Specific and Generalized Treatments of Male Infertility

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Abstract

Approximately, 10–15% of all couples have fertility problems, undergo fertility assessment, and seek treatment. Infertility is a common and complex disorder attributed to a number of etiological factors. Due to the complexity of this disorder, its diagnosis and treatment are not straightforward. There is no standardized drug available for the treatment of idiopathic infertility. Generally, medicinal therapy is recommended on the basis of actual or probable cause of infertility. Antiestrogen therapy is the most common treatment for idiopathic infertility. Besides this, vitamins and antioxidants are also prescribed as dietary supplements to improve the semen quality. However, assisted reproductive techniques can be used when medicinal therapy fails to restore fertility or initiate pregnancy. In this chapter, we have discussed specific and generalized therapies for the management of male infertility.

Keywords

Infertility treatment • Hormones and gonadotropins in male infertility Antiestrogens in male infertility • Antioxidants in male infertility

Key Points

- Due to highly complex nature of the disorder, there is no standardized form of male infertility treatment, which can be prescribed to most of the patients.
- Poor understanding of the etiology of male infertility is the prominent reason behind inadequate therapeutic measures available for treating it.

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- Specific treatment upon identification of the reason or generalized/empirical treatment in idiopathic cases is recommended to begin with.
- In many cases, vitamins and antioxidants are also prescribed as dietary supplements to improve the semen quality.
- Failure of the above treatments makes a case for assisted reproduction, and the patient may be advised to go for an appropriate method of ART.

24.1 Introduction

Approximately, 10–15% of all couples have fertility problems, undergo fertility assessment, and seek treatment. Infertility is a common and complex disorder attributed to a number of etiological factors. The list of etiological factors includes genetic (chromosomal abnormalities, classical and microdeletions), epigenetic (DNA methylation), environmental (exposure to hazardous chemicals), lifestyle, and nutritional (malnutrition) aspects (Oliva et al. 2001; Rajender et al. 2011; Bansal et al. 2016). Due to the complexity of this disorder, its diagnosis and treatment are not straightforward. Identification of an etiological factor would facilitate directed therapy with significant chances of success. The remaining cases are often prescribed empirical therapies, which are usually prescribed based on the theoretical concepts. Assisted reproductive techniques (ARTs) are recommended after the failure of initial treatment (Cocuzza and Agarwal 2007) and need a number of considerations.

In the case of male factor infertility, the main goal of management is to diagnose the causes of infertility and to provide appropriate medications to achieve improvements in semen parameters. After exploring all etiological factors, the cause of seminal abnormalities in 25% remains unknown (Greenberg et al. 1978). There is no standardized drug available for treatment of infertility of idiopathic infertility. A variety of non-specific medical treatments has been recommended to treat these patients. Some of these treatments have been effective in improvement in semen parameters, but none of them ensures improvements in pregnancy rates. Moreover, the efficacies of medical treatments are doubtful due to lesser number of studies being conducted on such therapies, inappropriate study designs, lack of the placebo/controls, and problems in patient's follow-up. Normally, empiric treatments last for more than 3–6 months to cover one spermatogenic cycle. In this chapter, we have discussed the current medical treatments available for male infertility.

24.2 Hormonal Treatments

Hypogonadotropic hypogonadism (HGH) or secondary hypogonadism is a clinical syndrome of undeveloped gonads due to either inadequate or absent hypothalamic GnRH secretion or less or no pituitary gonadotropin secretion. Pulsatile secretion of gonadotropin-releasing hormone (GnRH) by hypothalamic neurons is crucial for initiating the release of pituitary gonadotropins, secretion of sex steroids, pubertal development, and gametogenesis. HGH may be congenital (Kallmann syndrome,

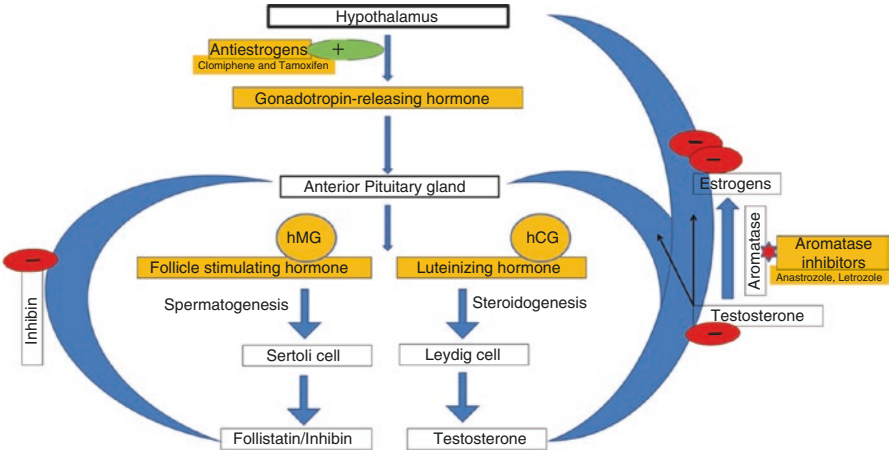

Fig. 24.1 Therapeutics and their targets for male infertility treatment

Prader-Willi syndrome), acquired (pituitary tumors, steroid abuse, panhypopituitarism, pituitary trauma, and testosterone replacement therapy), or functional (functional gonadotropin deficiency due to chronic systemic disease, malnutrition, acute illness, obesity, hyperprolactinemia). In Kallmann syndrome, this defect occurs at the level of hypothalamic GnRH secretion due to the malformation of the midline cranial structures (Cunningham and Lipshultz 1986). In HGH patients, testosterone therapy is given to the adult men to induce and maintain the secondary sexual characteristics and sexual function, but it does not restore fertility. When fertility is desired, gonadotropin therapy is given to induce spermatogenesis in HGH males (Ho and Tan 2013). Treatment protocols of gonadotropin therapy vary with the patient. In patients with acquired HGH, administration of exogenous GnRH or gonadotropins can restore normal spermatogenesis (Fig. 24.1).

24.2.1 Gonadotropin-Releasing Hormone (GnRH) Therapy

Gonadotropin-releasing hormone (GnRH) is secreted by hypothalamic neurons in a pulsatile manner and is transported to the anterior pituitary gland, which in turn secretes follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH control gonadal gametogenesis and steroidogenesis, respectively, in both sexes (Fink 1988). GnRH therapy has been used in the treatment of different reproductive endocrinopathies (Kiesel et al. 2002). Since GnRH has been discovered, many GnRH-I analogs have been made and studied broadly (Conn and Crowley 1994). Exogenous GnRH administration can increase the pituitary's production of FSH and LH and could potentially increase spermatogenesis. Badenoch et al. (1988) examined prolonged GnRH treatment in idiopathic OAT (oligoasthenoteratozoospermia) patients, but no effect was observed on either semen parameters or circulating gonadotropins.

Because GnRH is secreted in a pulsatile manner, a pulsatile GnRH therapy has also been tried using the portable mini-pumps. Pulsatile GnRH therapy has been effective in gonadotropin deficiency caused by hypothalamic or pituitary diseases (Mortimer et al. 1974; Crowley et al. 1985), but not in patients with loss of pituitary gonadotropin function (Wang et al. 1989). Moreover, GnRH therapy has been effective in restoring fertilization capacity in men undergoing the treatment of testicular tumors. In two different studies, men undergoing cisplatin and radiation therapy restored the fertility completely from germ cell damage when GnRH treatment was provided (Kreuser et al. 1990; Brennemann et al. 1994). However, the use of this therapy is restricted by the pituitary malfunction, formation of anti-GnRH antibodies (Lindner et al. 1981), the cumbersome wearing of the pulsatile pump, and high cost of the therapy.

24.2.2 Gonadotropins

The anterior pituitary gland produces and secretes two gonadotropins (FSH and LH), which stimulate spermatogenesis and steroidogenesis, respectively. hCG and hMG are also gonadotropins but are exogenous in nature. hCG is secreted by the chorionic cells of the placenta. It is analogous to LH and can stimulate the secretion of testosterone from the Leydig cells. hMG is extracted from the urine of postmenopausal women and has both FSH and LH activity. Generally, pituitary insufficiency is treated by hCG or hMG or urine FSH or recombinant human FSH (r-hFSH) alone or in combinations (Fig. 24.1). Treatment with gonadotropins has been very effective in the management of hypogonadotropic hypogonadism (HGH) (phenotypically hypogonadotropic oligozoospermia/azoospermia). Human chorionic gonadotropin (hCG), which contains LH-like activity, and human menopausal gonadotropin (hMG), which contains both FSH and LH activity, are used for replacement therapy in these patients. Normally, hCG, at the dose of 1500–3000 IU, is subcutaneously administered three times per week. However, in cases of congenital HGH, after 3 months of hCG therapy, FSH is administered intramuscularly at the dose of 37.5–75 IU three times/week. Semen parameters and testosterone levels are measured during the treatment. Normally, spermatozoa appear in ejaculate in 6–9 months, but can take much longer time. Once sperm concentration reaches to the satisfactory level, FSH administration can be stopped, and spermatogenesis may be maintained with hCG alone.

The significance of this therapy has been controversial in the treatment of normogonadotropic oligozoospermia (Siddiq and Sigman 2002). Moreover, the effects of this therapy on pregnancy rates/outcomes have been contradictory. Two randomized controlled trials have reported no improvement in pregnancy rates with either purified hMG (Matorras et al. 1997) or r-hFSH therapy (Kamischke et al. 1998), while one has shown positive outcomes after a post hoc analysis in a selected subpopulation (Matorras et al. 1997). The use of this therapy is limited by its expensiveness and the lack of studies showing its significance on pregnancy outcomes. Moreover, this therapy could not be prescribed to the men without demonstrable hormonal abnormalities.

In some patients, who do not respond to hCG/FSH combination therapy, GnRH therapy can be given. GnRH is administered intravenously or subcutaneously in a pulsatile fashion with a portable infusion pump. Pulsatile GnRH therapy depends on how well the anterior pituitary responds to exogenous GnRH. Pulsatile GnRH therapy is effective in gonadotropin deficiency caused by hypothalamic diseases (Mortimer et al. 1974), but not in the loss of pituitary gonadotropin function (Wang et al. 1989). GnRH therapy is also very effective in restoring fertility in men undergoing treatment for testicular tumors (Kreuser et al. 1990; Brennemann et al. 1994).

24.3 Inhibitors of Hormone Synthesis/Action

24.3.1 Antiestrogens

Antiestrogen therapy is a most common treatment for idiopathic infertility. Though estrogen is a female hormone, many studies have shown its role in male reproduction (Hess et al. 1997). Estrogen receptors are expressed on male germ cells, suggesting the importance of estrogens in spermatogenesis (Zondek 1934; Dorrington et al. 1978; Nitta et al. 1993; Carreau and Hess 2010). This hormone negatively regulates gonadotropin secretion (Finkelstein et al. 1991) and maintains the sexual behavior in adult males (Lauber et al. 1997). Antiestrogens work by blocking the estrogen and testosterone receptors in the hypothalamus, which increases the GnRH secretion, which in turn stimulates the secretion of FSH and LH from the anterior pituitary. The two commonly used antiestrogens are clomiphene and tamoxifen.

Clomiphene is a nonsteroidal drug, which has a structure similar to diethylstilbestrol (Fig. 24.1). Generally, clomiphene citrate is prescribed at a dose of 25 mg/day (doses range from 12.5 to 400 mg/day). The significance of clomiphene treatment on sperm count and pregnancy rates has been contradictory. Many randomized controlled studies on clomiphene citrate failed to show its efficacy over placebo (Foss et al. 1973; Paulson et al. 1977; Rönnberg 1980; Sokol et al. 1988). Only two studies have shown its positive effects on sperm count as well as on pregnancy rates (Wang et al. 1983; Check et al. 1988). Side effects of clomiphene treatment are mild and include headache, weight gain, nausea, change in libido, dizziness, allergic dermatitis, and gynecomastia. Moreover, regular monitoring of FSH, LH, and testosterone levels and frequent semen analysis are required in patients undergoing the clomiphene therapy because increased testosterone levels could negatively affect spermatogenesis (Gilbaugh and Lipshultz 1994).

Tamoxifen is also an antiestrogen and is commonly used for idiopathic male infertility treatment (Fig. 24.1). Tamoxifen citrate is prescribed at a dose of 10–30 mg orally per day. Recently, one study on infertile oligozoospermic men with different FSH levels revealed that tamoxifen citrate significantly increased the sperm count and concentration in men having lower FSH levels in comparison to those having higher FSH levels (Kadioglu 2009). Though uncontrolled studies have reported that tamoxifen citrate treatment increased sperm concentration/counts and pregnancy rates (Vermeulen and Comhaire 1978; Bartsch and Scheiber 1981; Buvat

et al. 1983), yet many controlled studies using tamoxifen citrate (at the dose of 10–20 mg/day) did not find such an association (Willis et al. 1977; AinMelk et al. 1987; Krause et al. 1992). Side effects of tamoxifen treatment are milder than clomiphene citrate because of its weaker estrogenic properties.

Antiestrogens are comparatively inexpensive and safe oral drugs for the treatment of idiopathic male infertility. However, the efficacy of this treatment is doubtful. Therefore, prolonged courses of this therapy should not be recommended.

24.3.2 Aromatase Inhibitors

In the testis, the Leydig and Sertoli cells have high aromatase activity (Inkster et al. 1995). Aromatase is an enzyme that converts circulating testosterone into estrogen in fat cells. Therefore, obese men might have an excessive conversion of testosterone into estrogen. Theoretically, changes in the ratios of estrogen and testosterone systemically or within the testes could manipulate pituitary levels of LH and FSH and impair sperm production (Kulin and Reiter 1972; Veldhuis et al. 1985). Aromatase inhibitors suppress the conversion of testosterone to estrogen and increase spermatogenesis (Ciaccio et al. 1978).

Aromatase inhibitors are expensive pharmaceutical agents that fall into two categories: steroidal (testolactone) and nonsteroidal (letrozole, anastrozole, and exemestane). Anastrozole are the fourth generation of aromatase inhibitors. They are highly potent as well as specific for the aromatase enzyme (Fig. 24.1). These drugs are safe and well tolerated. These drugs can be prescribed to men with idiopathic oligozoospermia with abnormal testosterone/estrogen ratio. During the treatment, patients are followed at regular intervals for serum testosterone, estrogen levels, and seminal parameters. Some studies have shown very impressive results with this treatment (Pavlovich et al. 2001; Raman and Schlegel 2002). Treatment with the aromatase inhibitor (testolactone at the dose of 50–100 mg twice daily) in infertile men with a low serum testosterone-to-estradiol ratio significantly increased sperm count and motility as well as corrected the hormonal abnormality (Pavlovich et al. 2001; Raman and Schlegel 2002). Similar changes were also observed when patients were treated with the more selective aromatase inhibitor, anastrozole, at the dose of 1 mg/day (Raman and Schlegel 2002). However, more numbers of placebo-controlled, randomized trials are required to assess the efficacy of aromatase inhibitors in idiopathic male infertility.

24.3.3 Hyperprolactinemia

Hyperprolactinemia is a condition of elevated serum prolactins, which results in HGH and infertility. Prolactin is a 198-amino acid protein (23kDa), which is secreted by lactotroph cells of the anterior pituitary gland. Normally, prolactin is present in both men and women in a small amount in their blood. Its main function is to enhance breast development in women during pregnancy and to induce

lactation after a baby is born. In men, prolactin regulates sperm production by controlling the secretion of GnRH. Normal fasting values of prolactin in men are less than 25 ng/mL. In hyperprolactinemia, elevated levels of prolactin inhibit the hypothalamic secretions of GnRH.

Hyperprolactinemia may occur due to pituitary tumors (micro- or macroadenomas), stress, hypothyroidism, medical illness, medications such as antidepressants and antihypertensives, and idiopathic factors. Pituitary micro- or macroadenomas are the most common causes of hyperprolactinemia. Generally, prolactin-secreting pituitary adenomas result in lowering of the gonadotropin and testosterone levels and elevation in prolactin levels. In macroadenomas, prolactin levels are high to greater than 250 ng/mL, while in microadenomas, the levels remain between 100 and 250 ng/mL.

In patients with hyperprolactinemia, pituitary MRI with gadolinium contrast is recommended to rule out a pituitary tumor. Prolactin levels are repeatedly checked many times in a day as prolactin levels vary throughout the day and with physical activity. In most of the patients with hyperprolactinemia or pituitary adenomas (especially microadenomas), medical therapy is the first line of treatment, but in macroadenomas where the condition is more serious, surgery may be recommended. In our body, prolactin levels are regulated by other hormones, called prolactin-inhibiting factors (PIFs), such as dopamine. Initially, in hyperprolactinemia, bromocriptine, a strong dopamine D_2 receptor agonist, is prescribed with doses ranging from 2.5 to 7.5 mg/day. Bromocriptine has been shown to significantly reduce the serum prolactin levels in oligozoospermic men with hyperprolactinemia and to increase the sperm count to a level sufficient for pregnancy initiation (Chuang and Howards 1998). In cases in which bromocriptine is not very effective and not well tolerated, a new long-lasting drug cabergoline is prescribed. Cabergoline shows fewer side effects and requires less frequent dosing than bromocriptine. Cabergoline is given at the dose of 1.0 mg/week. When prolactin levels get in normal range, the dose can be reduced to 0.5 mg/week (Verhelst et al. 1999).

24.4 Steroids and Antioxidants

24.4.1 Steroids for Anti-sperm Antibodies

Immunologic infertility is referred to as a condition in which anti-sperm antibodies (ASAs) are produced by the body as a response against sperm proteins. ASA may be present in serum and/or in seminal plasma or on the sperm surface. Normally, a man does not develop antibodies against his own spermatozoa because genital tract is a closed tube and is separated from the immune system. When blood cells and sperm come in contact, a male can produce antibodies against his own sperm. The presence of ASAs in the body fluids can block sperm-egg interactions via immobilizing and/or agglutinating the spermatozoa. They can also block the implantation and/or the development of embryo (Haas 1986; Koide et al. 2000). In all infertile couples with ASAs, IgG and IgA anti-sperm antibodies were found either on spermatozoa or in cervical mucus (Kremer et al. 1978).

ASAs have been found in a large number of infertile men and have been shown to compromise the male fertility (Rumke and Hellinga 1959). The most common causes of ASA include genital tract infections, surgical treatments such as testicular biopsy and vasectomy, testicular trauma, and testicular torsions (Broderick et al. 1989; Koide et al. 2000; Arap et al. 2007). In males, genital tract infections can weaken the blood-testis barrier (BTB), leading to the leakage of sperm and influx of immunologically competent cells. According to an estimate, 50–80% of men having undergone for vasectomy have circulating anti-sperm antibodies (Haas 1987). ASAs are one of the major causes of obstructive azoospermia associated with infertility after surgical treatments (Alexander and Anderson 1979; Linnet 1983; Mandelbaum et al. 1987). Moreover, ASAs are present in 80% of men having unilateral ductal obstruction (Hendry et al. 1986).

Generally, infertile men with ASAs are treated with oral corticoids to suppress the antibody production. However, no double-blinded, randomized trial has been done to confirm its efficacy till date. Prednisolone, a synthetic form of corticosteroid hormone, is the first line of the medical therapy. In a study, two men treated with 96 mg methylprednisolone per day for 7 days resulted in a slight decrease of the sperm-agglutination titer; however, no pregnancy was achieved (Kremer et al. 1978). In severe sperm autoimmunity, intracytoplasmic sperm injection (ICSI) may be a treatment of choice (Check et al. 2000). ICSI has shown no significant differences in clinical pregnancy rates (19% vs 12%) between ASA-positive and ASA-negative patient groups (Clarke et al. 1997). Recently, meta-analysis also revealed that semen ASAs are not related to the pregnancy rates after ICSI or IVF, indicating that both ART techniques can be used in infertile couples with semen ASAs (Zini et al. 2011).

24.4.2 Vitamins and Antioxidants

Elevated levels of ROS have been identified as an independent cause of male infertility (reviewed in Agarwal et al. 2006). In an estimate, increased levels of ROS in semen have been detected in 25–40% of infertile male patients (De Lamirande and Gagnon 1995; Padron et al. 1997). ROS can be beneficial or damaging depending upon the type and concentration of the ROS as well as length and location of the exposure to ROS (Agarwal and Saleh 2002). An excess amount of ROS can modify cell functions and increase cell death (Agarwal and Saleh 2002). Although ROS level in spermatozoa is controlled and maintained by the antioxidants present in seminal plasma, yet insufficient check on ROS could lead to oxidative stress, which in turn could be harmful to spermatozoa (Agarwal and Anandh Prabakaran 2005). Sperms are very susceptible to ROS because their plasma membrane has a large amount of polyunsaturated fatty acids (Alvarez and Storey 1995).

In most cases, damage induced by the ROS can be repaired. Seminal plasma has two different types of antioxidants to reduce the ROS level: enzymatic and nonenzymatic antioxidants. Enzymatic antioxidants include superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPX), and nonenzymatic antioxidants are vitamin E,

vitamin C, glutathione, pyruvate, and carnitine (Agarwal et al. 2004). In the treatment of infertility, antioxidants are often prescribed to idiopathic infertile men as a supplement to reduce the ROS level/oxidative stress. In a randomized, double-blinded controlled trial, asthenozoospermic patients were supplemented with oral vitamin E (300 mg/day). This treatment significantly decreased the malondialdehyde (MDA, a marker for lipid peroxidation) concentration and improved sperm motility (Suleiman et al. 1996). In another study, vitamin E and selenium supplementation significantly decreased the MDA concentration and improved sperm motility (Keskes-Ammar et al. 2003).

Vitamin C is a potent chain-breaking antioxidant and contributes up to 65% antioxidant capacity of the seminal plasma. Vitamin C concentration is ten times higher in seminal plasma than that in the blood plasma (Lewis et al. 1997). Fraga et al. (1991) reported that repletion of dietary vitamin C for 28 days (from 5 to 250 mg/day) doubled the vitamin C level in seminal plasma and reduced the 8-hydroxy-2′-deoxyguanosine (8-OHDG, a marker of oxidative stress) by 36%. This study indicated that dietary supplementation could be used to protect spermatozoa from endogenous oxidative damage. Some of the vitamins and their sources have been discussed in detail in Chap. 20.

24.5 Other Treatments

24.5.1 Genital Tract Infections

Genital tract infections account for about 15% of male infertility cases (Pellati et al. 2008). A number of microorganisms are involved in such infections. Some of them are *Streptococcus faecalis*, *Escherichia coli*, *Chlamydia trachomatis* (sexual transmission), *Ureaplasma urealyticum*, *Mycoplasma genitalium*, and *Mycoplasma hominis* (genital mycoplasma). According to one study, an overnight co-incubation of *M. hominis* with human spermatozoa showed small but statistically significant differences in sperm motility, morphology, and fertilization potential (Rose and Scott 1994). Moreover, *U. urealyticum* has been found to be associated with the generation of reactive oxygen species, even in the absence of leucocytospermia, and *M. genitalium* has been found to be attached to human spermatozoa (Taylor-Robinson 2002). Among viruses causing the infections in the genital tract are *herpesviruses (HSV)*, *human papilloma viruses (HPV)*, and *human immunodeficiency viruses (HIV).* The contribution of these infections to infertility has been discussed in detail in Chap. 12.

Once an infection of genital tract is identified, antibiotic therapy is given. In culture-negative patients, anti-inflammatory therapy can be prescribed. According to the presence of the microorganism, the following antibiotics can be prescribed: for *C. trachomatis* infection, azithromycin 1 g single dose orally or doxycycline 100 mg orally twice daily for 7 days can be given. For *N. gonorrhoeae* infection, ceftriaxone (125 mg intramuscularly single dose) or fluoroquinolones (ciprofloxacin 500 mg, ofloxacin 400 mg, levofloxacin 250 mg/day) can be prescribed. For *Mycoplasma*

spp., macrolides (erythromycin/roxithromycin) are usually given. These drugs are usually prescribed for 2–3 weeks, depending on the severity of the infections (Haidl and Schill 1991).

24.5.2 Disorders of Ejaculation

Ejaculatory dysfunctions in males include premature ejaculation (PE), delayed ejaculation (DE), anejaculation (AE), and retrograde ejaculation (RE). Except for PE, all other ejaculatory dysfunctions interfere with the delivery of sperms to the female genital tract and are important etiological factors for male subfertility. While PE and DE are common causes of sexual dissatisfaction in men and their partners, these disorders are not associated with male infertility (Barazani et al. 2012). On the other hand, men with RE and AE are not able to deliver sperm to the female genital tract and are subfertile. RE is referred to as a condition in which ejaculates flow abnormally backward and toward the bladder. RE is a common ejaculatory dysfunction but contributes to only 0.3–2% of male infertility (Vernon et al. 1988; Yavetz et al. 1994). The diagnosis of RE is made by the post-ejaculate urine test. In patients with low-volume ejaculates (<1.0 mL semen), the presence of sperm (>10–15/hpf) in urine indicates the etiology of RE. On the other hand, in patients with AE, the absence of sperms in the urine indicates the failure of emission.

Initially, pharmacologic therapy is recommended to the patients with RE. This therapy is only successful in patients who do not have bladder neck abnormalities (which are caused by the surgery done earlier for the treatment of other problems of genital tract, such as prostate surgery) and the problem of anejaculation. In treatment, alpha-adrenergic agonists such as ephedrine sulfate (25–50 mg q.i.d), pseudoephedrine (60 mg q.i.d), and imipramine (25 mg b.i.d) are prescribed. Moreover, medical therapy for ejaculatory dysfunction has to be synchronized with female's ovulatory cycles. This therapy is more effective if given at least 7–10 days before the ejaculation is planned. If medical therapy fails to recover the normal ejaculation, ART techniques can be used to achieve the pregnancy. In such situations, spermatozoa can be retrieved from the post-ejaculatory urine (Shangold et al. 1990); however, urine may damage the sperm by its acidity, contamination, and change in osmolarity (Crich and Jequier 1978).

24.5.3 Miscellaneous Treatment Regimens

Other non-hormonal treatments have also been used for the treatment of idiopathic male infertility. One of these treatments included L-carnitine, which is present in epididymal secretions. Approximately, 50% of total carnitine in human seminal plasma is found as acetyl-carnitine, which plays a major role in energy metabolism and sperm membrane stabilization. L-Carnitine is given as a nutritional supplement and is available over the counter. Carnitine also possesses antioxidant capacity that protects spermatozoa from oxidative stress/damage (Agarwal and Said 2004). However, studies

have shown no direct association between semen L-carnitine levels and fertility (Soufir et al. 1984). Uncontrolled studies have revealed improvements in semen parameters, but not in fertility rate (Costa et al. 1994; Vitali et al. 1995). Two randomized controlled trials using carnitine and acetyl-L-carnitine for idiopathic male infertility (Lenzi et al. 2003, 2004) reported statistically significant improvements in seminal parameters, but neither in carnitine levels in semen nor in pregnancy rates (Lenzi et al. 2003: 8%; Lenzi et al. 2004: 13%). There are little evidences on the effectiveness of carnitine treatment; therefore, more number of studies are required for validation of its efficacy.

Tamoxifen treatment has been prescribed either alone or in combination with kallikrein/testosterone. Tamoxifen has been effective in oligozoospermia while kallikrein in asthenozoospermia. In this context, the combination of these two should be useful in the treatment of oligoasthenozoospermia. Three studies using more than 84 oligoasthenozoospermic patients showed an increment in sperm count (Höbarth et al. 1990; Maier and Hienert 1990) and motility (Maier and Hienert 1990). However, these studies did not follow up the patients for pregnancy outcomes. Tamoxifen in combination with testosterone has been reported to be effective in men with idiopathic oligoasthenoteratozoospermia (OAT). Recently, one study using a combination of tamoxifen citrate and testosterone undecanoate has shown improvements in total sperm count, functional sperm count, and motility in men with OAT (Adamopoulos et al. 2003). Interestingly, they have also reported good pregnancy rates (Adamopoulos et al. 2003).

Conclusions

Selection of the therapy, whether specific or empirical, depends on the fertility status of infertile men. Once the etiology of the disorder is diagnosed, the treatment is provided accordingly. Generally, medicinal therapy is recommended for the treatment of idiopathic male infertility. However, ARTs can be used when medicinal therapy fails to restore fertility or initiate pregnancy. Empirical (nonspecific) therapy can be provided to patients when no specific etiology is identified. There are some side effects of these medicinal therapies; therefore, proper caution and regular checkups are required during the course of treatment. Nevertheless, prior to treatment, infertile couples should be informed about the inconsistency of therapy outcomes and low conception rates. If semen parameters do not improve significantly or a pregnancy is not achieved after at least two spermatogenic cycles, it is an indication to proceed with ART. Although few studies are available (even fewer studies have proper study designs) on the effectiveness of these therapies, more number of studies having better study designs are required.

In a large number of patients, the etiology remains unknown and treatment a challenge. Unfortunately, the number of such patients with male infertility is very high. Therefore, development of other therapeutic strategies is much needed. Inadequate treatment regimens for male infertility are in part due to poor understanding of the molecular cues to spermatogenesis and sperm fertility. Further research needs to focus on the identification of new molecular players critical to the process of

spermatogenesis. Identification of new molecular targets would open new avenues for drug development. Empirical therapies lack support by appropriately designed studies; nevertheless, it is not a bad idea to try these therapies in the cases where specific and targeted therapies are either not possible or fail to yield results.

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