Infertility: Urological Aspects

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Abstract

For the couple experiencing fertility problems, management is frequently directed by gynaecologists, who focus mainly upon treatment of the woman, often using in vitro fertilisation. However, in up to 40% of couples, the failure to conceive is attributable to a problem affecting the man. Consequently, the woman may undergo expensive and stressful procedures with limited success rates, whereas effective treatment could be provided by a urologist working in collaboration with the gynaecologist. In cases of obstructive azoospermia, for example, reconstructive surgery of the vas deferens or epididymis may successfully restore fertility.

Introduction

One in 10 couples experiences a delay of more than 2 years when trying to start a family, and the rate of infertility is increasing with the growing trend for couples to delay starting a family until their mid-30s. In approximately 60% of couples, the failure to conceive is attributable to a problem affecting the woman. However, in 20% of couples the problem lies with the man, while in a further 20% of couples factors in both partners contribute to the problem. Consequently, the treatment of both partners must be coordinated and good communication between the urologist and the gynaecologist is paramount.

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Diagnosis and Assessment of the Infertile Male

In the majority of cases, the man is referred to the urologist following a poor semen analysis. He will often attend the clinic with his partner and this allows a combined assessment of the couple. A careful clinical history will yield information to shape the course of the investigation and should include the length of the relationship, how long the couple has been trying to conceive and any problems with intercourse, the presence of any co-existing or previous medical conditions (e.g. diabetes, tuberculosis, mumps during adulthood, venereal disease) and lifestyle factors (e.g. alcohol consumption, smoking).

The Physical Examination

Physical examination of the man should be performed behind a screen without the female partner to minimise any possible feelings of humiliation. Features to note include the type of underwear – boxer shorts which allow air to circulate and cool the testicles are preferred to tight-fitting underpants – and the appearance of the scrotal skin, as eczema can cause scratching, leading to thickening and hyperaemia of skin and, consequently, elevated temperature. This condition is easily treated by referral to a dermatologist may be necessary.

An essential part of the examination is measurement of testicular size using a Prader's orchiometer. *It is important to record the volume of each testicle for future reference.* In a testis with a volume of 15 ml, the chances of normal sperm production are approximately 95% or more, whereas a testis with a volume of 5 ml or less is unlikely to function normally. Those of intermediate size should be further evaluated. An asymmetry may suggest a problem such as an obstruction of the better testicle.

To facilitate recognition of a varicocele, the patient should be examined while standing and in a good light. *It is important to diagnose and record the presence of a varicocele,* although the efficacy of treatment is debatable. It is also essential to bear in mind that each testicle may be affected by a different problem. For example, the patient with a varicocele affecting one testis may also have a previous unilateral epididymitis, causing an oedematous obstruction of the epididymis, affecting the contralateral testis. The appearance and texture of an obstructed testicle can be related to the characteristics of a vasectomised testicle.

Finally, the physical examination should include a rectal examination for detection of subclinical prostatitis or prostatovesiculitis producing pus cells which release superoxide radicals that can affect sperm motility. With the patient on his left side, rectal examination of the prostate may reveal discomfort on palpation. Any fluid that is expressed should be sent for microbiological analysis, to permit specific treatment of the causative organism rather than the use of a broad-spectrum antibiotic.

It is important to note that male fertility may be affected by any systemic disease and a full blood count, blood urea, fasting blood sugar and folic acid measurements along with liver function tests and routine urinalysis should form part of the investigation.

Testicular Temperature and Semen Analysis

Following the physical examination, a number of other possible factors that may interfere with sperm production, ejaculation or fertilisation should be assessed. *Testicular temperature is the most criticial factor affecting spermatogenesis.* The normal scrotal temperature should be no greater than 32°C, and it is valuable to quantify scrotal temperature using thermography after equilibration with the surrounding temperature and to *record it.* A significant varicocele may raise the temperature to 35°C, and contact thermography can be useful both in assessing the nature of a varicocele (unilateral or bilateral) and to evaluate the success of corrective surgery or embolisation. *Semen analysis must be performed according to WHO standards.* The volume, pH, fructose content, liquefaction time, concentration of spermatozoa, percentage of active spermatozoa, motility and progression should all be recorded. In addition, bacterial culture and assessment of antibiotic sensitivities should be per-

formed. Any positive cultures should be treated specifically. Electron microscopy of the semen sample may be used to distinguish pus cells due to prostatitis from abnormal sperm precursors, to identify microtubule abnormalities (e.g. absence of dynein arms) that may affect motility, and to detect the absence of an acrosome, in which case treatment using assisted reproductive technology (ART) is indicated.

A small-volume ejaculate, with acid pH and low fructose content, is characteristic of the absence of the vasa deferentia or seminal vesicles or of ejaculatory duct obstruction, all of which are diagnosed by transrectal ultrasound. Surgery is necessary to correct these defects.

Antisperm antibodies are most readily detected bound to the patient's own spermatozoa, using either the mixed antiglobulin reaction where sperm are mixed with sensitised red cells, or the immunobead (direct IB test) in which sperm are washed to remove unbound IgG in the seminal plasma. In addition the tray agglutination test (against donor spermatozoa) will give the antibody titre in the patient's serum and seminal plasma. If an antibody problem is suspected, the postcoital test (5 motile sperms or more per high-power field) is useful in confirming the ability of sperm to penetrate the cervical mucus.

Investigation of Hormonal Factors

The pituitary-gonadal axis supports normal spermatogenesis which provides negative feedback on follicle-stimulating hormone (FSH) whilst luteinising hormone secretion is controlled by circulating testosterone. *FSH levels should be interpreted in relation to the Johnson score (sperm count) and the size of the testicles.* For example, a grossly elevated FSH level in combination with azoospermia and small testes is diagnostic of an untreatable failure of spermatogenesis. In contrast, normal or slightly raised FSH levels with one or both testes of nearly normal size will require further investigation via scrotal exploration and testicular biopsy to assess spermatogenesis and exclude obstruction. Asymmetries of testicular function may result in oligozoospermia and raised FSH.

Table 1. The aetiologies of subfertility (% of couples)

Semen abnormality	35
Abnormality of female cycle	21
No known cause (a genetic cause may be suspected in most cases)	20
Tubal pathology	14
Severe semen abnormality (>1 million sperm/ml)	5
Disturbed sperm/cervix interaction	5

Hypopituitary hypogonadism, which is characterised by low FSH and small testes, is rare but generally responds well to gonadotrophin-releasing hormone replacement therapy. *Impotence with infertility requires full endocrinological investigation.* For example, low testosterone levels require detailed analysis of gonadotrophin levels whereas persistently raised prolactin levels in conjunction with relative impotence may indicate a pituitary tumour. As with all hormonal studies, *care must be taken to ensure that diurnal and other variations due to stress and drug therapy (e.g. phenothiazine) are excluded*. In addition, thyroid and adrenocortical hormone levels should also be checked if there is any clinical suspicion of abnormality.

Medical Treatment for Male Infertility

The term 'subfertility', defined as a failure to conceive within 12 months, is preferable to 'infertility' which implies an untreatable condition. Between 13 and 26% of couples in the Western world are subfertile, and 4–17% of these will be seeking medical help to conceive at any time. Despite all treatments, 3–4% of couples will remain childless.

A number of different causes of subfertility have been identified (table 1), but only 6% of subfertile men have a condition for which a specific treatment is available. *The challenge for the andrological urologist is to search for the treatable causes, to define prognostic factors and prevent couples going for premature ART.*

Conditions for which effective medical treatment is available include hypopituitary hypogonadism, hyperprolactinaemia and immunological male subfertility. Hypopituitary hypogonadism, which is rare, may have congenital (e.g. Kallmann's syndrome), iatrogenic or idiopathic causes. The treatment involves the administration of testosterone to initiate puberty, followed by pulsatile gonadotrophin-releasing hormone to promote spermatogenesis. Hyperprolactinaemia may be treated with bromocriptine, starting at 5 mg/day, with monitoring of the patient's prolactin and testosterone levels. It is important to exclude the presence of a prolactinoma in such patients, and this can be done with a CT scan of the sella turcica.

Double-blind studies of methylprednisolone for the treatment of immunological subfertility have provided no statistical evidence of improved pregnancy outcomes following steroid treatment [1]. *The use of pregnancy outcomes in such studies is important, since improved semen quality does not necessarily lead to a successful conception.* Cross-over studies comparing steroid treatment plus timed intercourse with intrauterine insemination plus ovarian hyperstimulation have shown the latter to be more effective [2]. Therefore, ART is the treatment of choice for immunological subfertility, especially as steroids at high doses may cause severe complications.

Empirical Medical Treatments

A number of empirical medical treatments, such as anti-oestrogens, pancreatic kallikrein, bromocriptine and continuous low-dose androgen therapy, have been employed in the treatment of male subfertility with varying levels of success. In a review of studies that have investigated the stimulation of Leydig cells by anti-oestrogens such as tamoxifen or clomiphene citrate, O'Donovan et al. [3] found that there were some non-significant beneficial effects of treatment on pregnancy and this treatment deserves wider assessment. *There is currently no convincing evidence to support the use of pancreatic kallikrein* to regulate sperm motility, migration and metabolism, and this treatment should be tested in better-quality studies. Empirical treatment with bromocriptine has been suggested in view of the inverse relationship between serum prolactin levels and sperm count. However, its effects have not been shown to be superior to those of placebo on either semen quality or pregnancy rates. Finally, *continuous low-dose androgen (testosterone) treatment is totally ineffective.* In general, empirical medical treatments represent an inefficient use of public health funds and may delay effective treatment. Their use needs to be investigated in properly controlled clinical trials with pregnancy as the outcome.

Treatment of Ejaculatory Dysfunction

Premature ejaculation has been shown in many studies to be the most common male sexual dysfunction, with an incidence varying from 4.8% in the Netherlands [4] to 40% in the USA [5, 6]. Management strategies include the application of genital desensitisers (e.g. 10% lidocaine), stop/start techniques during intercourse, the use of multiple condoms or repeated masturbation prior to coitus. *Serotonin re-uptake inhibitors, which increase serotonin levels in the midbrain, will increase the ejaculation latency time.* Several drugs, including fluoxetine (Prozac®) and paroxetine (Seroxat®), have been tested in well-randomised controlled trials. The tricyclic antidepressant clomipramine at a dose of 25 mg taken 12–24 h before coitus has also been found to considerably increase the ejaculatory latency time, although there is also some placebo effect [7].

Retrograde ejaculation is mostly encountered in young patients with neuropathy due to diabetes mellitus. Ultrasonography is useful to show the open bladder neck in such cases. Treatment with α-sympathomimetics to increase contractility of the bladder neck yields good results. For example, imipramine may be given in increasing doses (25–75 mg) with assessment of the results after 6 weeks. The patient may also be advised to ejaculate with a full bladder. In patients in whom such strategies fail, sperm may be retrieved from the optimised postejaculatory urine, following treatment of any urinary tract infection.

Ejaculatory dysfunction may be encountered as a side-effect of many drugs, such as antihypertensives and antipsychotics, which inhibit central arousal or alter the function of the bladder neck or accessory glands. The patient may be unaware of such effects and may also have a low-volume ejaculate. Changing the drug regimen usually improves both the quantity and quality of semen. *It is important, therefore, for the urologist to be aware of the co-morbidity of drugs, stress, disease and environment.*

Surgical Treatment for Obstructive Azoospermia and Ejaculatory Duct Obstruction

Obstruction of the seminal duct at any level due to congenital or acquired factors and which results in azoospermia requires careful evaluation and counselling of both partners before treatment with reconstructive microsurgery or sperm retrieval plus intracytoplasmic sperm injection (ICSI) or both methods at the same time. The choice of treatment depends on many different factors, the woman's age being the most important one. Generally, reconstructive surgery plus sperm cryopreservation as the first step followed, if necessary, by ICSI with cryopreserved sperm or ICSI with freshly retrieved sperm plus a second reconstructive procedure is recmmended to offer the greatest possibility of success.

Obstruction of the Epididymis

Seminal duct obstruction occurs most frequently at the level of the epididymis, and a variety of different causes have been identified, including congenital abnormalities (with or without the vas deferens – the cystic fibrosis gene is found in over 10% of these cases), inflammation (generally a local prostatic infection), association with respiratory disease (e.g. Young's syndrome), secondary to a more distal obstruction (e.g. vasectomy), iatrogenic (e.g. epididymal cystectomy), traumatic, neoplastic or secondary to cysts. *The majority of obstructions, however, are classified as idiopatic.*

Diagnosis of obstruction is based upon the observation of azoospermia in conjunction with a normal seminal volume and normal spermatogenesis as shown by testicular biopsy. This procedure should be performed by a single scrotal incision to allow observation of the head of the epididymis, which will be dilated. *Infection must be excluded before surgery to avoid re-obstruction of the anastomoses.* Transrectal ultrasonography may identify pathologies of the distal seminal duct that offer a poor prognosis following vasoepididymostomy.

Vasoepididymostomy

When performing a vasoepididymostomy, most microsurgeons now favour the end-to-side method of Thomas [8] and Wagenknecht et al. [9] (fig. 1) over the original end-to-end procedure described by Silber [10]. *The permeability of the vas deferens must be confirmed by injecting saline solution prior to opening the epididymal tube. Infrequently, it is possible to observe a more distal obstruction of the seminal duct.* The most distal part of the dilated epididymal tubule indicates the site for incision, and an avascular area of the tunica should be chosen if possible. *It is important to match the size of the incision to the lumen of the epididymis and the vas deferens.* The Silber classification is used to assess sperm motility in the emergent fluid in repeated samples. *Motile sperm are cryopreserved if possible* but, if no complete sperm are found, the tubule is opened more proximally. The anastomosis is made using 10-0 double-armed nylon sutures, which simplifies the procedure. It is important to release any tension in the vas deferens (fig. 2), and this may be provided by sutures between the epididymal tunica and the vas deferens muscular layer. A new invaginating technique using only two sutures appears to allow good control of the tubule [11]. Postsurgical semen analysis is continued for 1 year and, *if azoospermia persists, the cryopreserved sperm are used for ICSI without the need for further surgery.*

In the vasoepididymostomy series published, the permeability rates vary from 37 to 85% and the pregnancy rate between 13 and 42%. Good prognostic indicators for vasoepididymostomy are an acquired aetiology, a

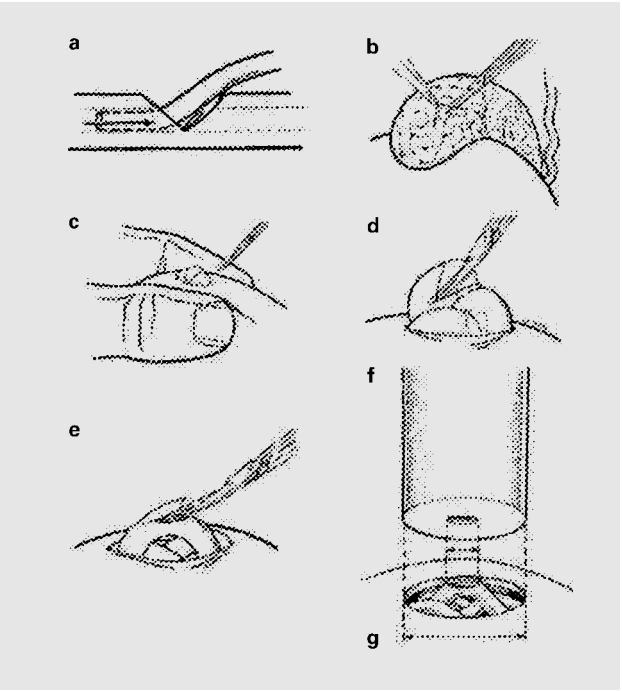

Fig. 1. The end-to-side technique for vasoepididymostomy of Thomas [8] and Wagenknecht et al. [9]. **a** Introduction of a No. 24 abbocat shield through the distal hemisectioned vas deferens. The injection of saline solution enables permeability of the distal vas deferens to be checked. **b** Circular opening of the epididymal tunic. **c** Compression of the epididymis between the thumb and the forefinger. **d** Section of the peritubular connective tissue. **e** Opening of the epididymal tube. **f** The diameters of the incisions in the epididymal tunic and tube must be similar to the diameters of the vas deferens and its lumen, respectively. Four 2.5-cm 10-0 nylon double-armed sutures are placed in the tubular wall approximately at 2, 5, 10- and 7-o'clock positions.

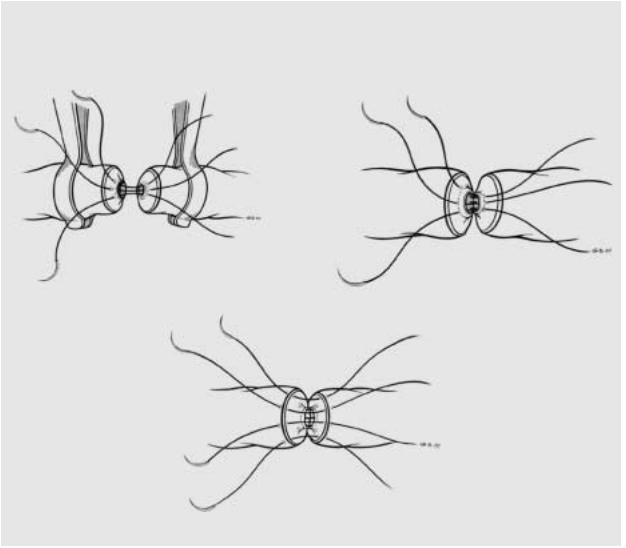

Fig. 2. a The cut end of the vas is brought without tension into opposition with the hole in the epididymal tunic and sutured in place with 3–5 sutures of 9-0 nylon. **b** The posterior tubular sutures are passed inside the posterior mucosal layer of the vas deferens. **c** The anterior tubular sutures are passed inside the anterior mucosal layer of the vas deferens. **d** Three to five sutures of 9-0 nylon are placed between the epididymal tunic and the anterior muscular layer of the vas deferens.

short duration of obstruction, distal obstruction, lack of antisperm antibodies and good surgical procedure. The prognosis is poorer for cases of idiopathic or congenital obstruction and those with infection or distal seminal duct abnormalities.

Obstruction of the Vas deferens

The vas deferens is infrequently obstructed, except by vasectomy, and diagnosis in iatrogenic cases (injury) and distal obstruction is via testicular biopsy and vasography to show the level of obstruction. Reconstructive surgery is almost impossible for distal obstructions; instead sperm retrieval from an implanted artificial spermatocele will permit repeated ICSI without further surgery. In cases of bilateral herniorraphy (complete or partial section of the seminal duct), it may be difficult to localise the distal end of the vas deferens and make an anastomosis, particularly where a segment is missing. Secondary epididymal obstructions often contribute further complications and worsen the prognosis.

Vasovasostomy

The recommended procedure for vasovasostomy is the two-layer anastomosis (fig. 3) performed under local anaesthesia. The obstructed segment of the vas deferens is removed and the distal permeability is checked by saline injection. *It is important to sample the fluid emerging*

from the proximal end for sperm motility as this information is valuable in postoperative assessment. The ends of the vas deferens are then approximated. Depending on the depth of the muscularis layer, a one- or two-layer anastomosis is indicated.

Azoospermia after surgery is infrequent and further vasovasostomy including cryopreservation of sperm is recommended if sperm were present during initial surgery, since this indicates a re-obstruction. Causal factors for re-obstruction include infection, irreversible epididymal dysfunction, strictured anastomoses or high sperm antibody levels.

The absence of sperm during the initial procedure could indicate the presence of a secondary epididymal obstruction, and this requires a vasoepididymostomy with sperm cryopreservation. The seminal fluid should be investigated for the presence of antisperm antibodies, which occur in the majority of these patients, but which may be treated.

Published results suggest success rates of between 75 and 99% for patency, and a pregnancy rate of 46–82%. *Even when no sperm are found during surgery, postoperative patency rates of 60% and pregnancy rates of 31% can occur following vasovasostomy* [12]. When the obstruction is secondary to an injury, vasovasostomy can be performed in only 30% of cases, and other techniques are required.

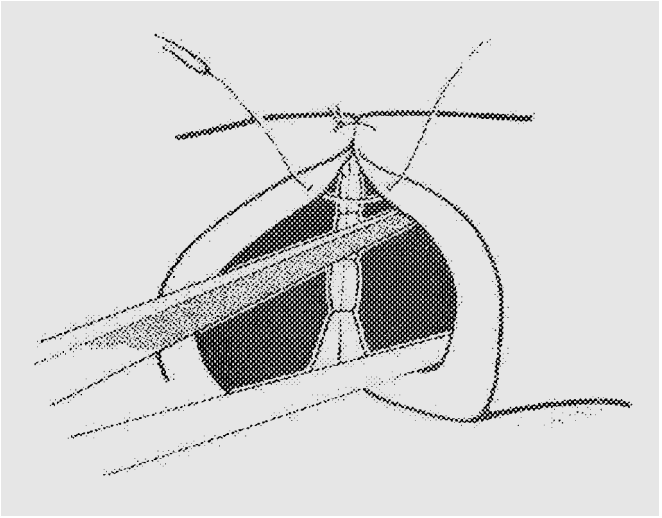

Fig. 3. Vasovasostomy in two layers allows good approximation and continuity of both lumens.

Ejaculatory Duct Obstruction

Ejaculatory duct obstruction is rare and specialist centres see only 2 or 3 cases per year. The causes are very variable, but diagnosis is based upon hypospermia, absence of fructose in the semen and a plapable vas deferens, and is confirmed by transrectal ultrasonography or vasography. It is important to collect sperm for cryopreservation during vasography because of the high incidence of re-obstruction following endoscopic surgery. Secondary epididymal obstruction is frequent, especially in congenital cases, and in these cases and where endoscopic surgery is not possible, sperm should be retrieved for ICSI from the most distal part of the system where their quality will be highest.

Endoscopic surgery is the treatment of choice and should be followed by methylene blue injection into the vas to confirm patency of the duct. Postoperative re-obstruction is indicated by hypospermia combined with azoospermia. If spermatozoa are present with hypospermia, then immediate cryopreservation is advised and intrauterine insemination is recommended. If secondary epididymal obstruction is suspected, the prognosis is poor and ART is indicated.

The Place of Sperm Retrieval, in vitro Fertilisation and ICSI with Notes on Genetic Screening

Although in vitro ferilisation (IVF) was first performed in 1978, it was not until 1983 that sperm retrieval procedures were introduced for men with no sperm in their ejaculate, and the first pregnancy fathered by a man with obstructive azoospermia was reported in 1984. Since then, ICSI has become available, making it possible for men who would otherwise remain infertile to father children. When

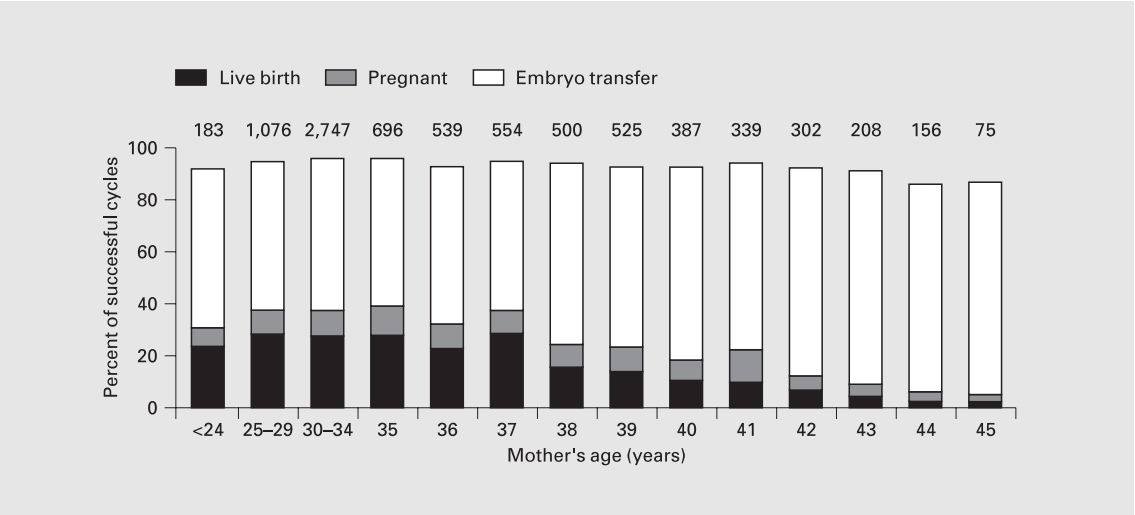

Fig. 4. The effect of aging on female fertility. Analysis of all IVF procedures at the Lister Hospital, London, 1988–1998.

deciding upon the most appropriate treatment for men with, for example, obstructive azoospermia, it is necessary to consider a number of factors including the likely success of reconstructive surgery as well as the age of the female partner, as a woman's fertility declines dramatically after 38 years of age (fig. 4).

Indications for Sperm Retrieval

Sperm retrieval may be indicated for a number of different conditions. It is used particularly in the management of men with obstructive azoospermia, especially in cases where reconstruction is not possible. Sperm may also be retrieved during reconstructive surgery in situations where it becomes apparent that a good outcome is unlikely, for example when the epididymis is scarred or fibrotic. Finally, *if the woman is older than 38 years of age, sperm may be retrieved during reconstructive surrgery for use in ART to increase the chances of pregnancy.* Sperm retrieval is also used in the management of men with testicular failure and azoospermia, and for men with ejaculatory failure.

Indications for IVF

Although some authorities recommend IVF for the management of couples in whom antisperm antibodies are the cause of infertility, *in couples where the woman is under 35 years it is preferable to treat the antisperm antibodies with increasing doses of methylprednisolone for 9 months before attempting IVF.* A multicentre, double-blind, cross-over study found that there was a pregnancy rate of 38% during treatment for antisperm antibodies, whereas there were no pregnancies during placebo treatment [13].

IVF is generally appropriate for use with sperm obtained from the vas deferens of men with ejaculatory failure, as such sperm usually have good motility and a high probability of achieving fertilisation. IVF should also be tried before ICSI in cases of unexplained infertility.

Indications for ICSI

ICSI has been the most important advance in the treatment of male factor infertility in the past decade. In contrast to the situation with standard IVF, in which approximately 50,000 sperms are introduced with each egg, ICSI requires only 1 sperm for each egg.

ICSI is indicated for couples where the sperm has been preserved, as frozen sperm is never as good as fresh sperm for standard IVF. ICSI is also indicated when no fertilised embryos have been produced as a result of standard IVF procedures. Finally, *ICSI is necessary in cases of azoospermia* where the sperm has had to be retrieved by a surgical procedure from either the epididymis (obstructive azoospermia due to conditions such as vasal aplasia, faild vasectomy or epididymal obstruction) or the testes.

The success rates with ICSI are good. A recent analysis of 1,783 cycles of treatment with ICSI performed at the Lister Hospital, London, between 1995 and 1999 found that there was a 30% pregnancy rate, while 23% of cycles resulted in live births.

Genetic Screening

It is well established that *the incidence of chromosome abnormalities is increased in men with defective spermatogenesis* [14]. It is essential, therefore, to warn the couple of the possibility that the children may be affected following a pregnancy resulting from ICSI. Nevertheless, in many cases the desire of the couple to have children is so strong that they choose to proceed with fertility treatment in spite of advice to the contrary from genetic counsellors.

The cystic fibrosis (CF) gene on chromosome 7 encodes the CF transmembrane conductance regulator gene. Men with congenital bilateral absence of the vas deferens have a 10% chance of being homozygous for CF and a 40% chance of being heterozygous. Many centres screen both partners for the CF gene, but it is only necessary to screen the man when the woman is known to be a carrier. In such cases, pre-implantation embryo biopsy should be considered.

Conclusions

Treatment of the infertile couple requires coordinated management of both the man and the woman, and effective teamwork by the gynaecologist and urologist is essential. The couple needs to be educated about the risks and likely success rates of the various treatment options, and it is important to recognise the key influence that the mother's age has on the chances of achieving a successful pregnancy. *The primary aim should be attempt to restore fertility rather than proceed immediately to ART.* Nevertheless, both IVF and ICSI ave an essential role to play in the management of infertility. Even men with Sertoli-cell-only syndrome may be able to father children with the assistance of ICSI.

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