The Role of Pharmaceutical Agents in the Alleviation of Male Infertility (Part-II)

1. ANTIOXIDANTS: FRIENDS OR ENEMIES OF THE SPERM QUALITY

Two review studies in this volume attempt to answer whether the administration of antioxidants improves sperm parameters and sperm fertilizing capacity and extensively discuss the balance between oxidative mechanisms and reductive mechanisms in sperm physiology (Table 1). These latter review studies emphasize that in certain doses, antioxidants may have a beneficial effect on sperm parameters. However, the excessive administration of antioxidants leading to reductive stress may have a detrimental effect on sperm physiology.

Oxidative stress (OS), caused by free radicals under the form of reactive oxygen species (ROS), has been investigated thoroughly in male infertility [1-8]. ROS such as superoxide anion, hydroxyl ion, and hydrogen peroxide are unstable and highly reactive molecules that have been linked with male infertility [1] as it was found that ROS are an independent risk factor for male infertility, irrespective of normal or abnormal semen parameters [9]. Their structure comprises unpaired electrons in their outermost valence shells. The short half-life time of these ROS makes them responsible for the insult caused by OS [2]. Spermatozoal mitochondria and leukocytes in the seminal plasma constitute the main sources of ROS in sperm [1].

Nevertheless, small amounts of ROS are crucial in the setting of basic cellular functions [1, 2]. Cellular regulations, signal-transducing, elicitation of apoptosis, and several effects on sperm physiology are among the most outstanding contributions which are highlighted in the current body of literature [1, 10]. These highly reactive compounds appear to be fine tuners of the physiologic function of spermatozoa since ROS are of paramount importance in the process of hyperactivation, sperm capacitation, and acrosome reaction [11]. It is well established that superoxide anion and hydrogen peroxide are major components of sperm hyperactivation, capacitation, and acrosome reaction [11]. During sperm capacitation, the total levels of tyrosine phosphorylation are spectacularly enhanced, and this process is regulated by the action of cyclic adenosine monophosphate and modulated by the redox status of the spermatozoon [12]. Thus, it appears that physiological levels of ROS exert a positive effect on tyrosine phosphorylation, as demonstrated in experimental and clinical studies [12, 13].

On the other hand, an excess of OS has many detrimental implications in the sperm and the male reproductive organs [1]. Structural and functional abnormalities of spermatozoa are the most evident consequences of OS combined with deleterious effects on both mitochondrial and nuclear DNA and sperm epigenome [2, 14]. Most importantly, increased DNA fragmentation, chromosomal microdeletions, and mitochondrial DNA mutations are mainly accused of DNA damage [14]. The structural properties of spermatozoa containing a high proportion of unsaturated fatty acids make them particularly vulnerable to the action of ROS, which leads to lipid peroxidation [15], increased sperm DNA damage, altered motility, diminished sperm viability, and ultimately damaged overall fertility potential [16].

The optimal oxidative environment of the human body is maintained by a variety of enzymatic and non-enzymatic mechanisms [14, 17]. Over the last few years, there was a critical shift towards the administration of exogenous antioxidants in an attempt to counteract the ROS-mediated infertility pathways and reduce OS-induced male infertility [2, 17]. Antioxidants typically aim to prevent or reduce the damage caused by ROS [2, 14]. Therefore they have been recognized as a viable treatment option targeting the body’s redox state, maintaining cellular homeostasis, and regulating optimal sperm function. However, the lack of enough elaborate randomized control trials and meta-analyses raises considerable concern about the wide and continuously expanding use of antioxidants. Currently, antioxidant supplementation is administrated irrespectively of the clinically quantified deficiencies leading to poor efficiency, risky over-exposure, and potentially detrimental effects. Several biological reactions in the human body are strictly regulated by a physiologic equilibrium between oxidative and reductive states. Any deviation from this balance shifts toward either oxidation or reduction, which may have detrimental effects on the tissue [14, 17]. In this way, the irrational use of antioxidants may disrupt the redox balance leading to detrimental effects on male fertility.

2. ADMINISTRATION OF PHARMACEUTICAL AGENTS BEFORE THE PERFORMANCE OF TESTICULAR SPERM EXTRACTION

Historically, the most challenging andrological cases are men with nonobstructive azoospermia (NOA-men). Microdissection testicular sperm extraction (micro-TESE) represents the procedure of choice for NOA-men. Combined with ICSI, micro-TESE allows NOA-men the opportunity to father their own biological children while minimizing testicular damage [18]. However, micro-TESE offers in these men a mean sperm retrieval rate of 50% [19]. In this context, any treatment option aiming to improve spermatogenesis the possibility of retrieving spermatozoa in these men is greatly anticipated.

Several empirical medical treatments have emerged and been employed to treat idiopathic male infertility with limited success. Hormonal manipulation has also been employed to stimulate spermatogenesis in severe testiculopathies [20], but controversy exists regarding the efficacy of preoperative hormonal treatment [21]. The rationale behind the hormonal administration is the increase of intratesticular testosterone levels, further stimulating spermatogenesis since there is evidence that improvement in serum testosterone levels may improve the production of the sperm. Corroborating to this hypothesis is the study by Hussein et al., who demonstrated that the administration of clomiphene citrate in NOA-men had a beneficial effect with the return of sperm to the ejaculate [22]. Similarly, NOA-men with Klinefelter syndrome had a better sperm retrieval rate with micro-TESE when responded to hormonal therapy [18]. However, a definitive conclusion on the
use of medical treatment in optimizing androgen production before TESE in NOA-men is difficult to be drawn since randomized trials and meta-analyses are still lacking.

3. HYPOGONADOTROPIC HYPOGONADISM

Gonadotropin-releasing hormone (GnRH) is the key molecule for the treatment of hypogonadotropic hypogonadism. This volume aims to focus on the influence of GnRH therapy on fertility and cognitive abilities. One of the objectives of this volume was to evaluate the current level of evidence for this therapeutic approach. The key messages for these aspects are highlighted. If fertility is not of major importance for a patient, testosterone therapy is the treatment of choice to induce and maintain secondary sexual characteristics and sexual function [23]. Spermatogenesis is usually detrimentally influenced in patients with hypogonadotropic hypogonadism.

Gonadotropin therapy or GnRH supplementary replacement therapy beneficially affects the exocrine function of the testis. Outcomes after combined treatment of FSH and hCG have been demonstrated to be superior compared with single pharmaceutical agents. Alterations in testicular size, testicular endocrine function, testicular exocrine function, and adverse effects after long-time combination therapy with hCG and FSH are extensively reviewed in this volume. Several studies mentioned and extensively discussed in this volume suggest that administration of gonadotropins is important in preserving reproductive potential in patients with hypogonadotropic hypogonadism.

4. HYPERGONADOTROPIC HYPOGONADISM

To alleviate infertility in males with hypergonadotropic hypogonadism, medical treatments are used either alone or in combination with assisted reproductive techniques. To treat the infertility status in men with hypergonadotropic aromatase inhibitors, recombinant gonadotropins, or gonadotropins, aromatase inhibitors, selective estrogen receptor modulators, and their combination are available as options. In this volume, several types of therapeutic pharmaceutical or surgical approaches for infertile men with hypergonadotropic hypogonadism are reviewed. Some pharmaceutical treatments have been shown to have a positive effect on male reproductive potential.

Table 1. Mechanisms mediating the effects of pharmaceutical agents on sperm parameters.

<table>
<thead>
<tr>
<th>Pharmaceutical Agent</th>
<th>Mechanisms Responsible for the Effects on Sperm Parameters and Function</th>
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<tbody>
<tr>
<td><strong>Hormonal</strong></td>
<td>-</td>
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<tr>
<td><strong>GnRH</strong></td>
<td>Stimulation of the pituitary-testicular axis</td>
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<tr>
<td><strong>Gonadotropins</strong></td>
<td>Stimulation of Leydig and Sertoli cellular secretory function</td>
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<tr>
<td><strong>Non-hormonal</strong></td>
<td>-</td>
</tr>
<tr>
<td><strong>NO donors</strong></td>
<td>Vasodilating effect on the vascular supply of the testis, epididymis, and prostate; increase in prostatic blood flow and nutrition; increase in prostatic secretory function</td>
</tr>
<tr>
<td><strong>Antioxidants and/or micronutrient supplements</strong></td>
<td>Protection of diploid or haploid testicular germ cell plasma membrane from oxidative stress/lipid peroxidation, and increase in the blood supply of the testis, epididymis, and prostate; increase in prostatic secretory function</td>
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</tbody>
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REFERENCES


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