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Oxidative and nitrosative stress and female reproduction: Roles of oxidants and antioxidants

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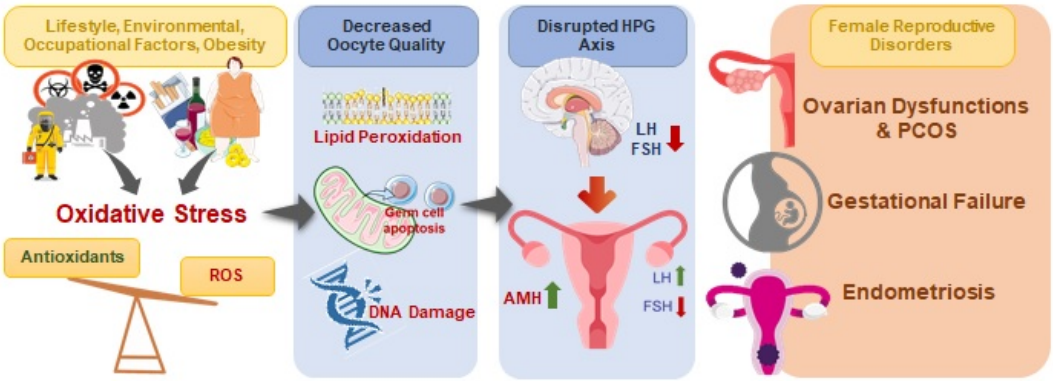
Review

ABSTRACT



Oxidative stress (OS), caused by an imbalance between oxidants and antioxidants in the body, is pivotal in influencing female reproductive health. This review explores the complex interactions of oxidizing agents and antioxidants on female reproductive functions, underscoring their impact on fertility, pregnancy, and reproductive outcomes. Primarily resulting from excessive reactive oxygen species (ROS), OS can detrimentally affect oocyte maturation, embryonic development, and endometrial receptivity. Although ROS naturally arise during cell metabolism, their overproduction or insufficient neutralization can damage cellular macromolecules, including lipids, proteins, and DNA. Such disruptions can lead to ovarian issues, recurrent pregnancy losses, and conditions like endometriosis and polycystic ovary syndrome (PCOS). Conversely, antioxidants combat excess ROS, promoting cellular balance and reproductive success. Emerging treatments underscore the benefits of boosting antioxidant levels to address OS-related disorders. However, caution is essential due to potential risks of excessive antioxidant intake. The review underscores the critical association between OS and female reproduction, suggesting therapeutic strategies for improved reproductive outcomes.

Keywords: female infertility; oocyte quality; oxidative stress; reactive oxygen species

INTRODUCTION

In the field of biomedical sciences, oxidative stress (OS) refers to a state in which there is a discrepancy between the production of reactive oxygen species (ROS) and the capacity of biological system to neutralize these reactive entities or amend the ensuing harm.[1] Essentially, ROS are radicals formed during metabolic activities. While their presence at regulated levels is essential for cell signaling and stability, an overabundance can be harmful, leading to damage of cellular constituents such as proteins, lipids, and DNA.[1, 2].

This intricate balance between oxidizing agents and antioxidant mechanisms is not just a molecular puzzle but a crucial foundation underpinning numerous biological functions.[1, 3] An optimal balance facilitates the seamless operation of physiological activities, ranging from gene transcription to cell multiplication. However, any deviation from this equilibrium, either due to excessive oxidants or insufficient antioxidants, might lead to adverse health consequences.[3]

In the context of female reproductive biology, which is complex and governed by various biological pathways and communication

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systems, the equilibrium between oxidants and antioxidants holds immense importance.[2] The roles of ROS and antioxidants are pivotal across diverse aspects of female reproduction, encompassing oocyte maturation, ovarian hormone production, embryonic growth, and the sustenance of pregnancy.[4] Given the sensitivity of reproductive mechanisms to subtle shifts in the cellular internal milieu, it is crucial to comprehend the dynamics and implications of OS. This review provides a comprehensive exploration of the interplay between OS and female reproductive health, clarifying the contributions of both oxidants and antioxidants, emphasizing their criticality in reproductive efficacy.

Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) Formation

The female reproductive system exhibits a complex environment, defined by periodic alterations and diverse cellular interplay.[5] Within this context, both ROS and RNS are formed, serving crucial functions in normal physiological actions and in pathological states.[5]

Origin of ROS in the Female Reproductive System

ROS represent a collection of molecules that are highly active and are oxygen derivatives. These encompass superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (•OH). Within the female reproductive anatomy, the main sources of ROS are cellular metabolic processes, especially those emanating from the mitochondria during the oxidative phosphorylation phase, the mechanism through which energy is produced by cells.[6, 7] Moreover, immune cells like neutrophils and macrophages, which are found in the reproductive system, are also capable of producing ROS during oxidative bursts, a defense against potential pathogens.[7] During the ovulation phase, leukocytes influx into the ovarian follicle, potentially elevating ROS production. The corpus luteum, a transient endocrine entity associated with menstrual and estrous phases, also becomes a probable ROS production site due to its heightened metabolic rate.[7]

Origin of RNS in the Female Reproductive System

RNS, which include compounds like nitric oxide (NO) and peroxynitrite ($ONOO^-$), are nitrogen derivatives.[8] Within the female reproductive system, the synthesis of NO from L-arginine is catalyzed by nitric oxide synthase (NOS) enzymes, which are present in diverse reproductive tissues such as the ovaries and endometrium.[2, 9] In conditions where both NO and O_2^- are coexistent, they can combine to produce the potent oxidant, peroxynitrite. RNS are integral to a variety of reproductive events. For example, NO plays roles in ovulation, implantation, and sustaining pregnancy. It serves as a vasodilator, adjusting blood circulation within reproductive structures and also influences cellular communication pathways.[9]

While ROS and RNS generation is an inherent component of cellular metabolism, maintaining a balance between their production and clearance is imperative. When present at optimal levels, these molecules participate in vital physiological activities, encompassing cellular communication, ovulation, and the luteal phase.[10] They also offer protection against potential pathogens within the reproductive system. Yet, if there is an overproduction of ROS and RNS or a diminished clearance mechanism, it results in oxidative and nitrosative stress.[11] Such imbalances can inflict harm on cellular entities such as DNA, proteins, and lipids. Relating to the female reproductive system, these stresses are associated with conditions like endometriosis, polycystic ovary syndrome, and even infertility.[12] Summarily, ROS and RNS are fundamental to the biochemistry of the female reproductive system. Grasping their origin and roles offers profound insights into reproductive wellness and potential treatment modalities for related conditions.

Biological sources of ROS/RNS

ROS and RNS are highly reactive molecules due to the existence of unpaired electrons. These species, encompassing free radicals, serve dual roles: they are essential for cellular signaling and also contribute to OS causing cellular injury. Various endogenous systems produce ROS and RNS.[13]

Mitochondrial Electron Transport Chain (ETC): The mitochondria stand as the predominant source of ROS in many cells, inclusive of those in females.[14] During oxidative phosphorylation in the ETC, some electrons may deviate, interacting with molecular oxygen, which results in the genesis of the superoxide radical (O_2^-•). Subsequent reactions, both enzymatic and non-enzymatic, transform this into hydrogen peroxide (H_2O_2) and the hydroxyl radical (•OH).[15]

NADPH oxidases (NOX): Representing a family of enzymes, their principal role is the production of ROS, particularly superoxide and hydrogen peroxide.[11] Distributed across various cellular types and tissues in females, they are pivotal in immunological responses, cellular proliferation, and endocrine synthesis.[14, 16]

Cytochrome P450 enzymes: Situated in the endoplasmic reticulum, these enzymes are instrumental in metabolizing drugs and synthesizing cholesterol, steroids, and other lipids. During these metabolic activities, the enzymes might unintentionally generate ROS.[17, 18]

Xanthine oxidase: This enzyme mediates the metabolic transformation of hypoxanthine to xanthine and subsequently xanthine to uric acid. During these conversions, it gives rise to superoxide and hydrogen peroxide.[5]

Endothelial nitric oxide synthase (eNOS): Residing in the endothelial cells that constitute the interior surface of blood vessels, eNOS synthesizes nitric oxide (NO•) as a signaling molecule for vasodilation. Nonetheless, under circumstances where the enzyme is misaligned due to factors like a dearth of its cofactor tetrahydrobiopterin (BH4), eNOS might produce superoxide instead.[19]

Myeloperoxidase: Located in neutrophils, this enzyme forms hypochlorous acid (HOCl) from hydrogen peroxide, enhancing the antimicrobial capability of these immune cells. Yet, HOCl is a potent ROS and has the potential to harm host cells.[20]

Hormonal variations: Regular menstrual cycles in females are orchestrated by oscillations in estrogen and progesterone concentrations.[21, 22] Although estrogen can act as an antioxidant, it might display pro-oxidative effects in specific scenarios, leading to ROS production. Additionally, during ovulation, the ovaries experience a short-lived elevation in ROS, which is crucial for the disruption of the ovarian follicle, facilitating ovum release.[23]

ROS AND RNS IN OVARIES AND THEIR PHYSIOLOGICAL ROLES

Oocyte maturation and ovulation

In the ovary, ROS have a crucial role during ovulation. During this process, ROS increase and signal the release of enzymes from small storage sacs called lysosomes. These enzymes break down the wall of the follicle, enabling the oocyte (or egg cell) to be released. Similarly, RNS, particularly nitric oxide, contribute to ovulation.[24] Nitric oxide causes blood vessel changes and helps in the release of the mentioned enzymes. It also controls an important stage in the oocyte's growth called meiosis resumption. The right amount of nitric oxide is critical for the proper growth of the oocyte.[11, 24]

Luteinization

Following ovulation, ROS help granulosa cells change into luteal cells. These luteal cells make a hormone called progesterone, which prepares the womb's lining for a potential embryo.[25] Nitric oxide influences how the corpus luteum (a temporary endocrine structure involved in ovulation and early pregnancy) functions and eventually breaks down. The balance between nitric oxide and agents that constrict blood vessels sets the blood flow to the corpus luteum, impacting its function.[26, 27]

Follicular development

ROS influence cellular communication routes, like the MAPK and PI3K/AKT pathways, which guide the growth and maturity of the follicle.[28]

The harmful effects of uncontrolled ROS/RNS

ROS and RNS are molecules with significant reactivity, produced during aerobic metabolism. Within physiological bounds, ROS/RNS concentrations are meticulously controlled by intracellular antioxidant systems, ensuring their beneficial contribution to cellular signaling, immune responses, and ovulation. Nonetheless, when their synthesis exceeds the intrinsic antioxidant capacity, oxidative and nitrosative stresses ensue. Elevated ROS/RNS concentrations can detrimentally influence female reproductive health, affecting both its structural and functional aspects.[4, 14]

Oocyte Maturation and Quality: Oxidative insult from ROS/RNS can induce lipid peroxidation, protein oxidation, and DNA lesions in oocytes.[29] These molecular perturbations can impede oocyte maturation, yielding suboptimal eggs with compromised fertilization potential. Additionally, heightened OS is linked with spindle irregularities and chromosomal missegregation during meiosis, potentially causing aneuploidy—a principal reason for miscarriages and birth defects.[29, 30]

Endometrial Receptivity and Early Embryo Development: Excessive ROS/RNS might diminish endometrial receptivity, pivotal for embryo implantation. An oxidatively stressed uterine milieu may obstruct the effective adherence of the embryo to the endometrial tissue, resulting in implantation failures or early gestational loss.[31] Furthermore, augmented ROS/RNS during embryonic stages can induce DNA disruptions in the embryo, precipitating developmental cessation or aberrations.[32]

Ovarian Follicular Progress and Ovulation: An optimal ROS equilibrium in the ovaries is crucial for follicular progression and ovulation. An imbalance caused by overwhelming ROS/RNS can hinder follicular growth. Consequently, this can affect the regular ovulatory cycle, potentially leading to disorders like polycystic ovary syndrome (PCOS).[33, 34]

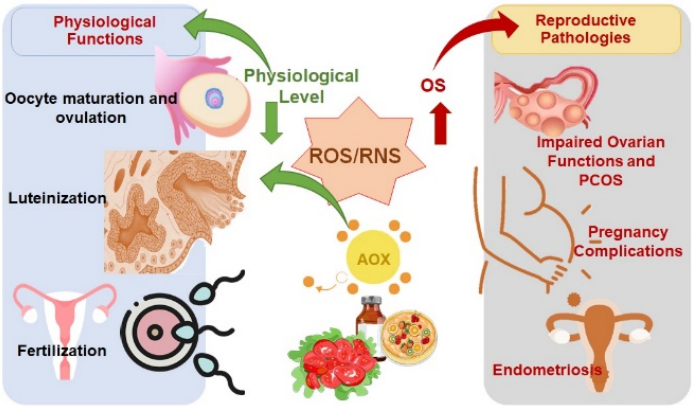

Figure 1. Physiological and pathological impacts of reactive oxygen species on female reproduction. Role of antioxidants on the mitigation of oxidative damage to the female reproductive system.

Impact on Mitochondrial Function: Due to their pivotal function in ATP synthesis and their close proximity to the electron transport chain, mitochondria are especially susceptible to oxidative impairments.[35] Oxidative harm to the mitochondria in reproductive cells can impede ATP synthesis, which is indispensable for essential cellular operations, culminating in cellular malfunction or apoptosis.[35, 36]

Increased Inflammatory Responses: Excess ROS/RNS can instigate the secretion of pro-inflammatory cytokines, fostering an enhanced inflammatory condition in the reproductive system.[37] Persistent inflammation is correlated with ailments like endometriosis, impairing fertility.[38, 39]

Thus, although ROS/RNS are indispensable in the physiological activities of the female reproductive system, their unchecked concentrations can cause a series of molecular and cellular disturbances. This emphasizes the necessity of a harmonious balance between oxidants and antioxidants, particularly concerning reproductive well-being. Surveillance and potential mitigation of oxidative and nitrosative stress could be pivotal approaches in addressing female reproductive anomalies and optimizing fertility outcomes**. (Figure 1)**

ANTIOXIDANTS: THE BODY'S DEFENSE MECHANISM

Natural enzymatic antioxidants

The female reproductive system is an intricate and adaptive structure vital for human species propagation. Within this system, achieving equilibrium between oxidants and antioxidants is paramount for optimal operation, given the association of OS with multiple reproductive pathologies.[40, 41] The enzymatic antioxidants, specifically superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), are central to sustaining this equilibrium.[42]

Superoxide Dismutase (SOD)

Superoxide dismutase encompasses a set of enzymes responsible for the conversion of superoxide radicals (O2•−) into hydrogen peroxide (H2O2) and elemental oxygen (O2).[41] This conversion is essential since superoxide radicals, being primary ROS in cells, can exert detrimental effects. Within the female reproductive system, SOD enzymes are localized in regions including the ovaries, uterus, and fallopian tubes, mitigating the adverse impacts of ROS. These impacts encompass disruption of cellular operations, damage to DNA, proteins, lipids, and perturbations in regular follicular maturation and ovulation.[41]

Catalase (CAT)

Subsequent to the SOD activity, hydrogen peroxide emerges. Even though it's less reactive than superoxide radicals, unchecked H2O2 concentrations can be deleterious. Catalase, an enzymatic antioxidant present in cell peroxisomes, mediates the breakdown of hydrogen peroxide into dihydrogen oxide (H2O) and elemental oxygen (O2), preventing H2O2 overaccumulation in cells.[40, 41] Within the female reproductive domain, catalase serves as an auxiliary protective barrier. It ensures regulation of H2O2 levels, thereby shielding gametes and reproductive tissues from oxidative damage, crucial for efficacious fertilization and embryo development.[43]

Glutathione Peroxidase (GPx)

Glutathione peroxidase, a selenium-reliant enzyme, is integral to the antioxidant defenses of the female reproductive system. Its main role is to catalyze the reduction of hydrogen peroxide and organic hydroperoxides into dihydrogen oxide and corresponding alcohols, utilizing glutathione (GSH) as the reductant. This reaction results in the conversion of GSH to glutathione disulfide (GSSG). This activity is not only pivotal for neutralizing H2O2 and hydroperoxides but also vital for conserving the intracellular reductive state. GPx is active within various reproductive regions including the ovary, uterus, and cervix, and is instrumental in preserving the structural and functional integrity of oocytes and associated granulosa cells.[40, 41, 43]

Thus, the inherent enzymatic antioxidants - SOD, CAT, and GPx - are integral for maintaining homeostasis within the female reproductive system. These enzymes orchestrate a sophisticated defense against OS by consecutively neutralizing and eliminating reactive entities. Their collective actions underpin the delicate equilibrium between pro-oxidants and antioxidants, which is crucial for reproductive events like ovulation, fertilization, and embryonic growth. A deeper comprehension of these enzymes' roles could elucidate the pathomechanisms of various reproductive ailments and potentially pave the way for innovative therapeutic interventions.[44]

Non-enzymatic antioxidants

The female reproductive system consists of specialized organs and functions designed to support conception, pregnancy, and childbirth. This system can be affected by OS from environmental sources, natural bodily reactions, or metabolic waste products.[45, 46] If not controlled, OS can harm reproductive organs, decrease fertility, and cause various reproductive problems. The body uses several defense methods against OS, with non-enzymatic antioxidants being especially important in the female reproductive system.[41, 47]

Vitamin C (Ascorbic Acid)

Vitamin C is a powerful water-based antioxidant known for its ability to combat ROS.[48, 49] It is present in the female reproductive fluids such as the follicular and oviductal fluids and the uterus. It helps in egg development, embryo growth, and luteal function. By fighting off free radicals, Vitamin C prevents damage to cells, DNA, proteins, and fats. A lack of Vitamin C can reduce fertility and increase the risk of luteal phase problems, highlighting its importance in reproductive health.[47]

Vitamin E (Tocopherol)

Vitamin E, a fat-loving antioxidant, is mainly known for protecting cell membranes as it can block lipid radicals and stop lipid oxidation. Within the female reproductive system, it can be found in the ovarian follicles, uterine fluid, and placenta. It ensures cell membrane health, especially for developing eggs and embryos.[50] Additionally, Vitamin E supports prostaglandin production, important for uterine contractions and ovulation.[51] Low Vitamin E levels can interfere with these functions, possibly reducing fertility.[52]

Glutathione

Glutathione, made of cysteine, glutamic acid, and glycine, is vital for controlling cell oxidation. In the female reproductive system, it has many roles.[53] Apart from being an antioxidant, it manages several cell functions including DNA creation, immune response, and detoxification. In the ovaries, it is crucial for shielding the maturing egg from oxidative harm. The amount of glutathione in an egg can show its quality, with less glutathione indicating a lesser quality. Also, glutathione is important for the fusion of sperm and egg, ensuring effective fertilization.[54]

Other Non-enzymatic Antioxidants

Besides the above antioxidants, others like zinc, selenium, and various carotenoids help maintain a stable oxidation balance in the female reproductive system. Working together with other antioxidants, they offer strong protection against oxidative damage.[18, 55]

Therefore, the female reproductive system is equipped with many non-enzymatic antioxidants. These antioxidants, including Vitamin C, Vitamin E, and glutathione, play distinct yet related roles in safeguarding reproductive health. They protect the reproductive system and create the best conditions for processes like egg release, fertilization, and embryo growth. Understanding these antioxidants can help in treatments for reproductive issues and guide diet and lifestyle decisions for those aiming to enhance their reproductive health.

OXIDATIVE STRESS AND FEMALE REPRODUCTIVE SYSTEM

Oxidative Stress in Folliculogenesis

Folliculogenesis pertains to the developmental progression of the ovarian follicle, culminating in the discharge of a mature oocyte at ovulation. In folliculogenesis' initial phases, a minimal ROS concentration is vital for the differentiation, growth, and steroidogenesis of the follicle.[56] ROS regulate multiple signaling pathways vital for the proliferation and longevity of follicular cells.[56] Nonetheless, an overabundance of ROS is deleterious.

Sustained OS can lead to DNA lesions, lipid peroxidation, and oxidation of proteins in granulosa cells and oocytes. Such damages can degrade oocyte quality and compromise the granulosa cells' tight junctions, jeopardizing the blood-follicle barrier's integrity. Additionally, elevated ROS concentrations can trigger granulosa cell apoptosis, resulting in follicular atresia. Thus, maintaining an equilibrium between ROS and antioxidants is paramount during folliculogenesis.[57, 58]

Oxidative Stress in Ovulation

Ovulation entails the expulsion of a mature oocyte from the ovarian dominant follicle. This event is precipitated by an upsurge in luteinizing hormone (LH) and consists of a sequence of synchronized molecular and cellular events. An ephemeral escalation in ROS is one such event, aiding the ovarian follicle rupture and oocyte release. Though ROS are essential for ovulation, their amounts must be strictly managed. During the periovulatory phase, the ovarian influx of immune cells, mainly neutrophils and macrophages, amplifies ROS production.[33] Nonetheless, inordinate OS can impair the extracellular matrix, destabilize the collagen infrastructure, and obstruct ovulation. Additionally, elevated ROS can harm the DNA of the cumulus cells encircling the oocyte, potentially affecting subsequent fertilization and embryogenesis.[33]

Oxidative Stress in Luteolysis

Post-ovulation, the residual fragments of the ruptured follicle evolve into a transient glandular entity, the corpus luteum, whose principal role is progesterone secretion, priming the endometrium for prospective conception. Absent pregnancy, the corpus luteum experiences degeneration, a phenomenon labeled luteolysis. OS is considered influential in modulating luteolysis.[59] As the corpus luteum matures, its antioxidant prowess diminishes, heightening its vulnerability to ROS mediated harmful effects. OS can elicit apoptosis in luteal cells, furthering corpus luteum degeneration. Additionally, ROS influence the creation of prostaglandins, notably prostaglandin F2α, a formidable luteolytic compound. An increased ROS presence can expedite the attrition of corpus luteum, curtailing the luteal phase.[60, 61]

Impact of OS on oocyte quality and embryo development

Oocytes, the reproductive gametes in females, display pronounced vulnerability to the deleterious impacts of OS. The proliferation of ROS can hinder oocyte maturation, competence, and its ability to fertilize. On a biochemical level, elevated ROS concentrations can lead to DNA lesions, lipid peroxidation, and protein oxidation within the oocyte.[62] Given the restricted DNA repair capabilities in mature oocytes, the resulting DNA damage can be substantial.[63] This undermines the genetic integrity of the oocyte, diminishing its capacity to give rise to a healthy embryo. Beyond the direct effects on oocytes, OS can also influence adjacent cumulus cells and granulosa cells, which are instrumental in aiding oocyte maturation and preserving its microenvironment. Impaired cumulus and granulosa cells can disrupt signaling pathways and essential nutrient interactions required for oocyte development, further degrading its caliber.[29, 64]

Post-fertilization, the persistent presence of OS can obstruct appropriate embryonic growth.[65] Escalated ROS concentrations can inflict cellular harm in the nascent embryo, possibly interfering with vital developmental operations such as cellular division, differentiation, and genomic imprinting. This might culminate in halted growth, atypical blastocyst generation, or amplified instances of embryonic aneuploidy.[66] Furthermore, OS during the initial embryonic phases can cast long-lasting impacts on post-implantation growth, shaping fetal development, organ formation, and even health after birth. For example, embryos exposed to OS might exhibit a heightened likelihood of developmental irregularities or could be more susceptible to specific ailments in their later life stages.[67]

Consequently, OS serves as a formidable perturber of both oocyte integrity and embryonic growth. Comprehending its underlying mechanisms and repercussions is pivotal to refining assisted reproductive methodologies and safeguarding the vitality and health of future progeny.

ROLE OF ANTIOXIDANTS IN FEMALE REPRODUCTION

Protective role of antioxidants in oocyte maturation and embryo development

The path of oocyte maturation is complex, necessitating a well-regulated setting. In this context, antioxidants are pivotal. They counteract the excess ROS, averting oxidative harm. This action preserves the cytoplasmic and genetic integrity of the oocyte, facilitating effective maturation and subsequent fertilization.[68] Furthermore, antioxidants bolster the energy-generating mitochondria in oocytes, ensuring adequate energy reserves for maturation activities.[69] Post-fertilization, the initial embryonic phases are vital and vulnerable to oxidative impairments. Antioxidants provide a shield by neutralizing free radicals, thereby facilitating undisturbed cellular division and differentiation. An optimal antioxidant milieu is associated with elevated rates of blastocyst formation and enhanced results during implantation in the realm of assisted reproductive methods.[70] Therefore, antioxidants play a crucial protective role, safeguarding the integrity and vitality of oocytes and evolving embryos. Ongoing research increasingly highlights their significance, suggesting promising prospects for augmenting results in both natural pregnancies and assisted reproductive procedures.[68, 71] Concurrently, the attention toward the potential benefits of antioxidant-rich diets and supplements in boosting reproductive health and outcomes is intensifying.

Antioxidants in assisted reproductive techniques (ART)

Assisted Reproductive Techniques (ART) have advanced significantly over time, providing solutions for couples grappling with fertility challenges. The primary objective of ART is to enhance the quality of gametes, promote superior embryo growth, and increase the likelihood of successful implantation, ultimately raising the probability of a fruitful pregnancy. Antioxidants have emerged as significant players in these procedures, especially in countering OS, which detrimentally affects fertility in both men and women.[68, 71]

While ROS are fundamental to processes such as oocyte maturation, sperm capacitation, and fertilization, their overabundance can be harmful. Elevated ROS concentrations can inflict DNA damage in sperm, hinder sperm movement, initiate lipid peroxidation in cellular membranes, and deteriorate the

quality of oocytes. These adverse impacts considerably diminish the prospect of achieving a prosperous pregnancy.[72]

Within the ART framework, antioxidants serve a central role in addressing these issues. Concerning male infertility, numerous research projects indicate that antioxidant supplements can improve various sperm metrics, including shape, number, and movement. For example, vitamins C and E, coenzyme Q10, and glutathione have proven efficacy in reducing oxidative harm in sperm, which in turn optimizes ART results.[73-75] Likewise, for females undergoing ART protocols, OS can adversely influence the milieu of the oocyte and the receptivity of the endometrium.[41, 76, 77] By incorporating antioxidants either in the culture medium or as nutritional supplements, there's potential to curtail oxidative harm, bolster embryo growth, and elevate the potential for successful implantation. Therefore, recognizing and leveraging the advantageous impacts of antioxidants in ART is essential. While comprehensive knowledge about specific antioxidant usage and precise protocols is still emerging, current data propose a vital role for antioxidants in boosting ART outcomes by counteracting the harmful impacts of OS on gametes and embryos. As ART methodologies evolve, the inclusion of antioxidants could become an integral component to optimize success ratios.[4, 68, 71]

Natural and supplemental antioxidants: Benefits and potential risks

Benefits of Antioxidants in Female Fertility

Natural Antioxidants: Dietary sources like fruits, vegetables, and certain nuts and seeds are abundant in inherent antioxidants including vitamin C, vitamin E, and selenium. Incorporating these foods in one's diet can bolster the body defenses against OS, possibly enhancing oocyte health and overall reproductive functionality.[78]

Supplemental Antioxidants: These are intensified antioxidant formulations available in capsule or powder form. Taking these supplements can be particularly advantageous for females with recognized antioxidant deficits or distinct reproductive challenges related to OS.[79]

Potential Risks of Antioxidants in Female Fertility

Over-Supplementation: While the therapeutic properties of antioxidants are acknowledged, over-supplementation can unexpectedly produce a pro-oxidant outcome. This suggests that instead of neutralizing free radicals, they may produce them in substantial amounts, resulting in amplified OS.[80, 81]

Interaction with Medications: Elevated intake of exogenous antioxidants may disrupt specific reproductive therapies or other medications. For example, an excessive consumption of vitamin E may possess anticoagulant properties, which could influence embryo implantation.[59]

Hormonal Imbalances: Preliminary research indicates that unchecked and excessive consumption of certain antioxidants may disrupt hormonal regulation, a paramount element in female reproductive health.[82]

Potential for Reduced Therapeutic Effect: Some investigations propose that over-reliance on antioxidant supplements might curtail the success of assisted reproductive procedures, like IVF.[83]

The delicate equilibrium between oxidizing agents and antioxidants is instrumental in female reproductive well-being. Inherent antioxidants, obtained from a well-rounded diet, present a prudent method to enhance fertility. Nonetheless, while exogenous antioxidants might provide advantages in certain situations, their unchecked and excessive intake can lead to unforeseen outcomes. It's imperative that any decisions about antioxidant supplementation be made with expert oversight and aligned with an individual's specific health circumstances.

PATHOLOGICAL ASPECTS OF OXIDATIVE STRESS IN FEMALE REPRODUCTION

Role of oxidative stress in endometriosis

Endometriosis is an intricate gynecological disorder characterized by the presence of endometrial-like tissue outside its customary location in the uterus, predominantly affecting the pelvic peritoneum, ovaries, and bowel. The exact causative factors of endometriosis are not yet fully understood despite comprehensive research.[39] Nevertheless, OS has been recognized as a key factor in the development and advancement of this disease. With regards to endometriosis[39], OS is central through several interconnected mechanisms:

Elevated ROS Levels: Elevated concentrations of ROS are frequently observed in the peritoneal fluid of women diagnosed with endometriosis. This heightened ROS presence can lead to DNA impairment, initiate inflammatory processes, and enhance the growth and persistence of ectopic endometrial cells.[84, 85]

Antioxidant Depletion: Research indicates a reduction in antioxidants, such as superoxide dismutase and glutathione, in the peritoneal fluid of endometriosis patients. This decline in antioxidant capability heightens the susceptibility of the pelvic region to oxidative injuries.[86]

Inflammation and Immune Dysregulation: A cycle exists where OS promotes an inflammatory environment, subsequently increasing ROS synthesis.[87] This repetitive process amplifies inflammation, thus favoring the growth and sustenance of ectopic endometrial tissues.[18, 88]

Enhanced Angiogenesis: OS triggers the secretion of factors that facilitate angiogenesis or new blood vessel formation. This process supplies ectopic lesions with nutrients, promoting their expansion and infiltration.[89]

Estrogen Dominance: The pathophysiology of endometriosis is closely tied to estrogen. OS intensifies local estrogen synthesis and impedes its breakdown, reinforcing an environment dominated by estrogen. Concurrently, estrogen can escalate ROS synthesis, establishing a self-reinforcing mechanism that intensifies oxidative stress.[90, 91]

Role of OS in polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is a complex endocrine disorder, primarily marked by irregular ovulation, heightened androgen levels, and the presence of multiple cysts in the ovaries.[92, 93] Advances in scientific research have identified OS as a key factor influencing the initiation and progression of PCOS.[94] Numerous investigations have demonstrated increased indicators of lipid peroxidation, protein oxidation, and DNA harm in women diagnosed with PCOS in contrast to their healthy counterparts, suggesting persistent oxidative challenges in these individuals. Moreover, the frequent occurrences of hyperinsulinemia and

insulin resistance in PCOS intensify OS. Specifically, insulin resistance has been connected to elevated ROS output as a result of mitochondrial anomalies and the triggering of particular cellular pathways promoting ROS formation.[94]

The consequences of OS in PCOS are diverse. It is potentially involved in the hormone imbalances typical of PCOS, such as excessive androgen levels. Moreover, the chronic inflammatory response and the compromised endothelial function seen in a substantial number of PCOS patients might be attributed to the detrimental outcomes of OS.[95] Recognizing the significance of OS in PCOS is crucial, both for grasping the foundational pathophysiological aspects of the condition and for the creation of therapeutic strategies addressing this oxidative discrepancy.[96] Upcoming research may introduce antioxidant-focused therapies or lifestyle modifications aimed at reducing the oxidative strain in individuals with PCOS.[96]

Role of OS in premature ovarian failure

Primary ovarian insufficiency (POI), or premature ovarian failure (POF), is a condition marked by the termination of regular ovarian activity before 40 years of age. Although various etiological factors may contribute to its emergence, recent research accentuates the central contribution of OS in the initiation and development of POI.[97]

The oocyte, a critical cellular element within the ovary, is particularly susceptible to damage instigated by ROS. Elevated ROS levels can inflict oxidative damage on the DNA, lipids, and proteins of the oocyte, thereby hindering its maturation, undermining its developmental viability, and promoting apoptosis.[98] This is of significant concern since females possess a limited reserve of oocytes from birth; thus, any ROS-induced detriment can hasten ovarian senescence. Additionally, OS can induce inflammation and can adversely affect granulosa cells, integral for endorsing oocyte maturation and steroidogenesis.[99] Dysfunctional granulosa cells might result in disturbed folliculogenesis and deviations in steroid hormone production, which are distinctive characteristics of POI.

Research has detected increased concentrations of OS indicators in POI-affected women, highlighting a probable link between ROS and ovarian dysfunction.[100, 101] In such individuals, the antioxidant defense systems, like superoxide dismutase, catalase, and glutathione, which counteract ROS, might be diminished, thereby exacerbating oxidative insult. Consequently, OS is intrinsically involved in the pathophysiology of primary ovarian insufficiency. The overproduction of ROS and the subsequent harm to ovarian cellular structures can hasten ovarian senescence, culminating in an early end to ovarian functionality. Prospective therapeutic interventions focusing on OS may offer promising approaches for the treatment and potentially the prophylaxis of POI.

OXIDATIVE STRESS, PREGNANCY, AND OBSTETRICAL OUTCOMES

ROS and placental function

The placenta is an indispensable organ during gestation, responsible for facilitating the transfer of nutrients and oxygen to the fetus while simultaneously removing waste. In addition to these primary tasks, the placenta synthesizes hormones and growth factors imperative for the sustenance of pregnancy and fetal growth. At the molecular spectrum, the role of ROS in placental functionality has become a significant research focus.[5]

In the context of placental biology, ROS exhibit dual functionalities — they can be advantageous or harmful based on their quantity and spatial distribution. At balanced concentrations, ROS function as secondary messengers, modulating multiple signaling cascades.[32] Notably, ROS participate in the differentiation and invasion of trophoblast cells, processes fundamental for the development of the placenta and the initiation of the maternal-fetal circulatory connection.[5] The journey and penetration of trophoblast cells into the maternal endometrium are essential for the secure attachment of the placenta and the restructuring of maternal spiral arteries. ROS adjust the expression of specific proteins, such as matrix metalloproteinases, aiding these mechanisms.[32] However, an overproduction of ROS or insufficient antioxidant mechanisms can culminate in OS. Within the placenta, OS correlates with various gestational complications, including preeclampsia, intrauterine growth restriction, and spontaneous miscarriage. An abundance of ROS can hinder placental functionality by inducing damage to its DNA, lipids, and proteins, thus compromising the structural integrity of the placenta and hampering its nutrient and oxygen transport capabilities to the fetus.[5]

Multiple elements can escalate ROS production within the placenta, encompassing maternal variables like smoking, obesity, and diabetes, infectious agents, and placental ischemia-reperfusion damage.[102-104] Placental ischemia, characterized by diminished blood supply to the placenta, can arise due to inadequate remodeling of the spiral arteries. The ensuing restoration of blood flow can instigate an intensified release of ROS, intensifying OS.[102] Thus, ROS exhibit a complex role in placental operations, acting as crucial signaling entities under standard conditions and simultaneously partaking in placental disturbances during OS scenarios.[32] Grasping the equilibrium between ROS generation and antioxidant countermeasures in the placenta is crucial for innovating therapeutic interventions to combat gestation-associated ailments stemming from OS.

Role of ROS and OS in gestational diseases like preeclampsia

Preeclampsia is a condition associated with pregnancy marked by elevated blood pressure and either notable proteinuria or end-organ impairment.[105] The exact origin of preeclampsia is not fully elucidated, yet increasing data indicate that OS plays a significant role in its development.[106] The development and functions of placenta are vital during gestation. In early pregnancy, the uterus's spiral arteries undergo modification to enhance blood supply to the placenta. However, in preeclampsia, this transformation is often suboptimal, leading to diminished placental blood supply.[105] Such decreased perfusion can cause ischemia-reperfusion injuries, consequently heightening the generation of ROS. Under these circumstances, the placenta emerges as a prominent ROS producer, intensifying the OS within the maternal circulatory system.[106]

This escalation in ROS and the subsequent OS can precipitate broad endothelial dysfunction, a distinguishing feature of preeclampsia. The endothelial cells that line the blood vessels sustain damage, becoming permeable and compromised. This damage can precipitate the vascular constriction observed in

preeclampsia, adding to the disease's hallmark elevated blood pressure.[107] Moreover, OS promotes the secretion of anti-angiogenic agents, such as soluble fms-like tyrosine kinase-1 (sFlt-1), which counters the effects of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF). This counteraction further undermines vascular functionality, contributing to the hypertension and renal impairment observed in individuals with preeclampsia.[107] Beyond its direct influence on the circulatory system, OS also instigates inflammation. Heightened ROS concentrations can trigger specific transcription factors, notably nuclear factor-kappa B (NF-κB), prompting the emission of pro-inflammatory cytokines and chemokines.[108] These compounds intensify the preeclamptic inflammatory reaction. Thus, the nuanced interplay between ROS and OS is central to the onset of gestational conditions like preeclampsia. It not only induces vascular irregularities and inflammation but also modifies vital physiological functions necessary for a successful pregnancy. Grasping this interrelation could offer avenues for specialized treatments to counteract the detrimental outcomes of OS in pregnancy-related disorders.[107]

Impact on fetal development and outcomes

During embryonic development, OS can exert profound effects. The fetus exhibits heightened susceptibility to alterations in its intrauterine surroundings. Recognizing that ROS influence cellular differentiation, proliferation, migration, and apoptosis, anomalous concentrations of ROS can interfere with the complex processes underpinning fetal growth.[11] Successful embryogenesis and organogenesis are fundamentally anchored in a balanced ROS equilibrium; its disturbance can yield catastrophic results.[18, 72, 109] There are myriad pathways that connect elevated OS during gestation to detrimental fetal outcomes.[109] These pathways encompass direct oxidative harm to DNA, proteins, and lipids, alongside indirect repercussions arising from the disruption of cell signaling pathways. For example, OS has been linked to fetal programming, potentially predisposing the progeny to certain diseases in their later life stages. Persistent exposure to elevated ROS concentrations can alter fetal gene expression, instigating lasting modifications that could render individuals more susceptible to disorders such as cardiovascular diseases, obesity, and type 2 diabetes.[109-111]

Fetal consequences associated with maternal OS encompass conditions like intrauterine growth restriction (IUGR), preterm birth, and neural tube anomalies. IUGR, delineated by the fetus's incapacity to achieve its inherent growth potential, has correlations with placental insufficiency, often concomitant with augmented OS.[112] When OS affects the placenta, the fetus may experience diminished nutrient and oxygen delivery, impairing its growth trajectory. Additionally, maternal pathologies like preeclampsia, a hypertensive ailment marked by systemic OS, endothelial malfunctions, and inflammation, can negatively influence fetal outcomes.[113] Multiple environmental and behavioral factors, such as tobacco use, alcohol intake, and exposure to environmental contaminants, can intensify OS during gestation, amplifying the likelihood of negative fetal consequences.[114] Hence, interventions aimed at curtailing OS during pregnancy, such as adhering to an antioxidant-rich diet or steering clear of recognized sources of ROS, might be indispensable for optimal fetal growth.[115] Thus, balance in ROS equilibrium is paramount for standard fetal developmental events. An imbalance, culminating in OS, can bear significant ramifications, impacting not just immediate fetal outcomes but also the subsequent health trajectory of the individual.[67] Delving into these underlying processes could pave the way for formulating strategies that enhance gestational outcomes and engender healthier descendants.

FUTURE DIRECTIONS AND CONCLUSIONS

The complex interplay between OS and female reproductive processes has become a central topic of scientific investigation in recent times. It is clear that maintaining a balanced redox equilibrium is crucial for ideal reproductive health. However, both elevated and diminished levels of ROS can detrimentally impact reproductive functions. The effects of oxidizing agents on events like oocyte maturation, ovulation, and embryonic development present conflicting data, emphasizing the need to determine the exact mechanisms and levels at which ROS influence these processes. Despite our advancements in knowledge, significant knowledge gaps persist. Delving deeper into the body's antioxidant systems and their interaction with ROS in a reproductive setting is of utmost importance. This is especially relevant in diseases such as polycystic ovary syndrome (PCOS) or endometriosis, where OS may have contributive roles. The potential long-term impacts of heightened OS on progeny health are not sufficiently studied. As we move further into the realm of precision medicine, individualized interventions become more prominent. The variability in OS response among females emphasizes the need for such personalized treatments. Interventions tailored to a person's specific redox state and reproductive health might lead to improved results. The therapeutic promise of antioxidants needs to be exploited judiciously to ensure safety and efficacy. Thus, while we have advanced our understanding of OS in female reproductive health, there are still many areas warranting further research, highlighting the continued significance of this field.

Conflict of Interest

The authors declare that none of them has any conflict of interest.

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