Management of male infertility

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Introduction

Male factors account for 20 to 30% of cases of infertility. Significant advances have been achieved in the recent decade in the treatment of infertility due to male factor. The management of patients with male infertility will depend on whether a cause can be found. Careful history taking, physical examination and appropriate investigations may identify specific and treatable causes. Therefore, the male partner should always be assessed carefully to find out whether there is any specific cause for the male infertility in general, men should be advised to stop smoking, limit their alcohol drinking, to wear loose underwear or trousers, and to avoid occupational or social situations that might cause testicular hyperthermia (Royal College of Obstetricians and Gynaecologists,1998).

Medical Management

In men with hypogonadotrophic hypogonadism, injections of human chorionic gonadotrophin three times per week may be effective in stimulating spermatogenesis if the hypogonadism occurred after puberty. In men whose onset is before puberty, the combination of hCG with human menopausal gonadotrophin (hMG) 150 IU three times weekly) will usually be required (Finkel et al, 1985). The dose of hCG (usually 1000-2500 IU two to three times per week) should be adjusted to the testosterone concentration, which should not exceed normal values. If the hypogonadism is hypothalamic in origin, the use of pulsatile gonadotrophin releasing hormone (GnRH) may be even more effective but it requires administration by a minipump which needs to be carried continuously by the men and it is inconvenient.

Hyperprolactinaemia in men causes loss of libido and impotence. Bromocriptine is an effective form of therapy for men with sexual dysfunction due to hyperprolactinaemia (Bommer et al,1979). It reduces the serum level of prolactin and improves the sexual function.

The relationship between male genital tract infection and infertility is controversial. When present, the infection should be treated. Leucocytospermia by itself does not appear to be correlated with infertility. There is no evidence that treatment with antibiotics in men with leucocytospermia can improve their fertility (Erel et al,1997). Empirical use of antibiotics in men with male infertility has also been shown to be ineffective in improving the pregnancy rate in men with asthenozoospermia (Baker et al, 1984).

There is no scientific evidence that the empirical use of androgens, antioestrogens, bromocriptine and kinin-enhancing drugs are effective in the treatment of male infertility. The use of systemic steroids for treatment of antisperm antibodies is still controversial especially since their use may be associated with potentially serious side effects. Therefore, they can be recommended only in the context of clinical trials (RCOG 1998).

Surgical treatment

There are still a lot of controversies in the

management of male infertility associated with varicocele. A systematic review by RCOG(1998) of published studies suggested that the semen quality and pregnancy rates might improve in oligozoospermic men after treatment of a clinically apparent varicocele while treatment of a varicocele in infertile men with normozoospermia has not been shown to be beneficial.

Obstructive lesions in the male genital tract may benefit from surgical correction, which should be performed by properly trained and experienced surgeons in a centre with proper facilities. Since the surgical exploration would provide an opportunity for sperm retrieval, the surgery should be done in centres with facilities for sperm cryostorage.

Ovarian stimulation and intrauterine insemination

Intrauterine insemination (IUI) has been used for a long time for the management of male infertility. Kerin et al (1984) first demonstrated that IUI was effective in the treatment of male infertility but the results of other trials are less favourable (Ho et al 1989). With the use of ovarian stimultion, the results were better (Ho et al 1992). A recent review of the results of IUI (Cohlen 1998) showed that IUI significantly improved the probability of conception compared with timed intercourse with a combined odds ratio (COR) 2.5 and 95% confidence intervals (CI) 1.6-3.9. In IUI treatment cycles, the use of ovarian stimulation with gonadotrophins improved the chance of success when compared with natural cycles (COR 2.0 and 95% CI 1.1-3.8). The use of gonadotrophins was more effective than the use of clomiphene citrate. The success rate of IUI combined with ovarian stimulation depends on the quality of the semen (Ho et al,1992). Previously, IUI was usually performed with spermatozoa prepared by percoll discontinuos density- gradient centrifugation method. However, some batches of percoll have been found to contain high levels of endotoxin making them unsuitable for clinical use. We have recently shown that Isolate is a useful replacement for Percoll (Makkar et al, 1999).

Assisted reproduction

In- vitro fertilisation

In severe cases of male infertility, or when simple measures like IUI fail, the couple can be treated with assisted reproduction. The most commonly used method is in-vitro fertilisation and embryo transfer (IVF). In this method, the embryos are transferred into the uterus after fertilisation of the oocytes in-vitro. In gamete intrafallopian transfer (GIFT), the prepared sperms and the oocytes were transferred directly into the fallopian tubes immediately after the aspiration of the oocytes. Some centres have reported better pregnancy rates with GIFT when compared with IVF. However, in women who fail to conceive with GIFT, it is difficult to assess whether successful fertilisation has occurred. Moreover, GIFT requires the use of laparoscopy and often general anaesthesia while IVF can be performed under local anaesthesia without the use of laparoscopy. Another method is pronuclear stage tubal transfer. In this method, the oocytes are fertilised in vitro and the fertilised oocytes are transferred into the fallopian tubes at the pronuclear stage. This method usually requires general anaesthesia and laparoscopy. Therefore, for most centres, IVF is the preferred method.

Intracytoplasmic sperm injection (ICSI)

When fertilisation fails in IVF, or when the fertilisation rate in IVF is low, the couple can be treated with ICSI. In this procedure, a single sperm is injected with a mircopipette directly into each oocyte after oocyte retrieval. The fertilisation rate, embryo development and implantation rates are comparable to those of standard IVF (Bonduelle et al, 1999).

In some men with obstructive azoospermia, the obstruction may not be correctable with surgery e.g.

congenital absence of vas. In these men,sperms may be aspirated from the epididymis with microsurgical techniques. As the quantity and quality of sperms obtained are usually suboptimal, ICSI is required for assisted fertilisation. Recently Tournaye (1999) reviewed the different methods of aspiration of sperms: microsurgical epididymal sperm aspiration (MESA), percutaneous epididymal sperm aspiration (PESA), testicular sperm aspiration (TESA) and testicular sperm extraction(TESE). MESA is invasive, expensive and requires microsurgical correction. Therefore, it is the preferred method in men with incomplete workup. In PESA, the sperms are aspirated blindly from the epididymis under local or regional anaesthesia with a percutaneous puncture using a 19 gauge needle. It is quick, simple and can be performed as an outpatient procedure. The sperm recovery is comparable to that of MESA. However, sometimes the blind puncture may lead to inadvertent damage to epididymal structures and uncontrolled bleeding. TESA is performed with a biopsy gun or 19- or 21- gauge needle under local or regional anaesthesia. In men with obstructive azoospermia, it is effective in recovering sperms in 96% of cases. In TESA, the sperms are obtained by open excisional biopsy. In obstructive azoospermia, the sperm recovery rate is 100%.

In some men with testicular failure(non-obstructive azoospermia), sperms can also be obtained from the testis by TESE. Results are less favourable than those with obstructive azoospermia. The sperm recovery rate is only about 50% and the fertilisation rate after ICSI is also lower than in men with normal spermatogenesis. Testicular sperms can also be obtained from frozen thawed testicular tissue. This allows ovarian stimulation to be timed and avoids cancellation of ovum pick-up when spermatozoa cannot be retrieved.

Genetic aspects of male infertility and implications for treatment.

With advances in molecular biology techniques, new genes have been isolated from the Y chromosome (Yen 1999) and microdeletions in the Y- chromosomes have been reported in men with severe oligozoospermia or azoospermia. The incidence in different reports ranged from 3.5% to 55% with most series reporting 10-15% in men with azoospermia or severe oligozoospermia. Most of the microdeletions occur in three non- overlapping regions on the long arm of the Y chromosome: AZFa, AZFb and AZFc, the most common site for microdeletion being AZFc. Since these men were infertile, the genetic defects would not be transmitted to the next generation. However, with the development of ICSI, these men can now become fathers and the genetic defect can be transmitted to their sons. Infertile men should be counselled on these risks before offering the treatment of ICSI. When facilities are available, tests for the microdeletions of the Y-chromosomes should also be offered.

Outcome of pregnancies conceived with ICSI

ICSI is an apparently invasive procedure and there is a lot of concern on its safety especially to the resultant children. Follow up studies showed that the pregnancy outcome of singletons conceived after ICSI is similar to those of spontaneous conceptions and the increased risk of pregnancy complications is mainly related to the occurrence of multiple pregnancies (Tarlatzis and Grimbizis 1999). Most of the follow up studies of the children conceived after ICSI showed that the incidence of major congenital malformations was similar to that of the general population. However, there does appear to be a higher risk for transmission of chromosomal aberrations of paternal origin as well as a higher risk of de novo, mainly sex chromosomal aberrations (Tarlatzis and Grimbizis 1999; Bonduelle et al, 1999).

Artificial insemination by donor sperms

One of the options of treatment for men with severe abnormalities in the semen is insemination by donor sperms. The semen samples are obtained from healthy

donors with normal semen parameters. The donors are screened to exclude genetic and infectious diseases. The semen samples are frozen and stored in liquid nitrogen while waiting for the results of the screening tests. Some of these tests e.g. HIV antibody need to be repeated 6 months after donation to exclude the possibility of infections. The recipient will be inseminated with the semen samples on the days of ovulation estimated either by cervical mucus, basal body temperature charts or tests for luteinizing hormone surge. IUI may give a better pregnancy rate than intracervical insemination but it involved semen preparation and it makes the procedure more complicated and expensive. The use of ovarian stimulation may also give a better pregnancy rate but the woman may be at risk of ovarian hyperstimulation and multiple pregnancy (Cooke 1998). These procedures may be reserved for those who fail to conceive with the simpler methods. Since the treatment involves gametes from third parties, careful counselling of both the donors and the recipient couples is required.

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