# ANTIOXIDANT THERAPY IN MALE INFERTILITY

*An Essay's*

Submitted for fulfillment
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*By*

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# LIST OF ABBREVIATIONS

| Abbrev. | Full term |
|---|---|
| **AR:** | Androgen receptors. |
| **ARTs:** | Assisted reproductive techniques. |
| **ATP:** | Adenosine triphosphate. |
| **cAMP:** | Cyclic adenosine mono phosphate. |
| **CK:** | Creatine kinase. |
| **CoQ10:** | Coenzyme Q-10. |
| **DHT:** | Dihydrotestosterone. |
| **EGF:** | Epidermal growth factor. |
| **ERC:** | Excess residual cytoplasm. |
| **FMLP:** | Formyl-methionyl-leucyl-phenylalanine. |
| **FSH:** | Follicle-stimulating hormones. |
| **G6PD:** | Glucose-6-phosphate dehydrogenase. |
| **GnRH:** | Gonadotropin-releasing hormone. |
| **GSH:** | Glutathione. |
| **H2O2:** | Hydrogen peroxide. |
| **HPG:** | Hypothalamic-pituitary-gonadal. |
| **ICSI:** | Intracytoplasmic sperm injection. |
| **IM:** | Immotility. |
| **IUI:** | Intra-uterine insemenation. |
| **IVF:** | In vitro fertilization. |
| **LH:** | Luteinizing hormone. |

# LIST OF ABBREVIATIONS (Cont...)

| Abbrev. | Full term |
|---|---|
| **LHRH:** | Luteinizing hormone releasing hormone. |
| **LPO:** | Lipid peroxidation. |
| **MAR:** | Mixed antiglobulin reaction. |
| **MDA:** | Malondialdehyde. |
| **NAC:** | N-acetyl-L-cysteine. |
| **NADPH:** | Nicotinamide adenosine diphosphate. |
| **NP:** | Non-progressive motility. |
| **NSAID:** | Non-steroidal anti-inflammatory drugs. |
| **OAT:** | Oligoasthenoteratozoospermia. |
| **OS:** | Oxidative stress. |
| **PMA:** | Phorbolmyristate acetate. |
| **PMNL:** | Polymorphonuclear leukocytes. |
| **PR:** | Progressive motility. |
| **PUFA:** | Polyunsaturated fatty acids. |
| **PVE:** | Prostato–vesiculo–epididymitis. |
| **ROS:** | Reactive oxygen species. |
| **SOD:** | Superoxide dismutase. |
| **TAC:** | Total antioxidant capacity. |
| **TGF:** | Transforming growth factor. |
| **TTP:** | Time-to-pregnancy. |
| **WHO:** | World health organization. |


*First of all, I wish to express my sincere thanks to ALLAH for guidance and generosity brought on me and my life.*

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# INTRODUCTION

Infertility is the inability of a sexually active non-contracepting couple to achieve pregnancy in one year. About 25% of couples do not achieve pregnancy within 1 year. Of these couples, 15% seek medical treatment for infertility and less than 5% remain unwillingly childless. Infertility affects both men and women. Male causes for infertility are found in 50% of involuntarily childless couples. If there is a single factor, the fertile partner may compensate for the less fertile partner. In many couples, however, a male and a female factor coincide. Infertility usually becomes manifest if both partners are subfertile or have reduced fertility ***(Dohle et al., 2007).***

In the era of evidence-based medicine, specific management of infertility should be based on identifying reversible causes of infertility and treating them with suitable medications. However, this may constitute a challenge, since in spite of extensive research; no identifiable cause can be found in over 25% of infertile males ***(March and Isidori et al., 2002).***

Recently, oxidative stress (OS) has become the focus of interest as a potential cause of male infertility. Oxidative

stress occurs when there is an imbalance between reactive oxygen species (ROS) production and antioxidant capacity ***(Aitken et al., 2003).***

ROS are free radicals that are derived from metabolism of oxygen. Under physiological conditions, spermatozoa produce small amounts of ROS, which are needed for capacitation, acrosome reaction and fertilization. However, excessive amounts of ROS produced by leukocytes and immature spermatozoa can cause damage to the normal spermatozoa, loss of sperm motility and decreased capacity for sperm-oocyte fusion by inducing lipid peroxidation and DNA damage ***(Agarwal et al., 2003).***

The seminal plasma contains an array of antioxidants that act as free radical scavengers to protect spermatozoa against OS. This defense mechanism compensates for the loss of sperm cytoplasmic enzymes occurring when the cytoplasm is extruded during spermiation, which in turn, diminishes endogenous repair mechanisms and enzymatic defenses ***(Smith et al., 1996).***

High concentrations of ROS may be detected in the semen of 30–80% of infertile men. In view of this, rational strategies with the goal of reducing concentrations of OS should be effective in the treatment of male infertility.

Initially, clinicians should identify and treat the cause for increased ROS production, for example reproductive tract infections, smoking, and varicocele. Following this, augmentation of the scavenging capacity of the seminal plasma by supplementation with antioxidants should be considered ***(Sharma et al., 2001)*.**

The human body has a number of mechanisms to minimize free radical-induced damage and to repair damage that has already occurred. Three different antioxidant protection systems provide the necessary protection against the damaging effect of free radicals: dietary antioxidants that are obtained as part of our regular diet; endogenous antioxidants that are the part of body's own defense mechanism; and the metal-binding proteins that combine with the metals and prevent their catalytic effect ***(Percival et al., 1996)*.**

# AIM OF THE WORK

The aim of the work is to review the effect of oxidative stress in male infertility and benefits of antioxidant therapy.

# MALE REPRODUCTIVE PHYSIOLOGY

Proper understanding of spermatogenesis and related pathology requires appreciation of the physiology of the testis, hormonal control of the testis. It is responsible for reproductive tract formation and development, maturation of fertility potential at puberty, and the maintenance of maleness in the adult.

## Hypothalamic-Pituitary-Gonadal Axis

The hypothalamic-pituitary-gonadal (HPG) axis plays a critical role during development and adulthood in four physiological processes:

1) Phenotypic gender development during embryogenesis.

2) Sexual maturation at puberty.

3) Testis endocrine function (testosterone production).

4) Testis exocrine function (sperm production).

## Components of the reproductive axis:

### *1-Hypothalamus:*

As the integrative center of the HPG axis, the hypothalamus receives neuronal input from the amygdala, thalamus, pons, retina, olfactory cortex and

many other areas **(Fig.1)**. The most important hypothalamic hormone for reproduction is gonadotropin-releasing or LH-releasing hormone (GnRH or LHRH). Currently, the only known function of GnRH is to stimulate the secretion of luteinizing hormone (LH) and follicle-stimulating hormones (FSH) from the anterior pituitary ***(Dode et al., 2003)*.**

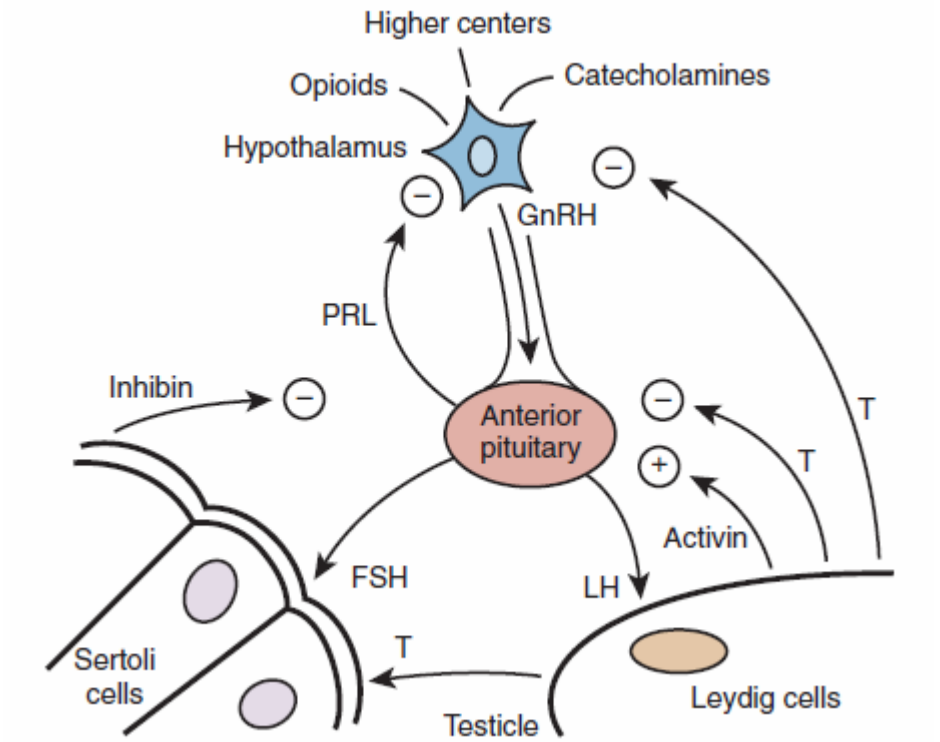


**Figure (1):** Diagram of the hypothalamic-pituitary-testis hormonal axis.

***In: Tanagho EA, McAninch JC, editors. Smith's urology. 16th ed. Stamford, CT: Appleton & Lange; 2008 [chapter 44–2].***

### *2-Anterior Pituitary:*

The pituitary has two lobes: posterior and anterior. The posterior lobe, or neurohypophysis, secrets two hormones, oxytocin and vasopressin. In contrast, the anterior pituitary or adenohypophysis is regulated by blood-borne factors and is the site of action of GnRH and secretion of LH and FSH hormones. LH and FSH are the primary pituitary hormones that regulate testis function. FSH and LH are only known to act in the gonads. In the testis, LH stimulates steroidogenesis within Leydig cells by inducing the mitochondrial conversion of cholesterol to pregnenolone and testosterone. FSH is essential for the initiation of spermatogenesis at puberty. FSH binds to Sertoli cells and spermatogonial membranes within the testis and is the major stimulator of seminiferous tubule growth during development. In the adult, the major physiologic role of FSH is to stimulate quantitatively normal levels of spermatogenesis ***(Goffin et al., 2002).***

### *3-Testis:*

Normal male virility and fertility requires the collaboration of the exocrine and endocrine testis. The interstitial compartment, composed mainly of Leydig cells, is responsible for steroidogenesis. The seminiferous tubules

produce spermatozoa. Testosterone is metabolized into two major active metabolites in target tissue:

(1) The major androgen dihydrotestosterone (DHT) from the action of 5α-reductase.
(2) The estrogen estradiol through the action of aromatases.

DHT is a much more potent androgen than is testosterone. The primary site of FSH action is on Sertoli cells within seminiferous tubules. In response to FSH, Sertoli cells produce androgen-binding protein, transferrin, lactate, ceruloplasmin, clusterin, plasminogen activator, prostaglandins, and growth factors. Through these FSH-mediated factors, seminiferous tubule growth is stimulated during development, and sperm production is initiated during puberty ***(Levallet et al., 1999).***

The testis also produces the protein hormones inhibin and activin:

(1) Inhibin is a 32-kD protein made by Sertoli cells that inhibits FSH release from the pituitary. Within the testis, inhibin production is stimulated by FSH and acts by negative feedback at the pituitary or hypothalamus.

(2) Activin, a testis protein with close structural homology to transforming growth factor–β, exerts a stimulatory effect on FSH secretion ***(Itman et al., 2006).***