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# Role of Vitamin E and Vitamin C in Oxidative Stress of Female Reproductive System

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# Role of Vitamin E and Vitamin C in Oxidative Stress of Female Reproductive System

Farah Laraib <sup>α</sup> & Rubaisha Ameer <sup>σ</sup>

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## I. INTRODUCTION

The main factor in the pathogenesis of most diseases is oxidative stress (OS) (Agarwal, Gupta, Sekhon, & Shah, 2008) which arises when antioxidant and prooxidant imbalances arise (Al-Gubory, Fowler, & Garrel, 2010). Due to OS-induced cell membrane damage, DNA damage, and apoptosis, OS is implicated in faulty and delayed embryonic development. Apoptosis leads to the development, with minimal changes to implant and mature, of fractured embryos (Muriel, 2006).

Due to the metabolic rate and the growth in mitochondrial activities, Placenta may be the primary source of OS. Placental tissues have low concentrations and key antioxidant functions during the first quarter, including catalase, glutathione peroxidase, and superoxide dismutase. This condition will cause oxygen-mediated damage to the embryonic trophoblast cells (Poston & Rajmakers, 2004). As oxygen stress rose at the beginning of the maternal bloodstream, a placental OS explosion had been observed in the second quarter. Analysis shows that this oxidative damage can have a detrimental effect on the placental remodeling and functions that may change the course of gestation (Metcalf & Alonso, 2010).

Excess prooxidants cause OS by either the production or inhibition of reactive oxygen species (ROS). ROS's reactivity is extremely unstable. They gain electrons from acid, lipid, protein, carbohydrate, or some other surrounding molecule that makes a chain of reactions stable. These reactions in the chain contribute

to cellular disruption and sickness. ROS can damage cell functions in the female reproductive system and can ultimately stop homeostasis intracellular and contribute to damage to cells (Mohd Mutalip, Ab-Rahim, & Rajikin, 2018).

Excess ROS also influences early embryonic development by altering the primary transcription factors modifying gene expressions (Dennerly, 2004). High levels of ROS can also adversely impact oocyte fertilization and hinder embryonic implantation in the female reproductive tract. High ROS development and reduced defense antioxidant potential may contribute to increased sensitivity to OS for the developing fetus (Sharma & Agarwal, 2004).

The overproduction of ROS is limited by antioxidants. They are in both enzyme and non-enzyme forms. They are there. The natural antioxidants or endogenous antioxidants are known as natural antioxidants or endogenous antioxidants are known as enzymatic antioxidants (SOD), catalase, but oxidase GSH, and reductase glutathione (GSH). Available from foodstuffs and vegetables are the non-enzymatic antioxidants, also known as the exogenous antioxidants. Taurine, hypotaurine,  $\beta$ -carotene, selenium, copper, vitamin C, and vitamin E are among others (Agarwal, Gupta, & Sharma, 2005).

As an antioxidant of female reproductive health, vitamin C and vitamin E are a good defense in retarding free radical cellular injury, shown to be helpful for breastfeeding and neonatal health, and have played an important role in disorders of fertility or pregnancy. Vitamin C serves as a reduction agent for cell safety against adverse OS effects (Shaik-Dasthagirisahab et al., 2013). Vitamin E acts to defend cell membranes from ROS and as a chain-breaking antioxidant, for example in protection against auto-oxidation by polyunsaturated fatty acid (PUFAs) (Traber & Atkinson, 2007).

The main element for the pathogenesis of most diseases is oxidative stress and when imbalances arise in the presence of antioxidants and pro-oxidants. Because of cell-membrane injury, DNA damage, and apoptosis triggered by OS, the incomplete and delayed embryonic growth includes OS. Apoptosis contributes to the development of broken embryos that are less likely to implant and increase. ROS and antioxidants remain in equilibrium in a balanced body and the reactive oxygen molecules. Oxidative stress (OS) happens when the

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equilibrium is broken to an overabundance of ROS. OS affects the entirety of a woman's reproductive life and even afterward OS stems from an excess of the capacity of the body to scarp prooxidants (antioxidants) and (free radical species) (Roth, 2017).

ROS is a double-edged weapon - signal molecules that act as the most important in physiological processes but also have a role in female reproductive processes. ROS affects many

physiological pathways, ranging from oocyte to fertilization, fetal growth, and conception. It was proposed that OS modulates the decrease in fertility associated with age. It plays a role in and initiates premature jobs during pregnancy and natural parturition. In the superficial epithelium, most ovary cancers occur, and prolonged ovulation was assumed to have caused them (Grandi et al., 2015).

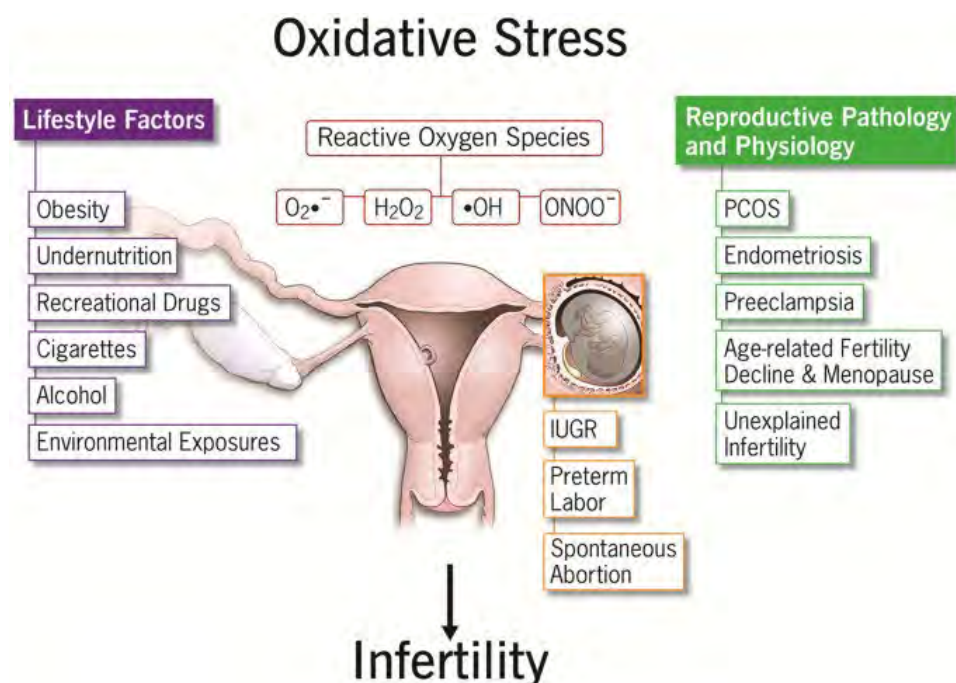


Figure 1.0: Oxidative Stress

OS findings of women's breeding are increasing in pre-eclampsia pathophysiology, hydatiform mole, free birth failures that lead to radical induction, and other conditions such as abortion. Many studies have shown that OS has a role to play in infertility and pathophysiology promoted fertility. Endometriosis, miscarriage, and unexplained infertility of tubes and peritoneal factor have shown their role. This article discusses the OS's role in ovaries, follicles, and endometrial cycling in daily circulation.

It also addresses female infertility associated with SA and how it impacts the effects of assisted reproductive techniques. The paper discusses the role of oxidation stress in conditions like abortion, pre-eclampsia, hydatidiform mole, fetal embryopathy, preterm labor, pre-eclampsia, gestational diabetes in a detailed way. The research also discusses the increasing role of nitrogen oxide species in women's reproduction. The functions played by nitric oxide species in endometrial or ovarian control, endometriosis etiopathology, or maintaining uterine relaxation, labor, and cervical ripening throughout gestation are addressed (Patel et al., 2015).

Radical species free and strongly reactive are unstable. It is stable when the electrons are obtained from nuclear acids, lipid, protein, and carbohydrates, or other molecules which, via chains, lead to cellular oxidative stress-induced. There are 2 main types of free radical molecules: reactive oxygen (ROS) and nitrogen species Reactive (NOS).

Vitamin E was first found to be a sexual substance in 1922. Vitamin E has been researched thoroughly and is now commonly recognized as a potent fat-soluble antioxidant after this discovery. The role of vitamin E as an antioxidant is increasingly interested since it has been discovered as an anti-cancer agent and lowers body cholesterol levels. Many studies have shown that the influence of vitamin E on cancer and anti-inflammatory activities include, anti-angiogenic anti-survival, anti-proliferative, and anti-apoptotic effects. Vitamin E's health benefits usually are recorded in different ways. Although it has initially been shown to be a reproduction-related vitamin, research concerning its effects is still missing in this field. This paper is therefore intended to explore the known functions of vitamin E in women's reproductive health as an antioxidant (Jung et al., 2012).

## II. OXIDATIVE STRESS

Julein Finaud et al. (2012) conducted a study to explain that what is oxidative stress. Free radicals are known as highly reactive compounds that are naturally produced in the human body. This study explained that oxidative stress has both positive and negative effects on the body. The positive effects of free radicals activate the immune system of an individual whereas the negative effect of free radicals in the oxidation of lipids, proteins, and DNA within the human body. There is a need for complex protection from the protection of harmful effects of these oxidation reactions this system is known as the antioxidant system. This study explained that the antioxidant system is comprised of antioxidant enzymes and non-enzymatic enzymes. Some examples of antioxidant enzymes of this system are catalase, superoxide dismutase, glutathione, and catalase, whereas the examples of non-enzymatic antioxidants are vitamin E, glutathione, vitamin A, uric acid, and vitamin C. The presence of an imbalance between the production of these free radicals and the antioxidant defense system leads to a state known as oxidative stress. The state of oxidative stress involved in the again processes and also leads to some diseases such as cancer and Parkinson's disease. When an individual has done physical exercise it increases the oxidative stress of an individual and results in the disruption of homeostasis. The training of individuals also imparts positive as well as negative effects on oxidative stress. The presence of this stress on the human body depends on the training load, basal level of training, as well as training specificity of an individual. This study also explained that oxidative stress results in Muscular

fatigue due to the presence of oxidative stress due to excessive training (Julien Finaud, 2012).

Helmut Sies et al. (2017) conducted a study to explain the facts about oxidative stress. This study explained that oxidative stress is two-sided such as it is beneficial for human beings but its excess may also cause multiple diseases within the human body. This study explained that the presence of oxidant challenge within the human body causes severe damage to the biomolecules, an essential component for the governing of life processes by redox signaling, maintenance of a physiological level of oxidant challenge, and also termed as the oxidative eustress. This study has determined that recent studies focused on the intricate ways by which all redox signaling of oxidative integrate its all converse properties. The maintenance of redox balance is done by the prevention, concomitantly, interception, and repair of the regulatory potential of molecular thiol-driven master switches. This study explained that these thiol-driven switches such as Nrf2/Keap1 or NF- $\kappa$ B/I $\kappa$ B are most commonly used for the oxidative stress response. This study explained that the presence of non-radical species such as hydrogen peroxide as well as singlet molecular oxygen performs its functions as a major second messenger function to prevent the disease. This study explained that chemokine-controlled NADPH oxidases as well as metabolically controlled mitochondrial sources, and thioredoxin-related pathways with the presence of a powerful enzymatic backup system imparts an important role in the fine-tuning of the physiological redox signaling. This study imparts an important role in redox medicine based on its nutritional science, molecular knowledge of the product, and environmental medicine (Helmut Sies, 2017).



Figure 2.1: Cells in Oxidative Stress

### III. VITAMIN E AND VITAMIN C AS DEFENCE PARTNERS

Alvin et al. (1993) conducted a study to explain that vitamin E and vitamin C are partners in the defense system. This study explained that free radicals and oxidative stress within the human body can also reduce by the presence of vitamin E and vitamin C. Enzymes are majorly involved in the removal of free radicals from the human body by act as scavengers of free radicals but the presence of some vitamins also act as the strong line of defense in reducing the free radicals by induced cellular damage. This study explained that various distinct pathways are used for the repairing of oxidized vitamin E in human cells have been identified in this study. This study explained that when arachidonic acid is imparted in the human body, after 0.5 minutes of this addition or installation the half of the platelet vitamin E added with the arachidonate was metabolized by enzymes named platelet cyclooxygenase and lipoxygenase pathways. This study explained that after the addition of nordihydroguaiaretic acid, which is a strong reductant and a lipoxygenase inhibitor was regenerated to form vitamin E. This study explained that

there is a need to test the various physiological and water-soluble reductants that helped in regenerating the vitamin E, lipoxygenase inhibitory, and eicosatetraenoic acid that is not antioxidant was used. The use of both ascorbate, as well as glutathione present in the human body, imparts a significant and remarkable role in the regeneration of vitamin E. the kinetic analysis of regeneration of vitamin E and previous studies about vitamin E explained that its regeneration is done by a system-denaturing system that revealed that ascorbate imparts an important role in its regeneration. The regeneration of vitamin E is done both either by use of enzymes or without the use of enzymes in enzymatically regeneration glutathione is included but in non-enzymatically ascorbate is used. This study determined that there is a remarkable and significant relationship present between the water-soluble and lipid-soluble molecules at the membrane-cytosol interface as well as vitamin C also involved in the repairing of oxidized vitamin E. Thus this study explained that vitamin E and vitamin C imparts an important role in the defense mechanism against the oxidative stress present in the human body (Chan, 1993).

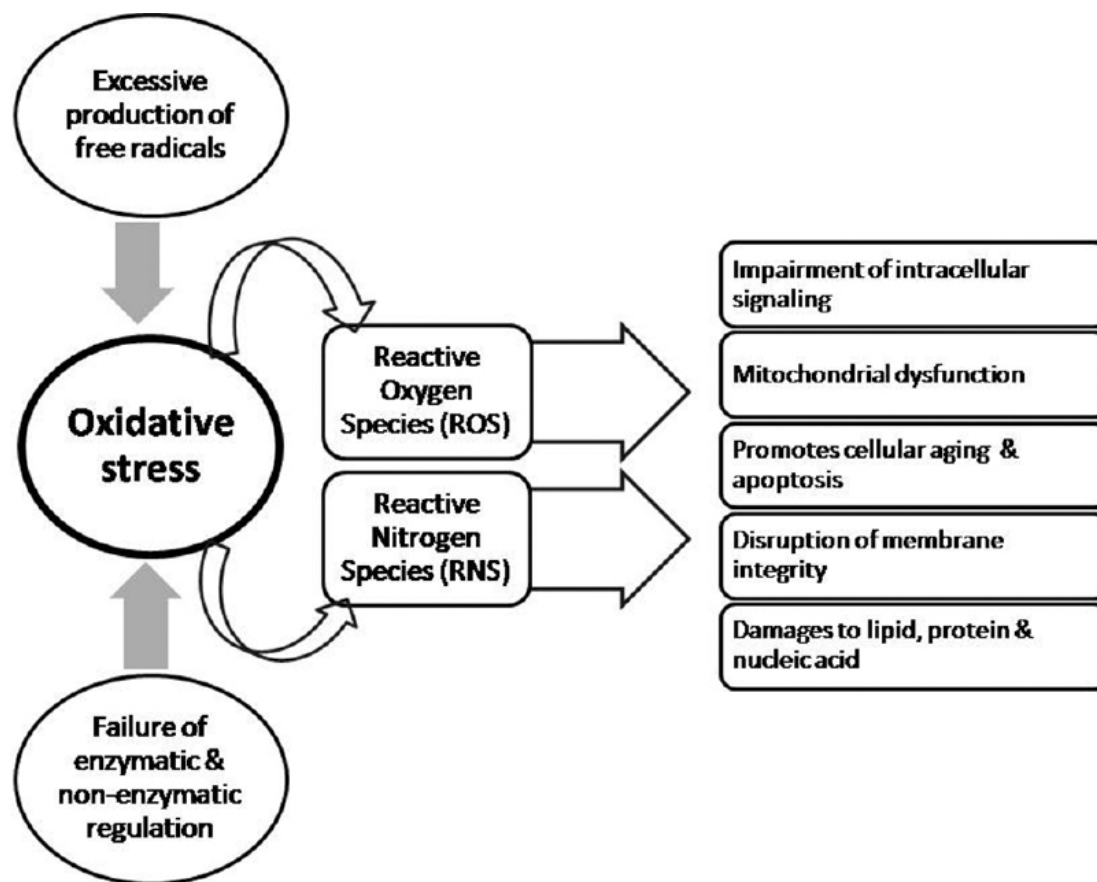


Figure 2.2: Excessive Production of Free Radicals

Senousey et al. (2018) conducted a study to explain the role of dietary vitamin C, vitamin E, and

alpha-lipoic acid supplementation on the antioxidant defence system and also immune-related gene

expressions exposed to oxidative stress by the dexamethasone. This study explained that vitamin C, vitamin E, and ALA are known as some of the potential nutritional antioxidants that impart an important role in enhancing the immunity of an organization. The powerful nutritional antioxidants Vitamin C, Vitamin E, and Alpha-lipoic acid (ALA) is helpful in the improvement of the immune. The effects of the vitamin C, vitamin E or ALA supplementation on the antioxidant system and the immune-related expression of the genes under oxidative stress generated by dexamethasone (DEX) in broilers were compared in this study. In all, 240 one day females Recessive White Rock have been allocated to basal diets, either with a vitamin C supplement (200 mg/kg diet), with vitamin E supplements (100 mg/kg), or ALA (500 mg/kg) randomly with a 28 d commencing from a hatch.

This study explained that at the 21d age, birds fed ALA-supplementation that imparts an important role in their total antioxidant capacity, increases the

superoxide dismutase, enhances the activities of glutathione peroxidase, and also lower the malondialdehyde activities. This study explained that the use of ALA supplementation also reduced the levels of mRNA gene expressions of interferon gammas as well as lipopolysaccharide-induced tumor necrosis factor- $\alpha$  factor. In the 3 therapeutic groups, the broilers were injected with DEX into the thigh muscle for 3 alternative days at the age of 23 d. The control group was also separated in 2 equal groups, one injected with saline and the other with DEX. At 28 d of age, the plasma and liver DEX-ALA ( $P < 0.05$ ), and the biggest decreases in the MDA, were at the highest levels of activity for T-AOC, T-SOD, and GSH-PX ( $P < 0.05$ ). Dietary ALA significantly lowered the interleukin  $1\beta$ , IL-6, IFN- $\beta$  and LITAF expression levels than other groups during oxidative stress by DEX. During the oxidative stress period the ALA was considerably less. Finally, this study indicates that ALA is higher in broilers (H.K.El-Senousey, 2018).

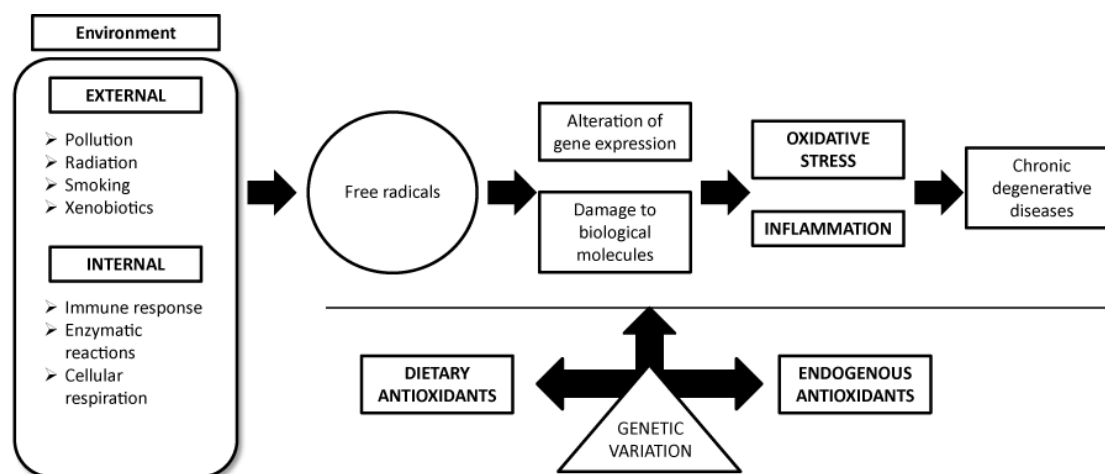


Figure 2.3: Genetic Variation

#### IV. ROLE OF VITAMIN E AND VITAMIN C IN OXIDATIVE STRESS OF FEMALE REPRODUCTIVE

##### a) Character of Oxidative Stress on the Reproduction of Female

A 2005 research by Ashok Agarwal et al. on the role of oxidative stress for women. This study determines that ROS and antioxidants present in our body on a balance and when this balance is disturbed the physiological functions of the human body are also disturbed. OS highly influenced the lifespan of a female reproductive system and after menopause, there is imbalance occurred between the ROS and antioxidants present in the body. ROS act as the signaling molecule present in the body and also have some pathological properties, especially in the female reproductive system. This study determined that ROS affects various

physiological processes such as fertilization, oocyte maturation pregnancy, and embryo development.

This study also explores the fact that OS is involved in age-related weakening infertility. OS imparts a significant character in the pregnancy, normal parturition, and also in the initiation of the preterm labor. It was determined that repetitive ovulation and surface epithelium were the main causative factors of ovarian cancer in the female reproductive tract. Antioxidant damage to the ovarian (Agarwal et al., 2005).

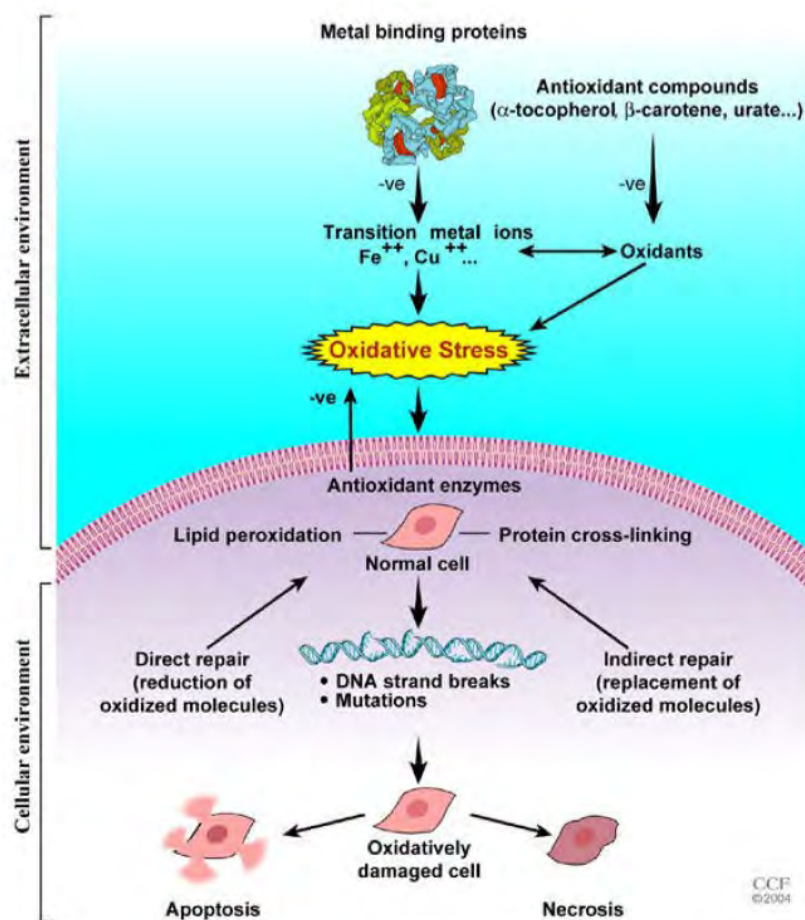


Figure 2.4: Metal Binding Proteins

Oxidative basis and damage to the DNA incurred by epithelial ovulation can also be prevented. OS literature is increasing with the involvement of pre-eclampsiological pathophysiology, mole-hydatide and free radical contamination, and in other cases, such as abortions. More and more detail is available. Many studies have shown that OS plays a part in infertility and fertility pathophysiology. The function of endometriosis, peritoneal and tubal infertility and unexplained infertility are seen.

In the aetiology of female reproductive disturbances, the dynamic interplay between cytokines and oxidative stress is discussed. The cell's oxidants modulate angiogenesis, which is crucial to follicular development, endometrial differentiation of corpus luteo formation and embryonic growth. Oxidative stress control techniques and reproductive enhancement are both normal and assisted. Early measures for pre-eclampsia prevention are mentioned. Trials exploring vitamin E and vitamin C intake in combination intervention methods are illustrated in pre-eclampsia prevention. Antioxidants are high and antioxidant supplements in the sexual breeding have been studied in several studies. However, in order to show the

effectiveness of antioxidant supplementation in female reproductive disorders, randomised controlled experiments with adequate strength are needed until doctors prescribing antioxidants. In longitudinal research, serial measurements of oxidative stress biomarkers may help delineate the aetiology of certain disorders such as preeclampsia for reproduction by females (Staff, 2019).

#### b) Impact of Oxidative Stress on Female Fertility

Elizabeth et al. conducted a study to determine the impact of oxidative stress on female fertility. This study determined that oxidative stress is related with decreased female fertility in multiple animals but there is no any direct relation with the women. Oxidative stress-related exposures and proofs of timing and sustaining a viable birth include risks of pregnancy (e.g. preeclampsia), extremes of body weight, alcohol and nicotine as well as caffeine use. The consumption of antioxidant nutrients, like multivitamins, has repercussions on the production of reactive species of oxygen and can support women's fertility. Infertility is a huge public health issue and frustrating, intrusive, and expensive diagnosis and care. An understudied and

convincing area of study is the role of the oxidative stress in female fertility. Identifying modifiable stress relief mechanisms may be an effective and invasive treatment for increased fertility in the gynaecological setting (Ruder, Hartman, & Goldman, 2009).

c) *Character of Oxidative Stress on the Reproduction of Female*

A research by Jiayin et al. to determine the role of oxidative stress in reproductive women was carried out. This research was carried out to examine the significance of oxidative stress in the reproductive system for the woman. There are multiple studies have been done on this topic as this topic become very common regarding the research. The oxidative stress (OS) analysis has become more and more common in recent years. The role of the OS in women's fertility is especially significant and closely oriented.

OS occur when overproduction is achieved by reactive oxygen species (ROS).

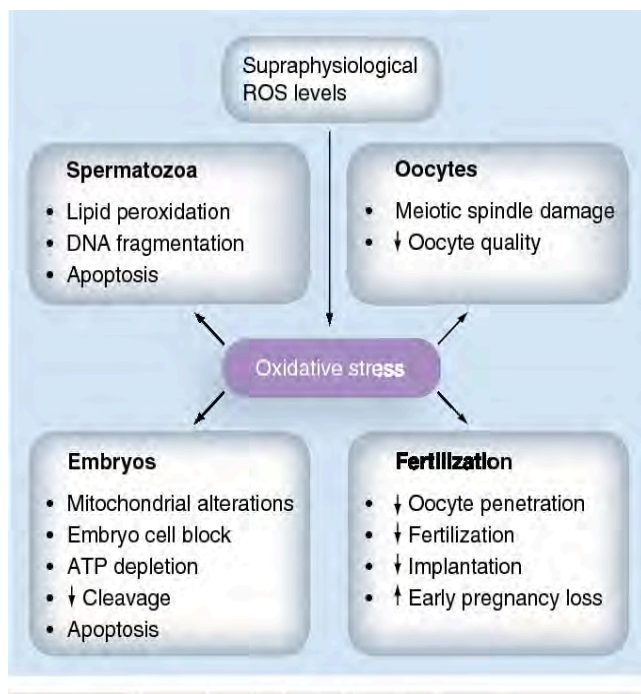


Figure 2.5: Supraphysiological ROS Levels

In certain intracellular cascades, ROS is a two-edged sword; as secondary Messengers, it not only plays an important part but it also has important effects on pathological processes involving women's genital tract. In this study it was explored that reactive oxidative stress as well as anti-oxidants imparts an important role in the regulation of the reproduction of both animals and humans. Both animals and people are governed by ROS and antioxidants for reproductive processes. Disorders between prooxidants and antioxidants may lead to many reproductive illnesses in women. This analysis focuse on the function of OS and a variety of reproduction processes for women, describing the role

of OS in women's reproduction and OS-generated reproductive diseases, including PCOS, endometriosis, preeclampsia, etc. A variety of signals affecting female fertility, including the OS-affected pathways of the Keap1-Nrf2, NF- $\kappa$ B, FOXO, and MAPK, offer new insights into processes of reproductive diseases (Lu, Wang, Cao, Chen, & Dong, 2018).

d) *Vitamin E and Vitamin C as Defence Partners*

The protective essence and relationship of vitamin C and vitamin E has been determined by Alvin Chan et al. Besides the enzyme free radical removal process, essential foods, such as vitamins E and C, that can scavenge free radicals, form a powerful protection to delay free radical damage to the cell. Different mechanisms have recently been established to fix oxidised vitamin E in human cells. About half the vitamin E platelet and the addition of arachidonate is metabolised by platelets cyclooxygenase and lipoxygenase pathways within 0,5 min of the addition of arachidonic acid to the human platelet homogenate. More than 60% of the oxidised vitamin E was regenerated after adding Nordihydroguaiaretic acid, a lipoxygenase inhibitor and a good reducing agent.

There were multiple physiological and water-soluble reducing agents were testes to explore that they may help in regenerating of the vitamin E as well as eicosatetraenoic acid that is a lipoxygenase inhibitor was used for this test. In testing of other physiologically soluble water-reducing agents, eicosatetraenoic acid, an inhibitor of lipoxygenase, which is not an antioxidant, can help regenerate vitamin E. Ascorbate and glutathione have been essential for the regeneration of vitamin E in this phase.

Kinetic analyses and analyses of the regeneration of vitamin E within a protein denaturation system have shown that ascorbate regenerates vitamin E by a nonmammal process, while glutathione enzymatically regenerates vitamin E. These studies indicate that essential interactions occur at the membrane cytosol interface between the water- and lipid-soluble molecules and that vitamin C can function in vivo to repair the membranous oxidising vitamin E (Wong et al., 2019).

e) *Review about Role of Oxidative Stress in Female Reproduction*

The Jiayin et al. researched the effect and role of oxidative stress within reproduction of women from various scientists. They performed a review. The oxidative stress (OS) analysis has become more and more common in recent years. The role of the OS in women's fertility is especially significant and closely oriented. OS arise when reactive oxygen species are overly production (ROS). In certain intracellular cascades, ROS is a two-edged sword; as secondary Messengers, it not only plays an important part but it also has major impacts on pathophysiological

conditions involving women's genital tract. Both animals and people are governed by ROS and antioxidants for reproductive processes. There were some imbalances occurred between the pre-oxidants and antioxidants and this imbalance imparts a great role in the production of multiple diseases of female reproductive.

ROS is a two-edged weapon in some intracellular cascades; as second Messenger it plays a critical role, and also has a significant effect on pathophysiological disorders affecting the reproductive tract of women. A large number of signalling pathways in female reproduction are identified, including the OS-affected Keap 1-Nrf2, NF- $\kappa$ B, FOXO and MAPK pathways, offering a new insight into reproductive disease mechanisms (Lu et al., 2018).

#### f) *Part of Oxidative Stress on Assistant Pregnancy*

The research by Gupta Sajal et al. has explored the role of oxidative stress on an adjunct. There were multiple disease s happened due to the presence of oxidative stress and also seen that this oxidative stress resulted in the failures of techniques by which pregnancy and fertilization has achieved. Oxidative pressure leads to the high rate of failing to accomplish fertilisation and conception in assisted reproduction techniques. Several experiments have been undertaken to explain the cause of oxidative stress on ART and to resolve the detrimental impact it has upon IVF and ICSI outcomes. This research deals with the use of metabolomics as a modern and non-invasive process to reliably and efficiently measure oxidative stress. A literature review on the results of various treatments to boost the levels of fertilization and conception is at the core of this research. This research aims to updates the current literature on findings from various therapies including the use of antioxidant supplementations for IVF cultures and patients to improve the fertilization and reproduction rates of key is to avoid patients receiving ART (Gupta, Sekhon, Kim, & Agarwal, 2010).

This study determined that oxidative stress is highly connected with the negative ART outcomes. Oxidative tension is associated to poor ART performance. The literature has been well developed for both exogenous and endogenous sources of reactive oxygen species during IVF/ICSI. In contrast to IVF, gamet susceptibility to endogenous oxidative stress sources in gametes is considered to reduce. There are multiple strategies present for the management of exogenous causes of oxidative stress include minimising visible/near sensitivity to UV light, the incorporation of metal chelators to cultivated media, preserving environmentally low oxygen voltage and the use of antioxidant therapy. A vitamin C, vitamin E and melatonin antioxidants supplement of culture media have been studied and conflicting results have been made (Khazaei & Aghaz, 2017).

Although oral antioxidant supplementation has been recognized for male patients and is currently performed, the efficacy of vitamin C, vitamin E, and melatonin supplementation for females undergoing ART is not being decided. A further study of the effectiveness and safety of antioxidant supplementation in culture media and patients is important in randomized controlled trials, along with a determination of the dose necessary for optimizing IVF/ICSI fertilization rates and pregnancy outcomes.

#### g) *Vitamin E for the Health of Female Reproductive System*

A research was performed to determine vitamin E as the health of women in the reproduction system by Syairah Mohd Mutalip et al. This study has been done to determine that how vitamin E imparts a significant part on the health of a female reproductive system. This study determined that the importance of vitamin E as a reproductive substance has been discovered in 1922. Vitamin E has been researched extensively and is commonly recognised as a strong lipid-soluble Antioxidant after the finding. Since it was seen to be less cholesterol in body and an anticancer agent, vitamin E's performance as an antioxidant has increased. Vitamin E has been noted in several trials for anti-proliferative, anti-survival, pro-apoptotic, anti-angiogenesis and anti-inflammatory roles in cancer (Wong et al., 2020).

Vitamin E gave the multiple benefits to the human health and is very important in the maintenance of healthy life of a female. It also imparts an important and positive role on the health of female reproductive system. Vitamin E's health benefits in general are recorded in different ways. While it is initially discovered as a reproductive vitamin, research on its effects in this region have been incomplete to date. In order to assess the known functions of vitamin E as an antioxidant for the reproductive health of women, this paper was therefore drafted.

#### h) *Effects of Vitamin E and Vitamin C Supplementation on Female Reproductive System*

Jennifer Mier-Cabrera et al. also conferred a review on peripheral oxidative stress markers and fertility rates in endometriosis women to examine the effects of vitamin E and Vitamin C supplementation. The basic purpose and goal of this research is to establish if the addition of Vitamin E and Vitamin C imparts a significant part on the health of female reproductive system. Vitamin C and Vitamin E reduces oxidative stressors in women with endometriosis and also increases pregnancy rates. The vitamin C and E bar (specifically 343 mg and 84 mg, respectively) and 6 months placebo were obtained by 344 women with endometriosis. Plasma and peritoneal fluid (MDA) and lipid hydroperoxides have been tested for both women and in both grades (LOOHs) (Vitale et al., 2018).

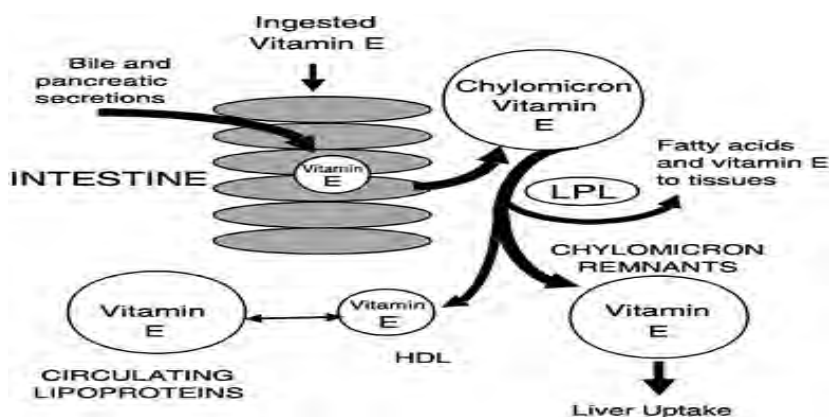


Figure 2.6: Bile and Pancreatic Secretions

The analysis of data is important to determine the actual result and conclude the outcomes of the study. The analysis of a data has been done by multiple ways such as t test, chi-square test, correlation, and other multiple test. Data for quantitative variables and a Summer Test of Man—Whitney, or a Kruskal-Wallis test for nonparametric data were tested by the t or 1-way study of variances. For comparing pregnancy rates, the exact Fisher test was used. After 4 months the MDA and LOOH were smaller than the control group. The difference was statistically meaningful in the fourth months for MDA and in the sixth month for LOOHs. The pregnancy rates were 19 percent and 12 percent in the supplementation and placebo categories, both of which showed no substantial difference. The conclusion is that a decrease in the oxidative stress markers in women with endometrosis is consistent with the supplementation of vitamins C and E. However, before or after the procedure the pregnancy rate did not change (Mier-Cabrera, Jiménez-Zamudio, García-Latorre, Cruz-Orozco, & Hernández-Guerrero, 2011).

#### i) Follicular Fluid and Serum Markers of Oxidative Stress in Women Infertility

Laura Prieto et al study's has measured follicular fluid and serum oxidative stress markers in women with endometriosis-related infertility. The goal is to investigate the levels of four oxidative stress markers in follicular fluid and plasms in endometriosis and control-related infertility patients. It is an experimental study design and conducted within a university affiliated hospitals and infertility center. Ninety one women has been participated in this study from which 23 women were infertile with endometriosis and 68 women control due to the presence of tubal factor, healthy egg donors, and male factors.

Endometriosis women demonstrated lower FF levels of vitamin C ( $12.7 \pm 5.9$  vs  $9.7 \pm 6.9$   $\mu\text{g/mL}$ ) and lower plasma levels of the superoxide dismutase ( $0.9 \pm 1.4$  vs.  $0.5 \pm 0.7$  U/mL) in comparison to controls. In women suffering from endometriosis ( $8.1 \pm 3.8$  vs.  $5.2$

$\pm 3.2$   $\mu\text{g/mL}$ ), Vitamin E plasma was substantially higher. Women with endometriosis have no significant tendency towards a lower plasma malondialdehyde concentration. These results indicate that infertile women with endometriosis have less antioxidant ability. While reactive oxygen species need a certain amount of physiological conditions, a changed equilibrium between pro-oxidant and antioxidant activities could influence folliculogenesis and adequate embryonic growth (Prieto et al., 2012).

#### j) Impact of Multivitamin and Supplementation on Fertilization

Okan et al. have completed a multivitamin and supplementation analysis to establish oxidative stress and antioxidant vitamin levels in women experiencing in vitro fécondation in serum and follicular fluid. The basic aim and objective of this study is to determine the impact of multi vitamin and supplementation modulates on the undergoing fertilization happened in vitro. In serum and follicular fluids, 56 women under IVF and 13 years of age have been tested for the effects of multivitamins and mineral additives on lipid peroxidation, diminished glutathione, glutathione peroxidase, vitamin A, vitamin C and vitamin E. We also hypothesised that the antioxidant protection mechanism may be improved by decreasing oxidative stress in the serum and follicular fluid of women suffering from IVF (Özkaya & Nazıroğlu, 2010).

#### k) The Position of Free Radicals in Women's Breeding Conditions

A research to determine the role of free radicals in female reproductive disorder and supporter reproduction was conducted by Ashok Agarwal et al. The basic aim and objective of this study is to determine and explore the role of free radicals in the female reproductive diseases. This study explored that infertility has become a very common problem that has been experienced by multiple couples. Infertility is a recurrent concern that many partners face. There are multiple treatment strategies and therapies for female infertility are available.

In certain cases, however, the procedure is observational, as the aetiology of infertility is not well known. Reactive oxygen species has been shown to play a major role in the day-to-day life of women and in infertility pathogenesis. Reactive oxygen species may also play a part in other diseases of women, such as endometriosis, and multiple sexual illnesses have arisen because of reactive species of oxygen.

If a disparity exists in the reproductive tract between ROS production or antioxidants scotching ability, oxidative stress occurs. Both normal and aided fertility are impaired. Since aided breeding approaches are widely utilized for the treatment of infertility, in vitro complications involving both fertilization and embryonic growth are important to recognize. Treatments that alleviate oxidative stress may benefit infected women suffering from diseases caused by this condition (Pashkow, 2011).

The techniques include the detection of the source of excess ROS generation, the treatment of the root cause and the supplementation of antioxidants in vitro and in vivo. Research is underway to describe and establish successful methods to combat oxidative stress in the aetiology of female reproductive diseases caused by ROS (Steller, Alberts, & Ronca, 2018).

#### *l) Human Reproductive Device Antioxidant Strategy*

Rosaria Meli et al. carried out an oxidative stress and BPA toxicity interaction analysis. In this study an oxidative approach has been used for the dysfunction of male and female reproductive system. Bisphenol (BPA) has been used and detected in many consumer goods and food stuffs as a non-persistent, anthropogenic and chemically pervasive compound and hence prolongs human display. Oversight of the fundamental molecular mechanism of BPA toxicity has been shown over the last ten years in several studies and the link between BPA-induced oxidatives, male and female genital defects and human diseases has been found.

The BPA exhibits tissue effects in target cells due to its hormone-like properties, inducing poisoning, Oxidative stress and inflammation-related cell responses in particular hormone receptors. It is a metabolic and endocrine disrupter. By raising oxidatively engaged mediators or decreasing the amount of antioxidant, BPA diminishes the redox homeostasis, induces mitochondrial dysfunction, modifies pathways for cell signals and contributes to apoptotic cell death.

This research analyzes BPA literatures, in which the oxidative stress induction of the toxic impact pathways of BPA that have pleiotropic reproductive effects can be called the 'fil rouge' (fil rouge). The positive properties observed in male and female reproductive functions for BPA counteract the protective properties of five forms of antioxidants, namely vitamins or co-factors (herbs or plant chemical compounds),

methyl donor, melatonin, and selenium products, are localized here (used individually or in a combination) (Zaid, Othman, & Kassim, 2018).

#### *m) Role of Vitamin C on Female Reproductive System*

Mustafa Saygin et al. conducted a study to determine the impact of electromagnetic radiation on the female reproductive system and also determine the role of vitamin C on the female reproductive system. The present research has researched the effects of the 2,45 GHz continuous electromagnetic (EMR), which could cause the ovarian, fallopian and uterine tissue changes in physiopathology or morphology. We proposed to reduce these extreme effects with the addition of vitamin C (Vitamin C). Eighteen sprague Dawley rats have been split randomly into three groups of five animals in each: EMR, EMR, 1 h/day for 30 days and Sham and Vitamin C.

In the EMR only category of ovarian tissues, the average status of oxidants and the oxidative stress index (OSI) improved ( $p = 0.011$  and  $p = 0.002$ , respectively). In the Vitamin C-treated community in fallopian tube, and ovarian, and uterine tissues ( $p < 0.05$ ) the TOS and OSI levels decreased substantially in all tissues. The level of anti-muller hormones in the EMR group ( $p < 0.05$ ) was slightly increased and in Vitamin C-treated groups was decreased. In the EMR group, estrogen (E2) levels had not been modified because of the statistically not relevant variations.

In the epithelial cells of the EMR Community ( $p < 0.05$ ), immune histochemical monitoring of the ovaries has shown substantial changes in Caspase-3 expressions. Hyperemia in uterine tissues was found in the EMR community. The EMR group was greatly improved by Caspase-3 and Caspase-8 ( $p < 0.001$ ). With the application of Vitamin C in ovarian and uterine tissues ( $p < 0.05$ ) Caspase-3 was substantially decreased. In the uterine tissues alone ( $p < 0.05$ ) Caspase-8 was greatly decreased.

These findings suggest that repeated exposure to EMR triggered changes in ovarian, fallopian and uterine tissues owing to oxidative damage to physiopathology's. Vitamin C will protect women's reproductive system from oxidative damage under the conditions of this study (Saygin et al., 2018).

The rate and number of deliveries by cesarean is directly associated with some of the maternal risks such as long surgery time, peripheral organ damage, need for intensive care, maternal death, bleeding and hysterectomy (Kaplanoglu, Bulbul, Kaplanoglu, & Bakacak2015). The mode of delivery is also associated with age such as chances of cesarean deliveries are most common at the age from 31-40. As the age increase, the chances of normal delivery or miscarriage enhance due to weak immunity. There are more complications at the time of delivery at the age from 21-30. Thus, it is clear that age is directly related with mode

of delivery as well as complications during delivery. The study showed that second mode of delivery depends on first mode for example, if a previous delivery mode of a woman was SVD than there are high chances of SVD for current delivery and vice versa (Rowlands, (2012). Thus, it is clear that the delivery modes highly depend on first delivery and women should go for SVD because there are less complication with SVD as compare to cesarean.

#### n) *Function of Menopause Oxidative Damage*

The role of oxidative stress in menopause has been determined by Sejal Doshi etcetera. The research addresses the idea of reproductive ageing that involves identifying menopause, its symptoms and the disorders predisposed to menopause. It will discuss the leading factors to menopause pathogenesis, with an emphasis on oxidative stress. This study would explicitly illustrate how oxidation stress is directly related to the decrease in oestrogen during reproductive ageing, in the form of free radically and antioxidant deficiency.

This paper will also address treatment strategies to reduce menopausal complications and hormones that can contribute to multiple disease processes. Options such as oestrogen treatment, supplemental antioxidants and dietary changes have been researched in order to determine their usefulness in treating and avoiding menopause symptoms and sequelae. PubMed and the National Library of Medicine have collected the bulk of the data in this study. While the bulk of references are original research papers, a handful of references are detailed evaluations (Doshi & Agarwal, 2013).

Kennare et.al conducted a study and compares the risks of second birth after first birth in cesarean and vaginal birth. In this study the data was collected from South Australian during the year of 1998 to 2003 and compare almost 2733 women who have vaginal first birth with the 8725 women who have cesarean first birth. The results of this study show that abnormalities due to cesarean are high after first birth and it may harm the mother and baby both. (Kennare 2010)

Silveiral et al. conducted a study to show a comparison of cesarean and vaginal birth deliveries. This study was conducted in Brazil in 2004 and all the mothers are investigated in hospitals during their stay in hospitals. Doctors and nurses asked from them about their previous family gestational history. The results of this study show that the overall rate of cesarean in Brazil is 45% in their government hospitals and 81% in private hospitals. This study shows that private hospitals have high rate of cesareans.

P Braveman et.al conuted a study to relate that how ethnicity depends on the cesarean. In this study he discussed that either race of women are dependent or not on cesarean delivery. It is a retrospective based study and this study is conducted in California in th year of 1991. This study shows that the chances of cesarean

in black women are 24% high then the white women. The result of this study was that ethnicity is highly effect the cesarean but other social activities of the women are not affected and be a cause of cesarean. (Braveman, P., Egerter, S., Edmonston, F. 19950)

Adriant Grant conducted a study to show that how cesarean reduce the morbidity or death of premature birth but it may cause abortion or risk of maternal. In this study the Cochrane pregnancy and childbirth methods are used to investigate. In this study the data of 122 women are taken and check the maternal abnormalities in these women and their new born babies. The results shows that the babies of these women have less chances of respiratory distress syndrome and neonatal seizures and very few deaths occurred but the mothers are at high risks.(Grant, A 2001)

Richard et.al conducted a study to discuss the causes, trends and solution of huge cesarean cases. In this study it is also determines that the vaginal birth rate is decreased day by day because most of the women choose cesarean because they have no tendency to bear the labor pains during pregnancy. This study also shows that the some strategies are applied to reduce the cesarean cases and induce the labor pains so that vaginal birth can be enhanced. (Porreco, R. P.1996)

E.L conducted a study to discuss the psychological effect in emergency cesarean case ad vaginal birth case. This study shows that psychology has a great effect on the type of birth either vaginal or emergency cesarean. If they are already known that they have cesarean it impacts negative effect on the health of mother and baby but if its an emergency case then it doesn't have more negative impact on the mother health. The results show that an unplanned cesarean delivery has less negative impact on health. (Ryding, E. L., Wijma, K.1998)

Kiel conducted a study to show that how obesity in women can alter the pregnancy and mode of delivery. This is a cohort study in which data was collected of 120251 obese pregnant women to check that how obesity affect the pregnancy. The results of the data shows that if there is no extra abdominal weight is gain the pregnancy is not altered or affected in obese patient. (Kiel, D. W., Dodson, E. A., Artal, R., Boehmer, T. K.2007)

Projestine S Muganyizi et.al conducted a study to discuss that how different age groups pregnant women affected by their delivery. This study is conducted in tertiary hospital of Tanzania and discusses that different age groups has no major effect on the pregnancy outcomes. This study indicates that mothers of high ages have more chances of cesarean delivery and less age group have less chances of cesarean delivery.

o) *Protective Part of Vitamin E on Nickel Induced Oxidative Stress in Ovary of Female Reproductive System*

Mandava et al. carried out an analysis to establish the protective effect of vitamin E in the ovary of the female reproductive system on nickel and chromium mediated oxidative stress. In the present study, nickel chloride (NiCl<sub>2</sub>) and potassium dichromate (K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>; 5 mg/kg body weight) were identified in vivo to adult mice. Overall, in vivo, adult mice were found to have a diagnostic effect. The vitamin E protective function (2 mg/kg body weight) was also analysed in accordance with its combination. The level of lipid peroxides in the ovary has risen with nickel and/or chromium to the mouse, followed by a substantial reduction in the levels of protein, glutathione, complete ascorbic acid, dismutase and catalase of superoxide's.

The vitamin E supplement with NiCl<sub>2</sub> + K<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub> decreased lipid peroxidation levels considerably and improved antioxidant status. The results of this study indicate that the safety of vitamin E from toxicity by avoiding lipid peroxidation and by shielding the anti-oxidant system in women's ovaries against nickel and/or chromium.

p) *Role of Reactive Oxygen Species in Female Reproduction*

Rizzo et al. carried out an analysis to determine the function of female breeding reactive oxygen species. Reactive oxygen molecules are the highly reactive oxidizing agents (ROS). Under aerobic conditions, cells offer ROS defense and a strong balance occurs under natural conditions between pro-oxidants and antioxidants. Oxidative stress happens, during which ROS accumulates and destroys the cells and organs, if the body is unable to remove ROS unnecessarily. In addition to the adverse effects, accumulation of evidence has shown the physiological impact of regulated and sufficient ROS levels.

Different experiments have verified the presence of ROS and transcripts in women's breeding tract. When ROS development is overcome by antioxidants, oxidative stress, which can endanger the anatomical and functional integrity of the genital tract, occurs. It deals with the major physiological and pathological roles played by ROS and its scavenging mechanisms in multiple processes that engage in the primary physiological functions of the women's and domestic animals' reproductive tract. The role of oxidizers in many reproductive processes, such as follicular growth, ovarian steroidogenesis, ovulation, luteolytic, germ cell functions, pregnancy maintenance and starting parturition, is studied in particular.

q) *Implication of Oxidative Stress on Female Infertility*

Ashok Agarwal et al. showed a learning to determine the oxidative stress and its implication in the female infertility. Reactive oxygen species (ROS) play a

significant role in gamete content modulation and gamete interaction. Spermatozoa and leukocytes contaminating ROS generation is inherent. Sperm, ovaries, eggs, and their environment are affected by ROS. Sperm membrane peroxidant damage is mediated by oxidative stress (OS), which causes nuclear DNA damage. ROS can modulate the sperm fertiliser ability. There is a wide variety of literature on OS and its working in male infertility and DNA damage and its effect on assisted reproductive techniques. Facts are obtained in the role of ROS in female reproduction.

In oocyte growth, ripening, follicular atresia, corpus luteum and luteolytic several animal and human studies have highlighted ROS' function. The precipitation mediated by the OS of reproductive pathologies in women is similar to the precipitation involving male infertility. OS affects the efficiency and the fertilization rates of the oocytes and embryos. In gamete activity modulation and efficient fertilization, ROS tends to production an significant role (Ramalho-Santos et al., 2009). In cultural media ROS may affect the production of post-fertilization, i.e. cleavage rate, blastocyst yield and efficiency (indicators of assisted reproduction outcomes).

Both natural and aided fertility are recorded to impact OS. The methods for antioxidants should be able to intercept extracellular as well as intracellular ROS. This analysis explores origins of ROS in media for the movement of IVF embryos and methods for OS control in in-vitro ripening of the oocytes, in-vitro cultivation and sperm preparation techniques.

In the aetiology of female reproductive disorders, the complex link between cytokines and oxidative stress is discussed. Cell regulation of Angiogenesis is important for follicular development, separating of dogmas and for embryonic growth of the formation of corpus lute. Techniques for controlling oxidative stress and improving fertility are both natural and supportive. Early pre-eclampsia preventive strategies are discussed. The pre-eclampsia avoidance illustrates tests for the discovery of vitamin C and vitamin E intake in combination treatment.

In some trials, high levels of antioxidant additives were examined in sexual breeding. But before doctors prescribe antioxidant to demonstrate the effectiveness of antioxidant supplementation in women's replicative disorders, randomized controlled trials with adequate intensity are needed. Duration studies may help to delineate the aetiology of certain disorders, such as preeclampsia for female reproduction by means of serial test measurements for oxidative stress biomarkers (Agarwal et al., 2005).

r) *Anti-Oxidant Nutrient and Lead Toxicity*

The analysis of the antioxidant nutrient as well as the lead toxicity in mammalian cells was carried out by Ping-Chi et al. Lead-induced oxidative stress leads to

pathogenesis of lead poisoning in mammalian cells to interrupt the fragile prooxidant/antioxidant balance. After lead treatment in in vitro experiments, production of reactive oxygen species (ROS) is increased. Studies in vivo indicate that lead toxicity contributes to ROS production and modification of the protection mechanism for antioxidants in animals and employees exposed to jobs. The mechanism for oxidative stress triggered by circuitry involves the impact of plumbing on membrane, DNA and cell protection antioxidant systems.

In epidemiological and animal research, there are differing responses from low to elevated levels of plum sensitivity to oxidative stress at various target sites such as lung, blood vessels, testes, sperm, liver and brain. The beneficial effect of antioxidant nutrients by exogenous enrichment of antioxidant molecules may thus be correlated with reducing the capacity for lead to interfere with essential biological molecules and causing oxidative harm or enhancing cell antioxidant defenses. Although a number of studies have researched the use of antioxidants to avoid lead toxicities, the functions of antioxidant nutrients are not entirely apparent by the re-equalization of the degraded prooxidant/antioxidant ratio. The analysis addresses their beneficial function in lead-induced oxidation stress by discussing the antioxidant nutrients namely, vitamin E, vitamin C, vitamin B6,  $\beta$ -carotene, zinc and selenium (Hsu & Guo, 2002).

It also deals with female SA infertility and how it influences the effects of aided breeding techniques. The paper explores in depth the role of oxidation stress in conditions such as abortion, preeclampsia, hydatidiform mole, foetal embryopathy. The thesis also addresses the increased role of nitrogen oxide species in reproduction by women in the literature. It covers the participation of nitrial oxide Dravidian in endometrial as well as ovarian structure planning, etiopathology of endometriosis, support of vaginal stimuli, initiation of work and maturation of the cervix.

Junichi Fuji et al. (2005) conducted a study to explore the basic roles of reactive oxygen species as well as protective mechanism in the female reproductive system. This study explored that controlled oxidation such as disulphide bind present at the nuclei of sperm during the ovulation imparts an important and basic role in female reproductive system. The presence of high oxygen causes oxidative stress that results into the dysfunction of all process of reproductive system. The presence of anti-oxidation reactions reduced the level of reactive oxygen species and imparts an important role in maintaining the quality of gametes as well as reproduction system. The presence of oxidative enzymes such as superoxide dismutase as well as peroxide imparts a significant role in elimination of these oxidative stress. The redox reactions present in female reproductive system are comprised of two main reactive

agents such as glutathione as well as thioredoxin that reduced the level of oxidized molecule and also reduced the oxidative stress in female reproductive system. Thus, this study determined that antioxidants as well as redox enzymes imparts an important role in providing protection to gametes as well as gametes in female reproductive system.

#### s) *Role of Oxidative Stress and Antioxidants in Assisted Reproduction*

Sajal Gupta et al. (2010) conducted a study to measure the role of oxidative stress and antioxidants in assisted reproduction. Oxidative stress correlates to an increased rate of failure to achieve fertilization and pregnancy in assisted reproductive procedures. Many studies have been carried out to elucidate oxidative stress sources for ART and therapies to overcome the unfavourable effects of IVF and ICSI. Oxidative stress sources were determined in this context. This article addresses the use of metabolomics as a unique, non-invasive tool for evaluating oxidative stress precisely and efficiently. The purpose of this study was to examine the current literature on the impact of several therapies, including the use of IVF culture supplements antioxidants in the field of fertilization well as rates of pregnancy in the subfertile patients undergoing ART.

Examination by Pubmed and the Cochrane databases of recent publications Outcome: Oxidative stress is linked to the unfavourable effects of ART. The IVF/ICSI is well-established in literature both exogenous and endogenous sources of reagent oxygen species. The exposure of gametes to endogenous sources of oxidative stress has been minimised by ICSI, compared with the IVF. Strategies to minimise oxidative stress sources within a randomized ART environment include limiting visible / close UV exposure, adding metal chelators to cultivation media, maintaining low environmental oxygen tension and using antioxidant treatment. The vitamin C, vitamin E and melatonin antioxidant addition of culture media has been researched and inconsistent findings have been produced. With the acceptance and practise of oral antioxidant supplements in male patients, there is no consensus on the usefulness of ART supplementation in females, vitamin E and melatonin. Further research into the efficacy and safety of antioxidant supplementation of culture medium and patients and the necessity for determination of the dosages required to promote fertilization and pregnancy are necessary in randomized controlled trials.

## V. CONCLUSION

It is concluded that oxidative free radicals present but the imbalance between these radicals leads into the oxidative stress. There are two ways to reduce the oxidative stress either by using enzymes or by vitamins as both act as the antioxidants. This study

explained that vitamin E and vitamin C imparts an important as antioxidant in the prevention of the side effects of oxidative stress. Due to the metabolic rate and the growth in mitochondrial activities Placenta may be the primary source of OS. Placental tissues have low concentrations and key antioxidant function during the first quarter, including catalase, glutathione peroxidase and superoxide dismutase. This condition will cause oxygen-mediated damage to the embryonic trophoblast cells.

Despite the gains made in the field of ART, antioxidant therapy has been a matter for much discussion and has been used to reduce the infertility burden by improving IVF and ICSI procedures. Although current information literature makes no definite conclusions about whether the specific antioxidant supplementation of patients with infertility and the culture media used for the use of ART will increase the success of the ART, important evidence suggests that this is a well-known contributor to ART failure and has the potential to fight oxidative stress. There is no question that an underlying relationship exists between OS and fertilization and possible IVF pregnancy. Thus, this study concluded that vitamin C and vitamin E imparts an important role in female reproductive system as an antioxidant.

#### Abbreviations

CVD Cardiovascular Disorders  
DNA Deoxyribonucleic Acid  
FA Formaldehyde  
GPx Glutathione Peroxidase  
LPO Lipid Peroxidation  
NOS Nitrogen Species Reactive  
OS Oxidative Stress  
PUFAs Polyunsaturated Fatty Acid  
ROS Reactive Oxygen  
SOD Superoxidase Dismutase  
VPA Valproic acid

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