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Original Research Article

Preeclampsia: Current Insights into Pathogenesis, Diagnosis, and Emerging Therapeutic Strategies

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Name of Author:
Dr. N Rachitha[1], Dr. Saumya[1], Dr. Kavya Manjunath[2], Dr Mahesh M Nosenoor[1], Dr. Usha D S[1]*, Dr. Shilpashree Bettadapura Muralidhar[1]

Affiliation: *[1]Department of Pharmacy Practice, KLE College of Pharmacy, Bengaluru 560010, KLE Academy of Higher Education and Research, Belagavi 590010, Karnataka, INDIA*
[2] Department of Pharmaacolgy, KLE College of Pharmacy, Bengaluru 560010, KLE Academy of Higher Education and Research, Belagavi 590010, Karnataka, INDIA

Corresponding Author:
Dr. Usha D S

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Abstract: Preeclampsia is a severe type of high blood pressure affecting 2-8% of pregnancies globally, leading to maternal and neonatal health issues. Risk factors include persistent high blood pressure, diabetes, autoimmune disorders, older age, obesity, and family history. Recent research has identified additional risk factors like sleep apnea and assisted reproduction treatments. The condition results from abnormal placental formation, inflammation, oxidative stress, and endothelial dysfunction. Biomarker tests, such as the ratio of soluble fms-like tyrosine kinase-1 to placental growth factor, may facilitate early prediction. Low-dose aspirin and vitamin D could prevent preeclampsia in high-risk women, with ongoing research exploring new treatment options.

Keywords: Preeclampsia, pregnancy complications, pathophysiology, biomarkers, diagnosis, treatment, maternal health.

INTRODUCTION

Preeclampsia, the origin of this word, dates back to the ancient Greek era. Breaking down the term, 'Pre', which means 'before', and '*eklampsís*', which is a Greek word for eclampsia and translates as a burst of lightning or a sudden onset (in literal terms) (*Etymonline, 2023)*. Preeclampsia is a condition seen in pregnant women (after 20 weeks of gestation) where there is a spike in the blood pressure, damaging the foetus *(American College of Obstetricians and Gynecologists, 2019), (World Health Organization, 2011)*. Eclampsia is a condition of the onset of seizure in women with preeclampsia. It occurs during or after delivery. Preeclampsia is a condition that occurs before eclampsia; hence, it is termed as pre-eclampsia, whereas eclampsia occurs in a pre-eclamptic condition along with seizures.

Pre-eclampsia is a complication of pregnancy wherein the blood pressure spikes to ≥ 140/90 mm

Hg *(Phipps et al., 2019)*. Though the etiology remains unclear, this condition causes maternal and fetal abnormalities. India suffers one-tenth of all maternal deaths due to pregnancy-associated complications *(World Health Organization, 2011)*.

The key symptom of Pre-eclampsia is new-onset hypertension, which generally occurs after 20 weeks of gestation along with proteinuria (300 mg per 24-hour urine collection) and end-organ damage*(Ma'ayeh & Costantine, 2020)*.

Diagnosing Pre-eclampsia is not only associated with the presence of the above two symptoms but also with other complications like new-onset renal insufficiency, impaired liver function, etc., and is not associated with any other etiology. Although delivery can resolve many signs and symptoms, it often persists in the form of Postpartum Preeclampsia *(American College of Obstetricians and Gynecologists, 2019)*.

The real meaning and understanding of Preeclampsia have evolved over centuries, ranging from the bizarre theories of ancient Greece by Hippocrates to research papers published by scientists all over the world, and the process is still in progress *(Bell, 2010)*.

Epidemiology:

Preeclampsia, affecting 2-8% of pregnant women, leads to approximately 500,000 fetal and 70,000 maternal deaths yearly. Its prevalence is rising in developed countries, particularly impacting African-American women more than other ethnicities. The National Hospital Discharge Survey noted a 5.9% incidence rate of hypertensive disorders of pregnancy in the USA, contributing to high rates of caesarean sections, prematurity, severe morbidity, and maternal death, with risks elevated 3-25 times in affected pregnancies. *(Phipps et al., 2019), (Ives et al., 2020), (Rana et al., 2019).*

Etiology:

Preeclampsia has an aetiology that is unknown. At the moment, the following 4 hypotheses are the focus of in-depth research:

1) Placental ischemia
2) Immune maladaptation
3) Very low-density lipoprotein vs toxicity-preventive activity
4) Genetic imprinting *(Dekker & Sibai, 1998*.

Risk factors:

According to the 2020 National Institute for Health and Care Excellence (NICE) guidelines, the risk factors for preeclampsia have been divided into 2 categories: i) Moderate and ii) high. NICE guidelines classify preeclampsia risk factors into moderate and high, including first pregnancy, family history, age over 40, BMI over 35, and long pregnancy intervals. Women are considered at high risk of preeclampsia if they have co-morbidities such as chronic kidney disease, type 1 or type 2 diabetes, autoimmune diseases such as systemic lupus erythematosus or antiphospholipid, chronic hypertension, or hypertension during previous pregnancy *(Barrett, 2020)*. Bartsch et al. identified preeclampsia risk factors, recommending aspirin, with oocyte donation increasing risk compared to IVF or natural conception. *(Fox et al., 2019)*.

Pathophysiology:

Preeclampsia, which has an impact on many organ systems, is a sophisticated disease progression that emerges from the maternal-fetal junction. The largest aspect of the condition, which may or may not always be associated with proteinuria, is hypertension [7]. Although this is a major field of ongoing international studies, the following mechanisms leading to the pathophysiology seem to be inadequately defined. Thus, preeclampsia (a placental condition) develops in 2 stages:

Stage 1: Abnormal placentation
Stage 2: A maternal syndrome in the latter 2nd and 3rd trimesters, which is marked by an increase of antiangiogenic elements *(Rana et al., 2019)*.

Stage 1: Abnormal Placentation:

This usually occurs in the 1st trimester of pregnancy. The early stages of preeclampsia are known as the placental syndrome. Preeclampsia can be developed only in the presence of a placenta and not a foetus, which is noticeable by the growth of the condition in a hydatidiform mole *(Phipps et al., 2019)*. Decidual vasculopathy in preeclampsia involves endothelial proliferation, fibrin deposition, and smooth muscle loss. Two patterns identified are acute atherosis and hypertrophic DV, contributing to preeclampsia *(Hecht et al., 2016)*.

Preeclampsia was not found to occur in other species except for humans. This may be because the human fetus has a high ratio of brain: body weight, and in the 3rd trimester of pregnancy, almost 60% of nutrition is exchanged from mother to foetus, whereas in other species, only 20% is exchanged *(Phipps et al., 2019).*

The myometrial spiral arteries are remodeled by trophoblast invasion during implantation to enhance blood flow to the fetus. Defective remodeling can lead to oxygen deprivation, oxidative stress, and ischemia, notably in hypertensive pregnancies *(Phipps et al., 2016).*

Thus, abnormal placentation includes the following factors:

a. Oxidative stress
b. Invasion of trophoblasts and hypoxia

c. The immune response

Oxidative stress

Pro-inflammatory oxidative stress results from an imbalance of oxidants and antioxidants, leading to reactive oxygen species' production, damaging redox signaling and contributing significantly to preeclampsia *(Aouache et al., 2018)*.

In healthy pregnancies, antioxidant mechanisms counter lipid peroxidation, but preeclampsia patients lack this capability, leading to oxidative stress imbalances. *(Chiarello et al., 2020*).

Invasion of trophoblasts and hypoxia

Hypoxia is significant in preeclampsia pathogenesis, linked to shallow trophoblast invasion and inadequate spiral artery remodeling *(Chiarello et al., 2020)*. In 1914, Young found that women with toxaemia, albuminuria, and eclampsia had more placental infarcts than those without. Studies in the 1960s noted significant differences in placentation between pre-eclamptic and normotensive pregnancies, highlighting arterial abnormalities. Pregnancy affects placental function, particularly in preeclampsia. HIF1 promotes trophoblast growth and regulates genes under hypoxia, peaking in the first trimester *(Phipps et al., 2019).*

sFLT1 generation, linked to maternal syndrome, is limited by 2-methoxyestradiol's inactivation of HIF-1, crucial in pre-eclampsia. Pre-eclamptic placentae show high HIF1/HIF2 levels and fail to downregulate upon oxygenation. Advanced MRI techniques can assess placental perfusion and suggest new non-invasive monitoring methods. *(Phipps et al., 2019), (Rana et al., 2019).*

Studies show that in 10 to 20% of women with severe preeclampsia, the HELLP syndrome (hemolysis, increased liver function tests, and low platelet count) develops; this incidence is almost 100 times that for other pregnancies (1 to 2/1000). Most HELLP syndrome pregnant women have proteinuria and hypertension, although some don't have either *(Dulay, 2019)*.

Ongoing discussions highlight that in pre-eclampsia, cytotrophoblasts fail to undergo pseudo-vasculogenesis, lacking typical endothelial markers. This differentiation issue suggests early mechanisms causing placental ischaemia, indicating pre-eclampsia stems from inadequate placentation and failure to remodel uterine spiral arteries. *(Phipps et al., 2019)*.

The immune response:

Understanding the immunological tolerance needed at the maternal-placental interface is essential in order to identify the underlying etiology of faulty placentation *(Phipps et al., 2019)*.

The complement system, crucial for immune response, causes inflammation and damage via liver-produced pathways. It defends against infections, especially in pregnancy, influencing placentation, though human studies yield inconsistent findings related to C1q deposition *(Collier et al., 2021)*.Pro-inflammatory macrophages secrete angiogenic chemicals, with M1 and M2 phenotypes influencing immune reactions and angiogenesis in pregnancies *(Aneman et al., 2020).*Pro-inflammatory cells are properly controlled and function, as well as their behaviors during invasion, thanks to Tregs and regulatory cytokines (Baker et al., 2009). It is widely known that Treg cells are crucial for maternal-fetal immunological tolerance in mice studies.(Faas and de Vos, 2017a). To generate immunological tolerance in the mother to the fetus, it is also thought that the dendritic cells (DCs) present in the decidua can encourage a dominating presence of T helper type 2 cells (Th2) in the uterus and placenta *(Raguema et al., 2020)*. PE is associated with Th1/Th17 cytokine imbalance and decreased Treg/Th2, resembling autoimmune patterns. *(Collier et al., 2021)*. Between 1980 and 2010, PE rates rose from 3.4% to 3.8%, with severe cases increasing 322% while moderate cases decreased; obesity significantly contributed to this rise *(Spradley et al., 2015)*.

Stage 2: A maternal syndrome in the latter 2nd and 3rd trimesters, which is marked by an increase of antiangiogenic elements.

Imbalance in Circulating Angiogenic Factors

Anti-angiogenic Factors are a group of proteins that prevent the formation of new blood vessels. One such protein is sFLT1, which acts by inhibiting the function of VEGF and PIGF. Anti-angiogenic factors prevent new blood vessel formation, with sFLT1 inhibiting VEGF and PIGF, vital for endothelial function in key organs. Studies link sFLT1 to preeclampsia, showing reduced PIGF in affected women and that sFLT1 injection induces preeclamptic symptoms. sENG, another factor inhibiting TGF-β1, correlates with preeclampsia severity, as seen in animal studies, affecting fetal growth and causing cerebral edema. s *(Rana et al., 2019*).

Inflammatory Cytokines and Immune Cell Alterations

Preeclampsia connects to inflammation via syncytial knots and microvesicles, influencing proinflammatory responses. Decreased IL-10 causes Th1 shifts, harming trophoblast invasion, while complement levels and Eculizumab offer treatment insights *(Rana et al., 2019)*.

Renin-Angiotensin Pathway

Preeclampsia pathogenesis involves altered renin-angiotensin-aldosterone pathways, increased sensitivity to angiotensin II, and AT1 autoantibodies. These factors lead to hypertension, endothelial dysfunction, and elevated antiangiogenic factors, highlighting a complex interplay in the condition's mechanisms *(Rana et al., 2019).*.

Sympathetic nervous system

Placental factors and maternal endothelial dysfunction are key in preeclampsia, but studies suggest the sympathetic nervous system's role as well. Increased sympathetic nerve activity and reduced baroreflex sensitivity are noted in preeclamptic women, linking it to placental ischemia-induced hypertension *(Rana et al., 2019).*

Diagnosis

Some screening methods used in 19-24 weeks of pregnancy for Preeclampsia are medical history and maternal demographic characteristics, mean arterial pressure (MAP), and uterine artery pulsatility index (UtA-PI) (alone or in combination) *(Litwinska et al., 2021)*

Presence of Biomarkers:

- According to Powe et al, levels of PlGF and sFlt-1 are altered in preeclamptic women (before and during the onset of clinical signs and symptoms) *(Powe et al., 2011)*
- This finding also supports the pathogenic function of Angiogenic factor.
- Normal pregnant women's serum levels of sFlt-1 are rather high at term, but they drop to non-pregnant levels 48 hours following birth.
- In preeclampsia, sFlt-1 levels start to rise at least 5 weeks before the start of the clinical disease and continue to be higher than in women who are not affected.
- Additionally, there is a correlation between sFlt-1 levels and disease severity.
- sEng levels in women with normal pregnancies are stable until approximately week 33 of pregnancy, when they rise, peaking at delivery *(Venkatesha et al., 2006).*
- In women with preeclampsia beginning before 37 weeks of gestation (preterm), levels of sEng begin to rise earlier, by 20 weeks of gestation, and rise more steeply after 33 weeks (Levine et al., 2006)
- Women with preeclampsia beginning after 37 weeks of gestation (term) also have elevated 3rd trimester sEng levels, but a slower rise, beginning at 25 weeks of gestation and rising steeply around 33 weeks of gestation.
- Preeclampsia is best characterised by a combination of sFlt-1, PlGF, and sEng levels, which connects the combined actions of many angiogenic factors to clinical preeclampsia *(Kusanovic et al., 2009).*
- Prior to the beginning of preterm preeclampsia, high circulating levels of both sEng and sFlt-1/PlGF are frequently seen *(Levine et al., 2004).*
- According to more recent research, maternal vascular dysfunction and reduced nitric oxide generation are linked to changes in sFlt-1, PlGF, and sEng in women with preeclampsia[27]
- The levels of sFlt-1, PlGF, and sEng have all been found to change in placental abruption brought on by pre-eclampsia *(Sandrim et al., 2008).*

RAAS Pathway

- A unique type of circulating oxidised angiotensinogen that promotes the production of angiotensin has recently been discovered in the blood of pre-eclamptic patients *(Zhou et al., 2010).*
- However, pre-eclamptic patients have decreased levels of circulating angiotensin II and aldosterone.
- To determine whether this oxidised form of angiotensinogen is altered before clinical illness, studies are required.

Cost-Effectiveness of Biomarker Testing

- When it comes to cost-effectiveness, some studies from various nations have demonstrated that using the sFlt-1/PlGF test to manage patients with suspected PE could result in cost savings by avoiding needless surgeries and hospitalization *(Venkatesha et al., 2006).*
- In Brazil, the calculated savings between public and private health care were R $185.06 and R$635.84 per patient, respectively *(Costa et al., 2022).*

Prediction in the First Trimester Using PlGF

The levels of PlGF in the blood differ significantly depending on maternal characteristics and co-morbidities; they are higher in pregnant women, smokers, and people of Afro-Caribbean, South Asian, and East Asian origin, and decreased in women with obesity or type 2 diabetes mellitus *(Lai et al., 2014).* Consequently, to standardise data and permit comparisons between research groups, adjustments must be made for these variables as well as other variances in biomarker testing and assay analysis. PlGF values can be reported as multiples of the expected median (MoM) in order to standardise the data *(Akolekar et al., 2008).*

The mean distribution of gestational age at birth with PE

is altered by the inclusion of specific maternal traits and biomarker values (MAP, UtPI, and PlGF) *(Wright et al., 2015)*.

Third and Fourth Trimesters PE prediction:

PE screening throughout the second and third trimesters tries to estimate the patient-specific risk, deciding the frequency and scope of a person's ongoing antenatal monitoring. Given the narrow window of opportunity for current prophylactic treatments, it is not primarily focused on PE prevention *(Roberge et al., 2018)* . First-trimester screening for early and preterm PE had a similar, if not superior, predictive value to the combination of maternal risk factors, mean UtPI, MAP, and PlGF According to studies, this combination screening between 19 and 24 weeks' gestation can accurately predict 46% of term PE, 85% of preterm PE, and 99% of early PE *(Gallo et al., 2016)* . Over 50% of instances of term PE are still missed by screening in the third trimester between 30 and 34 weeks, even though it can predict 98% of preterm PE cases *(Tsiakkas et al., 2016)*.

Serum PlGF and sFlt-1 in the Screening and Diagnosis of PE in Women with Suspected Disease:

NICE recommends four commercially available PlGF-based assays for diagnosing PE between 20 and 36 + 6 weeks' gestation. Each assay's thresholds differ, and second-trimester values can be converted to MoM for comparison. Angiogenic testing is now recommended *(Panaitescu et al., 2018)*.

Lacunae of Current Diagnosis:

Preeclampsia is diagnosed with elevated blood pressure and proteinuria. Current criteria may be inadequate; lab tests assess organ damage, but no definitive test exists yet. *(Black et al., 2019)*. The assessment of anti-angiogenic proteins helps identify preeclampsia in women with chronic disorders. Not all preeclampsia patients display altered sFlt1 and PlGF, and low levels may indicate misdiagnosis or a non-angiogenic illness form *(Levine et al., 2006)*.

Treatment

Given below, two research offer some potential therapies for preeclampsia.

Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia

Low-dose aspirin (150 mg daily) was tested in a multicenter, double-blind trial involving 1776 high-risk singleton pregnant women from 11 to 14 weeks to 36 weeks of gestation. Results showed 1.6% in the aspirin group had preterm preeclampsia, compared to 4.3% in the placebo group (odds ratio 0.38, P=0.004). Strong adherence (79.9% compliance) was noted, with no significant differences in neonatal adverse outcomes between groups, indicating aspirin reduces preterm preeclampsia risk. *(Story & Nelson-Piercy, 2018)*.

Vitamin D supplementation and incident preeclampsia:

Maternal vitamin D deficiency increases preeclampsia risk. A systematic review and meta-analysis of 27 RCTs showed that women receiving vitamin D throughout pregnancy had lower preeclampsia risk. Findings suggest that vitamin D supplements may help prevent preeclampsia. *(Fogacci et al., 2020)*.

Abbreviations

PE: Preeclampsia, **HDP**: Hypertensive Disorder of Pregnancy, **NICE**: National Institute for Health and Care Excellence, **BMI**: Body Mass Index, **IVF**: In Vitro Fertilisation, **DV**: Decidual Vasculopathy, **OS:** Oxidative Stress, **ROS:** Reactive Oxygen Species, **ETC**: Electron Transport Chain, **ER**: Endoplasmic Reticulum, **COX-2** : Cyclooxygenase-2, **XO** : Xanthine Oxidase, **NOX** : NADPH Oxidase, **NADPH** : Nicotinamide Adenine Dinucleotide Phosphate (reduced form), **L-arginine** : Amino acid, cofactor for nitric oxide synthesis, **BH4** : Tetrahydrobiopterin,
eNOS : Endothelial Nitric Oxide Synthase, ***NO** : Nitric Oxide, **$ONOO^-$** : Peroxynitrite, **GPX** : Glutathione Peroxidase, **HO** : Haem Oxygenase, **CO** : Carbon Monoxide, **LDL** : Low-Density Lipoprotein, **TNF** : Tumor Necrosis Factor, **PERK** : PKR-like Endoplasmic Reticulum Kinase, **TF** : Transcription Factor, **HIF** : Hypoxia-Inducible Factor, **VEGF** : Vascular Endothelial Growth Factor, **NO**: Nitric Oxide, **HELLP** : Hemolysis, Elevated Liver Enzymes, and Low Platelet Count, **VE** : Vascular Endothelial, **NCR**: Natural Cytotoxicity Receptor, **NK**: Natural Killer (cells), **Treg**: Regulatory T Cell, **DC**: Dendritic Cell, **Th**: T Helper (cell), **IL**: Interleukin **FOXO1**: Forkhead Box Protein 1, **M1/M2**: Macrophage Phenotypes (M1: pro-inflammatory, **M2**: anti-inflammatory), **sFlt-1**: Soluble fms-like Tyrosine Kinase-1, **PlGF**: Placental Growth Factor, **sEng** : Soluble Endoglin, **TGF-β1** – Transforming Growth Factor Beta 1, **PRES**: Posterior Reversible Encephalopathy Syndrome, **C1q, C3a, C4d, C5a, C5b9** – Complement Components, **MAC**: Membrane Attack Complex, **AT1-AA**: Angiotensin II Type 1 Receptor Autoantibodies, **C5**: Complement Component 5, **FDA**: Food and Drug Administration, **ET-1**: Endothelin-1, **AT1:** Angiotensin II Type 1 Receptor, **B2**: Bradykinin Type 2 Receptor **RAAS**: Renin-Angiotensin-Aldosterone System, **RCT**: Randomized Control Trial, **Arrb1**: β-Arrestin-1, **RUPP**: Reduced Uterine Perfusion Pressure,

MAP: Mean Arterial Pressure, **UtA-PI**: Uterine Artery Pulsatility Index, **MoM** : Multiples of the Median, **DR**: Detection Rate, **WHO:** World Health Organization.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest

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REFERENCES:

1. Etymonline. (2023, July 31). *Pre-eclampsia | Etymology, origin and meaning of pre-eclampsia.* https://www.etymonline.com/word/pre-eclampsia
2. American College of Obstetricians and Gynecologists (ACOG). (2019). *ACOG Practice Bulletin No. 202: Gestational hypertension and preeclampsia. Obstetrics & Gynecology, 133*(1), e1–e25.
3. World Health Organization. (2011). *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia.* Geneva: World Health Organization.
4. Phipps, E. A., Thadhani, R., Benzing, T., & Karumanchi, S. A. (2019). Pre-eclampsia: Pathogenesis, novel diagnostics and therapies. *Nature Reviews Nephrology, 15*(5), 275–289. https://doi.org/10.1038/s41581-019-0119-6
5. Ma'ayeh, M., & Costantine, M. M. (2020). Prevention of preeclampsia. *Seminars in Fetal and Neonatal Medicine, 25*(5), 101123. https://doi.org/10.1016/j.siny.2020.101123
6. Bell, M. J. (2010). A historical overview of preeclampsia–eclampsia. *Journal of Obstetric, Gynecologic & Neonatal Nursing, 39*(5), 510–518.
7. Ives, C. W., Sinkey, R., Rajapreyar, I., Tita, A. T. N., & Oparil, S. (2020). Preeclampsia: Pathophysiology and clinical presentations: JACC state-of-the-art review. *Journal of the American College of Cardiology, 76*(14), 1690–1702.
8. Rana, S., Lemoine, E., Granger, J. P., & Karumanchi, S. A. (2019). Preeclampsia: Pathophysiology, challenges, and perspectives. *Circulation Research, 124*(7), 1094–1112. https://doi.org/10.1161/CIRCRESAHA.118.313276
9. Dekker, G. A., & Sibai, B. M. (1998). Etiology and pathogenesis of preeclampsia: Current concepts. *American Journal of Obstetrics and Gynecology, 179*(5), 1359–1375.
10. Barrett, V. (2020). *NICE guidelines on pre-eclampsia.* Action on Pre-Eclampsia. https://action-on-pre-eclampsia.org.uk/wp-content/uploads/2020/01/NICE_guidance_on-Pre-eclampsia_VB2020.pdf
11. Fox, R., Kitt, J., Leeson, P., Aye, C. Y. L., & Lewandowski, A. J. (2019). Preeclampsia: Risk factors, diagnosis, management, and the cardiovascular impact on the offspring. *Journal of Clinical Medicine, 8*(10), 1625.
12. Hecht, J. L., Zsengeller, Z. K., Spiel, M., Karumanchi, S. A., & Rosen, S. (2016). Revisiting decidual vasculopathy. *Placenta, 42*, 37–43.
13. Phipps, E., Prasanna, D., Brima, W., & Jim, B. (2016). Preeclampsia: Updates in pathogenesis, definitions, and guidelines. *Clinical Journal of the American Society of Nephrology, 11*(6), 1102–1113.
14. Aouache, R., Biquard, L., Vaiman, D., & Miralles, F. (2018). Oxidative stress in preeclampsia and placental diseases. *International Journal of Molecular Sciences, 19*(5), 1496.
15. Chiarello, D. I., Abad, C., Rojas, D., Toledo, F., Vázquez, C. M., Mate, A., & Sobrevia, L. (2020). Oxidative stress: Normal pregnancy versus preeclampsia. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1866*(2), 165354.
16. Dulay, A. (2019). *Preeclampsia and eclampsia.* Merck Manuals Professional Edition. https://www.merckmanuals.com/professional/gynecology-and-obstetrics/abnormalities-of-pregnancy/preeclampsia-and-eclampsia
17. Collier, A. Y., Smith, L. A., & Karumanchi, S. A. (2021). Review of the immune mechanisms of preeclampsia and the potential of immune modulating therapy. *Human Immunology, 82*(5), 362–370.
18. Aneman, I., Pienaar, D., Suvakov, S., Simic, T. P., Garovic, V. D., & McClements, L. (2020). Mechanisms of key innate immune cells in early- and late-onset preeclampsia. *Frontiers in Immunology, 11*, 1864.
19. Raguema, N., Moustadraf, S., & Bertagnolli, M. (2020). Immune and apoptosis mechanisms regulating placental development and vascularization in preeclampsia. *Frontiers in Physiology, 11*, 98.
20. Spradley, F. T., Palei, A. C., & Granger, J. P. (2015). Immune mechanisms linking obesity and preeclampsia. *Biomolecules, 5*(4), 3142–3176.
21. Litwinska, M., Litwinska, E., Astudillo, A., Syngelaki, A., Wright, A., & Nicolaides, K. H. (2021). Stratification of pregnancy care based on risk of pre-eclampsia derived from biophysical and biochemical markers at 19–24 weeks'

gestation. *Ultrasound in Obstetrics & Gynecology, 58*(3), 360–368.

22. Powe, C. E., Levine, R. J., & Karumanchi, S. A. (2011). Preeclampsia, a disease of the maternal endothelium: The role of antiangiogenic factors and implications for later cardiovascular disease. *Circulation, 123*(24), 2856–2869. https://doi.org/10.1161/CIRCULATIONAHA.109.853127
23. Venkatesha, S., Toporsian, M., Lam, C., Hanai, J., Mammoto, T., Kim, Y. M., et al. (2006). Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nature Medicine, 12*(6), 642–649.
24. Levine, R. J., Lam, C., Qian, C., Yu, K. F., Maynard, S. E., Sachs, B. P., et al. (2006). Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *The New England Journal of Medicine, 355*(10), 992–1005.
25. Kusanovic, J. P., Romero, R., Chaiworapongsa, T., Erez, O., Mittal, P., Vaisbuch, E., et al. (2009). A prospective cohort study of the value of maternal plasma concentrations of angiogenic and anti-angiogenic factors in early pregnancy and midtrimester in the identification of patients destined to develop preeclampsia. *Journal of Maternal-Fetal & Neonatal Medicine, 22*(11), 1021–1038.
26. Levine, R. J., Maynard, S. E., Qian, C., Lim, K. H., England, L. J., Yu, K. F., et al. (2004). Circulating angiogenic factors and the risk of preeclampsia. *The New England Journal of Medicine, 350*(7), 672–683.
27. Sandrim, V. C., Palei, A. C., Metzger, I. F., Gomes, V. A., Cavalli, R. C., & Tanus-Santos, J. E. (2008). Nitric oxide formation is inversely related to serum levels of antiangiogenic factors soluble fms-like tyrosine kinase-1 and soluble endoglin in preeclampsia. *Hypertension, 52*(2), 402–407.
28. Signore, C., Mills, J. L., Qian, C., Yu, K. F., Rana, S., & Karumanchi, S. A. (2008). Circulating soluble endoglin and placental abruption. *Prenatal Diagnosis, 28*(9), 852–858.
29. Zhou, A., Carrell, R. W., Murphy, M. P., Wei, Z., Yan, Y., Stanley, P. L., et al. (2010). A redox switch in angiotensinogen modulates angiotensin release. *Nature, 468*(7320), 108–111.
30. Costa, M. L., Cavalli, R. C., Korkes, H. A., Cunha Filho, E. V. D., & Peraçoli, J. C. (2022). Diagnosis and management of preeclampsia: Suggested guidance on the use of biomarkers. *Revista Brasileira de Ginecologia e Obstetrícia, 44*(9), 878–883.
31. Lai, J., Garcia-Tizon-Larroca, S., Peeva, G., Poon, L. C., Wright, D., & Nicolaides, K. H. (2014). Competing risks model in screening for preeclampsia by serum placental growth factor and soluble fms-like tyrosine kinase-1 at 30–33 weeks' gestation. *Fetal Diagnosis and Therapy, 35*(4), 240–248.
32. Akolekar, R., Zaragoza, E., Poon, L. C. Y., Pepes, S., & Nicolaides, K. H. (2008). Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia. *Ultrasound in Obstetrics & Gynecology, 32*(6), 732–739.
33. Wright, D., Syngelaki, A., Akolekar, R., Poon, L. C., & Nicolaides, K. H. (2015). Competing risks model in screening for preeclampsia by maternal characteristics and medical history. *American Journal of Obstetrics and Gynecology, 213*(1), 62.e1–62.e10.
34. Roberge, S., Bujold, E., & Nicolaides, K. H. (2018). Aspirin for the prevention of preterm and term preeclampsia: Systematic review and meta-analysis. *American Journal of Obstetrics and Gynecology, 218*(3), 287–293.e1.
35. Gallo, D. M., Wright, D., Casanova, C., Campanero, M., & Nicolaides, K. H. (2016). Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 19–24 weeks' gestation. *American Journal of Obstetrics and Gynecology, 214*(5), 619.e1–619.e17.
36. Tsiakkas, A., Saiid, Y., Wright, A., Wright, D., & Nicolaides, K. H. (2016). Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 30–34 weeks' gestation. *American Journal of Obstetrics and Gynecology, 215*(1), 87.e1–87.e17.
37. Panaitescu, A., Ciobanu, A., Syngelaki, A., Wright, A., Wright, D., & Nicolaides, K. H. (2018). Screening for pre-eclampsia at 35–37 weeks' gestation. *Ultrasound in Obstetrics & Gynecology, 52*(4), 501–506.
38. Black, C., Al-Amin, A., Rolnik, D. L., et al. (2019). Midpregnancy testing for soluble fms-like tyrosine kinase 1 (sFlt-1) and placental growth factor (PlGF): An inter-assay comparison of three automated immunoassay platforms. *Placenta, 86*, 11–14.
39. Story, L., & Nelson-Piercy, C. (2018). Aspirin versus placebo in pregnancies at high risk for preterm pre-eclampsia. *Obstetric Medicine, 11*(2), 90–91. https://doi.org/10.1177/1753495X18775898
40. Fogacci, S., Fogacci, F., Banach, M., Michos, E. D., Hernandez, A. V., Lip, G. Y. H., et al. (2020). Vitamin D supplementation and incident preeclampsia: A systematic review and meta-analysis of randomized clinical trials. *Clinical Nutrition, 39*(6), 1742–1752.

