

## STUDY OF PREECLAMPSIA IN PLACENTA, KIDNEY, AND HEPATIC DISEASES

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## ABSTRACT

Preeclampsia (PE) have a high risk of pregnancy disorder and can cause liver and kidney disease. PE is a dangerous disease in Indonesia with a high risk of cardiovascular death. PE has biomarkers such as proteinuria, blood pressure, dipstick test, renin-angiotensin system, adipsin, calcium/creatinine (Cr) ratio, albumin/Cr ratio, and uric acid. Apoptosis occurs in the placenta's PE, where trophoblasts invade and overhaul the uterine spiral artery in the epidermal growth factor signaling system, and the expression of miRNA in PE is targeting genes in a variety of pathophysiological processes can cause kidney and hepatic disease. In this review, we will discuss role of HSP, miRNA, Immunology cell and the risk of kidney and hepatic disease of patient of Preeclampsia.

**Keyword:** Preeclampsia, Placenta, Kidney diseases, Hepatic diseases, mRNA.

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## INTRODUCTION

Preeclampsia (PE) is a dangerous and potentially life-threatening disease for the mother and fetus which occurs uniquely in Indonesia, so the improvement of the standard diagnostic approach with complement is very important for this problem and development of future treatment strategies [1,2]. According to Survei Demografi dan Kesehatan Indonesia in 2007, PE contributes to 24% of maternal mortality in Indonesia, makes it second cause of maternal death in Indonesia [3]. International non-governmental organization Forum on Indonesian Development states that Indonesia is a country in Southeast Asia with the highest maternal mortality of 359/100.000 births [4]. Chronic hypertension pre-pregnancy can lead to developmental rates of severe hypertension so that babies are premature and small [5]. One of the characteristics of PE is the syncytial node-forming process, the shedding of the syncytial aggregate, and the appearance of placental microparticles in the maternal and contributes to maternal vascular injury [6]. Strong evidence supports the involvement of deficient trophoblast survival, inadequate endovascular invasion, endothelial cell dysfunction, and a systemic maternal inflammatory response [7,8]. Failure of trophoblast invasion inhibits decidualization leading to poor placental blood supply in maternal vessels which further generates placental ischemia and apoptosis [9]. PE can cause diseases of the liver and kidneys. Those diseases may not be initiated by pregnancy, but interfere strongly with pregnancy. Exact diagnosis is therefore of high clinical relevance [10]. Not just in science, there is a direct and indirect relationship regarding the empowerment of PE prevention in pregnant women through the theory of social capital to Indonesia society [11].

## BIOMARKER IN PE

PE may be characterized by hypertension and proteinuria after 20 weeks of pregnancy and a change in the angiogenic factor [12,13]. Detected proteinuria can be used dipstick test with urine sample concentration with creatinine (Cr) is higher [14]. Massive Urinary Protein also has the potential to be associated with more severe clinical manifestations of PE [15]. Significantly, isolated gestational (IG) proteinuria was also a risk factor for PE and IGP-PE accounted for most (20%) of all PE [16]. Women who have higher levels of urea nitrogen in the blood have a higher incidence of PE; premature labor (women with kidney disease with  $p < 0.001$ ), 8/35 (23%); premature rupture of membranes; and intrauterine growth restriction [17-19]. Urinary protein, adipsin, was

found to increase significantly and the ratio of Cr to adipsin correlated with urine protein, for 24 h in 124 patients combined with elevated diastolic blood pressure ( $\geq 90$  mm Hg) [20]. It is important to know that increased activity of a local renin-angiotensin system (RAS) in the kidney, correlates with high blood pressure, and proteinuria in PE [21]. Oral labetalol is more efficacious and important for effective control of blood pressure in PE [22]. Hypertension, proteinuria, and renal function resolved normally over an average period of 35.8 days and neurologic complications, pulmonary edema, and multiple organ failure can be a cause of death [23]. No woman with protein: Cr ratio  $< 18$  mg/mM ( $n=20$ ) had significant proteinuria, but between 18 and 60 mg/mM [24]. To assess the effectiveness of the calcium/creatinine ratio (CCR) as a diagnostic test for PE predicted, CCR at 0.04 in spot urine samples was a good test, as a screening test on all asymptomatic pregnant women [25]. The first albumin/creatinine ratio (ACR), for maternal and neonatal outcomes, is also an independent prognostic factor for maternal and fetal outcomes in suspected PE [26].

Proteinuria-onset PE is associated with an increased adverse risk of PE with the onset of hypertension [27]. Hypertension and proteinuria are very common outside the postpartum period in Cameroonian women with severe PE and eclampsia [28]. In severe PE with proteinuria  $> 3$  g/L showed that the amount of proteinuria is not associated with severe PE, although proteinuria is detected, prematurity may occur [29]. Serum cytoglobin was significantly more effective and higher in patients with early-onset preeclampsia (EO-PE) and slow onset of preeclampsia (LOPE), compared with healthy pregnant women [30]. Uric acid with proteinuria can identify perinatal risk with high risk with gestational hypertension in women [31]. However, serum uric acid will increase after presentation of clinical symptoms of PE and cannot be a biomarker [32].

## ROLE OF HEAT SHOCK PROTEIN (HSP) IN PREECLAMPSIA

HSPs play an important role in the maintenance of cellular homeostasis, where these proteins constitute about 5–10% of the total protein of all normal cells and mediate protein assembly and proper intracellular localization [33]. HSP20 is widely expressed under normal physiological conditions and plays an important role in the dilation of blood vessels and the collection of platelet suppression and as a marker for predicting the onset of PE or severity with decline in the chorionic plate resistance artery and in serum female PE [34]. HSP27 was found to be a translation

initiation and signal transducer, transcription activator-3 (STAT3) level administrator, because HSP27 is a key protein during the development of placenta and differentiation of trophoblast cells, STAT3, and eukaryotic initiation factor of eukaryotic 4E is involved in regulating the differentiation/migration of extracellular trophoblast cells [35]. Upregulation of Hsp27 is a common phenomenon in pregnancy that is affected with PTB and PPRM. Downregulation of HSP70 and HSPBP1 also represents the unique feature of PPRM [36]. HSPs can be induced in cells as a protective mechanism and play a role in PE [37].

HSP70 is one factor that can mediate the effects of cytoprotective, antiapoptotic, and immune regulation, HSP70 serum concentrations were significantly higher in patients with PE than in the control group. Therefore, HSP70 may be identified as a diagnostic factor [38]. Serum HSP70 plays a protective role in tissue damage and a higher liver stiffness value in patients with biliary atresia, so serum HSP70 and liver stiffness may serve as a non-invasive parameter [39]. HIF-1 $\alpha$  and HSP70 have a close relationship with the origin and development of the disease for the diagnosis and treatment of the disease [40]. HSP70 and proliferation are associated with trophoblast cells and decidual cells in exhibiting highly proliferative activity, as demonstrated by PCNA immunohistochemistry, at the mid-gestational stage. However, the difference is the decrease in the percentage of PCNA-positive cells observed in the final stages [41]. HSP70s also protect cells from the proteotoxic stress associated with abnormal rapid proliferation, suppresses cell aging and provides resistance to stress-induced apoptosis including protection against cytostatic, drugs, and radiation therapy [42]. Recent data also showed that serum Hsp70 (HSPA1A) levels are elevated in diabetes mellitus types 1 and 2. However, further research is needed to determine whether Hsp70 is a cause in the pathogenesis of gestational diabetes [43].

#### ROLE OF IMMUNOLOGY CELLS IN PE

The immunologic mechanism also plays an important role in the pathophysiology of PE. Helper T-Cell 17 (Th17) as a new subset of effector T-cells and plays an important role in host defense in extracellular pathogens, autoimmune, and inflammatory in PE such as recurrent spontaneous abortion (RSA) [44]. T regulatory cells (Treg cells, FoxP3+) suppresses cytotoxic T-cells (CD8+) and responds to natural killer cells (NK) and increases immunological tolerance in the fetus [45]. Dendritic cells (DC) are also involved in the immune system, which regulates differentiation of Th17 and regulatory T-cells (Treg) participating in PE and RSA, but there is still a shortage in the intrahepatic cholesterol study of pregnancy (ICP) [46]. IL-17 and podocyte levels also had a positive association in serum and overreaction of microRNA-155 (miR-155) in PE patients, thus results in increased IL-17 production by CD4+ T-cells *in vitro*, and decreased nephrin expression in podocytes and apoptotic processes of podocytes [47]. In addition, high red cell distribution width can be a promising marker to predict low CD4 cell counts in HIV-positive reproductive women in antiretroviral therapy in PE women [48]. The effects of adiponectin on the cardiovascular system in hypertensive patients are believed to be partially mediated by activation of 5' active adenosine monophosphate protein kinase and pathway cyclooxygenase-2, reduces endothelial cell apoptosis, promotes the production of nitric oxide, decreased activity in tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and prevented atherosclerotic proliferation and smooth muscle cell migration [49]. In addition, there is a consensus strategy to improve early detection and enrichment of pathogenic genes in PE such as HSP90, PAK2, CD247, and others, included in the first 1% of the prioritized list, so it needs to be explored further on the pathogenesis of PE through an experimental approach [50]. Activation of endothelial antibodies is also a marker of cardiovascular system dysfunction and endothelial dysfunction as well as severe pathology, with multiple organ failure manifestations, which is evidence of the relevance of this area of research to a large number of patients [51]. Detyrosination and tyrosination of tubulin are also important for the stability and dynamics of microtubules and significantly reduces the level of detyr-tubulin in the placental biopsy, placental angiogenesis damage, and vascularization in cases of PE [52]. The implantation site macrophages comprised about

20% of the population leukocytes, and as a major mediator thereby increasing the expression of M-CSF, pro-inflammatory cytokines, IL-1b, or TNF- $\alpha$ , mainly through the NF- $\kappa$ B pathway signal to increase M-CSF expression in FTDCs, leading to M2 polarization of macrophages, and the phagocytic capacity of M2 macrophages is consistently improved, possibly through downregulation of SIRPa [53]. In gene levels, based on expression of 15 genes from C19MC, microRNAs (miR-512-5p, miR-515-5p, miR-516-5p, miR-517-5p, miR-518b, miR-518f-5p, miR-519a, miR-519d, miR-519e-5p, miR-520a-5p, miR-520h, miR-524-5p, miR-525, miR-526a, and miR-526b) were assessed in the placental tissue, miR-519a was found to be associated with severe PE. The longer the pregnancy-related disorder progresses, the wider the regulation of microRNAs decreases (miR-515-5p, miR-518b, miR-518f-5p, miR-519d, and miR-520h). Downregulation of some C19MC microRNAs is a common phenomenon that is shared between GH, PE, and FGR. On the other hand, some C19MC microRNAs are only derived only on PE [54]. In Egyptian women, There is a significant association between VEGF C 405 G and VEGF C 2578 A gene polymorphisms. Thus, the screening for PE mutations for all Egyptian pregnant women in order to set up an appropriate method of prophylaxis against these pre-eclamptic disorders [55].

#### APOPTOSIS OF PLACENTA IN PE

The main cause of PE is the placenta in the presence of trophoblast tissue that can cause apoptosis [56]. In addition, toxic effects of carbon monoxide from tobacco can damage mitochondria in pregnant smokers, resulting in reduced birth weight [57]. Apoptosis in the placenta was found to increase in PE and associated with the activation of caspase-8 on the extrinsic pathway, then caspase-3 activation [58]. FasL expression was significantly less and Bcl-2 expression was significantly greater in villous trophoblasts due to increased apoptosis and the formation of a synthetic node combination by reducing FasL expression may be involved in the pathophysiology of the mechanism of PE [59]. Increased apoptotic signaling leads to reduced nutrient transport capacity, which triggers the release of vascular factors in the placenta, maternal vascular produce response because the fetus must adapt to changes in the intrauterine environment, and this adaptation increases the risk of disease in offspring [60]. A danger signal in preeclampsia, that is, a high mobility group box 1 that participates in various inflammatory processes and processes in the placenta [61]. Fetal developmental disorders cause antioxidant enzymes not able to cope with increased levels of oxidative stress, resulting in epigenetic changes at the specific level of genes to transcribe antioxidant enzymes [62]. Telocytes which are a new type of stromal cells associated with signal transduction mechanisms in the regulation of fetal blood vessels in placenta PE can be damaged by oxidative stress and placental apoptosis of endothelial cells, and trophoblast cells [63]. For strong antioxidants, melatonin plus indoleamine has utility in the treatment of PE, intrauterine growth restriction, placental and fetal/reperfusion ischemia, etc [64].

Maintain a physiological balance between the proliferation of cytotrophoblast (CTB) with the placental vein and apoptosis is very important because of increased oxidative stress and apoptosis in the pathological placenta is not balanced [65]. Impaired nitric oxide pathways and excessive stress on endoplasmic reticulum (ER) have been observed in the stress response and iNOS that may be associated with increased apoptosis in the placenta of PE patients [66]. In HELLP syndrome, there is an increase in apoptosis, proliferation, and FAS ligand expression in the placenta compared with placenta PE and normal pregnancy [67]. One of the placental factors involved in triggering PE is trophoblast debris, which can pass the pathogen signals from the placenta to endothelial cells, where trophoblastic debris from the placenta of PE leads to endothelial cell activation [68]. Observation of trophoblast cells in the placenta can be done with Formalin-fixed paraffin-embedded (FFPE), observed with immunohistochemistry and calyculin, resulting in an increase in trophoblast cells in the placenta PE compared with normal trophoblast cells [69]. To determine cell apoptosis or cell fragments derived from CTB or syncytiotrophoblast, use E-cadherin staining together with markers for apoptosis [70].

During pregnancy, the subset of placental CTB differentiates into cells that aggressively invade the uterus and blood vessels [71]. The vasculosyncytial membrane (VSM) is a fetomaternal exchange when syncytiotrophoblast surrounds the terminal villi and makes close contact with the capillaries. The inverse relationship between the VSM and hypoxia in the fetus disrupts the syncytial PE [72]. Increased apoptosis, CTB necrosis, and syncytiotrophoblast may compromise placental function, including nutrient transport and cause increased shedding syncytiotrophoblast extracellular vesicles (STBEV) in PE, but relaxin (pregnancy hormone) may improve [73]. The release of extracellular vesicles (EVs) by syncytiotrophoblast (STB) is an important mechanism, in which placental signaling to the mother is important in the formation, maintenance of a healthy pregnancy and provides a real-time reading of placental health [74]. After delivery of the placenta, the rapidly restored state is caused by growth factors vascular endothelial signals which are impaired [75,76]. However, with the administration of 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) during pregnancy reduces the adverse outcome of PE [77]. Pomegranate juice can reduced oxidative stress on the placenta *in vivo* and *in vitro* induced by stimuli from trophoblast women PE [78]. A decreased enzymatic antioxidant capacity and increased oxidation in placental tissue from PE women, which may contribute to the pathogenesis of this complex disorder [79]. In the study, the presence of concentration nitric oxide in placenta PE was higher significantly than normal placenta. Hence, there was no significant difference caused by decrease markedly of ROS production [80].

The development of PE induced by apoptosis of trophoblast cells may decrease miR-34a which is an effective strategy for increasing apoptosis in the trophoblast cells [81]. Apoptosis in trophoblasts also invades and overhauls the uterine spiral artery in the signal system of epidermal growth factor signaling that regulates differentiation in trophoblasts [82]. The Wnt signaling path plays an important role in regulating trophoblast functions. Wnt signaling pathways were detected in the placenta in the third trimester, decreased placental expression of Wnt2, and increased placental expression of secreted frizzled-related protein 4 (SFRP4) [83]. Signaling is the function of the Wnt/ $\beta$ -catenin pathway in the placenta of PE is significantly inhibited, due to oxidative stress and apoptosis [84]. Excessive activation of the terminal pathway is associated with fetal growth restriction in preeclamptic women in the third trimester of human pregnancy [85]. In apoptosis, protein P53 is regulated in HUVECs which triggers the capture of G1, then P21 expression increases, decreases the regulation of cyclin E expression, and CDK2-cyclin E complex. Increased regulation of P53 also activates the Bax gene, suppresses the Bcl-2 gene, BIRC5 resulting increased Bax/Bcl-2 ratio, and then activated caspase cascade, eventually apoptosis [86]. At the moment advances in biomarkers, therapies and genetic profiles are becoming an effective treatment in PE [87]. Potential biomarkers of this disease, such as activin A may lead to increased nodal expression and further increase Nodal/ALK7 signaling to induce apoptosis of the trophoblastic cells [88]. Low-dose aspirin is also widely used in preventing PE and reduces apoptosis caused by H<sub>2</sub>O reduces the ability of caspase-3 activation and TNF- $\alpha$  expression levels in PE [58]. New mitochondrial proteins such as mitofusin-2 (Mfn2) in the placenta are detected by qRT-PCR, indicating mitochondrial dysfunction, decreasing trophoblast cell viability, and contributing to the multifactorial pathogen mechanism of PE [89]. The important role of mitochondrial activity changes in the adaptive response to the development of PE, due to increased OPA1 mRNA and protein expression in the placenta [90]. Potential genes such as STOX1 and ACVR2A were also identified determining their causality in PE disorders [91]. In PE, male fetal placenta is associated with much higher expression of inflammation, hypoxia, and apoptosis than female fetal placenta but reduces the expression of pro-angiogenic markers [92].

Complementary system activation is also involved in PE pathologic processes, such as complementary 5a (C5a) that plays an important role in placental abruption, regulate migration, and trophoblast angiogenesis and is also associated with maternal blood pressure

and arterial stiffness [93]. Calreticulin (CRT) is also an important ER resident protein (ER) that participates in the intracellular regulation of Ca<sub>2</sub> homeostasis, cell adhesion, and cell apoptosis [94]. Shedding of syncytiotrophoblast microparticles from the placenta to maternal blood occurs under normal circumstances of pregnancy and is enhanced during PE [95]. Placental on syncytiotrophoblast microvesicles (STBMs) in the maternal circulation during normal pregnancy is significant in PE and STBM proteins are involved in immune responses, coagulation, oxidative stress, apoptosis, and lipid metabolism [96]. Injection of light into pregnant mice also induces placental apoptosis, small fetuses, PE, hypertension, and proteinuria where light functioning through 2 receptors induces the secretion of fms-like tyrosine kinase-1 and endothelin-1, 2 pathogenic factors in PE [97].

#### PLACENTAL MICRORNA EXPRESSION IN PE

MicroRNAs (miRNAs) have emerged as major regulators in the stability of gene expression involved in cell proliferation and apoptosis, whereas their expression may be altered in association with a variety of pathological disorders, such as in PE and preterm delivery [98]. There are Target genes of miRNAs, that participate in organ/system development (cardiovascular and reproductive system), immunologic dysfunction, cell adhesion, cell cycle, and signaling in PE [99]. MicroRNA (miRNA) is a small non-coding RNA which regulates gene expression through mRNA degradation and translational suppression. As a result, the expression of miR-210 is regulated in the placenta causing repression. Thus, miR-210 has a major effect on placental mitochondria [100]. Three miRNAs (miR-17, -20a, and -20b) increased significantly in PE compared with normal placenta [101].

#### HEPATIC DISEASE IN PE

Liver disorders of PE may increased liver enzymes, low platelets (HELLP), acute fatty liver, hyperemesis gravidarum, intrahepatic cholestasis, and autoimmune liver [102]. Atypical hemolytic uremic syndrome in a woman pregnant who was given the diagnosis of gestational hypertension, and hemolysis, elevated liver enzymes, and low platelet count (HELLP) also occurs in preeclampsia [103]. In terms of age, elderly gravidae (age  $\geq$ 35 years) showed higher levels of urea and uric acid when compared with women <35 years, so increased age may increase the risk of impaired kidney and liver function [102]. Based on the Fibroscan results for 1–7 days postpartum, fibrosis was significantly higher in PE women (although within the normal range [104]. Most of the causes of liver function impairment during the third trimester were hypertension, which induced pregnancy with HELLP syndrome (37%), acute fatty liver pregnancy (37%), and viral hepatitis (20%) [105,106]. In PE disorders, non-hypoxia is also a pathway that may be involved in angiogenic changes and abnormal metabolism in PE because defects in angiogenesis and mitochondrial function in the placenta contribute to the pathogenesis of PE, but the upstream regulator of this path is unknown [107]. Trophoblastic mitochondrial damage is a common terminal path, as it may cause different changes in lipid metabolism [108]. LDL-c and HDL-c isolated from PE indicating oxidative damage to lipids and proteins. Antioxidants are needed to reduce oxidative stress and induce damage in the vascular endothelium [109]. Selenium is an important constituent that acts as an antioxidant and has some possible metabolic function in terms of treating PE with a certain concentration [110]. Extra Virgin Olive Oil (EVOO), in the form of extra virgin, contains a rich antioxidant tocopherol (Vitamin E) capable of controlling the induction of HSP70 serum levels are not excessive, so the process of apoptosis does not occur excessively, especially PE [111]. A significant effect of EVOO on TGF- $\beta$  expression in placenta and there was a positive and strong relationship ( $r=0.494$ ) as well as a very significant relationship ( $p<0.01$ ) between TGF- $\beta$  and the serum MDA [112].

On multivariate analysis, women with abnormal alanine aminotransferase level before pregnancy had a 1.21-fold increased risk of developing preeclampsia than those with normal alanine aminotransferase level before pregnancy [113]. Patients with intrahepatic cholestasis of pregnancy and elevated levels of alanine aminotransferase should be

followed up for perinatal normal results, so as to safeguard maternal and fetal safety [114]. Serum levels of liver fatty acid-binding proteins (LFABP) in PE women, correlated with the severity of PE, may be used to confirm the diagnosis [115]. HELLP syndrome can be measured by elastosonography acoustic radiation force impulse (ARFI) [116]. For the diagnosis of HELLP syndrome, elevated levels of ET-1, M30, and Angs-1 and -2 appear as promising apoptotic-associated biomarkers where serum M30 levels have the benefit of being the most promising test for predictive or differential diagnosis of HELLP syndrome in PE patients [117]. D-dimers can also be as biomarkers in fibrin formation and degradation where levels were significantly increased in Sudanese women with PE, with hemostatic abnormalities [118].

Women who have non-alcoholic fatty liver (NAFLD) before delivery of the fetus, increase the risk of pregnancy adversely independently of body mass index and diabetes and should be monitored carefully during antenatal care [119]. Prenatal serum bilirubin, plasma fibrinogen levels, and platelet counts are the predictors of postpartum recovery in the acute fatty liver of pregnancy (AFLP) [120]. Chronic alcohol consumption without AFLD can lead to significant circulation increases, as an inflammatory marker and may result in downregulation of oxidative stress production [121]. In addition to acute fatty liver of pregnancy (AFLP), intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease in pregnancy that causes hepatobiliary and immune-mediated cancers and cardiovascular disease [122]. In Western India, Hepatitis E is the most common cause of liver disease in pregnant women resulting in maternal mortality, predicted with high MELD scores [123]. Two rare causes of hepatitis, especially fulminant (rare complications of the herpes simplex virus) such as HSV-1 and HSV 2 are comorbid in the same patient [124]. Pregnancy in women with cirrhosis of the liver, portal hypertension, or esophageal varices leads to worse pregnancy and may warrant closer antenatal monitoring and patient counseling [125]. Different levels of bile acid and carnitine circulation can be altered in patients with primary biliary cirrhosis (PBC) as potential biomarkers [126]. The circulating levels of different bile acids and carnitines can be changed in patients with primary biliary. Liver infarction is dangerous and complications associated with hemolysis, elevated liver enzymes, and low platelet syndrome (HELLP), may cause cardiac arrest and fulminant liver failure [127]. Due to advances in obstetric and transplant medications, women with a history of liver transplants can have successful pregnancies. The transplanting process should have a relationship with maternal and fetal levels of high morbidity [128]. Liver transplantation also restores sexual function and fertility as early as, a few months after transplantation [129].

#### KIDNEY DISEASE IN PE

Renal function monitoring appears to be relevant for PE, especially since albuminuria should be evaluated in postpartum and are classified at high risk for impaired renal function [130]. Podocytes play a role in the development of kidney damage and prevention of long-term complications of PE [131,132]. The depletion of podocytes in the kidneys is associated with end-stage renal disease (ESKD). PE may also increase the risk of future ESKD [133]. The depletion of podocytes may also affect individuals with the APOL1 genotype against the risk of kidney disease in blacks [134]. Persistent proteinuria is the most important predictor of renal disease and sustained proteinuria, persistent hematuria, or renal function disorder after the postpartum period [135]. Proteinuria also results in the loss of fetuin-A, resulting in low molecular weight [136]. PE also causes transient renal disease, characterized by hypertension and proteinuria then induced hypertensive pregnancy (PIH) and HELLP syndrome [137]. In PE, deteriorating arterial gradients and hemodynamic venous abnormalities of gestational hypertension (GH) linearly correlate between proteinuria and renal interlobar vein impedance index (RIVI [138]). Chronic pregnancy renal disease (CKD) has a high risk and to evaluate renal function during pregnancy after renal transplantation can lead to higher preterm prevalence and a worse neonatal prognosis [139,140] and until now there have been no reports of maternal deaths, childbirths, or neonatal deaths in renal donors.

However, PE is more common in renal donors [141]. Acute kidney injury (AKI) is a serious problem during pregnancy and understanding the physiological kidney adaptation during pregnancy is essential for early detection, diagnosis, and appropriate management to prevent obstetric complications [142]. In pregnant women with type I diabetes mellitus (T1DM) at increased PE risk, urine albumin examination should be performed to prevent kidney complications [143]. Giving serum containing gelocalin-associated gelatinase (NGAL) can be correlated with renal inflammation in severe PE [144]. Tempol, a mimetic dismutase-antioxidant drug has been shown to weaken radical damage, exert beneficial effects on animal models of oxidative stress and hypertension, against chronic ischemic renal injury, and prevent renal dysfunction through antioxidants, vasodilators, and antihypertensive [145]. In addition, the plant-based diet should be limited, especially those containing proteins in PE patients, as it can control proteinuria in pregnant CKD women with segmental focal glomerulosclerosis [146].

PE is also associated with hypercoagulability, endothelial dysfunction, and inflammation, resulting in microparticles (MPs) in which microparticles of platelets (PMPs), endothelial cells (EMPs), and leukocytes (LMPs) which are a method of knowing the presence of endothelial dysfunction and inflammation involved in the pathogenesis of PE [147]. Glomerular damage kidneys are common in PE and can be identified with tubular channels such as 1-microglobulin (A1M), retinol-binding protein (RBP), molecule-1 (KIM1), C5b-9, metalloproteinase-2 (TIMP-2), and insulin growth factors binding protein-7 (IGFBP-7) [148]. Metalloproteinase-2 and IL-18 tissue inhibitors show that the kidneys have an increased inflammatory response during pregnancy and tubular epithelial tubular injury [149]. Biomarkers have also been found to differentiate CKD and PE, where the sFlt-1 rate increases significantly compared to CKD and control [150]. Levels of serum cystatin C, urine RBP, urine NGAL, and urine KIM-1 in the PE group were higher than in the normal pregnancy group. When four biomarkers are combined, the sensitivity and specificity is 100% and 98.20% respectively. Hence, urine KIM-1 biomarkers are the most common for kidney injury in PE [151]. Low-molecular-weight heparin (LMWH) can also control the condition of PE, protect kidney function, improve to fetal health, and protect kidney function by inhibiting apoptosis [152]. Nephron relative administration in patients increased after LMWH intervention and accompanied by decreased proteinuria. Glomerular nephron expression in L-NAME induced preeclampsia significantly decreased and down-regulation of nephron is involved in L-NAME induced proteinuria [153]. Molecularly recently, DNA-containing mitochondria with unmethylated CpG motifs and formyl peptides have been shown to damage the associated molecular pattern (DAMP) and induce immune responses and clinical cell injury mtDAMPs that cause increased urine protein in mice, resulting in damage to proteinuria and kidney [154].

#### CONCLUSION

Proteinuria, blood pressure, dipstick test, RAS, adipsin, CCR, ACR, and uric acid are biomarkers in PE diagnosis. Increased apoptosis, CTB necrosis, and syncytiotrophoblast may compromise placental function, including nutrient transport and cause increased shedding of extracellular vesicle syncytiotrophoblast (STBEV) so that compounds and antioxidant and antiapoptotic drugs are needed. MicroRNA in PE as major regulators in the stability of gene expression involved in cell proliferation and apoptosis. Liver and kidney disease in PE women have a high risk of pregnancy disorder, although until now no reports of maternal death, the birth of premature infants or neonatal death.

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## AUTHORS' CONTRIBUTION

Putri Cahaya Situmorang undertook the most part during preparation of manuscript and Syafruddin Ilyas acted as corresponding author with responsibility to review the content and english grammar.

## CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

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