Male infertility: a critical review of pharmacologic management

Alaa J Hamada*, Brian Montgomery* & Ashok Agarwal†
†Glickman Urological and Kidney Institute, Center for Reproductive Medicine, Cleveland Clinic, Cleveland, OH, USA

Introduction: Male factor infertility contributes partially and solely to the problem of childlessness in around 50% of the cases. Unfortunately, 30 – 50% of the etiologies of male infertility are unknown and therefore, no specific therapy can be instituted. Evidence-based medical therapy for male infertility is an attractive research area where a large number of clinical trials, controlled and uncontrolled, using different types of medications have been conducted yielding variable results and outcomes.

Areas covered: In this review, we summarize and evaluate the most important and most recent information pertaining to the use of different medications in male infertility and assign level of evidence to these medications. An extensive literature search was performed using the search engines: Pubmed, Science-direct, Ovid and Scopus.

Expert opinion: Male infertility represents a very challenging area of clinical medicine. Many different types of medications have been tried and very few have had satisfactory results. There is a huge need to advance and develop andrologic diagnostic techniques, focusing on the metabolomics and proteomics of the sperm, seminal plasma, and testicular tissue. Clarification of the causes of idiopathic male infertility and the discovery of novel molecular targets will help guide future innovative development of new pharmacologic agents.

Keywords: male infertility, medical treatment, pregnancy outcome, semen analysis

1. Introduction

The World Health Organization currently defines infertility as the inability of a sexually active couple (at least three times per month), not using contraception, to achieve pregnancy within one year. About 15% of sexually active couples are infertile [1,2] and male factor infertility contributes to about 50% of the infertility cases [2-4]. There are both known and unknown causes of male infertility, with idiopathic causes accounting for approximately 30 – 50% of all the cases of male infertility [2,3,5]. Idiopathic male infertility is also known as idiopathic oligoasthenoteratozoospermia (iOAT), which indicates that the patient has unexplained abnormalities in sperm parameters including low sperm concentration (≤ 15 × 10^6 per mL), reduced sperm motility (≤ 40%), and abnormal sperm morphology (≤ 4% normal forms) [6]. The list of known causes of male infertility is enormous and broadly includes: varicocele, urogenital infections, immunologic factors (e.g., anti-sperm antibodies), sexual/ejaculatory inadequacy, congenital disorders (e.g., Kallmann’s syndrome, Klinefelter’s syndrome, etc.), acquired urogenital abnormalities, and endocrine disorders [1-3,5]. Only a handful of the known causes of infertility have a pharmacologic option as the first line of treatment. Known causes of male infertility tend to have targeted and effective treatment options, whereas idiopathic cases of infertility have non-specific or empirical treatment options with questionable efficacy.
that pulsatile GnRH therapy is effective at increasing testicular size and inducing spermatogenesis (requires approximately 4 months of treatment) in patients with HH whose fertility potential is the main concern [8-13]. Pulsatile GnRH therapy induces spermatogenesis in approximately 40% of patients with HH [8] and small studies have found pregnancy rates in the 50 – 60% range [10,14]. Pulsatile GnRH therapy is very similar to gonadotropin therapy in terms of successful induction of spermatogenesis [10], although pulsatile GnRH possibly results in a more rapid initiation of spermatogenesis [12]. Overall, pulsatile GnRH is an effective and a generally well-tolerated treatment option for those individuals with HH. Pulsatile GnRH use is limited by its expensive cost, invasive delivery, and the need to regularly change subcutaneous needles. In addition, there are reported cases of anti-GnRH antibodies developing in a patient receiving pulsatile GnRH therapy [14].

Pulsatile GnRH has been considered as an empirical treatment option for idiopathic male infertility, but its invasive delivery and cost has limited its use. One underpowered (n = 19), randomized, placebo-controlled study found no hormone or semen parameters improvements in men with idiopathic infertility treated for 12 weeks with a GnRH analog or saline [15]. The European Association of Urology does not recommend empirical use of pulsatile GnRH based on the lack of controlled trials [5].

2.2 Gonadotropin therapy

As stated before, the anterior pituitary is responsible for producing and releasing the gonadotropins FSH and LH in response to GnRH. FSH and LH are responsible for inducing spermatogenesis and sex steroid production in the testes [7]. The gonadotropin hCG is of placental origin and has hormonal effects that are similar to those of LH because it contains subunits in its structure closely related to LH [16]. Purified urinary extractions of hCG, FSH, and hMG (similar to FSH activity), along with recombinant forms of FSH and LH are available to treat patients with pituitary lesions or GnRH deficiencies and have been also tried as an empirical therapy in idiopathic male infertility.

Multiple well-designed studies have shown that gonadotropins are an effective treatment option for HH [10,17-19]. Typical treatment is self-administered subcutaneous injections of 75 – 150 IU FSH or hMG thrice weekly plus 1500 – 2500 IU hCG twice weekly. Treatment is typically continued until sperm appear in the ejaculate and/or a pregnancy is induced. Studies have shown that gonadotropins induce spermatogenesis in 80 – 96% of patients with HH [10,18,19]. Median treatment time to first sperm has been shown to be approximately 5 – 7 months [18,19]. The median treatment time to achieve conception is about 28 months and the pregnancy rate is approximately 38 – 51% [10,18]. Gonadotropins have also been shown to increase testosterone levels and average testicular volume with relatively few side-effects (e.g., gynecomastia) [10,19].

There are really no appreciable differences in pregnancy rate and spermatogenesis induction when comparing gonadotropin

<table>
<thead>
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<th>Article highlights.</th>
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<tr>
<td>• About 15% of sexually active couples are infertile and male factor infertility contributes to about 50% of infertility cases.</td>
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<tr>
<td>• Idiopathic male infertility constitutes at least 30% of all cases of male infertility.</td>
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<td>• Medical therapy in male factor infertility is divided into specific (etiology is known) and non-specific or empiric (etiology is unknown).</td>
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<tr>
<td>• Specific medical therapy is successful in 20% of male factor infertility cases, particularly for certain etiologies of male infertility such as urogenital infections, hypogonadotropic hypogonadism, hyperprolactinemia, and erectile dysfunction.</td>
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<tr>
<td>• Idiopathic male infertility represents a challenging situation for clinicians, because many available medications have little or no beneficial effect.</td>
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<td>• Hormonal therapy, anti-oxidants, anti-inflammatory agents, phosphodiesterase inhibitors, anti-estrogens and aromatase inhibitors often have ambiguous benefits in men with idiopathic infertility and lack reproducibility in studies.</td>
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<td>• Testosterone is strictly contraindicated as a treatment option for men with idiopathic infertility.</td>
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<tr>
<td>• Anti-oxidant use in idiopathic male infertility modestly improves pregnancy rates and live birth rates, without serious side-effects.</td>
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This box summarizes key points contained in the article.

This review article will focus on the pharmacologic therapies currently available for treatment of male infertility and the latest data on the efficacy of those therapies (data on efficacy, indications, and level of evidence is shown in Table 1).

2. Hormonal treatment

2.1 Pulsatile gonadotropin-releasing hormone (GnRH)

GnRH is a decapeptide that is produced within the hypothalamus and released in a pulsatile fashion to stimulate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary. In men, FSH and LH are responsible for induction of spermatogenesis and steroidogenesis [7]. Pulsatile GnRH therapy attempts to simulate the normal physiology of GnRH secretion and is used to replace GnRH deficiency. Pulsatile GnRH, dosed at 5 – 20 µg every 120 min via a subcutaneous needle, has been unsuccessfully used as an empirical therapy for idiopathic male infertility and as an effective specific treatment option for male infertility due to hypogonadotropic hypogonadism (HH) (e.g., Kallmann’s syndrome, isolated and idiopathic HH).

In patients with HH, secondary sexual characteristics are easily induced by exogenous testosterone administration, but fertility is mainly induced by either pulsatile GnRH or a combination of LH and FSH analogs. Multiple studies have shown that pulsatile GnRH therapy is effective at increasing testicular
Table 1. Overview of pharmacologic agents used for male infertility.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Indication</th>
<th>Pregnancy rate</th>
<th>Other effects</th>
<th>Relative cost</th>
<th>Delivery</th>
<th>Level of evidence</th>
<th>Recommendation level</th>
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</thead>
<tbody>
<tr>
<td>Pulsatilin GnRH</td>
<td>HH</td>
<td>50 - 60%</td>
<td>η testicular size, η spermatogenesis</td>
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<td>subQ</td>
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<td>iOAT</td>
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<td>Gonadotropin (FSH, hCG, hMG)</td>
<td>HH</td>
<td>38 - 51%</td>
<td>η testicular size, η spermatogenesis</td>
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<td>subQ</td>
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<tr>
<td>iOAT</td>
<td>13.4%*</td>
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<td>Dopamine Agonist</td>
<td>HPRL</td>
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<td>-Normalize PRL, η sexual function</td>
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<td>iOAT</td>
<td>0 - 5%</td>
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<td>-None seen</td>
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<td>Anti-estrogen</td>
<td>iOAT</td>
<td>13 - 19%</td>
<td>-Improve sperm parameters</td>
<td>$</td>
<td>Oral</td>
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<td>Aromatase Inhibitor</td>
<td>iOAT</td>
<td>0%</td>
<td>-Improve sperm parameters</td>
<td>$</td>
<td>Oral</td>
<td>II-1</td>
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<td>Corticosteroid</td>
<td>ASA</td>
<td>18 - 31%*</td>
<td>-Improve sperm parameters</td>
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<td>Oral</td>
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<td>NSAIDs</td>
<td>Leuko-cytospermia</td>
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<td>Antibiotic</td>
<td>Leuko-cytospermia</td>
<td>47%*</td>
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<td>Anti-oxidant</td>
<td>iOAT</td>
<td>17%*</td>
<td>-Improve sperm parameters</td>
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<td>α-Agonists</td>
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<td>34%</td>
<td>-Antegrade ejaculation</td>
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<td>AE</td>
<td>2%</td>
<td>-Antegrade ejaculation</td>
<td>-Retrograde ejaculation</td>
<td>$</td>
<td>Oral</td>
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<tr>
<td>Parasympathomimetics</td>
<td>AE</td>
<td>2%</td>
<td>-Antegrade ejaculation</td>
<td>$</td>
<td>Oral</td>
<td>II-1</td>
<td>D</td>
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<tr>
<td>Mast cell blocker</td>
<td>iOAT</td>
<td>29%*</td>
<td>-Improve sperm parameters</td>
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<td>Oral</td>
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<td>PDE5i</td>
<td>iOAT</td>
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<td>-Improve sperm parameters</td>
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<td>PTX</td>
<td>iOAT</td>
<td>0%</td>
<td>-Improve sperm parameters</td>
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<td>Oral</td>
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Level of evidence based on U.S. Preventive Services Task Force (USPSTF) system: Level I: Evidence obtained from at least one properly designed randomized controlled trial; Level II-1: Evidence obtained from well-designed controlled trials without randomization; Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group; Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence; Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Recommendations based on U.S. Preventive Services Task Force (USPSTF) guidelines: Level A: Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients; Level B: At least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks. Clinicians should discuss the service with eligible patients; Level C: At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations. Clinicians need not offer it unless there are individual considerations; Level D: At least fair scientific evidence suggests that the risks of the clinical service outweigh potential benefits. Clinicians should not routinely offer the service to asymptomatic patients; Level I: Scientific evidence is lacking, of poor quality, or conflicting, such that the risk versus benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service.

*Statistically significant compared to placebo treatment.

therapy to pulsatile GnRH [10]. Gonadotropin therapy is an effective, well-tolerated treatment option for HH that is typically used as a first-line therapy over pulsatile GnRH therapy due to an easier route of administration. Patients are able to self-administer subcutaneous injections of FSH and hCG, whereas pulsatile GnRH requires a subcutaneous butterfly needle placed by a healthcare professional approximately every 2 days. Recombinant forms of FSH and LH are appealing when compared to urinary preparations because of their steady supply, dependable composition, purity, and specific activity [20].

Gonadotropins have been used to empirically treat men with idiopathic infertility. A large meta-analysis (n = 278) including four randomized controlled trials [21-24] showed that in comparison to placebo or no treatment, 3 months of gonadotropins therapy significantly increased pregnancy rate in men with idiopathic infertility (13.4 vs. 4.4%, OR 3.03, 95% CI 1.30 – 7.90) [25]. The number needed to treat to achieve one pregnancy was 12. Of note, two older meta-analyses found no significant improvement in pregnancy rate with gonadotropins treatment, but the inclusion criteria were not as strict and some patients included utilized assisted reproductive technologies (ART) [26,27]. One study included in the two meta-analyses mentioned in the previous section showed no statistically significant improvement in pregnancy rate with intrauterine insemination (IUI) [28]. However, natural pregnancy rate outside of the IUI cycle was 14.7% in the FSH treatment group versus 2.5% in the control group [23,24,28]. Gonadotropins show marginal improvements in pregnancy rates, but the high cost and invasive route of delivery limit the use. The European Association of Urology does not recommend the use of gonadotropins for idiopathic male infertility due to a lack of unambiguous efficacy, which mandates further conduction of additional well-designed randomized, controlled trials to show their advantages [5].

2.3 Dopamine agonists
Hyperprolactinemia is a known cause of male infertility and is clinically manifested with hypogonadism, impotence, and galactorrhea [29]. Causes of pathologic hyperprolactinemia in males include pituitary adenoma (prolactinomas, macro and microadenomas), idiopathic hyperprolactinemia, and empty sella syndrome [30]. Dopamine released from the hypothalamus is largely responsible for the tonic inhibition of prolactin secretion from the anterior pituitary [31]. Dopamine agonists have successfully been used to treat male infertility due to hyperprolactinemia, but have shown little promise as an empirical therapy for idiopathic male infertility [27,32].

Two dopamine agonists have been used and thoroughly studied for pathologic hyperprolactinemia, i.e., bromocriptine and cabergoline. Cabergoline (0.5 – 1 mg twice weekly) has been shown to normalize prolactin levels in 70% of bromocriptine-resistant patients and only about 4% of patients had to stop the medication due to side-effects (e.g., headache, postural hypotension, nausea, and sleepiness) [30]. Cabergoline has been shown to improve gonadal and sexual function in males with prolactinoma earlier than bromocriptine [34]. After 6 months of treatment, prolactin levels were 7.9 ± 2.2 μg/l in the cabergoline treatment group, whereas prolactin levels in the bromocriptine group were 16.7 ± 1.8 μg/l. In addition, at 6 months, the sperm concentration and motility were significantly higher in the cabergoline treatment group compared to the bromocriptine treatment group [34]. Similarly, Walia et al. reported a significant rise in seminal volume, sperm concentration, and motility following a 6-month course of cabergoline in patients with macroprolactinoma [35]. Interestingly, both De Rosa et al. and Colao et al. reported that cabergoline treatment for a longer period (24 months) leads to significant increases in sperm concentration and motility, whereas, short-term administration (6 months) can lead to a reduction in serum prolactin and increase in testosterone, LH, and FSH [36,37].

Pregnancies have been reported in very few studies [38]. Although normalizing prolactin levels in males improves gonadal and sexual function, there is a need for studies with live pregnancy rate as a primary outcome.

Bromocriptine is not effective as an empirical therapy for idiopathic male infertility and three studies showed no difference between bromocriptine and placebo in terms of pregnancy rate and sperm parameters [39-41]. Bromocriptine should not be used to treat idiopathic male infertility, but studies have not looked at newer dopamine agonists such as cabergoline in idiopathic oligozoospermia.

2.4 Estrogen receptor antagonist and aromatase inhibitors
Testosterone is aromatized peripherally by a P450 cytochrome enzyme into estradiol, which in turn provides negative feedback to the hypothalamus and pituitary. This feedback decreases GnRH pulse frequency and decreases pituitary responsiveness to GnRH, which ultimately decreases gonadotropin production [42]. Estrogen receptor antagonist and aromatase inhibitors both interfere with estrogen’s negative feedback, and therefore, may increase gonadotropin secretion (FSH and LH enhancers), which in turn would stimulate spermatogenesis and steroidogenesis. Another specific potential indication for estrogen receptor antagonist is direct interference with xenoestrogens which were found to be higher in semen of infertile men [43,44]. These two therapies have been explored as potential empirical therapies for idiopathic male infertility.

Estrogen receptor antagonists, also known as anti-estrogens, such as clomiphene and tamoxifen, act on both endogenous and exogenous estrogens. Tamoxifen is a pure anti-estrogen, whereas clomiphene citrate is a non-steroidal substance with a strong intrinsic estrogenic effect and anti-estrogenic properties. This difference is important because...
there is concern that the estrogenic effect of clomiphene can potentially have deleterious effects on spermatogenesis. However, Katz et al. and Whitten et al. showed that clomiphene can have substantial effects on serum testosterone levels in hypogonadal men [45,46]. Furthermore, Whitten et al. showed in small series that two of four hypogonadal men were able to induce pregnancy [46].

The role of clomiphene citrate in normogonadal idiopathic male infertility is controversial and the medication is considered as off-label use. World health organization conducted a randomized, double-blind study on 1308 couples when male partners received 25 mg of clomiphene citrate daily for 6 months and found no significant effects on pregnancy rates or semen quality [47]. Several authors, however, combined clomiphene with anti-oxidants and showed modest benefits. However, whether such improvement was attributed to clomiphene citrate or to the anti-oxidant is still unclear. Husseini et al. titrated doses of clomiphene in 42 men with idiopathic non-obstructive azoospermia to achieve testosterone levels of 600 ng/dL to 800 ng/dL. Only 36% of the participants remained azoospermic, but they had adequate sperm for intracytoplasmic sperm injection (ICSI) [48]. Adamopoulos et al. found that men with idiopathic infertility treated with tamoxifen (10 mg twice daily) for 3 – 6 months had a significant increase in sperm concentration, functional fraction, and testicular volume compared to placebo [49].

Studies looking at aromatase inhibitors to treat idiopathic infertility are limited and those that are available are small. Two types of aromatase inhibitors are available, steroidal (e.g., testolactone) and non-steroidal (letrozole and anastrozole). The latter is more effective at increasing the testosterone to estrogen ratio (T/E) and is less likely to cause interruption of the adrenal axis beyond aromatase inhibition. Anastrozole is the third most common medication used by American andrologists [50]. Aromatase inhibitors must be used with caution because they increase the risk of developing osteoporosis (11%) and joint disorders (17%). Indications for clinical use include infertile men with hyperestrogenemia or low T/E ratio (< 10). Elevated estrogen level or estrogen/testosterone ratio is obviously observed in men with significant obesity and is associated with idiopathic HH and Klinefelter syndrome.

A small study showed serum testosterone levels, sperm concentration, sperm motility, and ejaculate volume significantly increase in men with idiopathic infertility treated with letrozole (2.5 mg for 6 months) [51]. Another small study was unable to show any differences in testosterone, sperm concentration, semen quality, or pregnancy rate between men with idiopathic infertility treated with testolactone (2 g daily) or placebo [52].

Several studies have examined the role of aromatase inhibitors in infertile men with hyperestrogenemia (low T/E ratio) Raman et al. reported that therapy with testolactone (100 – 200 mg/day) and/or anastrozole (1 mg/day) resulted in a rise in T/E ratio and increase in semen parameters [53]. Gregoriou et al. treated two groups (n = 29) of infertile men with low T/E ratio with two different non-steroidal aromatase inhibitors (2.5 mg/day letrozole or 1 mg/day anastrozole) for 6 months [54]. Both forms of treatment resulted in a significant improvement in serum testosterone, T/E ratio, semen volume, sperm concentration, sperm motility, and reduced serum estradiol [54].

Interestingly, Ramasamy et al. demonstrated that medications that lead to endogenous testosterone secretion (e.g., aromatase inhibitors, clomiphene, or human chorionic gonadotropin) resulted in a better chance of sperm retrieval in men with Klinefelter’s syndrome with either normal or low baseline testosterone compared to men with Klinefelter’s syndrome who received exogenous testosterone to induce secondary sexual characteristics (77 vs. 55%) [55]. This observation can be attributed to the fact that exogenous testosterone suppresses the production of FSH and LH and, therefore, suppress spermatogenesis [55].

Due to a paucity of studies looking at pregnancy rate as a primary outcome, there is little evidence that anti-estrogens or aromatase inhibitors are effective empirical therapies for idiopathic infertility. Studies have indicated that these treatments may show more potential in infertile men with low T/E ratios.

2.5 Androgens
Testosterone is fundamentally important for maintenance of spermatogenesis and male sexual function. It was thought that raising serum testosterone could improve epididymal function and sperm maturation, whereas sudden withdrawal of testosterone would result in a transient rise in gonadotropins and sperm concentration, which has been termed the “rebound effect.” Testosterone, however, has contraceptive properties in men due to its negative feedback on hypothalamic-pituitary axis and thus inhibition of LH, FSH, and spermatogenesis. Various meta-analyses have demonstrated that androgen therapy does not improve pregnancy rates in men with idiopathic male infertility [26,27]. Based on the published literature, testosterone is contraindicated as a treatment option for male infertility. Surprisingly, a recent survey of 387 urologists belonging to the American Urologic Association reported that 25% of the responders are still prescribing androgens for infertile patients [50].

2.6 Combination therapy
Combinations of different hormonal therapies and hormonal therapies plus anti-oxidants have been studied as potential empirical treatments for idiopathic male infertility. A large study (n = 212) showed tamoxifen (20 mg daily) (estrogen antagonist and FSH and LH enhancer in adult men) plus testosterone undecanoate (120 mg daily) for 6 months significantly increases sperm concentration and spontaneous pregnancy rate (33.9 vs. 10.3%, RR 3.195, 95% CI 2.615 – 3.765) compared to placebo [56]. Another study found
that tamoxifen (20 mg daily) plus testosterone undecanoate (120 mg daily) resulted in a significant increase in sperm concentration, motility, normal morphology, functional fraction, and testicular volume when compared to placebo. The same study found tamoxifen plus testosterone improved sperm functional fraction when compared to tamoxifen or testosterone alone [49]. Clinicians frequently recognize harmful effects of testosterone administration on testicular function as it suppresses pituitary secretion of LH and FSH. However, the above two studies conducted by the same group of researchers demonstrated that testosterone undecanoate has minimal pituitary suppressive influence and it mainly promotes epididymal dihydrotestosterone (DHT) secretion [57]. Furthermore, FSH-enhancing effects of tamoxifen might explain the beneficial effects of the combination on the semen parameters.

A randomized, controlled trial (n = 30) found clomiphene citrate (25 mg) plus vitamin E (400 mg) daily resulted in a significant increase in pregnancy rate (36.7 vs. 13.3%, OR 3.76, 95% CI 1.03 – 13.64) and sperm concentration when compared to placebo [58].

A few combination therapies have been proven to be moderately effective in the treatment of idiopathic infertility, but there are still many potential combinations that have yet to be explored.

3. Anti-inflammatory therapy

3.1 Corticosteroids

Anti-sperm antibodies (ASA) interfere with sperm motility and sperm function, thereby reducing the chance of spontaneous pregnancy [59,60]. Corticosteroids have been tried as a specific therapy for male infertility associated with ASA. One randomized, double-blind crossover study (n = 43) compared prednisolone treatment to placebo. The men were treated with 20 mg of prednisolone twice daily for the first 10 days of their partner’s menstrual cycle and then received 5 mg daily for days 11 and 12. The treatment period was 9 months before crossover and alcohol use was forbidden. Pregnancy rate was 31% (9/29) in the prednisolone group versus 10% (2/20) in placebo group. There were no serious complications, but 60% of the patients experienced mild side-effects (acne, weight gain, dyspepsia, and irritable) [61]. Another randomized, controlled trial (n = 40) found 5 mg of prednisolone for 3 – 6 months significantly reduced the anti-sperm antibody titer, improved sperm motility, and increased pregnancy rate when compared to placebo (20 vs. 5%). No side-effects were reported in this study [62]. Six randomized, controlled trials, including the above two, were included in a meta-analysis with prednisolone doses ranging from 5 to 96 mg daily. The two studies mentioned above were the only studies to find a significant increase in pregnancy rate, but they were also the only studies where treatment lasted more than 3 months. Combining all the studies resulted in an 18.3% (30/164) pregnancy rate in the treatment group and 10.7% (16/150) pregnancy rate in the placebo group (OR 1.82, 95% CI 0.96 – 3.42) [27].

The benefits of prednisolone therapy are at most modest and only when used for greater than 3 months. Although rare, the potential risk for serious side-effects such as weight gain, generalized infections and avascular necrosis (AVN) of the femoral head makes prednisolone less preferable treatment option for infertile men with ASA [26].

3.2 Non-steroidal anti-inflammatories (NSAIDs)

Leukocytes are a common finding in seminal plasma of infertile males and have been shown to negatively affect sperm function [63], but the link between abacterial leukocystospermia and male infertility is not completely clear [64,65]. NSAIDs have been tried as an empirical therapy for infertile males with abacterial leukocystospermia. Two studies found that 25 mg of COX-2 inhibitors (rofecoxib) daily for 30 days significantly reduced leukocystospermia and improved sperm parameters (increased sperm concentration, motility, and normal morphology) [66,67]. Randomized, controlled trials with live birth rates as a primary outcome are needed to assess whether the improvement in sperm parameters with COX-2 inhibitors leads to increased fertility.

4. Antibiotics

Genitourinary (GU) infections are a potential cause of male infertility. Gallegos et al. found that GU infections increase sperm DNA fragmentation and decrease sperm concentration, morphology, and motility [68]. Appropriate antibiotic treatment of GU infections has been shown to significantly reduce sperm DNA fragmentation and improve sperm concentration and motility [68]. There are notable differences in the ability of different groups of antibiotics to penetrate the various areas of the male GU tract, and therefore, careful selection is critical.

Antibiotics have been tried as an empirical therapy in infertile men with low-level leukocystospermia (0.2 – 1.0 x 10^6 WBC/mL). One study administered doxycycline to 34 patients with low-level leukocystospermia and compared them to 27 historical controls. No significant changes in semen parameters were seen in either group, but leukocystospermia resolved in 56% of the treatment group versus spontaneous resolution in 25% of the historical controls. The natural pregnancy rate in the treatment group was significantly greater than the pregnancy rate in the historical controls (47 vs. 20%, OR 3.7, 95% CI 1.1 – 11.7, p = 0.04) [69]. Another study (n = 53) found that leukocystospermia resolved in 68% of infertile men treated with antibiotics and 53% of these men were able to induce pregnancy compared to only 6% of the men whose leukocystospermia was unresponsive to antibiotic and were able to achieve pregnancy [70]. Doxycycline, besides its broad anti-bacterial spectrum, has specific inhibitory effects on the generation of reactive oxygen species by leukocytes. The use of antibiotics in patients with low-level leukocystospermia appears to be an effective option.
5. Anti-oxidants

Increased rates of infertility have been found in men with seminal fluid containing high levels of reactive oxygen species (ROS) [71,72]. Seminal fluid from men with idiopathic infertility has been shown to be significantly associated with low total anti-oxidant capacity and high oxidative stress [73]. Spermatozoon membranes are largely composed of polyunsaturated fatty acids (PUFA), which makes them highly susceptible to free-radical lipid peroxidation [74]. ROS have been shown to reduce sperm motility [75-77], increase sperm DNA damage, and induce apoptosis of spermatozoa [78,79]. Anti-oxidant therapy has been utilized as an empirical therapy for idiopathic male infertility in an effort to reduce free radicals and in turn improve sperm function and fertility (see Table 2). Anti-oxidants are a broad medication category and are best classified as reducing agents which able to donate an electron to the free radical and become oxidized, e.g., ascorbic acid and lycopene, and catalytic agents which have no intrinsic electron donation property but it enhances the natural anti-oxidant system in the body, e.g., carnitine and N-acetyl cysteine.

Showell et al. recently analyzed 34 randomized, controlled trials with a total of 2876 couples dealing with idiopathic male infertility [80]. Table 3 provides a summary of the results from this meta-analysis. Interventions used in studies within this meta-analysis included: combinations of anti-oxidants, carnitines, Coenzyme Q10, docosahexaenoic acid (DHA), magnesium, N-acetyl cysteine (NAC), pentoxifylline (PTX), selenium, vitamin C, vitamin E, and Zinc. Three of the studies reported a total of 20 live births out of 214 couples, which was significantly greater than the controls (OR 4.85, 95% CI 1.92 to 12.24; p = 0.0008). Fifteen of the studies looked at pregnancy rate (96 pregnancies out of 964 couples) and found anti-oxidants had a significantly higher pregnancy rate when compared to controls (OR 4.18, 95% CI 2.65 to 6.59; p < 0.00001). Sperm motility significantly increased with 3 – 6 months of anti-oxidant therapy, but not with 9 months. Sperm concentration significantly increased with 6 months of therapy, but not with 3 or 9 months. These sperm parameter findings may diminishing sample size at 9 months or it may be a coincidence. Head-to-head comparisons of different types of anti-oxidants did not reveal any superior anti-oxidant in terms of pregnancy rate or sperm parameters, but this is likely due to low statistical power as there were only a limited number of studies for each specific anti-oxidant. No serious side-effects were noted and the most common anti-oxidant side-effect was GI upset, but it was statistically no different than the rate seen in the control group. Overall, the included studies were very low quality due to inadequate methodology descriptions, lack of head-to-head comparisons, wide confidence intervals, and high heterogeneity. Couples with idiopathic male infertility should be advised that current evidence on the effectiveness of anti-oxidants is inconclusive and that further randomized, placebo-controlled trials with pregnancy rates as an outcome are needed [80]. Two other meta-analyses had similar results, reporting that both sperm parameters and pregnancy rate improve with anti-oxidant therapy [81,82].

Comhaire and Declerq pooled data (1013 couples) that specifically looked at pregnancy rates from the two largest meta-analyses [80,81]. The pregnancy rate in the anti-oxidant group was 17.2% (88/512) versus 4.4% (22/501) in the control group (RR 3.91, 95% CI 2.49 – 6.14, p < 0.0001). The authors concluded that oral anti-oxidants quadrupled the probability of spontaneous pregnancy within 3 months and also reduced the cost per pregnancy by 60% [83].

In addition to the need for additional studies with pregnancy rate as an outcome, there is a need to further elucidate the physiologic mechanisms and actions of anti-oxidants. Before discussing the anti-oxidants in the following section, it is important to note that unless stated specifically, few of these studies measured levels (plasma, serum, seminal or sperm) of anti-oxidants in patients before or after treatment. If a specific deficiency was not demonstrated, it is possible the effects were merely coincidental. We have tried to discuss, where available, large randomized, placebo-controlled trials in an effort to minimize this issue.

5.1 Vitamin C

Vitamin C (ascorbic acid) is a water-soluble, natural anti-oxidant that is capable of scavenging reactive oxygen species (ROS). Ascorbic acid is found in seminal plasma at concentrations 10 – 60 times the concentration in serum, which emphasizes the importance of ascorbic acid in seminal plasma [84]. Low levels of seminal ascorbic acid are associated with significant increases in sperm-DNA damage [85]. Low levels of seminal ascorbic acid have also been found to be a risk factor for abnormal spermatozoa and idiopathic male infertility [86,87]. Ascorbic acid supplementation improves sperm parameters in healthy men [88] and protects sperm DNA from oxidative damage [89]. Akmal et al. found that men with idiopathic infertility receiving 1000 mg vitamin C twice daily had significant increases in sperm concentration, sperm motility, and normal sperm morphology [90], but randomized, controlled trials with pregnancy rate as an outcome are still needed.

5.2 Vitamin E

Vitamin E denotes a group of eight naturally occurring lipid-soluble compounds that contain chromanol rings (i.e., tocopherols α, β, δ, γ and tocotrienols α, β, δ, γ). However, only α-tocopherol (the natural dietary form RRR-α-tocopherol and the synthetic form 2R-stereoisomeric all racemic-α-tocopherol) is maintained in human plasma and retained in body tissues. Vitamin E forms are not interconvertible and only α & γ tocopherols are absorbed through the intestine and carried to the liver through chylomicrons. In the liver, the α-tocopherol transfer protein is responsible for preferential secretion of α-tocopherol in human plasma with very low-density, low-density, and high-density lipoproteins.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Positive effect on sperm*</th>
<th>Negative/no effect on sperm</th>
<th>Positive effect on pregnancy rate*</th>
<th>Negative/no effect on pregnancy rate</th>
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</thead>
<tbody>
<tr>
<td>Carnitines</td>
<td>Moradi et al., 2010 [100]</td>
<td>Sigman et al., 2006 [107]</td>
<td>Lenzi et al., 2004 [101]</td>
<td>Sigman et al., 2006 [107]</td>
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<td></td>
<td>Balercia et al., 2005 [105]</td>
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<td>Cavallini et al. 2004 [108]</td>
<td>Balercia et al., 2005 [105]</td>
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<td>Lenzi et al., 2004 [101]</td>
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<td>Cavallini et al. 2004 [108]</td>
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<td>Costa et al., 1994 [106]</td>
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<td>Vitali et al., 1995 [103]</td>
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<td></td>
<td>Moncada et al., 1992 [104]</td>
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<td>Carotenoids</td>
<td>Comhaire et al., 2005 [133]</td>
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<td>Comhaire et al., 2005 [133]</td>
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<td></td>
<td>Gupta &amp; Kumar, 2002 [138]</td>
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<td>Coenzyme Q10</td>
<td>Balercia et al., 2009 [112]</td>
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<td></td>
<td>Safarinejad, 2009 [113]</td>
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<td>Folate</td>
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<td>Wong et al., 2002 [139]</td>
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<td>Magnesium</td>
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<td>Zavaczi et al., 2003 [121]</td>
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<td>NAC</td>
<td>Ciftci et al., 2009 [132]</td>
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<td>Safarinejad, 2009 [117]</td>
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<td>Erkila, et al., 1998 [131]</td>
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<td>Oeda et al., 1997 [130]</td>
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<td>Omega-3 FA</td>
<td>Safarinejad, 2011 [142]</td>
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<td>Selenium</td>
<td>Safarinejad, 2009 [117]</td>
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<td>Scott et al., 1998 [118]</td>
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<td>Selenium +NAC</td>
<td>Safarinejad, 2009 [117]</td>
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<td>Vitamin C (≥ 1000 mg daily)</td>
<td>Colagar &amp; Marzony, 2009 [86]</td>
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<td>Scott et al., 1998 [118]</td>
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<td>Patel et al., 2009 [87]</td>
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<td>Akmal et al., 2006 [90]</td>
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<td>Song et al., 2006 [85]</td>
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<td>Fraga et al., 1991 [89]</td>
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<td>Dawson et al., 1990 [88]</td>
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<td>Vitamin E</td>
<td>Suleiman et al., 1996 [94]</td>
<td></td>
<td>Scott et al., 1998 [118]</td>
<td>Suleiman et al., 1996 [94]</td>
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<td></td>
<td>Kessopoulou et al., 1995 [95]</td>
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<td>Kessopoulou et al., 1995 [95]</td>
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<tr>
<td>Vitamin E+C</td>
<td>Greco et al., 2005 [143]</td>
<td></td>
<td>Rolf et al., 1999 [96]</td>
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<td>Vitamin E+Selenium</td>
<td>Keskes-Ammar et al., 2003 [146]</td>
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<td>Rolf et al., 1999 [96]</td>
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<td>Vezina et al., 1996 [145]</td>
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<td>Zinc</td>
<td>Colagar et al., 2009 [124]</td>
<td></td>
<td>Wong et al., 2002 [139]</td>
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<td></td>
<td>Omu et al., 2008 [73]</td>
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<td>Omu et al., 1998 [127]</td>
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<td>Omu et al., 1998 [127]</td>
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<td>Tikkiwal et al., 1987 [126]</td>
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<td></td>
<td>Hartoma et al., 1977 [125]</td>
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* = statistically significant effect (p<0.05).
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<th>Compound</th>
<th>Positive effect on sperm*</th>
<th>Negative/no effect on sperm</th>
<th>Positive effect on pregnancy rate*</th>
<th>Negative/no effect on pregnancy rate</th>
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<tr>
<td>Zinc+Folate</td>
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<td>Menevit</td>
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<td>Okada et al., 1997 [175]</td>
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<td>Tesarik et al., 1992 [171]</td>
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<td>Micic et al., 1988 [176]</td>
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<td>Marrama et al., 1985 [177]</td>
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<td>PDE5i</td>
<td>Dimitriadis et al., 2010 [165]</td>
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<td>Pomara et al., 2007 [166]</td>
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<td>Glenn et al., 2007 [168]</td>
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* = statistically significant effect (p<0.05).
Table 3. Results from Cochrane review on anti-oxidant use in male subfertility [80].

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of studies</th>
<th>No. of patients or couples (T, C)</th>
<th>Anti-oxidants used in trials</th>
<th>Duration of treatment</th>
<th>MD (95% CI) or OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sperm motility</td>
<td>10</td>
<td>514 (302, 212)</td>
<td>Combinations, Carnitines, CoQ10, DHA, Magnesium, NAC, PTX, Selenium, Vitamin C, Vitamin E, Zinc</td>
<td>≤ 3 months</td>
<td>MD 11.72 (6.94 to 16.49)</td>
<td>&lt; 0.00001</td>
</tr>
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<td></td>
<td>7</td>
<td>963 (625, 338)</td>
<td>Carnitines, CoQ10, NAC, Selenium, Vitamin E</td>
<td>6 months</td>
<td>MD 4.19 (3.81 to 4.56)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>320 (162, 158)</td>
<td>Carnitines, CoQ10</td>
<td>9 months</td>
<td>MD 1.38 (0.81 to 1.95)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>825 (536, 289)</td>
<td>Carnitines, CoQ10, NAC, PTX, Selenium</td>
<td>6 months</td>
<td>MD 5.25 (4.43 to 6.08)</td>
<td>&lt; 0.00001</td>
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<tr>
<td>Sperm concentration</td>
<td>3</td>
<td>332 (181, 151)</td>
<td>Carnitines, CoQ10</td>
<td>9 months</td>
<td>MD 1.61 (0.61 to 2.61)</td>
<td>0.002</td>
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<tr>
<td></td>
<td>1</td>
<td>64 (32, 32)</td>
<td>Vitamin C, Vitamin E</td>
<td>2 months</td>
<td>MD -13.80 (-17.50 to -10.10)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Sperm DNA fragmentation</td>
<td>15 (2 trials included couples using ART)</td>
<td>964 (515, 449)</td>
<td>Combinations, Carnitines, CoQ10, Magnesium, PTX, Selenium, Vitamin C, Vitamin E, Zinc</td>
<td>2 – 9 months</td>
<td>OR 4.18 (2.65 to 6.59)</td>
<td>&lt; 0.00001</td>
</tr>
<tr>
<td>Pregnancy rate per couple</td>
<td>3 (1 trial included couples using IVF or ICSI)</td>
<td>214 (116, 98)</td>
<td>Vitamin E, Zinc</td>
<td>3 – 6 months</td>
<td>OR 4.85 (1.92 to 12.24)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

ART: Assisted reproductive technology; C: Number of patients/couples in control group; CI: Confidence interval; CoQ10: Coenzyme Q10; DHA: Docosahexaenoic acid; ICSI: Intracytoplasmic sperm injection; IVF: In vitro fertilization; MD: Mean difference; NAC: N-acetyl cysteine; OR: Odds ratio; PTX: Pentoxifylline; T: number of patients/couples in treatment (anti-oxidant) group.
Vitamin E is described as a chain-breaking anti-oxidant that prevents the propagation of free-radical reactions [91]. Natural forms of vitamin E are sensitive to light and oxidation, and therefore, esterification of the labile hydroxyl group on the chromanol ring can extend its half-life. Natural forms of α-tocopherol (d-forms) are twice as active as synthetic forms and synthetic forms (dl-forms) are capable of inhibiting the natural forms from entering cell membranes [92,93].

A meta-analysis of two randomized, controlled trials [94,95] found men with idiopathic male infertility treated vitamin E had a live birth rate of 15% (10/67) compared to 0% (0/50) in the control groups (OR 6.44, 95% CI 1.72 – 24.04) [88]. However, different doses of synthetic forms were used in these studies (300 mg vs. 600 mg), which undermines drawing specific conclusions about the best form or dose of vitamin E that should be used to treat infertile men. Furthermore, contradictory results were reported by Rolf et al. in their randomized, placebo-controlled trial exploring the protective role of vitamin E in infertile men who were given 800 mg of vitamin E for 56 days [96].

These controversies point out the importance of measuring semen ROS levels before instituting vitamin E anti-oxidant therapy, due to the fact that anti-oxidant therapy may not be useful in infertile men without oxidative stress in their semen. In addition, high doses of vitamin E, especially synthetic forms, can act as pro-oxidants [97]. Due to these issues, studies are needed to assess the efficacy of natural forms of α-tocopherol and optimum doses required for the treatment of infertility in men suffering from oxidative stress.

5.3 Carnitines (L-acetyl carnitine and L-carnitine)

Carnitines play an important role in generating cellular energy via β-oxidation by transporting fatty acyl groups across the inner mitochondrial membrane. In mammals, the concentration of free L-carnitine is highest in epididymal plasma and spermatozoa where it accumulates in both the free and acetylated forms [98]. The increase in L-carnitine in the epididymal lumen corresponds with the initiation of sperm motility [98]. The mechanism of the anti-oxidant abilities of carnitines has not fully been elucidated, but carnitines have been shown to scavenge ROS and inhibit lipid peroxidation [99]. Multiple placebo-controlled studies have found that carnitines (2 – 3 g daily of LC plus LAC or LC alone for 3 – 6 months) significantly improves sperm straight progressive velocity, total oxyradical scavenging capacity, sperm motility, sperm concentration, and semen volume [100-106]. Sigman et al. found no significant improvement in semen parameters in men with idiopathic infertility taking LC plus LAC (2 – 3 g daily for 6 months), but the sample size was small (n = 12) [107]. Meta-analysis of four randomized, controlled trials [101,107,108] found LC plus LAC resulted in a pregnancy rate of 20% (19/96) in males with idiopathic infertility compared to 3.4% (3/87) in the placebo group (OR 4.48, 95% CI 1.77 – 11.36) [80]. Although these studies did not report that oral carnitine therapy could raise semen carnitine level, there is good evidence to suggest carnitines are mildly effective at improving the fertility rates of men with idiopathic infertility.

5.4 Coenzyme Q10

It is well known that coenzyme Q10 (ubiquinone) is a fundamental component of the electron transport chain, participating in aerobic respiration and the generation of energy in the form of ATP [109,110]. Coenzyme Q10 is ubiquitous in membranes throughout eukaryotic cells [111], which ideally places it to scavenge free radicals and prevent lipid peroxidation [110]. In addition to direct anti-oxidant activity, coenzyme Q10 helps restore other anti-oxidants, such as Vitamin E and C, to their reduced state [109,110]. Randomized, placebo-controlled trials have found coenzyme Q10 (200 – 300 mg daily for 6 months) can significantly improve sperm motility in males with idiopathic infertility [112,113]. Although statistical significance was not achieved, Balercia et al. found that treatment with 200 mg of Coenzyme Q10 daily for 6 months resulted in a 20% (6/30) pregnancy rate compared to a 10% (3/30) pregnancy rate in the placebo group [112]. These pregnancy rates are similar to those seen in other anti-oxidant studies. A lack of studies with live birth rate outcomes leaves efficacy questionable.

5.5 Selenium

Selenium is a non-metal element that is an essential component of important anti-oxidant enzymes such as glutathione peroxidase [114]. High levels of glutathione peroxidase and reductase found in sperms indicate that the glutathione system is an important defense mechanism against ROS [115]. Selenium also plays an important role in sperm maturation [116]. A randomized, placebo-controlled trial (n = 468) found selenium (200 µg daily for 6 months) significantly increases sperm motility, concentration, and normal morphology in men with idiopathic infertility when compared to placebo [117]. Another randomized, placebo-controlled study treated subfertile men with low plasma selenium levels (n = 69) with selenium, which significantly improved sperm motility, but had no effect on sperm concentration. An 11% pregnancy rate was seen in the treatment group versus 0% in the placebo group [118].

5.6 Magnesium

Magnesium is a co-factor for hundreds of enzymes involved in critical processes like nucleic acid synthesis and energy metabolism [119]. Magnesium deficiency correlates with increases in ROS and lipid peroxidation, but the exact mechanism of magnesium’s anti-oxidant activity remains unknown [120]. One small, randomized, placebo-controlled pilot study (n = 20) found 3000 mg magnesium-orotate for 3 months resulted in no significant improvement in sperm parameters or pregnancy rates [121]. This study was too small to assess the impact of magnesium on idiopathic male infertility. Larger studies are needed.
5.7 Zinc
Zinc acts as a cofactor for approximately 100 metalloenzymes and stabilizes effects and synergistically helps other anti-oxidants [122]. It is thought that zinc can occupy copper- and iron-binding sites, thereby preventing copper- or iron-initiated lipid peroxidation [122]. Zinc is also thought to have membrane-stabilizing effects and anti-apoptotic properties [123]. Low levels of zinc in seminal plasma are associated with male infertility [124]. Higher levels of zinc in seminal plasma correlate significantly with increased sperm concentration and normal sperm morphology [125,126]. Zinc sulfate (500 mg daily for 3 months) significantly improved sperm concentration, motility, and morphology [125,126]. Zinc sulfate (500 mg daily for 3 months) significantly improved sperm concentration, motility, and morphology [125,126]. Zinc sulfate (500 mg daily for 3 months) significantly improved sperm concentration, motility, and morphology [125,126]. Zinc sulfate (500 mg daily for 3 months) significantly improved sperm concentration, motility, and morphology [125,126]. Zinc sulfate (500 mg daily for 3 months) significantly improved sperm concentration, motility, and morphology [125,126].

5.8 N-acetyl cysteine (NAC)
NAC is a precursor for reduced glutathione (GSH), and therefore, can replenish this important anti-oxidant mechanism [128]. NAC can also directly scavenge ROS [128-130]. NAC has been tried as a potential therapeutic option in men with idiopathic infertility, because NAC has been shown to improve germ cell survival in seminiferous tubules [131], increase sperm motility, and reduce semen ROS [130]. Two randomized, placebo-controlled trials looked at the effect of NAC (600 mg daily for 6 months) on men with idiopathic infertility and found NAC significantly improved sperm parameters and semen oxidative status [117,132]. Once again data on pregnancy rates are absent, but needed to fully assess the impact of NAC on idiopathic male infertility.

5.9 Carotenoids (e.g., astaxanthin and lycopene)
Carotenoids are considered to be powerful anti-oxidants that can scavenge ROS and inhibit lipid peroxidation [133-137]. Comhaire et al. conducted a small, randomized, placebo-controlled trial that included 30 men with idiopathic infertility [133]. Treatment consisted of 16 mg of astaxanthin daily for 3 months. Astaxanthin therapy only resulted in a significant decrease in ROS and Inhibin B and a significant increase in sperm linear velocity. No significant changes were seen in other semen parameters, zona-free hamster oocyte test, testosterone levels, LH levels, or FSH levels. The pregnancy rate in the treatment group was 54.5% (6/11) versus 10.5% (2/19) in the placebo group [133]. The pregnancy rate in the treatment group seems excessively high which may be due to small sample size and emphasizes the need for larger studies.

Another study included 30 men with idiopathic male infertility that were all treated with 2000 µg of lycopene twice daily for 3 months [138]. Semen analysis at the end of the study revealed that 66% of the patients had an improvement in sperm concentration (p < 0.05), 53% had improved sperm motility (p <0.05), and 46% had improved sperm morphology. Of note, no changes were seen in patients with baseline sperm concentrations less than 5 million/mL, which may prove to be an important cut-off point for future studies. Six pregnancies (20%) were reported in this study, which is a comparable rate to that with other anti-oxidants discussed [138]. Larger, randomized, placebo-controlled trials are needed to truly assess the impact of carotenoids on idiopathic male infertility.

5.10 Folate
Folate is essential to DNA synthesis, which in turn is a vital component of spermatogenesis. Wong et al. conducted a randomized, placebo-controlled study (n = 103) in which men with idiopathic male infertility were treated with 5 mg of folate daily for 6 months [139]. There were no changes in sperm parameters and pregnancy rate was not included as an outcome [139]. This large study demonstrates that folate shows little promise as a treatment option for idiopathic male infertility.

5.11 Omega-3 fatty acids
Dietary omega-3 polyunsaturated fatty acids are thought to have anti-inflammatory and anti-oxidant properties [140,141]. Safarinejad conducted a double-blind, placebo-controlled, randomized study on 238 males with idiopathic infertility to look at the effects of omega-3 fatty acids on semen parameters [142]. Men in the treatment group received 1.84 g of eicosapentaenoic (EPA) and docosahexaenoic acids (DHA) daily for 32 weeks. Statistically significant improvement in sperm concentration, motility, and morphology was seen in the treatment group. In addition, concentrations of EPA and DHA were significantly greater in seminal plasma, RBCs, and sperm of the treatment group. Superoxide dismutase (SOD) and catalase-like activity were significantly greater in the treatment group after the treatment period. Seminal plasma levels of EPA and DHA positively correlated with semen parameters and seminal plasma SOD-like and catalase-like activity [142]. The inclusion of seminal and
sperm EPA and DHA levels made this an excellent model for future studies of other anti-oxidants, but the lack of pregnancy rate as a primary outcome leaves something to be desired.

5.12 Anti-oxidant combinations
Numerous studies have looked at combinations of anti-oxidants for the treatment of idiopathic male infertility. In addition, pharmaceutical companies are producing and marketing specific combinations of anti-oxidants for males with idiopathic male infertility. Greco et al. demonstrated in a randomized, controlled trial that 1 g of vitamin C plus 1 g vitamin E daily for 2 months significantly reduced (p < 0.001) the DNA fragmentation in spermatozoa when compared to placebo, but had no effect on semen parameters [143]. Rolf et al. conducted a similar study (1 g vitamin C plus 800 mg vitamin E daily for 56 days) and found no improvement in semen parameters or pregnancy rate [96]. Scott et al. found vitamin A, C, and E together had no effect on semen parameters in men with idiopathic infertility [118].

Another randomized, controlled trial (n = 42) treated patients for 3 months with vitamins A, C, and E plus NAC and zinc. This anti-oxidant combination significantly increased the odds of having a normal sperm concentration, but had no impact on pregnancy rate after 12 months of follow-up [144]. Vitamin E (400 mg daily) plus selenium (225 µg daily) supplementation for at least 3 months in men with idiopathic infertility has been shown to significantly improve sperm morphology and motility [145,146] and to decrease MDA (lipid peroxidation marker) concentrations [146]. Safarinejad found that men with idiopathic infertility taking 6 months of selenium (200 µg daily) plus NAC (600 mg daily) had significantly increased sperm motility, concentration, normal morphology, and ejaculate volume when compared to placebo [117]. One randomized, placebo-controlled study involving 60 men with idiopathic infertility looked at the use of a commercial combination of anti-oxidants as an adjuvant to IVF-ICSI treatment. The specific combination capsule contains 6 mg lycopene, 400 IU vitamin E, 100 mg vitamin C, 25 mg zinc, 26 mg selenium, 0.5 mg folate, and 1000 mg garlic. The study found a pregnancy rate of 64% (23/36) in the treatment group compared to 38% (6/16) in the placebo group (p = 0.077). There was also a significant improvement (p = 0.046) in viable pregnancies at 13 weeks in the treatment group (38%, 20/52) compared to placebo group (16%, 4/25) [147]. Of note, the pharmaceutical company provided the capsules for the study. The anti-oxidant combinations that have been studied thus far show no added benefit of certain anti-oxidants alone.

6. α-Agonists
Retrograde ejaculation is a rare cause of male infertility, but can arise secondary to surgical damage to the hypogastric plexus during retroperitoneal lymph-node dissection or pelvic operations [148] or can be due to neuropathy associated with medical diseases such as diabetes mellitus [149]. Drugs with α-agonist properties include chlorpheniramine, phenylpropanolamine, midodrine, and imipramine. α-Agonist therapy increases sympathetic tone at the bladder, thereby increasing pressures in the posterior urethra, which increases the likelihood of achieving antegrade ejaculation in a patient with retrograde ejaculation [148,150]. A recent review looked at six small studies involving pharmacologic management of retrograde ejaculation, including surgical causes, and found that 11 out of 40 patients (28%) treated with a sympathomimetic achieved antegrade ejaculation [151]. The use of anti-cholinergics resulted in 22% (11/50) achieving antegrade ejaculation [151]. Combinations of sympathomimetics and anti-cholinergics resulted in 39% (5/13) of patients achieving antegrade ejaculation [151]. The number of patients in the studies was too small for a valid statistical comparison [151].

A larger meta-analysis (44 studies) by Kamischke and Nieschlag found that the overall success rate of pharmacologic management in treating retrograde ejaculation is 50% and concluded that pharmacologic management should be considered a first-line treatment for retrograde ejaculation [152]. The highest success rate (79%) was seen with 50 mg chlorpheniramine plus phenylpropanolamine daily [152]. A 64% success rate was found with 25 – 75 mg of imipramine daily and a 56% success rate was found with 5 – 40 mg of midodrine daily [152]. A natural pregnancy rate of 34% (30/87) was seen with α-agonist therapy (19 studies) [152]. The most common side-effects of α-agonist therapy included dizziness, weakness, nausea, and sweating [152]. A newer meta-analysis (36 studies) found that imipramine and chlorpheniramine plus phenylpropanolamine have significantly higher reversal rates when compared to ephedrine [153].

α-Agonist therapy has also been used with less success to treat male infertility due to anejaculation. Causes of anejaculation in order of most to least common include spinal cord injury, retroperitoneal lymph node dissection, idiopathic, diabetes mellitus, multiple sclerosis, colorectal surgery, trauma, and myelitis [152]. A meta-analysis (29 studies) found that only 19% of patients with anejaculation (excluding spinal cord injury) achieved ejaculation [152]. Midodrine dosed at 5 – 30 mg daily had the greatest success rate at 54% [152]. Only two natural pregnancies were reported out of 127 patients [152]. A newer meta-analysis (40 studies) found α-agonist treatment of anejaculation was significantly inferior to parasympathomimetic treatment of anejaculation [153]. Of the α-agonist medications, midodrine was found to be significantly better at treating anejaculation than imipramine, pseudoephedrine, and ephedrine. α-Agonists are not recommended as a first-line treatment for anejaculation because electrovibration stimulation and electroejaculation have much higher success rates [153].

A large, randomized, controlled trial (n = 128) found that 7.5 – 15 mg of midodrine daily in a stepwise approach reversed anejaculation in 57.4% (29.5% achieved antegrade
ejaculation, 13.1% achieved retrograde ejaculation, and 14.8% achieved antegrade plus retrograde ejaculation) of patients with anejaculation, excluding patients with anejaculation secondary to spinal cord injury [154]. No patients (0/64) in the placebo group achieved antegrade or retrograde ejaculation. The most favorable responses were seen among patients with multiple sclerosis and least favorable responses were seen among patients with bilateral sympathectomy [154]. Strong evidence reveals α-agonists are an excellent therapeutic option for patients with retrograde ejaculation, but better therapies exist for patients with anejaculation.

7. Parasympathomimetics

To occur, antegrade ejaculation requires both sympathetic and parasympathetic stimulation [155]. Parasympathomimetics such as neostigmine and physostigmine have been used to treat anejaculation. Meta-analysis of 13 studies found a 51% overall success rate of parasympathomimetics in the treatment of anejaculation [152]. Only six natural pregnancies out of 396 patients were reported [152]. An updated meta-analysis found that parasympathetic drugs are significantly more successful than α-agonistic drugs in the treatment of anejaculation [153]. Neostigmine has been abandoned due to invasive intrathecal delivery and severe side-effects including autonomic dysreflexia and cerebral hemorrhage [156,157]. Physostigmine can be administered subcutaneously and has less severe side-effects (e.g., GI upset and orthostatic hypotension) [152].

8. Mast-cell stabilizers/blockers

Increased numbers of mast cells in seminal fluid have been associated with idiopathic male infertility [158,159]. Yamamoto et al. conducted a placebo-controlled, single-blind study in which 50 men with idiopathic infertility were randomly assigned to treatment with 300 mg of tranlast (mast cell blocker) daily or placebo for 3 months [160]. The mast cell blocker group had a significantly higher pregnancy rate than the placebo group (28.6 vs. 0%). The mast cell blocker group also had significantly improved sperm concentration and motility compared to placebo [160]. In an uncontrolled study, 55 men with leukocytospermia were treated with 2 mg of ketotifen daily for 3 months [161]. Sperm motility (p = 0.002) and sperm morphology (p = 0.002) significantly improved and semen WBC count significantly diminished to normal levels (p < 0.0001) after 12 weeks of treatment [161]. Ketotifen (2 mg for 3 months) was recently tried as a post varicocelectomy adjunct therapy in a randomized, controlled trial including 103 infertile men [162]. By 9 months post treatment, the mast cell blocker group had a significantly greater pregnancy rate compared to placebo (41.17% vs. 21.15%, p < 0.05). In addition, the mast cell blocker group had a significant improvement in sperm concentration, sperm motility, sperm morphology, and sperm protamine content, plus a significant reduction in the mean value of seminal white blood cells [162]. There is convincing evidence suggesting mast cell blockers are a good treatment option, but more studies are needed.

9. Phosphodiesterase-5 inhibitors (e.g., sildenafil, tadalafl, vardenafil)

Phosphodiesterase-5 inhibitors (PDE5-i) are well-known for their use in the treatment of erectile dysfunction, but they have also been considered as a possible treatment option for idiopathic male infertility. PDE5-i prevents the hydrolysis of cGMP, thereby increasing intracellular levels of cGMP [163]. It is thought that cGMP may play a role in sperm motility and function, especially the acrosome reaction [164]. One randomized trial (n = 70) treated men with idiopathic infertility with 10 mg of vardenafil daily or 50 mg of sildenafil daily or placebo for 3 months [165]. Sperm concentration, sperm motility, and normal sperm morphology significantly increased after treatment with PDE5-i [166]. PDE5-i also enhanced Leydig cell secretion of insulin-like-3 peptide [165]. Another prospective, randomized, double-blind, crossover study looked at the effects of sildenafil or tadalafl on 18 patients with idiopathic male infertility [166]. Patients received a single dose of sildenafil (50 mg) or tadalafl (20 mg) and semen samples were collected 1 or 2 h after each treatment. A significant increase in sperm motility was seen after sildenafil treatment when compared to baseline, but a significant decrease in sperm motility was seen after treatment with tadalafl. The difference is thought to be due to the fact that tadalafl also inhibits phosphodiesterase-11 (PDE11) [166]. PDE11 has been shown to play an important role in spermatogenesis, sperm motility, and capacitation [167]. Another study (n = 57) found that 100 mg of sildenafil significantly increases sperm motility at 1 and 2 h after treatment [168]. The study also found a statistically significant increase in the proportion of acrosome-reacted sperm after treatment, which may be detrimental to fertility [168]. This emphasizes the importance of including pregnancy rate as a primary outcome when investigating treatment options for male infertility.

10. Non-specific phosphodiesterase inhibitors (e.g., pentoxifylline)

Pentoxifylline’s mechanism of action involves the inhibition of phosphodiesterase, which subsequently leads to an increase in intracellular cyclic adenosine monophosphate (cAMP) [169]. cAMP is important to sperm motility, sperm respiration, and the acrosome reaction [170-173]. Pentoxifylline reduces superoxide anions in vitro [174,175] and significantly increases sperm motility and normal sperm morphology in men with idiopathic infertility [175-177]. A small, randomized, placebo-controlled trial (n = 46) showed that 1200 mg of
pentoxifylline daily for 6 months had no effect on pregnancy rate or sperm concentration in men with idiopathic infertility [178]. A larger, randomized, placebo-controlled trial (n = 254) utilizing a smaller dose of pentoxifylline (800 mg daily for 6 months) [179], found that treatment resulted in a statistically significant increase in sperm concentration, sperm motility, normal sperm morphology, and seminal SOD-like and catalase-like activity, but found no differences in serum hormones (testosterone, LH, FSH, PRL, TSH, and Inhibin B) [179]. Again, pregnancy rate as a primary outcome is absolutely necessary in further studies.

11. Conclusion

Pharmacologic therapy is only effective in a handful of known causes of male infertility. The pathophysiology behind these specific causes of male infertility is relatively well-defined and understood, which allowed for the development of specific pharmacologic agents to correct the problem. More research is needed to delineate the pathophysiology behind idiopathic male infertility in order to develop specific therapies. Based on current data, hormonal therapies in general are a poor choice for idiopathic male infertility due to questionable efficacy and restrictive cost. At present, anti-oxidants appear to be the best pharmacologic choice for empirical treatment of idiopathic male infertility due to their low cost, high availability, good safety profile, and modest efficacy.

Many studies on infertility tend to focus on semen parameters as a primary outcome, but this outcome doesn’t necessarily correlate well with fertility rates. Studying the treatment of male infertility is inherently difficult due to length of time to achieve pregnancy, the long human gestational period, and complexities of sexual relationships. A greater number of adequately powered randomized, controlled trials using live birth rates as a primary outcome are needed to determine the most effective anti-oxidant, dosing, and combination treatments.

12. Expert opinion

Medical treatment of male infertility is a fascinating field for urologists, reproductive biology researchers, scientists, and patients, as it allows for, when absolutely effective, reversal in the decline of man’s fertility potential by simply prescribing medications. Assisted reproductive techniques (ART) are expensive and their success rates are 40 – 60% in the best centers. Although further research is necessary, an important and growing area of infertility management is the use of adjunct medical therapies with ART. Some medical therapies may improve the success rates of ART and thus reduce the cost from repeated cycles.

Male infertility of unknown origin constitutes around 50% of male infertility cases and is very difficult to treat. Specific medical therapy is applied to around 20% of known etiologies of male infertility, where such therapy eventually culminates in improvement in semen parameters and pregnancy rates. HH, urogenital infections, erectile dysfunction, anejaculation, and retrograde ejaculation (due to medical causes) are the only areas where medical therapy has proven successful in restoration of male fertility.

Both pulsatile GnRH analogs and combined LH and FSH treatment are effective in reversing the basic hormonal defects in HH, resulting in successful manifestation of secondary sexual characteristics, testicular enlargement and induction of spermatogenesis (Level B). However, their therapeutic roles in idiopathic male infertility have not been reproducible. Furthermore, the devastating consequences of exogenous testosterone on infertile men, in the form of testicular atrophy and further deterioration of spermatogenesis, make it critical to avoid such practice.

Dopamine agonists are effective in mitigating the pathologic consequences of hyperprolactinemia on semen parameters, hormonal profile and erectile function (Level A); however, no studies on improvement of pregnancy rates were conducted. Again, their role in idiopathic male infertility is limited.

Anti-estrogens were tried in many studies on idiopathic male infertility as single agents or in combination with other agents and they generally have limited therapeutic benefits (Level I). To combat idiopathic and obesity-related hyperestrogenemia, several aromatase inhibitors were tested resulting in modest improvement in hormonal profile without substantial effects on pregnancy rates (Level I). In addition, long-term use of these medications may lead to development of osteoporosis and joint pain.

For immune infertility, intracytoplasmic microinjection of spermatozoa into the oocyte constitutes the best treatment option due to the fact that long-term use of high-dose corticosteroids can lead to development of serious side-effects with no clear advantages on pregnancy rates (Level C).

Although the recent Cochrane review on use of oral anti-oxidants highlighted the therapeutic role of anti-oxidants in idiopathic male infertility, such a conclusion may be jeopardized by the fact that the selected controlled studies used different therapeutic agents. Oral anti-oxidants are generally safe drugs even in high doses; however, it is unknown whether such a safety profile is applied to redox cells such as sperm. Use of anti-oxidants should be evidence-based and goal-directed. Therefore, estimation of the oxidative burden and specific anti-oxidant deficiency in semen can be a solid indication to select specific therapeutic anti-oxidant agents with gradual dose increase based on the observed improvement in semen parameters, semen anti-oxidant levels, oxidative stress parameters and pregnancy rates.

Idiopathic male infertility represents a challenging and frustrating situation for clinicians, because many different medications have no outstanding benefits. Regimens such as hormonal therapies, anti-oxidants, anti-inflammatory agents, and phosphodiesterase inhibitors have been utilized as a monotherapy or in combinations, in both controlled and uncontrolled studies, but their beneficial influences seem to
be ambiguous and lack reproducibility. There is a fundamental need for advances in andrologic diagnostic techniques, focusing on metabolomics and proteomics of sperm, seminal plasma, and testicular tissue. This will allow for the elucidation and categorization of causes of idiopathic male infertility. In addition, the discovery of novel molecular targets is required to guide innovative research activity and the creation of new pharmacologic agents directed at correcting specific irregularities.

The testes are immune-privileged organs, whose cells are protected by the blood-testis barrier. Many chemical compounds are unable to penetrate inside the testes and therefore can’t exert their effects. Modern thinking is directed toward enhanced delivery of these drugs to the testicular cells by non-toxic means such as nanotechnology. When these advances come to fruition, we can expect more efficient therapies and more consistent results.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (*) or of considerable interest (**) to readers.

** Randomized controlled study.
** Randomized controlled study.
** Randomized controlled study.
Male infertility: a critical review of pharmacologic management

male idiopathic infertility: a randomized, double-blind, placebo-controlled, clinical trial. Hum Reprod 1998;Mar13(3):596-603

- Randomized controlled study.


- Meta-analysis.


- Meta-analysis.


- Meta-analysis.


46. Whitten SJ, Nangaia AK, Kuloetis PN. Select patients with hypogonadotropic hypogonadism may respond to treatment with clomiphene citrate. Fertil Steril 2006;Dec86(6):1664-8


- Meta-analysis.


54. Gregoriou O, Bakas P, Grigoraidis C, et al. Changes in hormonal profile and


58. Ghanem H, Shaeer O, El-Segini A.


Male infertility: a critical review of pharmacologic management


109. Braverman DI, Braverman I. The role of coenzyme Q10 in preventing oxidative damage. Proc Natl Acad Sci USA. 1994;91(21):10005-8


Male infertility: a critical review of pharmacologic management


• Randomized controlled study.

Affiliation
Alaa J Hamada*1 MD, Brian Montgomery*2 & Ashok Agarwal†3 PhD HCLD
*Both authors are contributed equally
†Author for correspondence
1Research Fellow in Andrology/Male Infertility, Glickman Urological and Kidney Institute, Center of Reproductive Medicine, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA
2Research intern, Glickman Urological and Kidney Institute, Center of Reproductive Medicine, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA
3Professor, Lerner College of Medicine, Director, Center for Reproductive Medicine, Director, Andrology Laboratory, Cleveland Clinic, Desk A19.1, 9500 Euclid Avenue, Cleveland, OH 44195, USA
Tel: +1 216 444 9485; Fax: +1 216 444 6049; E-mail: agarwaa@ccf.org