Review Article ISSN 2639-9342

Gynecology & Reproductive Health

The Enigma in the Prediction of Pre-Eclampsia and the Relevance in Management

Rupalakshmi Vijayan, M.D[1], Ramesh Pundi, M.D[2], Alina Alvarez, M.D[3], Sagar Bhandari[4] and Miguel A. Diaz, M.D[3]

[1]*Department of Obstetrics and Gynecology, Kasturba Medical College, Mangalore, Karnataka, India.*

[2]*Peach Tree Health, Marysville, California, United States.*

[3]*Department of Family Medicine, Larkin Community Hospital, South Miami, Florida, United States.*

[4]*National Medical College, Birgunj, Nepal affiliated to Tribhuvan University.*

***Correspondence:**

Rupalakshmi Vijayan, M.D., Department of Obstetrics and Gynecology, Kasturba Medical College, Light House Hill Road, Mangalore 575001, Karnataka, India, Phone: +1(814)3152522

Received: 29 Jun 2022; **Accepted:** 04 Oct 2022; **Published:** 12 Oct 2022

Citation: Vijayan R, Pundi R, Alvarez A, et al. The Enigma in the Prediction of Pre-Eclampsia and the Relevance in Management. Microbiol Infect Dis. 2022; 6(5): 1-11.

ABSTRACT

The ultrasonographic markers are less sensitive and that the biochemical markers are not very beneficial. Various serum markers have been investigated as probable predictors in the first and second trimester of pregnancy. The markers utilized are both angiogenic and anti-angiogenic factors and related to the placentation. Appropriate screening for early-onset pre-eclampsia is reasonable in the first trimester of pregnancy with a high detection rate and a low false-positive rate. Furthermore, the biochemical markers are not very beneficial when used alone as a predictive tool of pre-eclampsia. A combination of the biochemical markers along with maternal history, clinical features, risk factors, demographic characteristics, Doppler velocimetry could be more effective in the prediction of pre-eclampsia. Besides, an antenatal check-up at 11-13 weeks when maternal risk factors and history is cumulatively assessed along with biophysical and biochemical parameters has been suggested by recent approaches.

Capsule

A combination of the biochemical markers and maternal history, clinical features, risk factors, demographic characteristics, and Doppler velocimetry could be more effective in predicting pre-eclampsia.

Keywords

Pre-eclampsia, Hypertension, Pregnancy, Screening, Detection, Management, Maternal health.

Introduction

The most common causes of perinatal and maternal complications are hypertensive disorders of pregnancy [1]. Pre-eclampsia is defined as new-onset hypertension after a 20 weeks period of gestation (POG) with proteinuria or without proteinuria but end-organ damage [1]. The diagnostic criteria, risk factors for pre-eclampsia and severe pre-eclampsia have long been established [Table 1-3].

Table 1: Risk factors of pre-eclampsia.

	Risk factors of pre-eclampsia_
1	Nulliparity
2	Multifetal Gestations
3	Pre-eclampsia in a previous pregnancy
4	Chronic hypertension
5	Pregestational diabetes
6	Gestational diabetes
7	Thrombophilia
8	Systemic lupus erythematosus
9	Pre-pregnancy Body Mass Index greater than 30
10	Anti-phospholipid antibody syndrome
11	Maternal age 35 years or older
12	Kidney disease
13	Assisted reproductive technology
14	Obstructive sleep apnea

Table 2: Diagnostic criteria of pre-eclampsia.

Diagnostic criteria of pre-eclampsia
Blood pressure with Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
OR
Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more.(Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).
AND
Proteinuria with 300 mg or more per 24-hour urine collection (or this amount extrapolated from a timed collection)or with Protein/creatinine ratio of 0.3 mg/dL or more or with a Dipstick reading of 2+ (used only if other quantitative methods not available)
OR
In the absence of proteinuria, new-onset hypertension with the new onset of ANY of the following:
Thrombocytopenia: Platelet count less than 100,000
Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/ dL or a doubling of the serum creatinine concentration in the absence of other renal diseases
Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
Pulmonary edema
New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Table 3: Diagnostic criteria of severe pre-eclampsia.

	Diagnostic criteria of severe pre-eclampsia
1	Systolic blood pressure of 160 mmHg or more, or diastolic blood pressure of 110 mmHg or more on two occasions at least 4 hours apart (unless antihypertensive therapy is initiated before this time)
2	Thrombocytopenia (platelet count less than 100,000)
3	Impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit normal concentration), and severe persistent right upper quadrant or epigastric pain unresponsive to medication and not accounted for by alternative diagnoses
4	Renal insufficiency (serum creatinine concentration more than 1.1 mg/ dL or a doubling of the serum creatinine concentration in the absence of other renal diseases) Pulmonary edema
5	New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
6	Visual disturbances

Currently, the standard methods for screening are not available, even though a plethora of protocols have already been studied with varying success.

There is sufficient evidence based on the Screening Program for Pre-Eclampsia (SPREE) study that combining biomarkers like Pregnancy-associated plasma protein-A (PAPP-A), mean arterial pressure (MAP), Placental growth factor (PGF), Uterine artery pulsatility index (UtA-PI) along with the maternal history and risk factors is a more effective screening procedure to predict pre-eclampsia [2] in contrast to The National Institute for Health and Care Excellence (NICE) guidelines [3]. The standard NICE-recommended method screened positive for all pre-eclampsia 30.4% and 40.8% for all preterm pre-eclampsia. In contrast, the new method combining maternal characteristics, MAP, and PAPP-A screened positive for 42.5% of all pre-eclampsia cases [4,5]. Including PGF and UtA-PI screened positive for 82.4% of all preterm pre-eclampsia cases [6]. New biomarkers based on fetal hemoglobin, microglobulin are also on the horizon [7].

Estimations suggest that pre-eclampsia complicates 2–8% of pregnancies worldwide [8,9]. Latin America and the Caribbean have a 26% incidence of maternal deaths attributed to hypertensive disorders [8]. In contrast, in Africa and Asia, 9% of maternal deaths are due to pre-eclampsia [10]. Even though maternal mortality is way lesser in high-income countries than in developing countries, 16% of maternal deaths are incriminated as hypertensive disorders [10,11]. In the U.S., the prevalence of pre-eclampsia has escalated dramatically in the last two decades [12,13].

Analysis over the last 20 years has witnessed the change in identification for aneuploidies from the 2nd to the 1st trimester of pregnancy, which has resulted in the discovery of a multitude of early biophysical and biochemical markers for abnormal placentation [14]. With the help of the Bayes-based method, which integrates maternal risk factors and significant history of medical conditions and interventions, UtA-PI, MAP, and PAPP-A along with PGF in the serum of the pregnant woman at 11–13 weeks of gestation (WOG) can identify the significant portion of pregnancies at high-risk for early-onset pre-eclampsia [4].

Currently, in practice, there is a dearth of a reliable and replicable screening tool in the 1st trimester of pregnancy with adequate accuracy to distinguish women at increased risk of developing pre-eclampsia in spite of the fact that umpteen number of factors, like defective placentation, may appear in the first or early second trimester [15]. Early stratification of high-risk pregnancy may aid in developing new plans for antenatal surveillance or prevention hence improving perinatal and maternal outcomes. This study aims to review the literature on the predictive markers of pre-eclampsia and their relevance.

Discussion

Pre-eclampsia is a multisystem disorder of pregnancy. Previous hypotheses and scientific discoveries have helped shape our current knowledge on pre-eclampsia. The etiology of pre-eclampsia is likely multifactorial, with genetic, environmental, and immunological factors implicated. The pathogenesis of pre-eclampsia is to date elusive [16-18].

Factors associated with the pathogenesis of pre-eclampsia include abnormal placentation, stress by oxidative species and on the endoplasmic reticulum, type-1 angiotensin II receptor autoantibodies, activation of thrombin as well as platelets, inflammation intravascularly, dysfunction of the endothelium, chronic uteroplacental ischemia, immune maladaptation very-low-density lipoprotein (VLDL) toxicity, genetic imprinting [16], increased trophoblast apoptosis or necrosis, an exaggerated maternal inflammatory response to deported trophoblasts and an anti-angiogenic state, among which an imbalance of angiogenesis

has been emerged as one of the key factors [19]. Overproduction of placental-derived HbF and depletion of hemoglobin/ heme scavenging mechanisms have a role in the pathogenesis of pre-eclampsia. The interaction of vasodilators prostacyclin and nitric oxide and vasoconstrictors thromboxane A2 (TXA2) and endothelin lead to intense vasospasm. When an ineffective attempt to correct the contraction of the intravascular space seen in pre-eclampsia is made with vigorous fluid therapy, due to frequent capillary leak and decreased colloid oncotic pressure can lead to elevation of the pulmonary capillary wedge pressure and higher chances of pulmonary edema. This hypothesis led to studies suggesting incorporating aspirin into the pre-eclampsia prevention protocol as it preferentially inhibits TXA2 at lower doses [20].

Hippocrates around 400 BC first identified that headache, heaviness, and convulsions in pregnancy were considered ominous. Bossier in 1739 first differentiated epilepsy from eclampsia. In 1894, Dr. John Lever first linked proteinuria to pre-eclampsia and derived its specificity to the disease. The invention of manometry finally helped link high blood pressure (B.P.) recordings to pre-eclampsia [21]. Since the 20th century, prenatal care and the identification of pre-eclampsia have mostly remained the same. Regular B.P. measurement and urinalysis are the basic surveillance methods since early signs, and symptoms of pre-eclampsia may not be easily recognized. Fetal monitoring has become very advanced in recent years. In our setup and all studies, the basic tools for predicting and diagnosing pre-eclampsia remain consistent from time immemorial [22].

Pre-eclampsia essentially does not meet the criteria of an ideal screening tool, but we still need predictive measures. A definitive predictive tool for early diagnosis of pre-eclampsia is essential to yielding maximum benefits of initiating prophylaxis with aspirin and calcium supplements in high-risk cases [23].

Numerous agents, including low molecular weight heparing, are under investigation [24], high-dose folate [25], vitamin D [26], and statins [27]. Establishing screening strategies with high sensitivity and specificity to identify populations at greatest risk of pre-eclampsia could increase the statistical and clinical validity of further trials, including all agents. In the Southeast Asian population, there is an increased incidence of pre-eclampsia and poor maternal and fetal outcomes. If any of the prophylactic regimens have marginal benefit, it will help improve fetal outcomes after delivery by prolonging in-utero duration. As the prevalence of pre-eclampsia in the obstetric population is usually low (1 - 7 %), a test would usually require significantly high sensitivity and specificity to predict or exclude the development of the disease accurately [28].

Early-onset pre-eclampsia develops before 34-week gestation (WOG) and late-onset pre-eclampsia develops after 34 WOG [29]. Clinical risk factors have been used to categorize women as high risk for developing pre-eclampsia. Many studies show the relationship between hypertensive complications and Body Mass Index (BMI), 1st-trimester B.P. recording, UtA-PI, and PAPP-A [30]. Several guidelines have been formulated on standard antenatal care to help stratify pregnant women into low risk and high risk for developing pre-eclampsia [31].

Predictors of early pre-eclampsia are the black racial group, women with chronic hypertension, previous pregnancy with pre-eclampsia, and the use of ovulation induction [32]. Late pre-eclampsia predictors are older age, raised BMI, and familial history of pre-eclampsia or previous pregnancy with pre-eclampsia [10]. These factors have been corroborated as predictors by large studies done. The majority of the studies on the maternal risk factors for the development of pre-eclampsia have been shown not to quantify the risks. Few studies have derived relative risk. Most of the studies are cohort,case-control, and retrospective studies. Maternal demographic characteristics inclusive of obstetric and medical history after being incorporated into a combined multivariate analysis are useful as a screening tool [32].

The highest incidence of pre-eclampsia has been witnessed in healthy nulliparous women with no known risk factors [31]. The reliability of maternal symptoms as a predictor is low. Right upper quadrant or epigastric pain is hypothesized to be because of focal parenchymal and periportal ongoing necrosis, liver cellular edema, or Glisson's capsule expansion, or a multitude of factors. Unfortunately, a decent correlation between the liver cell microscopy and histopathology and laboratory value discrepancies has failed to be noticed [33]. Elsewhere, studies have proved that the headache for diagnosis has been of low reliability and specificity. Hence, a definitive and an "umbrella" diagnostic approach is required. A screening method for predicting pre-eclampsia that has its basis on the maternal risk factors as well as biomarkers has been shown to have better performance as a standard method based than the one that bases itself on maternal characters as well as medical history. Historical risk factors only predict about 30 percent of the women who will develop pre-eclampsia [34].

The use of imaging and laboratory tests along with risk factors to calculate a woman's risk is hence an area of active investigation. However, current models have a low positive predictive value (PPV) as they fail to differentiate early and late-onset pre-eclampsia.

For women with high risk for pre-eclampsia, confirming gestational age, B.P. at first visit, and baseline blood reports that include platelet count, creatinine concentration, liver function tests, and 24 hr urinary protein estimation early in pregnancy can be useful later in differentiating pre-eclampsia from other disorders with comparable features [35]. Screening in low-risk women has reduced PPV. Hence, the majority of screen-positive patients would not develop the disease, and prophylaxis in this group would inadvertently expose a large number of patients who would not derive benefit from the interventions. The sensitivity and specificity for predicting early-onset pre-eclampsia using first trimester and second-trimester biochemical or biophysical parameters [36] are better than for late-onset pre-eclampsia.

The reason for this is hazy, but it is plausible that the timing of the injury to the fetal supply line or the fetal response might be different in early-onset and late-onset pre-eclampsia [37]. Up to half of the women with gestational hypertension will inevitably develop proteinuria or other end-organ dysfunction matching the diagnosis of pre-eclampsia, and the progression is noted when the hypertension is diagnosed before 32 WOG [38].

Screening by Maternal Biophysical Markers

Uterine Artery Doppler

The most promising screening test for pre-eclampsia is uterine artery Doppler velocimetry. The development of pre-eclampsia has a proposed mechanism of abnormal trophoblastic invasion of the mother's spiral arteries and the conversion of vessels to wide non-muscular channels**.** Impaired placental perfusion, as seen in raised UtA-PI, is noted with the development of pre-eclampsia. The MoM value of UtA-PI is markedly increased at 11–13 WOG in women who subsequently develop pre-eclampsia. In the first trimester of pregnancy, it has been studied that a combination of reduced maternal serum concentrations of PGF, and increased UtA-PI, identified 93.1% of patients who would develop pre-eclampsia requiring delivery before 34 WOG [14]. Although studies show high sensitivity, the predictive value is not uniform. Therefore, biomarkers and ultrasonography cannot correctly predict pre-eclampsia. Meta-analyses confirm uterine artery Doppler analysis as a predictor for women at increased risk of pre-eclampsia in second trimester Doppler [39].

Increased gestational age impedance is an early radiographic feature of pre-eclampsia and implies raised resistance [40]. Two types of uterine artery Doppler waveform analysis techniques have emerged for pre-eclampsia prediction, one being the presence or absence of diastolic notching of the arcuate uterine vessels and the other being flow waveform ratios. The use of uterine artery Doppler velocimetry for the prediction of pre-eclampsia was best illustrated in a 2008 systematic review of 74 studies, including almost 80,000 women [41]. It was found that uterine artery Doppler ultrasonography had higher accuracy for the prediction of pre-eclampsia if performed in the second trimester than in the first trimester.

Blood Pressure

In pre-eclampsia, hypertension develops due to vasoconstriction and reduced peripheral vascular compliance [42]. Even though hypertension is just a secondary sign of pre-eclampsia, there is enough evidence stating that an increase in B.P. in women destined to develop pre-eclampsia may be seen in the first and second-trimesters of pregnancy. MAP is another significant marker for pre-eclampsia [43]. MoM value of MAP is significantly increased at 11–13 WOG in women who subsequently develop pre-eclampsia [14].

Screening By Maternal Biochemical Markers

Umpteen numbers of biomarkers [Table 4] for pre-eclampsia have been detected in the maternal serum, reflecting on its complicated pathogenesis [44].

A unanimous biomarker is yet to be demonstrated with a decent predictive value for clinical use. Instead, they have been shown to have higher validity when utilized in clusters [44].

Markers of Placental Function

Pregnancy-associated plasma protein-A (PAPP-A) is regularly tested in the first-trimester for aneuploidy screening and plasma protein 13 (PP-13); both are reduced in those who later develop pre-eclampsia [45]. PAPP-A is a metalloproteinase derived from syncytiotrophoblast that enhances the mitogenic function of the insulin-like growth factors (that help in placental development) by breaking the complex formed between growth factors and their respective binding proteins [46].

Cystatin C

Cystatin C is a well-known marker for renal function, which increases when the glomerular filtration rate falls [47]. Raised serum levels of cystatin C in the first trimester are associated with the development of both early and late-onset pre-eclampsia. The

Table 4: Biochemical markers for pre-eclampsia.

Markers	Features	Origin/expression	Alteration in P.E.
PIGF, VEGF,sVEGFR-1 (SFlt-1)	Markers of angiogenesis	trophoblast	Raised (sFlt-1)
			reduced (VEGF, PIGF)
endoglin	Receptor of TEGFβ1&β3	trophoblast	Increased
TPO	Cytokine for thrombopoiesis	liver	Increased
P-selectin	Inflammation reactions	Platelets, endothelial cells	Increased
PP13	placental implantation, maternal vascular remodeling	Syncytiotrophoblast,	Decreased
PAPP-A	Insulin –like growth factor binding protein	trophoblast	Low initially
			Increased in late onset PE
ADMA	Inhibitor of NO composition	ADMA is formed by methylation of L-arginine	Increased
CRF & CRF-BP	Modulation of vascular tone	trophoblast	Raised (CRF)
			Low (CRF-BP)
PGH	Metabolism in pregnancy	Syncytiotrophoblast, extravillous cytotrophoblast	Decreased in late onset P.E.
			Increased before the onset
IGF1, IGFBP1	implantation	placenta	Decreased (2nd trimester)
Inhibin A &	TEGFβ- family	placenta	Increased
Activin A			

novel findings in the current study published by Thilanganathan et al. note that serum cystatin C levels are significantly elevated several months before women develop pre-eclampsia, not only in early-onset pre-eclampsia but in those manifesting at term [48]. Similar results were found in a recently published meta-analysis by Bellos et al., which showed that raised levels of Cystatin C were noted in the third trimester of pregnancy in the women who later developed pre-eclampsia, with 0.85 sensitivity and 0.84 specificity [49].

Maternal Inflammatory Response Marker

Increased levels of pentraxin 3 (PTX3) in the first trimester, was observed in patients who developed early-onset pre-eclampsia but were not noticed in women with late-onset pre-eclampsia [50,51]. Petraxin-3 is linked to the classical complement pathway and plays a role in modulating inflammation. Pentraxin-3 has an inhibitory effect on NO synthesis and cell proliferation, thereby altering the endothelial function [52]. Earlier studies report Increased levels of pentraxin 3 (PTX3) in the first trimester, which was observed in patients who developed early-onset pre-eclampsia but was not noticed in women with late-onset pre-eclampsia [53]. The latest case-control study published by Colmenares-Mejía CC et al. suggests a stronger correlation of Pentraxin-3 with HELPP syndrome than pre-eclampsia [54].

Angiogenic Agents

These include PGF and vascular endothelial growth factor (VEGF), decreasing in women prone to develop pre-eclampsia [55].

Soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng)

The sFlt-1 works together with sEng, an anti-angiogenic factor, whose reduced levels in the late first trimester are associated with pre-eclampsia. Ischemic trophoblast, a characteristic finding in pre-eclampsia, increases the production of anti-angiogenic proteins (sEng, sFlt1) and reduces the production of angiogenic proteins (VEGF, PGF). Changes in VEGF levels, PGF, sFlt-1, and sEng in maternal blood and urine appear several weeks to months prior to the onset of clinical pre-eclampsia and are appropriate to the disease severity [56]. However, when assessed by gestational age, most of the markers performed better after 30 WOG as opposed to the first half of pregnancy [57].

PGF

Urinary PGF does not have a good predictive value in early pregnancy as a screening test. However, the test was predictive of pre-eclampsia late in gestation. Low values were reported in patients who presented with pre-eclampsia later. Ratios of excretion could be advantageous over absolute levels of urinary factors for risk identification [36].

According to a recent meta-analysis conducted by Agrawal S et al., low PGF values were highly specific and sensitive to rule in pre-eclampsia, especially early-onset pre-eclampsia, as compared to late-onset pre-eclampsia. PGF cut-off value of 80-120 at >19 WOG is highly specific to predict the onset of pre-eclampsia. The accuracy of the test increases with the gestational age. It has been reported that the PGF levels start to fall from the second half of the pregnancy. Women with high PGF values have no risk of developing pre-eclampsia. In the clinical setting, this test can aid in the diagnosis of early-onset pre-eclampsia and adopting prompt measures to prevent maternal and fetal adverse outcomes [58].

In another clinical trial conducted by Duhig KE et al., they concluded that there was a notable decrease in the clinical confirmation time for pre-eclampsia with the availability of PGF test results. Moreover, PGF implementation was associated with a decreased incidence of adverse outcomes in females, consistent with the targeted and enhanced surveillance adoption as recommended in the clinical management algorithm for clinicians. Thereby suggesting that adoption and addition of PGF test in women with suspected pre-eclampsia could be noteworthy [59].

sFlt-1: PGF ratio

This may be the most promising test for predicting pre-eclampsia, but the above tests are not useful early in pregnancy. Previous studies report significant changes in the levels of the markers in the third trimester. No significant changes were noted until the second half of pregnancy [36]. According to a recent meta-analysis by Ohkuchi A et al., low PGF values were highly specific and sensitive to rule in pre-eclampsia, especially early-onset pre-eclampsia, as compared to late-onset pre-eclampsia. PGF cut-off value of 80-120 at >19 WOG is highly specific to predict the onset of pre-eclampsia. The accuracy of the test increases with the gestational age. It has been reported that the PGF levels start to fall from the second half of the pregnancy. Women with high PGF values have no risk of developing pre-eclampsia. In the clinical setting, this test can aid in diagnosis early-onset pre-eclampsia and adopting prompt measures to prevent maternal and fetal adverse outcomes [60]. A meta-analysis by Liu Y et al. based on 20 studies suggests that the sFlt-1/PlGF ratio for screening P.E. has a moderate accuracy rate and needs further evaluation on a larger scale [61].

Fetal Free Hemoglobin and a Microglobulin

The combination of HbF and α1-microglobulin and/or hemopexin may serve as a prediction model for pre-eclampsia combined with maternal risk factors and/or uterine artery Doppler ultrasound. HbF/Hb ratio and a-1 microglobulin have been seen to increase early in pregnancy, while hemopexin is low in women with a risk of pre-eclampsia [62].

In contrast, Murtoniemi K et al. suggests there are no differences in longitudinal Hemopexin and A1M concentrations from first to late second trimester in high-risk women who developed early-onset or late-onset pre-eclampsia or in women who developed severe or non-severe pre-eclampsia [63].

Inhibin A and activin A

They are proteins of placental origin, {transforming growth factor (TGF-b) family}, both are increased before 14 weeks in pre-

eclamptic pregnancies [62]. A small retrospective cross-sectional study found higher levels of Inhibin-A in the maternal serum at the beginning of the third trimester [64]. Market elevation of Inhibin-A in maternal serum at 15-19 WOG in the maternal serum of women who subsequently developed pre-eclampsia was reported [65].

Another study by Grobman et al., with small sample size, demonstrated no significant changes in the levels of maternal Inhibin-A in women who developed pre-eclampsia, especially late-onset pre-eclampsia. This study further stated that Inhibin-A elevation might be associated with early-onset pre-eclampsia [66]. Salomon et al. found that elevated Inhibin-A with a cut-off of 272 pg/ml at 7-13 WOG positively correlated with an increase in systolic and diastolic blood pressure seen at the time of diagnosis at 31 WOG on an average [67]. Combining maternal Inhibin-A and Activin-A measured in the early second trimester (16-18 WOG) and UtA-PI at 24-26 WOG was found to be useful in screening pre-eclampsia, but the improvement in predictability in the clinical setting was far less [68]. A prospective case-control study reported higher Activin-A levels in the maternal serum as early as 11-15 WOG who later developed pre-eclampsia [69].

Cell-free fetal DNA levels

A recent case-control study by Kwak et al. concludes that there is an increase in the levels of cell-free DNA in the second trimester in asymptomatic women with early-onset pre-eclampsia [70]. Higher than normal levels are seen in pregnancies with pre-eclampsia. A small retrospective case-control study about the validity of cell-free fetal DNA in the first trimester demonstrated a sensitivity and specificity of 100% for the development of pre-eclampsia [71].

Neutrophil Gelatinase-Associated Lipocalin (NGAL)

NGAL, a glycoprotein present in neutrophil granules, is increased in the first trimester of pregnancies which mostly develop early- or late-onset pre-eclampsia [72]. Elevated levels of NGAL were found in the maternal serum of women who later developed pre-eclampsia [73]. The levels of circulating NGAL are directly linked to the severity of pre-eclampsia and are positively correlated with proteinuria and systolic and diastolic blood pressure, as reported by a small case-control study [74]. Another case-control study demonstrated the same with a sensitivity rate of 75% and specificity of 94.5% with a 5.5% false-positive rate [75]. However, a case-cohort study states that NGAL is highly elevated in the maternal serum of women who develop early-onset pre-eclampsia but with poor screening results [76].

ADMA (asymmetric dimethylarginine)

ADMA, an anti-angiogenic factor that reduces VEGF expression in the endothelial cells and inhibits the formation of nitric oxide, is elevated in pregnancies that later manifest as pre-eclampsia [57]. ADMA is metabolized to citrulline and dimethylamine by Dimethy-hydrolase, which is inhibited by homocysteine. So elevated levels of ADMA are attributed to Hyperhomocysteinemia. Increased ADMA contributes to endothelial dysfunction by inhibition of the eNOS pathway, which is associated with pre-eclampsia [77]. According to meta-analysis, marked elevation levels of ADMA were seen in pre-eclamptic women at > 20 WOG compared to gestational age at < 20 weeks [78].

Thrombopoietin (TPO)

TPO is a significant cytokine for megakaryocytopoiesis and thrombopoiesis and the regulation of early hematopoiesis. TPO levels are markedly increased in pregnancies complicated by hemolysis, elevated liver enzymes, and low platelets syndrome (HELLP) [Frölich MA et al., 1998]. Lack of TPO potentiating for collagen activation by platelets in the first trimester has been noted with pre-eclampsia [79].

Uric Acid

The serum uric acid concentration increases significantly in pre-eclampsia [80]. The common theory is the higher reabsorption and lower excretion of uric acid in the proximal renal tubules. Systematic reviews have proved that serum uric acid concentration before 25 WOG has not been useful in identifying the group of women prone to develop pre-eclampsia and its complications.

Urine Protein -Prediction Dipstick & 24hr Urine

If quantitative methods are unavailable or rapid decisions are required, a urine protein dipstick reading can be substituted, though there are high chances of false-positive readings as confirmed by 24-hour urine protein tests [81].

Corticotropin-Releasing Factors, Corticotropin-Releasing Factors Binding Proteins, And Placental Growth Hormones

Perkins AV et al. demonstrated in their study that the corticotropin-releasing hormone (CRH), also known as corticotropin-releasing factor (CRF), was increased, the corticotropin-releasing factors binding proteins (CRF-BP) was decreased, and the free potentially bioactive hormone had a net increase in pregnancies complicated by pre-eclampsia suggesting their possible role in the pathogenesis of the disease [82]. Measuring the levels of CRF and CRF-BP could help predict pre-eclampsia in pregnant women at risk [83].

Screening for Anti-Phospholipid Antibodies

Anti-phospholipid antibody syndrome (APS) is associated with the development of severe early pre-eclampsia. In case of high-risk factors, screening could be carried out for APS. Di Prima et al. suggests that the association of pre-eclampsia and APS could be controversial due to smaller studies with conflicting results [84].

Screening for Inherited Thrombophilias

Thrombophilias are associated with severepre-eclampsia but not with mild pre-eclampsia. Therefore, not useful for predicting those at high risk of mild pre-eclampsia [85].

Placental Exosomes

They are extracellular vesicles that have the ability to transfer microRNA to target cells. Evidence elicits abnormal levels of circulating microRNAs in pregnancies affected by pre-eclampsia [86]. A recent prospective cohort showed that the levels of

circulating exosomes are increased in pregnancies complicated by pre-eclampsia [87].

Proteomic Studies

Increased MMP-7 before 22 weeks and low PGF after 22 weeks are the strongest predictors for the subsequent development of late-onset pre-eclampsia [88]. A recent longitudinal study reports elevated levels of MMP-7 (with a false-positive rate of 10%) at 16-22 WOG in the maternal serum of the women who later went on to develop early-onset pre-eclampsia [88]. According to another study, a high MMP-7 level with 70 % sensitivity and a false positive rate of 20% at 8-22 WOG has been seen in late-onset pre-eclampsia [88]. Increased MMP-7 before 22 weeks and low PGF after 22 weeks are the strongest predictors for the subsequent development of late-onset pre-eclampsia [88]. Marked elevation in gp-IIb-IIIa in the maternal plasma at 8-16 WOG in women who developed early pre-eclampsia was reported in a longitudinal proteomic study for the first time [89].

Multiparametric Tests

Combined tests increase predictive value than singular tests. Hence, for better predictive values, certain screening tools have been formulated [14].

National Institute for Health and Care Excellence (NICE) guidelines.

According to the guideline, if they have anyone major factor (history of hypertensive disorder in a prior pregnancy, chronic hypertension, autoimmune disease, chronic kidney disease, diabetes mellitus) or any two moderate factors (age at first pregnancy > 40 years, the interval between consequent pregnancies > 10 years, prepregnancy BMI > 35 kg/m^2 or family history of pre-eclampsia), women have a high risk of developing pre-eclampsia [3].

Bayes Theorem

This approach allows estimation of patient-specific risks of pre-eclampsia and combines risk from maternal characteristics and medical history with the reports of a plethora of combinations of biophysical and biochemical measurements [90]. It has helped identify four useful markers at 11-13 WOG, namely, MAP, UtA-PI, PAPP-A, and P1GF [89] [Table 5]. Bayes theorem was applied in the most recent trial and gave significant results [9].

Screening Program for Pre-Eclampsia (SPREE) Trial

In this trial, singleton pregnancies at 11-13 WOG had recordings of maternal characteristics and medical history and measurements of MAP, UtA-PI, P1GF, and PAPP-A. The performance of screening for pre-eclampsia by Baye's theorem-based method was compared to the predictability of the NICE method. It was found that the validity was higher with Baye's theorem-based method and also had higher compliance to the preventive strategy of aspirin intake [2].

Relevance of the Predictive Tests in Management

These tests help in the early prediction of both early and late pre-eclampsia and hence help in early preventive measures to be undertaken. Many studies report a significant reduction in severe pre-eclampsia and fetal growth restriction on starting low dose aspirin before 16 WOG compared to a modest reduction in pre-eclampsia when started on low dose aspirin after 16 WOG [91]. Women with any of the high-risk factors for pre-eclampsia and those with more than one of the moderate-risk factors should receive low-dose (81 mg/ day) aspirin for pre-eclampsia prophylaxis initiated between 12 weeks and 28 WOG (preferably before 16 WOG) and continuing until delivery [92]. One of the significant trials conducted was the ASPRE trial, which concluded that in women with a singleton pregnancy and at high-risk for pre-eclampsia, aspirin (150 mg/ day) *vs.* placebo from 11 to 14 until 36 WOG was associated with a significant reduction in the incidence of preterm pre-eclampsia, but had no significant effect on the incidence of term pre-eclampsia [93].

Most risk factors for pre-eclampsia are not modifiable; avoiding obesity and excessive gestational weight gain are notable exceptions. The use of metformin to prevent pre-eclampsia has been suggested but remains investigational [94]. Recent meta-analyses by Hofmeyr GJ et al. conclude that high dose calcium supplements (>1 g/day) help reduce the incidence of pre-eclampsia only in women with low dietary intake of calcium [95].

Conclusion

Appropriate screening for early-onset pre-eclampsia is feasible in the first trimester of pregnancy with a high detection rate and a low false-positive rate. The biochemical markers are not very

Table 5: Performance of screening for pre-eclampsia according to National Institute for Health and Care Excellence (NICE) guidelines and another method combining maternal factors and biomarkers.

Method of screening	Detection rate (n (%, 95% CI))		Difference in detection rates between methods (% (95% CI))			
			No adjustment for effect of aspirin		Adjustment for effect of aspirin*	
NICE guidelines	144	(30.4,	26.3-34.6)	12.1	(7.9-16.2)	11.3
Maternal factors + MAP + PAPP-A	201	(42.5,	38.0-46.9)			
NICE guidelines	58	(40.8,	32.8-48.9)			
Maternal factors + MAP + PAPP-A	76	(53.5,	45.3-61.7)	12.7	(4.7-20.7)	10.5
Maternal factors + MAP + PIGF	98	(69.0,	61.4-76.6)	28.2	(19.4-37.0)	24
Maternal factors + MAP + PIGF + UtA-PI	117	(82.4,	76.1-88.7)	41.6	(33.2-49.9)	35.1

MAP: mean arterial pressure; PAPP-A: pregnancy-associated plasma protein-A; PIGF: placental growth factor; UtA-PI: uterine artery pulsatility index

effective when used alone as a predictive tool of pre-eclampsia. Hence, a combination of these biochemical markers with other predictors such as maternal history, clinical features, risk factors, demographic characteristics, Doppler velocimetry could be more effective. Moreover, recent approaches suggest antenatal check-up at 11-13 weeks when maternal risk factors and history are cumulatively assessed along with biophysical and biochemical parameters. This would help in segregating cases who would benefit from prophylactic intervention. Also, ongoing research is on the path of discovering an effective integrated predictive tool for 30-33 WOG to improve perinatal outcomes. Larger studies are mandated to shed light on this topic further.

Ethical Approval

This study did not require ethical approval as data was obtained from already available databases, and patients were not directly involved.

References

1. Mammaro A, Carrara S, Cavaliere A, et al. Hypertensive disorders of pregnancy. Journal of Prenatal Medicine. 2009; 3: 1-5.
2. Tan MY, Koutoulas L, Wright D, et al. Protocol for the prospective validation study: 'Screening programme for pre-eclampsia' (SPREE). Ultrasound in Obstetrics and Gynecology. 2017; 50: 175-179.
3. Webster K, Fishburn S, Maresh M, et al. Diagnosis and management of hypertension in pregnancy: Summary of updated NICE guidance. The BMJ. 2019; 366.
4. Francisco C, Wright D, Benkő Z, et al. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11–13 weeks' gestation. Ultrasound in Obstetrics and Gynecology. 2017; 50: 589-595.
5. Francisco C, Wright D, Benkő Z, et al. Competing-risks model in screening for pre-eclampsia in twin pregnancy according to maternal factors and biomarkers at 11–13 weeks' gestation. Ultrasound in Obstetrics and Gynecology. 2017; 50: 589-595.
6. Wright D, Gallo DM, Gil Pugliese S, et al. Contingent screening for preterm pre-eclampsia. Ultrasound in Obstetrics and Gynecology. 2016; 47: 554-559.
7. Anderson UD, Gram M, Ranstam J, et al. Fetal hemoglobin, α1-microglobulin and hemopexin are potential predictive first trimester biomarkers for preeclampsia. Pregnancy Hypertension. 2016; 6: 103-109.
8. Abalos E, Cuesta C, Grosso AL, et al. Global and regional estimates of preeclampsia and eclampsia: A systematic review. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2013; 170: 1-7.
9. Wright D, Wright A, Nicolaides KH. The competing risk approach for prediction of preeclampsia. American Journal of Obstetrics and Gynecology. 2020; 223: 12-23.e7.
10. Jeyabalan A. Epidemiology of preeclampsia: Impact of obesity. Nutrition Reviews. 2013.
11. Khan KS, Wojdyla D, Say L, et al. WHO analysis of causes of maternal death: a systematic review. Lancet. 2006; 367: 1066-1074.
12. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: Age-period-cohort analysis. BMJ. 2013; 347: f6564.
13. Shih T, Peneva D, Xu X, et al. The Rising Burden of Preeclampsia in the United States Impacts Both Maternal and Child Health. American Journal of Perinatology. 2016; 33: 329-338.
14. Park HJ, Shim SS, Cha DH. Combined screening for early detection of pre-eclampsia. International Journal of Molecular Sciences. 2015; 16: 17952-17974.
15. Poon LC, Shennan A, Hyett JA, et al. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: A pragmatic guide for first-trimester screening and prevention. International Journal of Gynecology and Obstetrics. 2019; 145: 1-33.
16. LaMarca B. Endothelial dysfunction. An important mediator in the pathophysiology of hypertension during pre-eclampsia. Minerva Ginecologica. 2012; 64: 309-320.
17. Gathiram P, Moodley J. Pre-eclampsia: Its pathogenesis and pathophysiolgy. Cardiovascular Journal of Africa. 2016; 27: 71-78.
18. Palei AC, Spradley FT, Warrington JP, et al. Pathophysiology of hypertension in pre-eclampsia: A lesson in integrative physiology. Acta Physiologica. 2013; 208: 224-233.
19. Agarwal I, Karumanchi SA. Preeclampsia and the anti-angiogenic state. Pregnancy Hypertension. 2011; 1: 17-21.
20. Atallah A, Lecarpentier E, Goffinet F, et al. Aspirin for Prevention of Preeclampsia. Drugs. 2017; 77: 1819-1831.
21. Bell MJ. A historical overview of preeclampsia-eclampsia. Journal of Obstetric, Gynecologic, and Neonatal Nursing. 2010; 39: 510-518.
22. Henderson JT, Thompson JH, Burda BU, et al. Screening for Preeclampsia: A Systematic Evidence Review for the U.S. Preventive Services Task Force. 2017.
23. Briceo-Prez C, Briceo-Sanabria L, Vigil-De Gracia P. Prediction and prevention of preeclampsia. Hypertension in Pregnancy. 2009; 28: 138-155.
24. McLaughlin K, Scholten RR, Parker JD, et al. Low molecular weight heparin for the prevention of severe preeclampsia: where next?. British Journal of Clinical Pharmacology. 2018; 84: 673-678.
25. Greenberg JA, Bell SJ, Guan Y, et al. Folic Acid Supplementation and Pregnancy: More Than Just Neural Tube Defect Prevention. Reviews In Obstetrics & Gynecology. 2011; 4: 52-59.
26. Purswani JM, Gala P, Dwarkanath P, et al. The role of vitamin D in pre-eclampsia: A systematic review. BMC Pregnancy and Childbirth. 2017; 17: 231.

27. Katsi V, Georgountzos G, Kallistratos MS, et al. The role of statins in prevention of preeclampsia: A promise for the future?. Frontiers in Pharmacology. 2017; 8: 247.
28. Al-Rubaie ZTA, Hudson HM, Jenkins G, et al. Prediction of pre-eclampsia in nulliparous women using routinely collected maternal characteristics: A model development and validation study. BMC Pregnancy and Childbirth. 2020; 20: 23.
29. Valensise H, Vasapollo B, Gagliardi G, et al. Early and Late preeclampsia: Two different maternal hemodynamic states in the latent phase of the disease. Hypertension. 2008; 52: 873-880.
30. Kane SC. First trimester screening for pre-eclampsia. Obstetric Medicine. 2016; 18: 106-112.
31. Fox R, Kitt J, Leeson P, et al. Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring. Journal of Clinical Medicine. 2019; 80: 1625.
32. Poon LCY, Kametas NA, Chelemen T, et al. Maternal risk factors for hypertensive disorders in pregnancy: A multivariate approach. Journal of Human Hypertension. 2010; 24: 104-110.
33. Gupte S, Wagh G. Preeclampsia-eclampsia. Journal of Obstetrics and Gynecology of India. 2014; 64: 4-13.
34. Ukah UV, Payne B, Côté AM, et al. Risk factors and predictors of pre-eclampsia. The Figo Textbook Of Pregnancy Hypertension. 2019.
35. Brown MA, Magee LA, Kenny LC, et al. Hypertensive disorders of pregnancy: ISSHP classification, diagnosis, and management recommendations for international practice. Hypertension. 2018; 72: 24-43.
36. Anderson UD, Olsson MG, Kristensen KG, et al. Biochemical markers for prediction of preclampsia. Placenta. 2012; 33: S42-S47.
37. Roberts JM, Escudero C. The placenta in preeclampsia. Pregnancy Hypertension. 2012; 2: 72-83.
38. Von Dadelszen P, Magee LA. Preventing deaths due to the hypertensive disorders of pregnancy. Best Practice and Research: Clinical Obstetrics and Gynaecology. 2016; 36: 83-102.
39. Capucci R, Pivato E, Carboni S, et al. The use of uterine artery doppler as a predictive tool for adverse gestational outcomes in pregnant patients with autoimmune and thrombophilic disease. Journal of prenatal medicine. 2011; 5: 54-58.
40. Dall'Asta A, Brunelli V, Prefumo F, et al. Early onset fetal growth restriction. Maternal Health, Neonatology and Perinatology. 2017; 3: 2.
41. Myatt L, Clifton RG, Roberts JM, et al. The utility of uterine artery doppler velocimetry in prediction of preeclampsia in a low-risk population. Obstetrics and Gynecology. 2012; 120: 815-822.
42. Enkhmaa D, Wall D, Mehta PK, et al. Preeclampsia and vascular function: A window to future cardiovascular disease risk. Journal of Women's Health. 2016; 25: 284-291.
43. Townsend R, O'Brien P, Khalil A. Current best practice in the management of hypertensive disorders in pregnancy. Integrated Blood Pressure Control. 2016; 9: 79-94.
44. Petla LT, Chikkala R, Ratnakar KS, et al. Biomarkers for the management of pre-eclampsia in pregnant women. Indian Journal of Medical Research. 2013; 138: 60-67.
45. Spencer K, Cowans NJ, Chefetz I, et al. First-trimester maternal serum PP-13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. Ultrasound in Obstetrics and Gynecology. 2007; 29: 128-134.
46. Conover CA, Bale LK, Overgaard MT, et al. Metalloproteinase pregnancy-associated plasma protein A is a critical growth regulatory factor during fetal development. Development. 2004; 131: 1187-1194.
47. Grubb AO. Cystatin C-Properties and use as diagnostic marker. Advances in Clinical Chemistry. 2001; 35; 63-99.
48. Thilaganathan B, Ralph E, Papageorghiou AT, et al. Raised maternal serum cystatin C: An early pregnancy marker for preeclampsia. Reproductive Sciences. 2009; 16: 788-793.
49. Bellos I, Fitrou G, Daskalakis G, et al. Serum cystatin-c as predictive factor of preeclampsia: A meta-analysis of 27 observational studies. Pregnancy Hypertension. 2019; 16: 97-104.
50. Akolekar R, Casagrandi D, Livanos P, et al. Maternal plasma pentraxin 3 at 11 to 13 weeks of gestation in hypertensive disorders of pregnancy. Prenatal Diagnosis. 2009; 29: 934-938.
51. Cetin I, Cozzi V, Pasqualini F, et al. Elevated maternal levels of the long pentraxin 3 (PTX3) in preeclampsia and intrauterine growth restriction. American Journal of Obstetrics and Gynecology. 2006; 194: 1347-1353.
52. Angeli F, Angeli E, Trapasso M, et al. Pentraxin-3 and the pathogenesis of preeclampsia. Hypertension Research. 2020; 43: 979-981.
53. Hamad RR, Eriksson MJ, Berg E, et al. Impaired endothelial function and elevated levels of pentraxin 3 in early-onset preeclampsia. Acta Obstetricia et Gynecologica Scandinavica. 2012; 91: 50-56.
54. Colmenares-Mejía CC, Quintero-Lesmes DC, Bautista-Niño PK, et al. Pentraxin-3 is a candidate biomarker on the spectrum of severity from pre-eclampsia to HELLP syndrome: GenPE study. Hypertension Research. 2020; 43: 884-891.
55. Mustafa R, Ahmed S, Gupta A, et al. A comprehensive review of hypertension in pregnancy. Journal of Pregnancy. 2012.
56. Masuyama H, Nakatsukasa H, Takamoto N, et al. Correlation between soluble endoglin, vascular endothelial growth factor receptor-1, and adipocytokines in preeclampsia. Journal of Clinical Endocrinology and Metabolism. 2007; 92: 2672-2679.
57. Powe CE, Levine RJ, Karumanchi SA. Preeclampsia, a disease of the maternal endothelium: The role of antiangiogenic factors and implications for later cardiovascular disease. Circulation. 2011; 123: 2856-2869.
58. Agrawal S, Shinar S, Cerdeira AS, et al. Predictive performance of PlGF (Placental Growth Factor) for screening preeclampsia in asymptomatic women: A systematic review and meta-analysis. Hypertension. 2019; 74: 1124-1135.

59. Duhig KE, Myers J, Seed PT, et al. Placental growth factor testing to assess women with suspected pre-eclampsia: a multicentre, pragmatic, stepped-wedge cluster-randomised controlled trial. The Lancet. 2019; 393: 1807-1818.
60. Ohkuchi A, Hirashima C, Takahashi K, et al. Onset threshold of the plasma levels of soluble fms-like tyrosine kinase 1/ placental growth factor ratio for predicting the imminent onset of preeclampsia within 4 weeks after blood sampling at 19-31 weeks of gestation. Hypertension Research. 2013; 36: 1073-1080.
61. Liu Y, Zhao Y, Yu A, et al. Diagnostic accuracy of the soluble Fms-like tyrosine kinase-1/placental growth factor ratio for preeclampsia: a meta-analysis based on 20 studies. Archives of Gynecology and Obstetrics. 2015; 292: 507-518.
62. Youssef L, Erlandsson L, Åkerström B, et al. Hemopexin and α1-microglobulin heme scavengers with differential involvement in preeclampsia and fetal growth restriction. PLoS ONE. 2020; 15: e0239030.
63. Murtoniemi K, Kalapotharakos G, Vahlberg T, et al. Longitudinal changes in plasma hemopexin and alpha-1-microglobulin concentrations in women with and without clinical risk factors for pre-eclampsia. PLoS ONE. 2019; 14: e0226520.
64. Muttukrishna S, Knight PG, Groome NP, et al. Activin A and inhibin A as possible endocrine markers for preeclampsia. Lancet. 1997; 349: 1285-1288.
65. Aquilina J, Barnett A, Thompson O, et al. Second-trimester maternal serum inhibin A concentration as an early marker for preeclampsia. American Journal of Obstetrics and Gynecology. 1999; 181: 131-136.
66. Grobman W. Serum levels of activin a and inhibin a and the subsequent development of preeclampsia. Obstetrics & Gynecology. 2000; 96: 390-394.
67. Salomon LJ, Benattar C, Audibert F, et al. Severe preeclampsia is associated with high inhibin A levels and normal leptin levels at 7 to 13 weeks into pregnancy. American Journal of Obstetrics and Gynecology. 2003; 189: 1517-1522.
68. Ay E, Kavak ZN, Elter K, et al. Screening for pre-eclampsia by using maternal serum inhibin A, activin A, human chorionic gonadotropin, unconjugated estriol, and alpha-fetoprotein levels and uterine artery Doppler in the second trimester of pregnancy. Australian and New Zealand Journal of Obstetrics and Gynaecology. 2005; 45: 283-288.
69. Banzola I, Farina A, Concu M, et al. Performance of a panel of maternal serum markers in predicting preeclampsia at 11-15 weeks' gestation. Prenatal Diagnosis. 2007; 27: 1005-1010.
70. Kwak DW, Kim SY, Kim HJ, et al. Maternal total cell-free DNA in preeclampsia with and without intrauterine growth restriction. Scientific Reports. 2020; 10: e0200360.
71. Portelli M, Baron B. Clinical presentation of preeclampsia and the diagnostic value of proteins and their methylation products as biomarkers in pregnant women with preeclampsia and their newborns. Journal of Pregnancy. 2018.
72. Karampas G, Eleftheriades M, Panoulis K, et al. Maternal serum levels of neutrophil gelatinase-associated lipocalin (NGAL), matrix metalloproteinase-9 (MMP-9) and their complex MMP-9/NGAL in pregnancies with preeclampsia and those with a small for gestational age neonate: A longitudinal study. Prenatal Diagnosis. 2014; 34: 726-733.
73. Norwitz E, Luo G, Park JS, et al. 798: Neutrophil gelatinase-associated lipocalin (NGAL) is a novel urinary biomarker for severe preeclampsia. American Journal of Obstetrics and Gynecology. 2009; 201: S286.
74. Kim SM, Park JS, Norwitz ER, et al. Circulating levels of neutrophil gelatinase-associated lipocalin (NGAL) correlate with the presence and severity of preeclampsia. Reproductive Sciences. 2013; 20: 1083-1089.
75. D'Anna R, Baviera G, Giordano D, et al. Second trimester neutrophil gelatinase-associated lipocalin as a potential prediagnostic marker of preeclampsia. Acta Obstetricia et Gynecologica Scandinavica. 2008; 87: 1370-1373.
76. Pihl K, Sørensen S, Jørgensen FS. P 35 First trimester maternal serum neutrophil gelatinase-associated lipocalin (NGAL) in prediction of preeclampsia in nulliparous women. Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health. 2017; 9: 52-53.
77. Dymara-Konopka W, Laskowska M. The role of Nitric Oxide, ADMA, and Homocysteine in the etiopathogenesis of preeclampsia-review. International Journal of Molecular Sciences. 2019; 20: 2757.
78. Yuan J, Wang X, Xie Y, et al. Circulating asymmetric dimethylarginine and the risk of preeclampsia: A meta-analysis based on 1338 participants. Oncotarget. 2017; 87: 43944-43952.
79. Carroll RC, Owers RL, Elder RF, et al. Lack of thrombopoietin potentiation of platelet collagen activation in the first trimester is associated with preeclampsia. Thrombosis Research. 2005; 116: 51-54.
80. Johnson RJ, Kanbay M, Kang DH, et al. Uric acid: A clinically useful marker to distinguish preeclampsia from gestational hypertension. Hypertension. 2011; 58: 548-549.
81. Amin S V, Illipilla S, Hebbar S, et al. Quantifying Proteinuria in Hypertensive Disorders of Pregnancy. International Journal of Hypertension. 2014.
82. Perkins AV, Linton EA, Eben F, et al. Corticotrophin-releasing hormone and corticotrophin- releasing hormone binding protein in normal and pre-eclamptic human pregnancies. BJOG. 1995; 102: 118-122.
83. Florio P, Imperatore A, Sanseverino F, et al. The measurement of maternal plasma corticotropin-releasing factor (CRF) and CRF-binding protein improves the early prediction of preeclampsia. Journal of Clinical Endocrinology and Metabolism. 2004; 89: 4673-4677.
84. di Prima FAF, Valenti O, Hyseni E, et al. Antiphospholipid Syndrome during pregnancy: the state of the art. Journal of prenatal medicine. 2011; 5: 41-53.

85. Kupferminc MJ. Thrombophilia and pregnancy. Reproductive Biology and Endocrinology. 2003; 1: 111.

86. Salomon C, Guanzon D, Scholz-Romero K, et al. Placental exosomes as early biomarker of preeclampsia: Potential role of exosomalmicrornas across gestation. Journal of Clinical Endocrinology and Metabolism. 2017; 102: 3182-3194.

87. Shennan A, Duhig K, Vandermolen B. Recent advances in the diagnosis and management of pre-eclampsia. F1000Research. 2018; 7: 242.

88. Erez O, Romero R, Maymon E, et al. The prediction of late-onset preeclampsia: Results from a longitudinal proteomics study. PLoS ONE. 2017; 12: e0181468.

89. Tarca AL, Romero R, Benshalom-Tirosh N, et al. The prediction of early preeclampsia: Results from a longitudinal proteomics study. PLoS ONE. 2019; 14: e0217273.

90. Wright D, Syngelaki A, Akolekar R, et al. Competing risks model in screening for preeclampsia by maternal characteristics and medical history. American Journal of Obstetrics and Gynecology. 2015; 213: 62.e1-62.e10.

91. Roberge S, Nicolaides K, Demers S, et al. The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis. American Journal of Obstetrics and Gynecology. 2017; 216: 110-120.e6.

92. Committee on Obstetric Practice. Low-Dose Aspirin Use During Pregnancy. Obstet Gynecol. 2018; 132: e44-e52.

93. Rolnik DL, Wright D, Poon LCY, et al. ASPRE trial: performance of screening for preterm pre-eclampsia. Ultrasound in Obstetrics and Gynecology. 2017; 50: 492-495.

94. Bao P, Gao XL, Wen GQ. The Threat of Antibiotics and Heavy Metal Pollution to Human Health and Potential Solutions. BioMed Research International. 2020.

95. Hofmeyr GJ, Lawrie TA, Atallah ÁN, et al. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database of Systematic Reviews. 2014; 10: CD001059.