ICASH-A058

# UPDATE: METABOLIC DISORDERS OF PREECLAMPSIA A REVIEW

**Dian Aprilia Damayanti*, Mardiyono Mardiyono**

*Master of Applied Science in Midwifery, Poltekkes Kemenkes Semarang, Indonesia*

*Corresponding author email: apriliavalid229@gmail.com

**ABSTRACT**

***Background:*** *Preeclampsia is one of the contributors to the increased maternal morbidity and mortality rates in Indonesia. One of the disorders caused by the preeclampsia is metabolic disorders. The purpose of this study is to provide an overview of metabolic disorders that accompany preeclampsia.*
***Methods:*** *This was a literature review using electronic databases Science Direct and PubMed. Keywords used in searching literature were 'preeclampsia' and 'metabolism disorder of preeclampsia' with the year limit between 2010 and 2018. Articles published in English was chosen in this study.*
***Results:*** *The search found 3,823 articles, of which 14 articles were included in this study. Metabolic disorders that happened in the group of preeclampsia were higher RDW (Red blood cell distribution width), MTT (Biomarker), ADA (adenosine deaminase), CA-125 serum, triglycerides (TG), Angiotensin, cytokinin, CEC (Circulating endothelial cells), lipoprotein and cholesterol. Meanwhile, studies also found that preeclampsia caused the lower selenium serum, aromatase, and thiol-disulphide in the body.*
***Conclusion:*** *Preeclampsia proved causing the disorders of metabolic, mostly in the form of inflammation, endothelial cell damage and oxidative stress. Potential targets are needed for treatment of metabolic disorders in preeclampsia group both medically and non-medically especially for the lipid levels in preeclampsia.*

***Keywords:*** *Preeclampsia, metabolic disorders*

## INTRODUCTION

Pregnancy can be considered as a phase that is vulnerable to certain complications that can interfere with the health in pregnancy, one of which is preeclampsia. Preeclampsia is one of the contributors to the increased mortality and morbidity rates in Indonesia. Preeclampsia can be considered as a complex symptom so that the pathogenesis is unknown. Various sources explain that preeclampsia is caused by interference with placentation during early pregnancy which then causes progressive inflammation and endothelial cell damage [1]. Endothelial dysfunction will cause the release of a cytokine that is of a nature vasoconstrictor resulting in disruption of the production of vasodilate substances. this is the originator of the emergence of trias of symptoms of preeclampsia, namely hypertension, edema and proteinuria. Preeclampsia is a major complication in the mother, both acute and chronic (chronic), especially due to uncontrolled blood pressure [2]. Based on a meta-analysis conducted by Bellamy et al, the results show that preeclampsia in women will be increased risk of hypertension, heart disease, stroke, and venous thromboembolism [2].

There are several trigger factors for preeclampsia, include obesity, mothers with a history of hypertension, especially in primigravida mothers (first pregnancy) and in mothers with multiple pregnancies [3]. In developing countries, the effect of preeclampsia on pregnancy can reach 3-7% where

preeclampsia is diagnosed based on high blood pressure and proteinuria. Preeclampsia is a major cause of premature birth and also the birth of babies with low birth weight [4].

In the journal of Elizabeth Phipps (2016), it explains that the pathogenesis of preeclampsia is related to angiogenic factors, the pathway of heme oxygenase, the pathway of hydrogen sulfide, oxidative stress, nitric oxide, and protein [5]. According to other literature, several mechanisms are associated with the development of multifactorial syndrome in preeclampsia, including changes during placentation [6], oxidative stress [7], inflammatory responses [8], thrombosis, activation of the renin-angiotensin-aldosterone system [9] and endothelial dysfunction caused by changes in angiogenic profiles [10].

The pathogenesis of preeclampsia may also occur due to changes in the metabolism of PUFAs (polyunsaturated fatty acids) and lipoxin deficiencies, resolvins, protectins, maresins and nitrolipids. This implies that the administration of PUFA (polyunsaturated fatty acids), lipoxins, resolvins, protectins, maresin and nitrolipids can prevent and improve the condition of pre-eclampsia [11].

But at present, the causes of preeclampsia have not been clearly explained, but many say that it is likely the cause of placental insufficiency due to maternal blood vessels that do not work adequately [12]. This causes a complex process where in the circulation will contain cytotoxic factors [13].

The hypoperfusion of placenta is associated with an imbalance and complication in angiogenesis, vascular endothelial and cardiovascular especially inflammatory response. Oxidative stress will increase oxidative because uteroplacental hypoperfusion [14]. Common clinical symptoms in preeclamptic women can include vascular dysfunction in the mother, activation of the immune system that is chronic, kidney dysfunction, and intrauterine growth disorders (IUGR). This requires treatment because if it is not managed properly, preeclampsia can cause seizures in the mother, stroke, work failure of various organs, and death [1].

Within a year, there are around 63,000 cases of maternal death and 500,000 cases of infant mortality caused by preeclampsia where there are no action criteria for early diagnosis established in preeclampsia and there is no cure [15]. Changes that occur in placental oxygenation caused by the failure of spiral artery transformation are related of preeclampsia occurrence. New findings suggest that preeclampsia begins with imbalance factor in antiangiogenic [16].

Maternal systemic vascular dysfunction in preeclamptic women is a major feature that occurs and plays a role in increasing any problem such us peripheral vascular resistance, hypertension, and also proteinuria [17]. The mechanism of systemic vascular dysfunction in mothers with preeclampsia can include imbalances in the constrictor process and dilators in vascular cells, hyper-responsiveness to constrictor stimulus, reduce dilation based on the endothelium, to the occurrence of oxidative stress [18].

Many Journal have shown that related between circulatory and maternal endothelium factors contribute significantly to make vascular dysfunction. These circulation factors originate in part from the placenta, providing a relationship between the placenta and maternal vascular dysfunction [19]. The mother's will give a response depend on vascular blood vessel condition of the and will be very dangerous for the mother [18].

The diagnosis of preeclampsia is clinical and require proper examination. In the ACOG, establishing a diagnosis of preeclampsia requires a blood pressure check, wherein the blood pressure test results of 140/90 mmHg at 2 examinations are accompanied by the examination of urinary protein excretion with a yield of 300 mg/day. People can do laboratory tests for the liver, urine for protein detection and creatinine testing can help identify the extent of organ damage but are not specific in cases of preeclampsia [20].

Hyperuricemia is also one of the symptoms of preeclampsia which is more common in women with preeclampsia compared to normotensive pregnant women. Hyperuricemia has also been used as a diagnostic to help predict harmful effects in cases of preeclampsia [21].

Therefore, it is very important to identify the risk factors and diagnosis of preeclampsia so that it supports the results of effective treatment including prevention of complications during pregnancy. Other examinations are related to platelet counts, measurements of liver enzymes, evaluation of proteinuria, blood pressure, monitoring of weight gain, kidney analysis, and pulmonary function, and assessment of previous pregnancy history (eg premature labor, LBW) [22].

Endothelial dysfunction is strongly associated with preeclampsia. there are many effects caused by endothelial dysfunction, one of which is changes in lipid levels in preeclampsia. With a variety of complex pathogenesis in preeclampsia, further research is needed to produce treatment and prevention of preeclampsia, especially for lipid levels.

## RESEARCH METHODS

### *Searching Strategy*

Articles for this research is done by searching in the Science Direct and PubMed databases. Only articles that contain full text will be included in this study. Search is carried out by entering keywords namely "Preeclampsia" and "Metabolism Disorder of Preeclampsia" with the year limit between 2010-2018. There are 3823 studies related to "Preeclampsia" and "Metabolism Disorder of Preeclampsia". The scopes of this study here which limit only to the research study.

### *Inclusion and Exclusion*

The inclusion criteria were English-language articles; samples in the form of mice and pregnant women; type of case report research. While the exclusion criteria in this study are articles not in English; articles in the form of a thesis or thesis; book section; conference abstract; and also incomplete journals.

### *Data Extraction*

Searching for research articles was conducted on March 4, 2019 to March 9, 2019. The author extracted research articles obtained to be adjusted based on inclusion criteria and exclusion criteria, and detected duplication of research articles. The results of the extraction of research articles are written in the form of tables containing the article title, author's name, year, sample, and intervention.

## RESULTS

Searching for research articles through the Science Direct and PubMed databases received 3823 journals in English with a range of time between 2010-2018. In Science Direct there were 2414 journals and 1409 journals were found in PubMed. Furthermore, the articles are filtered by title, abstract, and keywords and reviewed based on the full text. Then after screening the article, 72 journals were related to *metabolic disorders of preeclampsia* and only 14 articles about research related to *metabolic disorders of preeclampsia.* The selected articles are shown in Table 1.

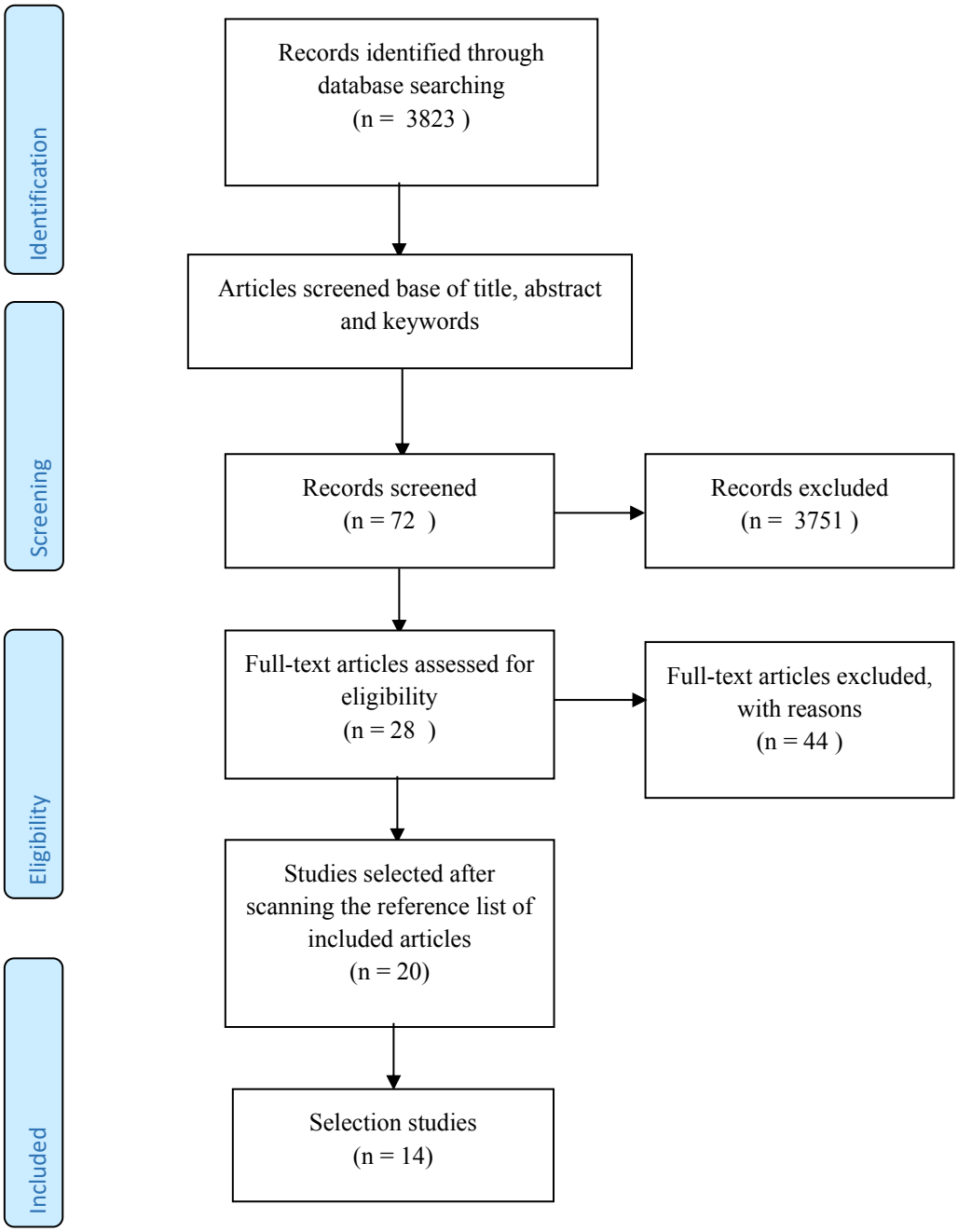


Figure 1. PRISMA Flow Diagram

Table 1. Summary of Selected Study

| Authors' | Source | Methods | Variables | Result |
|---|---|---|---|---|
| Zehra Vural Yılmaz, Elif Yılmaz, Tuncay Küçüközkan (2016) | Elsevier | Case-control | 1. *Preeclampsia*<br>2. Red blood cell distribution width | The RDW value (Red blood cell distribution width) significantly increases in preeclampsia. |
| Nadia Berkane, Philippe Liere, Guillaume Lefevre (2018) | PubMed | Randomized Trial | 1. *Preeclampsia*<br>2. Abnormal steroidogenesis and aromatase activity | Estrone/androstenedione ratio, pregnenolone sulfate and aromatase expression in preeclampsia have decreased. |
| Patrícia Nessralla Alpoim, Luiza Oliveira Perucci (2018) | Elsevier | Case-control | 1. *Preeclampsia*<br>2. Oxidative stress markers and thrombomodulin plasma levels | Level MTT (biomarkers) were higher in severe preeclampsia than in pregnancy normotensive. |
| Vanessa S. Giorgi, Steven S. Witkin, Camila F. Bannwart-Castro (2016) | Elsevier | Case-Control | 1. *Preeclampsia*<br>2. adenosine deaminase activity | ADA level (adenosine deaminase) has increased in the preeclampsia group. |
| Md. Mahodul Haque, Md. Mizanur Rahman Moghal, Md. Shahid Sarwar (2016) | Elsevier | Case-Control | 1. *Preeclampsia*<br>2. Serum selenium concentration | The average concentration of selenium serum in preeclamptic patients has decreased. |
| Erbil Karaman, Yasemin Karaman, _Ismet Alkıs_, Agahan Han, Gokhan Yildirim, Hasan Cemal Ark (2014) | Elsevier | Case-Control | 1. *Pre-eclampsia*<br>2. *maternal serum* | level of CA-125 (serum concentrations of cancer antigen-125) significantly higher in the preeclampsia group. |
| Pardis Keshavarz, B. Fatemeh Nobakht M., Seyed Reza Mirhafez (2017) | PubMed | Case-Control | 1. *Preeclampsia*<br>2. Lipid Profile, Zinc and Copper Levels and Superoxide Dismutase Activities. | Triglyceride Levels (TG) and SOD (superoxide dismutase) in plasma activity increased significantly but level of Zn and Cu significantly reduced. |
| Paula Rosas, Cecilia Tufiño, Bracho Ismael Valdes, Rosa A. Bobadilla Lugo (2017) | Elsevier | Experiment model | 1. *Preeclampsia*<br>2. *Angiotensin II* | Rat with preeclampsia have a significant increase in blood pressure. |
| Hilal Uslu Yuvac, Nermin Akdemir, Mehmet Suhha Bostanc (2016) | Elsevier | Case-Control | 1. *Preeclampsia*<br>2. level of thiol-disulfhide homeostasis | The original thiol count and total thiol in the severe preeclampsia group were found lower significantly. |
| Ifeoma Udenze, Casimir Amadi, Nicholas Awolola, Christian Chigozie Makwe (2015) | PubMed | Case-Control | 1. *Preeclampsia*<br>2. Cytokines | There is a significant correlation between CRP (C reactive protein) with systolic blood pressure, diastolic blood pressure, |

| Authors' | Source | Methods | Variables | Result |
|---|---|---|---|---|
| | | | | gout AST and ALP in preeclampsia. |
| Nick Anim-Nyame, Anshuman Ghosh, Nick Freestone, and Francesca IF Arrigoni (2015) | PubMed | Case-Control | 1. *Preeclampsia*<br>2. insulin resistance and circulating endothelial cells The | amount of CEC (Circulating endothelial cells) increases significantly in pre-eclampsia compared to normal pregnancy. |
| Yan-Ping Lin, Cai-Lin Xu, Kui-Sheng Lin (2018) | PubMed | Case-Control | 1. *Preeclampsia*<br>2. adipocyte fatty acids, proteins, glucolipid metabolism | Serum A -FABP, FINS, TG, TC, HOMA-IR, and A-FABP placenta were significantly higher in preeclamptic patients and HDL levels were clearly lower than in the control group. |
| Christine Contini, Martin Jansen, Brigitte König (2018) | PubMed | Case Control | 1. *Preeclampsia*<br>2. *Lipoprotein* | Pure elimination of Apolipoprotein B and plasma lipids is lower than theoretically estimated. |
| Lucia Maria Procopciuc, Gabriela Caracostea (2017) | PubMed | Case-Control | 1. *Preeclampsia*<br>2. *Lipid profile* | Cholesterol in preeclampsia is significantly higher, lower HDL levels. |

From the description, we found various changes that occur in cases of preeclampsia, including : RDW (Red blood cell distribution width), aromatase, MTT (Biomarker), ADA (adenosine deaminase), selenium serum, serum CA-125, triglycerides (TG) , Angiotensin, thiol-disulphide, cytokinin, CEC (Circulating endothelial cells), Serum A-FABP, FINS, TG, TC, HOMA-IR, and A-FABP placenta, lipoprotein and cholesterol. Some of these studies, obtained several studies that describe lipid levels in preeclampsia. There are differences in results on lipid levels where there are researchers who explains that lipid levels in preeclampsia become low and other studies declared lipid levels in preeclampsia increased.

## DISCUSSION

Many interpret that preeclampsia is a "disease theory" where it is intended that preeclampsia has a "two-stage model". The initial stage is the asymptomatic stage, characterized by placental formation and abnormal release of placental factors into the mother's circulation. The second stage is a symptom characterized by hypertension and proteinuria which results in angiospasm in the brain resulting in eclampsia/seizures [23]. Until now, effective facilities in the diagnosis and prediction of preeclampsia are still very lacking so that the therapy given has not been effective. If left untreated, preeclampsia can be life-threatening and may develop into eclampsia with complications of HELLP Syndrome (Increased liver enzymes, hemolysis, and low platelets), placental abruption, acute renal failure and pulmonary edema [24]. Several studies were conducted with the aim of describing various metabolic disorders in preeclampsia.

Research conducted by Zehra Vural (2016) shows that there is a significant relationship between *Red blood cell distribution width (RDW)* and also preeclampsia. Mothers with preeclampsia will have a higher *RDW* compared to women with normal blood pressure. *RDW is* described as having an association with inflammation and oxidative stress where the higher the value of *RDW*, the more likely the level of inflammation to be that can describe the condition of preeclampsia. Because inflammation occurs, preeclampsia will release cytokines that interfere with the maturation of red blood cells.

Therefore, immature red blood cells enter the maternal circulation. The study hopes for further studies with large samples to understand the role of the *RDW* against preeclampsia [25].

Research conducted by Nadia Barkane (2018) explained that angiogenic factors, especially the concentration of sFlt1 (soluble fms-like tyrosine kinase-1) in preeclampsia were significantly higher compared to the control group. While for PIGF concentration (placental growth factor) has a very low value in preeclamptic women. For estrogen concentrations, preeclamptic women have low levels of E1 (Estrone) and E2 (estradiol) compared to other group. The same was shown in the levels of pregnenolone into the estrogen precursors androstenedione (Δ4-ADIONE) which was found to be lower in women with preeclampsia. Other results also showed that mothers with preeclampsia had a much higher level of 20α-dihydroprogesterone (20α-DHP) and 20α-DHP / progesterone ratio than the control group. Whereas at the level of Pregnenolone sulfate, women with preeclampsia have low levels. In addition, it was also found that aromatase expression decreased in the preeclampsia group. The study expects further research to produce new strategies in the treatment of preeclampsia [26].

Research conducted by Patricia (2018) explains that plasma MTT levels (3- (4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide) are higher in women with preeclampsia than mothers with normal blood pressure. There is a positive correlation between plasma MTT levels (3- (4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide), hemoglobin levels and hematocrit levels. There is a negative correlation between MTT (3- (4,5-dimethylthiazol-2-yl) -2,5-diphenyltetrazolium bromide) and total bilirubin levels. TBARs (thiobarbituric acid reactive substances) tests have been widely used to detect and measure lipid peroxidation where oxidative stress in pregnancy shows that lipid peroxide has increased. This study expects further research on oxidative stress and endothelial lesions in evaluating the pathogenesis of preeclampsia [27].

Research conducted by Vanessa (2016) found that ADA (adenosine deaminase activity) levels were higher in preeclamptic women compared with pregnant women with normal tension and non-pregnant mothers. Adenosine deaminase (ADA) is an enzyme that can reduce/reduce the level of extracellular adenosine level by catalyzing hydrolytic deamination into inosine. In women with preeclampsia also experience an increase in serum uric acid levels which is associated with increased proinflammatory production of cytokines by peripheral blood mononuclear cells. Other results also show that there is a positive correlation between ADA (adenosine deaminase activity) activity and uric acid levels in preeclampsia. Furthermore, ADA and hyperuricemia have a close relationship in preeclampsia where this occurs because of the circulation of adenosine increases. ADA (adenosine deaminase activity) also has a positive correlation with an increase in NF-jB levels (Nuclear transcription factor kappa B) and proinflammatory cytokine production by peripheral blood mononuclear cells in preeclamptic women where this results from an increase in anti-inflammatory adenosine. It can be concluded that adenosine by ADA and the accumulation of uric acid play a role in increasing systemic inflammation which is a characteristic response in mothers with preeclampsia. The relationship between increased serum ADA concentration, increased production of pro-inflammatory cytokines and hyperuricemia suggests that ADA plays a role in systemic inflammation that damages the response in preeclamptic women [28].

The study conducted by Mahmodul Haque (2015) found that serum selenium levels in preeclampsia were significantly lower than for pregnant women with normal tension [29]. Superoxide reacts with polyunsaturated fatty acids and produces lipid peroxides where lipid peroxide will increase thromboxane synthesis by stimulating prostaglandin to inhibit prostate-clinical synthesis by inhibiting prostacyclin synthase. Thromboxane is a powerful vasoconstrictor and platelet aggregation stimulator, while prostacyclin inhibits platelet aggregation. The imbalance between thromboxane and prostacyclin causes an increase in blood pressure [30]. Peroxynitrite is a substance that oxidizes and considered as a potential nitrate produced in vivo from superoxide and nitric oxide to the endothelium [31]. Peroxynitrite levels will be significantly higher in preeclampsia compared with normotensive pregnant women [32]. During preeclampsia, different types of reactive oxygen such as nitric oxide (NO, superoxide ($O_2^-$), hydrogen peroxide ($H_2O_2$), hydroxyl radicals (OH), and peroxynitrite ($ONOO^-$) increase substantially and

antioxidants decrease [33] Decreased selenium levels in preeclamptic women can lead to the functioning of seleno-proteins and glutathione peroxidases where they will cause damage to the endothelium more quickly [34]. This study recommends further studies with selenium supplementation in preeclamptic patients to determine the effectiveness of selenium in preeclampsia and to regulate daily selenium administration [29].

Research conducted by Erbil Karaman (2014) found that serum CA-125 (cancer antigen-125) levels were very high in women with preeclampsia compared with normotensive pregnant women. Serum CA-125 levels in preeclampsia have a positive correlation of proteinuric and also blood pressure (systole and diastole). This study explains that a significant increase in serum CA-125 levels in preeclampsia is a result of ascites formation resulting from decreased albumin levels [35].

Research conducted by Pardis (2017) found that preeclampsia had triglyceride (TG) and SOD (superoxide dismutase) levels in plasma activity experienced increase while Zn and Cu decreased significantly. Increased levels (superoxide dismutase) are considered as a mechanism of antioxidant protection against OS (oxidative stress) so it was concluded that OS (Oxidative Strees) plays a role in preeclampsia. This study also explains that there is a relationship between changes in serum lipid profile in preeclampsia where these changes cause a decrease in prostacyclin/thromboxane A2 (PGI2 / TXA2) [36]. Changing prostaglandin levels can stimulate an increase in lipid peroxidation resulting in oxidative stress in preeclampsia. This study suggests research on lipid peroxidation in preeclampsia, fat peroxidation in pregnancy, antioxidant therapy, perhaps with a combination of omega-3 fatty acids, may be useful in shifting the balance of thromboxane-prostacyclin and maintaining the overall integrity of vascular endothelium [37]. Other research by Paula (2017) found that fetoplacental ischemia can occur so that Angiotensin II causes hypertension and hyperglycemia that occurs in mid-pregnancy [38].

Research conducted by Hilal Uslu (2016) explained that serum native thiol (-SH) and total serum thiol (-SS + -SH) were lower in women with severe preeclampsia compared with mild preeclampsia. Whereas Serum disulfide (-SS) was significantly lower in severe preeclampsia [39]. This research is in line with the results of the study of Llurba et al. Where the results showed that serum thiol levels in preeclampsia were significantly lower than controls [40]. Preeclampsia will have an effect on oxidative damage where thiol is the main component of serum. Thiol levels that exist in the mother can show the severity of preeclampsia but need to study with a larger sample to confirm.

Research conducted by Ifeoma Udenze (2015) found that there were statistically significant differences between mothers with preeclampsia and normotensive mothers on the results of systolic blood pressure, diastolic blood pressure, uric acid, AST (aspartate aminotransferase), ALP (alkaline phosphatase), creatinine, GGT (gamma glutamyl transferase), IL 6 (Interleukin 6), CRP (C reactive protein) and TNF α (tumor necrosis factor alpha. explains that there is a correlation between CRP (C reactive protein) with systolic blood pressure, diastolic blood pressure, uric acid, AST (aspartate aminotransferase), and ALP (alkaline phosphatase) [41]. In cases of preeclampsia, placental ischemia can contribute to endothelial dysfunction by increasing synthesis of IL6, TNF 5 and IL8 [42]. Research conducted by Nick Anim-Nyame (2014) get results that Circulating endothelial cells (CEC) and IR (Insulin Resistance) have increased in preeclampsia compared with normotensive mothers [43]. With the increase in Circulating endothelial cells (CEC), there will also be an increase in endothelial dysfunction [44]. Hyperglycemia causes endothelial dysfunction in the state of IR (Insulin Resistance) through oxidative stress [43].

The study conducted by Yan-Ping (2018) found that preeclampsia patients had adipocyte fatty-acid binding protein levels ( A-FABP) is high and the A-FABP level is correlated with IR (insulin resistance) and glucolipid metabolic index. High levels of A-FABP can cause functional disturbances in vascular endothelial cells and will worsen preeclampsia by causing abnormalities in glucolipid metabolism [45].

The study conducted by Christine (2018) found that lipid metabolism in preeclampsia occurs quickly so that the metabolism is not optimal then gives rise to the remaining metabolism in the form of cholesterol-rich lipoproteins where these remainder accumulates in the walls of blood vessels and cause endothelial

dysfunction. This study expects further research to determine lipid metabolism and its treatment [46]. Research conducted by Lucia (2017) on "Maternal / fetal eNOS-Glu298A genotypes and their influence on the severity, prognosis and lipid profile of preeclampsia", explains that the variant of eNOS-Glu298Asp (in mothers and newborns) has a relationship with dyslipidemia (increased cholesterol, LDL and TG, and decreased HDL levels) that can affect the bioavailability of NO (oxide nitrite) thus worsening the condition of preeclampsia [47].

Some of these descriptions are very closely related to preeclampsia with endothelial dysfunction and NO bioavailability (Nitrite Oxide). Endothelial dysfunction is considered the center of maternal manifestations associated with preeclampsia and can explain its various clinical complications. One of the complications that can occur is changes in lipid levels in preeclampsia. There are differences in results on lipid levels where there are researchers who explains that lipid levels in preeclampsia become low and other studies declared lipid levels in preeclampsia increased. [48].

## CONCLUSION

Preeclampsia is a complex syndrome with various pathophysiological pathways. Metabolic disorders that accompany preeclampsia can be seen from RDW (Red blood cell distribution width), aromatase, MTT (Biomarker), ADA (adenosine deaminase), selenium serum, CA-125 serum, triglycerides (TG), Angiotensin, thiol-disulphide, cytokinin, CEC (Circulating endothelial cells), lipoprotein and cholesterol. Potential targets are needed for treatment of preeclampsia to metabolic disorders both medically and non-medically especially for lipid levels in preeclampsia.

## CONFLICT OF INTEREST

No conflict of interest in this study

## REFERENCES

1. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. Lancet [Internet]. 2010;376(9741):631–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0140673610602796
2. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: Systematic review and meta-analysis. Br Med J. 2007;335(7627):974–7.
3. Al-Jameil. A Brief Overview of Preeclampsia. J Clin Med Res. 2013;6(1):1–7.
4. Robert Taylor James Roberts F. Cunningham Marshall Lindheimer. Chesley's Hypertensive Disorders in Pregnancy 4th Edition. 2014.
5. Phipps E, Prasanna D, Brima W, Jim B. Preeclampsia: Updates in Pathogenesis, Definitions, and Guidelines. Clin J Am Soc Nephrol. 2016;11(6):1102–13.
6. Pijnenborg R, Bland JM, Robertson WB, Brosens I. Uteroplacental arterial changes related to interstitial trophoblast migration in early human pregnancy. Placenta. 1983;4(4):397–413.
7. S. G, A. A, RKS The role of placental oxidative stress and lipid peroxidation in preeclampsia. Obstet Gynecol Surv [Internet]. 2005;60(12):807–16. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L41698019%5Cnhttp://dx.doi.org/10.1097/01.ogx.0000193879.79268.59%5Cnhttp://sfx.library.uu.nl/utrecht?sid=EMBASE&issn=00297828&id=doi:10.1097%2F01.ogx.0000193879.79268.59&atitle=The+
8. Kharfi A, Giguère Y, Sapin V, Massé J, Dastugue B, Forest JC. Trophoblastic remodeling in normal and preeclamptic pregnancies: Implication of cytokines. Clin Biochem. 2003;36(5):323–31.
9. Ramma W, Buhimschi IA, Zhao G, Dulay AT, Nayeri UA, Buhimschi CS, et al. The elevation in circulating anti-angiogenic factors is independent of markers of neutrophil activation in preeclampsia. Angiogenesis. 2012;15(3):333–40.
10. Khan F, Belch JJF, MacLeod M, Mires G. Changes in endothelial function precede the clinical disease in women in whom preeclampsia develops. Hypertension. 2005;46(5):1123–8.
11. Das UN. Cytokines, angiogenic, and antiangiogenic factors and bioactive lipids in preeclampsia. Nutrition [Internet]. 2015;31(9):1083–95. Available from: http://dx.doi.org/10.1016/j.nut.2015.03.013
12. Baumwell S, Karumanchi SA. Pre-eclampsia: Clinical manifestations and molecular mechanisms. Nephron - Clin Pract. 2007;106(2).
13. Mütze S, Rudnik-Schöneborn S, Zerres K, Rath W. Genes and the preeclampsia syndrome. J Perinat Med. 2008;36(1):38–58.
14. Eiland E, Nzerue C, Faulkner M. Preeclampsia 2012. J Pregnancy. 2012;2012:1–7.
15. Khan KS, Wojdyla D, Say L, Gülmezoglu AM, Van Look PF. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006;367(9516):1066–74.
16. Huppertz B, Weiss G, Moser G. Trophoblast invasion and oxygenation of the placenta: Measurements versus presumptions. J Reprod Immunol [Internet]. 2014;101–102(1):74–9. Available from: http://dx.doi.org/10.1016/j.jri.2013.04.003
17. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a Disease of the Maternal Endothelium. Circulation. 2011;123(24):2856–69.
18. Brennan LJ, Morton JS, Davidge ST. Vascular Dysfunction in Preeclampsia. Microcirculation. 2014;21(1):4–14.

19. de Groot CJM, Davidge ST, Friedman SA, McLaughlin MK, Roberts JM, Taylor RN. Plasma from preeclamptic women increases human endotheial cell prostacyclin production without changes in cellular enzyme activity or mass. Am J Obstet Gynecol. 1995;172(3):976–85.
20. Practice AC on O. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. American College of Obstetricians and Gynecologists. Int J Gynaecol Obs [Internet]. 2002;77(1):67–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12094777%5Cnhttp://ac.els-cdn.com/S0020729202800029/1-s2.0-S0020729202800029-main.pdf?_tid=175ee400-e1cd-11e5-a98f-00000aacb362&acdnat=1457070848_8d50b6d8ea2ad4e14fda863560065b29
21. Thangaratinam S, Ismail KMK, Sharp S, Coomarasamy A, Khan KS. Accuracy of serum uric acid in predicting complications of pre-eclampsia: A systematic review. BJOG An Int J Obstet Gynaecol. 2006;113(4):369–78.
22. Chaiworapongsa T, Chaemsaithong P, Yeo L, Romero R. Pre-eclampsia part 1: current understanding of its pathophysiology. Nat Rev Nephrol [Internet]. 2014;10(8):466–80. Available from: http://dx.doi.org/10.1038/nrneph.2014.102
23. Hladunewich M, Karumanchi SA, Lafayette RA. Pathophysiology of the clinical manifestations of preeclampsia. Clin J Am Soc Nephrol. 2007;2(3):543–9.
24. Arulkumaran N, Lightstone L. Severe pre-eclampsia and hypertensive crises. Best Pract Res Clin Obstet Gynaecol [Internet]. 2013;27(6):877–84. Available from: http://dx.doi.org/10.1016/j.bpobgyn.2013.07.003
25. Yılmaz ZV, Yılmaz E, Küçüközkan T. Red blood cell distribution width: A simple parameter in preeclampsia. Pregnancy Hypertens. 2016;6(4):285–7.
26. Berkane N, Liere P, Lefevre G, Alfaidy N, Nahed RA, Vincent J, et al. Abnormal steroidogenesis and aromatase activity in preeclampsia. Placenta [Internet]. 2018;69:40–9. Available from: https://doi.org/10.1016/j.placenta.2018.07.004
27. Alpoim PN, Perucci LO, Godoi LC, Goulart COL, Dusse LMS. Oxidative stress markers and thrombomodulin plasma levels in women with early and late severe preeclampsia. Clin Chim Acta [Internet]. 2018;483(February):234–8. Available from: https://doi.org/10.1016/j.cca.2018.04.039
28. Giorgi VS, Witkin SS, Bannwart-Castro CF, Sartori MS, Romão-Veiga M, Borges VTM, et al. Elevated circulating adenosine deaminase activity in women with preeclampsia: association with pro-inflammatory cytokine production and uric acid levels. Pregnancy Hypertens [Internet]. 2016;6(4):400–5. Available from: http://dx.doi.org/10.1016/j.preghy.2016.09.004
29. Haque MM, Moghal MMR, Sarwar MS, Anonna SN, Akter M, Karmakar P, et al. Low serum selenium concentration is associated with preeclampsia in pregnant women from Bangladesh. J Trace Elem Med Biol. 2016;33:21–5.
30. Staff AC, Dechend R, Pijnenborg R. Learning from the placenta: Acute atherosis and vascular remodeling in preeclampsia-novel aspects for atherosclerosis and future cardiovascular health. Hypertension. 2010;56(6):1026–34.
31. Radi R. Peroxynitrite, a stealthy biological oxidant. J Biol Chem. 2013;288(37):26464–72.
32. MYATT L, WEBSTER RP. Vascular biology of preeclampsia. J Thromb Haemost. 2008;7(3):375–84.
33. Sánchez-Aranguren LC, Prada CE, Riaño-Medina CE, Lopez M. Endothelial dysfunction and preeclampsia: Role of oxidative stress. Front Physiol. 2014;5(OCT):1–11.
34. Ghaemi SZ, Forouhari S, Dabbaghmanesh MH, Sayadi M, Bakhshayeshkaram M, Vaziri F, et al. A prospective study of selenium concentration and risk of preeclampsia in pregnant Iranian women: A nested case-control study. Biol Trace Elem Res. 2013;152(2):174–9.
35. Karaman E, Karaman Y, Alkiş I, Han A, Yildirim G, Ark HC. Maternal serum CA-125 level is elevated in severe preeclampsia. Pregnancy Hypertens. 2014;4(1):29–33.
36. Keshavarz P, Nobakht M. Gh BF, Mirhafez SR, Nematy M, Azimi-Nezhad M, Afin SA, et al. Alterations in Lipid Profile, Zinc and Copper Levels and Superoxide Dismutase Activities in Normal Pregnancy and Preeclampsia. Am J Med Sci [Internet]. 2017;353(6):552–8. Available from: http://dx.doi.org/10.1016/j.amjms.2017.03.022
37. Hubel CA, Roberts JM, Taylor RN, Musci TJ, Rogers GM, McLaughlin MK. Lipid peroxidation in pregnancy: New perspectives on preeclampsia. Am J Obstet Gynecol [Internet]. 1989;161(4):1025–34. Available from: http://dx.doi.org/10.1016/0002-9378(89)90778-3
38. Rosas P, Tufiño C, Bracho Valdes I, Bobadilla Lugo RA. Time course of angiotensin II dependent vascular and metabolic effects of preeclampsia. Pregnancy Hypertens [Internet]. 2017;10:51–6. Available from: http://dx.doi.org/10.1016/j.preghy.2017.06.005
39. Yuvaci HU, Akdemir N, Bostanci MS, Yazar H, Cevrioglu S, Ozden S, et al. Evaluation of the level of thiol-disulphide homeostasis in patients with mild and severe preeclampsia. Pregnancy Hypertens. 2016;6(4):394–9.
40. Gratacós E, Martín-Gallán P, Cabero L, Dominguez C, Llurba E. A comprehensive study of oxidative stress and antioxidant status in preeclampsia and normal pregnancy. Free Radic Biol Med. 2004;37(4):557–70.
41. Udenze I, Amadi C, Awolola N, Makwe CC. The role of cytokines as inflammatory mediators in preeclampsia. Pan Afr Med J. 2015;20:1–6.
42. M. Reslan O, A. Khalil R. Molecular and Vascular Targets in the Pathogenesis and Management of the Hypertension Associated with Preeclampsia. Cardiovasc Hematol Agents Med Chem. 2010;8(4):204–26.
43. Anim-Nyame N, Ghosh A, Freestone N, Arrigoni FIF. Relationship between insulin resistance and circulating endothelial cells in pre-eclampsia. Gynecol Endocrinol [Internet]. 2015;31(10):788–91. Available from: http://dx.doi.org/10.3109/09513590.2015.1065477
44. Clarke LA, Hong Y, Eleftheriou D, Shah V, Arrigoni F, Klein NJ, et al. Endothelial injury and repair in systemic vasculitis of the young. Arthritis Rheum. 2010;62(6):1770–80.
45. Xu CL, Weng BC, Gu HB, Chen L, Lin KS, Lin YP, et al. Study on the correlation between adipocyte fatty-acid binding protein, glucolipid metabolism, and pre-eclampsia. J Obstet Gynaecol Res. 2018;44(4):655–62.
46. Contini C, Jansen M, König B, Markfeld-Erol F, Kunze M, Zschiedrich S, et al. Lipoprotein turnover and possible remnant accumulation in preeclampsia: Insights from the Freiburg Preeclampsia HELP-apheresis study. Lipids Health Dis. 2018;17(1):1–11.
47. Maria Procopciuc L, Caracostea G, Maria Hazi G, Nemeti G, Zaharie G, Stamatian F. Maternal/fetal eNOS-Glu298Asp genotypes and their influence on the severity, prognosis, and lipid profile of preeclampsia. J Matern Neonatal Med. 2018;31(13):1681–8.
48. Johal T, Lees CC, Everett TR, Wilkinson IB. The nitric oxide pathway and possible therapeutic options in pre-eclampsia. Br J Clin Pharmacol. 2014;78(2):244–57.