# Drug Therapy for Idiopathic Male Infertility: Rationale Versus Evidence

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**Purpose:** About half of all infertile men who seek treatment have no specific cause that can be determined for the seminal abnormality. These men are often subject to a number of medical therapies with doubtful efficacy. We reviewed the rationale on which these therapies are advised and determined whether sufficient medical evidence exists to justify their use.

**Materials and Methods:** A literature search was performed using MEDLINE/PubMed, focusing on publications of the last 20 years of drug therapies for idiopathic male factor infertility. Therapies for specific abnormalities such as hypogonadism were excluded. Basic science, in vitro and animal studies suggesting the mechanism of action for male infertility were evaluated as the rationale part of the review, while controlled and uncontrolled human clinical trials were reviewed as evidence for drug use.

**Results:** There is no evidence in support of androgens and gonadotropins for enhancing male fertility. These agents may instead act as contraceptives with significant side effects. There is insufficient evidence regarding the role of antiestrogens, aromatase inhibitors and antioxidants. No drug therapy has proved to be clearly beneficial for idiopathic oligoasthenoteratospermia.

**Conclusions:** Drug therapy for idiopathic male infertility is at best empirical. There is no clear benefit of using any medication in these patients. Moreover, androgens should not be used because they may actually suppress spermatogenesis.

*Key Words: testis; infertility, male; oligospermia; antioxidants; drug therapy*

Infertility is a major heath problem affecting 15% of couples in the reproductive age group. The male partner is contributory in up to 50% cases and the cause of male infertility with abnormal semen parameters remains unknown in 25% of men.[1] These men with idiopathic infertility are prone to receive a number of empirical therapies. The basis of treatment is usually the fact that these products appear rational because of their mode of action, or because of animal studies or uncontrolled human studies. However, scientifically acceptable evidence of benefit is limited. We reviewed the literature regarding such a rationale and evidence supporting empirical therapy for idiopathic male infertility.

Semen analysis report is one of the basic objective parameters used for evaluating male fertility. Semen analysis varies tremendously in the same individual within short periods and multiple readings are essential to ensure a representative sample. Moreover, while 25% of men with sperm density below 12.5 million per ml could father a child through spontaneous conception, 10% with a normal female partner cannot contribute to pregnancy despite a count of up to 25 million per ml.[2] These findings suggest that there may be parameters other than those assessed during routine semen analysis that affect pregnancy and study outcomes based only on improvement in semen parameters are not enough. A more effective outcome parameter would probably be the pregnancy rate since that is the ultimate end point of therapy. Even while using pregnancy as the end point of treatment outcomes, it is important to consider the spontaneous pregnancy rate in supposedly infertile couples on no therapy. This background spontaneous pregnancy rate is about 1% monthly, attaining 26% cumulatively during 3 years.[1] Obviously any treatment option used should improve this result.

A PubMed/MEDLINE search was performed using the key words male infertility, treatment, therapy, oligospermia, asthenospermia, teratospermia, androgens, testosterone, gonadotropins, FSH, LH, GnRH, LH-RH, mesterolone, clomiphene, testolactone, tamoxifen, anastrazole, aromatase inhibitor, antiestrogens, antioxidant, lycopene, $\alpha$ tocopherol, vitamin E, glutathione (L-$\gamma$-glutamyl-L-cysteinylglycine), carnitine, CoQ10 and coenzyme Q10 in various combinations. Articles with abstracts that referred to the mechanism of action or a description of controlled and uncontrolled human trials were retrieved and reviewed. Those describing a proposed mechanism of action and animal or in vitro trials were used for the rationale section of each review. Articles that described human trials were used to evaluate the evidence for drug use. Initially we attempted to limit ourselves to recent (after 1985) controlled trials with or without randomization and to meta-analyses of such trials. We also evaluated pregnancy rates as the end point of drug therapy. However, this was hampered by the paucity of such reports for most drugs. Therefore, we included nonrandomized/controlled trials for drugs when such reports were not available. The nature of the trials is mentioned for each drug.

## HORMONAL AGENTS

### Androgens

***Rationale.*** Androgens are central to the development of the male phenotype and spermatogenesis. Testosterone secretion from the Leydig cells of the testis is under the control

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of pituitary LH, which itself is controlled by pulsatile release of hypothalamic GnRH. This centrality of testosterone in the maturation of sperm has been the rationale for its use for idiopathic infertility. Exogenous androgens are administered at a dose that should not influence pituitary gonadotropin secretion. The dose may have a direct stimulatory effect on spermatogenesis or influence sperm transport and maturation through an effect on the epididymis, ductus deferens and seminal vesicles. The most commonly used agent for direct stimulation is the oral testosterone derivative mesterolone. A newer undecanoate salt is also being promoted for similar use. Therapy consists of 2 to 150 mg mesterolone daily orally or 40 to 160 mg undecanoate salt orally daily. The duration of therapy is variable with no well-defined end points.

Excessive exogenous androgens can suppress the normal hypothalamic-pituitary axis with decreased spermatogenesis. Heller et al noted azoospermia after 10 weeks of exogenous steroids in infertile men.[3] However, they also noted a rebound increase in sperm counts above baseline after the cessation of therapy. This observation led to the theory of rebound spermatogenesis following exogenous androgens. Supranormal testosterone is achieved using injectable preparations, such as testosterone propionate and testosterone enanthate, for 3 to 6 months with twice or thrice weekly injections, followed by semen analysis 3 to 6 months after the cessation of therapy.

***Evidence.*** The direct and rebound forms of therapy gained popularity because of initial reports of favorable results with up to 52% of patients showing semen analysis at fertile levels, followed by pregnancy in the wives of 25%. Lamensdorf et al used large doses of testosterone to cause degeneration of the testicular germinal epithelium and subsequent rebound spermatogenesis.[4] They reported a 29% pregnancy rate in 131 patients, including an 8% pregnancy rate in men with initial azoospermia.

These data are not supported by meta-analyses or randomized controlled trials.[5,6] A WHO funded, placebo controlled trial of androgen supplements using mesterolone failed to show any significant improvement in pregnancy rates.[5] In a Cochrane database review Vandekerckhove et al evaluated 11 trials in a total of 930 subjects treated with exogenous androgens as a supplement or as rebound therapy.[6] Randomized trials of mesterolone or testosterone undecanoate as stimulatory therapy and testosterone enanthate or undecanoate as rebound therapy were included. They concluded that for stimulatory and rebound therapy androgens had little effect on sperm parameters. The pregnancy rate was similar to that of no treatment or placebo. Moreover, there was a significant risk of sustained azoospermia, hepatic dysfunction, gynecomastia and cholestasis.

## Gonadotropins

***Rationale.*** Abnormalities of the amount, half-life and pulsatility of gonadotropin secretion have been considered a potential cause of male infertility.[7] Gonadotropin abnormalities have been corrected by pulsatile LHRH treatment.[8] Immunoreactive FSH may not be the biologically active form and sperm ultrastructure may improve after FSH therapy, resulting in better embryo development and, thereby, increasing the probability of embryo implantation.[9,10] However, these findings have been questioned in studies in which such functional defects of hypothalamic LHRH secretion were not confirmed.[11,12]

***Evidence.*** The use of human chorionic gonadotropin for idiopathic infertility has been reported to improve semen parameters in up to 69% of patients with a pregnancy rate of up to 36%.[13,14] However, similar to the studies with androgens, these studies have been uncontrolled. Subsequent studies using a randomized, controlled design failed to demonstrate any benefit of such therapies.[12,15] This includes therapy with human chorionic gonadotropin, human menopausal gonadotropin, GnRH or recombinant FSH. This does not, of course, include their role in the management of hypogonadotropic hypogonadism, for which these agents are highly effective, representing the principal mode of therapy.

A few groups have suggested a role for FSH therapy in men with idiopathic semen defects before the use of sperm for assisted reproduction. In a randomized, controlled trial Ashkenazi et al used purified FSH in 39 men with oligoasthenoteratozoospermia before intracytoplasmic sperm injection and noted improved fertilization and pregnancy rates compared to those in an equal number of men not on FSH therapy.[9] However, the difference was not statistically significant. They failed to report any change in sperm structure or semen parameters resulting from the therapy. They also reported 4 spontaneous pregnancies occurring after therapy was stopped. Again, semen parameters in these patients and the possible explanation for the delayed effects of FSH therapy were not discussed. Similarly Caroppo et al treated 23 men with idiopathic oligoasthenoteratozoospermia who failed to achieve fatherhood after previous intracytoplasmic sperm injection attempts with recombinant human FSH for 3 months.[10] They noted a significant increase in testicular volume and sperm parameters. That group did not assess sperm structure and the improved fertilization rate was not statistically significant. They also failed to explain why the pregnancy rate should be higher in this group of patients.

## Aromatase Inhibitors

***Rationale.*** Testosterone and other androgens undergo peripheral conversion to estrogen and its derivatives through the action of the enzyme aromatase. Estrogen has a negative feedback effect on the production of gonadotropins. Oral inhibitors of aromatase, such as testolactone and anastrozole, are administered to prevent the conversion of testosterone to estradiol and, thus, block the inhibitory effects of estrogen on spermatogenesis.

***Evidence.*** There has been only 1 randomized, controlled trial of aromatase inhibitors for idiopathic male infertility. Clark et al treated 25 men who had idiopathic oligozoospermia with 2 gm testolactone orally daily or placebo for 8 months, followed by crossover to the other treatment for an additional 8 months.[16] They noted no change in total estradiol and testosterone during testolactone exposure. There was also no improvement in semen parameters and no pregnancies occurred during the 16-month study.

## Antiestrogens

***Rationale.*** Antiestrogens have been one of the oldest and most commonly prescribed forms of therapy for idiopathic male infertility. The basic rationale of use is similar to that of aromatase inhibitors. These drugs inhibit the negative