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OPINION

Male Infertility

More attention should be paid to the treatment of male infertility with drugs—testosterone: to use it or not?

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Testosterone replacement is strictly contraindicated for the treatment of male infertility was the advanced view from the ‘2013 European Association of Urology (EAU) guidelines on male infertility’, and this view brings extensive concern and questions. Although sufficient numbers of well-performed and controlled clinical trials that provide evidence supporting drug treatment of male infertility are not available at present, the opportunity to prove that these drugs are effective should not be prevented, and rigorous examination of drug therapy should be encouraged and strengthened. Therefore, I believe the above conclusion in the EAU guidelines is poorly conceived.

While reading the ‘2013 European Association of Urology (EAU) guidelines on male infertility’, I found some information that was difficult to interpret and acknowledge. According to the guidelines, ‘Testosterone replacement is strictly contraindicated for the treatment of male infertility. Grade of Recommendation is A.’¹ I was confused by the presentation of the new EAU guidelines for male infertility. Although the related references were listed in the 2013 EAU guidelines on male infertility, I propose that the objective facts that are described in the references should not serve as evidence for a class A (the highest level) recommendation and that the notes on the recommendation level that are given in the

guidelines are not ‘upgraded’ following panel consensus. This statement further confused me. After discussing and analyzing this information with some andrological experts in China and abroad, I decided to express my perspectives on this problem.

The estrogen receptor modulator, tamoxifen, when combined with testosterone undecanoate (TU), was shown to be an effective treatment choice for male infertility patients with idiopathic oligozoospermia.² Therefore, this approach was recommended as a first-line option for empirical therapy of male infertility and was also the only option that was recommended by the EAU for drug treatment of male infertility.^{3,4} It would appear that a large discrepancy exists between the suggestions for the application of testosterone in the treatment of male infertility that were provided by the above-mentioned guidelines and the evidence from previous studies. Regarding the treatment of idiopathic infertility, the 2012 EAU guidelines on male infertility stated ‘treatment by anti-oestrogens combined with testosterone may be effective for part of the patients’ and provided related references as evidence.⁴ However, this description was not present in the corresponding section of the 2013 EAU guidelines on male infertility, and the related references were absent. Considering that evidence-based facts such as ‘treatment by anti-oestrogens combined with testosterone may be effective for part of the patients’ had been previously recognized, I could not understand why the group compiling the guidelines made such a significant adjustment.

Based on the reasons listed below, I believe the conclusion that ‘testosterone replacement is strictly contraindicated for the treatment of male infertility’ was poorly conceived.

THE ‘TREATMENT WITH DRUG’ PRIORITY IS CONSISTENT WITH BASIC MEDICAL PRINCIPLES

Treatment for male infertility has achieved significant breakthroughs following the development of intracytoplasmic sperm injection since 1992. However, for individual male infertility patients, traditional approaches should be given importance, and medication is still one of those important, traditional treatments. Therefore, treatments that prioritize the use of drugs, which include androgen applications, are consistent with basic medical principles and are characterized as simple and noninvasive. Moreover, the treatment principle, which is indicated as ‘from simple to complex’, is the foundation of the medical model. For most male infertility patients, clear causes are difficult to determine; therefore, empirical therapies are widely applied that are consistent with basic medical principles.

Empirical treatment of male infertility was introduced in the late 1980s and aimed at overstimulating testicular function through agents that acted on the hypothalamic-pituitary-testis axis, drove Leydig and Sertoli cells to operate at their maximal capacity and exercised the accessory gland function. When upgrading gonadal function, it was hoped that sperm production and quality might improve to increase the chance of conception. Various types of empirical approaches for treatment have been employed, with variable rationales and some degree of success, in an effort to improve sperm parameters and the chance of conception in couples with idiopathic male infertility as the main cause of subfertility.^{5–7}

Despite the lack of strict support from evidence-based medicine, nearly all

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patients are willing to accept this nonspecific treatment. Therefore, traditional empirical drug treatment should be recommended by doctors as a first-line option. The efficacy and safety of these drugs have not been proven by clinical trials and data; however, I still believe that we should not be deprived of the opportunity to prove that these drugs can be effective.

LOW ANDROGEN LEVELS ARE AN UNFAVORABLE FACTOR FOR SPERMATOGENESIS

Testosterone plays an important role in the development and maturation of the male reproductive system and is of vital importance for spermatogenesis. Spermatogenesis requires that Leydig cells generate and maintain a high level of testosterone in the testicles and mainly acts on the spermatogenic epithelium to promote the generation of sperm. Low testosterone levels may cause spermatogenesis dysfunction.⁸ The testosterone level in human testicular veins can reach 50–1200 ng ml⁻¹, which is 250 times that in the surrounding venous blood and indicates that the development and maturation of spermatogenic cells require much higher testosterone levels in the testis than in the serum. After rat pituitary resection, testicular volume decreased significantly and spermatogenesis halted at the primary spermatocyte stage; however, spermatogenesis could be reinduced after supplementation with a high dose of testosterone. Experiments in rats demonstrated that decreased testosterone levels caused sperm elongation failure and resulted in sperm that could easily detach from the Sertoli cells and be absorbed.⁹ Some researchers believe that a synergistic effect between testosterone and follicle-stimulating hormone occurs that could inhibit the apoptosis of Sertoli cells.¹⁰ Additionally, testosterone is effective in promoting late-stage differentiation of sperm cells.¹¹

Recently, the influence of a low testosterone level on male physiological function and quality of life has gradually been realized. Studies have indicated that the percentage of patients with hypogonadism was approximately 38.7% in healthy males aged > 45 years when using testosterone levels that were lower than the standard 300 ng dl⁻¹.¹² Other data indicated that approximately 20%–30% of male infertility patients had a low testosterone level.¹³ A specific percentage of male infertility patients lack androgens, which may influence spermatogenesis, and diagnosing such patients with male infertility for which testosterone is contraindicated is unreasonable. Various clinical testosterone

deficiencies, such as congenital defects of testosterone synthase, Leydig cell hypoplasia, androgen receptor gene mutation induced by androgen insensitivity syndrome, Kallmann syndrome or other congenital or acquired defects of gonadotropin could cause disorders in spermatogenesis or even azoospermia. Therefore, we should not ignore the option of using testosterone as a treatment when testosterone-deficient male patients are diagnosed as infertility.

DRUG DOSAGE COULD CONTROL THE NEGATIVE FEEDBACK EFFECT OF ANDROGENS

Researchers who hold the opinion that testosterone replacement therapy is not suggested in treatment of idiopathic male infertility are mainly concerned that androgen would induce negative feedback on the hypothalamic-pituitary-gonadal axis,¹ resulting in decreased serum gonadotropins and intratesticular testosterone and thereby impairing spermatogenesis.¹⁴ This misgiving is derived from the one-way thinking that contraception could be achieved by using androgens. Authoritative opinions indicated that inhibiting spermatogenesis by negative feedback with androgens requires substitution that exceeds normal physiological values and a relatively long time course.³

To justify the use of testosterone administration in suppressing effects on basal and gonadotropin-releasing hormone-promoted pituitary gonadotropin secretion and on basal and human chorionic gonadotropin-stimulated Leydig cell function. Adamopoulos *et al.*¹⁵ administered short- (10-day) or long-term (3-month) TU (40 mg t.i.d.) to treat idiopathic oligozoospermia and demonstrated that no marked effect by any type of treatment, including TU administration at the dose that was given or in combination with tamoxifen, was seen in either central or peripheral secretory activity. Research has demonstrated that as little as 6 months of continuous TU injection at an initial dosage of 1000 mg followed by a monthly dosage of 500 mg could inhibit spermatogenesis in a clinically safe, comfortable and reversible way.^{16,17} Available data has demonstrated that a low dosage of TU (40 mg t.i.d.) combined with tamoxifen can be used in treating idiopathic male infertility, does not reduce sperm quality and enhances the pregnancy rate more than when tamoxifen is used alone.² Currently, TU is mainly used clinically at 40 or 80 mg per day for treating male infertility. Although well-performed and controlled clinical

trials that provide evidence for testosterone treatment are absent at the present time, low-dosage androgen supplements combined with other drugs might play a vital role in treating idiopathic male infertility, and the inhibition of spermatogenesis by negative feedback inhibition is not a major concern.

ANDROGENS MAY BECOME ONE OF THE MOST IMPORTANT OPTIONS FOR DRUG COMBINATION THERAPY

Evidence-based medicine is the best approach for integrating professional knowledge based on research with the preferences and values of an individual patient, and clinical judgment must be used to apply the currently available evidence to every patient. Because male infertility is characterized by multiple etiologies, multiple factors and obvious individual differences, many uncertainties exist surrounding its treatment. Therefore, drug combination therapy has gained consensus approval among most researchers and may benefit male infertility patients.¹⁸

Although gonadotropin has the potential to improve reproductive ability to some extent, various studies are still required for verification. The administration of tamoxifen to treat idiopathic male infertility has been evaluated in a number of trials, but its performance has not been sufficient to warrant general acceptance.¹⁹ Although an increase in sperm number has been demonstrated in some studies on the treatment of male infertility, beneficial effects on motility and morphology have not been observed.^{20,21} This phenomenon might be due to a lack of an effect on epididymal and accessory glands, which are mainly responsible for sperm maturation and capacitation. The relative androgen deficiency that occurred in aberrations of the sperm parameters was most likely not fully compensated by tamoxifen.²² In this context, administration of androgen at a low dose does not compromise central and peripheral hormone secretion and might be appropriate for stimulating epididymal function independently of Leydig cell activity, and thus, might improve sperm quality. In addition, TU administration (40 mg t.i.d.) could result in a marked increase in serum dihydrotestosterone (DHT) without appreciable gonadotropin changes;^{2,23} therefore, one may speculate that this increase is instrumental in bringing about the beneficial effects on sperm parameters after TU and tamoxifen coadministration. In addition, Hsieh *et al.*²⁴ demonstrated that intratesticular testosterone could be maintained during testosterone replacement therapy by

coadministration of a low dose of human chorionic gonadotropin, which could support continued spermatogenesis in patients on testosterone replacement therapy. Therefore, the rationale of combined tamoxifen or low doses of human chorionic gonadotropin with testosterone at an appropriate dose lies in the overstimulation of pituitary gonadotropin and Leydig/Sertoli cell secretion simultaneously with overstimulation of accessory gland secretion and epididymal function.

Despite the fact that research evaluating other forms of drug and combination therapy using randomized, controlled trials is still in its early stages, evidence-based medicine has revealed a preliminary conclusion: combination therapies using antiestrogens, antioxidants and androgens show promise. Research using combination drug therapy has demonstrated, in randomized, controlled trials with adequate courses, sample sizes and well-designed protocols, that patients may benefit from treatment with antiestrogens, levocarnitine, antioxidants and combinations of these drugs.¹⁸ Although mono-medicine treatment is not recommended for male infertility, combination therapy with androgens shows promising prospects. Therefore, this approach should be perfected and verified by well-designed clinical tests.

ANDROGENS IMPROVE REPRODUCTIVE ABILITY THROUGH VARIOUS PATHWAYS

Of the procedures employed in the treatment of male infertility, the most holistic approach was that of an all-out overactivation of the spermatozoa-producing apparatus and parts of the systematic regions of sperm maturation, for example, the testes and accessory glands.

Androgen receptors exist in reproductive organs, such as the testes and prostate, and in other organs, such as skin, bone, adipose tissue and brain. Therefore, androgen supplements improve reproductive organ development and sexual function-related symptoms, which keeps testosterone levels relatively stable in the testes (reducing the release of endogenous testosterone for organs) and causes extensive multiorgan effects.²⁵ Other research demonstrated that androgen supplements improved androgen deficiency-related symptoms and improved the mental state and quality of life of a patient.²⁶ All influences on sexual desire, erection, epididymis and prostate secretions, epididymis function, lipid metabolism, muscle tension, mental state and quality of life can contribute to a successful pregnancy. Therefore, we cannot ignore the multiple effects of androgens in improving reproductive capacity. Furthermore, the belief

that androgens only act on spermatogenesis is biased.

RESEARCH ON DRUG THERAPY FOR MALE INFERTILITY SHOULD BE DIRECTED AND ENHANCED

Antiestrogens, such as clomiphene and tamoxifen, initiate and maintain spermatogenesis by increasing endogenous levels of follicle-stimulating hormone, luteinizing hormone and testosterone.²⁷ Treatment of idiopathic oligozoospermia by tamoxifen combined with TU can effectively improve sperm parameters and showed higher efficacy than when tamoxifen was used alone.²⁸ Apart from tamoxifen and clomiphene, no other drugs have been approved and recommended for the treatment of male infertility. Due to the inability to identify the precise etiology of male infertility (especially for the idiopathic aberrations of sperm parameters), a rational form of treatment is not available. Furthermore, an ideal treatment will not be a realistic possibility until the full spectrum of causative factors that are involved is elucidated. What should be done to help those male infertility patients when there are a limited number of drugs that could be applied? Should we recommend that all patients accept assisted reproductive techniques (ART)? Obviously, doing so is not realistic. Taking into consideration the high cost and potential risks of ART, drug therapy is still the first-line option in the clinic for male infertility due to its potential to restore natural reproductive capacity, and it has become the basic therapy for surgery and ART.

No drug was recommended for the treatment of idiopathic male infertility in the 2013 EAU guidelines on male infertility, but empirical drug treatment is widely used and accepted. In research on empirical drug therapy for idiopathic male infertility that was conducted by the American Urological Medical Association, approximately 25% of urologists who were questioned prescribed androgen for patients who wanted reproductive benefits.²⁹ Treatment of male infertility by the coadministration of testosterone and other drugs has been employed as a first line of treatment by centers and specialists in various parts of the world, especially in those where ART are not available on technical, social, religious or economic grounds.³⁰ In general, approximately 60.5% of doctors would propose a 3- to 6-month empirical drug regimen for male infertility, and when professionally trained doctors were questioned, this percentage reached 70%. Specifically, two-thirds of American urologists

who were questioned would apply an empirical drug therapy approach.²⁹ According to national experience but without detailed data, empirical drug application (including testosterone supplementation) is perhaps applied even more widely, and experts and scientific teams cannot neglect the objectivity and rationale of this phenomenon. Furthermore, experts should standardize and guide drug application for the treatment of male infertility to make it more scientific, rational and effective instead of ignoring or stopping it.

EXAMINATION OF DRUG THERAPY FOR MALE INFERTILITY SHOULD BE ENCOURAGED AND STRENGTHENED (RATHER THAN SIMPLY FORBIDDEN)

Although ART has achieved significant success, most infertility patients still preferred to achieve their goal of being parents by natural rather than laboratory methods. Drug therapy priority is consistent with the basic medical principle, which is the gradual selection of simple to complex therapies. Despite unsuccessful experiences in treating male infertility using drug therapies, a lack of medical evidence does not mean further studies should be stopped; instead, guidelines should encourage clinical doctors to explore and accumulate related experiences. Exploration and endeavors in the empirical treatments of today would become the support for the evidence-based medicine of tomorrow, and the new EAU guidelines on male infertility seem to have become an obstacle to this beneficial exploration. The rapid development of symptomatic medical science (such as ART technology) is a double-edged sword, and to some extent, it prevents exploration of routine therapies for male infertility. We are unwilling to witness this limitation of the scientific territory available for exploration and the effects it will have.

In summary, in the treatment of male infertility, the question of whether to use testosterone attracts the attention of clinicians and specialists and provokes extensive responses that range from unreserved acceptance to a cautious or critical attitude. Empirical drug treatment of male infertility will remain empirical until it is validated by sufficient evidence-based medicine. Therefore, more attention should be paid to research on the treatment of male infertility with drugs, and exploration should be encouraged and strengthened. Any other effort and approaches toward the challenge of treating male infertility should not be discouraged

outside the framework of ART, which are also a type of empirical medicine.

As the highest standards for standardizing the clinical behavior of doctors, guidelines should express the consensus of the professional team, encourage exploration and discussion and promote the development of the subject. While formulating related treatment guidelines, the professional team should be cautious and rigorous. Based on the aforementioned discussions, I believe that any assertion that a drug should not be used to treat certain diseases should be based on sufficient evidence, especially when the assertion would hinder the further combination therapy of this drug. Male infertility is a complex disease with multiple causes for which combination therapy has reached consensus approval among professionals. Therefore, with the hope of stimulating extensive discussion among experts, I suggest that empirical drug therapy, including androgens, for male infertility requires further research to generate evidence, especially for the combined application of drugs, which would shed light on the efficacy of drug therapy for male infertility.

I have concerns regarding the guidelines and wish to present this controversial issue on male infertility treatment. I sincerely wish that the issue be discussed and refined in order to reach a consensus view among a greater number of experts. In such a case, the impartiality and authority of the EAU could be maintained, the guidelines could direct clinical practice more efficiently, and the guidelines could be perfected through practice and become more popular and widely accepted. Moreover, uncertain factors will be revealed in the formulation of any guidelines, progress in medical science will lead to a better understanding of certain diseases, and the authority for such guidelines will be continuously challenged. No guidelines are always correct, but they should reflect current knowledge and understanding. Academic controversies represent the greatest respect to science, because controversies lead to in-depth thinking and concerns regarding academic issues. Finally, I sincerely hope the guidelines advance with the times and guide clinical practice more efficiently.

COMPETING INTERESTS

The author declares no competing interests.

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