ELSEVIER

Contraception 72 (2005) 314–318

Contraception

Original research article

Treatment of male infertility

Aldo Isidori, Maurizio Latini, Francesco Romanelli*

Division of Andrology, Department of Medical Physiopathology, University of Rome "La Sapienza," Viale del Policlinico, 155-00161 Rome, Italy

Received 10 January 2005; revised 7 May 2005; accepted 24 May 2005

Abstract

Male factor infertility is a general term that describes a situation in which the inability to conceive is associated with an alteration identified in the male partner. This dysfunction may be associated with low sperm concentration (oligozoospermia), poor sperm motility (asthenozoospermia) or abnormal sperm morphology (teratozoospermia); however, generally, a disturbance of all these variables, oligoasthenoteratozoospermia, is mostly frequent in male subfertility.

For many andrological disorders, it is not possible to find a reasonable cause and various uncontrolled treatments have been applied to infertile men, often just on an empirical basis.

More recently, after the explosive development of modern assisted reproduction techniques (ARTs), feasible with a single spermatozoon [intracytoplasmic sperm injection (ICSI)], the treatment of male infertility has received new meaning and andrologists are no longer expected to achieve a quantitative increase in sperm number but are instead asked to improve the fertility potential of the single sperm cell in order to achieve better results in both in vitro fertilization and ICSI. Additional prospective studies are needed to better understand the possible role of therapy in ART candidate patients.

Keywords: ARTs; ICSI; male factor infertility; idiopathic infertility

1. Introduction

Subfertility is defined as failure to conceive after 1 year of unprotected regular sexual intercourse. For this reason, couples present to a physician to start a workup able to identify either partner's responsibility. Half of these couples will have a component of male factor infertility and almost 30% of infertilities will be caused solely by male factors [1].

Male infertility generally involves a status in which the incapacity to conceive is related to a modification present in the male partner. This alteration may be associated with low sperm production (oligozoospermia), poor sperm motility (asthenozoospermia) or abnormal sperm morphology (teratozoospermia); however, generally, a combination of these, oligoasthenoteratozoospermia (OAT), is considered to be the most common cause of male subfertility [2].

Semen analysis represents the initial test for evaluating male partner fertility; as a result of the information achieved, a consequent diagnostic protocol will follow to discover, where possible, the underlying cause of male subfertility [3].

Unfortunately, for a large number of andrological disorders, it is not possible to find an evident cause such that a great part of male infertility remains idiopathic. As a consequence, rational therapeutical approaches are still lacking and various uncontrolled treatments have been prescribed to infertile men with often questionable pathophysiological justification or merely just on an empirical basis [4].

However, if a treatable condition responsible of male factor infertility, such as hypogonadism, varicocele, infections, immunologic infertility, obstructions and cryptorchidism, is found, then it should be corrected using current medical and/or surgical therapies [5].

More recently, after the exponential growth of modern assisted reproduction techniques (ARTs), possible with a single spermatozoon [intracytoplasmic sperm injection (ICSI)], the treatment of male infertility has received a novel impulse. Actually, for candidate patients to undergo ARTs, andrologists are no longer requested to attain an increase in sperm concentration but are instead asked to improve fertility potential by the optimization of qualitative sperm parameters after their assessment through sperm function tests [6].

In this review, we will first discuss the known causes of male infertility describing the available specific therapies,

* Corresponding author.
E-mail address: francesco.romanelli@uniroma1.it (F. Romanelli).

0010-7824/$ – see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.contraception.2005.05.007

then the concept of idiopathic infertility and its nonspecific treatment will be addressed.

2. Known causes and specific therapies

Before considering any treatment, a correct diagnosis has to be established. Hence, the evaluation of subfertile men begins with a detailed history and physical examination. The history should identify the duration of attempted conception, intercourse timing and frequency, erectile function, ejaculation, lifestyle factors (alcohol, smoking, etc.) and any drug taken [7]. Other pertinent details include previous mumps orchitis, chemotherapy and/or radiation for cancer, cryptorchidism, previous reproductive tract infections, prior illnesses and any systemic disease.

Physical examination should seek any sign of hypogonadism (virilization, body proportions, gynecomastia, etc.); a careful genitourinary examination should be performed to evaluate testicular size and consistency, presence of masses and eventual penile pathology (hypospadias, etc.) and to identify the presence of the most common cause for male infertility — varicocele [8,9].

Varicocele is found in approximately 15% of the general male population, but the percentage rises to ~40% among men with infertility. Varicocele treatment remains controversial and there is no agreement as to the effectiveness of intervention on the improvement of the main seminal parameters (concentration, motility and morphology) [10–12]. According to World Health Organization guidelines, treatment of varicocele is recommended in men with abnormal semen parameters, with no other cause of infertility and who show normal testicular volume and a normal hormonal status whereas intervention is considered to be of minimal benefit in men with reduced testicular volume and increased values of follicle-stimulating hormone (FSH) [13].

The treatment modalities include sclerotherapy (retrograde or antegrade), embolization and open surgery, including microsurgical dissection. The choice of therapy is mainly influenced by each specialist's experience [14].

Although male subfertility is rarely caused by endocrine deficiency, the integrity of the hypothalamic-pituitary-gonadal (HPG) axis is necessary for normal reproduction. Abnormalities, at any level, of the hormonal secretions of the HPG axis have the potential for a negative impact on fertility in men, being responsible of androgen deficiency (male hypogonadism).

Male hypogonadism can be categorized as primary or hypergonadotropic and secondary or hypogonadotropic. In primary hypogonadism, the disorder is at the testicular level and can be consequent to congenital or acquired pathologies. In patients with primary hypogonadism, fertility is severely compromised ranging from severe oligozoospermia to azoospermia as occurs in the case of karyotype abnormalities such as that of the Klinefelter syndrome (47, XXY), which is considered to be the most common sex chromosome disorder. As a whole, these patients rarely achieve paternity through natural conception and the only treatment in the case of azoospermia is testicular sperm retrieval to be used in ICSI. Indeed, a focal spermatogenesis with mature cell production in localized seminiferous tubules may be found in those patients who show azoospermia; in particular, this may be the case of patients with the Klinefelter syndrome who do or do not have mosaicism (46, XY/47, XXY) or of patients with Y chromosome microdeletions. For such cases, available data have failed to identify clinically useful prognostic markers for successful sperm recovery and advanced knowledge poses ethical dilemmas about the risk for unbalanced chromosome complement transmission to offspring. In cases such as these and in every patient seeking help through ARTs, genetic counselling, including prenatal and preimplantation genetic diagnosis, should be offered [15].

Secondary hypogonadism can be congenital or acquired and is caused by a hypothalamic or pituitary disease. Endocrine deficiency leads to a lack of spermatogenesis and androgen production due to abnormal synthesis and/or release of gonadotropin-releasing hormone (GnRH) and subsequent reduced gonadotropin [FSH, luteinizing hormone (LH)] concentrations. Drug therapy is effective in achieving fertility and several approaches are available. In hypothalamic hypogonadism, in which the Kallmann syndrome is classified, pulsatile application of GnRH by means of a portable minipump most closely simulates normal physiology. The pump delivers a small bolus (~5–20 μg/pulse) of GnRH every 120 min with the consequent increase of gonadotropin secretion that stimulates gonadal steroid production and gamete maturation.

A valid alternative both for economic and compliance reasons is given by chorionic gonadotropin (hCG), purified from the urine of pregnancy women, and FSH (human menopausal gonadotropin), purified from the urine of menopausal women or as a recombinant form (r-FSH) that appears to be as effective as urinary FSH. In the near future, urinary hCG is also likely to be replaced by the recently available recombinant hCG or LH, for which studies in the treatment of infertile men are awaited.

Usually, treatment is initiated with hCG alone at a dosage of 2000–5000 IU/week, administered intramuscularly or subcutaneously, to which intramuscular or subcutaneous FSH, at a dosage of 450–525 IU/week, is added if no sperm has appeared after a period of at least 6 months [16–19]. The dosages of urinary and recombinant FSH are equivalent.

The combined treatment has to be continued until sperm appears in the ejaculate, and this may require treatment courses of at least 1 year.

Frequently, secondary hypogonadism is consequent to a pituitary adenoma interfering with gonadotropin release, either by way of direct compression or by hormonal secretions. In this regard, hyperprolactinemia, which is derived from a prolactin-secreting adenoma, interferes with the normal pulsatile release of GnRH with subsequent sexual dysfunction and infertility. Medical therapy with the dopaminergic agents bromocriptine and cabergoline,

radiation and surgery for larger lesions are considered effective treatments.

Another possible cause of male subfertility is represented by chronic genital tract inflammations and urogenital infections for which nonsteroidal anti-inflammatory substances in addition to specific antibiotic therapy are considered the treatments of choice [20–22], subsequent to microorganism identification whenever available. However, there is still a lack of concrete data with consistent evidence showing the inflammatory disease to have a negative influence on sperm quality and further studies are needed to define the effective relation of different forms of silent infection of male accessory glands and their therapies to infertility disorders.

Obstructive azoospermia can be described as the absence of both spermatozoa and spermatogenetic cells in semen because of a complete obstruction of seminal ducts. Once diagnosis has been performed (semen analysis, FSH values, biochemical markers of seminal ducts patency, genetic screening, spermatozoa search in urine after ejaculation, transrectal ultrasonography, vasography, etc.) [23,24], therapy consists of testicular sperm extraction (TESE) or microsurgical epididymal sperm aspiration (MESA), depending on the site of obstruction, to retrieve spermatozoa for immediate use in ICSI or cryopreservation [25,26].

Immunologic infertility, characterized by the presence of antisperm antibodies in the serum and/or in the seminal plasma, can be treated by corticosteroids as recommended by several authors [27,28]. Although no general agreement on this topic exists and corticosteroid treatment cannot always be recommended, current evidence indicates that it could be considered in patients with antisperm antibodies and previously failed fertilization in in vitro fertilization (IvF) or ICSI [28].

3. Idiopathic infertility and nonspecific therapies

For many patients with idiopathic OAT, use of several drugs [antiestrogens, aromatase inhibitors, androgens, r-FSH, pentoxyphylline, arginine, carnitine, glutathione, vitamins (A, C and E), oligominerals (zinc, selenium), etc.] has been attempted, although only rarely based on controlled studies, to achieve as well only a temporary improvement of impaired fertility that may allow the application of less-invasive methods of artificial fertilization such as intrauterine insemination instead of IvF or ICSI, using ejaculated spermatozoa instead of retrieved ones.

The rationale for administering antiestrogens such as tamoxifen and clomiphene is to indirectly stimulate the secretion of FSH and LH acting at the hypothalamic level where their competitive action with estrogens removes the negative feedback on GnRH secretion. This way, a stimulating effect on germ cell maturation and testosterone production can be achieved. Although some authors have questioned this type of approach, others have achieved good results but, as a whole, better selection criteria for antiestrogen treatment are needed [29,30].

Aromatase inhibitors block conversion of testosterone into estradiol and that of androstenedione into estrone; on this basis, aromatase inhibitors could be administered to patients with subnormal testosterone and high estradiol levels to increase testicular testosterone levels and stimulate spermatogenic activity [31]. However, no proven statistical effectiveness in the treatment of male infertility, especially concerning pregnancy rate and qualitative features of sperm, has been shown.

Several investigations have shown that pentoxyphylline can improve testicular microcirculation, sperm motility and sperm concentration. Such drug is used both in vitro during assisted fertilization techniques and in vivo. However, although its effectiveness has been confirmed in vitro, uncertain results have been shown in vivo and, as is the case of many other drugs used on empirical basis in idiopathic male infertility treatment, prospective studies based on suitable selection criteria are needed.

Many of the sperm alterations present in idiopathic infertility have recently been related to the presence of high levels of reactive oxygen species (ROS). Although ROS can be considered important mediators of normal sperm function (sperm hyperactivation, capacitation and acrosome reaction) [32,33], an increased production of ROS results in oxidative damage to cellular lipids, proteins and DNA [34]. Antioxidant treatment may reduce the oxidative damage and increase the fertilizing capacity of spermatozoa. Agents with antioxidative properties are tocopherol (vitamin E), ascorbic acid (vitamin C), acetylcysteine and glutathione. According to recent investigations, treatment with tocopherol has increased sperm motility and improved sperm functions (sperm–zona pellucida binding capacity) with consequent positive effects on the fertilization rates in IvF [35]. Glutathione can reach seminal plasma and concentrate there after systemic administration. After glutathione administration, increase in sperm concentration and improvement in sperm motility and morphology were shown in different studies [36,37]. Furthermore, a protective role on sperm motility was also shown when in vitro therapeutic effects of glutathione were evaluated.

Antagonizing the generation and effects of ROS by means of antioxidant therapies seems to be a promising approach; however, further controlled randomized trials are still needed to add further data to the available conflicting results. More recently, the effects of L-carnitine therapy in infertile patients were evaluated in a placebo-controlled, double-blind, crossover trial; the results obtained show a significant improvement in semen quality for sperm concentration and motility. However, these preliminary results need to be confirmed by larger clinical trials and in vitro studies [38].

If conventional treatment of male infertility does not lead to a pregnancy after a reasonable period or if the diagnostic measures show that no improvement of the impaired fertility status is possible, then measures of assisted reproduction should be considered.

ICSI is the ultimate treatment for male infertile patients, making fertilization possible with a single spermatozoon that can be even retrieved, in the case of extreme subfertility, from the epididymis (MESA) or the testis (TESE). However, the great potentiality offered by ARTs should not cancel the importance of clinical andrology but only modify the role of physicians, who are no longer asked to treat a probable unknown cause of male infertility but instead to improve the fertility potential of the single sperm cell in order to achieve better results in both IvF and ICSI. Hence, any medical treatment should be aimed at improving morphological and functional sperm parameters [39–42].

It is well known that FSH plays a major role in the spermatogenetic and spermiogenetic processes and several studies have evaluated the role of its administration in improving sperm morphology and fertilization rate in ARTs. Some evidence show that FSH treatment is able to improve sperm ultrastructure, to increase sperm DNA condensation, to improve spermatic function tests and to reduce sperm apoptosis with consequent increase in fertilization and pregnancy rates [43–45], but this approach is still controversial because studies showing a positive effect of FSH treatment on sperm parameters are few and have a small number of subjects. In this regard, the need for further well-controlled studies evaluating pregnancy outcomes is stressed.

In conclusion, modern ARTs have actually changed the approach to treating severely infertile patients, being able to overcome previously unsolvable situations; however, many questions are yet unanswered and the need of evidence-based data, coming from well-designed prospective studies, is stressed more than ever [46,47].

References

[1] Poland ML, Moghissi KS, Giblin PT, Ager JW, Olson JM. Variation of semen measures within normal men. Fertil Steril 1985;44: 396–400.

[2] Guzick DS, Overstreet JW, Factor-Litvak P, et al. Sperm morphology, motility, and concentration in fertile and infertile men. N Engl J Med 2001;345:1388–93.

[3] McLachlan RI, Baker HW, Clarke GN, et al. Semen analysis: its place in modern reproductive medical practice. Pathology 2003;35:25–33.

[4] Baker HW. Medical treatment for idiopathic male infertility: is it curative or palliative? Baillieres Clin Obstet Gynaecol 1997;11: 673–89.

[5] Liu PY, Handelsman DJ. The present and future state of hormonal treatment for male infertility. Hum Reprod Update 2003;9:9–23.

[6] Liu DY, Baker HW. Evaluation and assessment of semen for IVF/ICSI. Asian J Androl 2002;281–5.

[7] Petrelli G, Mantovani A. Environmental risk factors and male fertility and reproduction. Contraception 2002;65:297–300.

[8] Redmon JB, Carey P, Pryor JL. Varicocele: the most common cause of male factor infertility? Hum Reprod Update 2002;8:53–8.

[9] Fretz PC, Sandlow JI. Varicocele: current concepts in pathophysiology, diagnosis, and treatment. Urol Clin North Am 2002;29:921–37.

[10] De Kretser DM, Baker HW. Infertility in men: recent advances and continuing controversies. J Clin Endocrinol Metab 1999;84:3443–50.

[11] Nieschlag E, Hertle L, Fischedick A, Abshagen K, Behre HM. Update on treatment of varicocele: counselling as effective as occlusion of the vena spermatica. Hum Reprod 1998;13:2147–50.

[12] Evers JL, Collins JA. Assessment of efficacy of varicocele repair for male subfertility: a systematic review. Lancet 2003;361: 1849–52.

[13] Rowe PJ, Comhaire FH, Hargreave TB, et al. WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge (UK): Cambridge University Press; 2000.

[14] Weidner W, Colpi GM, Hargreave TB, et al. EAU guidelines on male infertility. Eur Urol 2002;42:313–22.

[15] Simpson JL, Lamb DJ. Genetic effects of intracytoplasmic sperm injection. Semin Reprod Med 2001;19:239–49.

[16] March MR, Isidori A. New frontiers in the treatment of male sterility. Contraception 2002;65:279–81.

[17] Romanelli F, Isidori A. Trattamento dell'infertilità maschile. In: Molinatti GM, Fontana D, editors. Andrologia. Fisiopatologia e clinica. Roma: Verduci Editore; 1997. p. 309–17.

[18] Conte D, Romanelli F, Isidori A. Treatment of male idiopathic sterility with gonadotropin. Minerva Endocrinol 1990;15:91–4.

[19] Isidori A, Conte D, Nordio M, et al. Medical treatment of oligozoospermia. In: Wong PC, editor. The fourth advanced course on clinical reproductive endocrinology & infertility. Hong Kong: Excerpta Medica; 1992. p. 15–9.

[20] Krieger JN. New sexually transmitted diseases treatment guidelines. J Urol 1995;154:209–13.

[21] Weidner W, Krause W, Ludwig M. Relevance of male accessory gland infection for subsequent fertility with special focus on prostatitis. Hum Reprod Update 1999;5:421–32.

[22] Haidl G. Management strategies for male factor infertility. Drugs 2002;62:1741–53.

[23] Layman LC. Genetic causes of human infertility. Endocrinol Metab Clin North Am 2003;32:549–72.

[24] Quinzii C, Castellani C. The cystic fibrosis transmembrane regulator gene and male infertility. J Endocrinol Invest 2000;23:684–9.

[25] Schwarzer JU, Fiedler K, Hertwig I, et al. Male factors determining the outcome of intracytoplasmic sperm injection with epididymal and testicular spermatozoa. Andrologia 2003;35:220–6.

[26] Levine LA, Dimitriou RJ, Fakouri B. Testicular and epididymal percutaneous sperm aspiration in men with either obstructive or nonobstructive azoospermia. Urology 2003;62:328–32.

[27] Lombardo F, Gandini L, Dondero F, Lenzi A. Antisperm immunity in natural and assisted reproduction. Hum Reprod Update 2001;7: 450–6.

[28] Shin D, Palermo GD, Goldstein M, Rosenwaks Z, Schlegel PN. Indications for corticosteroids prior to epididymal sperm retrieval. Int J Fertil Womens Med 1998;43:165–70.

[29] Dickey RP, Holtkamp DE. Development, pharmacology and clinical experience with clomiphene citrate. Hum Reprod Update 1996;2: 483–506.

[30] Adamopoulos DA, Nicopoulou S, Kapolla N, Karamertzanis M, Andreou E. The combination of testosterone undecanoate with tamoxifen citrate enhances the effects of each agent given independently on seminal parameters in men with idiopathic oligozoospermia. Fertil Steril 1997;67:756–62.

[31] Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. J Urol 2002;167:624–9.

[32] de Lamirande E, Gagnon C. Impact of reactive oxygen species on spermatozoa: a balancing act between beneficial and detrimental effects. Hum Reprod 1995;10(Suppl 1):15–21.

[33] Griveau JF, Renard P, Le Lannou D. Superoxide anion production by human spermatozoa as a part of the ionophore-induced acrosome reaction process. Int J Androl 1995;18:67–74.

[34] Alvarez JG, Storey BT. Assessment of cell damage caused by spontaneous lipid peroxidation in rabbit spermatozoa. Biol Reprod 1984;30:323–31.

[35] Geva E, Bartoov B, Zabludovsky N, Lessing JB, Lerner-Geva L, Amit A. The effect of antioxidant treatment on human spermatozoa and fertilization rate in an in vitro fertilization program. Fertil Steril 1996;66:430–4.

[36] Lenzi A, Gandini L, Lombardo F, Picardo M, et al. Polyunsaturated fatty acids of germ cell membranes, glutathione and glutathione-dependent enzyme — PHGPx: from basic to clinic. Contraception 2002;65:301–4.
[37] Lenzi A, Culasso F, Gandini L, Lombardo F, Dondero F. Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod 1993;8:1657–62.
[38] Lenzi A, Lombardo F, Sgro P, et al. Use of carnitine therapy in selected cases of male factor infertility: a double-blind crossover trial. Fertil Steril 2003;79:292–300.
[39] Oehninger S, Gosden RG. Should ICSI be the treatment of choice for all cases of in-vitro conception? No, not in light of the scientific data. Hum Reprod 2002;17:2237–42.
[40] Kruger TF, Coetzee K. The role of sperm morphology in assisted reproduction. Hum Reprod Update 1999;5:172–8.
[41] Cummins JM, Jequier AM. Treating male infertility needs more clinical andrology, not less. Hum Reprod 1994;9:1214–9.
[42] Baccetti B, Capitani S, Collodel G, Strehler E, Piomboni P. Recent advances in human sperm pathology. Contraception 2002;65:283–7.
[43] Acosta AA, Oehninger S, Ertunc H, Philput C. Possible role of pure human follicle-stimulating hormone in the treatment of severe male-factor infertility by assisted reproduction: preliminary report. Fertil Steril 1991;55:1150–6.
[44] Bartoov B, Eltes F, Lunenfeld E, Har-Even D, Lederman H, Lunenfeld B. Sperm quality of subfertile males before and after treatment with human follicle-stimulating hormone. Fertil Steril 1994; 61:727–34.
[45] Baccetti B, Strehler E, Capitani S, et al. The effect of follicle stimulating hormone therapy on human sperm structure (Notulae seminologicae 11). Hum Reprod 1997;12:1955–68.
[46] Jequier AM. Clinical andrology — still a major problem in the treatment of infertility. Hum Reprod 2004;19:1245–9.
[47] Brugh III VM, Lipshultz LI. Male factor infertility: evaluation and management. Med Clin North Am 2004;88:367–85.