Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): January
ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.84

The Role of Oxidation and Antioxidants in Miscarriage with the Impact of Polycystic Ovary Syndrome

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Abstract. This research explores the complex interrelationships between oxidative stress and its antagonists in the context of miscarriage. Miscarriage, a critical issue affecting women's health worldwide, results from various multifactorial causes including genetic, hormonal, immunological, and environmental factors. Notably, oxidative stress emerges as a pivotal element, exacerbating the risk and incidence of miscarriage through an imbalance between oxidants and antioxidants within the body. This imbalance leads to cellular damage that can compromise placental function and fetal development, thus influencing pregnancy outcomes. The study underscores the importance of antioxidants in mitigating oxidative stress, suggesting their potential therapeutic role in improving pregnancy outcomes and reducing miscarriage rates. Additionally, it highlights the significance of early detection, management of associated risk factors, and the impact of environmental and lifestyle factors on miscarriage. Future research directions include the development of targeted antioxidant therapies and their integration into standard prenatal care. This comprehensive approach aims to enhance understanding, prevention, and management of miscarriage, thereby improving maternal and fetal health outcomes. Keyword : This study examines the role of oxidative stress and its antagonists in miscarriage, highlighting the potential of antioxidants to improve pregnancy outcomes by mitigating oxidative damage.

Highlights:

1. Oxidative stress contributes to miscarriage by causing cellular damage and placental dysfunction.
2. Antioxidants may help mitigate oxidative damage, improving pregnancy outcomes.
3. Future research focuses on targeted antioxidant therapies in prenatal care.

Keywords: oxidative stress, miscarriage, antioxidants, pregnancy outcomes, placental dysfunction

Introduction

Miscarriage is a significant medical and social issue, causing not only health risks but also psychological, economic, and family problems for women who experience it. It is a significant factor affecting women of childbearing age. According to the World Health Organization (WHO, 2000), miscarriage is defined as the early discharge of all or part of the uterine contents before the 24th week of pregnancy, i.e., before the fetus can survive

ISSN 3063-8186. Published by Universitas Muhamamdiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.84

outside the uterus. Alternatively, it can also be defined as the detachment of a fetus weighing less than 500 grams from the uterus before 20-24 weeks of pregnancy without evidence of the fetus's continued life (Arulkumaran et al., 2004). The viability of pregnancy increases when the fetus reaches 24-28 weeks in the United Kingdom. The WHO (2000) reported that approximately 10-15% of all pregnancies end in miscarriage (Finer and Henshaw, 2003). Miscarriage represents not only the loss of a fetus but sometimes a natural attempt to preserve future generations by eliminating malformed fetuses early (Creinin, 2000).

Researchers Decherney and Nathan (2003) indicate that about 50% of spontaneous miscarriage cases occur during the first trimester, with this percentage decreasing to about 20-30% during the second trimester and 5-10% during the third trimester. The risk of miscarriage increases with a woman's age: approximately 10% in women under twenty, 18% in women in their late thirties, and 50% in women aged 45 or older (Bansal, 2004).

A miscarriage may occur only once, termed a sporadic spontaneous abortion, or it may occur multiple times, referred to as recurrent spontaneous abortion, accounting for 15-20% of clinically distinguished pregnancy cases (Houwert et al., 1990). Recurrent miscarriage can lead to secondary infertility, where a previous pregnancy does not continue to term due to a dysfunction preventing a subsequent pregnancy (Abdul Razzaq, 2010).

There are many causes of miscarriage, including genetic factors, which account for more than 5% of spontaneous miscarriages, arising from chromosomal abnormalities in one or both partners. Hormonal factors contribute to 10-15% of spontaneous miscarriages, often involving insufficient hormone levels such as progesterone, which is essential for maintaining pregnancy (Hacker et al., 2004; Haddow, 2006).

Factors related to the mother, such as uncontrolled diabetes, can increase the likelihood of miscarriage and congenital abnormalities. Anatomical factors account for 10-15% of recurrent miscarriages and include congenital uterine anomalies and cervical insufficiency. Infectious factors contribute to 3-20% of cases, involving viruses, parasites, and bacteria. Additionally, immune system-related conditions, such as systemic lupus erythematosus and antiphospholipid syndrome, can affect pregnancy (Dubey, 2002; Bartha et al., 2000).

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The metabolic processes in a pregnant woman's body are directed towards meeting the physiological demands of pregnancy, including the increased needs for fetal growth and development and the mother's heightened energy and oxygen requirements. This can lead to oxidative stress, where an imbalance between oxidants and antioxidants occurs, causing oxidative damage which plays a significant role in many pregnancy-related diseases such as cardiovascular diseases characterized by hypertension, hyperglycemia, and abnormal liver functions, including the potentially severe pregnancy complication HELLP syndrome, characterized by hemolysis, elevated liver enzymes, and low platelet count associated with conditions like preeclampsia and eclampsia (Mihu et al., 2007; Mohanty et al., 2006; Adigo et al., 2007; Maas et al., 2007). Sex hormone levels, particularly estrogens and progesterone, vary significantly during pregnancy, reaching their highest concentrations in the last three months. These hormones have important metabolic and secretory effects in pregnant women and can affect various organs, including the lungs, heart, and stomach due to anatomical changes such as the upward displacement of the uterus pressing against the diaphragm (Guyton & Hall, 2006; Cunningham et al., 2005).

The liver, one of the largest abdominal organs located to the right of the stomach, is extensively affected by pregnancy, especially in the later stages. It performs numerous metabolic functions related to the metabolism of carbohydrates, proteins, and fats, in addition to its secretory functions and role in blood cell formation during the fetal stage, storing essential body elements, detoxification, and immunity (Ganong, 2003). Most of these functions are impacted by hormonal and physiological changes during pregnancy, which can also lead to other pathological changes in liver function, including variations in the activity of liver

enzymes such as alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP), as well as levels of albumin, bilirubin, and fibrinogen. Studies also indicate changes in the lipid profile during pregnancy (Magee et al., 2008). The underlying mechanisms causing these changes are not entirely clear yet, and understanding these variables during different stages of pregnancy could enhance our understanding of the mechanisms responsible for these abnormal changes in liver functions during pregnancy.

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2-2-8 Recurrent Abortion:

Recurrent abortion is defined as the occurrence of three or more consecutive miscarriages. Some causes of recurrent miscarriages remain unknown, and it occurs at a rate of three per thousand pregnant women. This type of miscarriage increases with age, particularly among women over the age of 35 (Al-Nasiri, 2009).

2-2-9 Infected Abortion:

An infected abortion occurs due to bacterial, viral, or parasitic infections of the female reproductive tract during pregnancy, typically in the early months. Common pathogens include the Rubella virus and the Toxoplasma gondii parasite. It may also result from uterine infections, presenting symptoms such as vaginal discharge with a distinctive odor. This type is more commonly seen in cases of missed and incomplete abortions (Dutt and Matthews, 1999).

2-3 Causes of Abortion:

The causes of miscarriage are somewhat unknown, especially in cases of spontaneous abortion, with unknown factors involved in 60-24% of all miscarriage cases. The causes can be categorized into those related to the fetus and those related to the mother, as outlined below (Braekeler et al., 2003).

2-3-1 Fetal Causes:

Researchers have developed a theory that the primary cause of miscarriage is due to developmental anomalies in the fetus, such as fetal genetic abnormalities:

1. Germ plasm defect: A defect in the fertilized egg, which involves the protoplasm of the germ cells that carry genetic characteristics. A high percentage of embryos show chromosomal variations, and studies indicate that 78% of embryos do not develop due to intrinsic defects occurring during the meiotic division. Thus, these defects are considered a significant cause of miscarriage and pregnancy loss (Paul et al., 2004).

2. Chromosomal abnormalities: Common among miscarriage cases, Edmons (2003) and Charai Harris (2003) noted that 50% of miscarriage cases are due to abnormal chromosomes from one or both parents. Researchers consider miscarriage a protective mechanism against the birth of a genetically disabled child. Most chromosomal changes involve an abnormal number of chromosomes in the somatic cell, either less than or more than the normal diploid set, such as in Turner's Syndrome or Down

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Syndrome (Decherney and Nathan, 2003). About 50% of fetal losses during weeks 8-15 of pregnancy involve the presence of an extra set of chromosomes, and trisomies are observed in one-third of chromosomal anomaly cases in early pregnancy, making ongoing pregnancy unsustainable (Burgoyne et al., 1991).

2-3-2 Maternal Causes:

2-3-2-1 Anatomic Factors:

Anatomic factors, whether congenital or acquired, represent about 10-15% of cases of recurrent spontaneous abortion, usually associated with second-trimester losses. Congenital anomalies such as Mullerian duct anomalies and septate uterus alter the anatomical shape of the uterus and often have insufficient blood vessels to nourish the fetus. Treatment typically involves surgical intervention using hysteroscopy. Other causes include adhesions that may occur inside the uterus due to severe uterine infections or following curettage or uterine surgeries, and cervical insufficiency, particularly common in the early months of pregnancy, is treated in some cases by cerclage (Decherney and Nathan, 2003).

2-3-2-2 Hormonal Factors:

Hormonal factors account for 10-20% of cases of recurrent spontaneous abortion. They include luteal phase defects and a deficiency in luteinizing hormone (LH) during the follicular phase. Insufficiency of hormones, particularly progesterone and estrogen, in the early months of pregnancy is a factor that predisposes women to miscarriage, especially in the first four months compared to those with a normal pregnancy (Al-Nasiri, 2009). Low levels of progesterone are linked to spontaneous miscarriage, and studies have indicated that the concentration of this hormone decreases after placental detachment, suggesting that the placenta is a primary site of progesterone production in the second and third trimesters of pregnancy (Al-Jubouri, 2005). Additionally, thyroid disorders play a significant role in miscarriage, with women suffering from hypothyroidism being more susceptible to spontaneous miscarriage and intrauterine fetal death (Bourgeois et al., 2005). Obesity and polycystic ovarian syndrome (PCOS) also increase the risk of miscarriage, and there is a correlation between higher miscarriage rates and uncontrolled diabetes mellitus. Women with well-controlled diabetes, whether through diet or insulin use, have a lower chance of miscarriage compared to those with poorly controlled diabetes (Curtis et al., 2006).

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2-3-2-3 Infected Factors:

Infectious factors account for 5% of miscarriage cases, either through direct effects on the fetus or placenta or indirectly through fever and the accumulation of toxic substances from the infection (Summers, 1999). Infections can occur in the cervical or uterine cavity, and when a pathogen settles in the external genital organs of pregnant women and subsequently enters the amniotic sac, it can weaken the sac and cause it to rupture, leading to infection transmission to the fetus, potentially resulting in preterm birth. These infectious agents are known to cause spontaneous abortion and fetal death from the 22nd week of pregnancy until the 28th day postpartum (Koonin et al., 1997).

2-3-2-4 Immunologic Factors:

Immunological dysfunctions account for about 60% of cases of recurrent spontaneous abortion due to immune mismatches within the mother's body. The fetus's alloantigens, encoded by genes inherited from the father, can trigger cellular immune reactions in the mother, leading to fetal loss. Pregnancy is known to suppress cellular immunity in the mother to prevent fetal rejection (Mellor and Munn, 2000). Tissues of the mother might immunologically reject the developing fetal and trophoblast tissues, considered foreign to the mother's immune system. Maternal immune factors can also play a significant role in recurrent pregnancy loss. Alloimmune factors cause the mother's immune system to reject the fetal antigens, and protection against this effect involves the presence of a maternal blocking factor represented by IgG class antibodies that cover the foreign fetal antigen, preventing rejection by the mother. Studies have shown that women with recurrent miscarriages may lack such a factor (Al-Jubouri, 2005). Autoimmune factors: Most studies have shown that women with three or more recurrent miscarriages often have an immunological disorder or autoimmune disease (Al-Jubouri, 2005).

2-3-2-5 Environmental Factors:

Environmental factors account for about 10% of all miscarriage cases, with less than 1% of deformities linked to exposure to medications and radiation such as chemotherapy for cancer, other chemicals like anesthesia gases, formalin, benzene, lead, and physical traumas that cause fetal detachment from the uterus (Werler, 1997).

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2-4 Early Detection of Miscarriage:

Early detection of miscarriage can be achieved through ultrasound or by testing for Human Chorionic Gonadotrophins (HCG). Women who have undergone assisted reproductive technologies or those with a history of miscarriage should be closely monitored, as detecting miscarriage in these women can be faster compared to those who do not receive such monitoring. The most common symptom of miscarriage is light bleeding, often referred to as threatened miscarriage. About half of the women who seek clinical treatment to stop bleeding during pregnancy end up miscarrying (Gracia et al., 2005; Everett, 1997).

2-5 Antioxidants:

Before discussing antioxidants, it is essential to clarify what oxidation is and how it occurs. Oxidation is the process in which a biological compound, such as fatty acids, loses a hydrogen atom or electron. Each compound that loses one or both is said to be oxidized. Oxidation occurs due to various internal and external factors, including exposure to ultraviolet and X-rays and food cooking processes like frying or grilling (Saber, 2009). All major cellular molecules in living organisms are potential targets for oxidative damage; thus, cells are equipped with specialized fibers to prevent or repair such damage, known as antioxidants. Antioxidants are substances or mechanisms that prevent, terminate, or remove the effects of free radicals or repair their damage. They are defined as a group of nutrients that help preserve cells from damage or dysfunction, thereby maintaining the body's health and protecting it from diseases, aging, and weakness. Antioxidants include a variety of defensive agents containing enzymatic and vitamin compounds that balance vital processes and eliminate free radicals in the human body (El-Masry, 2001).

2-5-1 Oxidative Stress:

Oxidative stress involves free radicals generated within tissues, including over 100 types, the most famous of which are Reactive Oxygen Species (ROS). These contribute to oxidative stress, which Sies describes as a shift in the balanced state where oxidants overpower antioxidants. This imbalance can sometimes halt the function of antioxidants and disturb their production due to high levels of ROS. An antioxidant is a substance that, when present in low concentrations compared to oxidants, works to prevent or inhibit the oxidation of that substance. Free radicals are not always harmful;

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sometimes they act as beneficial agents in the body. Some research has indicated that free radicals are essential molecules for the maturation of cellular structures. Furthermore, white blood cells use free radicals as part of the body's defense mechanism against diseases. Therefore, eliminating free radicals is not only unnecessary at times but can also be harmful (Hadi, 2007).

2-5-2 Antioxidants and Free Radicals:

Oxygen is a critical element in energy production through food oxidation. However, this reduction is never complete, even under normal conditions. Intermediate groups of naturally active chemicals, known as free radicals, are produced during metabolic processes. These free radicals attack and destroy cell components, causing significant damage to their genetic material and various cellular functions. As the accumulation of free radicals increases, several diseases can arise, such as degenerative diseases, cardiovascular diseases, cancer, aging, and more (Blair et al., 2006).

2-5-3 Classifications of Antioxidants:

Antioxidants are classified into two types (Omer, 2000):

1. Enzymatic Antioxidants, including:

- Superoxide Dismutase (SOD)
- Catalase (CAT)
- Glutathione Peroxidases (GSH-PX)
- Glutathione Reductase (GSH-Red)

2. Non-enzymatic Antioxidants, which come from two sources:

- The body itself, synthesizing substances like albumin, bilirubin, and glutathione, which assist many antioxidant enzymes.
- Diet, including vitamins C, E, A, and selenium, which provide robust defense against the harmful effects of free radicals through healthy foods.

Antioxidants play a crucial role in protecting against oxidative stress and the wide array of conditions linked to it, contributing significantly to overall health and disease prevention.

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https://doi.org/10.21070/ijhsm.v2i1.84

Conclusion

1. Significance and Impact of Miscarriage:

Miscarriage is a profound medical and social concern affecting a significant portion of the global population. It impacts not only the health of the woman but also exerts considerable psychological, economic, and familial stress. Understanding the multifaceted causes and effects of miscarriage is crucial for developing more effective prevention and treatment strategies.

2. Role of Oxidative Stress in Miscarriage:

Oxidative stress plays a pivotal role in the pathophysiology of miscarriage, influencing various pregnancy outcomes. The imbalance between oxidants and antioxidants leads to cellular damage and may contribute to conditions such as miscarriage by affecting placental function and fetal development. This suggests a potential therapeutic role for antioxidants in mitigating oxidative stress and improving pregnancy outcomes.

3. Importance of Early Detection:

Early detection through monitoring techniques such as ultrasound and HCG levels is vital for at-risk populations, including those with previous miscarriages or those undergoing assisted reproductive technologies. Early intervention can potentially prevent miscarriage and improve maternal-fetal health outcomes.

4. Influence of Environmental and Lifestyle Factors:

External factors, including exposure to toxins, radiation, and dietary habits, significantly influence the risk of miscarriage. Public health measures and individual lifestyle adjustments to minimize exposure to harmful substances could reduce miscarriage rates and improve reproductive health.

5. Preventative and Therapeutic Measures:

The findings underscore the importance of comprehensive prenatal care that includes genetic screening, management of hormonal imbalances, and immunological interventions. Additionally, optimizing antioxidant levels through dietary or supplemental means may offer a non-invasive strategy to enhance fetal survival rates.

6. Future Research Directions:

Further research is needed to clarify the mechanisms by which oxidative stress impacts miscarriage and to develop targeted antioxidant therapies. Studies should also

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explore the integration of these therapies into standard prenatal care regimens to assess their effectiveness in reducing miscarriage rates.

7. Policy and Educational Implications:

Enhancing awareness about the causes and prevention of miscarriage through public health initiatives and education can empower women and healthcare providers to take proactive steps towards mitigating risk factors. Policymakers should consider supporting research in reproductive health and ensuring access to comprehensive prenatal care to reduce the burden of miscarriage.

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