Research article

Early screening for preeclampsia: A myth or a reality?

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Abstract

Preeclampsia (PE) is a hypertensive disorder in pregnancy affecting 2-8% of pregnancies worldwide and remains one of the leading causes of maternal and neonatal morbidity and mortality. PE is characterized by hypertension and end-organ damage secondary to oxidative stress, endothelial dysfunction, and vasoconstriction. The pathophysiology of the disease being elusive, early screening, diagnosis, and effective management of PE is challenging. Traditionally several predictive models including clinical and biochemical parameters have been used to stratify the risk of developing PE in pregnancy. Poor sensitivity and specificity of these models have been a limitation and has inspired the clinical world to explore more tools to screen and diagnose PE prior to the onset of clinical syndrome. This review attempts to highlight the recent developments in the newly developed screening tools and explores the future direction of preeclampsia screening research.

Key words: preeclampsia, screening, pregnancy, risk stratification

Introduction

Preeclampsia (PE) is a pregnancy specific hypertensive disorder associated with endothelial dysfunction, vasoconstriction, and end-organ damage. PE affects 2-8% of pregnancies worldwide and is responsible for 14% of maternal deaths annually[1,2]. In Sri Lanka, hypertensive disorders in pregnancy accounted for 4.5% maternal deaths in 2020[3]. PE results in variable short- and long-term maternal and fetal adverse outcomes. These include renal failure, liver failure and seizures (eclampsia; 2-3 vs 40-90 cases/10,000 live births in Europe vs developing countries, respectively) in short-term and 3.7 times higher risk of developing hypertension; 2.2 times higher risk of developing coronary heart disease; and 1.8 times higher risk of developing stroke in long-term in mother. Fetal complications include growth restriction, placental abruption, fetal death and complications of prematurity in surviving babies[4-6]. Low middle income countries are the most severely affected by the disease and financial burden.

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International Society for the Study of Hypertension in Pregnancy (ISSHP) defines pre-eclampsia as de novo hypertension after 20 weeks' gestation accompanied by one or more of the following features: (i) proteinuria; (ii) other maternal organ dysfunction (acute kidney injury, liver dysfunction, neurological complications, haematological complications); and/or (iii) utero-placental dysfunction[1].

The underlying pathophysiology of PE remains poorly understood and that limits the ability to (i) effectively screen for the disease prior to the onset of clinical syndrome; and (ii) to treat the disease with minimal morbidity and mortality. It is known that (i) PE occurs in trophoblastic tumours (without the presence of a fetus)[7]; (ii) PE is more prevalent in multiple pregnancies (with greater placental mass)[8]; (iii) PE occurs in ectopic pregnancies (excluding the involvement of uterine tissue)[9]; and (iv) by far the only definitive treatment for PE remains the delivery of placenta (irrespective of gestational age). Therefore, the placenta is believed to be the primary site to the pathogenesis of preeclampsia.

Recently the placental origin of pathophysiology of PE has been challenged. Follow up studies of women with PE has shown ample evidence for short-term and long-term cardiovascular changes suggesting maladaptation of the cardiovascular physiological changes in pregnancy as a possible etiology. Women developing PE demonstrate impaired cardiac output, an increase in systemic vascular resistance and left ventricular diastolic dysfunction especially in early-onset PE. There are persistent long term cardiovascular alterations and life-long increased risk of cardiovascular complications[10].

Extensive epidemiological studies have identified various maternal and paternal risk factors to stratify a pregnant woman into high, moderate, or low risk of developing PE, thereby facilitating the prioritization of resources. A pregnant woman has increased risk of PE if the partner was a product of preeclamptic pregnancy (OR-2.1; 95% CI: 1.0-4.3)[11]. Donor insemination increases the risk of PE compared to natural insemination (OR-1.6; 95% CI: 1.4-1.8)[12] and change of male partner increases the risk of developing PE by 1.6% in the female partner in the subsequent pregnancy[13]. Table 1 summarizes previously described risk factors[14].

Currently, PE is a clinical diagnosis based on a criterion adopted from the ISSHP definition (Figure 1). Early screening and diagnosis of preeclampsia (prior to the onset of clinical syndrome) has been challenging due to the limitations of existing predictive models (which lack good positive predictive value).

Table 1. Risk factors of preeclampsia

Risk factor	Mean RR	95% CI	High/Moderate risk[15]
History of PE in the past	7.19	5.85-8.83	High
Antiphospholipid syndrome	9.72	4.34-21.75	High
Insulin dependent diabetes	3.56	2.54-4.99	High
Multiple pregnancy	2.93	2.04-4.21	Moderate
Nulliparity	2.91	1.28-6.61	Moderate
Family history of PE	2.90	1.70-4.93	Moderate
Obesity	2.47	1.66-3.67	Moderate
Age > 40	1.96	1.34-2.87	Moderate
Pre-existing hypertension	1.38	1.01-1.87	High

Screening for preeclampsia

In thentext, screening refers to the utilization of a procedure or test on individuals, who do not exhibit any symptoms of a specific disease, with the aim of assessing the probability of them being affected by the disease. The screening procedure itself is not diagnostic of the illness. Patients who have a positive screening test result will need further evaluation with subsequent gold standard diagnostic test or procedure to confirm or rule out the diagnosis.

In 1968, Wilson and Jungner published "Principles and Practice of Screening for Disease", that presented 10 principles that govern the decision of screening for a disease (Figure 2)[16].

As previously highlighted, PE poses significant health burden causing short- and long-term adverse outcomes in mother and the fetus. PE is diagnosed based on clinical criteria and once the clinical syndrome has set in, the diagnosis is straight forward. Once PE is diagnosed, there are well established guidelines for managing the disease. The pathogenesis of PE is believed to start early in pregnancy and thus leaves a considerable latent period prior to the onset of clinical syndrome. Currently, the screening for PE in Sri Lanka is based on clinical risk factors and are checked via history and examination, and these clinical methods are widely acceptable to the Sri Lankan population. Even though the pathophysiology of the disease is not well understood to date, it is evident that the placental pathology begins early in first trimester followed by a latent phase until the mid-second trimester when the clinical syndrome becomes apparent (>20 weeks). The well-established clinical diagnostic criteria clearly differentiate preeclamptic women from normal pregnancy. Case finding for PE in Sri Lanka involves day-to-day clinical work and it is a continuous process. Thus, PE fits the principles of screening, and by employing an effective screening strategy, the resources could be prioritized to the high-risk pregnancies as opposed to low-risk pregnancies.

An effective screening test should have high sensitivity and specificity. Sensitivity measures how accurate the screening test is in identifying disease in people who truly have the disease and specificity focuses on the accuracy of the screening test in correctly classifying truly non-diseased people. Positive predictive value measures the probability of a subject with a positive screening test to truly have the disease and negative predictive value measures the probability of a subject with a negative screening test to truly not have the disease (Figure 3).

Diagnostic criteria:

Hypertension: Systolic blood pressure (SBP) ≥140 mmHg and/ or diastolic blood pressure (DBP) ≥90 mmHg on two or more occasions 4 hours apart.

AND

Proteinuria: ≥ +1 in dipstick analysis initially, followed by protein/creatinine ratio ≥ 30mg/mmol in spot urine.

OR

Acute kidney injury: Serum creatinine ≥ 90 μmol/L (or 1mg/dL) **OR**

Liver dysfunction: SGOT and/or SGPT ≥ 40 IU/L with or without right upper quadrant or epigastric abdominal pain **OR**

Neurological complications: Severe headaches, altered mental status, persistent visual scotomata, exaggerated tendon reflexes, clonus, seizures, and stroke **OR**

Haematological complications: Evidence of haemolysis, disseminated intravascular coagulation (DIC), and/or thrombocytopenia (platelet count ≥150000/μL) **OR**

Uteroplacental dysfunction: Fetal growth restriction, abnormal umbilical artery doppler waveform analysis, and/or stillbirth.

Figure 1. **Diagnostic criteria for preeclampsia based on ISSHP guidelines.**

1. The condition should be and important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic phase.
5. There should be a suitabble test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including a diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuous process and not a "Once and for all" project.

Figure 2. **10 principles of screening.**

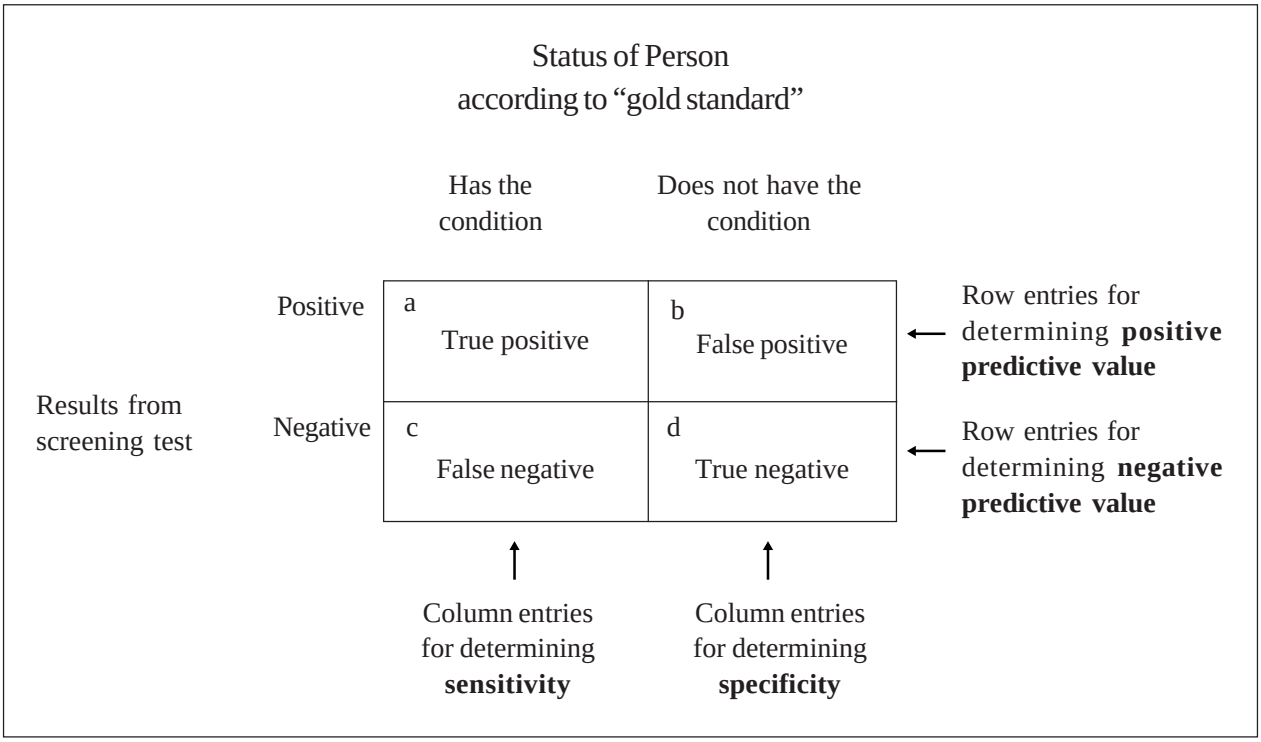

Figure 3. **Sensitivity, specificity, positive and negative predictive values.**

Screening for preeclampsia in Sri Lanka

In Sri Lanka, screening for PE at booking visit is based primarily on assessing clinical risk factors outlined in Table 1 based on NICE guidelines[15]. Recently it was shown that detection rates based on NICE recommendations were 41% and 34% for PE detected <34 weeks and <37 weeks respectively[17]. Presence of ≥ one high risk factor or ≥2 moderate risk factors deem the woman at high risk for developing PE. Those who are categorized as high risk undergo close supervision at tertiary health care setting with parallel shared care offered at the primary health care centres. Those who are deemed low risk are kept under surveillance for development of hypertension or PE with regular blood pressure and urine for protein monitoring at primary and tertiary health care settings. Any pregnant woman who records a SBP ≥140mmHg and/or DBP ≥ 90mmHg on two occasions, 2 hours apart in a primary care setting is referred to tertiary care setting for further evaluation[18].

Recent developments in screening and diagnosis of preeclampsia

In the current context, risk stratification for preeclampsia involves predictive tools based on clinical and biochemical features and measurement of soluble factors in maternal blood that are proven to be differentially expressed in preeclamptic women.

PE risk calculator

Fetal Medicine Foundation (FMF) has compiled an online PE risk calculator, which calculates risk of a pregnant woman in her first trimester to develop PE based on clinical and biochemical parameters. Internal validation of FMF risk calculator showed a detection rate of 90% and 75% for the prediction of PE cases <34 weeks and <37 weeks respectively[17]. PRSEIDE trial independently validated the calculator to predict 77.4% and 66.8% of cases with PE cases <34 weeks and <37 weeks respectively[19]. The risk calculator could be accessed online via: https://fetalmedicine.org/research/assess/preeclampsia/first-trimester

Measurement of soluble factors

Recent studies have found that soluble factors such as placental growth factor (PIGF), soluble fms-like tyrosine kinase-1 (sFlt-1) and endoglin play an important role in maternal physiology and pathology.

Placental growth factor is part of the vascular endothelial growth factor family and is responsible for angiogenesis. PlGF is predominantly released by placental tissue. Even though PlGF is expressed in other tissues such as heart, lung, thyroid gland, liver, skeletal muscle and bone, the relative expression was comparatively low compared to placental expression. Circulating level of PIGF was found to be reduced before the onset of symptoms in preeclampsia and was considered as an early screening biochemical test[20]. Thadhani, et al. demonstrated that serum PlGF levels were significantly lower in women with preeclampsia compared to normal pregnancies ($p<0.01$)[21]. Low serum PlGF (<5th centile) had high sensitivity (96%; 95%CI: 89-99%) and NPV (98%; 95%CI: 93-99%) for predicting development of PE in the following 2 weeks; but the specificity of the test was found to be low (55%; 95%CI: 48-61%)[22]. Another study reported that serum PlGF as a screening test had a sensitivity of 32% with a 5% false positive rate[20].

Soluble fms-like tyrosine kinase-1 is an alternatively spliced and truncated version of vascular endothelial growth factor receptor-1 (VEGFR-1). VEGFR-1 has (i) an extracellular ligand binding site for the proangiogenic factors-vascular endothelial growth factor (VEGF) and PlGF; and (ii) a transmembrane and cytoplasmic domain that regulates intracellular changes when the respective ligands bind the receptor. In contrast, sFlt-1 contains the extracellular ligand binding domain but lacks the transmembrane and cytoplasmic portions. Therefore, sFlt-1 can bind and reduce the circulating levels of both VEGF and PlGF. In PE, increased level of sFlt-1 is associated with decreased levels of free VEGF an PlGF resulting in a net anti-angiogenic state causing endothelial dysfunction[8,23-25]. Soluble fms-like tyrosine kinase-1 (sFlt-1) is found to be elevated and levels of free circulating VEGF and PlGF were found to be lower several weeks prior to the onset of clinical features in PE[26].

A multicenter case control study in Europe measured maternal serum concentrations of sFlt-1 and PlGF and reported that the concentrations of the soluble factors clearly differentiated women with PE from controls. The sFlt-1/PlGF ratio performed best (AUC 0.95) in the diagnosis of all PE compared to the sole measurement of sFlt-1 (AUC 0.91) or PlGF (AUC 0.92) ($p<0.05$). A cut off value of 85 resulted in the best sensitivity (82%) and specificity (95%) for the diagnosis of all PE and for the diagnosis of early-onset

PE (89% and 97%, respectively)[27]. On the other hand, a sFlt-1/PlGF ratio of 38 or lower was able to rule out PE in the following 7 days with a negative predictive value (NPV) of 99.3% (95% CI 97.9-99.9) with 80% sensitivity (95% CI, 51.9- 95.7) and 78.3% specificity (95% CI, 74.8-81.7)[28]. The ability of high NPV of the lower ratio to effectively rule out the risk of developing PE in a suspected woman with preeclampsia, enables the clinician to prioritize resources while simultaneously reassuring the patient.

Soluble endoglin (sEng) is a coreceptor for transforming growth factor – beta 1 (TGFβ1) and – beta 3 (TGFβ3), which is highly expressed on the cell membranes of vascular endothelial cells and syncytiotrophoblasts[29]. Soluble endoglin inhibits TGFβ1 signaling in vasculature and thus is anti-angiogenic. Placental expression of endoglin is up regulated in PE releasing more sEng into the maternal circulation[30]. Levine et al reported that circulating sEng levels markedly increased 2 to 3 months prior to the onset of preeclampsia[31]. Recently, it was reported that serum level of sEng was significantly elevated in PE compared to normal pregnancy (P<0.001) and a cut off value of 20.4 effectively distinguished PE from normal pregnancies (sensitivity of 92.1% and specificity of 90%)[32]. Increased level of sEng was usually accompanied by an increased ratio of sFlt-1:PlGF and the risk of developing PE was greatest among women with highest quartile of the control distributions for both biomarkers[31].

Leptin, pappalysin A1 (PAPPA-A1), human chorionic gonadotrophin-beta (β-hCG), alfa feto protein (AFP) and uric acid are few other circulating factors that are being investigated as potential markers for early screening and diagnosis of preeclampsia. Large scale studies and trials are needed to validate the above markers as effective screening tools.

Future direction in screening for preeclampsia

Extracellular vesicles (EVs) are membrane bound biomolecules released by various cells, and they carry various proteins and genetic material as its cargo. The syncytiotrophoblast layer of the placenta releases EVs (STB-EVs) into the maternal circulation from early first trimester and the amount of EV release increases as the pregnancy advances[33]. Preeclamptic placenta is known to release more STB-EVs compared to normal pregnancy[34]. STB-EVs in preeclampsia have been shown to regulate distant cells (such as endothelial cells) by depositing the contents of their cargoes causing vascular dysfunction, platelet activation, vasoconstriction, and endothelial activation[35-38]. Recently, the differential expression of cargoes carried within STB-EVs in PE and normal pregnancy have been explored and it could be the future of early screening, diagnosis, and monitoring disease prognosis[39,40]. EVs in general have been already used in the diagnosis of breast, pancreatic, and colorectal cancers[41-44].

Intervention

A pregnant woman deemed high risk for developing PE based on clinical risk factors is started on low dose aspirin (75mg-150mg) every night from 12 weeks until delivery of the baby. ASPRE trial confirmed that administration of aspirin reduced the incidence of preterm preeclampsia by 62% if started before 16 weeks, when compared with placebo[45,46].

The World Health Organization recommended daily dosage 1.5g to 2.0g calcium supplementation to prevent preeclampsia. Sri Lankan guidelines recommended daily intake of 1g of calcium, considering that routine calcium supplementation during pregnancy in Sri Lanka is 600 mg[18].

Vitamin D supplementation in prevention of preeclampsia is an area of controversy. In 2017, Sasan, et al. showed that vitamin D supplementation in first trimester contributed in preventing recurrence of preeclampsia (p<0.036)[47]. But this evidence was not strong enough to be generalized to the general population and warrants further research.

Conclusion

Sri Lanka is in par with most of the developed countries when it comes to diagnosing and managing preeclampsia. The recent advances in screening and ruling out possibility of developing preeclampsia in a woman suspected with symptoms suggestive of preeclampsia is an area that we need to explore and invest. Incorporating predictive tool or biochemical investigations in conjunction with the existing clinical risk categorization to effectively stratify the risk will help the clinicians to prioritize resources to the neediest patients while reassuring the low-risk women.

References

1. Brown MA, Magee LA, Kenny LC, et al. The hypertensive disorders of pregnancy: ISSHP classification, diagnosis and management recommendations for international practice. Pregnancy Hypertens. 2018; 13. doi: 10.1016/j.preghy.2018.05.004
2. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014; 2(6). doi:10.1016/S2214-109X(14)70227-X
3. Family Health Bureau. Analysis of Maternal Deaths - 2020; 2022. https://drive.google.com/file/d/1f42mGvTSYANxcVbgvZh6e_0U8lsrc5XV/view
4. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal Preeclampsia and Neonatal Outcomes. J Pregnancy. 2011; 2011: 1-7. doi:10.1155/2011/214365
5. Friedman SA, Schiff E, Kao L, Sibai BM. Neonatal outcome after preterm delivery for preeclampsia. Am J Obstet Gynecol. 1995; 172(6): 1785-92. doi:10.1016/0002-9378(95)91412-9
6. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. BMJ. 2007; 335(7627): 974. doi:10.1136/bmj.39335.385301.BE
7. Sotowright V, Bernstein M, Goldstein D, Berkowitz R. The changing clinical presentation of complete molar pregnancy. Obstetrics and Gynecology. 1995; 86(5): 775-9. doi:10.1016/0029-7844(95)00268-V
8. Bdolah Y, Lam C, Rajakumar A, et al. Twin pregnancy and the risk of preeclampsia: bigger placenta or relative ischemia? Am J Obstet Gynecol. 2008; 198(4): 428.e1-428.e6. doi:10.1016/j.ajog.2007.10.783
9. Hailu FG, Yihunie GT, Essa AA, Tsega W kindie. Advanced abdominal pregnancy, with live fetus and severe preeclampsia, case report. BMC Pregnancy Childbirth. 2017; 17(1): 243. doi:10.1186/s12884-017-1437-y
10. Melchiorre K, Giorgione V, Thilaganathan B. The placenta and preeclampsia: villain or victim? Am J Obstet Gynecol. 2022; 226(2): S954-S962. doi:10.1016/j.ajog.2020.10.024
11. Esplin MS, Fausett MB, Fraser A, et al. Paternal and Maternal Components of the Predisposition to Preeclampsia. New England Journal of Medicine. 2001; 344(12): 867-72. doi: 10.1056/NEJM200103223441201
12. Hoy J, Venn A, Halliday J, Kovacs G, Waalwyk K. Perinatal and obstetric outcomes of donor insemination using cryopreserved semen in Victoria, Australia. Human Reproduction. 1999; 14(7): 1760-4. doi: 10.1093/humrep/14.7.1760
13. Lie RT, Rasmussen S, Brunborg H, Gjessing HK, Lie-Nielsen E, Irgens LM. Fetal and maternal contributions to risk of pre-eclampsia: population based study. BMJ. 1998; 316(7141): 1343-7. doi: 10.1136/bmj.316.7141.1343
14. Kenny L, English F, McCarthy F. Risk factors and effective management of preeclampsia. Integr Blood Press Control. Published online March 2015: 7. doi:10.2147/IBPC.S50641
15. National Institute for Health and Care Excellence. Hypertension in Pregnancy: Diagnosis and Management 2019. https://www.ncbi.nlm.nih.gov/books/NBK546004/
16. Wilson JMG, Jungner G. Principles and Practice of Screening for Disease. World Health Organisation 1968. https://apps.who.int/iris/handle/10665/37650
17. Chaemsaithong P, Sahota DS, Poon LC. First trimester preeclampsia screening and prediction. Am J Obstet Gynecol. 2022; 226(2): S1071-S1097.e2. doi:10.1016/j.ajog.2020.07.020
18. Senadheera D, Jayasundara DMSC, Jayawardane IA, Ratnasiri UDP. Management of hypertensive disease in pregnancy. Sri Lanka Journal of Obstetrics and Gynaecology 2021; 43(4): 383-94. doi:10.4038/sljog.v43i4.8033
19. Riishede I, Rode L, Sperling L, et al. Pre-eclampsia screening in Denmark (PRESIDE): national validation study. Ultrasound in Obstetrics and Gynecology. 2023; 61(6): 682-90. doi:10.1002/uog.26183
20. Chau K, Hennessy A, Makris A. Placental growth factor and pre-eclampsia. J Hum Hypertens. 2017; 31(12): 782-6. doi:10.1038/jhh.2017.61
21. Thadhani R, Lemoine E, Rana S, et al. Circulating Angiogenic Factor Levels in Hypertensive Disorders of Pregnancy. NEJM Evidence. 2022; 1(12). doi:10.1056/EVIDoa2200161

22. Chappell LC, Duckworth S, Seed PT, et al. Diagnostic Accuracy of Placental Growth Factor in Women with Suspected Preeclampsia. Circulation. 2013; 128(19): 2121-31. doi:10.1161/CIRCULATIONAHA.113.003215

23. Maynard SE, Min JY, Merchan J, et al. Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. Journal of Clinical Investigation. 2003; 111(5). doi:10.1172/JCI17189

24. Levine RJ, Maynard SE, Qian C, et al. Circulating Angiogenic Factors and the Risk of Preeclampsia. New England Journal of Medicine. 2004; 350(7). doi:10.1056/NEJMoa031884

25. Rana S, Powe CE, Salahuddin S, et al. Angiogenic Factors and the Risk of Adverse Outcomes in Women with Suspected Preeclampsia. Circulation. 2012; 125(7). doi:10.1161/CIRCULATIONAHA.111.054361

26. Foidart JM, Schaaps JP, Chantraine F, Munaut C, Lorquet S. Dysregulation of anti-angiogenic agents (sFlt-1, PLGF, and sEndoglin) in preeclampsia-a step forward but not the definitive answer. J Reprod Immunol. 2009; 82(2): 106-11. doi:10.1016/j.jri.2009.09.001

27. Zeisler H, Llurba E, Chantraine F, et al. Predictive Value of the sFlt-1:PlGF Ratio in Women with Suspected Preeclampsia. New England Journal of Medicine. 2016; 374(1). doi:10.1056/NEJMoa1414838

28. Cerdeira AS, O'Sullivan J, Ohuma EO, et al. Randomized Interventional Study on Prediction of Preeclampsia/Eclampsia in Women with Suspected Preeclampsia. Hypertension. 2019; 74(4). doi:10.1161/HYPERTENSIONAHA.119.12739

29. Gougos A, St Jacques S, Greaves A, et al. Identification of distinct epitopes of endoglin, an RGD-containing glycoprotein of endothelial cells, leukemic cells, and syncytiotrophoblasts. Int Immunol. 1992; 4(1): 83-92. doi:10.1093/intimm/4.1.83

30. Venkatesha S, Toporsian M, Lam C, et al. Soluble endoglin contributes to the pathogenesis of preeclampsia. Nat Med. 2006; 12(6). doi:10.1038/nm1429

31. Levine RJ, Lam C, Qian C, et al. Soluble Endoglin and Other Circulating Antiangiogenic Factors in Preeclampsia. New England Journal of Medicine. 2006; 355(10): 992-1005. doi:10.1056/NEJMoa055352

32. Nikuei P, Rajaei M, Malekzadeh K, Nejatizadeh A, Mohseni F, AtashAbParvar A. Accuracy of Soluble Endoglin for Diagnosis of Preeclampsia and its Severity. Iran Biomed J. 2017; 21(5): 312-20. doi:10.18869/acadpub.ibj.21.5.312

33. Germain SJ, Sacks GP, Soorana SR, Sargent IL, Redman CW. Systemic Inflammatory Priming in Normal Pregnancy and Preeclampsia: The Role of Circulating Syncytiotrophoblast Microparticles. The Journal of Immunology. 2007; 178(9). doi:10.4049/jimmunol.178.9.5949

34. Goswami D, Tannetta DS, Magee LA, et al. Excess syncytiotrophoblast microparticle shedding is a feature of early-onset pre-eclampsia, but not normotensive intrauterine growth restriction. Placenta. 2006; 27(1). doi:10.1016/j.placenta.2004.11.007

35. Cronqvist T, Tannetta D, Mörgelin M, et al. Syncytiotrophoblast derived extracellular vesicles transfer functional placental miRNAs to primary human endothelial cells. Sci Rep. 2017; 7(1): 4558. doi:10.1038/s41598-017-04468-0

36. Germain SJ, Sacks GP, Soorana SR, Sargent IL, Redman CW. Systemic Inflammatory Priming in Normal Pregnancy and Preeclampsia: The Role of Circulating Syncytiotrophoblast Microparticles. The Journal of Immunology. 2007; 178(9): 5949-56. doi:10.4049/jimmunol.178.9.5949

37. Ermini L, Ausman J, Melland-Smith M, et al. A Single Sphingomyelin Species Promotes Exosomal Release of Endoglin into the Maternal Circulation in Preeclampsia. Sci Rep. 2017; 7(1): 12172. doi:10.1038/s41598-017-12491-4

38. Motta-Mejia C, Kandzija N, Zhang W, et al. Placental Vesicles Carry Active Endothelial Nitric Oxide Synthase and Their Activity is Reduced in Preeclampsia. Hypertension. 2017; 70(2): 372-81. doi:10.1161/HYPERTENSIONAHA.117.09321

39. Awoyemi T, Zhang W, Tanetta D, et al. Investigating the Roles of Small STBEV's Micrornas in the Pathogenesis of Early-Onset Preeclampsia through Bioinformatics. Placenta. 2021; 112: e24. doi:10.1016/j.placenta.2021.07.080

40. Awoyemi T, Jiang S, Bjarkadottir B, et al. Identification of Novel Syncytiotrophoblast

Membrane Extracellular Vesicles Derived Protein Biomarkers in Preeclampsia: A Cross-Sectional Study. medRxiv. Published online June 3, 2023. https://www.medrxiv.org/content/10.1101/2023.06.03.23290935v1

41. Giampieri R, Piva F, Occhipinti G, et al. Clinical impact of different exosomes' protein expression in pancreatic ductal carcinoma patients treated with standard first line palliative chemotherapy. PLoS One. 2019; 14(5): e0215990. doi:10.1371/journal.pone.0215990
42. Yokoyama S, Takeuchi A, Yamaguchi S, et al. Clinical implications of carcinoembryonic antigen distribution in serum exosomal fraction-Measurement by ELISA. PLoS One. 2017; 12(8): e0183337. doi:10.1371/journal.pone.0183337
43. Kimura H, Yamamoto H, Harada T, et al. CKAP4, a DKK1 Receptor, Is a Biomarker in Exosomes Derived from Pancreatic Cancer and a Molecular Target for Therapy. Clinical Cancer Research. 2019; 25(6): 1936-47. doi:10.1158/1078-0432.CCR-18-2124
44. Wang X, Zhong W, Bu J, et al. Exosomal protein CD82 as a diagnostic biomarker for precision medicine for breast cancer. Mol Carcinog. 2019; 58(5): 674-85. doi:10.1002/mc.22960
45. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. New England Journal of Medicine. 2017; 377(7): 613-22. doi:10.1056/NEJMoa1704559
46. Bujold E, Roberge S, Lacasse Y, et al. Prevention of Preeclampsia and Intrauterine Growth Restriction with Aspirin Started in Early Pregnancy. Obstetrics and Gynecology. 2010; 116(2): 402-14. doi:10.1097/AOG.0b013e3181e9322a
47. Behjat Sasan S, Zandvakili F, Soufizadeh N, Baybordi E. The Effects of Vitamin D Supplement on Prevention of Recurrence of Preeclampsia in Pregnant Women with a History of Preeclampsia. Obstet Gynecol Int. 2017; 2017: 1-5. doi:10.1155/2017/8249264