

Empirical medical therapy in idiopathic male infertility: Promise or panacea?

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Male factors account for 20%–50% of cases of infertility and in 25% of cases, the etiology of male infertility is unknown. Effective treatments are well-established for hypogonadotropic hypogonadism, male accessory gland infection, retrograde ejaculation, and positive antisperm antibody. However, the appropriate treatment for idiopathic male infertility is unclear. Empirical medical treatment (EMT) has been used in men with idiopathic infertility and can be divided into two categories based on the mode of action: hormonal treatment and antioxidant supplementation. Hormonal medications consist of gonadotropins, androgens, estrogen receptor blockers, and aromatase inhibitors. Antioxidants such as vitamins, zinc, and carnitines have also been widely used to reduce oxidative stress-induced spermatozoa damage. Although scientifically acceptable evidence of EMT is limited because of the lack of large, randomized, controlled studies, recent systematic reviews with meta-analyses have shown that the administration of gonadotropins, anti-estrogens, and oral antioxidants results in a significant increase in the live birth rate compared with control treatments. Therefore, all physicians who treat infertility should bear in mind that EMT can improve semen parameters and subsequent fertility potential through natural intercourse.

Keywords: Drug therapy; Infertility, male; Pregnancy outcome; Semen analysis

Introduction

Infertility, defined as the inability of a sexually active couple to conceive after 1 year of regular intercourse without contraception, affects approximately 15% of couples, and male factors are the cause in 20%–50% of cases [1-3]. Despite technological advances, the cause of male infertility is unknown in 25% of these cases. Infertility of unknown origin is classified into idiopathic male infertility and unexplained male infertility according to semen quality [3]. Idiopathic male infertility is known as idiopathic oligoasthenoteratozoospermia, which indicates that the men have an unexplained reduction of semen quality. In contrast, unexplained male infertility is defined as infertility of unknown

origin with normal sperm parameters [3]. Furthermore, optimal strategies for treating idiopathic male infertility have also remained unclear [4].

The medical treatment of infertility is divided into two main categories: specific and non-specific. Specific treatments are used for certain etiologies such as hypogonadotropic hypogonadism, male accessory gland infection, retrograde ejaculation, and positive antisperm antibody (ASA) [4-6]. Briefly, gonadotropin replacement is considered as an effective therapy in patients with hypogonadotropic hypogonadism that inhibits spermatogenesis and testosterone production. In male accessory gland infection, the presence of leukocytes and microorganisms are responsible for male infertility and antibiotics can be administered for 2 to 3 weeks. Alpha adrenergic agonists that increase the sympathetic tone of the internal sphincter and vas deferens have been used as an initial medical treatment in patients with ejaculation disorders. ASA can block sperm-egg interaction by immobilizing spermatozoa. Although the clinical significance of ASA is controversial, assisted reproduction techniques are considered to be the treatment of choice [4-6]. In contrast, empirical medical treat-

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ment (EMT), also known as non-specific treatment, has been used in men with idiopathic infertility. EMT can also be divided into two categories based on the mode of action: hormonal treatment and antioxidant supplementation [4-6]. However, scientifically acceptable evidence of EMT efficacy is limited because of the lack of large, randomized, controlled studies. Therefore, we conducted a literature review of studies dealing with commonly used EMTs and the evidence supporting the use of EMT for idiopathic male infertility.

Empirical treatment

1. Hormonal treatment

Hormonal treatment is widely used. It is minimally invasive and has few or no side effects. The hormonal agents employed include gonadotropins, androgens, estrogen receptor blockers, and aromatase inhibitors. These agents influence the hypothalamic-pituitary-gonadal axis to correct what has been termed subclinical endocrinopathy.

1) Gonadotropins

(1) Background

The naturally circulating gonadotropins FSH and LH play a key role in the process of spermatogenesis and steroidogenesis [7]. Furthermore, it is clear that gonadotropins are effective in the treatment of patients with hypogonadotropic hypogonadism. Purified urinary extractions of hCG, FSH, and hMG, along with recombinant forms of FSH and LH, are available for the treatment of idiopathic infertility [5-7].

(2) Results

Several clinical studies have shown that gonadotropin treatment significantly increases sperm parameters and improves some ultrastructural features of sperm [8-12]. A recent systematic review, including six randomized controlled trials with 456 participants, showed a beneficial effect of gonadotropin treatment in men with idiopathic infertility on live birth and pregnancy rate [13]. Five trials reported spontaneous pregnancies after gonadotropin treatment but only one trial reported live birth rates [10,13-17]. The reviewers concluded that gonadotropin treatment resulted in a statistically significant increase in live births and pregnancies [8]. However, there was no significant improvement in pregnancy rate after IUI and ICSI cycles within the gonadotropin treatment period [17,18]. In conclusion, further research is warranted, possibly in combination with artificial reproductive technologies, because of the small number of trials and participants.

2) Androgens

(1) Background

Androgens are fundamentally important for spermatogenesis. Moreover, male accessory glands that affect seminal constitution and

sperm motility, such as the epididymis and seminal vesicles, are also androgen-dependent [3]. Two main theories have been postulated to explain the effect of androgen treatment on male infertility: the direct stimulatory theory and the rebound theory. The stimulatory theory suggests that androgens have a direct stimulatory effect on spermatogenesis and facilitate sperm transport and maturation without influencing pituitary gonadotropin secretion. The rebound theory suggests that androgen therapy suppresses gonadotropin secretion and spermatogenesis, and that the sudden withdrawal of androgens leads to a transient rise in gonadotropins and spermatogenesis [19].

(2) Results

Only one randomized double blind study of androgen treatment has reported a marginally significant improvement in sperm morphology and a positive effect on pregnancy rate [20]. However, several meta-analyses have indicated that androgens do not improve pregnancy rates or sperm parameters in men with idiopathic infertility [19,21,22]. In addition, it is necessary to remember that exogenous testosterone suppresses the hypothalamic-pituitary axis, and thereby leads to a decrease in intratesticular testosterone and spermatogenesis [23,24]. Nonetheless, a recent American Urological Association (AUA) survey demonstrated that 25% of the responding urologists still use exogenous testosterone to treat idiopathic infertility. Surprisingly, a statistically significant difference in practice patterns was seen between general urologists and fellowship-trained urologists; general urologists are more likely to use testosterone than fellowship-trained urologists ($p=0.001$) [4].

3) Anti-estrogens and aromatase inhibitors

(1) Background

Estrogen, peripherally aromatized from testosterone by a cytochrome P450 enzyme, provides negative feedback to the hypothalamus and pituitary gland [3]. Anti-estrogens such as clomiphene and tamoxifen block endogenous estrogen by binding to estrogen receptors in the hypothalamus and pituitary. Aromatase inhibitors such as anastrozole, letrozole, and testolactone interfere with the normal synthesis of estrogen by blocking the aromatization of testosterone. Subsequently, these agents block negative feedback effects from estrogen with a resulting increase in gonadotropin secretion, which in turn stimulates spermatogenesis and steroidogenesis [25,26].

(2) Results

A Cochrane Database review showed that clomiphene and tamoxifen each have a beneficial effect on hormonal levels, such as increased serum testosterone levels, but not enough evidence exists for a positive effect on pregnancy outcomes [27]. However, there is the possibility of a type II error since the lower limit of the confidence interval

(CI) in the Cochrane review was 0.99 (odds ratio [OR], 1.56; 95% CI, 0.99–2.19). Moreover, a recent meta-analysis with 11 randomized controlled trials found that anti-estrogen therapy was associated with a statistically significant increase in the pregnancy rate (OR, 2.42; 95% CI, 1.47–3.94; $p=0.004$), sperm concentration (weighted mean difference [WMD] 5.24; 95% CI, 2.12–88.37; $p=0.001$), and sperm motility (WMD, 4.55; 95% CI, 0.73–8.37; $p=0.03$) [28]. In addition, the authors concluded that clomiphene (50 mg daily) or tamoxifen (20–30 mg daily) administered for 3–6 months had a statistically significant beneficial effect on the pregnancy rate [28].

Studies of the effect of aromatase inhibitors on pregnancy outcomes are limited in number and in the size of the study population. The only double-blinded crossover randomized trial using high-dose testolactone reported no improvement in semen quality and pregnancy rate during the 16 months of the study, despite the demonstration of a lower sex hormone-binding globulin (SHBG) binding capacity with an elevation of free testosterone [29]. Several small studies using letrozole or anastrozole showed a significant increase in sperm parameters as well as a correction of hormonal abnormalities [30,31]. In addition, aromatase inhibitors have been used to treat infertile men with high estrogen or low testosterone-to-estrogen (T/E) ratios (< 10); however, the normal T/E ratio is poorly defined and a Korean study has suggested that the proper T/E ratio for treatment is < 20 [32].

An AUA survey showed that clomiphene citrate and anastrozole are the most commonly used medications used in EMT for idiopathic infertility [4]. Nevertheless, their benefits are questionable, and further placebo-controlled randomized trials are necessary.

2. Antioxidant supplementation

Recently, there has been increasing interest in oxidative stress as an important cause of idiopathic male infertility. Oxidative stress occurs when reactive oxygen species (ROS), which are an inherent byproduct of aerobic life, overcome our natural ability to detoxify ROS-induced damage [33]. In fertile men, ROS production and total antioxidant capacity remain in balance. However, pathological conditions such as infections, autoimmune disorders, chronic disease, advanced age, alcohol consumption, smoking, stress, and obesity result in oxidative stress [34]. Antioxidant defense mechanisms against ROS may be enzymatic or non-enzymatic in nature. Scavenging enzymes within the cellular cytoplasm and antioxidants in the seminal fluid play a key role in antioxidant defense mechanisms [34]. However, relatively low concentrations of scavenging enzymes within the cytoplasm and large amounts of polyunsaturated fatty acids in membranes make spermatozoa susceptible to ROS from lipid peroxidation [35]. As a result, antioxidants in seminal fluid are the most important form of antioxidant defense available to spermatozoa. Antioxidants that are naturally found in semen include vitamins, superoxide dismutase, glutathione,

and thioredoxin [35]. Previous studies have reported that high levels of ROS in seminal fluid increased the risk of male infertility [36,37]. In this section, we will review the potential role of various antioxidants as EMT for male infertility. However, there is a possibility of publication bias and the findings are controversial. In addition, the choice and dosage of antioxidants employed are not consistent in the various studies [38].

1) Vitamins

(1) Background

Vitamin E can reduce lipid peroxy radicals through the formation of lipid hydroperoxide and the radical form of vitamin E during the lipid peroxidation process. These vitamin E radicals are subsequently reduced back to vitamin E by vitamin C [33]. Therefore, vitamins E and C act as a biological scavenging pathway to limit the peroxidation of polyunsaturated fatty acids in the spermatozoa membrane.

(2) Results

Two randomized trials have found that vitamin E significantly increases sperm motility and function [39,40]. Furthermore, a recent Cochrane Database review showed that vitamin E supplementation was associated with a statistically significant increase in the number of live births (OR, 6.44; 95% CI, 1.72–24.04; $p=0.006$) compared to placebo [41]. However, the dose of vitamin E was different in each study. Kes-sopoulou et al. [40] included couples who were undergoing IVF. Vitamin C supplementation improved sperm parameters, but there have been no randomized controlled trials measuring pregnancy rate as an outcome [42,43].

2) Zinc

(1) Background

Zinc (Zn) is a metalloprotein cofactor for DNA transcription and protein synthesis. Previous studies have suggested that Zn can act as an oxidation inhibitor by binding sulphhydryl groups in proteins, and by occupying binding sites for iron and copper in lipids, proteins, and DNA [44,45]. Zn concentrations are very high in the male genital organs, particularly in the prostate gland [46]. Recent studies have found that Zn concentrations in seminal fluid were lower in infertile males [47]. In addition, Zn is necessary for the maintenance of spermatogenesis and optimal function of the testis, prostate, and epididymis [46].

(2) Results

Wong et al. [48] found that there was no significant improvement in sperm parameters, with the exception of morphology, as determined according to strict criteria in subfertile men. However, Omu et al. [49,50] reported a statistically significant increase in the number of

births and pregnancies as well as an improvement in sperm parameters.

3) Carnitines

(1) Background

Carnitines (L-acetyl carnitine and L-carnitine) are essential compounds in cellular energy metabolism and stabilize spermatozoa membranes through mitochondrial β -oxidation of long chain fatty acids [51]. L-carnitine regulates the transport of an acetyl group through the cellular membrane by producing L-acetyl carnitine as a bioactive form. These carnitines affect sperm motility, maturation, and spermatogenesis. In addition, carnitines may be responsible for the reduction of excess toxic intracellular acetyl-CoA to protect spermatozoa from oxidative stress [51,52].

(2) Results

Multiple studies have found that carnitines have beneficial effects on sperm motility and concentration [53-55]. In addition, meta-analysis has shown significant improvement in pregnancy rate when treating men with idiopathic infertility [41,52]. However, there are some differences in the outcomes depending on the form of carnitine used (L-carnitine, L-acetyl carnitine, and L-carnitine plus L-acetyl carnitine) [41,53-55]. Furthermore, Lenzi et al. [54] showed that carnitine levels in seminal fluid did not change despite treatment.

4) Others

Coenzyme Q10 is a cofactor of the electron transport chain in mitochondria [56]. In 2013, a meta-analysis of three randomized, controlled trials found that coenzyme Q10 has a beneficial effect on sperm parameters, but no effect on either live birth or pregnancy rates [57]. In addition, selenium, folic acid, and N-acetyl cysteine have been also used as EMT and have significantly improved sperm parameters in idiopathic male infertility [48,58]. Additionally, pentoxifylline and magnesium, used in the treatment of idiopathic male infertility, have not been shown to be effective in improving sperm parameters or increasing pregnancy rates [59,60].

3. Combination therapy

Combination therapies have been studied to improve pregnancy rates. Combinations of different hormonal therapies (anti-estrogen, tamoxifen with an androgen, testosterone undecanoate) in 212 men with idiopathic oligozoospermia and 82 normozoospermic men with female factor subfertility significantly improved sperm parameters and the spontaneous pregnancy rate [61,62]. In the past, the European Association of Urology (EAU) guidelines stated that tamoxifen plus testosterone undecanoate appears to be an effective therapy for idiopathic male infertility [63]. However, this recommendation was

absent in the most recently published EAU guidelines [64]. Other small randomized trials using combinations of hormonal therapy and antioxidants (anti-estrogen, clomiphene with an antioxidant, L-carnitine or vitamin E) have shown a beneficial effect on sperm parameters and pregnancy rates [65,66]. In addition, other studies with various combinations of antioxidants have been performed. Paradiso Galatioto et al. suggested that commercial preparations of N-acetylcysteine and multi-vitamins are helpful in improving sperm parameters but not in improving the spontaneous pregnancy rate [67]. However, a recent meta-analysis has shown that antioxidants in combination had a positive impact on pregnancy rates [41]. Although there is some disagreement among these studies on the improvement of sperm parameters, treatment with various combinations of Zn, vitamins, selenium, and N-acetylcysteine improved sperm motility and/or concentration [50,58,68-70].

4. Adverse effects

With any prescribed therapy, the actual and potential adverse effects associated with each agent need to be considered. Gonadotropin injections may lead to local irritation at the injection site, gastrointestinal symptoms, and breast tenderness [71]. Anti-estrogen and aromatase inhibitor therapy may result in headaches, dizziness, flushing, visual disturbances, impotence, and decreased libido [13,28,31, 71]. Antioxidants commonly cause gastrointestinal symptoms such as nausea, vomiting, and abdominal discomfort [41]. Interestingly, Cavallini et al. [72] reported mild euphoria in all treatment and placebo groups. However, many of the adverse effects related to gonadotropins, anti-estrogens, aromatase inhibitors, and antioxidants are benign and resolve spontaneously. Furthermore, meta-analyses did not find any statistically significant differences between treatment and control groups [28,41].

Currently, testosterone replacement is commonly used in elderly males with late-onset hypogonadism. Testosterone is usually safe, but may cause or aggravate prostatic disease, male breast cancer, sleep apnea, and erythrocytosis [73]. In particular, androgens may have a harmful effect on male fertility via the suppression of the hypothalamic-pituitary axis resulting in decreased production of endogenous testosterone and impaired sperm parameters [23,24]. Although it is widely known that sperm parameters return to normal after cessation of exogenous androgens, we suggest that the various types of testosterone are an inappropriate option for EMT [74,75].

Conclusion

Many types of EMT have been used in the management of male idiopathic infertility. According to EAU guidelines, FSH may be beneficial in selected patients [64]. A Cochrane Database review showed

that treatment with oral antioxidants caused a significant increase in the live birth rate compared with control treatments [41]. Therefore, all physicians and urologists who treat infertility should remember that EMT can improve semen parameters and subsequent fertility potential through natural intercourse. Additionally, an effort should be made to establish consistent protocols and recommendations for the use of various forms of EMT.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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