Invited review

Medical and surgical treatment of male infertility

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Abstract

Although modern assisted reproduction techniques is helping to overcome severe male factor infertility, conventional treatment modalities are still the first approach to male fertility disorders. The critical step in treating male infertility is to evaluate properly every male partner of an infertile couple and to generate the suitable treatment strategy. Specific medical management of infertility is based on identifying reversible causes of infertility and treating them with appropriate medications to achieve a pregnancy. In addition, andrologists have an extensive arsenal of surgical options that are available including varicocele repair, reconstruction of obstructed reproductive system, or retrieve sperm for assisted reproduction. In the absence of a correctable etiology, patients can be managed with either empirical medical therapy or assisted reproduction. Although empiric medical therapy continues as a viable option, patients must understand that the success rates remain suboptimal.

Key words: male infertility, medical treatment, surgical treatment, oligospermia, drug therapy.

Introduction

Many different causes underlie male factor infertility and its treatment is difficult at best. The clinician first needs a thorough understanding of male reproductive anatomy and physiology. Most hormonal imbalances can be readily identified and successfully treated nonsurgically. However, the treatment of men with unexplained idiopathic infertility remains a challenge. Additionally, a large number of patients require surgery to improve sperm production or to improve sperm delivery. This article will discuss different aspects of medical as well as surgical management of male infertility. However, most of the recommendations are not based on controlled studies.

Specific medical treatment of male infertility

Specific medical management of infertility is based on identifying reversible causes of infertility and treating them with appropriate medications to achieve a pregnancy. While specific, treatable medical conditions comprise only a minority of causes of male subfertility, they represent an important subset because of our ability to potentially overcome their detrimental effects on reproduction.

In addition, medical therapy may describe the optimization of lifestyle factors potentially controllable by the patient. For instance, decreased

sperm density in smokers as compared with non-smokers has been demonstrated. Elevated serum prolactin and estradiol levels have been noted in smokers, and both have been proposed as a contributing cause for the subfertility noted in this population. Smoking also has been reported to exacerbate the effect of other causes of infertility, such as varicocele. Clearly, cessation of smoking is a simple specific step and enhances the fertility potential of the male patient [1].

Other lifestyle measures should include moderate alcohol consumption, healthy dietary habits, adequate exercising, as well as avoiding application of excessive heat to the testicles by discontinuing the use of saunas and hot tubs, and avoiding the use of common vaginal lubricants, which all may have spermatotoxic effects. If lubricants must be used, light vegetable oils, whole milk and egg whites are the least spermatotoxic.

Hypogonadotropic hypogonadism

Hypogonadotropic hypogonadism is the cause of infertility in a small percentage of patients and can be either congenital or acquired. One example of congenital hypogonadotropic hypogonadism is Kallmann syndrome, which is a malformation of the midline cranial structures [2]. In this syndrome, the defect is at the level of the hypothalamic secretion of gonadotropin-releasing hormone (GnRH) and may be associated with other congenital anomalies such as anosmia, deafness, cleft palate and renal anomalies. Other congenital forms include Prader-Willi syndrome and Laurence-Moon-Bardet-Biedl syndrome. Common causes of acquired hypogonadotropic hypogonadism include pituitary tumors, isolated gonadotropin deficiency, panhypopituitarism, pituitary trauma and anabolic steroid use.

Routine evaluation of patients should include a pituitary MRI to rule out a pituitary tumor [3], which can cause local destruction of the anterior pituitary. Serum prolactin level should be measured, and hyperprolactinemia must be ruled out and treated before starting gonadotropin replacement.

In patients with gonadotropin deficiency, normal spermatogenesis can usually be restored by treatment with exogenous gonadotropins or GnRH. Human chorionic gonadotropin (hCG) therapy, which contains LH-like activity, is the most commonly used treatment for economic and compliance reasons [4, 5]. Human chorionic gonadotropin initiates spermatogenesis but its completions is dependent on FSH administration. Human menopausal gonadotropin (hMG), which contains both follicle-stimulating hormone (FSH) and luteinizing hormone (LH), also has been used for replacement therapy in these patients.

Normally, subcutaneous administration of hCG at a dose of 1500-3000 IU three times per week [6] followed by intramuscular injections of FSH at a dose of 37.5 to75 IU three times per week after 3 months of hCG therapy [7] restores serum testosterone levels and normal spermatogenesis after 6 to 9 months of treatment [8]. Once sperm concentrations reach satisfactory levels, FSH can be suspended, and spermatogenesis may be maintained with hCG alone [9].

Treatment of hypogonadotropic hypogonadism with pulsatile GnRH analogs has been reported with similar success, but it cannot be used for acquired hypogonadotropic hypogonadism, since it requires an intact pituitary response. Normally, GnRH 5 at 20 mg/120 min is administered subcutaneously through an indwelling butterfly needle [10]. Intranasal GnRH can maintain previously induced spermatogenesis [11]. Crowley and Whitcomb reported that eight of nine patients desiring induction of fertility were able to father a child with the use of pulsatile GnRH therapy [12]. However, the high cost and the need for a 2-h dosing regimen makes this unfeasible to use as a first line therapy.

Hyperprolactinemia

Excessive production of prolactin inhibits the hypothalamic secretion of GnRH and disrupts LH binding to the Leydig cell in the testes, causing reproductive and sexual dysfunction. This condition may be caused by a pituitary tumor (macroadenoma or microadenoma), hypothyroidism, liver disease, stress or medications such as phenothiazines, tricyclic antidepressants and some antihypertensives. The most common causes of hyperprolactinemia are prolactin-secreting microadenomas (<10 mm) and prolactin-secreting macroadenomas (>10 mm) [13].

All patients with hyperprolactinemia should be evaluated with a pituitary MRI with gadolinium contrast to rule out a pituitary tumor. An elevation in peripheral prolactin should be followed with repeat testing because prolactin levels can vary widely throughout the day and with physical activity. Generally, in patients with prolactin-secreting pituitary adenomas, gonadotropin and testosterone levels are suppressed.

Although surgery and radiation therapy have been used in the past to treat patients with prolactin-secreting pituitary tumors, the vast majority of patients with idiopathic hyperprolactinemia or pituitary adenomas do not require surgery, and medical therapy is the initial treatment of choice [14]. However, patients with macroadenomas generally require surgical therapy.

Bromocriptine, a dopaminergic antagonist, can significantly reduce serum prolactin levels in oligospermic men with hyperprolactinemia and increase sperm counts to a level that may result in pregnancy [15]. Doses range from 2.5 to 7.5 mg per day and are given two to four times per day to

avoid gastrointestinal side effects. In most cases, the serum prolactin levels return to normal.

Cabergoline is a new long-acting dopamine agonist that is effective and well-tolerated in patients with pathological hyperprolactinemia. Cabergoline has been shown to be as effective as bromocriptine in lowering prolactin levels and reducing tumor size [16]. Moreover, cabergoline has the advantage of fewer side effects than bromocriptine and requires less frequent dosing. The median dose of cabergoline at the start of therapy is 1.0 mg/week, but once prolactin secretion is adequately controlled, the dose can be reduced to 0.5 mg/week, which further reduces therapy costs [16]. Normalization of prolactin level is achieved in 82% of treated patients [17]. Transsphenoidal surgery remains an option, especially for patients with microadenomas, when medical therapy is ineffective [14].

Isolated luteinizing hormone deficiency

Luteinizing hormone deficiency is often referred to as the "fertile eunuch syndrome", characterized by low serum testosterone, normal FSH levels, eunuchoid habitus, large testes, and small-volume ejaculates that may contain a few spermatozoa [18]. Treatment consists of intramuscular hCG therapy.

Isolated follicle-stimulating hormone deficiency

This disorder results in oligospermia or azoospermia, with normal virilization, LH and testosterone levels. Administration of hMG or FSH is adequate treatment [19].

Isolated testosterone deficiency

Rarely, hypogonadism may result from primary hypogonadism secondary to Leydig cell failure. Restoring the testosterone level to normal is possible with testosterone replacement and results in improvement of libido and sexual function. Unfortunately, the probablility of restoring normal spermatogenesis in these patients is low. Patients with a normal T/E2 ratio may respond to treatment with an estrogen receptor blocker or gonadotropin. In those with an abnormal T/E2 ratio, an aromatase inhibitor may enhance spermatogenesis [20].

Hypothyroidism

Hypothyroidism is responsible for 0.6% of male infertility cases [21], making this screening unnecessary during the patient work-up. Thyroxine replacement therapy generally restores fertility.

Congenital adrenal hyperplasia

The disorder is due to a deficiency in the enzyme 21-hydroxylase, resulting in decreased cortisol secretion and increased ACTH production. This in turn stimulates adrenal androgen production, inhibiting secretion of gonadotropins from the pituitary and suppressing spermatogenesis. Diagnosis in the normal, sexually mature male depends upon the demonstration of elevated levels of serum 17-hydroxyprogesterone and urinary pregnanetriol. Cortisol replacement reduces ACTH and androgen levels, stimulating gonadotropin release, testicular steroidogenesis and spermatogenesis [22].

Anabolic steroid abuse

Anabolic steroid use may induce hypogonadotropic hypogonadism by suppression of the hypothalamus and pituitary. The decreased gonadotropin activity results in a decrease in testosterone production by Leydig cells and a fall in intratesticular testosterone levels, acting as male contraceptives. In most cases, these abnormalities recover spontaneously without treatment when anabolic steroid use is discontinued. After discontinuation, the patient's pituitary and testicular function should be allowed to return to normal on their own. However, recovery of testicular function may take 3 months or more. For men who do not respond with adequate testosterone and spermatozoa production, replacement therapy with gonadotropins is indicated [23].

Immunologic infertility

An immunologic basis for some cases of infertility has been identified in a significant number of infertile men, suggesting that antisperm antibodies (ASA) may have a harmful effect on fertilization [24]. Immunologic infertility is characterized by the presence of antibodies against spermatozoa in the serum and/or in the seminal plasma or on the sperm surface. The presence of multiple ASA can lead to the immobilization and/or agglutination of spermatozoa, which blocks sperm-egg interaction. They can also prevent implantation and/or arrest embryo development [25, 26]. Common causes of ASA include previous genital tract infection, testicular biopsy, testicular trauma, testicular torsion and vasectomy [26-28].

The real significance of ASA in infertile men is controversial, and no standardized treatment regimens have been established [29]. Oral corticoids are commonly used to suppress antibody production, but to date, no double-blind, randomized trial has confirmed their efficacy. Studies following different protocols report pregnancy rates between 0 to 44% [30-33]. Studies in which treatment was continued for more than 3 months reported a significant increase in the number of pregnancies among those receiving prednisolone compared with placebo [34, 35]. However, a meta-analysis showed no significant improvement in pregnancy rates with prednisolone therapy [36].

Intracytoplasmic sperm injection (ICSI) is considered to be the treatment of choice for patients with severe sperm autoimmunity [37]. Clarke et al. showed no significant differences in fertilization rates (62 vs. 58%) or clinical pregnancy rates (19 vs. 12%) between sperm antibody-positive and sperm antibody-negative patient groups [38]. However, recently, higher fertilization rates in patients with antisperm antibodies were reported for *in vitro* fertilization (IVF) and immunosuppressive therapy compared with IVF alone [8, 39]. Thus, treatment of antisperm antibodies using corticosteroids should not be prescribed routinely, but it can be considered in patients with antisperm antibodies and earlier failed fertilization during IVF or ICSI.

Genital tract infection

The World Health Organization (WHO) defines leukocytospermia as a condition in which leukocyte levels are equal to or exceed 1×10^6/ml [40]. All men with elevated seminal white blood cell levels ($>1 \times 10^6$/ml) should be evaluated for a genital tract infection or inflammation, and a semen culture and a urethral swab for *Chlamydia*, *Ureaplasma* and *Mycoplasma* should be performed. Unexpectedly, approximately 80% of leukocytospermic samples are microbiologically negative [41, 42].

Most studies found that leukocytospermia is associated with decreased sperm motility and fertilization capacity [43-47]. Recent studies reported that even leukocyte counts below 1×10^6/ml were significantly correlated with production of seminal reactive oxygen species (ROS) as well as decreased sperm DNA integrity [48-51].

Testicular atrophy may occur following severe epididymo-orchitis with *Enterobacteriaceae*, *Chlamydia*, or *Neisseria gonorrhoeae*. Genital tract infections should be treated to prevent scarring to the seminiferous tubules and/or obstruction of the epididymis. Once the responsible microorganism has been identified, antibiotic therapy is initiated. However, culture-negative patients should be treated with anti-inflammatory therapy and frequent ejaculation because empiric antibiotic therapy generally provides no benefit and may be harmful [52, 53]. In cases of refractory leukocytospermia, sperm washing can be performed before intrauterine insemination (IUI) to remove the white cells.

Ejaculation disorders

The ejaculatory event is comprised of seminal emission and ejaculation. Seminal emission refers to the deposition of semen into the posterior urethra by contraction of the vasa deferentia and seminal vesicles. These events are mediated by the sympathetic nervous system *via* T10-L3 level preganglionic fibers. Ejaculation is the forceful expulsion of semen from the posterior urethra out the urethral meatus in an antegrade fashion. This event is secondary to the rhythmic contraction of periurethral and pelvic floor smooth muscle, mediated by parasympathetic (S2-S4) outflow and somatic efferents, and occurs in conjunction with closure of the bladder neck, which is sympathetically stimulated.

Retrograde ejaculation can be defined as the abnormal backward flow of semen into the bladder with ejaculation; the etiology may be anatomic, neurogenic, pharmacologic or idiopathic. Pharmacologic agents implicated in retrograde ejaculation include neuroleptics, tricyclic antidepressants, α-blockers used in the treatment of prostatism and certain antihypertensives [54-56]. The diagnosis of retrograde ejaculation is suspected in a patient with low or absent ejaculate volume and made by examining the post-ejaculate urine for sperm.

The strategy for treatment of retrograde ejaculation is the use of sympathomimetic agents orally to increase bladder neck tone. The agents commonly utilized include ephedrine sulfate (25 to 50 mg *q.i.d.*), pseudoephedrine (60 mg *q.i.d.*) and imipramine (25 mg *b.i.d.*). Medical therapy for ejaculatory dysfunction is administered on a cyclical basis timed to the female partner's ovulatory cycle. These medications are more effective if given for a period of at least 7 to 10 days before planned ejaculation, and tolerance may develop if they are administered continuously over several cycles. However, success is unlikely if no effect is observed within 2 weeks of treatment.

If medical therapy fails to restore normal ejaculation, spermatozoa may be retrieved from the post-ejaculatory urine before IUI [57]. Urine may damage spermatozoa because of its acidity, changes in osmolarity or contamination [58]. Several methods to circumvent these problems have been proposed, including neutralizing the urine pH with oral bicarbonate and hydrating the patient before sperm collection. Subsequent to ejaculation, urine is voided and processed for insemination. A more invasive method involves catheterizing the bladder with 30 cc of a buffered medium, which is discarded, and then instilling an additional 30 cc [59]. After ejaculation, the patient voids or is catheterized to retrieve the specimen. This procedure also is timed to coincide with ovulation in the female partner.

Anejaculation is a relatively uncommon condition that can occur as a result of spinal cord injury, retroperitoneal lymph node dissection, diabetes mellitus, transverse myelitis, multiple sclerosis or psychogenic disorders. If medical therapy with α-adrenergic agonists fails, anejaculation is treated with penile vibratory stimulation or rectal probe electroejaculation.

Reactive oxygen species and antioxidants

Spermatozoa generate a small quantity of ROS, which is necessary for normal physiologic cell function such as capacitation, hyperactivation, acrosome reaction and sperm-oocyte fusion [60, 61]. High ROS levels have been recognized as an independent marker of male factor infertility, irrespective of whether patients have normal or abnormal semen parameters [62]. Although the body employs a number of mechanisms to minimize ROS-induced damage, antioxidants in seminal plasma are the most important form of protection that sperm have against ROS insult [63]. These findings form the basis for the use of oral antioxidants as supplements to decrease oxidative stress and improve fertility.

The seminal plasma contains two different types of antioxidants to minimize free radical-induced damage: enzymatic and non-enzymatic antioxidants. The antioxidant protection mechanisms comprise three levels of defense: prevention, interception and repair. Avoidance of ROS formation is the first line of defense against an oxidative insult. As an example, the binding of metal ions, particularly iron and copper ions, prevents them from initiating a chain reaction [60]. Once transition metals become freely bound to ROS, they can generate more reactive oxidants, mainly OH^- [64]. Free radicals have a predisposition toward activating a chain reaction. The interruption of this reaction to avoid further injury is the process of deactivation, which leads to a non-radical end product formation [60]. Alpha-tocopherol, a chain-breaking antioxidant, restrains lipid peroxidation by scavenging peroxyl (RO^-) and alkoxyl (ROO^-) radicals. The capability of α-tocopherol to preserve a steady-state rate of peroxyl radical decline in the plasma membrane depends on the recycling of α-tocopherol by external reducing agents such as ascorbate or thiols. In this way, α-tocopherol is capable of functioning as a free radical chain-breaking antioxidant even if its concentration is low [65]. In most cases, free-radical induced damage can be repaired. However, spermatozoa plasma membranes contain large quantities of polyunsaturated fatty acids, and their cytoplasm contains low concentrations of scavenging enzymes. As a result, spermatozoa are unable to repair damage caused by excessive ROS [64-67]. The pathological levels of ROS detected in the semen of infertile men are more likely to be caused by increased ROS production than by reduced antioxidant capacity of the seminal plasma [61].

Current studies report the detection of increased ROS levels in the semen of approximately 30% of infertile men [68, 69]. Men classified as having idiopathic infertility usually present with higher seminal ROS levels and lower antioxidant properties than healthy controls [70]. Given the major role that oxidative stress plays in the pathogenesis of male infertility, reducing seminal oxidative stress levels is necessary for natural as well as assisted reproductive technologies [71]. Various clinical trials have demonstrated the beneficial effects of antioxidants in selected cases of male infertility [72-76], whereas others have failed to report similar benefits [77-79]. Pregnancy, the most relevant outcome parameter of fertility, was reported in only a few of these studies [75, 76, 80-82].

The majority of studies analyzed multiple antioxidant combinations, different doses and durations. Patient selection must also be considered in these studies since oxidative stress may not be the cause of male infertility in all selected patients. Recently, Agarwal et al., in an extensive review of the literature, concluded that the studies suffer from the lack of a placebo-controlled, double-blind design. Without such a study design, the effectiveness of antioxidant supplementation in infertile patients remains inconclusive [83].

Considering the etiology of infertility in various patients, antioxidants may not be effective [83]. Therapeutics directed against each specific etiological cause of elevated ROS should be attempted. Once the primary cause of infertility has been treated, or if no specific etiology can be identified, patients may be advised to take antioxidant supplements.

Nonspecific medical treatment of male infertility

Despite the advancements in diagnostic methodology, no identifiable cause can be found in 22.7% of infertile men [84]. These patients are treated with nonspecific medications in an attempt to improve semen parameters and subsequent fertility potential through intercourse. Empiric therapies also may be used for men with a known but otherwise untreatable cause of infertility, such as following surgery for cryptorchidism or torsion, as well as for certain instances of testicular failure. Additionally, empiric therapies may be tried for patients with identifiable and potentially treatable causes of subfertility who have failed to adequately respond to specific treatments.

Gonadotropin releasing hormone therapy

Exogenous GnRH administration can increase gonadotropin production and, potentially, spermatogenesis. GnRH seems to be a more physiologic agent for increasing the pituitary's production of FSH and LH, especially when it is administered in a pulsatile fashion in programmable, portable mini-pumps. Although GnRH therapy is effective in the treatment of patients with hypogonadotropic hypogonadism, two controlled studies failed to find efficacy of pulsatile

GnRH treatment for idiopathic oligo-asthenoteratozoospermia [85, 86]. Given the significant cost, inconvenience, and lack of efficacy, GnRH therapy is not recommended for the management of patients with idiopathic infertility.

Gonadotropins

The two gonadotropins, FSH and LH, stimulate spermatogenesis and steroidogenesis, respectively. Exogenous gonadotropin treatments include the use of hCG and hMG. Human chorionic gonadotropin is analogous to LH, and it stimulates the Leydig cell secretion of both testosterone and estradiol and inhibits FSH due to negative feedback. Human menopausal gonadotropin has both LH and FSH activity. The reason for gonadotropin administration in idiopathic oligozoospermia is based on observed efficacy in the treatment of HGH. However, their effectiveness for treating normogonadotropic oligospermia, either alone or in combination, is less clear [9].

A review by Schill of several uncontrolled studies of hMG and hCG indicated that patients with moderate oligozoospermia may have a much better response than men with sperm densities <10 million sperm/cc [87]. Nevertheless, the only available randomized double-blind, placebo-controlled, crossover study of hCG/hMG treatment of normogonadotropic men with idiopathic oligo-asthenoteratospermia failed to demonstrate any beneficial effect on semen parameters or pregnancy rates [88]. Although the treatment is safe, side effects include libido changes and acne. As with GnRH, these treatments are very expensive, and given the lack of convincing outcomes with controlled studies, this treatment is not routinely recommended in men without a demonstrable hormonal abnormality.

Recombinant FSH also has been used to treat idiopathic infertility. Acosta et al. demonstrated an increase in fertilization rates with IVF following treatment with pure FSH in men who had previously demonstrated poor fertilization rates, despite no actual change in semen analysis parameters [89]. Patients with oligoasthenoteratozoospermia treated with FSH for 12 weeks improved morphology and a higher percentage of integrity of subcellular organelles identified by electron microscopy [90]. Despite these results, once again a meta-analysis of studies using recombinant FSH showed no significant improvement on pregnancy rates [36].

Androgens

Men with idiopathic oligozoospermia may have subtle abnormalities of testosterone production or action that compromise androgenic activity and impair spermatogenesis but are undetectable using routine bioassays. Based on this theory, supplementary androgens have been used to treat idiopathic infertility despite the fact that androgen replacement suppresses spermatogenesis in the presence of an intact hypothalamic-pituitary-gonadal axis [9].

A WHO trial of mesterolone in men with idiopathic infertility failed to show any difference in pregnancy rates between the placebo group and the study group receiving either 75 or 150 mg [91]. Side effects include cholestatic jaundice, hepatic dysfunction and gynecomastia.

Testosterone rebound therapy

This therapy is based on the fact that high-dose exogenous testosterone suppresses gonadotropin secretion, resulting in a shutdown of the production of intratesticular testosterone and spermatogenesis. After withdrawal of therapy, spermatogenesis should resume within 4 months and the sperm count may be even higher.

A number of studies have described improvement in semen parameters and pregnancy rates following a course of large doses of parenterally administered testosterone [92, 93]. However, in the only placebo-controlled study to date, no pregnancies were initiated in the female partners of the 15 men after 6 months [94]. Furthermore, parenteral testosterone administration is associated with a 4-8% risk of persistent azoospermia or worsening of the semen parameters.

Anti-estrogens

Anti-estrogens are the most commonly used therapy for idiopathic infertility. The anti-estrogens indirectly stimulate the secretion of FSH and LH by blocking estrogen receptors in the hypothalamus and pituitary, which increases the release of GnRH. The major effect is stimulation of Leydig cells to produce testosterone and to facilitate sperm production. Two nonsteroidal anti-estrogens – clomiphene and tamoxifen – have been evaluated for empirical treatment of idiopathic male infertility.

Clomiphene citrate is a synthetic, nonsteroidal drug that is similar in structure to diethylstilbestrol. Although it has a mild estrogenic effect, it functions predominantly as an anti-estrogen. Clomiphene citrate is normally prescribed in a 25-mg daily oral dose. Men treated with clomiphene citrate consistently demonstrate an elevation in serum FSH, LH and testosterone levels. As a result, serum gonadotropins and testosterone must be monitored to ensure that the testosterone level remains within normal limits because higher levels may negatively influence spermatogenesis. In addition, patients should be cautioned that a small number of patients have suffered a deterioration in semen quality with anti-estrogen therapy. Therefore, frequent semen analysis is essential during

follow-up [3]. Side effects of clomiphene therapy are usually mild and occur in less than 5% of patients [9]. They include nausea, headache, weight gain, alterations in libido, visual field changes, dizziness, gynecomastia and allergic dermatitis.

Many well-designed prospective, randomized, controlled studies of clomiphene citrate failed to identify any efficacy over placebo [77, 95-98]. Only two studies revealed a positive effect on both sperm counts and pregnancy rates [94, 99]. However, a multi-center WHO study of 190 couples randomized to receive 25 mg clomiphene daily or placebo showed only an 8% pregnancy rate in the treatment arm [100].

Tamoxifen citrate is an antiestrogen that exhibits less estrogenic activity than clomiphene citrate and has been used in the treatment of male infertility. Doses range from 10 to 30 mg orally per day. Side effects are similar to those seen with clomiphene citrate but occur with lower frequency because of its weaker estrogenic properties. Although initial uncontrolled studies reported impressive results, including increased sperm densities and pregnancy rates [101-103], all controlled studies using tamoxifen 10 to 20 mg per day reported negative results [104-106].

Given the conflicting data in well-controlled studies, meta-analyses have been performed to resolve these differing conclusions. Kamischke and Nieschlag performed a meta-analysis of antiestrogen therapy (clomiphene and tamoxifen) that included randomized, placebo-controlled trials, and they concluded that treatment with anti-estrogens had no significant influence on pregnancy rates in the 459 patients analyzed (odds ratio 1.33, 95% confidence interval 0.78-2.28) [36]. More recently, a Cochrane database review assessed 10 studies involving 738 men with idiopathic infertility in which anti-estrogen therapy was administered for at least 3 months [107]. Only five trials specified the randomization protocol. In these studies, the overall analysis showed improved testosterone, but the pregnancy rate was no better than that of the controls.

Anti-estrogens are reasonably inexpensive and safe oral medications for the treatment for idiopathic male infertility, which explains their popularity. Nevertheless, their efficacy is in doubt, and prolonged courses of empirical anti-estrogen therapy should not be used as a substitute for more effective modes of management.

Aromatase inhibitors

The majority of estrogen production occurs within fat cells, where the enzyme aromatase converts circulating testosterone into estrogen. Hence, markedly obese men may have an excessive endogenous conversion of testosterone into estrogen. In theory, an alteration in the ratio of estrogen and testosterone systemically or within the testis could decrease pituitary levels of LH and FSH and impair sperm production [108, 109]. Aromatase inhibitors block the conversion of testosterone to estrogen, thereby enhancing spermatogenesis. Additionally, aromatase inhibitors block the inhibitory feedback of testosterone on the hypothalamic pituitary gonadal axis by reducing the amount of testosterone that is converted to the more potent inhibitory signal, estrogen. In the testis, aromatase activity is primarily located in the Leydig and Sertoli cells [110].

Aromatase inhibitors are relatively expensive pharmaceutical agents and may be steroidal (testolactoma) or nonsteroidal (anastrozole, letrozole and exemestane). Anastrazole represents the fourth generation of aromatase inhibitors. Although highly potent and specific for the aromatase enzyme, it differs from earlier steroid-based inhibitors in that it is less likely to exhibit agonist or antagonist steroidal properties. The drug is safe and well-tolerated and can be administered orally in men with idiopathic oligozoospermia. One indication for treatment is an abnormal T/E2 ratio. However, normal ratio ranges have not yet been standardized. Serum testosterone, estrogen concentrations and seminal parameters are followed at regular intervals. In addition, serum liver function tests should be performed because transaminase elevations are common but tend to resolve after therapy is stopped [9].

In older studies, treatment with testosterone aromatase inhibitors produced conflicting results [111]. Most recently, treatment of infertile men with a low serum T/E2 ratio using the aromatase inhibitor testolactone 50 to 100 mg twice daily significantly was shown to increase sperm count and motility and correct the hormonal abnormality [20, 112]. Similar changes were seen after treatment with the more selective aromatase inhibitor anastrozole 1 mg/day [20]. Aromatase inhibitors may be useful in a subpopulation of subfertile men, especially in those with subnormal testosterone and high estradiol levels. However, the T/E2 ratio remains to be defined in men with normogonadotropic idiopathic infertility. Placebo-controlled, randomized studies are still needed to assess definitively the effect of aromatase inhibitors in patients with idiopathic male infertility.

Growth hormone

Growth hormone (GH) is a pituitary hormone that is essential for normal pubertal testicular maturation. In GH-deficient states, onset of puberty is delayed and steroid production is reduced. GH is thought to stimulate the release of testicular insulin-like growth

factor-I (IGF-I), which contributes to normal spermatogenesis as an autocrine/paracrine growth factor. For the treatment of idiopathic oligozoospermia, GH is administered in doses of 2-6 IU/day, given subcutaneously. Side effects occur in up to 60% of patients and include paresthesia of the fingers, arthralgia, joint swellings, elevation in liver transaminases, increased serum creatinine and hemoglobin A_{1c}.

Carnitine

L-carnitine is a known component of epididymal secretions and is now available as an over-the-counter nutritional supplement for the treatment of idiopathic male infertility. In human seminal fluid, approximately 50% of total carnitine exists as acetyl-carnitine. The compound plays a critical role in intracellular energy metabolism as well as spermatozoa membrane stabilization. Carnitine also has an antioxidant capacity, and it protects sperm from oxidative damage [113]. However, studies have not shown a direct relationship between semen L-carnitine levels and fertility or that orally administered carnitine increases levels within the epididymis [114]. Uncontrolled studies demonstrate improvement in semen parameters but not fertility [115, 116]. Two recent randomized, controlled trials of carnitine and acetyl carnitine for idiopathic infertility [82, 117] reported statistically significant improvements in seminal parameters, but they have certain drawbacks. Carnitine levels in semen did not change despite therapy. Reported pregnancy rates were only 8% [82] and 13% [117]. Although improvements in the motile sperm count were statistically significant, they may not be clinically relevant as it was only 9 million per ml in the treated group and 7.4 million per ml in the controls. At this time, there is little evidence that carnitine therapy has any clinical benefit. Thus, the use of carnitine supplementation in idiopathic male infertility remains questionable.

Kallikrein

Kallikrein is a polypeptide enzyme, found in a variety of tissues and serum that will cleave kininogen to produce kinins, such as bradykinin and kallidin. These polypeptides act locally in the inflammatory response and are closely related to the coagulation and fibrinolysis systems. The kallikrein-kinin system has been shown to play a role in the regulation and stimulation of sperm motility [118]. The most common used regimen is an oral dose of 600 IU daily.

Pentoxifylline

Pentoxifylline is a phosphodiestarese inhibitor, and its initial use in male infertility was based on the possibility of improved testicular microcirculation. Pentoxifylline also inhibits the breakdown of cyclic adenosine monophosphate (cAMP) increasing ATP production, which in turn, could result in increased sperm motility. Oral pentoxifylline is administered in doses of 400 mg 3 times daily.

Surgical treatment of male infertility

In the past, surgical procedures for the infertile male were considered by many urologists to fall into two categories: diagnostic and therapeutic. With the advent of testicular sperm extraction (TESE) and ICSI, little remains in the diagnostic category except perhaps vasography, which is incorporated into treatment as a part of the surgical correction for obstruction.

A testis biopsy still may be defined as diagnostic, although it is probably best used as a prognostic tool to determine the chance of successful reconstruction for men with obstruction or to define for a couple the probability of being able to perform surgical sperm retrieval in cases of non-obstructive azoospermia.

Varicocelectomy

A varicocele is defined as a dilatation of the pampiniform venous plexous that surrounds the testis. The surgical correction of a varicocele, known as varicocelectomy, is the most commonly performed operation for the treatment of male infertility worldwide. Varicoceles have been found in 15% of the normal male population and in up to 40% of patients with male infertility [119]. Additionally, varicocele is an underlying cause of secondary infertility in 70% of patients [120].

The precise pathophysiologic mechanism as to how a varicocele affects the sperm quality of some men is yet unknown. The prevailing theory is that poor venous drainage leads to disruption of the counter-current exchange of heat from the spermatic cord, which elevates scrotal temperatures. The elevated scrotal temperature leads to impaired spermatogenesis. Thus, a unilateral varicocele may have effects on both testicles [121, 122]. Increased scrotal temperatures have been shown to result in decreased testosterone synthesis by Leydig cells, injury to germinal thermolabile cell membranes, decreased protein biosynthesis, decreased amino acid transport, and altered Sertoli cell function and morphology [123-125].

Impaired spermatogenesis in varicocele patients also is associated with oxygen deprivation, poor

venous drainage that leads to impaired drainage of gonadotoxins from the testis and increased oxidant level in semen. Studies in subfertile men with varicocele demonstrate the existence of an excessive release of nitric oxide within dilated spermatic veins that might be responsible for spermatozoa dysfunction [126]. Seminal ROS levels show a positive correlation with varicocele grade. Men with varicocele grade 2 and 3 have significantly higher seminal ROS levels compared with men with varicocele grade 1 [127]. A recent meta-analysis reported that oxidative stress parameters (such as ROS and lipid peroxidation) are significantly increased and antioxidant concentrations significantly decreased in varicocele patients as compared with normal sperm donors [128].

Varicocelectomy should be offered to the male partner of an infertile couple in the following situations: (1) the female partner has normal fertility or a potentially correctable cause of infertility; (2) the couple has documented infertility; (3) the man has clinical varicoceles; and (4) the male partner has one of more abnormal semen parameters or sperm function test results [129].

A variety of techniques have been described to perform varicocelectomy. They include the use of open surgery through a retroperitoneal, inguinal or subinguinal incision, laparoscopic clipping and percutaneous embolization. The most common complications after a varicocele repair are the hydrocele formation, varicocele recurrence and testicular artery damage. The complication rates after varicocele repair have declined substantially after the introduction of the microscope and intraoperative Doppler [130-133].

Although most studies suggest that varicocele repair improves semen quality and pregnancy rates, most of these data come from retrospective, poorly controlled studies. Only two randomized, prospective, controlled studies have been performed; they have different findings in respect to pregnancy rates, but they agree that varicocelectomy improved semen parameters significantly [134, 135]. A recent meta-analysis reported that the odds of spontaneous pregnancy after varicocelectomy for palpable varicocele were 2.87, compared with no or medical treatment (95% CI 1.33-6.20) [136].

Identifying predictive factors to assess which male patients would most benefit from varicocele repair has attracted considerable interest. Recently, the impact of varicocele grade on the magnitude of improvement in semen quality after varicocele repair has been discussed. Early reports suggested that varicocele size had no relation to the outcome following varicocele repair in infertile men [137]. These findings led to the conclusion that non-palpable varicoceles detected by radiological image studies should be candidates for treatment as well. However, subsequent studies have suggested that subclinical varicocelectomy is of questionable benefit. While there are mild improvements in postoperative semen parameters, pregnancy rates were not improved with ligation of these subclinical varicoceles [138-140]. This was also confirmed by the only randomized prospective study [141]. Current evidence supports the importance of varicocele size and that infertile patients receiving varicocele repair for large varicoceles are more likely to show seminal parameter improvement than are patients with smaller varicoceles [142].

Patients with higher pre-repair sperm counts have significantly greater absolute improvement in semen parameters than those with more severe oligospermia [143]. Marks et al. described that pre-ligation sperm motility of 60% or more is associated with an improved post-ligation pregnancy rate [144]. Also, reduced presurgical testicular volume or elevated FSH concentrations were identified as negative predictors for post-ligation outcome [144, 145]. Men with poor seminal parameters and Y chromosome microdeletions might have an incidental varicocele for which surgical repair is unlikely to improve fertility [146].

Vasovasostomy

The incidence of ductal obstruction among infertile men has been reported as 7.4%. Causes of ductal obstruction include congenital absence or hypoplasia of a part of the ductal system, ductal stricture following infection, functional obstruction and vasectomy. Approximately 750,000 vasectomies are performed annually in the United States, and 2 to 6% of these men request a reversal [147].

Owen and Silver individually reported their results regarding vasectomy reversal using a microscopic technique. Modifications of their techniques are currently the standard operating procedure for most urologists performing vasovasostomy [148, 149].

However, the success of reconstructive procedures remains somewhat unpredictable, because it depends on the individual patient. Preoperative prognostic factors include prior fertility of the spouse, partner's age at the time of reversal and the interval of obstruction. The Vasovasostomy Study Group reported in 1991 that patency and pregnancy rates decrease with the time of obstruction. If the reversal is performed at less than 3 years, 98% had sperm return and 74% established pregnancies. At the other end, at an obstruction interval of more than 15 years, 71% had sperm in their ejaculate and only 30% achieved a pregnancy [150].

Intraoperative observations are also linked to a higher success when performing vasovasostomy. The presence of a sperm granuloma at the distal end of the proximal vas has been associated with better grades of sperm quality and less dilatation of the testicular end of the vas [151]. Most physicians believe that vasovasostomy should be performed when the intravasal fluid containing sperm or sperm parts is encountered at the time of reversal. If clear or copious fluid is found without sperm, vasovasostomy may also be performed. The absence of fluid or the presence of thick, inspissated, toothpaste-like fluid is generally believed to be an indication of epididymal obstruction; therefore, a vasoepididymostomy is indicated. Witt el al. reported a correlation between higher quality of intravasal fluid characteristics with a testicular vasal remnant longer than 2.7 cm [152].

Vasoepididymostomy

Azoospermia secondary to epididymal obstruction may be caused by congenital malformation, bacterial or viral infections, iatrogenic injury, trauma and pressure blowouts due to more distal vas deferens occlusion. Vasoepididymostomy consists of anastomosing a patent epididymal tubule directly to the vas deferens, thus bypassing any obstruction in the epididymis distal to the tubule. Multiple techniques have been described, although three variations are currently used: direct end-to-end, direct end-to-side, and end-to-side intussusceptions [153]. Significantly lower patency and pregnancy rates have been reported after vasoepididymostomy compared with vasovasostomy [154].

Transurethral resection of the ejaculatory ducts

Ejaculatory duct obstruction may result from seminal vesicle calculi, Müllerian duct or Woffian duct cysts, postsurgical or postinflammatory scar tissue, calcification near the verumontanum, or congenital atresia of the ducts [155].

Ejaculatory duct obstruction classically is suspected in azoospermic men with at least one palpable vas deferens, a low semen volume, an acidic seminal pH, and negative or low semen fructose levels. In contrast, partial obstruction may present with oligoasthenoteratozoospermia and normal seminal fructose levels.

The essential step in the evaluation of ejaculatory duct obstruction is transrectal ultrasound which may demonstrate a midline cystic lesion or dilated ejaculatory ducts and seminal vesicles. The presence of motile sperm within the aspirate of the seminal vesicle indicates that an obstruction is present [156]. Seminal vesicle chromotubation guided by transrectal ultrasound combined with cystoscopy is the most accurate way to diagnose complete or incomplete ejaculatory duct obstruction [157].

Indications for transurethral resection include coital discomfort, recurrent hematospermia and infertility. Following resection, sperm may return to the ejaculate in 50 to 75% of cases, and pregnancy results in 25% of couples [158]. Reflux of urine into the ejaculatory ducts and seminal vesicles may impair sperm quality and lead to chronic epididymitis [159].

Take-home message

Currently, approximately 15% of all couples will seek infertility services due to the later age of first pregnancy attempt. In at least half of these cases, a male factor is involved. Management of male infertility is a difficult task, due to the fact that the pathologic process is in the majority of cases is poorly understood.

Although assisted reproduction techniques can help overcome severe male factor infertility, the use of this technology in all infertile couples would certainly represent overtreatment. As a result, identifying reversible causes of infertility and treating the male factor may allow couples to regain fertility and conceive through natural intercourse. A watchful diagnostic workup is essential prior to beginning any andrological treatment so that adequate treatment options can be elected for each patient.

In the absence of a correctable etiology, patients can be managed with either empirical medical therapy or assisted reproduction techniques. However, physicians and patients must be aware of the success rates and collateral effects of pharmacological empirical therapies.

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