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The Role of Antioxidants in Female Fertility: Mechanisms and Clinical Implications

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ABSTRACT :

Female fertility is a complex interplay of hormonal, genetic, and environmental factors, with oxidative strain playing a pivotal function in reproductive health and dysfunction. The difficult balance of oxidative stress and antioxidant defences performs a critical role in female reproductive fitness. Reactive oxygen species (ROS) and oxidative stress are identified as key elements that can adversely affect oocyte quality, follicular development, and universal reproductive consequences. Antioxidants, both endogenous and exogenous, counteract those effects by neutralizing ROS and supporting cell function. The biochemical pathways via which antioxidants have an impact on ovarian physiology, oocyte maturation, and embryo improvement are tested. Also, numerous antioxidants, together with vitamin C and E, melatonin, and polyphenols including quercetin, resveratrol, and baicalin, carotenoids like β-carotene, lycopene, and lutein, in conjunction with trace elements in addition to low-molecular-weight antioxidants which includes glutathione and uric acid, are explored alongside their efficacy in improving reproductive outcomes in animal models and scientific studies. This overview highlights ability therapeutic applications of antioxidants in conditions like polycystic ovary syndrome, endometriosis, and unexplained infertility, presenting a critical analysis of modern-day research and identifying gaps for future investigation. Emerging evidence suggests that targeted antioxidant therapy might also enhance fertility in women experiencing oxidative stress-related infertility. This review highlights the capacity of antioxidants as therapeutic agents in reproductive medicine, emphasizing the need for personalized approaches and comprehensive medical reviews.

Keywords: Infertility, oxidative stress, Reactive Oxygen Species, Antioxidant

Introduction

Infertility, a reproductive system disorder, characterized by the inability to achieve a clinically recognized pregnancy despite engaging in normal unprotected sexual intercourse for 365 days or longer, impacts approximately 15% of all couples. Notably, almost a quarter of these cases lack an identifiable causative issue [1]. Unexplained infertility refers to infertility in which the reason stays unidentified even after a thorough infertility evaluation. This situation accounts for about 20–35% of couples experiencing infertility [2]. The occurrence varies across areas and is encouraged by factors such as age, socioeconomic repute, and underlying fitness conditions. In industrialized countries, delayed schedule childbearing due to career pursuits, educational aspirations, and converting social norms has contributed to an upward push in infertility rates. Additionally, life-style elements which includes smoking, weight problems, and environmental pollution can impair reproductive feature and increase the threat of infertility [3]. Around 84% of couples normally achieve conceiving within the first year of engaging in sexual intercourse, and this percent increases to 92% by the end of the second year. [4]. In recent decades, there has been a decline in semen quality amongst Asian men, probably contributing to the increasing instances of infertility attributed to male elements [5]. Conversely, woman infertility influences an estimated 48 million women globally, with the highest incidence located in South Asia, Sub-Saharan Africa, North Africa, Middle East, Central Europe, and Central Asia [6]. While both male and woman factors together account for 20–30% of total infertility instances, the etiology in the majority (40–50%) is frequently attributed to the female companion [7]. The mechanisms through which various factors have an effect on female fertility are still not profoundly understood. Some studies advise that the incidence of this circumstance is expected to increase, especially in developed countries of the world, due to the trend of deferral of childbirth [8,9]. Nevertheless, comprehensive literature has documented studies inspecting the pathology of infertility in couples, in particular focusing on the role of oxidative stress (OS) inside the pathophysiology of woman infertility [7]. Oxidative stress arises from an imbalance among the production of reactive oxygen species (ROS) and the body's capability to counteract these harmful substances, resulting in cellular damage [10]. When cells utilize oxygen for their survival, they inevitably produce reactive oxygen species (ROS) as by-products. While a certain range of ROS is essential for the regular functioning of cells, which include reproductive cells and tissues [11], excessive quantities can emerge as unfavourable, leading to DNA damage and potentially triggering apoptosis. Elevated ROS ranges can result from both endogenous and exogenous elements. In reproductive cells, common exogenous causes of oxidative stress include environmental pollution, smoking, alcohol consumption, insufficient nutrients, and weight problems. Endogenous reasons might involve infections, chronic ailments, and autoimmune problems [12]. Optimal levels of reactive oxygen species (ROS) play important roles in signal transduction

pathways concerned in oocyte maturation, folliculogenesis, luteolysis, and fetoplacental improvement. Nevertheless, an excessive presence of ROS can result in harmful results. Given their intimate association with reproductive features, retaining tightly regulated ROS level is essential [13]. Reactive nitrogen and oxygen species (RNOS) at controlled levels play important signalling roles in diverse aspects of female reproductive health. They make a contribution to ovulation in the ovaries and facilitate the recovery and regeneration of the uterine lining post menstruation without inflicting scarring. Moreover, they help processes like energy production, blood vessel formation (angiogenesis), and regulate inflammation during different phases of menstrual cycle, thereby influencing fertility undoubtedly [14].

To counteract oxidative damage or stress, the body has advanced an antioxidant defence mechanism. Antioxidants are able to directly scavenging reactive oxygen species (ROS), rendering them inactive, and repairing the ensuing damage [15]. The body possesses natural antioxidants, which exist in both enzymatic and non-enzymatic forms. Enzymatic antioxidants encompass catalase, superoxide dismutase, glutathione peroxidase, and glutathione reductase. Non-enzymatic antioxidants contain substances along with ascorbic acid (Vitamin C), alpha-tocopherol (Vitamin E), ferritin, and transferrin [16]. Naturally occurring antioxidant compounds are found in fruits, veggies, medicinal plants, and different nutritional sources can be classified widely into 3 corporations: vitamins, carotenoids, and phenolic compounds.

Regulation of Female Reproductive system by Reactive Oxygen and Nitrogen Species:

Oxidative stress occurs when the body's ability to neutralize harmful substances, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), is submerged by their production, leading to an imbalance. This imbalance can greatly affect the specific lifespan of female reproductive health [17]. Reactive oxygen and nitrogen species play an important role in regulating various aspects of female reproductive processes. They look after ovulation, oocyte maturity, ovarian steroid production, breakdown of corpus luteum (luteolis) and its livelihood during pregnancy. In addition, they control the development of follicles and blastocysts, the implantation of the blastocyst and their signalling functions [18,19,20]. Severe oxidative stress in follicular fluid is associated with low oocyte quality and fertilization rate, which is likely due to DNA damage in eggs, alterations in the follicular microenvironment, and reduced antioxidant availability. This can ultimately result in lower pregnancy rates. It is essential to acknowledge that oxidative stress is only one of several factors affecting oocyte and follicle development, and further research is required to fully comprehend its influence on fertility outcomes. [21].

2.1 Role of Reactive Oxygen Species (ROS) in Follicular Development and Ovary and Uterus Physiology

The 3 major types of reactive oxygen species (ROS) are superoxide ($O2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl ($OH^{\bullet -}$). Superoxide radicals form when electrons escape out from the electron transport chain. Superoxide dismutation produces hydrogen peroxide. The relatively reactive hydroxyl ion can alter purines and pyrimidines and cause DNA strand breaks, leading to DNA damage [22,23]. Standard levels of physical ROS are required for follicular development and oocyte maturation. In the ovaries, oxidative stress is associated with conditions such as endometriosis and polycystic ovarian syndrome, causing impaired oocyte mitochondrial function, DNA fragmentation and fertilization. These mitochondrial dysfunction results in suboptimal oocyte growth and maturation [21]. Human granulosa and luteal cells make a response to hydrogen peroxide by defeating gonadotropin action and hampering progesterone secretion [24]. In cultures of human chorionic gonadotropin-stimulated luteal cells, hydrogen peroxide exposure leads to decreased production of progesterone and estradiol. This reduction in steroidogenesis occurs through both cAMP-dependent and non-cAMP-dependent pathways [25]. Studies have investigated the impact of human chorionic gonadotropin (hCG) on the expression of the antioxidant enzyme superoxide dismutase (SOD). Corpora lutea collected from patients undergoing hysterectomy or surgery for ectopic pregnancy were analyzed. The expression of Cu-Zn SOD in the corpora lutea was found to correlate with progesterone levels, reaching its peak during the mid-luteal phase and declining as the corpus luteum regressed. However, in pregnant patients, mRNA expression of Cu-Zn SOD was significantly higher compared to midcycle corpora lutea. This increased luteal Cu-Zn SOD expression is likely influenced by hCG, highlighting its essential role in sustaining corpus luteum function during pregnancy [26]. The levels of three oxidative stress biomarkers—conjugated dienes, lipid hydroperoxide, and thiobarbituric acid—were measured in preovulatory follicles. A concentration gradient was observed, with significantly lower levels of these markers in follicular fluid compared to serum. This suggests the presence of a strong antioxidant defense system within the preovulatory follicle, which becomes depleted under conditions of intense peroxidation [27]. Studies have shown that women with endometriosis exhibit increased levels of autoantibodies linked to oxidative stress (OS), resulting in higher serum autoantibody titers against oxidatively modified low-density lipoproteins [28]. In women with endometriosis, oxidative stress (OS) has been linked to increased autoantibody titers in the peritoneal fluid. Additionally, elevated levels of lysophosphatidylcholine—a key marker of lipid peroxidation and a strong chemotactic factor for monocytes and T-lymphocytes—have been detected in the peritoneal fluid of these patients [29].

2.2 Nitric oxide signalling in female reproductive system

The appearance of nitric oxide (NO) assembly in the human fallopian tube has been confirmed by positive NADPH diaphorase activity, which indicates the presence of an endogenous NO system within the tubes. NO involves in a crucial role in relaxing smooth muscles and regulating tubular contractility. Deficiency of NO can lead to impaired tubal motility, resulting in ovum retention, delayed sperm transport, as well as infertility. While elevated NO levels in the fallopian tubes exhibit cytotoxic effects against invading microbes, they may also negatively impact spermatozoa [30]. Endothelial and inducible nitric oxide synthases are present in the human endometrium and its blood vessels. Endothelial NO synthase is principally present in glandular surface epithelial cells, where it participates in regulating the microvasculature required for menstruation. These two forms of NO synthase contribute in the preparation of the endometrium for implantation. Inducible NO synthase, which supports implantation and early gestational development, is specifically expressed in decidualized stromal cells and early pregnancy tissues [20]. Nitric oxide participates in ovarian folliculogenesis and steroidogenesis as a local regulator. It turns on a number of iron-containing enzymes, including guanylate cyclase, a heme-containing enzyme, which subsequently stimulates cyclic GMP production [31]. Nitric oxide is found to suppress ovarian steroidogenesis. Human corpora lutea also has endothelial

NO synthase. Its higher expression is observed during the mid and early luteal phases, which diminishes in the late luteal phase. It has inhibitory effect on steroidogenesis in the corpus luteum as well and is associated with luteolytic action, which involves the elevation of prostaglandins and induction of apoptosis [32,33].

Impact of Antioxidant Systems in Female Reproduction :

To counteract oxidative stress (OS), a diverse range of both enzymatic and non-enzymatic antioxidant systems exist in human body. Enzymatic antioxidant protection depends on some vital enzymes such as catalase (CAT), glutathione peroxidase (GPX), glutathione reductase (GSR), and superoxide dismutase (SOD). These enzymes participate in preserving the integrity and functionality of cell membranes by preventing lipid peroxidation [34]. Enzymatic antioxidants, also known as natural antioxidants, prevent cellular structure damage by neutralising excess reactive oxygen species (ROS). These antioxidants for instance superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, also diminish hydrogen peroxide to water and alcohol [20]. Non-enzymatic antioxidants can be acquired through dietary intake or synthesized within the body and encompass a wide array of compounds. These comprise of polyphenol compounds such as quercetin, resveratrol, and baicalin, carotenoid compounds such as β-carotene, lycopene, and lutein, as well as low-molecular-weight antioxidants such as glutathione and uric acid. Furthermore, trace elements like zinc and selenium, vitamins A, E, C, and B9, and other substances like L-carnitine, melatonin, and acetylcysteine also contribute to the body's antioxidant defense system [35,36]. Endogenous antioxidants typically conserve a stable level within the body, activate only when needed. On the other hand, exogenous antioxidants are obtained from food and exhibit variable levels that fluctuate according to dietary intake [37,38].

Polyphenol, a dietary micronutrient, plays a crucial role in the maintenance of human fertility. Quercetin, a flavonoid with antioxidant properties is employed as an ideal agent for antioxidant treatment [16]. Resveratrol, a non-flavonoid polyphenol displays both structural and functional similarities to estrogen, empowering it to bind to nuclear estrogen receptors (ER) and modulate their activity [39]. Resveratrol shows potentiality in the treatment of endometriosis and uterine fibroids by remarkably bringing down both the number and volume of endometrial implants [40].

Glutathione is broadly considered as the primary natural antioxidant due to its extraordinary ability to detoxify and regulate the cellular redox state. It participates in maintaining the vital equilibrium between reactive oxygen species (ROS) and antioxidants. Additionally, glutathione plays a crucial role in the maturation of oocytes [41].

Essential trace elements, such as zinc (Zn), selenium (Se), copper (Cu), chromium (Cr), cobalt (Co), iodine (I), manganese (Mn), and molybdenum (Mo) are crucial for human body as they play key role in the active sites of enzymes and as components of transcription factors. Deficiency of these trace elements, particularly Zn and Se, are often associated with reproductive disorders like endometriosis and polycystic ovary syndrome (PCOS), along with pregnancy complications such as prolonged labor and pregnancy-induced hypertension. Zinc is essential in maintaining endocrine and redox balance, modulating inflammatory processes, along with regulating glucose and lipid metabolism. Furthermore, it plays a crucial role in controlling cell proliferation, gene expression, and supporting the immune system [42,43]. Zinc, together with copper, act as a cofactor for the essential antioxidant enzyme zinc superoxide dismutase (Zn-SOD) or zinc superoxide dismutase 1 (Zn-SOD1), which plays a critical role in women's ovulation and menstrual cycles by scavenging reactive oxygen species (ROS) [44]. Selenium inhibits NF-κB and inflammatory cytokine expression while enhancing antioxidant capacity by activating Nrf2. This action assists in diminishing the cytotoxic effects resulting from the reactive oxygen species (ROS) [45]. Selenium, as a component of selenoproteins like GPx and thioredoxin reductase, is essential for redox reactions within the uterus, granulosa cells, and follicles [46].

Research on the mechanisms of action of vitamins, A, C, E, and B9 as antioxidants is a significant landmark, as serum concentrations of these antioxidants are linked to steroidogenesis. These vitamins play a vital role in protecting cell compartments from oxidative damage and regulating the physiological development of uterine and ovarian cells throughout the menstrual cycle [47]. The antioxidant properties of vitamin E exhibit effectiveness in addressing disorders associated with reproduction and pregnancy [48]. As an antioxidant, vitamin E provides advantage for reproductive health by enhancing endometrial thickness, especially favorable for women experiencing implantation failure [49]. A blend of vitamin E with supplements like zinc, selenium, iron, and L-arginine has the potential to uplift ovulation and increase the likelihood of pregnancy [48]. Ascorbic acid, famously referred to as vitamin C, is a component of the ascorbate peroxidases-glutathione reductase (APXs-GR) antioxidant system, and plays a vital role in neutralizing superoxide ($O_2^{\bullet-}$) and hydroxyl (•OH) radicals. This process leads to production of ascorbate radicals, which exhibit enhanced antioxidant activity compared to the catalase or superoxide dismutase antioxidant systems [50]. Giving vitamin C supplementation to women undergoing a luteal phase defect demonstrated elevated serum progesterone levels, consequently leading to an improved pregnancy rate [50,51]. Vitamin C along with vitamin A have potential in preventing pre-eclampsia and preterm birth, as evidenced by investigation [53]. Furthermore, they also effectively take part in reducing pain levels in women suffering from endometriosis [53,54]. The antioxidant properties of carotenoids, such as fat-soluble vitamin A, involve the absorption of peroxyl radicals and singlet oxygen [55]. Vitamin A plays fundamental role in signal transduction during embryonic development by initiating the activation of retinoic acid receptor (RAR) and retinoid X receptor (RXR) transcription factors. These factors help in the activation of developmental genes essential for embryogenesis by binding to specific sites called RARE sites in DNA, bringing about the [56]. Folate, a water-soluble vitamin B9, resembling vitamins C and E, exhibits dynamic antioxidant properties that contribute to the maintenance of reproductive health in vivo [57]. In female reproductive system folate plays a critical role in various stages including oocyte quality and maturation, implantation, embryogenesis, placentation, as well as fetal growth and organ development all through pregnancy [58]. Administering folate is connected with reducing the risk of pregnancy-related disorders including intrauterine growth retardation, neural tube defects such as anencephaly and spina bifida, as well as lowering the likelihood of premature births and miscarriages [59].

L-carnitine (LC) and its acetylated counterpart, Acetyl-L-carnitine (ALC), are derived naturally from the amino acids lysine and methionine. Supplementing L-carnitine in oocytes and embryos enhances energy production through the β-oxidation of fatty acids. It also helps scavenging reactive oxygen species (ROS), and exhibits anti-apoptotic and anti-inflammatory properties. These properties ultimately lead to an elevated pregnancy rate, along with improved cryo-tolerance [60]. Additionally, L- carnitine reduces apoptosis through the inhibition of TNF-α, IFN-γ, and IL-2/4/6, and enhances the production of PGE1/2, thereby promoting cytokine release. This prevents uterine defects such as endometriosis and helps in regulating their apoptotic

and inflammatory characteristics [61]. For women diagnosed with PCOS, L-carnitine illustrates positive effects on ovulation and pregnancy rates, enhances endometrial thickness, and raises serum estradiol levels, thus improving reproductive outcomes [62].

Melatonin, commonly known as N-acetyl-5-methoxytryptamine, is a naturally produced peptide hormone, which is generated from the pineal gland and various extra-pineal tissues like the uterus, ovaries, and placenta. It plays an essential role in regulating responses to darkness, immune functions, inflammation, and microenvironmental angiogenesis [63]. Melatonin also help in detoxifying reactive oxygen species (ROS) and reactive nitrogen species (NOS), while indirectly stimulating enzymatic antioxidants and suppressing pro-oxidants [64]. Melatonin plays a significant role in female reproduction during childhood and puberty by regulating the reproductive endocrinological system and affects the ovulation process [65,63]. Reduced levels of melatonin in the follicular fluid may be linked to anovulation and the production of poor-quality oocytes in patients with PCOS. Consequently, treatment with melatonin has the potential to enhance oocyte quality during follicular maturation [66].

Conclusion:

Antioxidants play a crucial role in female reproduction by protecting cells from oxidative stress (OS) caused by reactive oxygen species (ROS) like superoxide radicals ($O2•^-$), hydrogen peroxide (H2O2), and hydroxyl radicals (•OH). An imbalance between ROS and antioxidants can negatively affect fertility. Supplementing with antioxidants can enhance endometrial thickness, aiding embryo implantation and potentially improving assisted reproduction outcomes. Antioxidants may also prevent pre-eclampsia and preterm birth and benefit conditions like PCOS, endometriosis, and functional hypothalamic amenorrhea. However, certain antioxidants, such as resveratrol and quercetin, should be avoided during pregnancy despite their benefits for gynaecological health.

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