

Serum Markers for the Prediction of Preeclampsia

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Abstract

Preeclampsia is one of the major causes of perinatal morbidity and mortality. There is urgent need for a first trimester marker for the prediction of the disease. Ultrasonographic markers when used alone are not very sensitive. Several biochemical serum markers have been investigated as possible predictors in the first and second trimester of pregnancy. The markers which have been studied extensively are both angiogenic and antiangiogenic factors as well as factors related to the process of placentation. However, the biochemical markers when they are used alone are not extremely effective for the prediction of PE. The combination of these markers with other predictors such as maternal history, clinical features, risk factors, demographic characteristics, uterine arteries Doppler will develop in the future more effective prediction models.

Keywords: Preeclampsia; Prediction; Serum biochemical markers

Risk factors for preeclampsia

Introduction

Preeclampsia (PE) is a leading cause of maternal and perinatal morbidity and mortality worldwide affecting 3% to 5% of pregnant women [1] and it is associated with the development of cardiovascular disease, obesity, renal damage and diabetes in adults [2-4]. It is a systemic syndrome which clinically arises in the second half of pregnancy and it is presented with the onset of hypertension (arterial pressure exceeding 140/90 mmHg on 2 occasion, at least 6 hours apart) and proteinuria (>300 mg/dL/24h or a dipstick of >= 2+) after 20 weeks of gestation, in a previously normotensive women [5].

According to World Health Organization, in developing countries with limited access to health care, PE is estimated to be responsible for more than 60000 maternal deaths per year, whereas in the developed countries the burden of this disease falls on the neonates because of the high rate of iatrogenic preterm deliveries performed to preserve the maternal health [6]. The perinatal and neonatal mortality rate due to PE is about 10%, worldwide [7].

In clinical practice, there is currently no reliable screening method in the first trimester of pregnancy with sufficient accuracy to identify women at high risk to develop PE despite the fact that many predisposing factors, including defective placentation, may already be apparent in the first or early second trimester. However, the ability of identification women at high-risk has increased considerably during the past decade. Early identification of high-risk pregnancy may help the development of new strategies for antenatal surveillance or prevention and thus improve maternal and perinatal outcome. The early identification of patients with increased risk for PE is therefore one of the most important goals in obstetrics. The aim of this study was to review the literature on the predictive serum markers of PE.

A high number of pre-pregnancy and pregnancy related factors have been associated with PE. Several medical conditions, such as chronic hypertension, renal disease, pre-gestational diabetes mellitus, uncontrolled hyperthyroidism, polycystic ovary syndrome, urinary tract infections, connective tissue disease (rheumatoid arthritis, lupus erythematosus), obesity, insulin resistance, antiphospholipid syndrome and thrombophilia, are some of these factors [8,9]. Moreover, maternal low birth weight, primipaternity, pregnancies conceived after donor insemination, oocyte or embryo donation, limited sperm exposure of the mother, maternal infections, partner who fathered preclampsic pregnancy with another woman and chromosomal abnormality (triploidy, trisomy 13) are risk factors for PE [8,9]. Conditions associated with increased placental mass, such as multifetal gestation and hydatidiform mole may also predispose to PE. Smoking during pregnancy has been found to decrease the risk of PE. In addition PE is higher in pregnant women younger than 20 and older than 40 years [10].

Maternal demographics including ethnic group, parity, body mass index (BMI), and personal or family history of PE are well-known risk factors [11]. Among women considered as high-risk, approximately 25% will develop PE compared to 5% in the general population [12]. The presence of PE in a first-degree relative increases a woman's risk of severe PE two to four fold [13], while a history of PE on fathers' mother increases the risk [14]. Most cases of PE occurs in nulliparous, in whom the incidence of PE may be as high as 7.5%, but multiparous with a new partner seem to have similar risk for preeclampsia to that of nulliparous women [15]. Although risk factors are not useful as an effective screening test by themselves [16], they can help on the identification of high risk populations in which other predictive test may perform better [17,18].

In a large study, Poon et al. showed that by using certain risk factors could predict early- and late-onset PE. Predictors of early-PE were black race, chronic hypertension, prior history of PE and the use of ovulation drugs. Late-PE predictors were advanced maternal age,

increased body mass index and family or personal history of PE. Using maternal factors the detection rates of early and late-PE were 37% and 28.9% respectively, for a 5% false positive rate [19].

Pathogenesis

The pathogenesis of preeclampsia is complicated and has not been fully elucidated. However, it is evident that this disorder involves multiple organ systems. Pathogenetic mechanisms implicated in preeclampsia include defective placentation, oxidative and endoplasmic reticulum stress, autoantibodies to type-1 angiotensin II receptor, platelet and thrombin activation, intravascular inflammation, endothelial dysfunction and the presence of an antiangiogenic state, among which an imbalance of angiogenesis has been emerged as one of the most important factors [20]. Angiogenesis is necessary for the establishment of adequate placental perfusion, which is important for providing the optimum in utero environment to support fetal development. Defective placental angiogenesis is associated with several pregnancy complications, the most clinically important of which is preeclampsia [21]. Nevertheless, it seems clear that placenta is the principal contributor to the pathogenesis of preeclampsia since the clinical syndrome will not develop in the absence of a placenta and the delivery of placenta remains the only treatment for the clinical disease.

Trophoblastic invasion has specific characteristics in human placentation. It is limited in depth, ending in the intern third of the myometrium and it is orientated to the spiral arteries. In normal pregnancies, extravillous cytotrophoblasts of fetal origin invade the uterine spiral arteries of the decidua and myometrium [22]. These invasive cytotrophoblasts replace the endothelial layer of the maternal spiral arteries, transforming them from small, high-resistance vessels into large-caliber vessels. These changes are essential to allow adequate blood supply to the placenta. In PE this transformation is incomplete [23]. Cytotrophoblast invasion of the spiral arteries is adequate only to the superficial decidua and does not reach the myometrium [24]. This reduced uteroplacental perfusion, which develops as a result of abnormal cytotrophoblast invasion of spiral arterioles, triggers the cascade of events leading to the maternal disorder. Placental ischemia causes the release of soluble placental factors, many of which are classified as anti-angiogenic or pro-inflammatory [25]. The endothelial dysfunction in its turn leads to hypertension, proteinuria and nondependent edema which are the characteristic clinical manifestations of PE [26].

Biomarkers

During the last decades, a lot of biochemical markers have been investigated based on pathophysiological observations of PE. In this review, the most important new biochemical markers for the prediction of PE which are responsible for placental dysfunction, inflammatory response and activation of the coagulation system are presented (Table 1).

Markers	Features	Origin/expression	Alteration in PE
PIGF, VEGF, sVEGFR-1(sFlt-1)	Markers of angiogenesis	of trofoblast	^(sFlt-1)
			v(VEGF, PIGF)
sEndoglin	Receptor of TEGFβ1&β3	trophoblast	^

TPO	Cytokine for thrombopoiesis	liver	^
P-selectin	Inflammation reactions	Platelets, endothelial cells	^
PP13	placental implantation, maternal vascular remodeling	Syncytiotrophoblast,	v
PAPP-A	Insulin –like growth factor binding protein	throphoblast	v initially ^>onset PE
ADMA	Inhibitor of NO composition	ADMA is formed by methylation of L-arginine	^
CRF&CRF-BP	Modulation of vascular tone	trophoblast	^(CRF) v(CRF-BP)
PGH	Metabolism in pregnancy	Syncytiotrophoblast, extravillous cytotrophoblast	v >onset PE ^ before the onset
IGF1, IGFBP1	implantation	placenta	v (2nd trimester)
Inhibin A & Activin A	TEGFβ-family	placenta	^

Table 1: Biochemical markers for PE prediction; VEGF :vascular endothelial growth factor, PIGF: placental growth factor, sFlt1: soluble membrane –bound fms-like tyrosine kinase 1, sEng: Soluble endoglin, TPO: Thrombopoietin, PP13: Placenta protein 13, PAPP-A: Pregnancy –associated plasma protein, ADMA: Asymmetric dimethylarginine, CRF-BP: Corticotropin releasing factor –binding protein, CRF: Corticotrophin-releasing factor, PGH: Placental growth hormone , IGF-1: Insulin like growth factor-1, IGFBP1: Insulin like growth factor binding protein-1

Angiogenic Factors

As a response to hypoxia, placenta produces pathogenic factors, which enter the maternal blood stream and are responsible for the endothelial dysfunction and other clinical manifestations of the disease including hypertension and proteinuria [26]. One of the most intensely studied pathways in the manifestation of PE is that which is related to vascular endothelial growth factor signalling [17,27]. Among the various angiogenic factors expressed by the placenta, vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) play a very important role [17,28]. Angiogenic molecules such as VEGF, PIGF, and antiangiogenic molecules such as soluble membrane –bound fms-like tyrosine kinase 1(sFlt1) may be important regulators of early placental development and pseudovasculogenesis. In fact, it has been shown that exogenous sFlt1 inhibits placental cytotrophoblast invasion in vitro [29].

VEGF is a potent angiogenic protein which promotes vasodilatation by inducing nitric oxide and prostacyclin synthesis by endothelial cells [30]. The function of VEGF is to promote sustenance, migration and differentiation of endothelial cells and vascular permeability [31]. It acts through two receptors tyrosine kinases, VEGF receptor-1(fms-like tyrosine kinase) and VEGF receptor-2, which are selectively expressed

on the vascular endothelial cell surface. The VEGF receptor -1 has 2 isoforms: a transmembrane isoform and a soluble isoform (sFlt) [32].

PlGF is an angiogenic growth factor that amplifies VEGF signalling by displacing VEGF from the Flt-1 receptor and allows it to bind to the more active kinase-insert domain receptor [33]. Increased sFlt-1 during preeclampsia is associated with decreased free VEGF and free PlGF in the blood (25). The major source of PlGF is placental trophoblast, and it is expressed as several different isoforms which bind only to VEGF receptor 1 (VEGFR1) [34].

Inappropriate modification of maternal uterine spiral arteries results in increased production of sFlt-1. sFlt-1 is a circulating soluble receptor for both VEGF and free PlGF. Increased sFlt-1 levels in maternal plasma lead to less circulating free VEGF and free PlGF, thus preventing their availability to stimulate angiogenesis and maintain endothelial integrity [35]. sFlt-1 antagonizes the pro angiogenic factors VEGF and PlGF by adhering to the receptor binding domains of VEGF and PlGF [36]. In the kidney this inactivation of free VEGF is believed to cause endotheliosis and proteinuria [35]. Abnormal expression of an endogenous sFlt-1 has been shown to be involved in PE cases [37].

Several studies have shown a decrease in serum levels of VEGF and PlGF with simultaneous increased levels of sFlt-1 in preeclamptic compared to normal pregnant women [36,38-40]. Inhibition of pro-angiogenic factors by increased levels of sFlt-1 leads to endothelial dysfunction which can be restored in vitro by exogenous PlGF and VEGF.

Maternal blood levels of sFlt-1 are related to the severity of preeclampsia. In an opposite manner the levels of bioactive VEGF and PlGF are significantly decreased in patients with severe symptoms, compared to normal pregnant woman or women with mild PE [35,38,41]. The sFlt-1/PlGF ratio has been reported as a better index for the angiogenic activity and can be used as a screening test for early onset preeclampsia [42].

Soluble Endoglin

Soluble endoglin (sEng) is another antiangiogenic factor, which acts together with sFlt-1 to induce a severe preeclamptic syndrome. Endoglin is a co-receptor for transforming growth factor (TGF)- β 1 and TGF- β 3 that is highly expressed on cellular membranes of the vascular endothelium and on syncytiotrophoblast [43,44]. It is involved in the angiogenesis and the regulation of the vascular tone [45]. Soluble endoglin (sEng) is a circulatory form of endoglin which consists of the extra cellular part of the molecule that may be produced through the proteocleavage of the placental membrane bound form. It acts as a potential anti-angiogenic factor by interfering with the binding of TGF- β 1 to its receptors, which ultimately affects the production of nitric oxide (NO), vasodilation and capillary formation by endothelial cells [45,46].

Similar to levels of sFlt-1, sEng levels are high among women with PE. Women with preeclampsia have elevated sEng (4-fold higher) in the third trimester with levels rising 4-5 weeks prior to clinical diagnosis [47]. sEng is significantly increased in women who will develop PE by 9-14 weeks [48], while effective prediction can be achieved at 11-13 wk gestation [49].

The measurements of both sEng and sFlt-1 may be a better predictor of preeclampsia. Combined analysis of sEng and sFlt1 is able to predict early-onset preeclampsia with a sensitivity of 100% and a

specificity of 93.3% [50]. The sFlt-1/PlGF ratio and more specifically (sFlt-1 + sEng)/PlGF ratio is a better predictor of PE than the individual markers [51].

Thrombopoietin

Thrombopoietin (TPO) is a major cytokine for megakaryocytopoiesis and thrombopoiesis, and also plays an important role in the regulation of early hematopoiesis. TPO is a 94 KD protein primarily made in the liver and secreted into the circulation, while there is no storage form. TPO activates a number of signal pathways to exert its biological function by binding to its receptor (c-mpl). Most of the circulating TPO is cleared by platelets (and possibly megakaryocytes) by binding to the TPO receptor, followed by internalization and catabolism of the bound ligand [52]. Therefore the circulating TPO level is inversely related to the rate of platelet production. When platelet production is low, less TPO is cleared and its levels rise, whereas when platelet production is elevated, more TPO is cleared and its levels fall [53].

In 1998 Frolich et al. reported for first time that TPO levels were significantly greater in pregnancies complicated by the hemolysis, elevated liver enzymes and low platelets syndrome (HELLP)[54]. Moreover, it has been found that infants with thrombocytopenia associated with preeclampsia have increased circulating levels of TPO[55]. On the contrary, Albert et al. found that preterm infants born to women with preeclampsia (n = 11) had lower TPO levels than NTP infants with a similar gestation age (<41 pg/ml vs 95 pg/ml) [56]. In addition lack of TPO potentiation of platelet collagen activation in the first trimester has been associated with preeclampsia [57].

P-selectin

P-selectin is a member of the selectin family of cell surface adhesion molecules. It is expressed by platelets and endothelial cells upon activation and it is involved in leucocyte-endothelial interactions. Its role is crucial in inflammatory reactions by supporting the recruitment and activation of circulating leucocytes [51,58].

During pregnancy, maternal P-selectin expression occurs exclusively at the implantation site and may provide a mechanism for maternal and fetal cell interaction to enable the trophoblast to implant within the uteroplacental vessel lumen [59]. P-selectin is released from the cell surface and circulates as a soluble molecule in the maternal plasma [60]. Both the membrane form and the soluble form of P-selectin are agonists of the processes of thrombosis and inflammation [61]. As PE is associated with extensive platelet activation, increased p-selectin expression may play an important role in the pathophysiology of the disease [62].

In a study by Laskowska M et al. it was found that elevated levels of soluble P-selectin are associated with PE. This may confirm the presence of platelet and endothelial activation, which may be due to the systemic inflammatory response in this serious pregnancy disorder [63].

Aksoy et al. suggested that P-selectin may be an additional risk marker for PE, and may be useful in distinguishing women with mild or severe PE and normal pregnancy [64].

In another study Bosio et al. supported an inflammatory model for PE, in which endothelial cell activation may be secondary to a primary

inflammatory response. In this study, plasma P-selectin had significant potential as a first trimester clinical marker of PE [65].

Last, Holmes et al. showed that P-selectin concentration is significantly higher in the second and third trimester of pregnancy when compared to non-pregnant controls [66].

Placenta Protein 13

Placenta protein 13 (PP13) is a small protein (32,kD) which is produced by the placenta, specifically the syncytiotrophoblast. It binds to protein on the extracellular matrix between the placenta and the endometrium and is thought to be involved in placental implantation and maternal vascular remodeling [67,68].

Recently this protein has been attracted as a potential marker for early diagnosis of PE [69]. The PP13 serum levels slowly increase during a normal pregnancy. Decreased levels of PP-13 have been found in patients who developed PE, particularly in cases with early onset disease [70]. In a study by Nicolaides et al. in patients with severe PE who gave birth before 34 weeks, the PP13 serum levels were lower than in the normotensive individuals. They suggested that effective screening for PE requiring delivery before 34 weeks can potentially be provided by assessment of a combination of maternal serum PP-13 and uterine artery Doppler in the first trimester of pregnancy [71]. Another study, analyzed maternal serum PP-13 levels at 9-12 weeks gestation and found lower levels in women who went on to develop preeclampsia compared with controls [72].

Romero et al. concluded that maternal serum first-trimester PP13 appears to be a reasonable marker for risk assessment for preterm preeclampsia, but a weak marker for severe PE at term and ineffective for identifying mild preeclampsia at term [73].

Pregnancy –Associated Plasma Protein (PAPP-A)

PAPP-A (pregnancy-associated plasma protein A) is a disulfide bond linked homodimeric peptidase of 1628 amino acids and a mass of 400 KDa produced by growing trophoblast which indirectly induces aggression to the endometrium [74]. It is an insulin-like growth factor binding protein (IGFBP) protease with specificity for IGFBP 2 and 4. Reduced levels of PAPP-A may result in increased amounts of insulin-like growth factor (IGF) being bound to its carrier proteins and hence not available at the cell receptor level to stimulate fetal growth and trophoblast invasion of the decidua [75]. Decreased levels of PAPP-A are associated with a higher risk of PE, but its predictive value is not as precise as PP13 and Doppler ultrasonography [76]. Decreased PAPP-A levels, are seen in all trimesters in women with PE [77]. It is not clear whether early evaluation of risk factors using PP13 and PAPP-A, alone or in combination, can improve pregnancy outcome [78]. The predictive values of placental function markers such as PP13 and PAPP-A in the second trimester has not been clearly defined and there is controversy among studies [79].

Moslemi Zadeh et al. suggested that it is possible to increase the predictive value of each test by combining the measurements of PAPP-A and PP13 in the first and second trimester [80].

Poon et al. showed that the PAPP-A serum levels in the first trimester was under the fifth percentage in 21.9% and 6.5% of patients with early and late PE, respectively. They noted that the PAPP-A-related patient-specific risk for PE can be modified by the measurement of uterine arteries Doppler PI (UtA-PI) [81].

D' Anna et al. also concluded that the first trimester PAPP-A is not useful in predicting late onset PE, as the levels of PAPP-A were significantly reduced only in the early onset PE, while the levels of PAPP-A in late onset preeclampsia did not differ from that of controls [82].

Asymmetric Dimethylarginine (ADMA)

ADMA (asymmetric dimethylarginine) is an antiangiogenic factor that decreases VEGF expression in endothelial cells and prevents the formation of nitric oxide (NO) from nitric oxide synthases (NOS) [83]. Through the action of protein arginine-N-methyltransferases, L-arginine can be methylated to form asymmetric dimethylarginine (ADMA) [84].

Elevated levels of ADMA have been implicated in the pathophysiology of other microvascular diseases and are a prognostic marker for major cardiovascular events and mortality in patients with established cardiovascular disease as well as in the general population [85]. Increased ADMA levels in endothelium-dependent vascular dysfunction were also detected in diabetic, hypertensive, and hypercholesterolemic patients [86-88]. ADMA levels may decrease at the beginning of a normal pregnancy [89] but its concentration increases significantly in PE as it has been reported in several studies [90-92]. Several studies have reported elevated ADMA levels in PE. It seems that ADMA is involved in the pathogenesis of PE as it inhibits the NO synthesis in rodents during pregnancy and produces signs similar to that of preeclampsia [93,94].

Corticotrophin-Releasing Factor (CRF), Corticotropin Releasing Factor –Binding Protein (CRF-BP)

In pregnancy, CRF (corticotropin-releasing factor) has a paracrine action inducing placental adrenocorticotropin hormone (ACTH) release, as well as an endocrine function modulating fetal pituitary-adrenal cortex axis [95,96]. Corticotropin-releasing factor-binding protein (CRF-BP) is a 37-kDa protein of 322 amino acids, which is expressed in human trophoblast and intrauterine tissues during pregnancy [97]. It modulates the activity of the hypothalamus-pituitary-adrenal axis during pregnancy, counteracting the actions of circulating or locally acting CRF [98]. Petraglia et al. showed an inverse correlation between reduced plasma CRF-BP levels and increased CRF levels in the maternal circulation of patients with pregnancy-induced hypertension. They also showed that these hormonal changes did not occur before the onset of disease, suggesting that the measurement of these polypeptides in maternal plasma does not predict the development of hypertension [99]. Florio et al. measured maternal plasma concentrations of two placental neurohormones, corticotropin-releasing factor (CRF) and CRF-binding protein (CRF-BP), in 58 at-risk pregnant women consecutively enrolled between 28 and 29 weeks to evaluate whether their assessment may predict third trimester-onset preeclampsia. CRF and CRF-BP levels were significantly higher and lower, respectively, in the patients who later developed PE [100].

Placental Growth Hormone (PGH)

Placental growth hormone (PGH) is a pregnancy-specific hormone that has been proposed to play a role in trophoblast invasion [101] and fetal growth [102], as well as maternal adaptation to pregnancy [103]. It is expressed by syncytiotrophoblast and extravillous cytotrophoblast [104]. PGH can be detected in maternal blood at as early as 5 weeks of

gestation [105] and increases throughout pregnancy until term at which time its concentration may remain stable or slightly decrease [106,107].

Sifakis et al. investigated whether maternal PGH serum concentration at 11–13 weeks' gestation, is altered in pregnancies that deliver small for gestational age (SGA) neonates. They found that maternal serum PGH at 11–13 weeks' gestation is unlikely to be a useful biochemical marker for early prediction of SGA. Moreover, they observed that PGH level is normal during the first trimester in pregnancies that subsequently developed PE, suggesting that this hormone is unlikely to play a role in the pathogenesis of the disease [108].

Mittal et al. tried to determine whether maternal serum concentrations are different in women with PE, women with PE who deliver a small for gestational age neonate (PE + SGA), and those with SGA alone. They concluded that PE is associated with higher median concentrations in both the maternal and the fetal circulation compared to normal pregnancies. Patients with PE + SGA had lower concentrations than preeclamptic patients without SGA. They suggested that may play a role in the pathogenesis of PE as well as of fetal growth restriction [109].

Insulin like Growth Factors (IGFs)

Insulin-like growth factor-I (IGF-I) is a strong mitogen that promotes cell proliferation and differentiation and has a critical role in many aspects of placental development and regulation of fetal and postnatal growth [110]. It increases the differentiation of cytotrophoblasts into syncytiotrophoblast and extravillous trophoblasts. Moreover, it increases the proliferation of placental fibroblast and trophoblasts and it enhances the trophoblast invasion [111]. The actions of IGF-1 in the circulation and the extracellular matrix are modulated by the presence of the IGF-binding proteins (IGFBP), mainly 1 and 3 (IGFBP-1 and IGFBP-3). Insulin-like growth factor I and II regulate the life cycle of trophoblast in the developing human placenta [111]. In the non-pregnant state, IGFBP-1 is produced in the liver and it is strongly regulated by insulin. In pregnancy, IGFBP-1 is also produced by the placenta, resulting in higher maternal concentrations of this protein [112]. IGFBP-3 is the most abundant IGFBP in the circulation, while both IGFBP-1 and -3 prolong IGF half-life in plasma and provide an IGF reservoir for target tissues [113]. Sifakis et al. reported that in pregnancies destined to develop PE the circulating levels of IGF-I and IGFBP-1 are already decreased from the first-trimester of pregnancy [114,115]. The IGFBP-3 levels are increased in women who will develop late- but not early-onset PE. Finally, the absence of significant association between serum IGF-I, IGFBP-1 and IGFBP-3 and uterine artery Doppler PI, suggests that the possible implication in the pathogenesis of PE is mediated by a mechanism unrelated to impaired placental perfusion [116].

Inhibin A, Activin A

Inhibin A and Activin A are glycoproteins, members of the transforming growth factor b family, and during pregnancy, are largely released by the placenta. Term placental cells secrete increased levels of inhibin A and activin A in the presence of inflammatory cytokines (increased in pre-eclampsia) which are potent stimulators of inhibin A and activin A [117]. In normal pregnancy, concentrations of both hormones rise in the third trimester, and levels have been shown to be elevated approximately 10-fold in the women with established

preeclampsia [118]. Serum levels can be raised as early as 10–15 weeks of pregnancy in women who subsequently develop pre-eclampsia compared with gestational age-matched control pregnant women [119]. Second trimester levels of inhibin A have been shown to be elevated in both serum and amniotic fluid [120] in women who went on to develop severe preeclampsia. The second trimester levels of both inhibin A and activin A have been reported to add significant prognostic information when measured in women with abnormal uterine artery Doppler studies [121]. On the contrary Davidson et al. in second trimester serum samples of 39 women who subsequently developed preeclampsia found significantly elevated Activin A levels but not elevated inhibin A levels [122].

Combination of Markers

Many investigators attempted to improve the predictive value by combining different maternal serum biomarkers with clinical characteristics and Doppler ultrasonography. The use of multiple markers increases the specificity and sensitivity of the screening possibly because they reflect different pathways to the disease process. Spencer et al. investigated the potential value of the combination of uterine artery Dopplers and the measurement of maternal serum pregnancy-associated plasma protein-A (PAPP-A), free β -human chorionic gonadotropin (β -hCG), activin A and inhibin A at 22 + 0 to 24 + 6 weeks' gestation. These maternal serum markers were measured in samples obtained from women with singleton pregnancies who participated in a screening study for pre-eclampsia by transvaginal color flow Doppler measurement of the uterine artery pulsatility index (PI). A search was made of the database to identify those who subsequently developed preeclampsia (n = 24) and a group of controls with normal outcome (n = 144). They suggested that in the PE group, compared with controls, the uterine artery mean PI and the maternal serum levels of PAPP-A, free β -hCG, activin A and inhibin A were significantly increased. The detection rates of PE, for a false positive rate of 5%, was 50% by uterine artery mean PI, 5% by PAPP-A, 10% by free β -hCG, 35% by inhibin A and 44% by activin A. Screening by a combination of uterine artery mean PI and maternal serum activin A and inhibin A could detect 75% and 92% of patients who subsequently developed pre-eclampsia, for a false positive rate of 5% and 10%, respectively [123]. Wald et al. in a nested case control study that carried out on 96 women with preeclampsia and 5 controls for each case, added a screening process for PE to an existing Down syndrome screening programme using the quadruple test markers (AFP, uE (3), hCG (total or free beta) and inhibin-A) they could detect over 40% of pregnancies with PE at an acceptable false-positive rate of 6% and with minimal additional cost [124].

Spencer et al. in a nested case control study of PE that carried out on 446 controls and 44 cases with early PE where delivery was induced prior to 35 weeks and a further 44 cases with PE in which delivery was not induced before term, observed that first trimester PP-13 levels may be useful in predicting PE and early-onset PE, and the accuracy of the method increases when coupled with second-trimester uterine arteries Doppler PI measurement. Moreover, first-trimester PAPP-A provided some prediction for PE when used in combination with uterine arteries Doppler PI, but did not add to the prediction of early-onset PE when PP-13 and uterine arteries Doppler PI were used together [125]. Nicolaides et al. investigated the value of maternal serum placental protein 13 (PP-13) measurements and uterine artery Doppler during first-trimester screening in the prediction of early pre-eclampsia. They carried out a nested case control prospective study of pregnancies at

11+ 0 to 13 + 6 weeks of gestation. In the cases that developed preeclampsia requiring delivery before 34 weeks, compared with the unaffected pregnancies, the median uterine artery PI was higher (1.43 MoM) and the median serum PP-13 level was lower (0.07 MoM; $P < 0.001$). This model predicted that for a 90% detection rate of preeclampsia requiring delivery before 34 weeks, the false-positive rate of screening by PP-13 was 12%, by uterine artery PI was 31% and by a combination of the two methods was 9%. A policy of contingency screening, whereby all women are screened by maternal serum PP-13 and only the 14% at highest risk are then screened by Doppler, achieved a detection rate of 90% with an overall false-positive rate of 6%. They suggested that effective screening for severe PE requiring delivery before 34 weeks, could potentially be provided by assessment of a combination of maternal serum PP-13 and uterine arteries Doppler in the first trimester of pregnancy [126]. Poon et al. tried to establish a method of screening for pregnancy hypertension by a combination of maternal variables, including mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A, and placental growth factor in early pregnancy. The base-cohort population constituted of 7797 singleton pregnancies, including 34 case subjects who developed preeclampsia (PE) requiring delivery before 34 weeks (early PE) and 123 with late PE, 136 with gestational hypertension, and 7504 cases subjects (96.3%) who were unaffected by PE or gestational hypertension. Logistic regression analysis was used to derive algorithms for the prediction of hypertensive disorders. They estimated that with the algorithm for early PE, 93.1%, 35.7%, and 18.3% of early PE, late PE, and gestational hypertension, respectively, could be detected with a 5% false-positive rate and that 1 in 5 pregnancies classified as being screen positive would develop pregnancy hypertension [127]. Akolekar et al. investigated the potential value of maternal plasma inhibin A in the first-trimester screening for PE. The concentration of inhibin A at 11-13 weeks was measured in samples from 121 pregnancies that developed PE, 87 cases of gestational hypertension (GH) and 208 normal controls. The authors found that the combination of maternal factors, plasma inhibin A and uterine arteries Doppler PI had a detection rate for early and late PE of 88% and 42%, respectively, for a false positive rate of 10% [128]. Last, in another study the concentration of PIGF at 11 + 0 to 13 + 6 weeks' gestation was measured in samples from 127 pregnancies that developed PE, including 29 that required delivery before 34 weeks (early PE) and 98 with late PE, 88 cases of gestational hypertension (GH) and 609 normal controls. In this study by combining maternal characteristics (maternal weight, cigarette smoking racial origin), obstetric history, serum PIGF and uterine arteries Doppler PI, the detection rate for early- and late-onset PE were 90% and 49%, respectively, for a false-positive rate of 10% [129].

Conclusion

The biochemical markers are not effective when they are used alone for the prediction of PE. The combination of these markers with other predictors such as maternal history, clinical features, risk factors, demographic characteristics, Doppler velocimetry will develop more effective models.

The identification of first trimester markers will contribute to a better understanding of the pathophysiology of PE and will give us a clinically validated screening procedure for a better management of this disorder. In addition the early identification of high-risk cases will offer the opportunity for prophylactic therapy, thus improving the perinatal outcome.

Recently published data suggest that studies on metabolomics, proteomics, fetal free DNA/RNA and other new techniques which aim to generate new predictive markers of PE, are promising prognostic tools of PE. PE is a multifactorial disorder. Therefore there is a need for large scale multicenter studies including women with different demographic characteristic and different risk of developing the syndrome in order to have a significant predictive model for a routine use in clinical settings. The goal for future studies will be to identify the best combination of markers that would result in optimal screening prediction for PE.

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