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ISCHEMIA-MODIFIED ALBUMIN (IMA) AS A BIOMARKER OF OXIDATIVE STRESS IN PREGNANCY

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ABSTRAK

Tujuan dari studi ini adalah untuk mengetahui kadar IMA sebagai penanda stres oksidatif yang terjadi pada kehamilan ektopik dan preeklampsia. Metode studi ini adalah dengan melakukan skrining dengan memanfaatkan data sekunder yang diperoleh dari tinjauan literatur yang ditemukan dari jurnal nasional maupun internasional, dengan kata kunci 'Stres Oksidatif' atau 'IMA' dan 'Kehamilan'. Artikel memenuhi kriteria inklusi jika diterbitkan pada jurnal nasional atau internasional dengan topik yang sesuai dengan tujuan penelitian dalam rentang waktu 2014 - 2024, akses teks lengkap, baik dalam Bahasa Inggris maupun Bahasa Indonesia. Kadar serum IMA ditemukan meningkat pada preeklampsia dan kehamilan ektopik dibandingkan dengan kehamilan normal. IMA dapat menjadi biomarker pada penyakit terkait kehamilan khususnya adalah preeklampsia dan kehamilan ektopik. Hasil sensitivitas dan spesifisitas yang lebih tinggi pada preeklampsia dibandingkan kehamilan ektopik menjadikan tes IMA lebih baik digunakan untuk mengidentifikasi preeklampsia dibandingkan kehamilan ektopik.

ABSTRACT

Ischemia-Modified Albumin (Ima) As A Biomarker Of Oxidative Stress In Pregnancy. This study aims to determine IMA levels as a marker of oxidative stress that occurs in ectopic pregnancy and preeclampsia. The method of this study is screening using secondary data obtained from literature searches found in national and international journals, with the keywords 'Oxidative Stress' or 'IMA' and 'Pregnancy'. Articles are included in the inclusion criteria if they are published in national or international journals with topics in accordance with the research objectives in the period 2014 - 2024, full-text access, both in English and Indonesian. It was found that serum IMA levels were increased in preeclampsia and, In comparison to normal pregnancy, ectopic pregnancy. This literature study concludes that IMA can be a biomarker for pregnancy-related diseases, especially preeclampsia and ectopic pregnancy. Higher sensitivity and specificity results in preeclampsia compared to ectopic pregnancy, the IMA test is better used to identify preeclampsia compared to ectopic pregnancy.

INTRODUCTION

Oxidative stress is frequently linked to the underlying mechanisms of various diseases. It refers to an imbalance between free radicals (pro-oxidants) and antioxidants, resulting from a deficiency of antioxidants and an overproduction of free radicals.[1] *Reactive oxygen species* (ROS) are molecules that can generate free radicals because they contain at least one oxygen atom. Oxidative stress has been associated with reproductive problems, including infertility, miscarriage, preeclampsia, and congenital disorders related to diabetes. According to the WHO, 800 women die daily due to childbirth complications. A study conducted at Uganda Hospital found that 27.4% (78/285) of women experienced pregnancy complications. The most common conditions were anemia (10.9%, 31/285), eclampsia (8.1%, 23/285), and abortion (4.9%, 14/285).[2–4]

Pregnancy is known to increase oxidative stress. Various metabolic changes are obtained in normal pregnancy, including increased basal oxygen consumption, because the fetus and placenta take in large amounts of oxygen. Pregnancy growth requires a normal placenta with a sufficient supply of nutrients and oxygen for fetal development. Insufficient blood flow to the placenta can cause hypoxia, which, if reoxygenation occurs, can cause reperfusion, resulting in increased free radical formation and oxidative tissue damage.[5]

Oxidative stress is commonly observed in complicated pregnancies, including ectopic or extrauterine pregnancy. Ectopic or extrauterine pregnancy is a complication that occurs in the early stages of pregnancy, where a fertilized egg attaches outside in a location other than the uterine cavity. Ectopic or extrauterine pregnancy is thought to result from Disrupted embryo transport and changes in the tubal environment, which can lead to premature implantation. Increased oxidative stress affects the tubal environment, causing the epithelial cells in the tube to be replaced by collagen fibers. This process reduces the movement of cilia in the tubes, ultimately slowing down the transport of the fertilized egg.[5,6]

Another complication of pregnancy that is characterized by oxidative stress is preeclampsia. Preeclampsia is a set of symptoms in pregnancy that include hypertension and protein in the urine (≥ 300 mg/24 hours) following the 20th week of pregnancy, most often occurring before the pregnancy reaches its full duration of pregnancy.[7] Preeclampsia is caused by the failure of the spiral artery's vascular remodeling process, resulting in vasoconstriction of the spiral artery, which then leads to blockage of blood flow to the placenta. As a result, hypoxia and ischemia occur in the placenta. Placental cytotoxic factors are then released into the mother's circulation, triggering an inflammatory response and systemic endothelial activation. This condition leads to the formation of free radicals, which can cause oxidative stress in large quantities.[8]

One biomarker that can be used to assess oxidative stress is Ischemia-modified albumin (IMA). IMA is a highly responsive biomarker, and the variant version ceases to maintain its capacity to interact with transition metals when subjected to oxidative damage induced by hypoxia, acidosis, or ischemia. A study by Dogan in 2022 reported that IMA levels may increase during pregnancy, ectopic pregnancy, and preeclampsia.[9] IMA can act as a marker for intrauterine hypoxia and oxidative stress; the two can significantly impair the normal development of trophoblasts in the early stages of pregnancy. In a study by Jaiswar, oxidative stress was found to be elevated in ectopic or extrauterine pregnancy and preeclampsia compared to normal pregnancy. It was proposed that IMA could serve as a biological marker for both ectopic or extrauterine pregnancy and preeclampsia.[9,10] This study aims to assess IMA levels as an indicator of oxidative stress in ectopic or extrauterine pregnancy and preeclampsia.

METHOD

The method used in this *literature review* is to screen secondary data from literature searches in national and international journals, with the keywords 'Oxidative Stress' or 'IMA' and 'Pregnancy'. Articles are included in the inclusion criteria if published in national or international journals with topics by the research objectives in the 2014-2024 period and access to full text, both in English and Indonesian. Figure 1 illustrates the flow chart outlining the article selection process for the review.

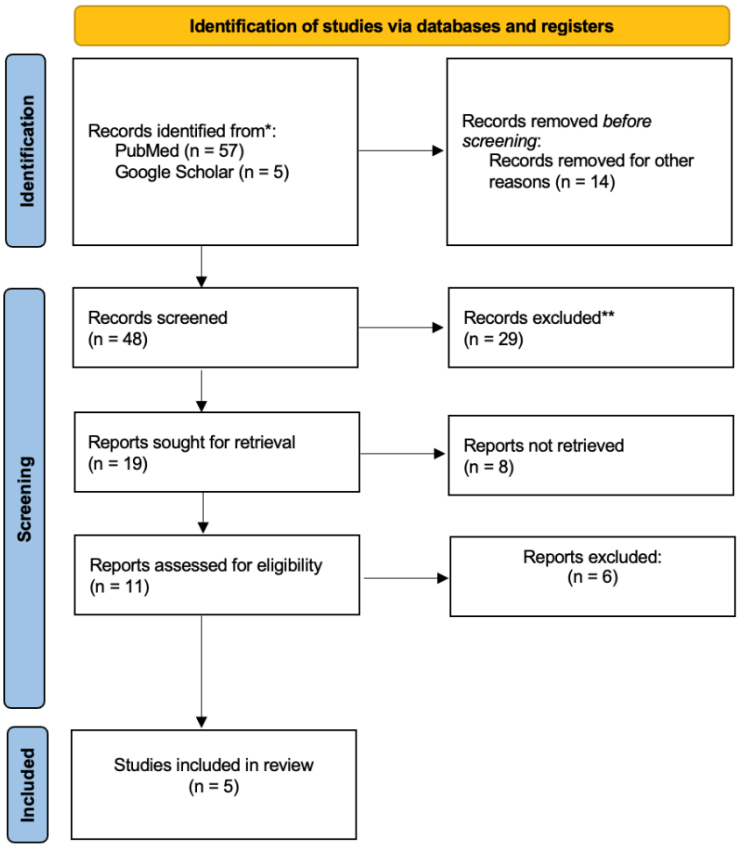

Figure 1. Flow Diagram of Article Selection

A table is created to organize The articles and journals that fulfill the criteria and correspond with the goals of the review, including details such as the author's name, publication year, research title, and key findings. Subsequently, these extracted articles and journals are analyzed, discussed, and used to conclude.

RESULT

The literature search identified five articles that met the criteria for analysis and were included in this literature study. The details retrieved from these five studies are displayed in Table 1 beneath..

Table 1. Findings on Ischemia-Modified Albumin (IMA) in Research As a Biomarker of Oxidative Stress in Pregnancy

Author (years)	Research Title	Relevant Findings
Ureyen, et al. 2022 [11]	Evaluation of Oxidative Stress in Ectopic Pregnancies	This study aims to show the relationship between oxidative stress and ectopic pregnancy. The result of this study is that ectopic pregnancy is associated with oxidative stress, which is characterized by increased IMA levels and decreased thiol levels.
Dogan, et al. 2022[9]	Ischemia-modified albumin (IMA) levels in ectopic pregnancy and early pregnancy loss	This study aims to compare IMA levels in cases of ectopic pregnancy, normal pregnancy, and early miscarriage. The study concludes that IMA is not a reliable biomarker for diagnosing early pregnancy complications.
Bozkaya, et al. 2019[6]	Evaluation of maternal serum ischemia modified albumin and total antioxidant status in ectopic pregnancy	This study aimed to compare IMA levels and total antioxidant status between ectopic and normal pregnancies and to evaluate the potential of IMA as a biomarker for diagnosing ectopic pregnancies. The results showed a significant difference in IMA levels between ectopic and normal pregnancies, indicating that IMA can serve as a biomarker for ectopic pregnancy.
Karasin, et al. 2020[12]	The Role of Ischemia-modified Albumin as a Biomarker in Preeclampsia	This study aimed to compare serum IMA levels between normotensive pregnancies and preeclampsia and to assess their relationship with the severity of the disease. The results indicated that serum IMA levels were elevated in preeclampsia patients compared to those with normal pregnancies.[13] However, no significant correlation correlation was found between IMA levels and the severity of preeclampsia .[12]
Jaiswar, et al. 2022[10]	Association of Maternal Serum Ischemia Modified Albumin (IMA) with Placental Histopathological Changes and Fetomaternal Outcome: A Prospective Case-Control Study in Normotensive and Pre-eclamptic Women	This study aims to compare IMA levels and evaluate changes in placental histopathology between preeclampsia and normal pregnancies. The results of this study were found to have higher IMA levels in preeclampsia compared to normal pregnancy and hypoxic histopathological lesions in the form of corangiosis, fibrin intervilus, and hyalinization.

DISCUSSION

Pregnancy-related oxidative imbalance

Pregnancy is a condition in which the result of conception is implanted in the uterus or another location in the body. During pregnancy, the woman's body undergoes significant changes that affect every physiological system to support fetal development. Pregnancy is linked to elevated oxidative stress caused by a whole-body inflammatory reaction that produces reactive oxygen

species (ROS) in the blood.[7] The primary organ responsible for this is the placenta, which plays a central role in the organ that regulates the condition and is the primary source of ROS during pregnancy. This increase in oxidative stress has the potential to cause tissue damage. However, this can be offset by increased antioxidant synthesis. When oxidative stress exceeds the antioxidant defenses in the placenta, it may cause oxidative damage that extends to other tissues.[14]

Placental development and maturation involve the regulation of trophoblastic invasion, along with the differentiation and proliferation of trophoblasts in the maternal decidua. During the initial stages of pregnancy (8-10 weeks), trophoblast cells are subjected to reduced oxygen levels, where the partial pressure of oxygen (pO2) in the placental lining is approximately 18 mmHg (2.5% O2). As a result, A cellular response is triggered in the uterine lining via hypoxia-inducible factors (HIF-1α and HIF-2α proteins).[7] A low-oxygen environment reduces the regulation of mitochondrial oxygen consumption, which helps prevent teratogenic effects caused by ROS produced by the mitochondria. This decrease in mitochondrial regulation seeks to avoid the harmful developmental consequences of ROS originating from mitochondria.[7] This process results in increased NO formation, which can inhibit trophoblastic apoptosis, thereby facilitating the proliferation, migration, and invasion of trophoblasts extravilate. Although oxidative stress is found to be normal in early pregnancy, it is also found in some pregnancy complications, such as preeclampsia and ectopic pregnancy.[4]

Oxidative Stress In Preeclampsia

Characterized by high blood pressure and proteinuria (≥ 300 mg/24 hours), preeclampsia is a condition related to pregnancy occurring beyond the 20th week of gestation, typically occurring before term.[15] Generally, preeclampsia appears towards the end of pregnancy (gestational age ≥ 34 weeks) and is known as late-onset preeclampsia (PEAL). About 10% of preeclampsia cases occur before 34 weeks of gestation, which is referred to as early-onset preeclampsia (PEAD). Factors that affect the occurrence of preeclampsia include genetics, nutrition, primigravida, education level, and socioeconomic conditions.[16,8]

Preeclampsia is linked to abnormalities in the vascular remodeling of the spiral artery and trophoblast invasion. This condition results from the stiffness of the muscle lining in the spiral artery, causing unstable placental perfusion and Repeated cycles of oxygen deprivation and restoration. These changes markedly disrupt angiogenesis, lead to vascular endothelial damage, lead to cardiovascular issues, and initiate an overactive inflammatory response. Additionally, hypoxia facilitates the transformation of xanthine dehydrogenase into xanthine oxidase, a major source of superoxide production, particularly in cytotrophoblasts, syncytiotrophoblasts, and stromal villus cells. This process impacts placental harm to tissues caused by reactive molecules. In preeclampsia, due to insufficient perfusion, placental ischemia releases syncytiotrophoblastic microvesicles into the maternal bloodstream. These microparticles are elevated in preeclampsia and are linked to the activation of maternal neutrophils, which contribute to endothelial dysfunction.[8]

Free radicals released by decidium cells can cause damage to endothelial cells. Reactive oxygen (ROS) molecules, including hydroxyl radicals and superoxide ions, increase platelet aggregation and convert unsaturated fatty acids on phospholipid membranes into lipid peroxides. The formation of this lipid peroxide makes free radicals more toxic and causes further damage to endothelial cells. During preeclampsia, hypoxia/reoxygenation of the uteroplacental increases oxidative stress, adversely affecting the health of the mother and fetus.[17]

Oxidative Stress In Ectopic Pregnancy

Ectopic pregnancy is a complex state where the embryo implants situated outside the uterine cavity, this can lead to maternal death from hemorrhaging, especially if diagnosed late. The most common site for ectopic pregnancies is the fallopian tubes, although it can also occur in the ovaries, cervix, intraligaments, and abdomen. During a typical pregnancy, fertilization and the initial stages of embryo development occur in the fallopian tubes. The cilia within these tubes help move the embryo toward the uterine cavity, where implantation occurs. The epithelial cells of the fallopian tubes secrete various factors crucial for embryonic development, including growth factors, cytokines, and embryotropic factors.[18,19]

Tubal ectopic pregnancy is thought to arise from impaired embryo transport to the tubes and alterations in the tubal environment that promote early implantation. Oxidative stress is associated with a variety of reproductive complications, including infertility, miscarriage, preeclampsia, fetal growth retardation, and premature labor. Due to increased oxidative stress, the tubal environment can change, potentially replacing tubal epithelial cells with collagen fibers, causing impaired cilia movement and smooth muscle contraction. This can adversely affect embryo transport. In addition, the accumulation of ROS interferes with the embryo's development and survival, so it can potentially cause implantation outside the uterus, such as in the fallopian tubes.[20] Furthermore, it has been found that the abnormal formation of nitrous oxide isoforms by synthase can decrease the activity of tubal cilia and smooth muscle contraction, which may interfere with embryo transfer, contributing to tubal ectopic pregnancy.[21]

IMA Biomarkers

From the explanation above, it can be said that oxidative stress can cause pregnancy complications such as preeclampsia and ectopic pregnancy. These conditions promote ischemic and hypoxic states in the placenta, further enhancing the production of IMA, that are dangerous for the fetus and mother. Therefore, examinations are needed to diagnose preeclampsia and ectopic pregnancy early. With the discovery of various biomarkers to detect oxidative stress in pregnancy, it is possible to diagnose early and as an intervention for complications that will occur in the future. Ischemia-modified albumin (IMA) is one of the biomarkers tested through several studies to detect oxidative stress due to ischemia.[22] IMA is a protein that increases in plasma due to oxidative stress, making it a valuable marker for detecting oxidative stress.[23] Oxidative stress initiates systemic inflammation and endothelial dysfunction, causing ischemia and hypoxia, stimulating the production of reactive oxygen species (ROS) and free radicals. These reactive molecules oxidize and modify the structure of the N-terminal region of albumin, impairing its ability to bind transition metals such as cobalt, a key feature of IMA.

A study conducted by Eda Ureyen in 2022 identified oxidative stress using biomarkers thiol and IMA. The study was conducted on 31 pregnant patients aged 18-45 years at 5-8 weeks gestation who were diagnosed with tubal ectopic pregnancy. The blood sample method was used for the research subjects, which was carried out through clinical chemical analysis. Thiol levels are significantly lower, while IMA levels are notably higher in cases of ectopic pregnancy.[24]

These findings suggest that ectopic pregnancy may be linked to increased oxidative stress, particularly in the early stages of pregnancy when an ectopic pregnancy is suspected.[11] Another study conducted by Dogan in 2022 on 91 pregnant women with a gestational age of 5-6 weeks who were grouped into three groups: the healthy pregnancy group, the ectopic pregnancy group, and the abortion group or treated for dilation and curettage. This study collected participants' blood

samples to measure IMA levels using a double antibody sandwich ELISA kit. This study showed no significant difference in IMA levels among the three groups, which did not support IMA as a reliable biomarker for pregnancy complications. This may be attributed to the small number of cases and the inclusion criteria, which only covered the first 5-6 weeks of pregnancy. A limitation of the study was the small sample, so additional research with more participants is necessary to confirm these findings. The study concluded that IMA could not definitively differentiate between potential pregnancy failure, ectopic pregnancy, or normal pregnancy, particularly in the first five to six weeks of pregnancy.[9]

Study on 38 women with ectopic pregnancies and 42 women with normal pregnancies.[17] Blood samples were collected to assess serum IMA levels using an albumin-cobalt binding test, employing the rapid calorimetry detection method to evaluate the decrease in cobalt-binding capacity to albumin.[22] This study's results showed no statistically significant difference between ectopic pregnancies and normal pregnancies in terms of age, body mass index (BMI), gravidity, parity, and the occurrence of spontaneous abortion.[6] A notable difference was found in the levels of IMA and, A-IMA and IOS between ectopic and normal pregnancies. The increase in IMA levels is attributed to albumin modification caused by tive stress, which decreases the ability to bind cobalt.[6] Although further research is needed, the study concluded that IMA could serve as a diagnostic marker for ectopic pregnancy. A study involving 90 pregnant women aged 18-45 years. IMA serum concentrations were assessed using an enzyme-linked immunosorbent assay (ELISA) in (group 1) 30 women with preeclampsia symptoms of severe disease, (group 2) 30 women with preeclampsia, and (group 3) 30 women with normotusia pregnancy. The study results indicated that the IMA level was markedly reduced in individuals with normal blood pressure than in the other two groups. Based on the IMA values, a considerable difference was found in correlation between the preeclampsia group and healthy pregnant women. However, IMA levels do not correlate with disease severity. One of the reasons is that preeclampsia is multifactorial, and the number of research subjects is limited. The study concludes that the increased concentration of IMA in serum suggests that the measurement of this biomarker may be valuable for tracking pregnancy and detecting the onset of preeclampsia.[12]

Another study discussed the relationship between maternal IMA levels and placental histopathological changes and fetomaternal outcomes in normotensive and preeclampsia women. This study was conducted on 80 pregnant women with a gestational age between 34 and 40 weeks, divided into two groups. The group consisted of 40 pregnant women diagnosed with preeclampsia, while the control group included 40 normotensive pregnant women.[10] IMA levels were analyzed using blood samples from patients, measured with the Sun Red-1043 (SB) biotechnology ELISA kit, which employs a quantitative sandwich enzyme immunoassay technique. The results were then compared between both groups regarding systolic and diastolic blood pressure, proteinuria, liver and kidney function, serum LDH, uric acid, IMA levels, fetomaternal outcomes, and changes in placental histopathology.[25] The results revealed that, in the preeclampsia group, the average serum IMA levels were notably elevated than in the normotensive group. Higher IMA levels were strongly linked with an increased incidence of preterm birth, birth weight ≤ 2 kg, and histopathological lesions, including hypoxia, chorangiosis, fibrin intervillous deposits, and hyalinization. Chorangiosis is a vascular alteration in the terminal chorionic villi of the placenta caused by prolonged hypoxia in placental tissue, often seen in cases of intrauterine growth restriction (IUGR), diabetes, and preeclampsia.[10] The study concluded that measuring serum IMA levels in early pregnancy could help

predict preeclampsia and potentially prevent complications related to severe preeclampsia in the future.[10,26]

The five articles' main result is that Ischemia Modified Albumin (IMA) holds significant potential as a biomarker for detecting oxidative stress during pregnancy. In conditions such as preeclampsia and ectopic pregnancy, serum IMA levels are elevated compared to normal pregnancy. While the serum IMA test is commonly recognized as a clinical marker for myocardial infarction, it has been found that non-cardiac diseases, including pregnancy and pregnancy-related conditions, can also lead to increased IMA levels.[6] Elevated IMA levels in pregnancies affected by fetal growth restrictions, indicating its association with placental insufficiency and fetal hypoxia. These findings support early identification of maternal serum IMA levels in pregnancy, which would be highly beneficial in detecting cases for prompt intervention. This, in turn, could help prevent co-morbidities related to the condition of the mother and fetus.[27] In addition, it was found that the serum IMA test had high sensitivity and specificity to identify preeclampsia (sensitivity of 65% and specificity of 87.5%) compared to ectopic pregnancy.[23]

CONCLUSION

Ischemia Modified Albumin (IMA) is a biomarker used to indicate that can be used to signal oxidative stress, being a modified form of albumin that loses the ability to bind to transition metals when exposed to oxidative stress due to hypoxia, acidosis, or ischemia. IMA can be a marker for intrauterine hypoxia and oxidative stress, which can inhibit the development of physiological trophoblasts in early pregnancy. This literature review concluded that IMA could serve as a promising future biomarker for monitoring pregnancies, particularly the development and severity of preeclampsia and ectopic pregnancy. With higher sensitivity and specificity results in preeclampsia compared to ectopic pregnancy, the IMA test is better used to identify preeclampsia than ectopic pregnancy. This could enable earlier diagnosis and intervention in preeclampsia cases, helping to optimize outcomes for both the mother and fetus.

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