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The Clinical Management of Male Infertility

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ABSTRACT

Male infertility is a common cause of subfertility for which sperm disorders are the single most common cause. Genetic abnormalities, for example, microdeletions associated with the Y chromosome, defects in the androgen receptor gene and cystic fibrosis have gained recent prominence and it is envisaged that many of the 60% of men for which no cause is found may have a genetic basis for their subfertility. Although an abnormal semen analysis is commonly the first indicator of a male factor problem, further tests are usually required. Empirical treatment with hormones, varicocelectomy and immunological treatment have been proven to be disappointing whilst the treatment of infection and obstruction do not always translate into significantly higher fertility rates. Ejaculatory disorders and impotence can be effectively treated today whilst donor insemination can be offered to men with untreatable infertility. The advent of assisted reproduction and micromanipulation has greatly improved prospects for fertility of men with very poor semen quality. However, the genetic implications of these procedures have to be quickly addressed so that fertility is maximised without risk to the progeny.

Keywords: male subfertility, androgen receptor gene, IVF, ICSI

INTRODUCTION

Subfertility affects about 15% of all married couples[1]. In about one third of these cases, a male factor is the primary problem and in another third, problems in both the male and female contribute to subfertility. As a single cause of subfertility, sperm disorders are the most frequent. With a few rare exceptions, it was traditionally regarded that male infertility was a condition which was very difficult to treat. This was mainly because the problem is not an entity but reflects a variety of different pathological conditions and effective treatment strategies were not available.

Even today, recognisable causes are present in only about 40% of men with infertility. The other 60% have normal gonadotrophin and testosterone levels and the pathophysiology remains to be elucidated although, new studies on the deletions or mutations in a number of genes may explain a substantial proportion of this group[2]. This would explain why until recently, the therapy remained mostly empiric and unsuccessful. However, advances in the field of micromanipulation techniques have revolutionised the management of the male factor in assisted reproduction and has now given hope to many men who would otherwise be unable to father a child. The optimism for this has been tempered by the genetic implications of men with very low and abnormal sperm counts, as will be seen later.

AETIOLOGY

There are many ways to divide the aetiological factors and a simple method based on a functional viewpoint as described by Skakkebaek et al[3] is shown in Table I. Although this list is by no means exhaustive, it shows the wide variety of conditions that can give rise to fertility problems. Many of the conditions on the list (eg. pre-testicular genetic causes) are quite rare but proper identification would be crucial with respect to the modality of treatment and counselling required.

Absent testicular tissue

This is a very rare cause of male subfertility. As the chance for natural fertility is nil, it is important that appropriate counselling be given early so that all the options could be explored with the couple. It is also important to exclude genetic and/or chromosomal disorders in such men.

Impaired sperm production and function

Genetic causes of male infertility

Genetic factors including chromosomal abnormalities that can impair sperm production and function are numerous but rare[4]. A high index of suspicion is necessary when taking a history and examining these men. Genetic defects are associated with a variety of clinical presentations ranging from gonadotrophin-releasing hormone deficiency to spermatogenic failure and obstructive azoospermia.

Recent discoveries have now firmly focused the attention on genetic disorders as an important component in the aetiology of male infertility. Testosterone is paramount in spermatogenesis in all mammals and acts via the androgen receptor (AR) which is encoded by the AR gene on the X-chromosome. Since most males with infertility have normal androgen levels, attention is now focused on the AR apparatus as a cause of defective spermatogenesis. Defective androgen binding has been

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Table I – Causes of male infertility

Mechanism	Cause
Absent testicular tissue	Anorchia Bilateral castration
Impaired sperm Production/function	Hypogonadotrophic hypogonadism
	Genetic abnormalities
	■ Pre-testicular cause
	■ Kallman's syndrome ■ Prader-Willi syndrome ■ Bardet-Biedl syndrome ■ Cerebellar ataxia ■ Thalassemia
	■ Testicular cause
	■ Klinefelter's syndrome ■ XYY syndrome ■ AZF and AR gene defects ■ Noonan's syndrome ■ 46XX male
	■ Post-testicular cause
	■ Cystic fibrosis ■ Congenital absence of vas ■ Androgen insensitivity syndrome ■ 5 alpha reductase deficiency ■ Young's syndrome ■ Polycystic kidney disease (autosomal dominant)
	Cryptorchidism Cancer of testis Varicocele Sertoli-cell-only Irradiation Drug induced Environmental agents
Impaired sperm transport	Autoimmune infertility Blockage of the vas Ejaculatory failure Previous vasectomy Impotence Kartegener's syndrome
Disturbances in sperm-oocyte fusion	Abnormal egg-binding proteins – clinical significance unknown

detected in 12% – 15% of infertile males and mutations of the ligand-binding domain of the AR can lead to defective spermatogenesis[5,6] in otherwise normal males. Other defects in the AR gene have now been shown to be associated with various conditions from androgen insensitivity syndromes to prostatic cancer and spinal bulbar muscular atrophy.

Another important genetic factor identified is the azoospermic factor (AZF) gene on the long arm of the Y chromosome. Studies on azoospermic and severely oligospermic men have shown that 12% – 18% of these men have deletions in a consistent specific portion in the AZF gene[7,8]. Clinical testing for defects in the AR gene and the AZF gene is now available and it is envisaged that more men with severe oligospermia or azoospermia will undergo such studies in the future.

Other causes

Patients with thalassemia major (which is prevalent in South East Asia) develop infertility resulting from iron deposition in the pituitary gland and testes[9]. Men with an undescended testis usually have impaired spermatogenesis that also affects the normal testis[10]. The same is true of men with testicular cancer where there is severe impairment of spermatogenesis in 25% of cases[11]. Hypogonadotrophic hypogonadism may be congenital as in Kallman's syndrome or acquired as in pituitary adenomas (eg. prolactinoma), craniopharyngioma and other brain tumours.

There are many drugs which have deleterious side effects on sperm production and function. Examples include sulphalazine (for inflammatory bowel disease), anabolic steroids and anticancer drugs (eg. cyclophosphamide, procarbazine, cisplatin). The role of environmental toxins have also become prominent in recent years. Some spermatotoxic compounds identified include pesticides (eg. DBCP, chlordecone, carbaryl, ethylenedibromide), glycol ethers (used in paints, printing inks and adhesives) and metals (lead, cadmium and mercury). Other toxins have been shown to have oestrogenic properties and have been implicated in the gradual decrease in sperm counts in men this century[12]. Finally, the influence of alcohol, smoking, recreational drugs and nutrition on fertility potential of the male should not be neglected.

Varicoceles are present in 10% – 15% of men in the general population. Although it has been strongly implicated in spermatogenic failure[13], the management of this problem has become a contentious issue in recent years.

Impaired sperm transport

Approximately 5% of men with infertility have identifiable anti-sperm antibodies. The role of sperm antibodies remains highly controversial. Although it is possible that the presence of antibodies on sperm has better prognostic value than those in serum or in seminal plasma, it is likely that infertility will occur when antibodies bind to a relevant sperm antigen involved in a specific fertility function[14]. This may explain the variation in functional defects seen in immunological infertility. Sexually transmitted diseases are an important cause of epididymitis and can lead to blockage of the ductal systems. Congenital absence of some part of the ductal system is a rare condition and may have genetic implications (eg. congenital absence of the vas deferens and cystic fibrosis[15]).

Anejaculation and retrograde ejaculation may occur in diabetics, after retroperitoneal lymph node dissection, spinal cord injury and bladder neck surgery. Sexual dysfunction and impotence may also masquerade as infertility.

MANAGEMENT

In many clinics, male infertility is diagnosed after evaluation of the semen sample. Although it is not necessary for the man to be examined in every case of infertility, it becomes a necessity when the sperm parameters are abnormal. This is because a thorough history, physical examination and relevant investigations will reveal a cause in up to 40% of cases.

Simply trying to overcome the problem with assisted reproduction techniques is both unscientific and dangerous[16].

History and physical examination

A thorough history may reveal an aetiology even though in the majority of cases, a negative history is more common. Some important points to note include a history of hernia surgery in childhood, trauma and torsion (possible damage to the vas or testis). A past history of genitourinary infections like orchitis (eg. mumps, syphilis, tuberculosis) or epididymitis (eg. gonorrhoea, chlamydia, tuberculosis) may indicate a more serious effect on fertility. Chronic infection of the prostate and seminal vesicles are characterised by painful ejaculation, haematospermia and pain in the perineum.

A delayed onset of puberty may indicate a gonadotrophin deficiency whilst a history of recurrent chest infection and bronchiectasis may be associated with epididymal obstruction (Young's syndrome), absent sperm motility (immotile cilia syndrome), and agenesis of the vas (cystic fibrosis). Testicular and sexual dysfunction may be caused by many chronic disorders such as renal failure, liver disease, malignancy and diabetes. Environmental and occupational exposure to toxins as well as a good drug history should be sought for. Some cases of infertility may have its seed in sexual dysfunction and it is imperative to establish that normal vaginal intercourse with intravaginal ejaculation occurs with regularity.

A general physical examination should be carried out and should include the height, weight, body habitus and secondary sexual development. Abnormalities in these basic parameters alone may be a clue to some of the rarer genetic causes of male subfertility (eg. obesity, lack of secondary sexual characteristics, hypotonia, tall/short stature).

If androgen deficiency (eg. eunuchoid, lack of facial and pubic hair, small testes, decreased libido) is suspected, look for gynaecomsatia, cryptorchidism, hypospadias, anosmia and visual field defects. Testicular volume measurement with a Prader orchidometer may give the key finding in differentiating between azoospermia due to testicular failure (small volume) and duct obstruction (normal volume). The normal adult testicular volume for Asian men is between 12 mL and 35 mL. Testicular size also indicates the degree of testicular development in hypogonadotrophic patients and of testicular atrophy in those with various forms of primary testicular pathologies. An irregular contour, induration or abnormal consistency of the testis suggests previous orchitis, surgery or malignancy.

An enlarged and tense caput epididymis may be palpable in cases of obstructive azoospermia. Irregularity and induration of the epididymis and vas suggest previous infection. The presence of a varicocele should be documented and graded (grade 1 – detected on doppler on Valsalva manoeuvre, grade 2 – palpable, grade 3 – visible). A chronic prostatic infection may reveal an irregular consistency and tenderness on rectal examination.

INVESTIGATIONS

Semen analysis

This remains the most important basic investigation of the male factor. However, conventional parameters of semen analysis such as sperm density, percentage of motile sperm, quality of sperm movements and sperm morphology are subjective and do not give an accurate assessment of the fertility potential of an individual. Also, as sperm counts can be quite variable in the same person, it is standard practice to do 2 to 3 analyses[18]. The extent to which standard parameters of semen analysis implicate a male factor is debatable and the conventional view that any sperm concentration under 20 x 106 sperm/mL indicated male infertility has been challenged[19]. The majority of men who are investigated for male factor subfertility have oligoasthenoteratozoospermia of unknown cause. In view of the severe limitations of a conventional semen analysis, new tests of sperm function have been introduced but they also have limited practical applications. Among these tests include those on strict morphology evaluations, acrosomal assessment and sperm-zona binding[20,21].

The presence of sperm antibodies can be detected by the mixed antiglobulin reaction test. The predictive value of this for fertilisation is variable and it has been shown that the nature of the antigen against which the seminal antisperm antibody is directed may be as important as the antibody concentration in affecting sperm function[22]. Cervical hostility towards semen is further assessed by the sperm-cervical mucus penetration (Kremer) test. The link between white cell count (pyospermia), infection and male infertility is still being debated[23]. Accessory gland function can be assessed by measurement of seminal fructose to assess the seminal vesicles and acid phosphatase or citrate to assess the prostate gland. In the presence of infection, the concentrations are lower although a normal value does not exclude it. If infection is strongly suspected, then the semen could be cultured for pathogenic organisms like gonococcus and chlamydia.

Hormonal profiles

The measurement of serum follicle-stimulating hormone (FSH) is a useful test to distinguish patients with azoospermia due to obstruction (normal FSH) from those with testicular damage (high FSH). In about one third of men with severe oligozoospermia or azoospermia from testicular damage, luteinising hormone (LH) levels are high whilst testosterone levels are low. The measurement of FSH, LH and testosterone levels are also useful in diagnosing men with hypogonadotrophic hypogonadism (low levels for all 3 hormones) as this condition is treatable. Testosterone and LH measurements are also indicated if there is a clinical suspicion of androgen deficiency and steroid secreting lesions such as congenital adrenal hyperplasia or hormone secreting adrenal/testicular tumours. High serum prolactin levels may cause decreased libido (and sexual dysfunction) and may also indicate pituitary disease causing secondary testicular failure.

Chromosomal and genetic studies

Men with azoospermia (or very severe oligospermia), high FSH and small testes (2 mL – 6 mL) should undergo these studies. The most common chromosomal abnormality in such cases is Klinefelter's syndrome (47 XXY) which accounts for up to 20% in some series. Screening for cystic fibrosis is required in patients with congenital absence of the vas deferens[24]. Partial androgen insensitivity syndrome should be excluded in men with a history of cryptorchidism or orchidopexy. Molecular techniques are now available to look for deleted DNA sequences in the DAZ or RBM regions on the Y chromosome as well as checking for mutations of the androgen receptor gene[25]. Micro-deletions of the Y chromosome are also found in up to 15% of men with idiopathic oligoasthenoteratozoospermia or azoospermia[26].

Testicular biopsy

The usefulness of this procedure, which had declined significantly in the last decade for various reasons, has had a recent resurgence. The decline was mainly due to the use of hormonal measurements to differentiate between obstruction and testicular failure as well as the increasing success of micromanipulation techniques. If the clinical diagnosis is uncertain or if testicular malignancy has to be excluded (eg. in men with a history of cryptorchidism), this procedure would be a useful adjunct to the other standard investigations. Testicular biopsy is now done routinely to check for spermatogenesis in non-obstructive azoospermia to determine whether it would be worthwhile to offer ICSI[27,28]. It may also be done for men who undergo exploration of the vas to check for blockage. An added advantage of a testicular biopsy is the detection of carcinoma-in-situ in testicular cancers.

Miscellaneous

Testicular ultrasound facilitates the detection of hydroceles and other abnormalities of the scrotum[29]. Doppler ultrasound and venography can be used to detect varicoceles but are of limited usefulness as the efficacy of varicocele treatment is still unproven. If retrograde ejaculation is suspected, then a post-ejaculatory specimen of urine should be obtained to confirm the presence of semen.

TREATMENT

While the exact cause of infertility is still unknown in the majority of men, we anticipate that within a decade, almost all of these would be ascribed to a genetic cause. Hence the use of logical or effective treatments affect only a small proportion (5% – 10%) of cases. In the majority, the treatment is more empirical and even if semen variables have improved after treatment, it does not correlate with increased conception rates. With major advances in micromanipulation techniques, there is at last a reasonable chance of fertility for these men and assisted reproductive techniques is now an important treatment modality for such men.

Treatments of no proven benefit

It is now certain that hormonal therapy has no beneficial effect on the infertile male except for the rare case of Kallman's syndrome or pituitary deficiency. Hence, use of anti-oestrogens (clomiphene citrate[30] and tamoxifen) to stimulate Leydig cells in idiopathic oligozoospermia, low dose androgen therapy[31], bromocriptine and vitamin E are largely ineffective. Similarly, the use of growth hormone in the treatment of male infertility has been disappointing[32].

The management of varicoceles is also a contentious issue. Several large, well controlled studies have shown that varicocelectomy has no beneficial effect on sperm count although the procedure is still commonly performed in some centres[33-35].

The role of anti-sperm antibodies is also controversial[14]. Immunological treatment of such men (eg. with steroids[36,37] has been largely ineffective compared to assisted reproduction. Intrauterine insemination (IUI), involving the deposition of prepared spermatozoa directly into the uterine cavity for men with oligozoospermia, also did not significantly improve the conception rates. If IUI is offered, it is usually done with ovarian hyperstimulation to couples who are normospermic and for a short duration only (eg. 3 cycles)[38]. More recently, the use of tubal perfusion (i.e. "flooding" the fallopian tubes with a sperm suspension) has also been tried; its efficacy is still to be determined[39].

Untreatable infertility

This include men with primary and acquired testicular failure (eg. Klinefelter's syndrome, undescended testes, idiopathic primary seminiferous tubule failure, trauma and exposure to cytotoxic drugs/radiation causing atrophy). They should be carefully counselled about the lack of effective therapy for themselves. Those with features of androgen deficiency should be given androgen replacement therapy.

Couples in this situation may accept either donor insemination (DI) or consider adoption as a solution. Donor insemination produces pregnancy rates of 10% – 15% per month and by 6 months, approximately 50% of women are pregnant[40]. If not pregnant by 6 months, it may be more efficient to convert to in vitro fertilisation (IVF) with donor sperm. With this method of management, there is an 80% chance of having a child within 2 years.

Infection

Men with genital tract infection should be treated with broad spectrum antibiotics such as erythromycin, doxycycline and metronidazole. However, permanent damage to the ducts and accessory glands may have already occurred and fertility may not be improved significantly.

Gonadotrophin deficiency

Although a rare condition, such men will respond successfully to treatment with human FSH and LH or human chorionic gonadotrophin (hCG) or by pulsatile GnRH therapy. As spermatogenesis takes 70 days, the treatment cycle is naturally long but results

indicate that up to 50% of such men will father a child even with reduced sperm counts[41].

Obstructive lesions

Patients with obstructive azoospermia should be offered epididymo-vasostomy with microsurgical techniques. Patients going for vasectomy reversal should also be offered epididymo-vasostomy as opposed to re-anastomosis of the vas. This is because the pressure increase after vasectomy leads to secondary epididymal obstruction which is the cause of failure of otherwise successful vasovasostomies[42].

Disorders of ejaculation

Men with impotence and erectile failure should be assessed to see if any treatable conditions (eg. diabetes) are present. Otherwise, they are usually managed by a combination of sexual counselling, pharmacologic therapy (eg. prostaglandin E1) and mechanical aids (eg. vacuum pumps).

Some cases of retrograde ejaculation may be treated successfully with sympathomimetic drugs. If this does not correct the problem, assisted reproductive techniques with spermatozoa isolated from the urine after previous adjustment of the urinary pH and osmolarity should be offered to the couple. More recently, vibration and electroejaculation have been introduced for treatment of retrograde ejaculation or anejaculation, mostly in tetraplegic and paraplegic patients[43]. In this procedure, an electrical current is passed via a rectal electrode to stimulate contractions of the pelvic muscles and accessory glands, resulting in erection and ejaculation.

In vitro fertilisation (IVF)

When no specific aetiological factors are found in subfertile men, it is common practice to resort to IVF as a therapeutic option. Usually, IVF is offered to couples with low sperm counts as the procedure theoretically allows the fewer number of available sperm a greater opportunity for direct contact with the ovum. The overall clinical pregnancy rates with male factor subfertility with IVF is between 17% to 27% with delivery rates comparable with IVF performed for other types of infertility[45].

Micromanipulation techniques and ICSI

The field of micromanipulation to assist conception came onto the clinical scene in 1988 and has since revolutionised the management of male infertility. The advent of intracytoplasmic sperm injection (ICSI)[46] has allowed men with 100% abnormal sperm morphology and severely compromised sperm motility to father children. Presently, when the total number of motile spermatozoa in the ejaculate is less than 5 x 10^6 per mL (severe oligoasthenozoospermia) or if the total motile sperm count after sperm preparation is less than 1.5 x 10^6 motile sperm or when progressive motility after sperm preparation is poor or when abnormal forms are high, success rates with IVF is poor[47]. Hence, ICSI is more suitable and the results are good with fertilisation rates above 60% and clinical pregnancy rates above 30% being reported[48,49].

The success of the micromanipulation techniques is dependent on a few important factors. Firstly, the quality of the oocytes retrieved should be good. Hence, a stimulation regime that results in a higher recovery of mature oocytes may result in a higher pregnancy rate[50]. The age of the woman is another crucial factor with a lower success rate in older women[51]. The other negative influence on the success of ICSI is when the sperm is completely immotile[52], which is probably a reflection of total necrozoospermia. Finally, the technique must be faultless[53].

ICSI has also been demonstrated to be the treatment of choice for patients with male immunological infertility[54]. The use of testicular sperm for ICSI in obstructive azoospermia has also resulted in viable pregnancies[55] and in azoospermia due to testicular failure, ICSI has a successful implantation rate of 18%[56]. ICSI has also been extended for use in cases where there is need for a high fertilisation rate eg. natural cycles[57] and immature oocytes which have matured in vitro[58]. Couples who have failed IVF as well as men with spermatogenic failure due to external causes (eg. drugs, chemotherapy, radiotherapy) have also benefited from this technique.

Although ICSI has revolutionised the management of severe male factor infertility, the genetic implications of the procedure have only recently come into prominence. There have been reports of increased incidence of sex chromosome abnormalities after ICSI[59]. At least 3 types of nuclear DNA mutations have some relation to spermatogenesis. It has been shown that severe oligospermia has been linked to deletions present on the long arm at the azoospermia factor (AZF) region of the Y chromosome[60]. Mutations in the androgen receptor (AR) gene on the X chromosome have also been shown to cause sperm defects[61]. The treatment of one such patient with androgen therapy has resulted in a successful pregnancy[5]. Mutations in mitochondrial DNA have also been reported in sperm with reduced motility. It has been recommended that screening for defects in the Y chromosome and the androgen receptor gene be done routinely for patients undergoing ICSI. Cystic fibrosis should also be excluded in patients with bilateral congenital absence of the vas deferens[15].

CONCLUSION

It has become clear that the application of assisted reproductive technology to male infertility represents a major advance in the last decade. With further advances in molecular biology in understanding the molecular basis of male infertility, more improvements and refinements in treating such men should become available. At the same time, we should not ignore the ethical considerations that come with such new treatment strategies so that the fertility prospects of such men can be realised with minimal risks to their progeny.

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