

## BLOOD BIOMARKERS TO PREDICT OF THE ONSET AND ADVERSE OUTCOMES OF PREECLAMPSIA : A SYSTEMATIC REVIEW

\*I Made Elga Aldela Paramerta

*\*Dr. Harjono General Hospital, Ponorogo Regency, Indonesia*

**Corresponding Author :**  
[elgaparamerta@gmail.com](mailto:elgaparamerta@gmail.com)

---

### ABSTRACT

**Background:** Pre-eclampsia is one of the most common pregnancy complications, and a major cause of fetal and maternal morbidity and mortality globally. Diagnosis currently takes place in the third trimester based on clinical symptoms. This systematic review sought to determine the blood biomarkers that are associated with pre-eclampsia, and in particular, the biomarkers that could predict pre-eclampsia in early pregnancy.

**Methods:** By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.

**Result:** In the PubMed database, the results of our search brought up 257 articles, whereas the results of our search on SagePub brought up 78 articles. The results of the search conducted for the last year of 2013 yielded a total 198 articles for PubMed and 54 articles for SagePub. In the end, we compiled a total of 5 papers, 4 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

**Conclusion:** PlGF and sFlt-1 are the most used in clinical practice, even if their specificity and sensitivity do not justify a default implementation into guidelines to screen all pregnant women. Their role is limited to rule-out a diagnosis of pre-eclampsia in women presenting with symptoms highly suggestive of the disease. Therefore, their current application is not useful for an early prediction of pre-eclampsia. Novel lines of research are needed to identify molecules able to detect pre-eclampsia in a timely manner and which have a predictive value high enough to justify the costs associated with routine measurements in the general pregnant population.

**Keyword:** Biomarkers, blood, pregnancy, preeclampsia

## INTRODUCTION

Preeclampsia is a pregnancy-specific disease, affecting 3-5% of all pregnancies. Its hallmark features are high blood pressure (hypertension) and endothelial dysfunction, leading to widespread end-organ injury. This includes the liver, blood, kidneys, brain and placenta. Preeclampsia is a significant contributor to maternal morbidity (including outcomes as severe as liver rupture, renal failure, seizures (eclampsia) and stroke) and mortality worldwide. With delivery the only current cure, preeclampsia also contributes significantly to prematurity, neonatal morbidity and perinatal mortality.<sup>1,2</sup>

Preeclampsia (PE) is a progressive, multisystem pregnancy disorder that can be a serious, even fatal condition. It affects 2%–4% of pregnancies worldwide and is responsible for nearly 46,000 maternal deaths and around 500,000 fetal and neonatal deaths every year. PE not only leads to adverse health outcomes for mothers and babies but also produces a substantial financial burden on the healthcare system. The healthcare cost for pregnancies with PE is significantly higher than uncomplicated pregnancies, including higher inpatient costs, birth costs, and postpartum costs, especially for newborns admitted to Neonatal Intensive Care Unit (NICU).<sup>3</sup>

The etiology of PE is still not fully understood, but the understanding of this disorder has been greatly improved. Increasing evidence has shown that PE is a complex and heterogeneous disorder, as reflected in several aspects, such as pathophysiology, clinical phenotypes, screening effectiveness, aspirin prevention performance, and clinical outcomes. Previously, PE was diagnosed as a new onset of hypertension and proteinuria after 20 weeks of gestation. The diagnostic definition was broadened in 2018 by the International Society of the Study of Hypertension in Pregnancy (ISSHP). The latest ISSHP guideline (2021) characterizes PE as hypertension arising *de novo* plus one or more other conditions, including proteinuria, maternal organ dysfunctions, and uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery Doppler, and imbalance of angiogenic markers (increased soluble fms-like tyrosine/placental growth factor (sFlt/PlGF) ratio or reduced PlGF) at or after 20 weeks.<sup>3</sup>

Previous research divided PE into early and late forms, whereas there is no consistent classification of PE subtypes. The gestational age of 34 or 37 is the cut-off value and is defined by the time of disease onset, diagnosis, or delivery. PE is widely accepted to be subclassified into early-onset (<34 weeks) and late-onset ( $\geq 34$  weeks), or preterm (delivery <37 weeks) and term (delivery  $\geq 37$  weeks). Despite the early and late subtypes sharing similar clinical symptoms, recent studies suggest that they have varied pathophysiology. Moreover, subtyping PE based on etiology has been proposed.<sup>4</sup>

Recently, there has been increased interest in predictive biomarkers for preeclampsia. An effective predictive test would facilitate early diagnosis, targeted surveillance and timely delivery. A biomarker able to predict high risk women in *early* pregnancy (less than 16 weeks) has clinical utility in preventing preterm preeclampsia (and associated preterm birth and perinatal morbidity) through administration of low-dose prophylaxis with aspirin to reduce preterm disease.<sup>5,6</sup>

A biomarker is an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention that could be used to predict, diagnose, and monitor diseases. This broad definition contains different types of biomarkers, such as molecular, histologic, radiographic, or physiologic characteristics. Useful biomarkers like biochemical markers (PlGF) or biophysical markers (mean arterial pressure, MAP) could improve the effectiveness of risk stratification for PE pregnancies, thereby creating a window of opportunity for clinicians to take preventative actions for high-risk women. Nevertheless, much previous research predicted PE as one type, and some focused more on reporting prediction achievement for the early form of PE. Apart from that, many biomarker studies tried to discover candidate predictors by using blood samples collected during PE diagnosis or placenta samples obtained after delivery, while those altered biomarkers may show better diagnostic value and reflect pathogenesis than the prediction.<sup>4</sup>

With a global incidence among pregnancies of 5%, pre-eclampsia (PE) is one of the major causes of maternal morbidity and mortality worldwide.<sup>7</sup> As established by the International Society for the Study of Hypertension in Pregnancy (ISSHP), a diagnosis of pre-eclampsia can be made where there is new-onset hypertension (systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg on two different occasions, 4 h apart) after 20 weeks of gestation with simultaneous proteinuria ( $\geq 300$  mg/24 h urine collection or protein/creatinine ratio  $\geq 30$  mmol/L or dipstick urine reading  $\geq 1$ ).<sup>8</sup> Severe clinical features of end-organ damage typical of pre-eclampsia include thrombocytopenia, hepatic and renal insufficiencies, pulmonary oedema, new onset of cerebral and visual symptoms and utero-placental dysfunction (such as growth restricted fetus).<sup>9</sup> Eclampsia is a life-threatening complication, requiring urgent medical treatment, and is defined by the occurrence of generalized seizures in a woman with pre-eclampsia.<sup>10</sup> Depending on the clinical onset of symptoms, pre-eclampsia can be classified as early-onset (first clinical presentation before 34 gestational weeks) and late-onset (disease develops at or after 34 weeks of gestation). More commonly, the former is associated with severe disease in both the mother and the child, including frequent development of fetal growth restriction; the latter is often accompanied by mild symptoms only.<sup>11</sup>

As established by the Food and Drug Administration (FDA) and the National Institute of Health (NIH), a biomarker is 'a defined characteristic that is measured as an indicator of normal processes, pathogenic processes or responses to an exposure or intervention.'<sup>12</sup> Blood, urine and imaging biomarkers have been widely used during pregnancy, with maternal

serum human chorionic gonadotropin (hCG) and progesterone being the most frequently adopted biomarkers to predict adverse pregnancy outcomes in early pregnancy.<sup>13</sup> The identification of a reliable, inexpensive, and non-invasive biomarker to predict the onset of pre-eclampsia in early pregnancy would be widely beneficial in reducing maternal and fetal complications by allowing better categorization of the disease according to its severity, monitoring its progression closely and detecting the disease before the clinical onset of any symptoms.<sup>14</sup> There may also be economical benefits, since early detection of disease could mean a reductions in healthcare costs. However, a biomarker with the characteristics has not been identified yet. Currently guidelines exist to stratify women at high risk of pre-eclampsia in the first trimester simply by using maternal characteristics and medical history, but the sensitivity for disease identification is very low. A more reliable screening for early (first trimester) detection of pre-eclampsia has been developed, which looks at mean arterial BP, Doppler ultrasound, and Placental Growth Factor (PIGF) blood measurements but has not been implemented into routine clinical practice due to the associated costs. Finally, the combination of PIGF and sFlt-1 during the third trimester (but before 37 gestational weeks) is used to rule out a diagnosis of pre-eclampsia when the disease is suspected, as recommended by NICE guidelines.<sup>12</sup>

**METHODS**

**Protocol**

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

**Criteria for Eligibility**

For the purpose of this literature review, we review the blood biomarkers to predict the onset and adverse outcomes of preeclampsia. This is done to provide an explanation and improve the handling of treatment at the patient. As the main purpose of this paper, to show the relevance of the difficulties that have been identified as a whole.

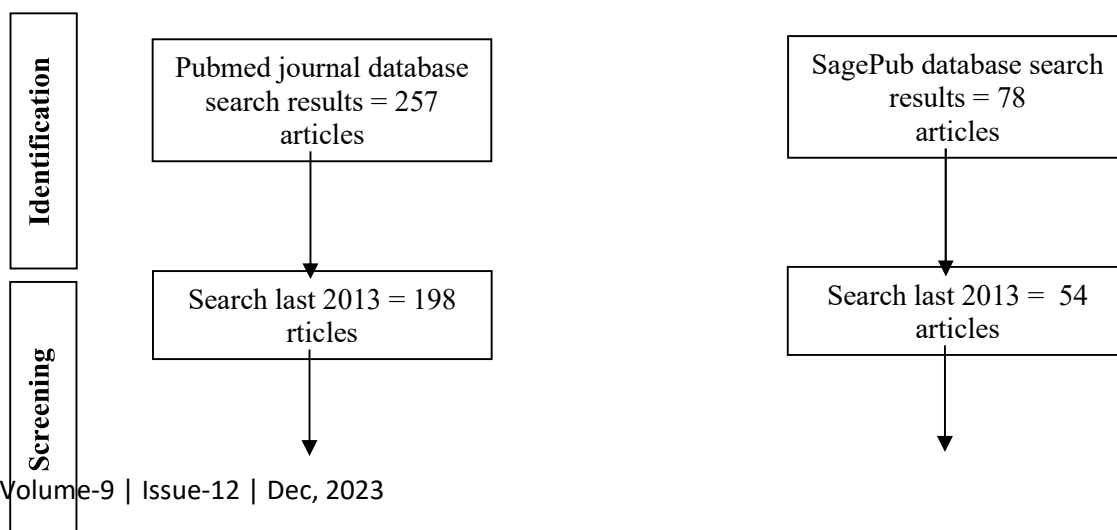
In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

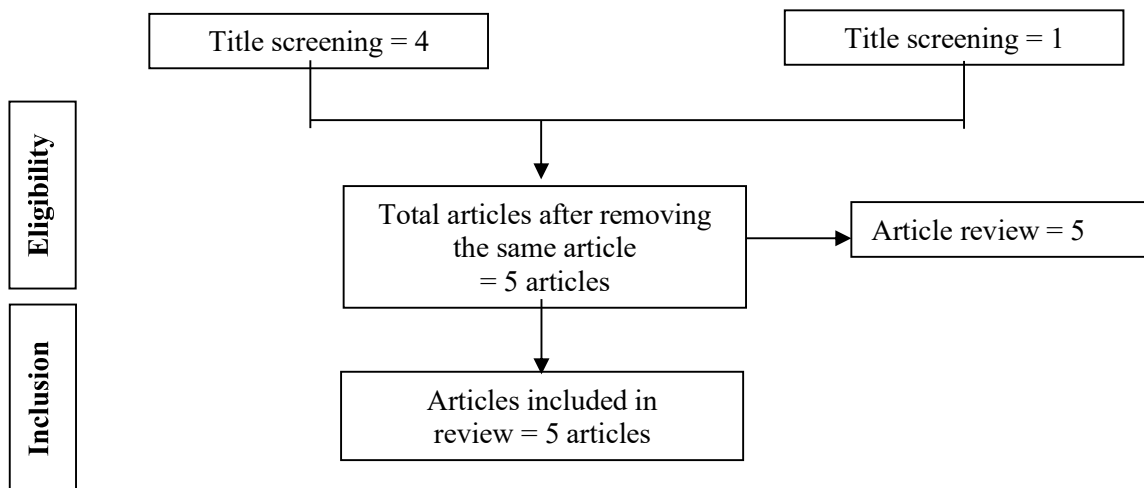
**Search Strategy**

We used "biomarkers" and "preeclampsia" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *("biomarker s"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields]) AND ("age of onset"[MeSH Terms] OR "age"[All Fields] AND "onset"[All Fields]) OR "age of onset"[All Fields] OR "onset"[All Fields] OR "onsets"[All Fields] OR "onsetting"[All Fields]) AND ("outcome"[All Fields] OR "outcomes"[All Fields]) AND ("pre eclampsia"[MeSH Terms] OR "pre eclampsia"[All Fields] OR "preeclampsia"[All Fields]) AND (2013:2023[mdat])* used in searching the literature.

**Data retrieval**

After reading the abstract and the title of each study, the writers performed an examination to determine whether or not the study satisfied the inclusion criteria. The writers then decided which previous research they wanted to utilise as sources for their article and selected those studies. After looking at a number of different research, which all seemed to point to the same trend, this conclusion was drawn. All submissions need to be written in English and can't have been seen anywhere else.





**Figure 1. Article search flowchart**

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

**Quality Assessment and Data Synthesis**

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. In order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

**RESULT**

In the PubMed database, the results of our search brought up 257 articles, whereas the results of our search on SagePub brought up 78 articles. The results of the search conducted for the last year of 2013 yielded a total 198 articles for PubMed and 54 articles for SagePub. In the end, we compiled a total of 5 papers, 4 of which came from PubMed and 1 of which came from SagePub. We included five research that met the criteria.

Barjaktarovic, et al<sup>15</sup> (2019) showed that high total hCG concentration in early pregnancy is associated with an increased risk of pre-eclampsia. The effect of high hCG concentration on the balance between pro- and anti-angiogenic factors during pregnancy may have a role in the pathophysiology of pre-eclampsia.

Widmer, et al<sup>2</sup> (2015) showed that angiogenic biomarkers in first half of pregnancy do not perform well enough in predicting the later development of pre-eclampsia.

Honarjoo, et al<sup>16</sup> (2019) showed that the results of the study showed that the high levels of  $\beta$ hCG would cause 5.65 times increase and the low levels of PAPP-A would cause 2.09 times increase in the chance of developing PE.

**Table 1. The literature include in this study**

Author	Origin	Method	Sample	Result
Barjaktarovic et al, 2019 <sup>15</sup>	Netherlands	Prospective Cohort Study	7754 patients	High hCG concentration was associated with a 1.5–2.7-fold increased risk of pre-eclampsia ( $P = 0.0001$ ), depending on the cut-off used, and with increased sFlt-1/PIGF ratio during early pregnancy ( $P < 0.0001$ ). The association between high hCG and pre-eclampsia attenuated by roughly 40% after adjustment for early-pregnancy sFlt-1/PIGF ratio ( $\beta$ -estimate change from $0.19 \pm 0.10$ ( $P = 0.052$ ) to $0.12 \pm 0.10$ ( $P = 0.22$ )).
Widmer et al, 2015 <sup>2</sup>	Multiple Country	Prospective Study	5121 patients	Pre-eclampsia was diagnosed in 198 of 5121 women tested (3.9%) of whom 47 (0.9%) developed it early. The median maternal serum concentrations of index tests were significantly altered in women who subsequently developed pre-eclampsia than in those who did not. However, the area under receiver operating characteristics curve at $\leq 20$ weeks' gestation were closer to 0.5 than to 1.0 for all biomarkers both for predicting any pre-eclampsia or at $\leq 34$ weeks' gestation. The corresponding sensitivity, specificity and likelihood ratios were poor. Multivariable models combining sEng with clinical features slightly improved the prediction capability.
Honarjoo et al, 2019 <sup>16</sup>	Iran	Cohort Study	4605 study	In the PE group, the mean MOM PAPP-A was significantly lower (1 vs. 1.09 with $P = 0.006$ ) and MOM $\beta$ hCG was significantly higher (1.51 vs. 1.14 with $P = 0.001$ ) than the group without PE. RR and OR for PE in subjects with MOM PAPP-A $< 0.4$ were reported as follows: RR = 2.49, ( $p = 0.001$ ) and OR = 2.09, ( $p = 0.001$ ). RR and OR for PE in subjects with MOM $\beta$ hCG $> 3$ were also reported as follows: RR = 4.02, ( $p = 0.001$ ) and OR = 5.65, ( $p = 0.001$ ). Adjusted OR for MOM PAPP-A $< 0.4$ and MOM $\beta$ hCG $> 3$ was obtained as follows: OR = 2.09 ( $P = 0.001$ ) and

				OR = 5.65 (P = 0.001), respectively.
Sharma et al, 2018 <sup>17</sup>	India	Prospective Study	2000 patients	Out of 2000 women, 199 women developed hypertension and 1454 women remained normotensive throughout their pregnancy. Among 199 hypertensive women, 151 (9.13%) cases had gestational hypertension, 45 (2.72%) had preeclampsia (PE) and 3 (0.18%) had eclampsia (E). First trimester mean arterial pressure (MAP) ( $p < 0.001$ ) and body mass index (BMI) ( $p < 0.001$ ) were found significantly higher in hypertensive women when compared with normotensive women. Maternal serum levels of PAPP-A ( $p < 0.001$ ) were significantly low in hypertensive women as compared to normotensive women, while free $\beta$ -hCG ( $p = 0.59$ ) was high, but the difference was not statistically significant. TNF- $\alpha$ ( $p < 0.001$ ) and INF- $\gamma$ ( $p = 0.014$ ) both were high in hypertensive women. When all biomarkers were combined we found the positive predictive value (PPV) of 51.6% an negative predictive value (NPV) of 71.4%.
Chen et al, 2021 <sup>18</sup>	China	Prospective Cohort Study	1041 patients	In unadjusted models, higher serum UA, GGT, ALP, and LDH levels, as well as lower eGFR and AST/ALT, were associated with higher BP levels during pregnancy and an increased risk of HDP. After adjustment for maternal age, pre-pregnancy BMI and other potential confounders, UA, GGT, ALP, and LDH remained positively associated with both BP and HDP. However, eGFR and AST/ALT were not associated with HDP after adjusting for potential confounders. When including all 6 biomarkers simultaneously in multivariable analyses, increased UA, GGT, and ALP significantly associated with gestational hypertension and preeclampsia.

Sharma, et al<sup>17</sup> (2018) showed that increased levels of proinflammatory cytokines suggest the role of underlying inflammation in pathogenesis of pregnancy hypertension, and low PAPP-A may be attributed to impaired implantation. Combining biomarkers may improve the prediction of pregnancy hypertension in the early stages of gestation. NPV of 71.4% depicts that if woman has all biomarkers in normal ranges during first trimester, she will have 71.4% chances of remaining normotensive during pregnancy.

Chen, et al<sup>18</sup> (2021) showed that increased UA, GGT, and ALP in early-pregnancy are independent risk factors of gestational hypertension and preeclampsia.

## DISCUSSION

The outcomes of this systematic review suggests that PlGF may be a useful diagnostic tool for pre-eclampsia diagnosis in the third trimester. However, its predictive value in early pregnancy is not high enough for an early diagnosis, and it generally becomes more reliable as the pregnancy progresses. Results from sFlt-1 meta-analysis were inconsistent. Other biomarkers have been included in this systematic review, but further meta-analyses have not been performed due to lack of sufficiently homogenous data. Consistent results among studies have been highlighted for PAPP-A, leptin, sEng, sFlt-1/PlGF, hemoglobin, CRP, and cystatin.

A search of multiple databases together with a comprehensive search strategy are among the main strengths of this systematic review. Furthermore, no language, date, or gestational week restrictions have been applied. Publication bias and study quality were both assessed, and a meta-analysis was performed for one biomarker. High quality and prospective studies only have been included in this systematic review. However, meta-analysis was not performed for the remaining biomarkers due to lack of homogenous data. Because of the high volume of research, we decided to analyze blood biomarkers only, thus not considering ultrasound, urinary or salivary molecules. Also, another important limitation of this systematic review was the lack of homogenous data due to the use of different laboratory methodologies and different kits throughout the included studies. Furthermore, the effect of different confounding factors among the study populations must be considered when interpreting the results. Due to the great variety of study designs and methods used, confounding factors could not be assessed when analyzing the results. Their effect should be statistically investigated in a larger single study using single patient data. Finally, no individual patient data was extracted and consequently no clinical difference between single patients can be appreciated.

To the best of our knowledge, this is the first systematic review that has no limit in terms of language or year of publication and that has investigated all blood biomarkers for the prediction or diagnosis of pre-eclampsia. The systematic review findings indicate that we currently lack an ideal biomarker for the early detection of preeclampsia. The use of PlGF to predict pre-eclampsia in the third trimester has been confirmed by this meta-analysis, but further studies are needed to investigate its role as a predictor of pre-eclampsia in early pregnancy. Biologically, PlGF is a proangiogenic molecule with a predominant role between the second and third trimester of pregnancy (26–30 weeks of gestation). At this time, PlGF is responsible for inducing systemic vasodilation in the placenta bed by stimulating cells to produce prostacyclin and nitric oxide, hence transforming placental vessels from high-resistance to low-resistance vessels. Consequently, low levels of PlGF in late pregnancy would result in placental hypoperfusion predisposing to pregnancy complications, in particular, pre-eclampsia.<sup>19</sup>

## CONCLUSION

Despite a better understanding of its pathophysiology, pre-eclampsia remains one of the most severe pregnancy complications. Several biomarkers have been evaluated throughout the years with the aim of a more accurate and earlier prediction of the disease. So far, PlGF and sFlt-1 are the most used in clinical practice, even if their specificity and sensitivity do not justify a default implementation into guidelines to screen all pregnant women. Their role is limited to rule-out a diagnosis of pre-eclampsia in women presenting with symptoms highly suggestive of the disease. Therefore, their current application is not useful for an early prediction of pre-eclampsia. Novel lines of research are needed to identify molecules able to detect pre-eclampsia in a timely manner and which have a predictive value high enough to justify the costs associated with routine measurements in the general pregnant population.

## REFERENCE

- [1] Say L, Chou D, Gemmill A, Tuncalp O, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health* [Internet]. 2014 [cited 2023 Dec 5];2(6):323–33. Available from: [https://www.thelancet.com/journals/langlo/article/PIIS2214-109X\(14\)70227-X/fulltext](https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(14)70227-X/fulltext)
- [2] Widmer M, Cuesta C, Khan KS, Conde-Agudelo A, Carroli G, Fusey S, et al. Accuracy of angiogenic biomarkers at  $\leq 20$  weeks' gestation in predicting the risk of pre-eclampsia: A WHO multicentre study. *Pregnancy Hypertens*. 2015;5(4):330–8.
- [3] Magee LA, Nicolaides KH, von Dadelszen P. Preeclampsia. *N Engl J Med*. 2022;386(19):1817–32.
- [4] Fox A, McHugh S, Browne J, Kenny LC, Fitzgerald A, Khashan AS, et al. Estimating the Cost of Preeclampsia in the Healthcare System: Cross-Sectional Study Using Data From SCOPE Study (Screening for Pregnancy End Points). *Hypertension*. 2017;70(6):1243–9.

- [5] Roberge S, Bujold E, Nicolaides KH. Aspirin for the prevention of preterm and term preeclampsia: systematic review and metaanalysis. *Am J Obstet Gynecol*. 2018;218(3):287–93.
- [6] Rolnik DL, Wright D, Poon LC, O’Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. *New England Journal of Medicine*. 2017 Aug 17;377(7):613–22.
- [7] Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *European Journal of Obstetrics & Gynecology and Reproductive Biology* [Internet]. 2013 [cited 2023 Dec 5];170(1):1–7. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0301211513001966>
- [8] Yang Y, Le Ray I, Zhu J, Zhang J, Hua J, Reilly M. Preeclampsia Prevalence, Risk Factors, and Pregnancy Outcomes in Sweden and China. *JAMA Netw Open*. 2021;
- [9] *Obstet Gynecol.* ] Hypertension in pregnancy. Report of the American college of obstetricians and gynecologists’ task force on hypertension in pregnancy. 2013;
- [10] Brown MA, Magee LA, Kenny LC, Karumanchi SA, McCarthy FP, Saito S, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis & management recommendations for international practice. *Pregnancy Hypertens* [Internet]. 2018 [cited 2023 Dec 5];13:291–310. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S2210778918301260>
- [11] Magley M, Hinson MR. Eclampsia. *NCBI Bookshelf*. 2023;
- [12] Memtsa M, Jurkovic D, Jauniaux ERM. Diagnostic Biomarkers for Predicting Adverse Early Pregnancy Outcomes. *BJOG Int J Obstet Gynaecol* [Internet]. 2019 [cited 2023 Dec 5]; Available from: [https://discovery.ucl.ac.uk/id/eprint/10068533/1/Memtsa\\_Diagnostic%20Biomarkers%20for%20Predicting%20Adverse%20Early%20Pregnancy%20Outcomes%20Scientific%20Impact.pdf](https://discovery.ucl.ac.uk/id/eprint/10068533/1/Memtsa_Diagnostic%20Biomarkers%20for%20Predicting%20Adverse%20Early%20Pregnancy%20Outcomes%20Scientific%20Impact.pdf)
- [13] MacDonald TM, Walker SP, Hannan NJ, Tong S. Clinical tools and biomarkers to predict preeclampsia. *The Lancet* [Internet]. 2022 [cited 2023 Dec 5];75. Available from: [https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964\(21\)00574-0/fulltext](https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00574-0/fulltext)
- [14] Zeisler H, Llurba E, Chantraine F, Vatish M, Staff AC, Sennström M, et al. Predictive Value of the sFlt-1:PIGF Ratio in Women with Suspected Preeclampsia. *New England Journal of Medicine*. 2016 Jan 7;374(1):13–22.
- [15] Barjaktarovic M, Korevaar TIM, Jaddoe VWV, de Rijke YB, Peeters RP, Steegers EAP. Human chorionic gonadotropin and risk of pre-eclampsia: prospective population-based cohort study. *Ultrasound Obstet Gynecol* [Internet]. 2019 [cited 2023 Dec 5];54(4):477–83. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6856821/>
- [16] Honarjoo M, Kohan S, Zarean E, Tarrahi MJ. Assessment of  $\beta$ -human-derived chorionic gonadotrophic hormone ( $\beta$ hCG) and pregnancy-associated plasma protein A (PAPP-A) levels as predictive factors of preeclampsia in the first trimester among Iranian women: a cohort study. *BMC Pregnancy Childbirth* [Internet]. 2019 [cited 2023 Dec 5];19:464. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6894335/>
- [17] Sharma K, Singh R, Kumar M, Gupta U, Rohil V, Bhattacharjee J. First-Trimester Inflammatory Markers for Risk Evaluation of Pregnancy Hypertension. *J Obstet Gynaecol India* [Internet]. 2018 [cited 2023 Dec 5];68(1):27–32. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5783907/>
- [18] Chen Y, Ou W, Lin D, Lin M, Huang X, Ni S, et al. Increased Uric Acid, Gamma-Glutamyl Transpeptidase and Alkaline Phosphatase in Early-Pregnancy Associated With the Development of Gestational Hypertension and Preeclampsia. *Front Cardiovasc Med* [Internet]. 2021 [cited 2023 Dec 5]; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8554001/>
- [19] Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. Vol. 31, *Journal of Human Hypertension*. Nature Publishing Group; 2017. p. 782–6.