Male subfertility: concepts in 1995

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Progress in male subfertility

A process of dispelling the myths

Until recently, male infertility has carried a poor prognosis for treatment, and the majority of couples with a significant male factor needed to consider donor insemination to achieve a pregnancy. In-vitro fertilization (IVF) raised the potential of generating embryos *in vitro*. However, although occasional pregnancies could be achieved after IVF and embryo transfer (Yovich and Stanger, 1984), the early techniques were found to be of limited benefit in males with severe oligozoospermia, asthenozoospermia, antispermatozoal antibodies in the semen or abnormal sperm morphology. It was found to be difficult to achieve fertilization, and the degree of difficulty was directly proportional to the severity of the semen disorder (Yovich *et al.*, 1985; Matson *et al.*, 1986) or the number of abnormal semen parameters. Consequently, pregnancy rates for IVF and embryo transfer remained low.

Subsequently, when the gamete intra-Fallopian transfer (GIFT) technique (Asch *et al.*, 1984) was introduced, new hopes were raised because the method was considered to have the benefit of being closer to the natural process of fertilization and would therefore be a more successful procedure for all non-tubal forms of infertility. However, GIFT proved to have major limitations for male factor infertility, but proved to be more effective than IVF and embryo transfer for many other categories of infertility (Yovich and Matson, 1990). A modified protocol (Matson *et al.*, 1987), involving the transfer of greater numbers of spermatozoa, enabled reasonable pregnancy rates to be achieved in cases of moderate oligozoospermia, but it was shown subsequently that the pregnancy wastage rate was higher (Rodriguez-Rigau *et al.*, 1989; Yovich *et al.*, 1989) possibly because of polyspermic fertilizations and the inability to control the quality of embryos available *in vivo*.

The problem of managing the male factor in IVF is made even more difficult because of diagnostic limitations, particularly with respect to the reliance on semen analysis, the complex and often multifactorial nature of infertility, the finding that some relatively 'normozoospermic' men fail to achieve IVF and the generally poor level of understanding of the aetiological nature of male infertility.

Significant improvements are now occurring as a result of determined efforts focused on understanding the limitations of the IVF procedures. This process has involved the reconsideration of virtually every aspect of sperm function and the fertilization process. Accordingly, many traditional 'myths' have been dispelled enabling useful and sometimes dramatic progress in managing male infertility. Examples of a more enlightened viewpoint include: (i) there is important information to be gained from the clinical examination of the male partner; (ii) where clinical assessment is undertaken, varicocoeles may be relevant, and it is also useful to biopsy the testes of azoospermic men who have raised follicle-stimulating hormone concentrations; (iii) semen analysis does not provide an accurate assessment of male fertility potential; (iv) morphologically abnormal spermatozoa are not necessarily genetically abnormal; (v) sperm–mucus interaction testing can be useful; (vi) the female partner still needs to be investigated even if the male is severely oligozoospermic or azoospermic; (vii) there is no clear 'bottom line' for sperm numbers to achieve fertilization *in vitro* (or even *in vivo* in the case of intrauterine insemination); (viii) spermatozoa, which can achieve normal fertilization when microinsemination is applied,

are not necessarily those that are motile, morphologically normal spermatozoa or 'mature', i.e. those spermatozoa collected more distal from the testes along the male genital tract; and (ix) azoospermia resulting from Klinefelter's or supposed Sertoli cell-only syndromes may now sometimes be offered treatment with the germ cells of the husband.

The road to 1995

Clinical andrology

Until recently, and despite constant appeals to the contrary, infertility treatment has often been undertaken by doctors who saw almost no value in direct consultation with the male partner, let alone conducting a physical examination. The male was represented by his semen analysis report. Occasionally, men whose semen analysis showed azoospermia or severe oligozoospermia were referred for further assessment by a urologist (Spark, 1988). The appraisal included a clinical assessment to check testicular volumes (comparative with Prader orchidometer), to identify dilatation and distension of the epididymides as a sign of distal obstruction, to detect the presence of varicocoele(s) and to undertake the palpation of the vasa and a rectal examination to determine the pathology of the seminal vesicles and prostate gland. Occasionally, Müllerian duct cysts may be detected clinically. Investigations included a chromosomal analysis to exclude Klinefelter's syndrome (considered untreatable), and serum gonadotrophin and testosterone estimations to detect hypogonadotrophic (treatable) and hypergonadotrophic states (reflecting spermatogenic failure; considered untreatable). Further investigations of men with normal testicular volumes included a scrotal exploration with vasography (for an evaluation of the distal genital structures and genital tract patency), along with a testicular biopsy for a histological evaluation. This could reveal a range of findings, from germinal aplasia (Sertoli cell-only syndrome), through maturational arrest to hypospermatogenesis, all conditions with largely unexplained causes, although maldescent of testes, specific infections, trauma (e.g. unrelieved haematomas from 'petrol tank slap' during motorcycle accidents), chemotherapy and irradiation are sometimes identified. Occasionally cystoscopic evaluations are useful to examine the ejaculatory ducts, prostate, prostatic utricles and seminal vesicle cysts. The identification of post-viral orchitis, or past infection through sexually transmitted disease, can often explain disturbances in semen quality by lesions left after inflammation.

More recently, the clinical examination of the male has been incorporated into the combined management of couples within dedicated clinics offering a comprehensive evaluation and treatment service [World Health Organization (WHO), 1993]. The prevalence of different male factor categories can be presented according to the treatment potential, and it is estimated that 12% of cases are untreatable and sterile, 13% are potentially treatable and 75% have untreatable subfertility (Baker, 1994). The comprehensive approach has evolved from the set-up required for IVF procedures, and may often incorporate an ultrasound assessment of the genito-urinary tract of the male (Martin, 1992). This has led to a more accurate volumetric assessment of the testes, greater specificity of varicocoele detection and grading by duplex or even triplex scanning systems incorporating colour Doppler, and the improved detection of intrapelvic features by intracavity scanning. The genetic basis for the subfertility of some individuals is now also being recognized (Chandley, 1995).

Laboratory investigations

The laboratory investigation of the male partner of an infertile couple has seen many advances over the years. Nevertheless, the real value of the laboratory tests in helping make an accurate diagnosis and prognosis is often not apparent. It is particularly disappointing to see basic and accepted tests being challenged constantly and found wanting, and so it might be more informative to examine here the reasons for this and to learn some salutary lessons, rather than simply cataloguing those tests which have become available, details of which are given elsewhere (Mortimer, 1994).

The purpose of the majority of tests applied to the man under investigation is to assess his potential fertility, and the most common test is semen analysis. While it is regarded as an important investigation, semen analysis has been shown recently to have limited value in predicting the chance of conception (Polansky and Lamb, 1988). An examination of the history and rationale of this test shows that the expectations placed upon it may be too demanding, as illustrated below.

Introduction and rationale

For any test of male fertility to be of value, it must have some firm biological basis and be able to

reasonably discriminate between nominally fertile and infertile groups. Unfortunately, semen analysis has been unable to satisfy this requirement with any degree of reliability. The examination of semen is a descriptive practice, enabling men with no spermatozoa present in their ejaculate to be identified. However, the value of the test as a predictor of fertility for men with spermatozoa in their semen has always been in doubt. Early attempts to develop a threshold of sperm concentration which demarcated the fertile and infertile men looked at respective populations and arrived at a figure of 60×10^6/ml as the lowest sperm concentration compatible with fertility (Macomber and Sanders, 1929). However, further analysis of a larger population showed that there was no difference in the frequency distribution of sperm counts between the fertile and infertile men except at concentrations $<20 \times 10^6$ spermatozoa/ml (Macleod and Gold, 1951); even then, 5% of fertile men had sperm concentrations below this value compared with 16% of infertile men. Nevertheless, a threshold of 20×10^6 spermatozoa/ml is commonly used as a limit of normality (WHO, 1992), even though Macleod (1971) concluded some 20 years later that there is 'good reason to believe that a reasonable chance of pregnancy is present at lower count levels if the wife has passed the usual tests and if the sperm motility is good'. The notion of the test being a good discriminator between fertile and infertile men was therefore flawed from the outset.

Variability in the result

For a test to be useful, some degree of reproducibility must be seen so that the repeat investigation of a patient will not give conflicting results. Technical variability has been addressed for semen analysis by the recommendation of standardized protocols (Eliasson, 1971; WHO, 1992) and internal quality control procedures (Mortimer *et al.*, 1986; Neuwinger *et al.*, 1990). Nevertheless, a large degree of inter-laboratory variation in the performance of semen analyses can be demonstrated with an external quality assessment programme (Matson, 1995). Biological variability can also compound the problem of test reproducibility, and this is clearly seen for semen analyses where samples from the same man can be oligozoospermic or normozoospermic on different occasions (Schwartz *et al.*, 1979; WHO, 1992). This then brings into question what the test can really be expected to achieve. It is apparent that it is only the ejaculate which is able to be assessed and therefore only a limited aspect of the potential of spermatozoa to successfully meet and fertilize an oocyte (Amann, 1989). Repeat tests are required to build up a composite picture of the man's overall fertility.

General principles

Being so far down the road in the development and application of numerous sophisticated tests in the investigation of male fertility, it seems trite to consider the reasons why the basic investigations have not satisfied our requirements. Yet it is important to identify these problems so that we can maximize the true potential of the newer tests and avoid making some elementary mistakes.

Any new test must have a definite rationale. However, we must be very clear about the particular aspect of male fertility which is being assessed so that unfair expectations of the test are not made. This may help with the establishment of a panel of tests which complement each other and assist in building an overall picture. Nevertheless, each test must satisfy the rigours required of any investigative technique before being applied in general clinical practice. This means that attention must be given to the validity of the test in terms of its reproducibility (by virtue of the technical variation in the laboratory and the biological variation between samples), its ability to successfully identify men with reduced fertility (but at the same time not having an unacceptably high rate of false identification) and its robustness to prove useful in the hands of different laboratories.

Available treatments

A standardized investigation of the couple (WHO, 1993) is now recommended. Unfortunately the past management of males in isolated urological consultations has been associated with very few successes. In fact, the separation of male and female partners, as found in many unenlightened clinics, has failed to recognize the multifactorial basis of most cases of infertility, and simply led to a delay in the comprehensive management of the couple. It also caused an often inaccurate focusing on one or other individual as 'causing' the infertility problem, with associated anguish and often withdrawal from considering further management when treatment trials of the male failed to achieve pregnancy or donor insemination was suggested. Of further interest, busy donor insemination clinics discovered that a significant portion of their referred cases required additional treatment of the female partner (e.g. ovarian stimu-

lation, pelvic surgery, intrauterine insemination preparations and even IVF or related procedures) to achieve pregnancy with high-grade donor spermatozoa (Chaffkin *et al.*, 1991).

In the evaluation of males for specific treatments, clinicians attempt to delineate whether the problem relates to genital tract obstruction or diminished sperm production. The former may sometimes be corrected by specific surgery (e.g. vasovasostomy and vasoepididymostomy, and preferably by microsurgical techniques and opening blocked ejaculatory ducts by transurethral resection). The question of varicocoele correction remains controversial (Hargreave, 1993), possibly because treatment trials have relied on clinical evaluations only, and conventional surgical techniques have high failure or recurrence rates. We would like to see data utilizing high-resolution duplex or triplex scanning with the laparoscopic resectioning of testicular veins performed within a dedicated infertility clinic setting to decide on the value of the procedure. The most effective treatment of sperm antibodies is still unclear. Nevertheless, the use of steroid therapy to help reduce the level of antibodies (Hendry *et al.*, 1990) or the stripping of antibodies from the spermatozoa (Grundy *et al.*, 1992) seem effective strategies. However, the removal of the ipsilateral testis in cases of unilateral non-correctable obstruction with high antisperm antibody levels (Hendry *et al.*, 1994) seems a controversial and drastic approach, and we feel it to be entirely unnecessary given the recent advances in IVF techniques.

A wide range of options have been described in the treatment of male subfertility (Baker, 1994). For non-obstructive cases, the gonadotrophin treatment of hypogonadotrophic hypogonadism is highly effective even when sperm concentrations achieved are low (Burris *et al.*, 1988), although there are few such cases. The majority of cases have unexplained (normogonadotrophic hypozoospermia) causes, and no treatment has withstood investigation within randomized controlled studies. Treatments have included gonadotrophin therapy by either follicle-stimulating hormone or luteinizing hormone alone or in combination (human menopausal gonadotrophin), androgen therapy, indomethacin, clomiphene and tamoxifen. In our experience with these treatments ranging over 20 years, only prolonged treatment by tamoxifen has seemingly produced a few cases of improved sperm profiles and function. Growth hormone has recently been suggested of potential benefit, but early unpublished results are not encouraging. The use of anti-oxidant vitamins (C and E) along with zinc is widely prescribed for theoretical reasons but is of unproved value.

Cases of hypergonadotrophic hypozoospermia have generally been regarded as beyond specific therapeutic consideration.

Achievements and challenges for 1995

As we approach the next century, it is worth reflecting on what has been achieved to date and identifying the challenges of tomorrow.

Investigation of the male partner

The clinical assessment of the male partner should become more extensive (Honig *et al.*, 1993), using revealing procedures such as ultrasound (Martin, 1992) and fine-needle biopsy of the testes (Mallidis and Baker, 1994). Such techniques are likely to play an increasing role in the assessment of men with azoospermia and severe oligozoospermia. In particular, the use of rectal ultrasound may well prove helpful in identifying the causes of treatable non-symptomatic deep pelvic infection (Purvis and Christiansen, 1993). Nevertheless, the extensive clinical evaluation of the moderately oligozoospermic or normozoospermic man is at present unlikely to reveal any underlying cause of subfertility in the majority of cases, and remains a constant challenge.

The laboratory role in the diagnosis of male subfertility is becoming clearly divided into that of service and research as experience and the availability of facilities increase. The provision of even the most fundamental of tests, such as semen analysis and sperm antibody detection, can now be performed using external quality assessment schemes to ensure the reliability of results (Matson, 1995). Attention to the relatively uninspiring, and often humbling, world of quality assurance is of prime importance at a time when laboratory accreditation and formal proficiency testing are becoming widespread. It is essential that a thorough evaluation of current and new diagnostic tests under routine conditions is performed before they are introduced into the clinical laboratory. At present, this is being undertaken with the acrosome reaction to ionophore challenge test in terms of quantifying the assay variability and biological variability (Calvo *et al.*, 1994; Troup *et al.*, 1994). It is hoped that promising tests such as the measure-

ment of sperm creatinine kinase (Huszar, 1994) will follow. The continued progress of laboratories engaged in high-quality meticulous research is important in the development of new diagnostic tests. However, the transition from a promising to a proven test is a step to be undertaken with great care and following rigorous scrutiny.

Treatment of male subfertility, 1995

Specialized sperm preparation techniques, particularly using pentoxifylline for enhancement, now enable many couples to be treated using their own gametes (Yovich, 1995). Intrauterine insemination treatment is usually sufficient for cases of moderate sperm disorder (Yovich and Matson, 1988), whilst severe cases will progress to IVF. Very severe cases will require additional microinsemination techniques to generate embryos (Cohen *et al.*, 1994). This is now also possible for azoospermic men, where spermatozoa can be collected from the epididymis (microsurgical epididymal sperm aspiration; Hirsh *et al.*, 1994) or testicular biopsy samples (Hirsh *et al.*, 1993). In fact, current developments indicate that small numbers of testicular spermatozoa can be collected from men with maturational arrest and even Klinefelter's syndrome, with high-quality embryos generated following intracytoplasmic sperm injection (Harari *et al.*, 1995). These results have even been achieved using cryopreserved testicular spermatozoa, immotile spermatozoa and also spermatids. Using these procedures, pregnancies can now been achieved in the female partners of hypergonadotrophic men, considered impossible until now.

Given these frontier developments in IVF and microinsemination procedures, we have now begun to change our work-up of the male where severe sperm disorders or azoospermia exist. Such cases still undergo conventional clinical work-up and investigations, as outlined previously. In addition, at scrotal exploration, epididymal and testicular sperm samples are teased into culture medium by the semenologist prior to fixing in Bouin's solution for histological evaluation. This process considerably enhances treatment options for the couple and provides a back-up situation for surgery in the event of a failure of anastomotic procedures. For those not interested in corrective surgery, testicular biopsy samples with spermatozoa recovery can be undertaken by simple needling under local anaesthesia. Whatever the recovery technique, such cryopreserved specimens can be utilized in IVF by microinsemination in an ordered schedule which does not rely on trying to undertake procedures on the husband and wife on the same day. Clearly these new developments extend the andrology side of infertility management extensively, creating a larger range of treatment options and reducing the demand for donor semen.

Future challenges

While we have come a long way in our ability to identify and treat subfertile couples with a male factor present, there is still much to learn. The papers presented in this supplement summarize the areas of interest and concern that will be the focus of our attention for the next few years. These include our basic understanding of spermatogenesis, the events which enable spermatozoa and oocytes to interact successfully, the short-term benefits and long-term limitations of new techniques such as intracytoplasmic sperm injection, the relative merits of different treatment strategies along with the choice of the most appropriate for individual patients, and possible ways of improving embryo quality and on-going pregnancy rates. Finally, we must not forget the other major benefit that will inevitably arise from our improved understanding of male reproductive physiology, namely that of male contraception.

References

Amann, R.P. (1989) Can the fertility potential of a seminal sample be predicted accurately? *J. Androl.*, **10,** 89–98.

Asch, R.H., Ellsworth, L.R., Balmaceda, J.P. and Wong, P.C. (1984) Pregnancy following translaparoscopic gamete intrafallopian transfer (GIFT). *Lancet*, **ii,** 1034.

Baker, H. (1994) Clinical male infertility. II. Critical evaluation of the prospects for therapy. *Reprod. Fertil. Dev.*, **6,** 9–12.

Burris, A.S., Clark, R.V., Vantman, D.J. and Sherins, R.J. (1988) A low sperm concentration does not preclude fertility in men with isolated hypogonadotropic hypogonadism after gonadotropin therapy. *Fertil. Steril.*, **50,** 343–347.

Calvo, L., Dennisonlagos, L., Banks, S.M. and Sherins, R.J. (1994) Characterization and frequency distribution of sperm acrosome reaction among normal and infertile men. *Hum. Reprod.*, **9,** 1875–1879.

Chaffkin, L., Nulsen, J., Luciano, A. and Metzger, D. (1991) A comparative analysis of cycle fecundity rates associated with combined human gonadotropin (hMG) and intrauterine insemination (IUI) versus hMG or IUI alone. *Fertil. Steril.*, **55,** 252–257.

Chandley, A.C. (1995). The genetic basis of male infertility. *Reprod. Med. Rev.*, **4**, 1–8.

Cohen, J., Schattman, G., Suzman, M., Adler, A., Alikani, M. and Rosenwaks, Z. (1994) Micromanipulating human gametes. *Reprod. Fertil. Dev.*, **6**, 69–83.

Eliasson, R. (1971) Standards for investigation of human semen. *Andrologie*, **3**, 49–64.

Grundy, C.E., Robinson, J., Guthrie, K.A., Gordon, A.G. and Hay, D.M. (1992). Establishment of pregnancy after removal of sperm antibodies *in vitro*. *Br. Med. J.*, **304**, 292–293.

Harari, O., Bourne, H., Baker, G., Gronow, M. and Johnston, L. (1995) High fertilization rate with intracytoplasmic sperm injection in mosaic Klinefelter's syndrome. *Fertil. Steril.*, **63**, 182–184.

Hargreave, T.B. (1993) Varicocele — a clinical enigma. *Br. J. Urol.*, **72**, 401–408.

Hendry, W.F., Hughes, L., Scammell, G., Pryor, J.P. and Hargreave, T.B. (1990) Comparison of prednisilone and placebo in subfertile men with antibodies to spermatozoa. *Lancet*, **335**, 85–88.

Hendry, W.F., Parslow, J.M., Parkinson, M.C. and Lowe, D.G. (1994) Unilateral testicular obstruction: orchidectomy or reconstruction. *Hum. Reprod.*, **9**, 463–470.

Hirsh, A., Montgomery, J., Mohan, P., Mills, C., Bekir, J. and Tan, S.-L. (1993) Fertilisation by testicular sperm with standard IVF techniques [Letter]. *Lancet*, **342**, 1237–1238.

Hirsh, A.V., Mills, C., Bekir, J., Dean, N., Yovich, J.L. and Tan, S.L. (1994) Factors influencing the outcome of in-vitro fertilization with epididymal spermatozoa in irreversible obstructive azoospermia. *Hum. Reprod.*, **9**, 1710–1716.

Honig, S.C., Thompson, S. and Lipshultz, L.I. (1993) Reassessment of male-factor infertility, including the varicocele, sperm penetration assay, semen analysis, and in-vitro fertilization. *Curr. Opin. Obstet. Gynecol.*, **5**, 245–251.

Huszar, G. (1994) The role of sperm creatine kinase in the assessment of male infertility. *Reprod. Med. Rev.*, **3**, 179–197.

Macleod, J. (1971) Human male infertility. *Obstet. Gynecol. Surv.*, **26**, 335–351.

Macleod, J. and Gold, R. (1951) Male factor in fertility and infertility: spermatozoon counts in 1000 men of known fertility and in 1000 cases of infertile marriage. *J. Urol.*, **66**, 436–449.

Macomber, D. and Sanders, M. (1929) The spermatozoa count: its value in the diagnosis, prognosis and treatment of sterility. *N. Engl. J. Med.*, **200**, 981–984.

Mallidis, C. and Baker, H.W.G. (1994) Fine needle tissue aspiration biopsy of the testis. *Fertil. Steril.*, **61**, 367–375.

Martin, B. (1992) *Atlas of Scrotal Ultrasound*. Springer-Verlag, Paris, France.

Matson, P. (1995) External quality assessment for semen analysis and sperm antibody detection: results of a pilot scheme. *Hum. Reprod.*, **10**, 620–625.

Matson, P.L., Turner, S.R., Yovich, J.M., Tuvik, A.I. and Yovich, J.L. (1986) Oligospermic infertility treated by in-vitro fertilization. *Aust. N.Z. J. Obstet. Gynaecol.*, **26**, 84–87.

Matson, P.L., Blackledge, D.G., Richardson, P.A., Turner, S.R., Yovich, J.M. and Yovich, J.L. (1987) The role of gamete intrafallopian transfer (GIFT) in oligospermic infertility. *Fertil. Steril.*, **48**, 608–612.

Mortimer, D. (1994) *Practical Laboratory Andrology*. Oxford University Press, New York, NY, USA.

Mortimer, D., Shu, M. and Tan, R. (1986) Standardisation and quality control of sperm concentration and sperm motility counts in semen analysis. *Hum. Reprod.*, **1**, 299–303.

Neuwinger, J., Behre, H. and Nieschlag, E. (1990) External quality control in the andrology laboratory and experimental multicenter trial. *Fertil. Steril.*, **54**, 308–314.

Polansky, F. and Lamb, E. (1988) Do the results of semen analysis predict future fertility? A survival analysis study. *Fertil. Steril.*, **49**, 1059–1065.

Purvis, K. and Christiansen, E. (1993) The role of pelvic organ inflammation in the etiology of sperm pathology. *Int. J. Fertil.*, **38**, 372–379.

Rodriguez-Rigau, L.J., Ayala, C., Grunert, G.M., Woodward, R.M., Lotze, E.C., Feste, J.R., Gibbons, W., Smith, K.D. and Steinberger, E. (1989) Relationships between the results of sperm analysis and GIFT. *J. Androl.*, **10**, 139–144.

Schwartz, D., Laplanche, A., Jouannet, P. and David, G. (1979) Within-subject variability of human semen in regard to sperm count, volume, total number of spermatozoa and length of abstinence. *J. Reprod. Fertil.*, **57**, 391–395.

Spark, R.F. (1988). *The Infertile Male: The Clinician's Guide to Diagnosis and Treatment*. Plenum Publishing, New York, NY, USA.

Troup, S.A., Lieberman, B.A. and Matson, P.L. (1994) The acrosome reaction to ionophore challenge test: assay reproducibility, effect of sexual abstinence and results for fertile men. *Hum. Reprod.*, **9**, 2079–2083.

World Health Organization (1992) *WHO Laboratory Manual for the Examination of Human Semen and Sperm–Cervical Mucus Interaction*. 3rd edn., Cambridge University Press, Cambridge, UK.

World Health Organization (1993) *WHO Manual for the Standardised Investigation and Diagnosis of the Infertile Couple*. Cambridge University Press, Cambridge, UK.

Yovich, J. (1995). Sperm preparation in assisted

conception. In Grudzinskas, J. and Yovich, J. (eds), *Gametes — the Spermatozoon.* Cambridge University Press, Cambridge, UK, pp. 268–281.

Yovich, J.L. and Matson, P.L. (1988) The treatment of infertility by the high intrauterine insemination of husband's washed spermatozoa. *Hum. Reprod.*, **3,** 939–943.

Yovich, J.L. and Matson, P.L. (1990) The influence of infertility aetiology on the outcome of in vitro fertilization (IVF) and gamete intrafallopian transfer (GIFT) treatments. *Int. J. Fertil.*, **35,** 26–33.

Yovich, J.L. and Stanger, J.D. (1984) The limitations of in vitro fertilization from males with severe oligospermia and abnormal sperm morphology. *J. In Vitro Fertil. Embryo Transf.*, **1,** 172–179.

Yovich, J.L., Stanger, J.D. and Yovich, J.M. (1985) Management of oligospermic infertility by in-vitro fertilization. *Ann. N.Y. Acad. Sci.*, **442,** 276–286.

Yovich, J.L., Edirisinghe, W.R., Yovich, J.M., Cummins, J.M. and Spittle, J.W. (1989) Dyspermiae and GIFT or PROST & TEST. In Capitanio, G.L., Asch, R.H., De Cecco, L. and Croce, S. (eds), *GIFT: From Basics to Clinics.* Raven Press, New York, NY, USA, pp. 411–424.