Empirical Drug Therapy for Idiopathic Male Infertility: What is the New Evidence?

Harshit Garg and Rajeev Kumar

Idiopathic male infertility is empirically managed using a number of drugs. We reviewed 64 articles published in the last 10 years on such drug therapy. There was severe heterogeneity in data along with poor definition of outcome parameters. Pregnancy or live birth rate was not reported in many studies. Antiestrogens appear to improve pregnancy rates while there is some data supporting the use of aromatase inhibitors. Antioxidants significantly increase the rate of both live birth and pregnancy but the data are limited. However, valid end-points based on data are limited for the empirical use of drugs in idiopathic male infertility. UROLOGY 86: 1065–1075, 2015. © 2015 Elsevier Inc.

The World Health Organization (WHO) defines infertility as the inability to conceive within 12 months of regular sexual intercourse.[1] The male partner is believed to be contributory when there is abnormality in semen parameters involving motility, morphology, or concentration in at least two semen analyses. Since abnormalities of these 3 parameters often coexist, the condition is referred to as oligoasthenoteratozoospermia or OAT. In up to 30% men, no specific etiology can be identified and they are considered to have idiopathic OAT.

OAT can be managed using therapy specifically targeted at the etiology (infection, varicocele, hormonal abnormality), bypassed using assisted reproductive technology, or subjected to empirical drug therapy. In the absence of a definitive therapy, these men are often administered a number of empirical drugs, including hormonal preparations and antioxidants, without clear benefit.

In an earlier article,[2] we had reviewed the Pubmed/Medline database for literature on empirical treatment of idiopathic male infertility and concluded that there was no drug with clear evidence in its favor. Although a number of drugs were postulated to have a possible role in the management of male infertility, very few controlled or randomized trials existed to study their impact. Certain therapies such as androgens and gonadotropins were found to actually impair spermatogenesis or lead to complications. As a number of new molecules and studies have appeared since the publication of that article, we aimed to review the new data on drug therapy for idiopathic male infertility.

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From the Department of Urology, All India Institute of Medical Sciences, New Delhi, India

Address correspondence to: Rajeev Kumar, M.Ch., All India Institute of Medical Sciences, New Delhi, 110029, India. E-mail: rajeev02@gmail.com

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MATERIALS AND METHODS

The Pubmed/Medline database was searched using the following keywords in various combinations: male infertility, treatment, drug therapy, oligoasthenoteratozoospermia, oligospermia, asthenospermia, teratospermia, hormonal agents, gonadotropins, follicle-stimulating hormone (FSH), luteinizing hormone (LH), gonadotropin releasing hormone (GnRH), luteinizing hormone releasing hormone (LH-RH), clomiphene, tamoxifen, anastrozole, aromatase inhibitor, antiestrogens, antioxidants, lycopene, alpha-tocopherol, Vitamin E, glutathione (L-γ-glutamyl-L-cysteinylglycine), carnitine, coenzyme Q10, and arginine. Articles with abstracts, published after 2005 (except for arginine for which the search included all data since 1985), describing mechanism of action, animal or in vitro studies, and human trials were retrieved and reviewed. Full texts were retrieved either through the journal access from the library or a request to the author. If full-text access was not possible, only the abstracts were reviewed, and such studies are clearly identified in the tables listing the reviewed articles. Articles describing combination therapies were excluded from the review. Articles describing case reports or studies involving patients fewer than 10 also were excluded.

RESULTS AND DISCUSSION

A total of 64 articles were included in the review. Three manuscripts involved study of more than 1 drug but not as a combination therapy. Full texts were retrieved for 51 articles and only abstracts could be retrieved for remaining 13 studies. Supplementary Table 1 lists the total number of studies, full articles, and abstracts reviewed for each medical agent.

HORMONAL AGENTS

Gonadotropins

Gonadotropins form the principal mode of therapy in the management of hypogonadotropic hypogonadism.[3] However, their role in idiopathic male infertility is far less established. Our earlier review suggested that

gonadotropins play a role in the improvement of sperm parameters, especially in assisted reproduction, but they do not significantly increase the rate of pregnancy.[2]

Evidence. Studies on the use of gonadotropins in idiopathic male infertility are given in Table 1. Attia et al[7] reported a meta-analysis of 6 randomized controlled trials in 2013. This meta-analysis involving 456 participants concluded higher spontaneous pregnancy rate in the treatment group compared to placebo. There was no significant difference between groups when intracytoplasmic sperm injection (ICSI) or intrauterine insemination was performed. On the contrary, Colacurci et al[6] reported a randomized controlled trial to study the role of gonadotropins in 129 infertile men and found no increase in sperm parameters or hormonal levels. They did not measure pregnancy rates as an outcome of the study.

Aromatase Inhibitors

Aromatase inhibitors decrease the conversion of androgens to estrogen and its derivatives. Estrogen has a negative feedback on production of gonadotropins and impairs spermatogenesis. Adipose tissue forms one of the major sites of conversion of androgens to testosterone in men and hence aromatase inhibitors have potential application in men with low testosterone-to-estradiol ratio.

Evidence. Table 1 lists the prospective studies available on the use of aromatase inhibitors. Although Saylam et al[8] showed significant improvement in sperm parameters and hormonal profile after treatment with letrozole for 6 months in 27 infertile men with oligo-azoospermia, the mean sperm count and motility did not reach normospermia after treatment. Gregoriou et al[9] did not find any significant difference between letrozole and anastrozole on seminal parameters before and after treatment even though anastrozole led to numerically higher sperm counts after treatment. Cavallini et al[10] studied 46 patients with idiopathic male infertility with low testosterone-to-estradiol ratio (<10). They found significant increase in sperm concentration and motility after treatment with letrozole for 6 months. However, the mean sperm concentration and progressive sperm motility improved from 450/ml and 2% to 1.3 million/ml and 18%, respectively, and hence failed to achieve normozoospermia. This study did not measure pregnancy as the outcome parameter.[10]

Antiestrogens

Antiestrogens decrease the negative feedback of estrogen on the hypothalamus and pituitary, leading to an increase in FSH and luteinizing hormone that stimulates testosterone production and spermatogenesis. Up to 41% men with infertility may have clinical or subclinical hypogonadism with testosterone levels below 300 ng/dl.[11] Antiestrogens such as clomiphene citrate, as well as aromatase inhibitors such as anastrozole, have been shown to increase testosterone levels.[12]

Evidence. Clomiphene is generally used at a dose of 25-50 mg/day whereas tamoxifen is used in dosage of 10-30 mg/day. Antiestrogens have been extensively studied in a number of trials (Table 2). Patankar et al[13] and Moradi et al[15] found improvement in sperm concentration and motility after treatment with clomiphene citrate at 25 mg/day for 3 months. Moradi et al[15] reported improvement in mean sperm concentration and motility from 20.3 million/ml and 23.7% to 42.5 million/ml and 43.3% after treatment, thereby, achieving normozoospermia. Cakan et al,[14] in a prospective single-blinded randomized controlled trial, reported significant improvement in sperm concentration and motility after treatment with tamoxifen. However, the mean sperm concentration and motility after treatment failed to achieve normal levels. Tang et al[16] also found significant improvement in sperm concentration but not in sperm morphology and motility. In a recent study, Nada et al[17] found tamoxifen improved sperm concentration and morphology but not sperm motility. Pregnancy rates were not reported in these studies.

Antiestrogens are also used in assisted reproduction cycles for improving retrieval of sperms for ICSI (Table 2). Hussein et al[19] reported 100% retrieval of sperms for ICSI in 42 azoospermic men after treatment with clomiphene for a mean duration of 5 months. They also reported resolution of azoospermia on testicular biopsy in 64.3% cases. Moein et al[20] also inferred similar results with 100% successful retrieval of sperms after treatment with tamoxifen for 3 months.

A recent Cochrane review of 11 clinical trials included 9 trials that reported pregnancy rate as an outcome.[18] The meta-analysis concluded there was a 2.4 times higher chance of pregnancy after treatment with antiestrogens compared with controls ($P = .0004$). In a subgroup analysis, clomiphene 50 mg/day and tamoxifen 20-30 mg/day were found to have 5 times ($P = .003$) and 2.8 times ($P = .003$) higher chances of pregnancy, respectively, as compared to controls. However, clomiphene at a dose of 25 mg/day was not significantly associated with increased pregnancy rate.

ANTIOXIDANTS

Spermatozoa are rich in polyunsaturated fatty acids and are susceptible to oxidative damage. Reactive oxygen species are principally derived from leukocytes and sperm cytoplasm. Increased generation or impaired clearance of reactive oxygen species leads to oxidative stress, thereby causing DNA fragmentation, membrane disintegration, and hence infertility.[21] A number of antioxidant agents have been used in idiopathic male infertility.

Glutathione

Glutathione forms an integral part of enzyme glutathione peroxidase (GPX). GPX in spermatids scavenges hydrogen