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Nonsurgical Treatment of Male Infertility: Specific Therapy

Erkek İnfertilitesinin Cerrahi Dışı Tedavisi: Spesifik Tedavi

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ABSTRACT

Approximately 15% of married couples undergo a fertility examination. Approximately half of the infertility cases have a male factor. Numerous advances have been made in reproductive medicine in the last few years. Infertile couples who previously were considered untreatable now have a chance at genetic paternity. Although it is possible to solve the problem with assisted reproductive techniques in cases with severe male factor, applying these treatment methods to all infertile partners is extra treatment, the cost increases, and rare but serious risks such as ovarian hyperstimulation may occur in the female partner. Prior to any andrological treatment, a serious diagnostic work-up should be performed and treatment should be individualized, providing adequate treatment options in selected cases. Primarily, specific therapeutic therapy directed against the etiological cause of infertility should be attempted. Specific medical treatment of infertility is based on identifying the causes of reversible infertility and treating it with appropriate drugs. Infertility causes such as hormonal disorders, i.e. congenital hypogonadotropic hypogonadism, hyperprolactinemia, genital tract infections, and sexual dysfunctions can be easily diagnosed and successfully treated with medical methods that do not require surgery. In this review, reversible causes of male infertility and nonsurgical specific medical treatment methods are discussed in the light of the current literature.
Keywords: Male infertility; nonsurgical; specific therapy.

ÖZ

Evli çiftlerin yaklaşık %15'i fertilite incelemesine maruz kalmaktadır. İnfertilite vakalarının yaklaşık olarak yarısında erkek faktörü bulunmaktadır. Son yıllarda üreme tıbbında çok sayıda ilerleme kaydedilmiştir. Daha önce tedavi edilemez olduğu düşünülen infertil çiftlerin artık genetik olarak babalık şansı olmaktadır. Her ne kadar şiddetli erkek faktörü bulunan vakalarda yardımcı üreme teknikleri ile sorunu çözmek mümkün ise de, bütün infertil eşlere bu tedavi yöntemlerini uygulamak fazladan tedavi olur, maliyet yükselir ve kadın partnerde ovaryen hiperstimülasyon gibi nadir ancak ciddi riskler meydana gelebilir. Herhangi bir androlojik tedaviden önce ciddi bir tanısal çalışma yapılmalı ve seçilmiş vakalarda yeterli tedavi opsiyonları sunularak, tedavi kişiselleştirilmelidir. Öncelikle infertilitenin etiyolojik nedenine yönelik spesifik terapötik tedavi denenmelidir. İnfertilitenin spesifik medikal tedavisi, geriye dönüşlü infertilite nedenlerinin ortaya çıkarılması ve uygun ilaçlar ile tedavi edilmesi esasına dayanmaktadır. Konjenital hipogonadotropik hipogonadizm gibi hormonal bozukluklar, hiperprolaktinemi, genital sistem enfeksiyonları ve cinsel fonksiyon bozuklukları gibi infertilite nedenlerinin tanısı kolaylıkla konulabilmekte ve cerrahi gerektirmeyen medikal yöntemlerle başarılı bir şekilde tedavi edilebilmektedir. Bu derlemede, erkek infertilitesinin geriye dönüşlü nedenleri ve cerrahi dışı spesifik medikal tedavi yöntemleri mevcut literatür ışığında tartışılmıştır.
Anahtar kelimeler: Erkek infertilitesi; cerrahi dışı; spesifik tedavi.

INTRODUCTION

Infertility is defined as the inability of a sexually active, non-contraceptive couple to achieve spontaneous pregnancy within one year (1). Primary infertility refers to couples that have never had a child and cannot achieve pregnancy after at least 12 consecutive months of having sex without using birth control methods. Secondary infertility refers to infertile couples who have been able to achieve pregnancy at least once before (with the same or different sexual partner).

About 15% of the couples do not achieve pregnancy within one year and seek medical treatment for infertility. One in eight couples encounters problems when attempting to conceive a first child and one in six when attempting to conceive a subsequent child (2). In 50% of involuntarily childless couples, a male-infertility-associated factor is found, usually together with abnormal semen parameters (1). For this reason, all male patients belonging to infertile couples should undergo a medical evaluation by a urologist trained in male reproduction.

Infertility services are increasingly being utilized due to the later age of first pregnancy and associated reduction in female fertility. Assisted reproductive technology (ART) remains an effective option for infertile couples. However, the cost is considerable, and there is a small but definite risk of ovarian hyperstimulation as well as fetal and maternal consequences associated with multiple gestation and developmental defects. In half of the infertility cases, a male factor is involved. Thus, identifying the pathology and treating the male may allow couples to regain fertility and conceive through natural intercourse. The goal of specific medical management of infertility is to diagnose reversible causes of infertility and treat them with appropriate medications to achieve seminal improvement and pregnancy (3).

Management of male infertility is always a difficult task, and the pathologic process is often poorly understood. Even though modern ART can help overcome severe male factor infertility, the application of these methods in all infertile couples would definitely represent over-treatment. Several conditions can interfere with spermatogenesis and reduce sperm quality and production. A careful diagnostic work-up is necessary before any andrological treatment can be initiated so that adequate treatment options can be selected for individual patients. Most hormonal imbalances can be readily identified and successfully treated nonsurgically. However, the treatment of men with unexplained idiopathic infertility remains a challenge. In the absence of a correctable etiology, patients are managed with either empirical medical therapy or ART. Empiric medical therapy continues as a viable option. However, physicians and patients must understand that the success rates with any of the pharmacological therapies remain suboptimal (4).

In this review, we discussed the specific nonsurgical treatment of male infertility including congenital hypogonadotropic hypogonadism (CHH), hyperprolactinemia, genital tract infection, and male sexual dysfunction in light of current literature.

CONGENITAL HYPOGONADOTROPIC HYPOGONADISM (CHH)

It is possible to classify hypogonadism in two or three ways; i) primary hypogonadism, it is of testicular origin, may be due to congenital or acquired causes; ii) secondary hypogonadism, it originates from the pituitary gland, it may be due to congenital or acquired causes; iii) tertiary hypogonadism, it is hypothalamic, may be due to congenital and acquired causes (5).

In some sources, secondary and tertiary hypogonadism together are defined as only secondary hypogonadism. Since the pathologies leading to hypogonadism are numerous, in this review, isolated hypogonadotropic hypogonadism and male infertility, which only cause secondary and tertiary hypogonadism and are the most common endocrine problems in the clinic, will be discussed. Two important spectrums of diseases that cause isolated hypogonadotropic hypogonadism are Kallmann syndrome and idiopathic hypogonadotropic hypogonadism (IHH). The main problem in these two diseases is gonadotropin releasing hormone (GnRH) deficiency or GnRH receptor resistance, which has been reported in very few cases. Other than that, other hypothalamo-pituitary axis functions are usually normal. While only hypogonadism is seen in IHH, Kallmann syndrome can be seen with anosmia or hyposmia, hearing loss, color blindness, congenital heart diseases, adrenal diseases, nervous system diseases, psychiatric diseases, and many other system pathologies (6).

Hypogonadotropic hypogonadism cases are seen in 0.5-1% of all infertile men, in addition to impaired spermatogenesis at varying rates, androgen deficiency may also have systemic effects such as mild anemia, deterioration in coagulation parameters, decrease in bone density, muscular atrophy, and regression in sexual and cognitive functions. Diagnosis and treatment are extremely important (4).

In planning the treatment of hypogonadism; it is important whether the onset time of hypogonadism is congenital, pre-pubertal, or post-pubertal, and whether there is a desire for fertility after puberty. These must be taken into account in the treatment. Since fertility is not possible in hypergonadotropic hypogonadism, the mainstay of treatment is testosterone replacement therapy (TRT). Unlike hypergonadotropic hypogonadism in IHH; since fertility is possible, the aim is not only to develop secondary sex characteristics but also to provide fertility if there is a desire for children. For this purpose, GnRH or gonadotropin therapy (conventional or unconventional) is applied, taking into account the level of gonadotropin secretion disorder. After fertility is achieved, gonadotropin treatment is discontinued and treatment is continued with TRT (7,8).

Pulsatile GnRH Treatment

It is effective in providing fertility in IHH due to hypothalamic insufficiency. It is done by means of a pump placed under the skin and injecting GnRH rhythmically. Quite successful results can be obtained in selected cases (9). It is not effective in pituitary-induced hypogonadism and GnRH receptor resistance.

Gonadotropin Treatment

It is used to provide fertility in IHH due to both hypothalamic and pituitary insufficiency. There are two types of gonadotropin therapy, conventional and unconventional (4,7).

Conventional Gonadotropin Therapy

It is done by using human chorionic gonadotropin (hCG) and human menopausal gonadotropin (hMG). Both of these hormones are obtained from human urine by

purification. hCG is similar in structure to luteinizing hormone (LH), and just like LH, it binds to Leydig cells and causes testosterone secretion (10). There are studies reporting that hCG, albeit to a lesser extent, binds to tubule cells and has an intrinsically follicle stimulating hormone (FSH)-like effect (9). hMG, on the other hand, has a similar structure to FSH and can stimulate spermatogenesis like FSH. hMG has a slightly LH-like effect, but the dose used to induce spermatogenesis is not sufficient to stimulate Leydig cells. Therefore, hCG should be used to ensure adequate testosterone production (11-13). Conventional gonadotropin therapy is first started with hCG therapy. hCG is administered by intramuscular or subcutaneous injection. Usually, 1000-2500 IU is given 2-3 times a week. The dose is adjusted to keep the testosterone level within the normal range. Spermatogenesis may begin during this time, sometimes due to residual FSH secretion. Treatment continues in this way for at least 8-12 weeks. Then, hMG or recombinant FSH, which can be administered intramuscularly or subcutaneously, is added to the treatment. It is recommended to apply 75-150 IU 2-3 times a week (4,7-9,11). Antibodies to gonadotropins may occur sometimes form during gonadotropin therapy. This may result in treatment failure. In some patients, gynecomastia may develop as a result of increased testosterone level and aromatization into estradiol during hCG treatment (14,15).

Unconventional Gonadotropin Therapy

It is performed with highly purified urinary human follicle stimulating hormone (u-hFSH) and recombinant human follicle stimulating hormone (r-hFSH). 95% of hMG preparations currently in use contain coprified protein. This protein both reduces the FSH-like effect of hMG and is responsible for allergic events. To overcome these drawbacks and increase specific activity, u-hFSH and r-hFSH have been developed. u-hFSH is obtained from human urine by advanced purification techniques. r-hFSH is obtained by administering genes isolated from human fetal liver cells to Chinese mice. Its specific activity is more and allergic events are less frequent. There is no intrinsic LH activity (11,14-16). Antibodies to hCG may occur and allergic events may occur during the use of hCG preparations that are still in use. Therefore, efforts to develop recombinant human LH (r-hLH) have yielded results, but doses for use in men have not yet been reached. Promising results have been reported in treatments with recombinant hCG in recent years (17). Although there are few studies comparing the clinical efficacy of conventional and unconventional gonadotropin therapy, there is no consensus on this issue yet (16-19). New studies are needed.

Testosterone Replacement Therapy (TRT)

The TRT is used in the treatment of hypergonadotropic hypogonadism and in the maintenance treatment of IHH after spermatogenesis is achieved. The aim of testosterone therapy is to keep the serum testosterone level within physiological limits as much as possible and to maintain the secondary sex characteristics and sexual functions.

In men with IHH, hCG therapy has advantages over testosterone therapy. One of them is testicular enlargement, and hCG promotes testicular growth. This is particularly evident in cases in the prepubertal period. With hCG therapy, better libido and less fluctuating testosterone levels are achieved. In addition, hCG therapy stimulates intratesticular testosterone production and initiates spermatogenesis. The disadvantages of hCG therapy are that it is more expensive than testosterone therapy and requires more frequent injections. In some patients, serum estradiol levels may be elevated with hCG therapy. These patients may experience decreased libido and gynecomastia. In some patients, antibodies to hCG may develop and the effect of hCG is reduced (20). In cases with a testicular volume of less than 4 ml, who have not completed pubertal development, both LH and FSH treatments are required to initiate spermatogenesis. After the initiation of spermatogenesis with this combination therapy, the treatment is continued with hCG alone. Spermatogenesis can be achieved with hCG therapy alone in patients with partial gonadotropin deficiency in the prepubertal period with a testicular volume of more than 4 mL. If this treatment is not sufficient and fertility cannot be achieved, hMG can be added to the treatment. A semen analysis can be done every three months. If adequate sperm count and sperm parameters are not achieved in six months, the dose can be doubled (20). Patients with IHH usually have a deficiency in pulsatile GnRH secretion. Even if, these patients respond to gonadotropin treatments, low-dose pulsatile GnRH therapy is a more physiological treatment for these patients. The LH-FSH combination is an effective therapy for restoring spermatogenesis in male patients with gonadotrophin deficiency. Ortac et al. (21), reported in a retrospective study that; investigated the efficacy and safety of gonadotropin therapy for the restoration of spermatogenesis in 112 CHH patients. In addition, the potential effect of baseline factors on treatment outcomes was also explored. The authors reported, approximately 85.7% (96/112) of the patients had detectable sperm in ejaculates during treatment. Dwyer et al. (22) and the European Metrodin HP Study Group (23) reported that FSH/hCG treatment induced spermatogenesis in 84% and 89.3% of patients with hypogonadotropic hypogonadism, respectively. A meta-analysis of 30 studies by Rastrelli et al. (24), reported the overall success rate of gonadotropin therapy on gonadotrophin-deficient male patients was 75% (range, 69-81%). Treatment of hypogonadotropic hypogonadism may take a long time to induce successful spermatogenesis. Dwyer et al. (22), reported that the time to develop spermatogenesis ranges from 3 to 19 months and 9 to 12 months for mono and combined gonadotrophin treatments, respectively. Different time periods for stimulation of sperm production may reflect different population groups and treatment regimens (22). In some studies, the mean time to achieve spermatogenesis was 9.4 months, consistent with other studies reporting the median time of the first appearance of sperm appearance reported as 9-12 months (23-28). Matsumoto et al. (27), found that the median time of first sperm appearance was 12.9 (range, 6.1-17.1) months. However, Liu et al. (25) reported a longer median time of 15 months to obtain sperm in the ejaculate. They speculated that this difference may relate to longer treatment sessions with lower dose hCG treatment and longer follow-up time. Several studies have focused on the predictive factors for successful spermatogenesis in patients with hypogonadotropic hypogonadism (29,30). Ortac et al. (21), reported that larger basal testicular

volume, older age, and a lower incidence rate of undescended testis were positive predictive factors for achieving sperm in the ejaculate. Testicular size increased significantly after gonadotrophin therapy in patients with induced spermatogenesis. The authors concluded that these findings support previous studies in which basal testicular volume and the rate of undescended testis were reported as the main prognostic factors for the restoration of spermatogenesis. The relationship between testicular development and sperm restoration is expected since it is known that normal testicular function is an essential part of a functional hypothalamic-pituitary-gonadal (HPG) axis in healthy adult men (31). It was proposed that mean testicular volumes >4 mL defined an important threshold for the success of sperm restoration (32). Spratt et al. (33), reported that patients with partial/normal nocturnal LH pulses had larger testicular volume (4 mL) compared with those without LH pulses.

We have reported in a currently published study (34); there are several treatment methods for patients with CHH.

1. The patients do not wish to have children: TRT in oral, intramuscular, or transdermal form is commonly used due to its low cost. The oral form is avoided if possible due to the toxic effects on the liver. Transdermal administration has two forms of application, to the scrotum or other body areas. Due to their wide availability in our country, we mostly used the transdermal and intramuscular forms.

2. The patients who wish to have children: These cases were treated using three different protocols.

a. Pulsatile gonadotropin releasing hormone (GnRH) therapy: This treatment is applied with a mini-pump at 5-20 μg/120 min for 12-24 weeks. This is an expensive method with no commercial preparation available in Turkey; therefore, we did not use it in any of our cases.

b. Conventional LH and FSH therapy: We first applied 1500 IU hCG (LH-effective) twice a week for 3-6 months, followed by hCG+hMG or recombinant FSH (150 IU three times a week) for a minimum of 18 months.

c. LH and FSH therapy with an incremental dose: Based on the idea that each patient's hormone requirement is different, some health centers prefer to use this treatment protocol and report favorable outcomes in recent years. In this protocol, serum hormone levels are monitored, and the dose of hCG is increased to 5000 IU and the dose of FSH up to 225-450 IU. In the examination of the patient files, the majority of our patients were seen to have been treated with this method. The patients who did not wish to have children immediately received TRT and those who wanted to have children were treated with hCG+FSH. Initially, only hCG therapy was applied, and when the serum T level was above 400 ng/dL, FSH therapy was added. The initial hCG treatment was planned as 1500 IU twice a week, but this dose was not sufficient in approximately 80% of patients (52 patients); that is, the serum T levels were observed to be below 400 ng/dL; thus, the dose of hCG was increased to 2500 IU twice a week. The time to achieve serum T levels greater than 400 ng/dl was 3 to 6 months. However, during this period, no sperm was observed in the ejaculate of any patient. When the serum T levels were above the threshold, the hCG therapy was continued at the same dose with the addition of FSH. Recombinant FSH preparations were not available at the beginning; thus, urinary FSH was used (15 patients); then, recombinant FSH was added to the treatment (40 patients). The initial FSH dose was 150 IU two to three times a week. In cases where sperm was not detected in the ejaculate within 6 months, the dose of FSH was increased to 450 IU twice a week. At the end of the second year, the mean testicular volume reached 8±4 mL, with the lowest volume being 8 mL and the highest being 14 mL. It was observed that the testicular volume increased more in patients with initial testicular volumes of >4 mL. However, the testicular volume did not reach healthy adult levels in any of the patients. Starting from the sixth month of the treatment, the semen volume of the patients was observed to gradually increase from 0.2 to 2±0.5 mL. At the beginning, all cases were azoospermic, with their semen containing no sperm for the first 6 months. The sperm was detected in the ejaculate only after the 9th month. When all cases were evaluated, five (7.7%) patients did not have any sperm in the semen despite the long-term treatment (>2 years), and in 10 (15.3%) cases, sperm was seen at the 9th month. The ejaculate contained sperm at the 12th month in 35 (53.8%) patients, the 15th month in 42 (64.6%) patients, the 18th month in 52 (80%) patients, and the 24th month in 60 (92.3%) patients. At the end of the second year, the sperm count of the patients with sperm-containing ejaculate ranged from 2×106/mL to 82×106/mL. Interestingly, the rate of progressive motility was >80%.

In the literature, spontaneous recovery has been reported in 10% of IHH cases, which were attributed to the constitutional delay of puberty (35). Although IHH is usually diagnosed easily, its treatment continues to be challenging since it presents as a wide spectrum of diseases, rather than a single form. There is no clear treatment protocol because the doses of medication and the duration of use required for the treatment vary from one patient to another. In addition, the necessity of lifetime treatment may be wearisome for the patient, his spouse, and the treating physician. For this reason, the patient and spouse should be convinced by the physician that the treatment will eventually be successful, but will last a lifetime and may need occasional modifications. Testosterone, GnRH, and gonadotropins are used in the treatment. Although TRT is sufficient for secondary sexual development and general body health, this treatment cannot achieve fertility. The intratesticular testosterone required for spermatogenesis should be at least 50-150 times more than that in the peripheral blood, and it is not possible to reach this amount using TRT. Therefore, treatments that increase intratesticular testosterone, for example, GnRH and hCG/LH, should be undertaken. TRT is easily applicable and cost-effective, and thus it is widely applied in cases where fertility is not of any concern at the time. However, patients wishing to have children should stop taking TRT approximately 2 years before the desired time of conception, and GnRH or hCG/LH+FSH treatment should be initiated (11,18,36,37). Gonadotropins therapy depends on whether the patients who wanted to have children. The success rate generally accepted for fertility is an increase in sperm count to 1.5×106/mL. At this limit, approximately 80% of patients achieve success at the end of the 18th month. Long-term results regarding pregnancy outcomes have not been reported in these series (38,39). In our currently published study, the spouses of 42 (64.6%) of the 65 patients had spontaneous pregnancy, while 8 (12.3%) achieved pregnancy

through intrauterine insemination (IUI), and 10 (15.3%) through in vitro fertilization (IVF) using the sperm ejaculate. The remaining five (7.6%) patients did not have any sperm in the ejaculate; thus, microsurgical testicular sperm extraction (micro-TESE) + intracytoplasmic sperm injection (ICSI) was attempted to achieve pregnancy. However, in only 3 of the 5 patients, sperm could be retrieved, and the remaining 2 patients did not respond to a repeat micro-TESE. Interestingly, there was no statistically significant difference between the total motile sperm count and pregnancy rates. Compared to the literature, our series has the longest follow-up, and highest pregnancy and success rates. This can be explained by our approach that included persuading the patients to undergo long-term treatments, and increasing the dose of medicine without hesitation (34).

HYPERPROLACTINEMIA

Prolactin inhibits the aging of spermatozoa by affecting spermatozoa in an intrinsic way and plays a direct role in the functioning of sperm functions. Prolactinemia is seen at a rate of 1% in andrology practice (40). In a study in which 30 patients with hyperprolactinemia were examined, although the prolactin level decreased with bromocriptine administration, there was no improvement in semen parameters (41). Hyperprolactinemia, defined as an excess of the hormone prolactin, is among the major endocrinopathies related to male infertility (41). The diagnosis is rather straightforward, as hyperprolactinemia may be found with routine serum tests; however, determining the origin of the condition can be difficult. Hyperprolactinemia can arise as a result of hypothyroidism, liver illness, stress, and the use of certain drugs (such as phenothiazines and tricyclic antidepressants), as well as in the presence of functional pituitary adenomas (41,42). The symptoms of excess prolactin may be asymptomatic in some cases or lead to a hypoandrogenic state or galactorrhea, while reduced libido and erectile dysfunction are reported in other cases (43). Hyperprolactinemia can cause male infertility due to its inhibitory effects on the hypothalamus (44). As a result, the hypothalamus is unable to secrete gonadotropins, which in turn affects testosterone production and spermatogenesis. Prolactin levels that are too high are associated with a decreased ability to produce testosterone (44). Because of the numerous impacts on the HPG axis, a patient may present with a variety of symptoms, including diminished sexual desire, erectile dysfunctions, and reduced semen quality (41). Once hyperprolactinemia has been diagnosed, the practitioner should order a magnetic resonance imaging (MRI) scan of the pituitary gland to rule out any other potential causes. If a prolactinoma is discovered, it can be classified according to its dimension and form. The most important distinction is between microadenomas, which are lesions smaller than 10 mm in diameter, and macroadenomas, which are lesions larger than 10 mm in diameter.

The medical treatment for prolactinoma is focused on inhibiting the release of prolactin with the use of dopamine agonists if the tumor is found to be present, which include, pergolide, cabergoline, bromocriptine, and quinagolide, with cabergoline and bromocriptine being the most well-characterized agents (45). Bromocriptine is an ergo derivative. The plasma half-life is 3.3 hours. Due to its short duration of action, it should be used 2-3 times a day. The initial dose is 0.625-1.25 mg daily. The dose is gradually increased to 5-7.5 mg/day once a week. Short-acting forms to slow-release forms are preferred. Side effects of bromocriptine are nausea, vomiting, dizziness, headache, nasal congestion, dry mouth, constipation, dizziness due to orthostatic hypotension, and syncope.

Cabergoline is an ergo derivative. Its half-life is 65 hours. Therefore, taking it 1-2 times a week is usually sufficient. Cabergoline is the first choice because it has more tumor-reducing effect and less side effects. Usually, 0.5-1 mg/week dose is sufficient, while increasing the maximum dose (7 mg/week) in rare cases may be required.

Quinagolide is not an ergo derivative. It binds to the dopamine receptor. It starts with 25 μg per day for the next three days and continues with 50 μg per day for the next three days. Recommended from the seventh day the dose is 75 μg per day. The maintenance dose is usually 75-150 μg per day.

These agonists take advantage of dopamine's inherent suppression of prolactin release to achieve their effects. In certain cases, this can really result in the tumor shrinking, albeit the process usually takes months to complete. Nausea, vomiting, and postural hypotension are among the side effects that can occur after using dopamine agonists. However, despite the fact that inhibition of excess secretion of prolactin prevents disruption of the HPG axis, few studies have examined the effects of dopamine agonists on reproductive functions. Bromocriptine was used in a 1974 trial to treat men with functional prolactinomas and hypogonadism, and the results revealed no increase in sperm motility (46). De Rosa et al. (47) treated 43 patients with hyperprolactinemia and impaired semen parameters by administering cabergoline for 24 months and compared the results with 60 healthy men at the end of the treatment. Significant improvements in semen quality were achieved in patients with normal prolactin levels. The seminal fluid characteristic values were found close to the control group. However, viable spermatozoa count, sperm membrane function, sperm kinetic index, and sperm nuclear DNA integrity remained abnormal in 9.3-53% of patients. On the other hand, a study compared cabergoline and bromocriptine in the same cohort of patients, and both treatment regimens showed significant improvements in sperm quantity, motility, rapid advancement, and morphology in a period of six months (47). In a later study conducted at the same institution, seminal fluid parameters were compared between men who had prolactinomas and men who did not. According to a study conducted on healthy control males, after 2 years of treatment with cabergoline (starting dose 0.5 mg weekly, gradually titrated to prolactin levels), the majority of men had regained testicular functions in comparison to the healthy control. When bromocriptine and cabergoline are compared, it is observed that cabergoline has higher effectiveness at normalizing levels of prolactin and regressing tumor load (48). Furthermore, when comparing cabergoline to bromocriptine, a higher percentage of individuals demonstrate a clinical response to cabergoline. Finally, compared to bromocriptine, cabergoline has a considerably better rate permanent remission rate and fewer side effects (49). All things

considered, cabergoline is frequently the initial treatment option for males with prolactinomas after other options are exhausted. In many situations, treatment of prolactinomas with dopamine agonists is beneficial; nonetheless, a considerable proportion of men may still remain persistently hypogonadotropic despite receiving treatment. The use of clomiphene citrate, according to a study, may be a successful therapy option for these men. Hypogonadal men treated with clomiphene (50 mg per day for 3 months) had increased levels of testosterone as well as improved sperm motility (49). Prolactinomas can be treated with ablative therapies such as radiation therapy or transsphenoidal excision, which are both effective. Ablative therapy is usually reserved for patients who have failed to respond to medical treatment. Ablative treatments work by removing the prolactin source and, as a result, the suppression of GnRH secretion that is occurring. It is still vital to monitor the patient's gonadotropin levels after treatment since additional intervention with exogenous gonadotropins may be required to maximize therapeutic benefit (50).

GENITAL TRACT INFECTIONS

Infection of the male urogenital tract is a potentially curable cause of male infertility (51). The World Health Organization (WHO) considers urethritis, prostatitis, orchitis, and epididymitis to be male accessory gland infections (MAGIs) (52). A systematic review of the relationship between sexually transmitted infections, such as those caused by *Chlamydia trachomatis*, genital mycoplasmas, *Neisseria gonorrhoeae*, *Trichomonas vaginalis*, and viruses, and infertility was unable to draw a strong association between sexually transmitted infections and male infertility due to the limited quality of reported data (53).

The clinical significance of an increased concentration of leukocytes in the ejaculate is controversial (54). Although leukocytospermia is a sign of inflammation, it is not necessarily associated with bacterial or viral infections, and therefore cannot be considered a reliable indicator (55). The deleterious effects of chronic prostatitis (CP/CPPS) on sperm density, motility, and morphology have been demonstrated in a recent systematic review based on case-controlled studies (56). Both *C. trachomatis* and *Ureaplasma* spp. can cause decreased sperm density, motility, altered morphology, and increased DNA damage. Treatment of CP/CPPS is usually targeted at relieving symptoms. The indications and aims of therapy are the reduction or eradication of micro-organisms in prostatic secretions and semen, normalization of inflammatory (e.g., leukocytes) and secretory parameters, and improvement of sperm parameters associated with fertility impairment. Only antibiotic therapy of chronic bacterial prostatitis (NIH II according to the classification) has provided symptomatic relief, eradication of micro-organisms, and a decrease in cellular and humoral inflammatory parameters in urogenital secretions. Although antibiotics might improve sperm quality, there is no evidence that treatment of CP/CPPS increases the probability of natural conception (51-56).

Asymptomatic presence of *C. trachomatis* and *M. hominis* in the semen can be correlated with impaired sperm quality, which recovers after antibiotic treatment. However further research is required to confirm these findings (57). The aim of treatment of epididymitis is as follows; microbiological cure of infection, improvement of clinical signs and symptoms, prevention of potential testicular damage, prevention of transmission, and decrease of potential complications such as infertility.

Considering that male genital tract infections are in their majority caused by bacterial pathogens, such infections can be treated with antibiotics and anti-inflammatories and are therefore potentially correctable causes of male infertility. Yet, it is to be noticed that many of these pathogens are sexually transmitted. Therefore, both partners have to be treated after proper diagnosis and administration of a suitable antibiotic after semen culture. Whereas guidelines for the treatment of acute bacterial epididymitis, epididymo-orchitis, and specific granulomatous orchitis have been published, this is not the case for chronic infections and inflammations. Hence, treatment of these diseases rather relies on empirical and a small number of uncontrolled studies.

On the other hand, for viral infections such as mumps orchitis, a systemic treatment with 2β-interferon was used to prevent testicular atrophy (58,59). Lesions due to the inflammatory processes can be alleviated with an antiphlogistic therapy, with both corticosteroids and non-steroids, and have shown significant positive effects on various semen parameters. In addition, antioxidant therapies to counteract oxidative stress may be considered, but are still debated (60). A new study reported that MAGIs are not clearly associated with impaired natural conception, antibiotic treatment often only eradicates micro-organisms; it has no positive effect on inflammatory alterations and cannot reverse functional deficits and anatomical abnormalities. Although antibiotic treatment for MAGIs may result in an improvement in sperm quality, it does not enhance the probability of conception (61).

Treating MAGIs may improve sperm quality, although it does not necessarily improve the probability of increasing conception. Weak data are insufficient to conclude whether antibiotics and antioxidants for the treatment of infertile men with leukocytospermia improve fertility outcomes. Weak refer sexual partners of patients with accessory sex gland infections that are known or suspected to be caused by sexually transmitted diseases for evaluation and treatment.

MALE SEXUAL DYSFUNCTION

Sexual dysfunction is more common in infertile men than in the normal population. Sexual dysfunctions may be the result of infertility as well as the cause of infertility. Therefore, every infertile man should be evaluated for sexual dysfunction. While erectile dysfunction, decreased libido, and premature ejaculation are mostly the result of infertility, retrograde ejaculation and unejaculation are more common causes of infertility. Erectile dysfunction can be easily treated with PDE5 inhibitors. If there is no response to PDE5 inhibitors and there is a decrease in libido, serum total testosterone level should be checked. These patients should not be given exogenous testosterone to preserve fertility but should be given selective estrogen receptor modulators, aromatase inhibitors, or hCG, which increase endogenous testosterone production. If the patients had anejaculation and used antipsychotics or

alpha-blockers, these drugs should be temporarily discontinued until pregnancy occurs. Retrograde ejaculation is the most important sexual dysfunction that causes male infertility. If retrograde ejaculation is due to anatomical reasons such as prostatectomy or bladder neck resection, medical treatment cannot be achieved and ART should be used in these patients. If retrograde ejaculation is not anatomical but neurogenic, medical treatment should be attempted (62).

Retrograde ejaculation occurs due to many reasons such as diabetes mellitus, spinal cord pathologies, intra-abdominal surgical interventions, and surgical interventions for the urinary system, and may cause infertility (63-65).

The traditional medical treatment of patients who are infertile due to retrograde ejaculation is the use of sympathomimetic agents. Pseudoephedrine is widely used in the treatment of these patients and the rate of obtaining sperm in the ejaculate reaches up to 58% (66).

Some studies reported successful pregnancies in patients with retrograde ejaculation by using midodrine, the alpha agonist methoxamine, or the antihypotensive amazinium and theophylline (66-69).

In their recent study, Hu et al. (70) investigated the effect of amoxapine, a norepinephrine reuptake inhibitor, in patients with retrograde ejaculation. They administered vitamin B12 to 13 patients and amoxapine to 13 patients, and found the rate of sperm retrieval in the groups to be 16% and 80%, respectively (70).

In another study, patients with retrograde ejaculation due to diabetes mellitus were divided into three groups, and the groups received 25 mg of imipramine twice a day, 120 mg of pseudoephedrine twice a day, and the combined form of these two agents twice a day. The sperm retrieval rate in the groups was 38.5%, 47.8%, and 61.5%, respectively (71).

CONCLUSION

Numerous advances have been made in reproductive medicine in the last few years. Infertile couples who previously were considered untreatable now have a chance at genetic paternity. ART provides a great opportunity to families with infertility. The increasing use of ICSI as an efficient therapy for cases of male infertility has become an applicable means to overcome multiple sperm deficiencies. Even men with potentially treatable causes of infertility can be treated with ART instead of a specific therapy. However, the potential medical risks such as those of multiple-gestation pregnancies and the associated costs cannot be ignored. Primarily, specific therapeutic therapy directed against the etiological cause of infertility should be attempted. Specific medical management of infertility is based on identifying reversible causes of infertility and treating them with appropriate medications. However, if no specific etiology can be identified, empiric therapy can be introduced in an attempt to improve semen parameters and subsequent fertility potential through natural intercourse. It is mandatory that a treatment timeline and endpoints be established prior to the initiation of empiric therapy. Many of the empiric therapies do hold a potential benefit, and as greater understanding is gained of what is now considered idiopathic infertility, a more specific application of these therapies may yield more successful results.

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REFERENCES

1. Rowe PJ, Comhaire FH, Hargreave TB, Mellows HJ. WHO manual for the standardized investigation and diagnosis of the infertile couple. Cambridge: Cambridge University Press; 1993.
2. Greenhall E, Vessey M. The prevalence of subfertility: a review of the current confusion and a report of two new studies. Fertil Steril. 1990;54(6):978-83.
3. Cocuzza M, Agarwal A. Nonsurgical treatment of male infertility: specific and empiric therapy. Biologics. 2007;1(3):259-69.
4. Zitzmann M, Nieschlag E. Hormone substitution in male hypogonadism. Mol Cell Endocrinol. 2000;161(1-2):73-88.
5. Özbey İ, Ziypak T. Erkekte hipotalamus-hipofiz-testis aksı. In: Aşcı R, Çayan S, Erdemir F, Orhan İ, Yaman Ö, Usta MF, et al, editors. Erkek üreme sistemi hastalıkları ve tedavisi. 1. Baskı. İstanbul: İstanbul Medikal Yayıncılık; 2013. p.39-54. Turkish.
6. Özbey İ. Hipogonadotropik hipogonadizm tedavisi. Turkiye Klinikleri J Urology-Special Topics. 2017;10(1):19-27. Turkish.
7. Jockenhövel F. Male Hypogonadism. Bremen: UNI-MED; 2004.
8. Melmed S, Kleinberg DL. Anterior pituitary. In: Larsen PR, Kronenberg HM, Melmed S, Polonsky KS, Wilson JD, Foster DW, editors. Williams textbook of endocrinology, 10th ed. Philadelphia: Saunders; 2003. p.177-279.
9. Ley SB, Leonard JM. Male hypogonadotropic hypogonadism: factors influencing response to human chorionic gonadotropin and human menopausal gonadotropin, including prior exogenous androgens. J Clin Endocrinol Metab. 1985;61(4):746-52.
10. Özbey İ. İntratestiküler testosteron: Üretimi ve klinik önemi. Androloji Bülteni. 2015;17(61):129-131. Turkish.
11. Barrio R, de Luis D, Alonso M, Lamas A, Moreno JC. Induction of puberty with human chorionic gonadotropin and follicle-stimulating hormone in adolescent males with hypogonadotropic hypogonadism. Fertil Steril. 1999;71(2):244-8.
12. Özbey İ, Aksay Y, Polat Ö. Erkekte izole folikül stimüle edici hormon ve izole luteinize edici hormon eksikliği. Androloji Bülteni. 2002;4(9):11-12. Turkish.
13. Erol B, Çeltik M, Kendirci M, Özbey İ, Kadıoğlu A, Özsoy C. Isolated FSH deficiency: Rare but treatable cause of male infertility. The Journal of Urology. 2003;169(4S):11.

14. Snyder PJ, Peachey H, Berlin JA, Hannoush P, Haddad G, Dlewati A, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab. 2000;85(8):2670-7.
15. Kliesch S, Behre HM, Nieschlag E. Recombinant human follicle-stimulating hormone and human chorionic gonadotropin for induction of spermatogenesis in a hypogonadotropic male. Fertil Steril. 1998;69(2):21s-3s.
16. Esteves SC, Papanikolaou V. Clinical efficacy, safety and tolerability of recombinant human chorionic gonadotropin to restore spermatogenesis and androgen production of hypogonadotropic hypogonadal men. Fertil Steril. 2011;96(3):230.
17. Young J, Couzinet B, Chanson P, Brailly S, Loumaye E, Schaison G. Effects of human recombinant luteinizing hormone and follicle-stimulating hormone in patients with acquired hypogonadotropic hypogonadism: study of Sertoli and Leydig cell secretions and interactions. J Clin Endocrinol Metab. 2000;85(9):3239-44.
18. Thau RB, Goldstein M, Yamamoto Y, Burrow GN, Phillips D, Bardin CW. Failure of gonadotropin therapy secondary to chorionic gonadotropin-induced antibodies. J Clin Endocrinol Metab. 1988;66(4):862-7.
19. Wilson JD. Hypogonadotropic hypogonadism. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al., editors. Harrison's principles of internal medicine. 14th ed. New York: McGraw-Hill; 1998. p.1984.
20. Young J, Xu C, Papadakis GE, Acierno JS, Maione L, Hietamäki J, et al. Clinical management of congenital hypogonadotropic hypogonadism. Endocr Rev. 2019;40(2):669-710.
21. Ortac M, Hidir M, Salabas E, Boyuk A, Bese C, Pazir Y, et al. Evaluation of gonadotropin-replacement therapy in male patients with hypogonadotropic hypogonadism. Asian J Androl. 2019;21(6):623-7.
22. Dwyer AA, Raivio T, Pitteloud N. Gonadotrophin replacement for induction of fertility in hypogonadal men. Best Pract Res Clin Endocrinol Metab. 2015;29(1):91-103.
23. European Metrodin HP Study Group. Efficacy and safety of highly purified urinary follicle-stimulating hormone with human chorionic gonadotropin for treating men with isolated hypogonadotropic hypogonadism. Fertil Steril. 1998;70(2):256-62.
24. Rastrelli G, Corona G, Mannucci E, Maggi M. Factors affecting spermatogenesis upon gonadotropin-replacement therapy: a meta-analytic study. Andrology. 2014;2(6):794-808.
25. Liu PY, Baker HW, Jayadev V, Zacharin M, Conway AJ, Handelsman DJ. Induction of spermatogenesis and fertility during gonadotropin treatment of gonadotropin-deficient infertile men: predictors of fertility outcome. J Clin Endocrinol Metab. 2009;94(3):801-8.
26. Warne DW, Decosterd G, Okada H, Yano Y, Koide N, Howles CM. A combined analysis of data to identify predictive factors for spermatogenesis in men with hypogonadotropic hypogonadism treated with recombinant human follicle-stimulating hormone and human chorionic gonadotropin. Fertil Steril. 2009;92(2):594-604.
27. Matsumoto AM, Snyder PJ, Bhasin S, Martin K, Weber T, Winters S, et al. Stimulation of spermatogenesis with recombinant human follicle-stimulating hormone (follitropin alfa; GONAL-f): long-term treatment in azoospermic men with hypogonadotropic hypogonadism. Fertil Steril. 2009;92(3):979-90.
28. Bouloux P, Warne DW, Loumaye E; FSH Study Group in Men's Infertility. Efficacy and safety of recombinant human follicle-stimulating hormone in men with isolated hypogonadotropic hypogonadism. Fertil Steril. 2002;77(2):270-3.
29. Pitteloud N, Hayes FJ, Dwyer A, Boepple PA, Lee H, Crowley WF Jr. Predictors of outcome of long-term GnRH therapy in men with idiopathic hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2002;87(9):4128-36.
30. Ishikawa T, Ooba T, Kondo Y, Yamaguchi K, Fujisawa M. Assessment of gonadotropin therapy in male hypogonadotropic hypogonadism. Fertil Steril. 2007;88(6):1697-9.
31. Silveira LF, Latronico AC. Approach to the patient with hypogonadotropic hypogonadism. J Clin Endocrinol Metab. 2013;98(5):1781-8.
32. Dwyer AA, Raivio T, Pitteloud N. Management of endocrine disease: reversible hypogonadotropic hypogonadism. Eur J Endocrinol. 2016;174(6): R267-74.
33. Spratt DI, Carr DB, Merriam GR, Scully RE, Rao PN, Crowley WF Jr. The spectrum of abnormal patterns of gonadotropin-releasing hormone secretion in men with idiopathic hypogonadotropic hypogonadism: clinical and laboratory correlations. J Clin Endocrinol Metab. 1987;64(2):283-91.
34. Yılmazel FK, Karabulut I, Yılmaz AH, Keskin E, Bedir F, Ozbey I. A review of hypogonadotropic hypogonadism cases followed up in our clinic in the last decade. Urologia. 2021;88(1):50-5.
35. Raivio T, Falardeau J, Dwyer A, Quinton R, Hayes FJ, Hughes VA, et al. Reversal of idiopathic hypogonadotropic hypogonadism. N Engl J Med. 2007;357(9):863-73.
36. Delemarre EM, Felius B, Delemarre-van de Waal HA. Inducing puberty. Eur J Endocrinol. 2008;159(Suppl 1):S9-15.
37. Segal TY, Mehta A, Anazodo A, Hindmarsh PC, Dattani MT. Role of gonadotropin-releasing hormone and human chorionic gonadotropin stimulation tests in differentiating patients with hypogonadotropic hypogonadism from those with constitutional delay of growth and puberty. J Clin Endocrinol Metab. 2009;94(3):780-5.
38. Farshchi HR, Shahnazi A, Azizi F. Effects of testosterone and gonadotropin therapy in men with hypogonadotropic hypogonadism. Int J Endocrinol Metab. 2009;7(4):242-7.
39. Bouloux PM, Nieschlag E, Burger HG, Skakkebaek NE, Wu FC, Handelsman DJ, et al. Induction of spermatogenesis by recombinant follicle-stimulating hormone (puregon) in hypogonadotropic azoospermic men who failed to respond to human chorionic gonadotropin alone. J Androl. 2003;24(4):604-11.
40. Özbey İ. Prolaktinoma tanı ve tedavisinde güncel yaklaşım. Androloji Bülteni. 2006;8(27):320-3. Turkish.

41. Nishimura K, Matsumiya K, Tsuboniwa N, Yamanaka M, Koga M, Miura H, et al. Bromocriptine for infertile males with mild hyperprolactinemia: hormonal and spermatogenic effects. Arch Androl. 1999;43(3):207-13.
42. Singh P, Singh M, Cugati G, Singh AK. Hyperprolactinemia: An often missed cause of male infertility. J Hum Reprod Sci. 2011 May;4(2):102-3.
43. Sohrabvand F, Jafari M, Shariat M, Haghollahi F, Lotfi M. Frequency and epidemiologic aspects of male infertility. Acta Med Iran. 2015;53(4):231-5.
44. Tsutsumi R, Webster NJ. GnRH pulsatility, the pituitary response and reproductive dysfunction. Endocr J. 2009;56(6):729-37.
45. Liu X, Tang C, Wen G, Zhong C, Yang J, Zhu J, et al. The mechanism and pathways of dopamine and dopamine agonists in prolactinomas. Front Endocrinol (Lausanne). 2019;9:768.
46. Thorner MO, McNeilly AS, Hagan C, Besser GM. Long-term treatment of galactorrhoea and hypogonadism with bromocriptine. Br Med J. 1974;2(5916):419-22.
47. De Rosa M, Colao A, Di Sarno A, Ferone D, Landi ML, Zarrilli S, et al. Cabergoline treatment rapidly improves gonadal function in hyperprolactinemic males: a comparison with bromocriptine. Eur J Endocrinol. 1998;138(3):286-93.
48. Gillam MP, Molitch ME, Lombardi G, Colao A. Advances in the treatment of prolactinomas. Endocr Rev. 2006;27(5):485-534.
49. Ribeiro RS, Abucham J. Recovery of persistent hypogonadism by clomiphene in males with prolactinomas under dopamine agonist treatment. Eur J Endocrinol. 2009;161(1):163-9.
50. Sengupta P, Dutta S, Karkada IR, Chinni SV. Endocrinopathies and male infertility. Life (Basel). 2022;12(1):10.
51. Rowe PJ, Comhaire FH, Hargreave TB, Mahmoud AMA. WHO manual for the standardized investigation, diagnosis and management of the infertile male. Cambridge: Cambridge University Press; 2000.
52. 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(5):421-32.
53. Fode M, Fusco F, Lipshultz L, Weidner W. Sexually transmitted disease and male infertility: a systematic review. Eur Urol Focus. 2016;2(4):383-393.
54. Trum JW, Mol BW, Pannekoek Y, Spanjaard L, Wertheim P, Bleker OP, et al. Value of detecting leukocytospermia in the diagnosis of genital tract infection in subfertile men. Fertil Steril. 1998;70(2):315-9.
55. Weidner W, Ludwig M, Miller J. Therapy in male accessory gland infection--what is fact, what is fiction? Andrologia. 1998;30(Suppl 1):87-90.
56. Comhaire FH, Rowe PJ, Farley TM. The effect of doxycycline in infertile couples with male accessory gland infection: a double blind prospective study. Int J Androl. 1986;9(2):91-8.
57. Ahmadi MH, Mirsalehian A, Sadighi Gilani MA, Bahador A, Afraz K. Association of asymptomatic Chlamydia trachomatis infection with male infertility and the effect of antibiotic therapy in improvement of semen quality in infected infertile men. Andrologia. 2018;50(4):e12944.
58. Solomon M, Henkel R. Semen culture and the assessment of genitourinary tract infections. Indian J Urol. 2017;33(3):188-193.
59. Yapanoglu T, Kocaturk H, Aksoy Y, Alper F, Ozbey I. Long-term efficacy and safety of interferon-alpha-2B in patients with mumps orchitis. Int Urol Nephrol. 2010;42(4):867-71.
60. Steiner AZ, Hansen KR, Barnhart KT, Cedars MI, Legro RS, Diamond MP, et al. The effect of antioxidants on male factor infertility: the Males, Antioxidants, and Infertility (MOXI) randomized clinical trial. Fertil Steril. 2020;113(3):552-60.e3.
61. Henkel R, Offor U, Fisher D. The role of infections and leukocytes in male infertility. Andrologia. 2021;53(1):e13743.
62. Liu Y, Wang Y, Pu Z, Wang Y, Zhang Y, Dong C, et al. Sexual dysfunction in infertile men: a systematic review and meta-analysis. Sex Med. 2022;10(4):100528.
63. Birch N, Shaw M. Retrograde ejaculation after anterior lumbar interbody fusion. Spine (Phila Pa 1976). 2004;29(1):106-7.
64. Ellenberg M, Weber H. Retrograde ejaculation in diabetic neuropathy. Ann Intern Med. 1966;65(6):1237-46.
65. Yavetz H, Yogev L, Hauser R, Lessing JB, Paz G, Homonnai ZT. Retrograde ejaculation. Hum Reprod. 1994;9(3):381-6.
66. Shoshany O, Abhyankar N, Elyaguov J, Niederberger C. Efficacy of treatment with pseudoephedrine in men with retrograde ejaculation. Andrology. 2017;5(4):744-748.
67. Soler JM, Previnaire JG, Plante P, Denys P, Chartier-Kastler E. Midodrine improves ejaculation in spinal cord injured men. J Urol. 2007;178(5):2082-6.
68. Ichiyanagi O, Sasagawa I, Suzuki Y, Matsuki S, Itoh K, Miura M, et al. Successful treatment of retrograde ejaculation with amezinium. Arch Androl. 2003;49(3):215-7.
69. Ebner T, Shebl O, Mayer RB, Moser M, Costamoling W, Oppelt P. Healthy live birth using theophylline in a case of retrograde ejaculation and absolute asthenozoospermia. Fertil Steril. 2014;101(2):340-3.
70. Hu J, Nagao K, Tai T, Kobayashi H, Nakajima K. Randomized crossover trial of amoxapine versus vitamin b12 for retrograde ejaculation. Int Braz J Urol. 2017;43(3):496-504.
71. Arafa M, El Tabie O. Medical treatment of retrograde ejaculation in diabetic patients: a hope for spontaneous pregnancy. J Sex Med. 2008;5(1):194-8.