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# Epidemiology, Pathogenesis and Management of Preeclampsia

**Muhammad Shahid Nadeem[1]*, Saima Iftikhar[2], Bibi Nazia Murtaza[3], Inam Ullah[4], Iram Sarwar[5], Mahnoor Murtaza[2], Imran Kazmi[1] and Muhammad Naeem Riaz[6]**

*[1]Department of Biochemistry, Faculty of Science, King Abdulaziz University Jeddah 21589, Saudi Arabia.*
*[2]School of Biological Sciences, University of the Punjab, Lahore, Pakistan.*
*[3]Department of Zoology, Abbottabad University of Science and Technology, Abbottabad 22310, Pakistan.*
*[4]Institute of Molecular Biology and Biotechnology, University of Lahore, Lahore, Pakistan.*
*[5]Department of Gynaecology, Ayub Medical College, Abbottabad, Pakistan*
*[6]Department of Pharmacy, COMSATS University, Abbottabad, Pakistan.*

## ABSTRACT

Preeclampsia (PE) is a pregnancy associated complication mainly demonstrated by the onset hypertension, proteinuria, foetal growth restriction, and maternal organ dysfunction including renal, cerebral and hepatic diseases before or after 34 weeks of gestation. As a cause of prenatal and maternal morbidity and mortality, it remains a major health concern to females worldwide. In this context, we aimed to provide an accumulative account of recent developments about the risk factors, pathophysiology, consequences and management of PE. Several genetic, acquired and environmental risk factors have been associated with the progression of PE. Pre-existing hypertension, chronic renal disease, family history, obesity, multi-foetal pregnancies and history of miscarriage are main risk factors. The disease is initiated by abnormal placentation, incomplete remodelling of spiral artery, utero-placental hypoperfusion leading to placental hypoxia and ischemia. Many molecules of foetal origin are released in to circulation and result in the dysfunction of maternal endothelium which is the hallmark of PE. The disease also has postpartum impacts on maternal and foetal health, the main consequences include cardiovascular complications, hypertension, diabetes, neurodevelopmental issues and dementia to the mother and offsprings. In the recent past, the revelation of antiangiogenic molecules and pathways has provided critical information about the pathogenesis of PE. Several molecules such as sFLT1 (soluble fms-like tyrosine kinase 1), Eng (soluble endoglin), angiotensin II, PIGF (placental growth factor), and VEGF (vascular endothelial growth factor) are regulated differently during the pathogenesis of PE. These molecules not only offer the candidate biomarkers for early disease detection but also provide therapeutic targets. Many surveillance and management strategies reported in the recent literature have also been included in the present review. Studies have emphasized that PE has a long-term threat to the health of mother and child. Therefore, the development of interventional strategies for the prevention and management of postpartum cardiovascular complications poses a challenge.

KEY WORDS: Preeclampsia, Hypertension, Pathogenesis, Risk factors, Treatment

## INTRODUCTION

Pregnancy-induced hypertension (PIH) is characterized as systolic and diastolic blood pressures after 20 weeks of gestation that includes gestational hypertension (GH) and preeclampsia (PE)[1,2]. According to estimates, more than 10% of pregnant women are affected by hypertension, it may be pre-existing chronic hypertension or pregnancy induced gestational hypertension. The chronic and gestational hypertension may be differentiated on the basis of their timings i.e. the chronic hypertension is a systolic and diastolic blood pressure above 140 mmHg and 90 mmHg before pregnancy or before 20 weeks and persists after pregnancy, GH is the hypertension that starts due to physiological changes after 20 weeks of pregnancy[3-5]. In some cases, hypertension is accompanied by increased levels of proteins in the urine

*Corresponding author: shahid.nadeem.hu@gmail.com
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known as Preeclampsia (PE). According to the definition by the International Society for the Study of Hypertension in Pregnancy (ISSHP), preeclampsia a condition characterized by a combination of gestational hypertension with organ damage and proteinuria at 20 weeks of gestation[6-8].

Preeclampsia affects up to 5% pregnancies worldwide[9,10] resulting in the death of 0.5 million infants and 76,000 women during pregnancy, causalities are many times higher in the developing countries[9]. More than 300 mg of total urine proteins per 24 h and a random urine protein to creatinine ratio above 0.30 are used to diagnose preeclampsia[11]. In 2013, proteinuria was excluded by the American College of Obstetricians and Gynaecologists as an essential criterion for the diagnosis of PE, now the GH with end-organ dysfunction is considered sufficient in diagnosis[12]. At present, the aetiology of PE is not properly understood, several risk factors have been associated with the onset of condition. The serum levels of uric acid in pregnant women also indicates the chances of preeclampsia[13]. Anaemia during pregnancy, history of GH, and previous second trimester abortion are associated with increased incidence of preeclampsia[14]. Preeclampsia is induced by many maternal, placental, foetal factors, genetic, and environmental factors[15-18]. The hypertension associated complications increase with the number of foetuses, singletons were found 6.5%, twins 12.7%, and triplets were found to have 20% chances of complications[19], females with twins have shown 14% and those with triplets have 30% chances of preeclampsia[20,21]. Mothers with stage-1 hypertension have an increased chances of GH and PE[22]. Many mother associated risk factors include insulin resistance, abnormal lipid metabolism, obesity, family history, and late age during pregnancy[23,24].

Pathogenicity of PE has been reported as a two stage process. The blastocyst implantation into the endometrium leads to its growth into an outer trophectoderm an inner cell mass that develop outer villi and embryo respectively. Placenta is developed from the outer villi and gets attached to the mother's uterus resulting in the remodelling of spiral artery. Problems in the invasion of trophoblast to the spiral arteries result in the uteroplacental malperfusion and vascular dysfunction (stage 1)[25]. Ischaemia-reperfusion in the placental tissue initiates the production and of reactive oxygen species (ROS), antiangiogenic factors, and cytokines and their subsequent release into the mother's circulatory system resulting in the systemic inflammation and endothelial dysfunction (stage 2)[26,27]. All the above hypertensive disorders enhance the risk of cardiovascular and renal complications during life after pregnancy[28,29]. GH and PE also promote the insulin resistance by increase in the ROS production via NF-kB-mediated pathway[30]. The low birth weight, premature delivery or mortality, and cardiac complication in infants are also associated with GH and PE[31,32]. Administration of aspirin can significantly (35% to 66%) reduce the chances of PE development in women with high risk of disease. Therefore, aspirin is recommended internationally to reduce the chances of PE[33-35]. Once the disease is diagnosed, delivery remains the ultimate solution for PE[36,37]. The recent developments in aetiology, health impacts and management of GH and PE are the areas of concern for the gynaecologists in particular and for the physicians in general. In this context, the present review article was aimed to accumulative account of recent developments in GH and PE.

## RISK FACTORS AND EPIDEMIOLOGY

Concept of GH and PE as two different manifestations of the same disease or separate entities with similar symptoms is not very clear. In many PE patients, hypertension occurs before proteinuria on the other hand, GH does not always progress to PE[38]. Studies on the risk factors of GH and PE can improve the understanding of aetiological mechanisms and treatment options of these diseases[39-41]. According to the hypothesis considering PE as a syndromic condition, GH and PE being the progressive stages of the same disorder, the common risk factors can suggest common aspects of aetiology[42]. Many risk factors of PE are based on the environment, drug applications, and genetics of mother and foetus. Genetics of PE is complicated, more than 178 potentially associated genes have been described. However, the mechanism of its inheritance is not clearly understood[43]. Some of the prominent risk factors have been tabulated (Tables I, II).

Some other risk factors include maternal smoking habits, age at gestation, number of pregnancies, pre-gestation obesity, diabetes, hypertension, chronic kidney disease, multifetal pregnancies, trisomy 13, family history, and foetal genetics[44,45]. A great deal of heterogeneity is found in the epidemiology, representative clinical characteristics, and morbidity of preeclampsia. The condition can be established after 20 weeks or after 34 weeks of gestation[46,47]. Restriction of intrauterine growth and maternal obesity lead to early and late onset of disease. Clinically, the both types of preeclampsia are represented differently but the pattern of gene expression is similar in both cases indicating a common mechanism of maternalvascular damage[83]. Some of the above-mentioned proteins including PAPP-A, PlGF, sFlt, PP13, and sEng are used as diagnostic markers for PE.

**Table I. Gestational hypertension and PE associated genetic risk factors (genes, genetic polymorphism).**

| Description of risk factors | | References |
|---|---|---|
| **Candidate gene (Gene product)** | **Physiological role** | |
| *STOX1* (Storkhead box 1) | Coagulation, trophoblast development, hypoxia, inflammation | 48 |
| *FOXD1* (Forkhead box D1) | Development, inflammation, immune system | 49,50 |
| *NLRP* (Nod-like receptor protein family) | Immune system, reproductive system | 51 |
| *TRIM28* (Tripartite motif containing 28) | Transcription inhibition, histone modification | 52,53 |
| *EPAS1* (Hypoxia-inducible factor 2-alpha (HIF-2α)) | Regulation of physiology at different oxygen levels | 54 |
| *NOS3* (Nitric oxide synthase 3) | Production of nitric oxide, blood circulation control | 55 |
| *OXGR1* (2-oxoglutarate receptor 1) | Transcription regulation | 56 |
| *IGFBP1* (Insulin like growth factor binding protein 1) | Binds both insulin-like growth factors to enhance its half life | 57 |
| *MTHFR* (Methylen etetrahydrofolate reductase) | Re-methylation of Hcy to methionine | 58-60 |
| *AGT1/AGT2* (Angiotensinogen) | Regulation of blood pressure | 61, 62 |
| *AGTR1* (Angiotensin II receptor type 1) | Regulation of blood pressure, salts and fluids | 63, 64 |
| *TNF-α* (Tumour necrosis factor-alpha) | Multifunctional proinflammatory cytokine | 65,66 |
| *RGS2* (Regulator of G protein signaling 2) | Regulates G protein-coupled receptor ignalling cascades | 67,68 |
| *VDR* (Vitamin D receptor) | Cellular response to vitamin D | 69,70 |
| *CTLA-4* (Cytotoxic t-lymphocyte antigen-4) | Immune response | 71 |
| *TGFB1* (Transforming growth factor beta 1) | Immunoregulation | 72 |
| *LEP* (Leptin) | Hormone | 73,74 |
| *PAPP-A* (Pregnancy-associated plasma protein A) | Regulates the insulin growth factor in pregnancy | 75-78 |
| *PLGF* (Placental growth factor) | Plays important role in vasculogenesis and angiogenesis | 79,80 |
| *sFlt* (Fms-like tyrosine kinase 1) | Circulating antiangiogenic protein prepared by placenta | 81,82 |
| *PP13* (Placental protein 13 produced by trophoblasts) | Vasodilation and vascularization during placenta formation | 83-85 |
| *sENg* (Soluble endoglin) | Angiogenesis | 86-87 |

## PATHOGENESIS

Although a considerable progress has been made during the last two decades yet the pathophysiology of PE is not clearly understood. The structural components and biochemical substances and processes contribute to the pathogenesis of PE. As for example, structure and physiology of placenta play a vital role in the pathogenesis of PE[84]. Placenta a link between the circulatory systems of mother and foetus is a vascular organ consisting of capillaries with about 550 km in length and 15m$^2$ surface area[90]. The extensive vasculogenesis process required for the normal physiology of placenta is influenced by proangiogenic and antiangiogenic factors. The concentration of circulating placental growth factor (PIGF) increases that interacts with a membrane anchored receptor known as fms-like tyrosine kinase 1 resulting in the activation of endothelial cells and initiation of angiogenesis. During the 30 weeks of pregnancy, highest levels of circulatory PIGF are found that helps in the maturation of vessels between uterus and placenta[91]. On the other hand, PIGF also interacts with a soluble fms-like tyrosine kinase 1 (sFLT1) has antiangiogenic properties. It reduces the availability of PIGF to the anchored receptor, reduces nitric oxide levels, promotes the effects of proinflammatory cytokines with endothelial cells consequently resulting in the vasoconstriction[92,93]. Hence, a balances of proangiogenic and antiangiogenic factors is necessary for the normal placental development and physiology. According to some reports the women suffering from PE have low concentrations of PIGF and higher concentrations of soluble fms-like tyrosine kinase 1 that is contrary to those with normal pregnancies[94,95].

**Table II. Mother and foetus associated risk factors.**

| Risk factor | Function | References |
|---|---|---|
| Use of selective serotonin reuptake inhibitors (SSRIS) (Used as antidepressants, mood control, depression control) | Directly interact the transporter protein and inhibit the reuptake of serotonin / Reportedly, promote GH and PE | 96,97 |
| Assisted reproductive technology (ART) modern technology applied to treat infertility including IVF (*in vitro* fertilization), ICSI (intracytoplasmic sperm injection) etc. | Increased the chances of GH and PE | 98 |
| Elevated plasma uric acid levels (produced by the breakdown of purine nucleotides. Meat, dried beans are rich sources of purines) | Promotes GH and PE | 13 |
| Threatened miscarriage (Signs and symptoms like lower abdominal pain, little vaginal bleeding or spotting) | Enhanced the chances of GH and PE | 99 |
| High BMI (Body mass index) of mother (Higher BMI is also known as obesity) | High BMI at gestation time increases the chances of GH and PE | 100 |
| High consumption of soft drinks (carbonated drinks) | Excessive consumption of soft drinks during pregnancy increase the chances of GH and PE | 101 |
| Oocyte donated pregnancies (In case of IVF, if the female have weak egg, it can be donated by some healthy woman) | Pregnancies based on donated eggs have been associated with an increased chances of GH and PE | 102 |
| Obstructive sleep apnea (Blockage of air pathways by the relaxation of throat muscles and disturbance in breathing that results in snoring or obstruction in the sleep). | Reportedly increases GH and PE | 103 |
| Dysbiosis of gut microbiota (The disturbance in the normal (healthy) ecology of gut microbes) | Enhance the chances of GH and PE | 104,105 |
| Oxidative stress (Effect of reactive oxygen species (ROS)) | Promotes the onset of GH and PE | 106 |
| Pregnancies with twins (The pregnancies with two or more foetuses) | Such pregnancies have 2 to 3 times increased risk of GH and PE development | 107 |
| COVID-19 infection (COVID-19 infection during pregnancy increases the levels of pro-inflammatory cytokines) | Chances of GH and Pe are enhanced in if pregnant women suffer from COVID-19 | 108 |

Structurally, placenta consists of many different types of cells that constitute its internal and external architecture. The inner cells that differentiate in to embryo include pericytes, endothelial cells, and smooth muscle cells. The syncytial outer layer consists of trophoblasts with an ability to invade the wall of uterine and differentiate in to the outer layer of foetus and placenta. These cells forming a thick layer are known as syncytiotrophoblasts. The surface of villi are covered by the syncytiotrophoblasts which brings these cells in direct contact with the maternal circulation [109,110]. Preeclampsia is a human specific disease, not found in other mammalian species. This due to the high brain to body ratio of human foetus. During the third trimester of pregnancy human foetus requires up to 60% nutritional exchange from mother's circulation whereas in other mammalian species the nutritional exchange demand is about 20%[111]. Therefore, the normal development and physiology of placenta is necessary to meet the nutritional requirements of foetus[112-114]. Pathogenesis of PE is a multi-step process mainly initiated by the abnormal placentation. Uterine arteries divide into several branches that provide blood to decidua (blastocyst attachment area), myometrium or open as spiral arteries in the intravillous space. Invasion of defective trophoblasts into the spiral arteries cause injuries to the walls of blood vessels and result in the incomplete subsequent remodelling. This invasion may occur long before the detection of pregnancy and long before the symptoms of the disease are apparent [115-117]. Under the normal conditions the decidualization process is prolonged to the most of the areas of endometrium and increase the chances of blood supply to the foetus by remodelling of spiral arteries. However, the molecular mechanism involved in the remodelling of spiral arteries is not clearly known[118,119]. A series of experiments involving the analysis of placental biopsy samples has shown that the spiral arteries from preeclamptic samples were significantly narrow (200 µm) as compared to those from the normal samples (500 µm). This may result in the high velocity blood flow and uterine hypoperfusion in preeclampsia[120-122].

The abnormal placentation and failure to the remodelling of spiral arteries are central to the PE pathogenesis. Studies on the analyses of placental metabolic profiles during the first trimester have revealed that energy needs remain unaffected.

Even under hypoxia, the trophoblast manage the routine proliferation by increasing the levels of HIF1α (hypoxia-inducible factor 1α), a transcription factor that also regulates the expression of nitric oxide (NO) synthase and vascular endothelial growth factor (VEGF)[123,124]. Normally, the level of HIFα increases at early weeks of pregnancy and then decreases. A continuously elevated level of HIFα indicates the chances of PE development[125]. The two stage model for the establishment of PE is supported by preclinical and clinical studies[126,127]. First stage is represented by incomplete remodelling of spiral artery resulting in ischemic placenta and hypoxic conditions, in the second stage ischemic placenta releases antiangiogenic factors into the maternal circulation with subsequent endothelial dysfunction (Fig. 1).

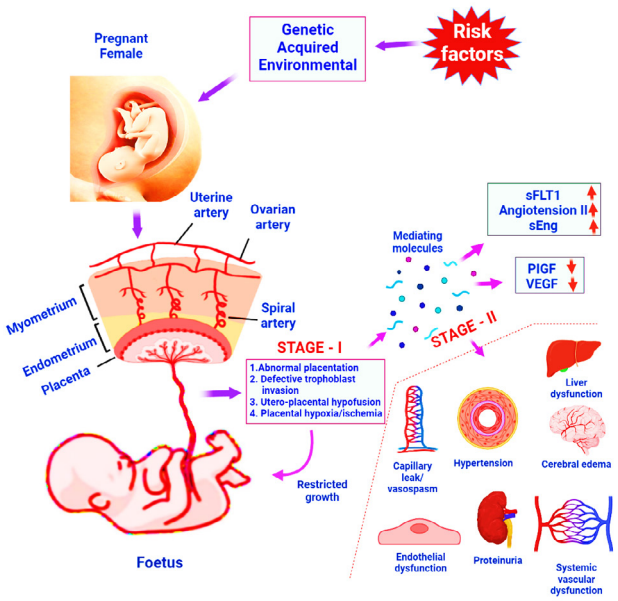


Fig. 1. Schematic representation of stage I and stage II of preeclampsia pathogenesis.

According to some studies, during spiral artery remodelling, the syncytiotrophoblast cells undergo apoptotic conditions and release a large number of syncytiotrophoblast-derived extracellular vesicles (SDEVs) into the blood circulation of mother. The level of SDEVs increase in the normal mother and becomes maximum during the third trimester. Its highest level can be found much earlier in case of PE due to hypoxic and ischemic placenta-e. A big (10% to 250%) difference of plasma SDEVs levels can be found in normal pregnancies and during PE. The difference in biological activities of these vesicles in case of normal and PE cases has been suggested[128,129]. In fact, the SDEVs produced during PE are strong promoters of inflammation, coagulation, endothelial damage, anti-angiogenic and vesoconstritive conditions as compared to those produced during normal pregnancies[130-132]. These processes not only enhance the injuries to the endothelial cells but also damage the placental vasculature and vessels of vital organs[133].

## MOTHER AND FOETUS ASSOCIATED POSTPARTUM OUTCOMES OF PREECLAMPSIA

According to the growing evidence, preeclampsia is not only a pregnancy disease but the patients suffering from PE have higher risk of negative health outcomes. According to the American Heart Association the mothers with PE have a long term risk of cardiovascular diseases (CVDs), and it should be considered during CVD risk evaluation[134-136]. According to meta-analysis the mothers with PE history have up to 4.2 times, 2.5 times, 1.8 times, and 6.7 times increased risk of heart failure, coronary artery disease, stroke, and hypertension respectively. According to similar reports such women have a double risk for thromboembolism and 4 times risk of diabetes mellitus in future[137,138]. The mothers with a history of PE have 3.8 times higher risk of periphery artery disease (PAD)[139], more than 30% of them suffer from asymptomatic atherosclerosis[140]. The studies have reported increased risk of left ventricular hypertrophy or dysfunction among the mothers with PE[141-142]. However, the risk of all the above conditions is variable among the women from different ethnic and geographic groups[143]. The individuals born after PE influenced pregnancy remain at high risk of stroke and hypertension at their adult age[144,145]. A study conducted on 45000 individuals born to preeclampsic pregnancy has demonstrated 2.39 mmHg and 1.35 mmHg increase systolic and diastolic blood pressures, respectively. These findings suggest 8% increased risk of ischemic heart disease and 12% increased chances of stroke. The cases when the mothers had early onset of preeclampsia, the children had up to 6 mmHg increase in the overall systolic blood pressure[146], these individuals have a specific hypertensive vascular structure[147]. Offsprings born after GH and PE pregnancy have problems in the cardiac structure and function[148]. The vascular remodelling demonstrates an increased risk of neuronal damage, especially the white matter and dementia[149-151]. An inverse relationship between the severity of GH, PE and development of foetus has been reported[152].

The women with preeclampsia have high risk of diabetes postpartum. The chances of diabetes onset increases up to 2 times in the presence or absence of GE[153,154]. Such women are prone to microalbuminuria and potential kidney disease[155], the risk of end stage renal disease (ESRD) was reportedly increased up to 15.5% in case of three PE pregnancies[156]. Histopathological studies have shown focal segmental glomerulosclerosis (FSGS) associated with PE[157-159]. Preeclampsia associated oxidative stress, dysregulation of immune system, and growth factor has been reported to

increase the risk of neurodevelopmental problems[160]. Studies have been conducted to associate the risk of migraine in case of PE[161].

## ASSESSMENT AND MANAGEMENT OF PREECLAMPSIA

The efficient management of PE depends on three main factors, disease prevention measures, availability of methods for early diagnosis and targeted procedures for the treatment. Gynaecologists can evaluate women for the risk factors, the high-risk individuals with pre-existing hypertension, antiphospholipid syndrome or renal disease should be advised according to established guidelines[162,163]. Women with suspected disease onset may be subjected to placental growth factor, sFlt-1/PlGF ratio, and proteinuria evaluation[164-167]. Plasma levels of sEng and sFlt1are significantly high among the women with PE as compared to those with normal pregnancy, the elevated levels can be used to determine the severity of PE[168-172]. Starting before gestation to 36 weeks post gestation a moderately high dose of calcium (above 1g/day) can reduce the risk of PE[173-175]. Once PE is diagnosed, regular and continuous surveillance is recommended by urine, blood pressure test, accurate anomaly and dating scans along with the assessment of foetal growth at every 4 weeks intervals. In case of severe indications of disease plasma electrolytes, liver, kidney function tests, umbilical artery Doppler test, regular measurement of respiration rate, heart rate and blood pressure are recommended after short intervals. Medicine can be prescribed or therapeutic strategies may be adopted by the physicians after the consideration of symptoms and intensity.

In case of mild PE, the experts are recommended to prescribe fluorinated steroids before 34 weeks of gestation to promote the maturation of foetus. In case of severe PE before 34 weeks of gestation termination of pregnancy is recommended after 34 weeks of gestation immediate delivery remains the only solution[176]. According to studies, the delayed delivery in severe PE cases can result in pulmonary edema, severe hypertension, HELLP syndrome, and liver damage to the mother. It can also cause abnormal heart rate, growth retardation, prenatal death, reverse end-diastolic flow in the umbilical artery that can be determined by Doppler ultrasound, and abruptio placentae to the foetus[177]. Several therapeutic strategies have also been recommended to prolong safe pregnancy in case of PE, some of these strategies are being discussed here:

Antihypertensive medication is aimed to prevent hypertensive encephalopathy, intracranial haemorrhage, and pulmonary edema. There is a universal consensus that there should not be an abrupt decrease in the blood pressure to maintain utero-placental blood flow. A 10 to 20 mm of Hg decrease in 10 to 20 min is recommended by some studies[178,179]. The medicines can be prescribed by a qualified physician, there is no clear advantage of one medicine on the other. According to recommendations labetalol and calcium channel blockers can be used as a first line drug against hypertension. According to some other reports the use of ketanserin, nitroprusside, chlorpromazine, and diazoxide should be avoided. $MgSO_4$ has shown no significant effect on severe hypertension[180,181]. The use of antihypertensive medicines during pregnancy with PE can reduce the risk of stroke but have shown hazardous impacts to the mother[182,183]. According to a study involving 2200 individuals, the chances of PE are reduced up to 50% if a low dose aspirin is used from 12-16 weeks before gestation to 36 weeks of gestation[173,184-186]. In another clinical study 1776 pregnant females diagnosed with low PIGF levels were enrolled, a treatment with 150 mg of aspirin per day reduced the onset of PE up to 62% as compared to placebo. On the basis of these results, low dose of aspirin is recommended to the females at high risk of PE[187-189]. Non-specific antioxidants have not shown significant effect in prevention of PE. The studies on the sources of oxidative stress are required to define the therapeutic targets[190-192].

Statins have been widely used for the activation of vascular function by stimulating the expression of haem oxygenase (HO), nitric oxide synthase (NO) and reducing the decrease in sFLT1 by placenta[193,194]. These medicines have shown promising results to prevent PE in pre-clinical studies[195,196]. Similar results have been reported in clinical studies by using pravastatin[197-199]. Pre-clinical studies have been conducted by using the ligands of sFLT1 such as recombinant VEGF121for the therapy against PE in rats. The results have shown an inhibition of hypertension and amelioration against renal disease without any adverse effects to the foetus[200,201]. Preclinical studies conducted on rodents and primates, recombinant PIGF another ligand of sFLT1 exhibited promising results against PE and hypertension. PIGF is highly specific for sFLT1 and dose not bind with sFLT2 and has no adverse effects[202-204]. Pre-clinical studies have shown that a pregnancy associated protein known as relaxin has potential therapeutic effects against PE induced hypertension and improves utero-placental perfusion in rats[205]. Apheresis is a procedure used in medical sciences in which the blood from a person is passed through an equipment to separate a specific ingredient and the remaining blood is returned to the person's circulation. It provides an attractive option to remove antiangiogenic proteins from the blood of pregnant mothers who are at high risk of PE[206]. Studies have been conducted to remove LDL and sFLT1from the blood of patients that give significant positive effects[207,208]. The studies on the application of small molecules in the PE therapy have also been reported. Placental hypoxia plays a vital role in the pathogenesis of PE, the production of hypoxia induced factors i.e. HIF1, HIF2, and sFLT1 are inhibited by ouabain and digoxin resulting in the reduction of hypertension in rats with ischemic placenta[209]. Metformin is a drug that improves the sensitivity to insulin and used to treat diabetes type 2, it has been beneficial in the management of PE[210-212]. Small

interfering RNA (siRNA) that are used to inhibit the synthesis of specific cellular proteins. The specific siRNA has been used to target sFLT1 in cell lines[213].

## CONCLUSIONS

Preeclampsia, a pregnancy associated complication has serious health threat to the mother and child worldwide. The characteristic signs and symptoms of disease include onset of hypertension at before or after 34 weeks of pregnancy, release of proteins in the urine, and subsequent damage to the kidneys, liver and cerebral part of brain. There are several genetic and environmental risk factors associated with the disease. The pathophysiology of disease is not completely understood. However, a two-stage mechanism of pathogenesis is well established. According to this mechanism PE is triggered by structural and functional problems in the placenta, production of defective trophoblasts, failure in proper remodelling of spirl artery, problems in the blood flow between mother and the foetus. These conditions result in the ischemic placenta, hypoxic conditions, regulation of expression of several genes including those coding for proangiogenic and antiangiogenic factors. The consequence of all these changes from normal pregnancy conditions is the onset of PE. Disturbance in the balance between proangiogenic and antiangiogenic factors is the hallmark of PE and these factors provide biomarkers for the early detection of disease. The disease is not restricted to the pregnancy periods, it has severe postpartum consequences including CVDs, hypertension, neurological and developmental problems for the mother and child. In case of severe PE, delivery is the only treatment. However, under minor to mild conditions aspirin, antihypertensive medicines and other biochemical therapies can be adopted. Restoration of angiogenic balance during the future pregnancies by administration of proangiogenic factors, removal of antiangiogenic factors can provide a useful measure to prevent PE. However, the development of strategies against postpartum outcomes for the child and mother need extensive research.

## DECLARATIONS

*Authors' contribution*

Conceptualization: MSN, BNM, IK. Writing original draft preparation: MSN, IU. Writing review and editing, critical revision: MNB, SJG, MMG, SIA, AU, SA.

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