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Evaluating Selenium's Therapeutic Benefits for Preeclampsia: A Comprehensive Review

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ABSTRACT

Preeclampsia (PE) is a multifaceted condition that affects multiple systems throughout pregnancy, with oxidative stress (OS) playing a significant role in its development. Selenium (Se) is a crucial micronutrient that plays a vital role in human health. The involvement of Se in the production of natural antioxidants is extensively documented, and a notable decrease in Se levels has been observed in women with PE. The significance of Se as a vital trace element is connected to its function as selenocysteine in several selenoproteins, such as antioxidant enzymes *glutathione peroxidases* (GSH-Pxs), *thioredoxin reductases* (TrxRs), and selenoprotein P (SePP). These enzymes provide protection to tissues against the harmful impact of reactive oxygen species (ROS) and other naturally occurring byproducts of cellular metabolism that are involved in DNA damage and have the potential to cause mutations, cell death, and the development of cancer. Insufficient levels of Se in the body and decreased activity of antioxidant enzymes during pregnancy lead to oxidative stress in tissues, which increases the risk of premature birth, miscarriage, preeclampsia, and intrauterine development retardation. Due to the strong reliance of placenta growth on oxygen levels, unregulated production of ROS is likely to be harmful. Notwithstanding these discoveries, the significance of Se and Se-dependent enzymes in pregnancy is still a subject of debate. The purpose of this review is to investigate the relationship between selenium (Se) levels during pregnancy and negative consequences. The effects associated with reduced antioxidant activity and elevated oxidative stress will be emphasized.

Keywords: Selenium, Preeclampsia, Pregnancy, Oxidative Stress

INTRODUCTION

Preeclampsia is a type of hypertension that occurs during pregnancy.[1] Globally, almost 10 million pregnant women suffer from preeclampsia, and roughly 76,000 women lose their lives due to preeclampsia and associated hypertension illnesses. Women in impoverished countries are seven times more likely to develop preeclampsia. These cases kill mothers 10-25% of the time.[2]

In Indonesia, particularly in the province of Aceh, preeclampsia accounted for about 40-60% of maternal mortality in 2022.[3] Preeclampsia patients have maladaptation, which causes hypoxia in trophoblast tissue. This leads to an elevated formation of free radicals, specifically reactive oxygen species (ROS), as a result of the activation of neutrophils, macrophages, and T lymphocyte cells.[4]

Free radicals are atomic or molecular entities that possess unpaired electrons, rendering them extremely reactive. Their high reactivity initiates cascading reactions

that result in molecular-level damage, and subsequently affect tissue integrity. Free radicals are often generated through physiological processes. However, in pathological situations such tissue ischemia, their quantity rises considerably.[5] If the body is unable to combat this condition, an imbalance arises between pro-oxidant reactive oxygen species (ROS) and internal antioxidants, resulting in the development of several illnesses.[6] In patients with preeclampsia, this imbalance leads to oxidative stress in the placenta, resulting in an increase in the growth of trophoblasts and their discharge into the mother's bloodstream. This elicits a detrimental immunological response, resulting in impaired functioning of the endothelium and the appearance of symptoms associated with preeclampsia.[7] Antioxidants are chemical or biological substances that have the ability to counteract the potential harm produced by free radicals. Recent studies have discovered that antioxidants can serve as a therapeutic approach for treating preeclampsia. Selenium is a sort of antioxidant.[8]

Selenium (Se) is an essential micronutrient for human health. There are two types of selenium: organic selenium, which includes *selenocysteine* and *selenomethionine*, and inorganic selenium, which includes selenite and selenate.[9] Food is the main source of Se, which is determined by soil concentration. Plant selenium content depends on species and soil selenium uptake. Foods like meat and fish account for 40-50% of selenium intake and maintain constant levels.[10]

Selenium boosts the immune-endocrine system, regulates metabolic processes, maintains cellular balance, and prevents certain diseases, according to studies.[11] Additionally, selenium acts as an antioxidant through the activity of *glutathione peroxidase* (GPx), an enzyme that plays a major role in protecting against oxidative stress.[12] Decreased blood selenium levels are believed to cause the production of oxidative stress compounds in the body.

This literature review seeks to analyze the effect of selenium in modulating reactive oxygen species (ROS) in preeclampsia. The literature review will comprehensively assess the potential of selenium in treating preeclampsia, focusing on its clinical consequences and suggesting areas for future research.

MATERIALS & METHODS

We conducted a comprehensive search on PubMed, Google Scholar and Scopus using keywords such as selenium, preeclampsia, pregnancy, selenoproteins and oxidative stress. We included accessible papers in both Indonesian and English, encompassing systematic reviews, meta-analyses, articles and literature reviews.

LITERATURE REVIEW

OXIDATIVE STRESS AND FREE RADICALS IN THE DEVELOPMENT OF PREECLAMSIA

Oxidative stress (OS) refers to a state when there is an imbalance between the production of Reactive Oxygen Species (ROS) or Reactive Nitrogen Species (RNS) and the ability of the cell to counteract their harmful effects through antioxidants. ROS consists of free radicals, such as superoxide (%O2-), hydroxyl radicals (%OH), as well as non-radical intermediates such hydrogen peroxide (H2O2) and singlet oxygen (1O2). RNS includes nitric oxide (NO%), a compound with reduced reactivity, as well as its derivative peroxynitrite (ONOO-). These compounds are generated through enzymatic reactions (such as respiratory chain, phagocytosis, prostaglandin synthesis, and cytochrome P450 system) and non-enzymatic reactions (such as oxygen reacting with organic compounds or ion exposure) that take place in the body. They are primarily produced in peroxisomes, the endoplasmic reticulum, and most notably in mitochondria, as part of normal cellular metabolism.[13]

ROS and RNS have important functions in cellular metabolism and a wide range of biological processes. ROS play a role in activating genes that are involved in processes such as oxygenation, cell differentiation, proliferation, and mitogenic pathways. During pregnancy, decreased levels of ROS stimulate the formation of new blood vessels (angiogenesis) by increasing the activity of a specific transcription factor called E26 *Transformation Specific Oncogene Homolog* 1 (Ets-1). This transcription factor enhances the production of *Vascular Endothelial Growth Factor* (VEGF) and promotes the invasion of *Kruppel-like Factor* 8 (KLF8), which in turn activates matrix metalloproteinase 9 (MMP-9).[4]

ROS stimulate the activation of *Mitogen Activated Protein Kinase* (MAPK) in mitogenic pathways. MAPK has a crucial role in the growth, specialization, and shaping of the placenta. Overstimulation of MAPK by OS can decrease MMP activity and negatively impact trophoblast cell invasion.[14] The overproduction of ROS and RNS is known to have harmful consequences on cellular function.

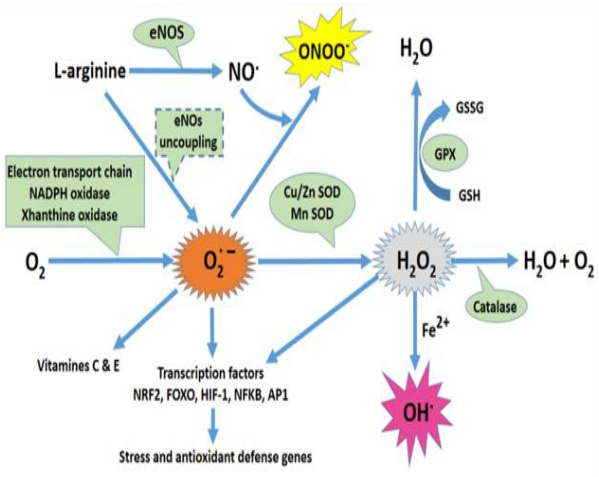

Figure 1. The Role of Oxidative Stress in the Physiopathology of Preeclampsia6

OS can also arise due to an insufficiency of antioxidants.[15] There are two categories of antioxidants: enzymatic and non-enzymatic.

Enzymatic Antioxidants:

- **Superoxide Dismutase (SOD)**: Catalyzes the redox reaction of O2•− to O2 and H2O2.
- **Hemoxygenase (HO-1)**: Plays a role in oxidative stress response.
- **Catalase (CAT)**: Rapidly neutralizes H2O2 by breaking it down into H2O and O2.
- **Glutathione Peroxidase (GPx)**: A selenium (Se)-dependent enzyme crucial for reducing hydrogen and lipid peroxides. It uses glutathione (GSH) as a cofactor to reduce H2O2, resulting in the formation of oxidized glutathione (GSSG).
- **Thioredoxin (TRX)**: An oxidoreductase enzyme that facilitates the reduction of other proteins by forming disulfide bridges between cysteine residues.

Non-Enzymatic Antioxidants:

- **Glutathione (GSH)**: Neutralizes ROS (especially H2O2) and helps maintain vitamin C and E in their reduced forms.
- **Vitamin C and E**: Play significant roles in protecting cells from oxidative damage.
- **Nicotinamide Adenine Dinucleotide (NADH) and Nicotinamide Adenine Dinucleotide Phosphate (NADPH)**: NADPH, in particular, is involved in protecting against ROS by enabling the regeneration of GSH.

Because OS can occur in different cellular compartments and through various mechanisms, the capacity of antioxidants to block ROS or RNS heavily depends on their local production (or import) and the oxidative stress environment.[6] In summary, both enzymatic and non-enzymatic antioxidants play critical roles in maintaining cellular redox balance, thereby protecting against oxidative damage.

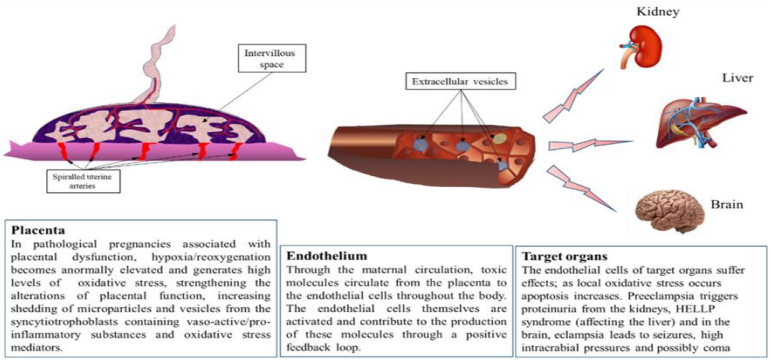

Figure 2. Vesicles Influencing Gene Expression in Maternal Endothelial and Immune Cells[6]

In addition to trophoblasts, OS can originate from endothelial cells in placental tissue, stromal cells of the villi, or immune cells (Hofbauer cells). OS modifies trophoblasts through gene expression. The placenta achieves this by producing extracellular vesicles that enter the maternal circulation and affect various cells (Fig 2). This process increases and occurs in preeclampsia (PE), as recently demonstrated by Verma et al in their study.

SELENIUM

A. SOURCE

Selenium is abundant in seafood, nuts, and liver. Additional sources encompass grains, wheat, and dairy products. In certain geographical places, the level of selenium present in drinking water is not nutritionally significant. The selenium level in plant-based diets is contingent upon the selenium concentration in the soil, as well as other parameters such as soil pH and organic matter. These additional elements influence the plant's capacity to absorb selenium.[16]

Food	Micrograms (mcg) per serving	Percent DV*
Brazil nuts, 1 ounce (6–8 nuts)	544	989
Tuna, yellowfin, cooked, dry heat, 3 ounces	92	167
Halibut, cooked, dry heat, 3 ounces	47	85
Sardines, canned in oil, drained solids with bone, 3 ounces	45	82
Ham, roasted, 3 ounces	42	76
Shrimp, canned, 3 ounces	40	73
Macaroni, enriched, cooked, 1 cup	37	67
Beef steak, bottom round, roasted, 3 ounces	33	60
Turkey, boneless, roasted, 3 ounces	31	56
Beef liver, pan fried, 3 ounces	28	51
Chicken, light meat, roasted, 3 ounces	22	40
Cottage cheese, 1% milkfat, 1 cup	20	36
Rice, brown, long grain, cooked, 1 cup	19	35
Beef, ground, 25% fat, broiled, 3 ounces	18	33
Egg, hard boiled, 1 large	15	27
Bread, whole wheat, 1 slice	13	24
Baked beans, canned, plain or vegetarian, 1 cup	13	24
Oatmeal, regular and quick, unenriched, cooked with water, 1 cup	13	24
Milk, 1% fat, 1 cup	8	15
Yogurt, plain, low fat, 1 cup	8	15
Lentils, boiled, 1 cup	6	11

Figure 3. Selenium Content in Selected Foods[16]
Daily Value (DV): A benchmark used to compare the nutrient content of foods and dietary supplements within the context of a total daily diet.

B. METABOLISM OF SELENIUM

In recent periods, the concept of free radicals causing OS has inspired research into the pathophysiology of diseases for therapeutic purposes. When free radicals enter the body, they tend to trigger chain reactions, potentially leading to sustained and permanent damage. The human body has an endogenous defense system against free radical attacks, which occurs through normal cellular metabolism and inflammation. The use of antioxidants to reduce oxidative stress caused by free radicals in the body has been a focal point of research. Selenium is one of these antioxidants. It helps to neutralize free radicals, thereby preventing the chain reactions and subsequent damage they can cause.

Selenium is incorporated into proteins as the amino acid selenocysteine, which is essential for the synthesis of selenoenzymes such as *Glutathione Peroxidase* (GPx), *Thioredoxin Reductase* (TRX), and selenoprotein P.[12] These selenoenzymes are known for their strong antioxidant effects. There are six groups of GPx enzymes, including GPx, GPx1, GPx3, GPx5, and GPx6. GPx enzymes play a crucial role in protecting cells from oxidative damage by reducing ROS and RNS. They reduce harmful peroxides, such as hydrogen peroxide (H2O2), hydroxyl radicals, nitric oxide, and peroxynitrite, to less reactive forms.

Thioredoxin (TRX), an additional antioxidant enzyme containing selenium, serves as a substrate to sustain the Trx/TrxR system by diminishing the elimination of

detrimental hydrogen peroxide. There are three distinct forms of TRX: *cytosolic* TrxR1, *mitochondrial* TrxR2, and *spermatozoa-specific* TrxR (SpTrxR). Mounting evidence indicates that selenoproteins have a crucial function as antioxidants, safeguarding against detrimental attacks from ROS and RNS.

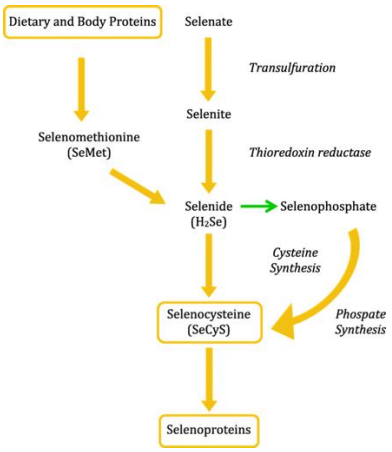

Figure 4. Stages of Selenium Metabolism before Selenocysteine Formation[17]

C. SELENIUM REQUIREMENTS DURING PREGNANCY AND BREESTFEEDING

A study conducted by Rayman et al found that the utilization of Selenium supplements decreased the occurrence of *Pregnancy-induced Hypertension* (PIH) and PE.[18] According to the second study, Se dramatically lowered sFLT-1, or *soluble vascular endothelium growth factor receptor* 1, a biomarker in PE.[19] To lower the risk of PE, it is advisable to increase selenium intake by ingesting more than two servings of fish/seafood per week or by taking Se supplements of 50-100 µg per day, either upon discovering pregnancy or while preparing to get pregnant.[18] The National Institutes of Health (NIH) recommends that pregnant and nursing women should ingest around 60 and 70 µg of selenium (Se) daily. The maximum tolerable dose for individuals over the age of 19, as well as pregnant and breastfeeding women, is 400 µg of Se per day. Exceeding this amount can have harmful consequences on health[16]. The following outlines the guidelines for dosing Se in micrograms (mcg):

Tabel 1. Suggestions for Administering Selenium[20]

Table 1: Recommended Dietary Allowances (RDAs) for Selenium [6]

Age	Male	Female	Pregnancy	Lactation
Birth to 6 months	15 mcg*	15 mcg*		
7–12 months	20 mcg*	20 mcg*		
1–3 years	20 mcg	20 mcg		
4–8 years	30 mcg	30 mcg		
9–13 years	40 mcg	40 mcg		
14–18 years	55 mcg	55 mcg	60 mcg	70 mcg
19–50 years	55 mcg	55 mcg	60 mcg	70 mcg
51+ years	55 mcg	55 mcg		

D. LEVEL OF SELENIUM IN WOMEN WITH PREECLAMSIA

Se is a constituent of several crucial enzymes involved in antioxidant action. Consequently, decreased levels of Se in the bloodstream can lead to several disease processes in PE. The decline in Se levels in pregnant women is a result of the transfer of Se to the developing fetus facilitated by SEPP1 (Plasma Selenoprotein P) through the *apoER2*.[19] Pregnancy exerts strain on Se stocks, which are inadequate in pregnant women to adequately supply the fetus's requirements. Bark et al validated this in a study involving two pregnant mice, where they found two Se transport pathways. Plasma GPx and SEPP1 are transported through uterine fluid (by pinocytosis) in the early to mid stages of pregnancy. However, in the latter half of pregnancy, SEPP1 is transferred to the maternal placenta through the *ApoE2* receptor. During late pregnancy in mice with normal plasma Se levels, the concentrations of selenoprotein P (SEPP1) decline fast. However, following birth, these concentrations increase dramatically.[21]

A study conducted by Rayman et al. involved the division of 230 pregnant women into two distinct groups. One group was administered daily Se supplements of 60 µg, whereas the other group received dummy pills. The treatment commences during the 12th to 14th week of gestation and persists till childbirth. Serum Se levels were measured in women during early pregnancy, specifically in the first trimester and at the 35th week of pregnancy. Furthermore, plasma SEPP1 concentrations

were also assessed after a duration of 35 weeks. The findings demonstrated a considerable increase in blood Se levels among the participants who used Se supplements, whereas the pregnant women in the placebo group saw a notable fall in selenium levels. Women who were taking Se supplements at week 35 showed noticeably higher levels of selenium in their whole blood and SEPP1 concentrations compared to those in the placebo group.[19]

The normal range for Se in pregnant women is not mentioned. The acceptable range for Se levels in the human body, as defined by the National Health Service (NHS) for individuals aged 14 years and older, is 0.66-1.57 µmol/L.[22] In their study, Eze et al conducted a comparison between the average serum Se levels and prevalence in pregnant women with PE and pregnant women without hypertension. The average Se in women with PE was 0.67±0.27µmol/l, which was lower than the average Se in women with normal blood pressure, which was 1.20±0.46µmol/l. The incidence of Se deficiency was higher in women with preeclampsia (n=33, 56.9%) and in those with normal blood pressure (n=10, 17.2%).[23]

DIET DURING PREGNANCY

Maintaining a nutritious diet is highly beneficial for pregnant women. Proper diet is essential to fulfill the increasing requirements during pregnancy. The objective is to achieve a harmonious balance between sufficient nutritious intake to facilitate the growth of the fetus and the maintenance of an optimal body weight.[24]

The significance of pre- and perinatal nutrition in mitigating the likelihood of developing preeclampsia.[25] A diet abundant in fruits, nuts, seeds, legumes, seafood, and vegetable oils offers defense against hypertension diseases.[26] The World Health Organization (WHO) advises consuming at least 400 grams of fruits and vegetables daily to maintain overall health. Pregnant women should adhere to a diet that is abundant in fish. Consuming 8 ounces of mixed seafood per week can lead to an intake of at least 250 mg of DHA+EPA per day. To decrease the likelihood of developing PE, it is advisable to restrict consumption of foods that are rich in fat, salt, and sugar, such as sweetened beverages, as well as to decrease consumption of processed red meat.[25]

CONCLUSION

The blood level of selenium decreases during pregnancy due to hemodilution and its transport to the developing fetus. Given selenium's antioxidant properties, it may be a valuable supplement during gestation to combat increased oxidative stress. Selenium's potential in managing preeclampsia is promising, particularly as a natural adjunct to traditional ROS-lowering therapies. Its ability to enhance oxidative stress breakdown and reduce inflammation complements existing treatments, potentially improving patient outcomes.

However, most research to date has been based on animal studies and in vitro investigations. Therefore, large-scale clinical trials are necessary to validate these findings. Future research should focus on determining optimal dosing, safety, and efficacy in diverse patient populations. Although some clinical trials have shown promise, others have produced conflicting results, highlighting the need for well-designed studies to confirm selenium's therapeutic potential for pregnancy complications and blood pressure control. Integrating selenium with advanced technologies could further enhance its effectiveness. This review encourages continued research to firmly establish selenium as a therapeutic agent for mitigating preeclampsia and improving patient outcomes.

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