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Nonsurgical Treatment of Male Infertility: Non-Specific Therapy

Erkek İnfertilitesinin Cerrahi Dışı Tedavisi: Spesifik Olmayan Tedavi

Emre TOKUÇ
0000-0002-5885-9278
Metin İshak ÖZTÜRK
0000-0002-1868-2316

Department of Urology, University of Health Sciences Haydarpaşa Numune Training and Research Hospital, İstanbul, Türkiye

ABSTRACT

In male infertility, all possible known causes should be carefully evaluated and if detected, targeted treatment options for the cause should be implemented. The known causes of male infertility such as hypogonadotropic hypogonadism, hyperprolactinemia, genital tract infections, disorders of ejaculation, thyroid hormone disorders and varicocele can be treated efficiently by targeted therapies or surgical corrections. Unfortunately, these known causes cover about 20% of male infertility and the rest remains idiopathic. On the other hand, management of idiopathic, unexplained male infertility, in which no etiological factors can be found, is a challenge for both the clinician and couples seeking solutions. In the era of assisted reproductive technology, few medical options in this regard are still available with limited benefits and low scientific foundation based on theoretical concepts but empirical medical therapy continues as a mostly off-label option for obtaining a natural pregnancy. Comprehending the hypothalamic-pituitary-gonadal axis and the regulation of hormones is crucial in this regard. Empirical therapies have the potential to overcome overtreatment with assisted reproductive technology yet clinicians and couples must be aware of the limitations of empirical therapies and should be counseled in this direction. In this review, non-specific medical treatment options for idiopathic male infertility were covered.
Keywords: Male infertility; medical treatment; empiric therapy.

ÖZ

Erkek infertilitesinde bilinen tüm olası nedenler dikkatlice değerlendirilmeli ve tespit edilirse o neden için hedefe yönelik tedavi seçenekleri uygulanmalıdır. Erkek infertilitesinin hipogonadotropik hipogonadizm, hiperprolaktinemi, genital sistem enfeksiyonları, boşalma bozuklukları, tiroid hormon bozuklukları ve varikosel gibi bilinen nedenleri, hedefe yönelik tedaviler veya cerrahi düzeltmeler ile etkili bir şekilde tedavi edilebilir. Ne yazık ki, bu bilinen nedenler erkek infertilitesinin yaklaşık %20'sini kapsamaktadır ve geri kalanı idiyopatik olarak kalmaktadır. Öte yandan, etiyolojik faktörlerin bulunamadığı, idiyopatik, açıklanamayan erkek infertilitesinin yönetimi hem klinisyen hem de çözüm arayan çiftler için zorlu bir süreçtir. Yardımcı üreme teknolojisi çağında, teorik kavramlara dayanan sınırlı yararları ve düşük bilimsel temeli olan bu konuda hala birkaç tıbbi seçenek mevcuttur, ancak spesifik olmayan tıbbi tedavi, doğal bir hamilelik elde etmek için çoğunlukla endikasyon dışı bir seçenek olarak devam etmektedir. Hipotalamus-hipofiz-gonad aksını kavramak ve hormonların düzenlenmesi bu konuda çok önemlidir. Ampirik tedaviler, yardımcı üreme teknikleriyle yapılacak olan aşırı tedavisinin üstesinden gelme potansiyeline sahiptir, ancak klinisyenler ve çiftler, ampirik terapilerin sınırlamalarının farkında olmalı ve bu yönde danışmanlık almalıdır. Bu derlemede, idiyopatik erkek infertilitesi için spesifik olmayan tıbbi tedavi seçenekleri ele alınmıştır.
Anahtar kelimeler: Erkek infertilitesi; medikal tedavi; ampirik tedavi.

Corresponding Author
Sorumlu Yazar
Metin İshak ÖZTÜRK
drmetinozturk@gmail.com

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INTRODUCTION

Infertility is defined as the failure of obtaining pregnancy after 12 months or more of regular unprotected sexual intercourse. Of all couples, about 15% are infertile. Male factor accounts for 50% of all infertility. The known causes of male infertility such as hypogonadotropic hypogonadism, hyperprolactinemia, genital tract infections, disorders of ejaculation, thyroid hormone disorders and varicocele can be treated efficiently by targeted therapies or surgical corrections. Unfortunately, these known causes cover about 20% of male infertility and the rest remains idiopathic (1).

In idiopathic male infertility, empirical therapies have been used for many years which are based on hypotheses and theories. Clinicians have to consider the treatment duration as at least 3-6 months based on the coverage of a full 74-day spermatogenetic cycle. Couples should be aware that these treatments have a low to moderate success chance when compared with assisted reproductive technology (ART). Clinicians should not insist on giving empirical therapy options to couples that lack improvement in seminal parameters and fail to have pregnancy after at least two spermatogenetic cycles. In this review, current empirical, non-specific therapy options for the nonsurgical treatment of male infertility have been discussed and summarized.

Lifestyle Changes

Environmental and lifestyle factors have the potential to contribute to idiopathic infertility (2). Therefore, simple changes in these factors can affect the sperm parameters in a positive manner. Firstly, few studies suggest that weight loss has a positive impact on sperm parameters (3,4). However, a meta-analysis of 28 cohorts and 1022 patients suggested that after bariatric surgery, sperm quality and function do not change in morbidly obese men (5). Weight loss has a clear advantage of the elimination of excess fat in the body which causes secondary hypogonadism. Similarly, physical activity has positive effects on the hormonal profiles of men, and also a recent meta-analysis has documented that moderate and high-intensity training can result in better seminal parameters (6). Cessation of smoking and heavy chronic alcohol consumption has proven positive effects on seminal parameters as well (7,8).

Gonadotropin Releasing Hormone Treatment

As known, the hypothalamus plays a crucial role by secreting pulsatile gonadotropin releasing hormone (GnRH) which induces the secretion of gonadotropins (follicle stimulating hormone, FSH, and luteinizing hormone, LH) from the anterior pituitary gland. These hormones are responsible for providing intratesticular testosterone levels and the normal process of spermatogenesis. This axis is a well-regulated system with multiple feedback mechanisms. Although exogenous GnRH administration is mostly used for a known etiology, hypogonadotropic hypogonadism, it may also be hypothesized to be used for empirical therapy with its beneficial effects on spermatogenesis. The underlying pathophysiology of the empirical use of GnRH is due to a subclinical endocrinopathy (9).

Despite being very effective in hypogonadotropic hypogonadism, administrating exogenous GnRH in idiopathic infertility has major drawbacks. Firstly, in the current literature, there is no evidence of the efficacy of this therapy when used empirically. Up-to-date, there are two randomized controlled studies which both fail to show a benefit of pulsatile GnRH in idiopathic male infertility (10,11). The seminal parameters were comparable and the pregnancy rates did not differ in both studies. In addition to the lack of scientific evidence, the high economic cost of this treatment, limited availability, and the difficulty of giving it in a pulsatile fashion with pump systems deter its clinical use. The use of pulsatile GnRH in idiopathic infertility is not recommended in the current European Association of Urology (EAU) guidelines (12).

Gonadotropins

Two major gonadotropins, FSH and LH are secreted from the anterior pituitary gland for the induction of spermatogenesis and steroidogenesis. Also, human chorionic gonadotropin (hCG), as an analog of LH, activates Leydig cells for the production of sex steroids, and human menopausal gonadotropin (hMG), having both LH and FSH activity, can be used for gonadotropin replacement. Usage of gonadotropins has failed to show a satisfying benefit and efficacy in numerous studies in terms of seminal parameters and pregnancy rates (13-15). In a review published in 2006, it is suggested that the seminal parameters were better with gonadotropin usage but not significantly different in pregnancy rates (16). On the other hand, a Cochrane database analysis of six randomized placebo-controlled studies showed better pregnancy rates in the treatment group (17). A more recent review by Jung and Seo (18) in 2014 concluded that seminal structure and pregnancy rates are better with gonadotropin therapy but the literature still lacks satisfactory evidence of empirical use of gonadotropins and combination with ART. Since in idiopathic infertility, most men have a testicular failure, resulting in azoospermia or severe oligoasthenoteratozoospermia. The feedback mechanism in testicular failure results in mostly elevated FSH and LH levels and the rationale to give more gonadotropins to these men is unclear (19). It may be stated that larger sample-sized placebo-controlled randomized studies are needed in this regard. It must be noted that the use of exogenous testosterone replacement to treat male infertility is contraindicated as it inhibits spermatogenesis (12).

Aromatase Inhibitors

Anastrozole, letrozole, exemestane, and testolactone are labeled aromatase inhibitors that inhibit the conversion of testosterone to estrogen. Also, these agents block the negative feedback of testosterone on the hypothalamic pituitary axis by lowering the converted estrogen which is a more potent inhibitory signal. Conversion of testosterone to estrogen takes place mostly in fat cells and therefore, the underlying mechanism of idiopathic infertility in obese men with high estrogen levels may be due to aromatase activity. These oral drugs are relatively safe and well-tolerated in men.

Even though its tolerability and convenience, indecisive results about aromatase inhibitors are attained when the literature is scanned. A double-blinded, placebo-controlled, cross-over study by Clark and Sherins (20) did not show an improvement in seminal parameters and pregnancy rates after 8 months of treatment with testolactone. Another study evaluated 27 oligospermic patients and concluded that letrozole 2.5 mg per day for over 6 months

increased the sperm counts and hormonal profile but failed to achieve normal levels (21). Similar results were achieved in an older study by Raman and Schlegel (22) in 2002 with anastrozole in infertile men with low serum testosterone/estrogen ratio. Overview of the studies conducted with aromatase inhibitors lead to the conclusion that these agents have potential in men with abnormal hormonal levels but the optimal testosterone/estrogen ratio for normal spermatogenesis remains vague and studies are still needed for this purpose. The latest systematic review published in 2020 about aromatase inhibitors on idiopathic male infertility documented 8 trials and reported that all agents have significantly improved the hormonal and seminal outcomes (23). While the evidence is promising, the lack of prospective studies makes the empirical use of aromatase inhibitors for idiopathic infertility off-label and debatable, especially in normogonadal men.

Antiestrogens / Selective Estrogen Receptor Modulators

These agents block the inhibitory feedback pathway of estrogen to the hypothalamus and anterior pituitary gland, resulting in an increase in GnRH and stimulating FSH and LH (24). For idiopathic infertility, antiestrogens are the most commonly used treatment for many years. Clomiphene citrate, tamoxifen citrate, toremifene, and raloxifene with various dosages have been used in this regard. The key point of this treatment is to monitor the serum gonadotropins and testosterone levels as higher levels may influence spermatogenesis negatively. The side effects cover weight gain, gynecomastia, libido changes, dizziness, headache, and nausea which are seen below 5% of patients and considered acceptable.

When the literature is scanned for efficacy, controversial results are seen. A randomized, double-blind study conducted by the World Health Organization evaluated the efficacy of clomiphene 25 mg for 6 months in 1308 men with idiopathic infertility. Semen quality and pregnancy rates did not differ from control after treatment in this study (25). A review by Cocuzza and Agarwal (26) in 2007 indicates that there are only two studies that reveal better semen quality and pregnancy rates with clomiphene citrate, with many studies suggesting the opposite. The same argument is present with tamoxifen citrate. As many trials suggest different results in this subject, meta-analyses have been conducted to clear the doubtful conclusions. In the meta-analysis by Kamischke and Nieschlag (27), antiestrogens showed no significant influence on pregnancy rates. Contrarily, a meta-analysis of 11 studies indicated that antiestrogens improve the pregnancy rate by 2.4 fold in total. In subgroup analysis, clomiphene citrate 50 mg improved the pregnancy rate by 5 fold and tamoxifen 20-30 mg by 2.8 fold. Clomiphene citrate 25 mg did not improve the pregnancy rate (28). Similar results were confirmed by a more recent meta-analysis of 16 studies (24). Antiestrogen use for normogonadal men with idiopathic infertility is still off-label and is still debated.

Miscellaneous Treatments

Besides the treatment modalities which focus on hormonal parameters, nutritional supplements, vitamins, anti-inflammatory, and antioxidant agents need to be referred. Mostly, these treatments target the improvement of sperm quality by a variety of mechanisms such as reactive oxygen species (ROS), production of prostaglandins, and enhancing the kallikrein-kinin system. The main goal of supplementary treatments is to ensure the integrity of sperm DNA and intracellular energy and membrane metabolism.

The enzymatic antioxidant mechanism in semen consists of superoxide dismutase, catalase, and glutathione peroxidase. On the other hand, glutathione, pantothenic acid, coenzyme Q10, l-carnitine, vitamin A, E, C, and minerals such as zinc, selenium, and copper are some of the non-enzymatic mechanisms of antioxidation. The imbalance between ROS and antioxidant agents leads to a low fertile potential (29).

The clinical studies that evaluate the effect of antioxidant supplements on sperm quality and function are mostly not randomized controlled studies which have a low scientific value. In a systematic review of 17 randomized studies that included 1665 infertile men evaluating the antioxidant agents' power, 14 studies showed an improvement in either semen quality or pregnancy rates after treatment. In terms of seminal parameters, motility was improved by 63%, sperm count was improved by 33% and morphology improved by 17% (29). Although these encouraging results, this review had its own limitations, studies were not controlled and their methodic designs were different. A very recent randomized controlled trial by Steiner et al. (30) in 2020 concluded that antioxidants do not improve semen parameters or DNA integrity and pregnancy and live birth rates. In a Cochrane database meta-analysis including 61 studies with 6264 subfertile men, although antioxidant treatment positively affected seminal parameters, pregnancy, and live birth rates, there is a high risk of bias in the studies, and the level of evidence was concluded as "very low" (31). Up-do-date, there are no specific recommendations on the use of antioxidant agents in the treatment of idiopathic male infertility and these agents remain completely empirical in terms of both dosage and duration of treatment.

CONCLUSION

For all possible known causes of male infertility, the goal is to target the treatment in order to get satisfactory outcomes. ART has become a major opportunity for couples with infertility and its use has become a routine practice. In cases of idiopathic male infertility, empirical treatment options can be discussed with couples in order to enhance the fertility potential with "natural" intercourse. Clinicians should be aware of the time and should set a deadline for this therapy. Over years, a better understanding of the "idiopathic" male infertility will lead to more specific directions of empirical therapies, and therefore better results.

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