms of the disease. Abnormal karyotypes, microdeletions of the Y chromosome and abnormalities in the cystic fibrosis transmembrane conductance regulator gene may be associated. The microdeletions have been found clustered in the azoospermia factor (AZF) a, AZFb, and AZFc regions (11). Genetic screening is impor-

tant, not only to define the etiology of severe oligospermia, but also because it gives precious information for a more appropriate clinical management of the patient and his future male offspring. Genetic screening for cystic fibrosis, chromosomal abnormalities and Y chromosome deletions is recommended in these patients. The patient should be informed about the risk of carrying a genetic abnormality (12), and genetic counselling should be offered to patients with genetic risk factors.

PYOSPERMIA

Infection of the seminal ducts or genital tract can cause male subfertility. An increased number of leukocytes (greater than one million/mL) in semen are associated with disorders of sperm function. Leukocytes and immature germ cells look alike under wet mount microscopy, so cytological staining or immunohistochemistry is used to make a diagnosis. *Streptococcus fecalis*, *Escherichia coli*, *Chlamydia trachomatis* and *Ureaplasma urealyticum* are the commonly involved pathogens. Identification of the organism and appropriate antibiotic treatment are recommended (3).

ANTISPERM ANTIBODIES

Patients exhibiting oligospermia with associated sperm agglutination and asthenospermia may be infertile due to antisperm antibodies. Risk factors for the development of antisperm antibodies include conditions that may disrupt the tight blood-testis barrier: acute epididymitis or orchitis, cryptorchidism and genital trauma. There is also an association with testicular torsion, varicocele, testis biopsy and sexually transmitted diseases. Antibodies can affect sperm function at several levels, such as impaired cervical penetration, inhibition of sperm capacitation, premature induction of acrosome reaction, impairment of zona binding or fertilization of the ova. Antisperm antibodies can be detected in 10% of infertile men.

FEVER AND OLIGOASTHENOSPERMIA

It has been shown that fever episodes can lead to a 0.4% to 7% decline in sperm concentration and a 0% to 23% decline in motility two to six weeks after the fever episode. The values come back to normal after two to three months in most patients. This implies that any abnormal sperm tests found during this period of transient impairment should be repeated after an interval of at least three months (13). The same phenomenon may be seen in patients exposed to high temperature.

CHEMOTHERAPY, RADIATION AND GONADOTOXINS

Cytotoxic chemotherapy and radiation therapy can adversely affect spermatogenesis. The possibility of testicular failure depends on the drug and the dose (14). In children, as little as 600 rads to the gonads may result in sterility later in life. Smoking, drugs and exposure to toxins can also have serious effects on fertility. Low sperm counts

have been seen in workers exposed to pesticides. Exposures to toxic medications, cocaine, marijuana, excessive hot tubs and saunas all have a negative impact on spermatogenesis. Athletes sometimes use androgenic steroids to increase their muscle mass and performance. This leads to the inhibition of the pituitary gonadal axis, which seriously impairs sperm production. When occupational hazards, environmental hazards or exposure to intoxicating agents are suspected to cause oligospermia they should be prevented (1).

OBSTRUCTIVE OLIGOSPERMIA

Genital duct obstruction is a potentially surgically curable cause of male infertility. It is found in 7% to 12% of all infertile men but is much more common in azoospermic men. Obstruction may be unilateral or bilateral and may occur at multiple locations simultaneously. It may be acquired secondary to infection or result from stricture, or it may be congenital due to the absence or malformation of ductal structure (15). Complete obstruction is easier to diagnose than partial obstruction. Typically, the patient presents with low volume and fructose-negative ejaculate, and diagnosis is confirmed by vasography or seminal vesiculography. With partial obstruction of the ducts, neither the diagnosis nor the treatment is simple. Low volume oligoasthenospermia often raises the suspicion of partial obstruction. Transrectal ultrasound and endorectal magnetic resonance imaging are useful tools to diagnose the cause of obstruction. Dilation of ejaculatory ducts, presence of prostatic cysts, and calcification and dilation of seminal vesicles are associated with diagnosis of obstruction (16). For more information about obstruction, please refer to the article on azoospermia (17).

EVALUATION

The key step for the evaluation of oligoasthenospermia is a thorough history and physical examination as described in Dr Bénard's article (18). Sexual history should include the evaluation of potency, use of lubricants, and awareness of the timing and frequency of intercourse or masturbation. Many patients are found to perform either too much or too little intercourse. Prolonged abstinence impairs motility. Sometimes patients use lubricants that are toxic for sperms; most lubricants including K-Y jelly (Johnson & Johnson, USA), Surgilube (Fougera, USA) and petroleum jelly may impaired the sperm motility. Vegetable oil, peanut oil, saliva and raw egg white do not interfere with the sperm function. High-grade fever can produce oligospermia lasting for up to three months or more (13). In such patients semen analysis should be repeated after three months to see any improvement. History of sexually transmitted diseases or other genitourinary infection is important. Childhood diseases such as mumps, orchitis and cryptorchidism have a deleterious effect on sperm production. Testicular trauma and torsion are also associated with decreased sperm production. Occupational history and history of exposure to gonadotoxins are equally important.

In addition to a general systemic examination, as described in Dr Bénard's article (18), patients should be examined for signs of androgen deficiency. Small and soft testes indicate testicular loss of spermatogenesis. The epididymis should be examined for tenderness, induration or cyst (possible signs of obstruction). Palpation for varicocele is an important component of physical examination. Digital rectal examination is done to detect prostatic and seminal vesicle abnormalities.

LABORATORY TESTS

Semen analysis

Semen analysis is the most important laboratory test, and should be carried out after an abstinence of two to three days. Two specimens one month apart should be analyzed (19).

An increased number of leukocytes (greater than one million/mL) in semen alters the sperm function and is often associated with genital tract infection. Leukocytes and immature germ cells look alike under wet mount microscopy, so cytological staining or immunohistochemistry is used to make a diagnosis. Patients with sperm agglutination and asthenospermia or with risk factors for these disorders require test for antisperm antibodies (20).

Endocrinological evaluation

In oligospermia, serum testosterone and FSH levels should be investigated initially. If serum testosterone is low then tests for LH, prolactin and estradiol are performed. Free and total serum testosterone is also repeated. Other endocrinological tests for pituitary, thyroid or adrenal abnormalities should be performed when indicated.

Transrectal ultrasound

Transrectal ultrasound is suggested if there is low volume ejaculate with palpable vasa deferentia and normal testicular size. Partial obstruction of the ejaculatory ducts can be diagnosed with the help of this modality (21).

MANAGEMENT

The aim of evaluation is to find out whether there are reversible causes for the oligoasthenospermia and to offer specific therapy to eliminate the cause if feasible. If the cause is irreversible the patients should be evaluated for ART. Some patients may require pharmacological treatment in association with ART to improve sperm quality. In cases where an underlying systemic disease is discovered, patients should be treated accordingly. Patients with idiopathic oligospermia may benefit from empirical medical treatment.

SPECIFIC SURGICAL THERAPY

Varicocele

Patients exhibiting oligospermia who have fertile female partners should be offered varicocele repair as primary treatment. It has the potential to reverse the disease process and to cure infertility. ART should be reserved for only those patients who do not respond to this treatment. Age and reproductive health of the female partner should always be

considered while making a decision (20). For more information, we refer you to Dr Zini's article (5).

Genital duct obstruction

Please refer to Dr Chan's article on azoospermia (17).

Other diseases

Patients with prolactin secreting pituitary adenoma or adenoma compressing the pituitary stalk are referred for specific therapy. Similarly patients with other brain tumours or other endocrinological abnormalities are referred to the respective specialties for specific treatment (22).

SPECIFIC PHARMACOLOGICAL THERAPY

Hypogonadism

In primary hypogonadism (hypergonadotropic hypogonadism) the disorder lies at the testicular level. Klinefelter's syndrome is a congenital disorder of this type. Acquired causes include orchitis atrophy, chemotherapy or radiotherapy. These patients often have severely compromised fertility. Pharmacological treatments to improve the fertility potential are rarely of help and these patients must rely on ART. In congenital hypogonadotropic hypogonadism (low FSH, LH and testosterone) the defect is of hypothalamic GnRH secretion. These patients can be treated with gonadotropin replacement either by pulsatile GnRH therapy or human chorionic gonadotropin along with menotropins or FSH. Dose is stratified according to the level of testosterone, gonadotropins and testicular volume. This therapy is effective if the pituitary is responsive (23-25).

Immunological infertility

When antisperm antibodies are present, two approaches are possible: an attempt may be made to suppress antibody formation or the unbound spermatozoa may be used, with or without processing, for the ART. The systemic treatment with corticosteroids has been associated with inconsistent changes in antibody titres, semen parameters and pregnancy rates. The advantage and risks of prednisone therapy must be weighed against the chance of pregnancy with ART. In this situation, we usually encourage patients to go for ART.

Impaired testosterone to estradiol ratio

Aromatase inhibitors can improve this problem in subfertile oligospermic men, as seen in obese patients, and improve sperm concentration and motility indices. Testolactone (100 to 200 mg/day) and amastazole (1 mg/day) have been found effective, but these drugs are not available in Canada (4).

EMPIRICAL THERAPY

In idiopathic oligospermia, patients can derive benefit from empirical medical pharmacological treatment. If empirical therapy is being used, it should be given for a minimum of three to six months to incorporate at least one full spermatogenic cycle. If this is unsuccessful, ART should be employed. Empirical treatment may be used in combination with ART (especially intrauterine insemination) to improve semen parameters.

Antioestrogen therapy

Clomiphene and tamoxifen citrate have been used for more than two decades. It is thought that they increase hypothalamic activity by blocking feedback inhibition leading to an over secretion of pituitary gonadotropins (FSH and LH). Some direct action of tamoxifen at the testicular level has also been described. There is some controversy in the literature about their efficacy. The majority of investigators have found pregnancy rates lower than 30% (1).

FSH and gonadotropins

Gonadotropins have been available as human chorionic gonadotropin or human menopausal gonadotropin purified from the urine of pregnant and menopausal women, respectively. Now, more purified as well as recombinant forms are available. FSH has been shown to improve sperm index, sperm count and the fertility potential of sperms. These treatments are very expensive and their efficacy is limited in idiopathic cases. These therapies are not recommend in men without a demonstrable hormonal abnormality (26,27).

Testosterone rebound therapy

This treatment involves the administration of excess doses of testosterone to suppress the activity of the HPG axis.

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The androgen therapy is then stopped in the hope that the system will rebound and improve the production of sperm. This therapy is not recommended because other and better therapies are available and because some patients have persistent azoospermia after this treatment. The same recommendation is made for any treatment used in combination with testosterone (27).

Miscellaneous treatments

Tranilast, a mast cell blocker, has also been used in idiopathic oligospermia and improved the sperm concentration by 41.1% (28). Other nonspecific treatments include pentoxifylline, arginine, carnitine, acetylcysteine, vitamins A, C and E, zinc, selenium and glutathione. Their efficacy is still doubtful.

CONCLUSION

Although ART have revolutionized the treatment of infertile couples, we still must try to find the cause of infertility in the male. Oligoasthenospermia can be treated or improved in many cases, and the method of treatment depends on the etiology. Nonspecific therapy has the potential to improve the fertility of sperms in some men with idiopathic oligospermia. ART remain available for those patients who did not respond to the therapy or for couples who prefer this type of therapy.