Chapter 34
Can empiric medical treatments improve idiopathic male infertility?

Jared M. Bieniek and Kirk C. Lo

Infertility is a frustrating condition affecting 15% of couples with identifiable male factors contributing to half of cases. Evaluation of the infertile man includes a thorough medical history, focused physical examination, and initial laboratory testing including a semen analysis and reproductive hormones. Targeted medical management or surgical therapies may be offered for specific findings. Idiopathic infertility, defined as the presence of semen analysis abnormalities with no historical infertility risk factors, a normal physical examination, and normal endocrine testing, often proves more challenging.

The major components of a comprehensive semen analysis describing sperm quantity and quality include sperm concentration, motility, and morphology (sperm shape) (Chapter 22). Decreased sperm concentration, motility, or an increased number of abnormal forms can be seen in men with idiopathic male infertility (IMI). These abnormal findings may often present together. The prevalence of IMI among infertile men ranges between 30-40%.

Despite the frequent finding of IMI, treatment options remain limited. Recent American Urologic Association (AUA) and European Association of Urology (EAU) guidelines on male infertility both review supplements and various hormonal medications specific to IMI treatment. Extensive reviews also detail the status of many of these prescription and non-prescription options. This chapter summarizes the data and recommendations for empiric medical treatment of men presenting with IMI.

Supplements

Supplements as a class include a wide variety of vitamins, antioxidants, and nutritional supplements. Antioxidants in particular have been extensively studied for the treatment of male infertility given

the link between increased oxidative stress and male subfertility. Reactive oxygen species, which form as a result of oxidative stress, can impair sperm function and DNA integrity. Various single antioxidants or combination regimens have been reported including vitamin C, E, selenium, zinc, folic acid, carnitine, lycopene, and coenzyme Q10 among others.

The most recent 2019 Cochrane meta-analysis included 61 randomized controlled trials (RCTs) with over 6,000 men and concluded that antioxidant supplementation led to slightly improved pregnancy and live birth rates. However, many of the included studies were of low quality with no evidence of increased live birth rate when excluding studies with high risk of bias. The more recent Males, Antioxidants, and Infertility (MOXI) trial randomized 174 men with abnormal semen parameters to an antioxidant combination or placebo. Over six months of treatment, no significant changes in semen parameters, pregnancy, or live birth rate were found. Antioxidant use appears to be safe with no increase in miscarriages and low risk of gastrointestinal (GI) symptoms.

The use of supplements for treatment of male infertility is of "questionable clinical utility" based on available literature per the 2020 AUA & American Society of Reproductive Medicine guideline on male infertility. It is not possible to recommend any specific antioxidant formulation owing to the variability of reported regimens. The 2021 EAU guideline acknowledges the weak evidence supporting antioxidants in improving semen parameters in IMI but likewise does not make any formulation recommendations.

The heterogeneity and quality of studies on antioxidant supplementation make it challenging to draw conclusions for the clinical treatment of IMI. The availability, relative safety, and general low cost of supplements may make them an appropriate option in selected individuals with risk factors for oxidative stress. Antioxidants in higher-than-recommended doses should be avoided due to the risk of conversion to reductive stress, which can also be detrimental to sperm.

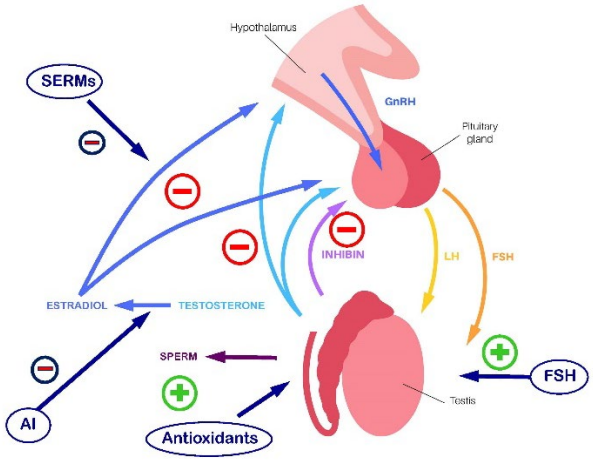

Figure 1: Hypothalamic-pituitary-gonadal axis with mechanisms of action of empiric male infertility treatments (dark blue text corresponds to medication or supplement class; AI = aromatase inhibitor, FSH = exogenous follicle stimulating hormone, SERMs = selective estrogen receptor modulators)

Selective Estrogen Receptor Modulators (SERMs)

Prescription medical treatments for male infertility target the hypothalamic-pituitary-gonadal (HPG) axis to increase signaling and downstream sperm production (Figure 1) (Chapter 2). Briefly, natural pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus leads to release of gonadotropins, follicle stimulating hormone (FSH) and luteinizing hormone (LH), from the anterior pituitary. FSH in turn stimulates Sertoli cells which support spermatogenesis while LH acts on Leydig cells to cause testosterone production. Testosterone, estradiol, and inhibin, a protein secreted by Sertoli cells, provide negative feedback to the hypothalamus-pituitary axis to maintain homeostasis.

SERMs represent a class of medications that exert agonistic or antagonistic effects on estrogen receptors based on medication and tissue type. These medications are useful for treatment of male infertility due to their blockade of estrogen receptors in the hypothalamus and pituitary, thus increasing GnRH, gonadotropins, and driving sperm and intratesticular testosterone production (Figure 1). Clomiphene and tamoxifen are the most commonly selected

SERMs for treating male infertility though neither is approved for this use, thus they are considered off-label.

While the use of SERMs and other hormone stimulating medications is supported for the treatment of infertile men with low testosterone, the data is mixed among men with IMI who, by definition, have normal endocrine values. A meta-analysis in 2013 including 11 studies found significant improvements in sperm count and pregnancy rates in men with IMI treated with SERMs. However, the overall effect on pregnancy rate remained small with few studies reporting complications associated with SERMs that can include blurred vision, breast tenderness, and low risk of thromboembolism.

Again many of the individual studies included in the above reviews are low quality leading guidelines to conclude that SERMs offer limited benefit to men with IMI, providing minimal improvements to fertility outcomes and possibly delaying future treatments. While the goal of SERM use is to drive the HPG axis forward and improve semen parameters, the benefits may not be realized for men with IMI who already have normal endocrine values. Relative to empiric SERMs, assisted reproductive techniques (ART), such as intrauterine insemination or *in vitro* fertilization, offer greater fertility success and should be discussed as a part of shared decision making. SERMs remain a valuable tool in selected men with IMI, particularly those with borderline endocrine values or those who cannot pursue ART due to cost or religious reasons. Additional research may better define men with IMI who can derive the greatest benefits from empiric SERM administration.

Aromatase Inhibitors

Estradiol, present in low concentrations in men, is an important male hormone but when elevated can cause excessive negative feedback on the HPG axis (Figure 1). Multiple cell types, particularly adipocytes and Leydig cells, contain aromatase, the enzyme responsible for estradiol production via aromatization of testosterone. Increases in serum testosterone or adiposity can lead to an increased estradiol level, low testosterone/estradiol (T/E) ratio (defined as <10 when T is reported in ng/dL and E in pg/mL), and downstream effects on spermatogenesis.

Men with IMI have normal endocrine parameters but those with abnormally low T/E ratio may be logical candidates for empiric treatment with an aromatase inhibitor (AI). AIs inhibit

estradiol production and associated central HPG negative feedback, leading to increased hypothalamic and pituitary signaling and testicular function. AIs may also be combined with a SERM to reduce excessive aromatization of testosterone with estrogen receptor blockade. Commonly used AIs for male infertility include anastrazole and letrozole, both of which are off-label, much like SERMs.

Most trials evaluating empiric AI use include subfertile men with low testosterone, not truly IMI. As expected, a 2019 meta-analysis of eight such studies demonstrated significant improvements in endocrine and semen parameters. Pregnancy outcomes were not reported in the included trials. A low number of men (3.2%) stopped therapy due to side effects with no bone metabolism disorders identified. High-quality prospective studies are needed to evaluate the role of empiric AIs specifically in men with IMI.

The EAU male infertility guideline notes insufficient evidence to support AI use for treatment of IMI The AUA guideline recommends considering AI administration for infertile men with low testosterone levels but does not mention empiric AIs for IMI. The use of AIs for IMI may be appropriate for selected patients with abnormal or borderline T/E ratios who are not candidates for or wish to avoid ART. Potential adverse effects to discuss before prescribing include GI upset, decrease in libido, abnormal bone metabolism with chronic use, and low risk of thromboembolism.

Exogenous FSH

Exogenous FSH is approved only for use in men with hypogonadotropic hypogonadism and can be administered as a subcutaneous injection. Given in purified or recombinant forms, it acts directly at the testicular level on Sertoli cells to support sperm production (Figure 1). Exogenous supplementation in men with IMI having normal FSH has been extrapolated to likewise increase sperm count, quality, and fertility outcomes.

An updated 2013 Cochrane systematic review included six RCTs with 456 men comparing FSH treatment to placebo or no treatment for idiopathic subfertility. Despite varying protocols, exogenous FSH treatment resulted in higher pregnancy rates (16% vs 7%). No differences were found in a subgroup analysis of couples utilizing ART. A more recent 2015 meta-analysis reviewed 15 controlled trials comprised of over 1,200 men. Spontaneous

pregnancy rates were similarly improved with FSH use (11% vs 2%). Pregnancies after ART demonstrated a small but significant increase with FSH in this review. Optimal FSH dosing for IMI remains uncertain.

Available studies on FSH analogues for IMI led the EAU guideline committee to conclude, albeit weakly, that treatment may improve sperm concentration in men with low sperm concentration. The AUA guideline recommends considering exogenous FSH to improve sperm concentration and fertility outcomes but admits that the cost-effectiveness of treatment is questionable. In clinical practice, FSH analogues must be used for three months or longer with significant associated cost and limited improvements in pregnancy outcomes. Due to limited cost-effectiveness for IMI, shared decision making discussions are necessary before embarking on FSH treatment.

Summary

Despite reported improvements in semen parameters and fertility outcomes with empiric IMI treatments, the heterogeneity of studies makes it challenging to draw conclusive recommendations. Supplements, particularly antioxidants, offer a cost-effective option for men with IMI but the literature is not sufficient to support a specific formulation. SERMs and AIs may be considered for carefully selected individuals, particularly those wishing to avoid ART. The use of FSH analogues is supported by limited evidence but the cost, duration, and limited effectiveness of treatment challenge its practicality. Exogenous testosterone should always be avoided due to its suppressive effects on the HPG axis. Ultimately, IMI has limited empiric medical treatment options and ART should be an option in any treatment discussion, particularly for couples with a female partner age of 35 or greater.

Suggested reading

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