Review Article

Empiric medical therapy with hormonal agents for idiopathic male infertility

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ABSTRACT

Introduction: Infertility affects approximately 15% of all couples, and male factor contribute to up to 50% of cases. Unfortunately, the cause of male infertility is unknown in about 30% of these cases. Infertility of unknown origin is classified as idiopathic male infertility when abnormal semen parameters are present. Despite not having a definable cause, these men may respond to treatment. This review focuses on the use of empiric hormonal therapies for idiopathic male infertility.
Methods: A detailed PubMed/MEDLINE search was conducted to identify all publications pertaining to empiric use of hormonal therapies in the treatment of idiopathic male infertility using the keywords "idiopathic," "male infertility," "empiric treatment," "clomiphene," "SERM," "gonadotropin," "aromatase inhibitor," and "androgen." These manuscripts were reviewed to identify treatment modalities and results.
Results: Gonadotropins, androgens, aromatase inhibitors, and selective estrogen receptor modulators (SERMs) have all been used with varying results. The studies on these treatments are of variable quality. The most well-studied agents are the SERMs which show a modest increase in semen parameters and pregnancy rates. Aromatase inhibitors are most effective in non-idiopathic patients. Gonadotropin treatment is limited by their inconvenience and relative ineffectiveness in this population. Testosterone suppresses spermatogenesis and should not be used to treat infertility.
Conclusion: Gonadotropins, SERMs, and aromatase inhibitors may improve semen parameters and hormone levels in men with idiopathic infertility with the best results from SERMs. Testosterone should never be used to treat infertility. Large multicenter randomized controlled studies are needed to better determine the success of empiric use of hormonal therapy on pregnancy rates.

INTRODUCTION

Infertility, defined as the inability to conceive after 12–24 months of unprotected intercourse, affects 15% of all couples.[1] About half of these couples will have male factor pathology as diagnosed by an abnormal semen analysis.[2] Nearly 30% of these men will have severe oligospermia or azoospermia.[3] Despite our modern techniques, an identifiable cause is found in only 50% of patients[4] and the remainder of these patents are classified as having idiopathic infertility. These men are usually left to choose between assisted reproductive techniques or empiric medical therapy (EMT). To make things more difficult, there is a lack of Food and Drug Administration (FDA) approval for the majority of empiric therapies to treat male factor infertility in the United States and there is still no consensus on the proper treatment of this subset of patients.[5] This review will focus on the empiric use of hormonal agents for idiopathic male infertility, with specific focus on gonadotropins, androgens, aromatase inhibitors, and selective estrogen receptor modulators (SERMs).

METHODS

A detailed PubMed/MEDLINE search was conducted to identify all publications pertaining to empiric use of hormonal therapies in the treatment of idiopathic male infertility using

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the keywords "idiopathic," "male infertility," "empiric treatment," "clomiphene," "SERM," "gonadotropin," "aromatase inhibitor," and "androgen." This search was limited to the English language and included reviews, clinical trials, observational studies, and case reports in humans. In various combinations, this yielded 42 articles for treatment with SERMs, 25 articles for treatment with aromatase inhibitors, 89 articles mentioning gonadotropins, and 59 articles with androgens. These abstracts were reviewed to identify study population, treatment modalities, and results. After screening for studies and reviews that included men with idiopathic male infertility treated with EMT (from one of the above classes of medications), 28 relevant manuscripts were reviewed.

GONADOTROPINS

This is the only class of medications currently approved for the treatment of male factor infertility due to hypogonadotropic hypogonadism by the FDA and includes gonadotropin releasing hormone (GnRH), luteinizing hormone (LH), follicle stimulating hormone (FSH), and human chorionic gonadotropin (hCG).

While the use of GnRH in hypogonadotropic hypogonadism has been well documented, this article focuses only on idiopathic infertility. Empiric use of GnRH, on the other hand, has failed to show significant improvements in semen parameters. In the first study, Badenoch *et al.* randomized 19 infertile men to receive buserelin, a GnRH agonist, or saline for 12 weeks. At the end of the study, there was no significant difference in sperm concentrations between the two groups.[6] In a slightly larger study, 28 infertile men with oligoasthenozoospermia were randomized to GnRH or placebo. There was a slight improvement in semen parameters in the treatment group, but this did not predict pregnancy rate, as there was no significant difference between the two groups (three births in the placebo group and five births in the treatment group).[7] Given the available evidence, we currently do not recommend the use of GnRH for idiopathic male infertility.

hCG has the biological activity of LH and can increase intratesticular testosterone concentrations up to 100 times that of peripheral blood. It's most common clinical use is to assist in the recovery of spermatogenesis in patients on testosterone for hypogonadism. It is also used for the treatment of idiopathic hypogonadotropic hypogonadism, often in conjunction with GnRH and/or FSH. In this setting, it is very effective. Unfortunately, these results have not translated to the idiopathic infertility population. One randomized, placebo controlled trial of men with idiopathic infertility and severe oligospermia treated with hCG (and human menopausal gonadotropin [HMG]) allocated 19 men to the treatment group for 13 weeks. Two pregnancies were reported in this group compared to none in the placebo group. Interestingly, semen analysis was similar between the two groups throughout the study period.[8] The drug also has high costs and requires injections and is not routinely recommended in idiopathic infertility patients.

FSH has been utilized in various forms for the treatment of male infertility. It was first purified from urine, followed by the creation of recombinant FSH. In a representative study, Paradisi *et al.* showed that in 30 men with idiopathic oligoasthenozoospermia, high dose FSH induced a marked increase in sperm count, a slight increase in sperm motility and no change in morphology.[9] Their study did not look at pregnancy rates. A Cochrane review on the effects of gonadotropins on idiopathic male infertility reviewed six randomized studies with 456 participants.[10] They determined that the live-birth rate was 27% versus 0% (odds ratio [OR], 9.31; 95% confidence interval [CI], 1.17–73.75) and the spontaneous pregnancy rate per couple was 16% versus 7% (OR, 4.94; 95% CI, 2.13–11.44) when compared to the no treatment arm. Because of the small number of studies and poor quality, the authors concluded that the results are encouraging, but the evidence is insufficient to allow final conclusions.

In a randomized prospective study, Colacurci *et al.* found that men with idiopathic oligoasthenoteratozoospermia (OAT) treated with FSH had a decrease in their DNA fragmentation index (DFI) (as measured by the TUNEL assay) but no difference in semen parameters. The treated group saw a decrease in DFI from 23.7% to 12.6% with a larger decrease seen in patients with higher DFI ($P < 0.05$).[11]

We believe that gonadotropins are best used in the setting of hypogonadotropic hypogonadism and have little use in the setting of idiopathic male infertility. Although there is some evidence that gonadotropins may improve pregnancy rates in this population, these studies are too small and low quality to recommend this type of treatment at this time.

AROMATASE INHIBITORS

As the name suggests, these compounds inhibit aromatase thus blocking the conversion of testosterone to estradiol (T/E), the main source of estrogen in men. Aromatase inhibitors have been used in idiopathic infertility with the intent of reducing estrogen's effect on spermatogenesis and reducing feedback inhibition of the hypothalamic–pituitary–gonadal axis. Two types of aromatase inhibitors are used clinically: Nonsteroidal (reversible) inhibitors and steroidal (irreversible) inhibitors. The steroidal inhibitors, such as testolactone, formestane, and exemestane have been supplanted by the nonsteroidal inhibitors in male infertility.[12] Letrozole and anastrozole are nonsteroidal inhibitors that cause reversible enzyme inhibition and can increase endogenous testosterone production and serum testosterone levels in men. They can do this without the

associated increase in estrogen seen with estrogen receptor modulators such as clomiphene.[13] Most studies on aromatase inhibitors were not controlled or used inhibitors that are no longer available or used clinically. An early study from 1989 treated 25 men with idiopathic infertility with testolactone or placebo for 8 months followed by crossover with treatment in the other arm for another 8 months. There was no change in semen parameters, and surprisingly, no change in testosterone or estradiol levels. No pregnancies were reported during the study.[14]

Pavlovich *et al*. found that men with severe male infertility had a T/E ratio of 6.9, and men with normal spermatogenesis had a mean T/E ratio of 14.5. Based on these observations, they proposed a T/E ratio of 10 as the lower limit of normal.[13] Saylam *et al*. found that in 27 men with idiopathic infertility and a T/E ratio <10 treated with letrozole, serum testosterone and all semen parameters improved while estradiol levels decreased. Total motile sperm counts improved from 2.37 ± 1.14 to 6.76 ± 2.37 (P = 0.009). In the patients with idiopathic oligospermia, two men (20%) achieved spontaneous pregnancy. They also saw return of sperm to 4/17 patients with azoospermia.[15] A blinded, placebo controlled, pilot study randomized 46 patients to either letrozole or placebo. The majority of these patients had idiopathic cryptozoospermia, whereas the remainder were azoospermic. The treatment group had increase in sperm concentration and motility, FSH, LH, and testosterone levels compared to the placebo group. No natural pregnancies occurred in either group after 6 months. The authors reported that the lower the T/E ratio and FSH, and the higher BMI and testicle volume, the greater improvement in sperm count after letrozole administration.[16]

Aromatase inhibitors are best used in men with hypogonadism with low T/E ratios and has been associated with improved semen parameters. In the idiopathic male infertility population, there is minimal evidence supporting their use. At our institution, we do not use aromatase inhibitors for idiopathic infertility patients with normal T/E ratios.

ANDROGENS

Androgens are essential for the development of the male reproductive system, sexual function, and puberty. High levels of intratesticular testosterone are also needed for induction and maintenance of spermatogenesis. This is partially due to the fact that the testes lack 5-alpha-reductase enzyme and are therefore not exposed to the more potent dihydrotestosterone. While testosterone is vital to spermatogenesis, exogenous testosterone inhibits pituitary LH and FSH production resulting in a drop of intratesticular testosterone levels and ultimately causing spermatogenesis to cease. In fact, exogenous testosterone has been studied as a possible form of male birth control.[17]

In a study of 59 men on testosterone who presented to an infertility clinic, 88% were azoospermic, and 65% recovered spermatogenesis 6 months after discontinuing testosterone.[18] A meta-analysis by the hormonal male contraception summit group attempted to investigate the rate, extent, and predictors of reversibility of exogenous testosterone use. In their analysis of 1549 men, the probability of recovery to a sperm count 20 million/ml was 67% within 6 months, 90% within 12 months, 96% (92–98) within 16 months, and 100% within 24 months. This study allows the provider to effectively counsel patients on the return of spermatogenesis after stopping exogenous testosterone.

Exogenous testosterone should never be used to treat infertility. While it is true that many of the medications described in this review increase endogenous testosterone, exogenous sources will stop spermatogenesis and may take up to 2 years to recover. Unfortunately, these studies have not stopped up to 25% of urologists from prescribing testosterone in an attempt to improve fertility.[5] In this population, we will use clomiphene to help increase testosterone levels and potentially hasten the return of spermatogenesis once they have stopped their testosterone, though this has not been studied to the best of our knowledge.

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Clomiphene and tamoxifen are SERMs that block negative feedback at the level of the hypothalamus and the pituitary. This blockade of negative feedback indirectly enhances LH and FSH excretion from the anterior pituitary, increasing both testosterone and spermatogenesis. Because of this, clomiphene is not as effective in patients with a pretreatment elevated FSH or in patients lacking a posttreatment FSH "surge."[19]

Studies have demonstrated improvement in LH and FSH, as well as semen parameters in patients with unexplained infertility.[20,21] Improvements in pregnancy rates have been harder to prove. A multicenter, randomized double-blind placebo controlled trial was performed in 1992 and included 190 men with idiopathic infertility who were treated with either clomiphene or placebo for 6 months. The pregnancy rates at 8 months were 11.7% and 8.1% in the placebo and clomiphene groups, respectively. There were no significant differences in semen parameters between the two groups.[22] A study from India found that 25 men with severe oligospermia had an increase in mean sperm count from 3.84 ± 0.32 to 8.2 ± 1.58 (P < 0.05) after 3 months of clomiphene therapy. In that same study, 40 men with oligospermia had an increase in counts from 13.05 ± 0.48 to 24.55 ± 1.73 (P < 0.001).[23] Another study looked at empiric clomiphene treatment for men with idiopathic azoospermia to see if their counts would rise enough to allow for intracytoplasmic sperm injection (ICSI). Forty-two patients from three international centers were included.

Initial testicular biopsy demonstrated maturation arrest in 42.9% and hypospermatogenesis in 57.1% of patients. After clomiphene, 64.3% of the patients demonstrated sperm in their semen analysis. The counts ranged from 1 to 16 million sperm/mL, with an average concentration of 3.8 million/mL. Patients that remained azoospermic (35.7%) underwent testicular extraction of sperm and were able to have sperm retrieval sufficient for ICSI. This study also showed that the level of maturation arrest improved with clomiphene therapy, with the majority of patients having maturation arrest at the level of spermatocytes before treatment, and at the level of spermatids after.[24]

A small study of azoospermic men treated with tamoxifen therapy for 3 months found that six patients from the original 32 had return of sperm to their ejaculate.[25] Two other studies looked at empiric use of tamoxifen in conjunction with antioxidants in the treatment of idiopathic infertility. The first study divided 183 patients into three groups: Tamoxifen only, tamoxifen + coenzyme Q10, and coenzyme Q10 only. Interestingly, sperm motility and morphology increased significantly in the tamoxifen + coenzyme Q10 and coenzyme Q10 groups ($P < 0.05$), but only slightly in the solo tamoxifen group ($P > 0.05$).[26] A second study looked at the efficacy of tamoxifen and l-carnitine on semen parameters, sperm ultrastructure in sixty idiopathic OAT patients. In a similar design to the previous study, participants were divided into a tamoxifen only, tamoxifen + l-carnitine, and l-carnitine only groups. The tamoxifen only group showed a significant improvement in sperm concentration, sperm morphology, ultrastructural head, acrosomal, and mitochondrial anomalies ($P < 0.01$). The group treated with both tamoxifen and l-carnitine showed improvement in all semen parameters and all ultrastructural anomalies ($P < 0.01$). The l-carnitine only group also saw significant improvements in sperm motility and sperm morphology, but to a lesser extent when compared with the tamoxifen containing groups.

A Cochrane review of clomiphene and tamoxifen for idiopathic oligoasthenospermia was completed in 2000. This systematic review included 10 randomized controlled trials of anti-estrogen therapy for 3 months or more in subfertile males where the infertility was attributed to the male alone. Although the treated men demonstrated improved endocrine/hormone parameters (OR 1.56, 95% CI 0.99–2.19), there was no change in pregnancy rates. The authors concluded that there is not enough evidence to evaluate the use of SERMs for improving idiopathic infertility. These 10 trials varied significantly in treatment parameters, use of placebo and other factors, limiting the reviews conclusions and the review has since been withdrawn since it had not been updated in over 10 years.[27] A more recent meta-analysis was performed by Chua *et al.* in 2013 analyzed 11 randomized controlled trials that evaluated SERMs (clomiphene or tamoxifen) as EMT for idiopathic male infertility. They found that the use of SERMs was associated with a statistically significant increase in sperm concentration of 5.24 million sperm/mL (95% CI, 2.12–88.37; $P = 0.001$) and 4.55% increase in sperm motility (95% CI, 0.73–8.37; $P = 0.03$). Most importantly although, the meta-analysis revealed an increase in pregnancy rates (OR, 2.42; 95% CI, 1.47–3.94; $P = 0.004$) which was not seen in the prior Cochrane review.[28]

The treatment of idiopathic male infertility with SERMs (specifically clomiphene) is the best studied of the empiric treatments discussed in this review. It also has the most promising results. The most recent randomized trials and meta-analysis show a modest increase in sperm concentration, motility, and pregnancy rates although the CIs are wide. Side effects are minimal and tend to be well tolerated but can include hot flashes, enlargement of the breast tissue, headache, and nausea. Serious complications are very rare but can include pulmonary embolus, palpitation, and seizures. There is also a small chance that clomiphene therapy can worsen semen parameters and hence it is important to order semen analyses periodically. At our institution, we routinely prescribe clomiphene for idiopathic male infertility when the sperm concentration is below 10 million sperm/ml. We will check a semen analysis at 3 months and again at 6 months. We will usually not keep a patient on continuous therapy for more than 2 years.

CONCLUSION

Many types of EMT have been used over the years for idiopathic male infertility but hormonal modulators remain the most commonly used agents. The main-stays of hormonal therapy are the SERMs and aromatase inhibitors. Exogenous testosterone should never be used for the treatment of male infertility as it inhibits spermatogenesis. No large high quality studies have evaluated gonadotropin (hCG, FSH, GnRH) use in idiopathic male infertility, but a few smaller studies show some improvement in pregnancy rates. Given the paucity of data and the fact that other treatments such as clomiphene are cheaper and easier to administer and monitor, gonadotropins should not routinely be used in the idiopathic setting. Aromatase inhibitors are potentially useful in the treatment of idiopathic infertility, but mostly in men with low serum testosterone and elevated estradiol levels. In the setting of normal testosterone and estradiol, their use remains controversial given the lack of data. SERMs, specifically clomiphene, have been used for decades to improve male fertility although there still remains a shortage of high quality randomized placebo-controlled trials to prove efficacy. However, based on current evidence, SERMs are the safest and most effective empiric treatment for idiopathic male infertility. There is no long-term safety data on any of these medications so all of these agents should be discontinued if no improvement is seen in semen parameters or pregnancy.

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