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ORIGINAL ARTICLE

Systemic review of antioxidant types and doses in male infertility: Benefits on semen parameters, advanced sperm function, assisted reproduction and live-birth rate

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KEYWORDS

Male infertility;
Antioxidants;
Reactive oxygen species;
Semen analysis;
Sperm DNA fragmentation

ABBREVIATIONS

ART, assisted reproductive therapy;
coQ10, co-enzyme Q10;
DDS, DNA degraded sperm;

Abstract ***Objective:*** To explore the current evidence concerning the effect of oral antioxidant supplementation on various male fertility outcomes, as antioxidants are widely available compounds that are commonly used for the treatment of male infertility.

Materials and methods: PubMed, Medline and Cochrane electronic databases were searched according to a modified Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines looking for studies investigating the effect of antioxidant therapy on infertile men. The studies were explored looking for antioxidants: (i) types and doses; (ii) mechanism of action and rationale for use; and (iii) effect on the different outcome measures reported.

Results: In all, 26 studies reported a significant positive effect of antioxidant ther-

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ICSI, intracytoplasmic sperm injection;
IVF, *in vitro* fertilisation;
LAC, L-acetyl carnitine;
LC, L-carnitine;
MeSH, Medical Subject Heading;
NAC, *N*-acetyl cysteine;
OAT, oligoasthenozoospermia;
OS, oxidative stress;
PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses;
ROS, reactive oxygen species;
SDF, sperm DNA fragmentation

apy on basic semen parameters, advanced sperm function, outcomes of assisted reproductive therapy, and live-birth rate. Vitamin E, vitamin C, carnitines, *N*-acetyl cysteine, co-enzyme Q10, zinc, selenium, folic acid and lycopene were most commonly used. The vitamins' mechanism of action and reported doses is presented in Tables 1 and 2.

Conclusion: Antioxidants generally have a favourable effect on male fertility. Further studies are needed to identify the optimal antioxidant regimen that can be used safely and efficiently in clinical practice.

Introduction

Infertility is defined as the inability to conceive after at least 12 months of regular, unprotected intercourse with a prevalence of 15% of couples worldwide. Male factors contribute to almost half of the reported cases [1,2] and are thought to occur secondary to derangement in testicular function or obliteration of the reproductive passages. Several causes of male factor infertility have been recognised; however, in most cases the exact cause remains unknown [1]. Efforts aimed to unravel the idiopathic causes of male infertility at the molecular level have highlighted the significant contribution of oxidative stress (OS), a term given to describe the imbalance of the bodies' redox state caused either by too high levels of oxidants or too low amounts of antioxidants.

Reactive oxygen species (ROS) or 'free radicals' are highly reactive oxygen-derived molecules characterised by having unpaired electrons in their outer valence orbital. They include oxygen-centred radicals (hydroxyl radical, nitric oxide radical, and superoxide anion radical) and non-radical derivatives (hydrogen peroxide, peroxynitrite anion, and hypochlorous acid) [3]. ROS play an important role in cell signalling and homoeostasis. They are produced by the sperm cell in small quantities providing beneficial functional effects including initiation of sperm capacitation, regulation of sperm maturation, and enhancement of cellular signalling pathways [4]. However, high levels of ROS may have paradoxical effects on sperm function, ultimately resulting in infertility. Increased DNA damage and lipid peroxidation are noticeable effects of exaggerated ROS levels in seminal plasma [5]. Several endogenous (immature spermatozoa, leucocytes, varicocele) and exogenous (testicular hyperthermia, environmental and habitual exposures) conditions have been recognised as potential causes of increased ROS production.

ROS are counterbalanced by antioxidants that help maintain the equilibrium in the redox potential desired for optimal sperm function [6]. Seminal fluid is rich in antioxidants that nourish and protect the sperm. They exist in two forms; an enzymatic and a non-enzymatic antioxidant system [7]. The enzymatic system is comprised of glutathione peroxidase, superoxide dismutase, and catalase. These enzymes are naturally occurring in the sperm cell or seminal plasma and are thought to originate from the prostate. The non-enzymatic system, on the other hand, is composed of multiple compounds that are consumed through diet or as supplements.

When excessive amounts of ROS are produced, or when antioxidant activity fails, the equilibrium state between oxidation and reduction is disrupted, resulting in OS. Spermatozoa are particularly vulnerable to OS. They contain very low levels of enzymatic antioxidants, which are insufficient in protecting the sperm against high ROS levels. Furthermore, the exceptionally high amounts of polyunsaturated fatty acids, especially docosahexaenoic acid, in the sperm cell's plasma membrane are appealing reactants for ROS-induced oxidation reactions.

Major advances have been witnessed in the field of male infertility over the past few decades. Tests of sperm function, such as sperm DNA fragmentation (SDF), and measures of OS have been added to the clinician's armamentarium to provide a better understanding of the true male fertility potential [8]. Also, the breakthroughs per-

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