Medical management of male infertility: now and future

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Purpose of review
Medical therapy for idiopathic male infertility has historically been empiric and based on small observational studies rather than larger well designed clinical trials. This review is timely and relevant because of the recent publication of several studies that are less susceptible to bias because of being placebo-controlled and more highly powered.

Recent findings
The largest proportion of recent publications covered antioxidants, with eight randomized controlled trials (RCTs) included in this review. The Males, Antioxidants, and Infertility (MOXI) trial is of particular interest, being a large multicenter RCT, which demonstrated no improvement in semen parameters or live-birth rates with antioxidant use. In addition, phosphodiesterase-5 inhibitors (PDE5i) have been shown to improve semen parameters, while duloxetine use was not associated with any adverse effects on sperm. Progress was also made in the realm of regenerative medicine, with the realization of the first successful primate model of sperm production from pluripotent stem cells.

Summary
It may be time to stop recommending antioxidants for idiopathic male infertility given recent studies suggesting lack of efficacy, but given their relative safety, it is reasonable to continue their use until the evidence is overwhelming. Otherwise, stem cell therapy is another anticipated area of research interest.

Keywords
azoospermia, idiopathic infertility, male infertility

INTRODUCTION

Male factor infertility has many potential causes, but is frequently multifactorial or idiopathic. If the cause is known, pharmacologic treatments tend to be well established. However, up to a quarter of male infertility cases are idiopathic. For these cases, treatment options are empiric and have less definitive outcome data to support use of these agents.

In this review, we summarize the most recent developments in the medical management of male infertility and speculate on developing therapies to look forward to. Most recent publications build upon existing treatment options, which are mainly drugs targeting the hypothalamic–pituitary–gonadal (HPG) axis. A large proportion of these studies focus on the effect of antioxidant use on semen parameters, as it has long been posited that increased oxidative stress may play a factor in idiopathic male infertility. An update on this topic is much needed, as previous data came from uncontrolled studies with variable designs. One experimental treatment under investigation that will also be given attention in this chapter is the use of stem cells to restore spermatogenesis in nonfunctioning testes.

METHODS

A PubMed search was conducted using the search terms 'male infertility treatment', 'male factor infertility', and 'medical management of male infertility' with a filter applied to only show articles published in the past 2 years. This yielded over 2000 articles, of which 40 were ultimately selected after careful review of all titles and abstracts. Inclusion criteria included primary source clinical trials or prospective

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KEY POINTS

- Drugs traditionally used for hypogonadal hypogonadism, such as gonadotropins, aromatase inhibitors, and selective estrogen receptor modulators may also have some limited benefit in idiopathic male infertility, though use remains primarily off-label.
- A recent meta-analysis demonstrated significant improvement in semen parameters with phosphodiesterase-5 inhibitor (PDE5i) use.
- Although many small-scale studies exist demonstrating improvement in semen parameters with use of various antioxidants, the true clinical utility of this treatment is called into question by the Males, Antioxidants, and Infertility (MOXI) trial, which is a large multicenter trial demonstrating no improvement in semen parameters or live-birth rates with antioxidant use.
- A randomized placebo-controlled trial on duloxetine use was not associated with any adverse effects on semen parameters, suggesting that at least serotonin and norepinephrine reuptake inhibitors (SNRIs) and perhaps selective serotonin reuptake inhibitors (SSRIs) are well tolerated for use in men desiring fertility.
- Advances are being made in the realm of stem cell therapy, with the first successful primate model of sperm production from pluripotent stem cells being realized in 2021.

studies on human patients, meta-analyses of existing treatments, and speculative articles on the future of male infertility. We excluded studies on herbal supplements not commonly used in the United States, animal models of infertility, and systematic reviews without statistical analysis.

MEDICAL TREATMENTS

Gonadotropins

Gonadotropins such as human chorionic gonadotropin (hCG), follicle-stimulating hormone (FSH), or human menopausal gonadotropin (hMG) have a proven benefit in men with hypogonadotropic hypogonadism who are unable to secrete their own gonadotropins. Traditional first-line therapy consists of hCG, though a consensus dosing regimen does not exist. After establishing a eugonadal state, recombinant FSH or hMG may be added for further spermatogenic stimulation. However, there is limited data on the use of these agents for otherwise normogonadotropic men with idiopathic infertility. Only two studies were published in the past 2 years on gonadotropin use for male infertility.

One study was a meta-analysis, which included five randomized controlled studies on use of FSH for normogonadotropic patients with idiopathic oligozoospermia (total sperm count under 39 E6 per ejaculate) compared with placebo [1]. A total of 372 patients and 294 controls were analyzed. Trials were classified by FSH dose, which was characterized as low (175–262.5 IU weekly), intermediate (350–525 IU weekly), or high (700–1050 IU weekly). The meta-analysis concluded that high-dose FSH, in particular, was effective in increasing sperm concentration, total sperm count, and progressive motility.

The other was a prospective case–control study where researchers evaluated the effect of FSH on 40 men with azoospermia because of spermatogenic dysfunction who underwent a prior unsuccessful microscopic testicular sperm extraction (microTESE) [2]. These patients were divided into two groups, with one group undergoing 1 month of testosterone downregulation in conjunction with FSH followed by 3 months of FSH treatment, while the control group had no treatment. Patients underwent a second microTESE, and it was noted that the control group had no positive sperm retrievals while the treatment group had two positive retrievals out of 20 patients. This was not statistically significant, but is an observation that certainly would warrant study in a larger trial prior to acceptance into clinical practice. A recent retrospective publication by Ozman *et al.* [3] that cited an 18.4% successful sperm retrieval rate following repeat microTESE without any medical intervention, demonstrating the lack of clarity for these difficult scenarios and questioning whether the findings of Verdi *et al.* would hold true in a larger study population.

Aromatase inhibitor therapy

Aromatase inhibitors such as anastrozole work by competitively inhibiting the peripheral conversion of androgens to estrogens, thereby reducing the inhibitory effect of estrogen on the HPG axis and increasing intra -testicular testosterone and spermatogenesis. A recent study suggests an important additional effect of aromatase inhibitors on Leydig cell aromatase activity suggesting a potential therapeutic target for the intratesticular testosterone : estrogen ratio, which is independently associated with spermatogenesis [4▪]. Aromatase inhibitors have been used as an off-label drug for the treatment of idiopathic male infertility.

Over the past year, only one low-quality retrospective trial has been published. This study focused on the use of anastrozole for hypogonadal and subfertile men with a BMI over 25 kg/m^2. After 5 months of therapy, these men were observed to

have improved hormonal profiles and semen parameters with a 46% rate of clinical pregnancy [5▪].

Selective estrogen receptor modulators

Selective estrogen receptor modulators (SERMs) are a class of drugs that upregulate gonadotropin secretion from the pituitary, primarily by binding estrogen receptors and thereby preventing the negative feedback effect of estrogen on gonadotropin production. SERMs such as clomiphene citrate and tamoxifen have a well established off-label role in the treatment of hypogonadal men with infertility. However, American Urological Association guidelines caution on the limited benefit of SERM therapy relative to assisted reproductive technologies (ART) [6].

There is no consensus on the testosterone cutoff needed to initiate SERM therapy. A recent retrospective study attempted to establish that cutoff by hypothesizing that hypogonadal men with idiopathic infertility and a total serum testosterone under 265 ng/dl would have more significant improvement with SERM use than those with a higher baseline testosterone [7]. The study included 83 male individuals with unexplained infertility who received 50 mg clomiphene daily for over 90 days, and were found to have a significant improvement in testosterone levels and sperm concentration regardless of baseline serum testosterone. These researchers found that their linear regression pattern of improvement was the same regardless of the testosterone value they chose to represent the cutoff for hypogonadism. They, therefore, recommended consideration of clomiphene for any patient with idiopathic male infertility with a testosterone level below 400 ng/dl, which is the cutoff suggested by the Endocrine Society.

One systematic review of 384 men from 11 different studies did note a paradoxical worsening in semen parameters in up to 17% of patients treated with clomiphene citrate, a decline that did not improve with discontinuation of therapy [8▪]. This effect has not been fully explored and is not currently understood.

Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 inhibitors (PDE5i) are the gold standard treatment for erectile dysfunction, and a few older studies exist that suggested an improvement in semen parameters with PDE5i use. In the past year, one meta-analysis was performed on nine RCTs involving 1211 participants from multiple countries who were given various regimens of PDE5i and had their semen parameters measured before and after treatment. This was compared with men treated with a sham treatment. They found a significant improvement in sperm concentration, motility, and morphology. Some limitations of this study are that most of the existing RCTs were small and did not take into account each patient's demographic factors that may contribute to bias [9▪▪].

Antioxidants

Antioxidants are an attractive area for study as reactive oxygen species (ROS), and oxidative stress have long been proposed to play a role in idiopathic male infertility or subfertility. Of the many antioxidants under investigation, the ones that have historically shown some benefit for the treatment of male infertility include vitamin C, Coenzyme Q10 (CoQ10), L-carnitine, and glutathione. There have also been small-scale studies to evaluate the role of antioxidants in preventing damage to sperm during cryopreservation, which is an important component of in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) success. Some common problems cited for these studies include the high risk of bias because of poor reporting methods of randomization, lack of follow-up of live birth rates and pregnancy, high patient attrition, and small overall sample sizes, which prevents definitive consensus statements on the use of antioxidants for idiopathic male infertility [10▪].

A total of eight relevant randomized controlled trials (RCTs) were published in the past 2 years, of which six were placebo-controlled. These studies were small scale, and although some combinations did demonstrate an improvement in semen parameters, the differences tended to be small, and no studies demonstrated a significant difference in pregnancy rates. The antioxidant combinations, which showed improvement in sperm parameters include CoQ10 [11▪,12▪], L-carnitine, N-acetyl-cysteine [13▪,14▪,15▪,16▪,17], and vitamin D [18▪].

One study that attempted to address the issue of studies being inadequately powered is the Males, Antioxidants, and Infertility (MOXI) trial, which was a multicenter double-blind randomized controlled trial conducted at nine fertility centers in the United States from 2015 to 2018. This trial enrolled 174 men who were randomly assigned to either a treatment arm consisting of a commercially available mix of vitamin C, vitamin E, selenium, L-carnitine, zinc, folic acid, and lycopene ($n = 85$) or placebo ($n = 86$). Primary outcome was live birth, with secondary outcome being pregnancy within 6 months of treatment. An internal pilot was also conducted with primary outcomes being semen

parameters and DNA fragmentation index after 3 months of treatment. This study initially concluded in 2020 that antioxidants neither improved semen parameters nor increased live-birth rates [19▪▪]. A secondary analysis of this trial was also conducted where baseline serum levels of vitamin E, zinc, and selenium were analyzed and found to have no significant impact on semen parameters or birth rates [20▪▪].

Another recently published prospective study with findings similar to the MOXI trial assessed the impact of 3 months of lifestyle changes in conjunction with oral antioxidants (including a mix of multivitamins, CoQ, omega-3, and oligo-elements) on semen parameters [21]. This study was conducted in 93 patients with a history of failed IVF or ICSI, with 10 healthy male individuals serving as controls. This study observed no differences in sperm parameters or static oxidation–reduction potential in the treatment group.

Antidepressants

The impact of antidepressant use on male fertility is an avenue worth studying because of the increasing prevalence of these medications. There has historically been a paucity of research on the topic, though some in-vitro, animal, and observational studies have shown potential negative effects of selective serotonin reuptake inhibitors (SSRIs) on semen parameters [22]. This negative association was recently called into question by a double-blind placebo-controlled RCT from Cornell, which concluded that administration of duloxetine had no effect on bulk semen parameters [23▪▪]. These results are encouraging as this is the first adequately powered human study to be published and suggests that at least duloxetine is well tolerated for use in men desiring fertility.

Stem cell therapy

Stem cells therapy is a promising avenue of scientific research that is increasingly being explored for male infertility. Although no human clinical trials have been conducted to date, there are promising results shown in many in-vitro and in-vivo studies on the topic [24▪,25▪].

Stem cells are cells that can differentiate into any cell of the human body under the right conditions. One type of stem cell deemed relevant to male infertility include mesenchymal stem cells (MSCs), which are multipotent stromal cells that may be derived from either cord blood, bone marrow, or adipose tissue. These cells can theoretically be transplanted into azoospermic testes to either induce spermatogenesis via its paracrine function or differentiate into new germ cells [26▪]. Another type of stem cell under investigation are induced pluripotent stem cells (iPSCs), which are artificially created from adult somatic cells through retrovirus-mediated transduction of specific transcription factors into fibroblasts. This allows researchers to bypass the use of embryos as a source for the stem cell, which has historically been restricted for ethical reasons, and negates the risk of immune rejection (as iPSCs are created from autologous tissue).

It has long been known that it is possible to create sperm using mice stem cells, but the clinical relevance of this was uncertain given the significant differences between mouse and human reproduction. In 2021, Khampang *et al.* [27▪▪] published a study, which reported the successful production of functional sperm from pluripotent stem cells in rhesus monkeys. Given the similarities between humans and primates, this represents an exciting advancement that suggests that a viable stem cell therapy for azoospermic men may be on the horizon. More in-vivo studies are needed to definitively prove the viability of this treatment for use in humans, and ethical debates surround the utilization of such techniques.

In addition, because the process of creating iPSCs involves reprogramming of the cell using transcription factors, there is a risk of mutation in the genome of the cell. Reducing the oncogenic potential of these stem cells is another challenge to be surmounted before they can safely be used in patients [28▪].

DISCUSSION AND FUTURE PERSPECTIVES

Antioxidant use for treatment of male infertility has been a topic of interest for decades, and while we appear to be closer to a consensus opinion, there is still more work that needs to be done in this area. The sheer number of antioxidant agents available is so large that many drug combinations are possible, and there is high heterogeneity in trial design. To date, there are only a few studies, which may be considered good-quality placebo-controlled RCTs, and these tend to be small scale. Many studies focus on the effect of drugs on semen parameters or sperm fragmentation, with only a few studies including reproductive outcomes (fertilization rate, pregnancy rate, and live birth rate) as a primary outcome. This makes it difficult to assess the clinical relevance of these studies, particularly given recent publications that have found a lack of correlation between factors like sperm DNA fragmentation and live pregnancy rates [29▪]. In addition, pregnancy occurrence is multifactorial, and it would be unrealistic to fully

attribute any pregnancy outcome to the administration of antioxidant therapy alone. However, given the demonstrated safety of antioxidant use and the presence of many small-scale studies demonstrating improvement in the quality of sperm, it may be reasonable to recommend these drugs for use in idiopathic infertility.

On the more experimental front, stem cell therapy is an avenue, which holds promise for the treatment of idiopathic male infertility and has been shown to be viable in animal models. We look forward to further research into this potential treatment option.

CONCLUSION

Medical treatment for idiopathic male infertility remains largely provider-dependent and empiric. Clinicians may exercise their judgment on what medications to prescribe based on the patient's individual characteristics and taking into account past medical history and baseline hormonal and semen function. Larger scale randomized trials are needed to definitively reach a consensus opinion on treatments.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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