Angiogenic growth factors in the diagnosis and prediction of pre-eclampsia

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ABSTRACT

The pathogenesis of pre-eclampsia is still not completely known; however, in the recent decade, there have been tremendous research efforts leading to impressive results highlighting the role of a disturbed angiogenic balance as one of the key features of the disease. Numerous studies have shown the key role of the placenta in the pathogenesis of pre-eclampsia. A shift in the sFlt-1 (soluble Fms-like tyrosine kinase-1)/PlGF (placental growth factor) ratio is associated with the disease. Although pre-eclampsia seems to be a clearly defined disease, clinical presentation, and particularly the dynamics of the clinical course, can vary enormously. The only available tools to diagnose pre-eclampsia are blood pressure measurement and urine protein sampling. However, these tools have a low sensitivity and specificity regarding the prediction of the course of the disease or maternal and perinatal outcomes. The only cure for the disease is delivery, although a timely diagnosis helps in decreasing maternal and fetal morbidity and mortality. The sFlt1/PlGF ratio is able to give additional valuable information on the status and progression of the disease and is apt to be implemented in the diagnostic algorithm of pre-eclampsia. In the present review, we aim to provide an overview of the vast literature on angiogenesis and anti-angiogenesis factors in pre-eclampsia that have been published over the last decade. We introduce work from basic research groups who have focused on the pathophysiological basis of the disease. Furthermore, we review studies with a clinical focus in which the sFlt-1/PlGF ratio has been analysed along with other candidates for routine clinical assessment of pre-eclampsia.

INTRODUCTION

Pre-eclampsia is a pregnancy-related disorder defined as the new onset of hypertension and proteinuria in the second half of pregnancy [1]. The adverse acute and chronic clinical impact on the mother and the child is severe, and the cost to society is immense [2,3]. Although pre-eclampsia seems to be a clearly defined disease, the clinical presentation and clinical course vary enormously. Moreover, autoimmune disorders and renal diseases can mimic pre-eclampsia. Contributing forces leading to pre-eclampsia include immunological, genetic and environmental factors. Clinical diagnosis requires blood pressure measurements and urine protein determinations.
in addition to knowledge regarding these variables. However, these tools have a low sensitivity and specificity regarding the prediction of severe maternal and perinatal outcomes [4–6]. The pathogenesis of the disease is far from understood; however, the last decade has brought a plethora of new and interesting information, particularly regarding the role of the angiogenic balance in the disease. Studies have shown that pre-eclampsia features a shift in angiogenesis and anti-angiogenic factors towards a maladaptive placental circulation. Circulating sFlt1 (placental growth factor) levels are reduced, whereas a shortened soluble gene splice variant of the VEGF-R [VEGF (vascular endothelial growth factor) receptor], sFlt-1 [soluble Flt-1 (Fms-like tyrosine kinase-1)], is markedly increased [7–9]. In the placenta, mRNA and protein expression of sFlt-1 is significantly enhanced [10]. Sensitive sFlt1 and sFlt-1 assays could contribute to decision making, if available in the clinical setting. Conceivably, morbidity and mortality rates, as well as health care costs, could be reduced. An analysis of samples from a large pre-eclampsia intervention trial support that view [11,12]. Recently, new automated tests have been developed that allow the fast and easy measurement of PlGF and sFlt-1 in the outpatient and hospital setting [13–15]. With these automated assays, the step from bench-to-bedside has apparently succeeded; however, hurdles remain. Every diagnostic assay system must be evaluated in terms of sensitivity and specificity, and positive and negative predictor values. Large prospective cohort studies in populations with high and low incidences of pre-eclampsia will be necessary to address these issues.

**BASIC RESEARCH ON ANGIOGENESIS AND ANTI-ANGIOGENESIS**

Early work by Brosens and co-workers [16,17] studied spiral artery remodelling and highlighted the importance of trophoblast invasion in the pathogenesis of pre-eclampsia. Normal placentaion involves a two-stage process, including the formation of a branching vessel network within the chorionic villi of fetal origin. These networks are subsequently followed by modifications of the existing vascular networks and transformation from a high-resistance, relatively hypoxic, vascular bed into a low-resistance circuit with increased oxygen tension [18,19]. Hypoxia, caused by defective placentaion, is a key event in the pathogenesis of pre-eclampsia. Placental ischaemia/hypoxia probably triggers the altered angiogenic balance, promoting the anti-angiogenic state [20,21]. Hypoxic conditions stimulate the expression of pro-angiogenic proteins in endothelial cells such as VEGF and its receptor Flt-1 [22–24]. The HIF (hypoxia-inducible factor)-1α transcription factor regulates VEGF and Flt-1 gene transcription [25]. HIF-1α and HIF-2α protein levels are significantly elevated in the pre-eclamptic placenta [26]. VEGF is up-regulated in the placenta by hypoxia; however, free circulating VEGF and PlGF are low, suggesting an anti-angiogenic state as the net result [27,28]. Furthermore, Lash et al. [29] have shown an association between angiogenic growth factors and trophoblast invasion. They demonstrated that VEGF increased trophoblast motility and invasion in vitro, and also raised the idea that functional receptors on extravillous trophoblasts mediate these actions. The effect has been verified and elucidated further by subsequent studies [30,31]. These findings indicate that dysregulation of angiogenesis is not only implicated in inducing the maternal syndrome, but is also involved in abnormal placentation. VEGF has previously been identified as a direct modulator of vascular function. In important pioneering work, Philip Baker’s group first showed that plasma of pre-eclamptic women directly alters vascular relaxation. This group subsequently identified that incubation of isolated human myometrial resistance vessels in vitro with VEGF results in a decrease in endothelium-dependent relaxation that mimicked the reduction induced by plasma from women with pre-eclampsia [32,33]. Here, a putative role of VEGF as a modulator of vascular resistance and possible inductor of endothelial dysfunction was introduced [32,33].

Maynard et al. [10] introduced the notion that placental sFlt1 could act as a VEGF and PlGF antagonist. They showed that sFlt1 is up-regulated in pre-eclampsia, leading to increased systemic levels of sFlt1, which fall after delivery. They also demonstrated that increased circulating sFlt1 in patients with pre-eclampsia were associated with decreased circulating levels of free VEGF and PlGF, resulting in endothelial dysfunction in vitro that could be rescued by exogenous VEGF and PlGF. In contrast with the work of Brockelsby et al. [32,33] on VEGF in human myometrial arterioles, Maynard et al. [10] showed that VEGF and PlGF caused microvascular relaxation of rat renal arterioles in vitro and that this was blocked by sFlt1. Administering sFlt1 to pregnant rats induced a pre-eclampsia-like condition with hypertension, proteinuria and glomerular endotheliosis in the animals [10]. Their observations ushered in the idea that sFlt1 contributes to the pathogenesis of pre-eclampsia (Figure 1). The same laboratory subsequently produced evidence that sEng (soluble endoglin) also exerts angioangiogenic effects in pre-eclampsia [8]. Li et al. [34] used adenoviral sFlt-1 expression to induce a pre-eclampsia-like syndrome in an animal model, which was antagonized with infusion of VEGF [35]. In these experiments, however, high serum concentrations of circulating sFlt-1 were measured in the treated rats (3–12.9 μg/ml) [34], and these were in contrast with the first report of the group [10], where mean serum concentrations in the adenovirus-treated rats were...
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Figure 1  Effects of the altered angiogenic and anti-angiogenic factor expression in pre-eclampsia

(A) The angiogenic ‘balance’ is shifted towards an increased anti-angiogenic sFlt-1 and a decreased PlGF in the maternal circulation. The result is a shift towards an anti-angiogenic state. (B) Receptors and ligands involved in angiogenesis with relevance to pre-eclampsia are given. VEGF and PlGF bind to Flt-1 on many cells. A gene splice variant of this receptor, sFlt-1, acts as a scavenger receptor. (C) VEGF and PlGF are needed for endothelial cell homoeostasis. Circulating sFlt-1 in the maternal blood leads to a net decrease in PlGF and VEGF in the vasculature. Endothelial cell homoeostasis (upper panel) is disturbed by the altered angiogenic balance and may result in endothelial dysfunction (lower panel).

7.3 ± 3.2 ng/ml, which is in line with concentrations measured in the serum of women with pre-eclampsia.

Furthermore, sFlt-1 expression was increased in both in vitro and in vivo models of placental hypoxia [28]. Makris et al. [35] have shown that uteroplacental ischaemia induced in primates results in a pre-eclampsia-like condition accompanied by elevated circulating sFlt-1 levels. These findings suggest that placental ischaemia/hypoxia may be sufficient to induce pre-eclampsia, and sFltI up-regulation may contribute to this induction. However, whether or not placental ischaemia is necessary for the induction of human pre-eclampsia remains to be conclusively defined.

Two research groups independently described a human-specific sFlt-1 transcript. Sela et al. [36] also reported that a specific transcript, called sFlt-1-14, is the predominant form, which is expressed in placenta and is induced in the circulation of pre-eclamptic women [36]. Thomas et al. [37], on the other hand, found similar levels of sFlt1-14 and sFlt1 in placenta; another limitation regarding PlGF. Although at least four PlGF isoforms have been described in humans, only one isoform has been found in rats and mice, which represents PlGF-2. They all share the same function in binding to VEGF-R1. Although all PlGF isoforms are secreted, PlGF-2 remains membrane-associated, owing to its heparin-binding domain [38].

However, there are substantial limitations in using rodent models of hypertensive pregnancy disorders. Pre-eclampsia has only been described occurring naturally in humans. However, a pre-eclampsia-like syndrome can be induced in rodents, especially rats, which resembles certain aspects of the disease. Although exhibiting major anatomical and physiological differences, both rats and humans feature the haemochorial type of placentation. Therefore, despite marked differences in the pathways of trophoblast invasion and depth of decidualization, rats are regularly used as a model for human placentation. The haemodynamic differences, however, with branching of the uterine artery into arcuate and spiral arteries of 10–12 placental sites per rat, hamper the translation of animal models to the human situation [39–41]. Moreover, although the alternatively spliced variants of VEGF are present in rats [42,43], they have not yet been described in mice. Nonetheless, the RUPP (reduced uterine perfusion pressure) rat model exhibits up-regulated sFlt-1 levels [44,45].

Since pregnancy involves a major immunological adjustment, the idea that pre-eclampsia could involve defective immunological tolerance has emerged. Agonistic autoantibodies that are capable of activating the AngII (angiotensin II) AT_1 (AngII type 1) receptor (AT1-AAs) were initially identified in patients with malignant hypertension and in patients with pre-eclampsia [46,47]. Thereafter, they were found in renal transplant patients undergoing humoral rejection. AT1-AAs exert many actions that are potentially related to the pathophysiology of pre-eclampsia [48,49]. The autoantibodies link pre-eclampsia to the RAS (renin–angiotensin system) [50]. AngII levels are not increased in pre-eclamptic patients; however, Gant et al. [51] showed that AngII sensitivity is greatly increased in pre-eclamptic women, compared with pregnant women without the condition. The increased AngII sensitivity begins before the onset of the clinical syndrome and persists even after delivery [52]. The RAS is intertwined with angiogenic mechanisms in various ways. Following the passive transfer of AT1-AAs in mice, Zhou et al. [53,54] have shown an up-regulation of sFlt-1 in the placenta of the animals that also exhibited a pre-eclampsia-like syndrome. However, in a transgenic pre-eclampsia rat model, in which AT1-AAs are also present, serum levels of sFlt-1, VEGF and PlGF were unchanged [55]. Nonetheless, a host of additional factors that could influence trophoblast invasion and placental implantation have been implicated in pre-eclampsia. In addition to the angiogenic factors, a genetic
prevalence, epigenetic dysregulation, pro-inflammatory cytokines, syncytiothrophoblast fragment microparticles and reactive oxygen species have been proposed to connect abnormal placentation and pre-eclampsia.

Another approach to the pathogenesis of pre-eclampsia involves the investigation of endothelial dysfunction [56,57]. A role for ADMA (asymmetric \(\omega-N^G,N^G\)-dimethylarginine), an endogenous inhibitor of NOS (NO synthase), was identified as being important in pre-eclampsia [58]. These studies raised the possibility of a link between endothelial dysfunction and the altered angiogenic balance. Eremina et al. [59,60] have provided a convincing connection between the anti-angiogenic balance and pre-eclampsia-associated target-organ damage. They have shown that the kidney requires VEGF to maintain normal glomerular endothelial cell fenestration. The glomerular injury in pre-eclampsia has been investigated previously and is termed endotheliosis. Foot process fusion and loss of fenestration are commonly observed. Furthermore, patients treated with the monoclonal anti-VEGF antibody bevacizumab develop hypertension and proteinuria [61,62]. These observations could connect anti-angiogenesis, renal target-organ damage and pre-eclampsia-related mechanisms. However, additional evidence is required for this attractive hypothesis. The relationship between low placental VEGF levels and placental PlGF production requires additional delineation. The trapping and inactivation of VEGF by sFlt-1 and sEng could be an important pathogenic mechanism for endothelial dysfunction. However, VEGF levels are very low or undetectable in normal pregnancy, and PlGF is the major angiogenic molecule during pregnancy [10]. Experimental proof that inactivation of PlGF is related to endothelial dysfunction is controversial and less clear compared with findings regarding VEGF.

The pathophysiology of pre-eclampsia remains to be fully elucidated and much work needs to be done. However, basic research has made in-roads into unravelling the disease. The two-stage theory of pre-eclampsia has gained new attention by the research developments on angiogenic and anti-angiogenic factors. Environmental, immunological and genetic factors could lead to the initial pre-eclampsia-predisposing ‘lesion’ involving placental mal-implantation and subsequent dysfunction. This state of affairs could initiate retarded fetal intra-uterine growth and result in altered placental expression of angiogenic and anti-angiogenic factors such as sFlt-1 and PlGF. The shifted expression and resulting altered circulating serum concentrations may produce the pathogenic and temporal connecting link to the maternal syndrome, consisting of hypertension and proteinuria and possible progression to generalized seizures (eclampsia), and to HELLP (haemolysis, elevated liver enzyme and low platelet) syndrome. The shifted angiogenic balance may affect endothelial cells and promote target-organ damage. Angiogenic and anti-angiogenic factors are a promising research direction and could indeed develop into clinically useful diagnostic tools. A schematic outline of sFlt-1-related mechanisms is given in Figure 2.

PATIENT-ORIENTED RESEARCH

The ramifications of sFlt-1 and sEng were tested by Levine et al. [12] in a nested case-control study of healthy nulliparous women within the CPEP (Calcium for Pre-eclampsia Prevention) trial. The authors found that sFlt-1 levels increased approximately 5 weeks before the onset of pre-eclampsia. Furthermore, PlGF levels were significantly lower in women who later had pre-eclampsia than in the controls beginning at 13–16 weeks of gestation. The greatest difference occurred during the weeks before the onset of pre-eclampsia, which coincided with the increase in sFlt-1 levels. Alterations in the levels of sFlt-1 and free PlGF were greater in women with an earlier onset of pre-eclampsia and in women in whom pre-eclampsia was associated with an SGA (small for gestational age) infant. However, there was an overlap between healthy and pre-eclamptic patients when they were near term. In the second retrospective nested case-control analysis, Levine et al. [11] found that circulating sEng levels increased 2–3 months before the onset of pre-eclampsia. Beginning at 17–20 weeks of gestation, sEng levels were significantly higher in women in whom preterm pre-eclampsia later developed than in controls. An increased level of sEng was usually accompanied by an increase in the sFlt-1/PlGF ratio. The risk of pre-eclampsia was greatest among women in the highest quartile of the control distributions for both biomarkers, but not for either biomarker alone. These two studies raised the possibility that sFlt-1, PlGF and sEng could be suitable biomarkers for pre-eclampsia prior to the development of the syndrome.

Other investigators have also studied these issues and not all of the findings are consistent. Torry et al. [9] were the first to show that pre-eclampsia is associated with a decrease in circulating PlGF serum levels. A host of supportive evidence has since been found. A possible role for VEGF in the pathophysiology of pre-eclampsia was suggested by Kupferminc et al. [7] and Lyall et al. [63]. Kupferminc et al. [7] found higher serum VEGF concentrations in the plasma of pre-eclamptic women compared with controls. Cooper et al. [64] observed differing expression earlier in the placentas of pre-eclamptic women. Some investigators have found that VEGF is increased in pre-eclamptic women [65,66], whereas others have found that it decreased [67–69]. All those who found elevated VEGF used an RIA or an ELISA that measured total bound and unbound VEGF. Those who observed
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decreased VEGF levels in pre-eclamptic pregnancies relied on a commercially available ELISA kit (R&D Systems) that determined free (unbound) VEGF. Thus VEGF levels were not found to have a diagnostic use, possibly because the growth factor is a local phenomenon rather than a hormone. However, the substantial placental PlGF secretion in pregnancy makes this related peptide a better candidate for serum assessment.

Results regarding the possible alterations of angiogenic factors in pregnancies with IUGR (intra-uterine growth restriction) or SGA are inconsistent. A number of studies have shown that the angiogenic balance is shifted in pregnancies complicated by IUGR and SGA, mainly when umbilical perfusion is impaired [70–72]. Other studies, however, have suggested that the balance was unaltered [73,74]. This contradiction may result from the differently used definition of IUGR and SGA. The ‘SGA’ cohort with fetuses below the 10th percentile, although adjusted for gestational age and gender, covers a rather heterogeneous group of fetuses with widely different reasons for their low birth weight. In contrast, IUGR means that a fetus does not reach its own theoretical normal growth potential as a result of disturbed placental function. IUGR is used to denote a pathological process resulting in the restriction of fetal growth and altered placental factors, whereas SGA refers to a statistical grouping of fetuses below a percentile. There is certainly a considerable overlap between these groups.

Pregnancy-related disorders such as molar pregnancy, parvovirus-induced hydrops, the unusual association of fetal and placental hydrops with maternal pre-eclampsia termed the ‘Mirror’ syndrome [75], twin-to-twin transfusion syndrome [76], placental abruption [77], and fetal death of unexplained aetiology [78] have all been attributed to angiogenic imbalance. However, the initial trigger for the up-regulation of the angiogenic factors is still unclear. Obviously, distinct pathological processes can lead to the common sFlt-1 increase.

Prediction of pre-eclampsia

In routine clinical practice, the obstetrician can assess the uterine impedance to blood flow by means of Doppler sonography [79]. The resistance of the uterine artery is increased in pre-eclampsia, reflecting the mal-implantation of the trophoblast and insufficient spiral artery remodelling [80,81]. Nonetheless, Doppler assessment has a low positive predictive value in pre-eclampsia detection [82]. Numerous studies have evaluated a combination of serum tests with Doppler sonography to improve the screening ability of this method [83–86].

Studies on the effectiveness of the sFlt-1/PlGF ratio as a very early prediction marker in the first trimester have yielded contradictory results. Thadhani et al. [87] showed that, in the first trimester, low PlGF levels were associated with a risk of developing pre-eclampsia or delivering an SGA infant; however, sFlt-1 levels did not differ from women not developing pre-eclampsia in the first trimester. Baumann et al. [88] measured maternal serum concentrations of sFlt-1, sEng and PlGF in women with normal pregnancies and in patients who subsequently developed late-onset pre-eclampsia. They found that the maternal serum concentrations of PlGF and the sFlt-1/PlGF ratio were not different between cases and controls [88]. Akolekar et al. [89] reported that maternal PlGF serum concentrations in women who subsequently developed early- and late-onset pre-eclampsia were significantly lower than that of controls [89]. They found that disease detection was as high as 90% in the first trimester when maternal serum PlGF concentrations

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were combined with maternal characteristics, obstetrical history and uterine artery Doppler flow studies. Foidart et al. [90] presented similar results, highlighting a role for PlGF and sEng in first trimester screening for pre-eclampsia. However, these studies must be interpreted in the light of a very high pre-test probability in the study population.

Numerous studies have examined the use of sFlt-1 and PlGF as a second trimester screening tool in different populations [91–93]. The use of these markers as an aid in prediction and an aid in diagnosis of pre-eclampsia was especially useful when a ratio was calculated. Raised sFlt-1/PlGF ratios indicated women with pre-eclampsia in earlier studies and some reports evaluated the use of a urinary sFlt-1/PlGF ratio [94]. Levine et al. [12] were the first to provide evidence that the sFlt-1/PlGF ratio is able to predict the later onset of the disease in women at risk for developing pre-eclampsia [12]. Kusanovic et al. [92] screened 1622 consecutive singleton pregnancies and, among other marker combinations, they investigated the PlGF/sEng ratio. This ratio had a predictive performance with a sensitivity of 100%, a specificity of 98–99% and likelihood ratios for a positive test of up to 90% [92]. The use of a ratio of sFlt-1 and PlGF, in this case the PlGF/sFlt-1 ratio, proved to be a reliable tool for the second trimester prediction of pre-eclampsia in that impressive study. The additional measurement of the sFlt-1/PlGF ratio has been shown to improve the sensitivity and specificity of Doppler measurement in predicting pre-eclampsia. In the largest prospective study thus far, Espinoza et al. [95] showed that the combination of PlGF and pathological uterine Doppler ultrasound was associated with an odds ratio of 44 for the occurrence of early-onset pre-eclampsia and an odds ratio of 37 for the later-onset of severe disease. It has to be mentioned that these results on the test performance were obtained in a high-risk cohort and not in an unselected low-risk population. Table 1 shows an overview of the prospective and case-control studies evaluating the utility of the sFlt-1/PlGF ratio in pre-eclampsia. In 2009, Roche introduced new automated assays to measure sFlt-1 and PlGF. These assays allow a fast and easy assessment of these factors in the clinical context. In contrast with previous research involving ELISAs with a limited sample number, the automated platform allows a standardized inexpensive measurement on widely spread machines with a high capacity flow. The assay can be performed in 18 min.

A nagging remaining question is: what can be done when the pre-eclampsia tests suggest that the condition will occur? Currently, delivery is the only known treatment. Dietary interventions and antioxidant strategies have yielded limited prospects. Low-dose aspirin remains in favour, and a Cochrane analysis identified a slight reduction in pre-eclampsia-related complications, such as iatrogenic preterm birth (8% risk reduction, 29 studies, 31151 women (relative risk, 0.92). The overall pre-eclampsia complication risk was decreased by 10%; however, no particular subgroup profited more than any other from low-dose-aspirin therapy [96]. In a recent meta-analysis, Bujold et al.

### Table 1  
Studies reporting the utility of the sFlt-1/PlGF ratio in the diagnosis or pre-eclampsia prediction

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients with PE (control)</th>
<th>Patients</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Before onset of PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stepan et al. (2007) [35]</td>
<td>12 (38)</td>
<td>All patients</td>
<td>62</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>9 (28)</td>
<td>Early-onset PE</td>
<td>67</td>
<td>51</td>
</tr>
<tr>
<td>Kim et al. (2007) [172]</td>
<td>46 (100)</td>
<td>All patients</td>
<td>80.4</td>
<td>78</td>
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<td>Crispi et al. (2008) [143]</td>
<td>38 (76)</td>
<td>Early-onset PE</td>
<td>84.2</td>
<td>90</td>
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<tr>
<td>Diab et al. (2008) [169]</td>
<td>33 (108)</td>
<td>All PEs</td>
<td>100</td>
<td>85</td>
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<tr>
<td></td>
<td>8 (108)</td>
<td>Early-onset PE</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>De Vivo A. et al. (2008) [134]</td>
<td>52 (52)</td>
<td>All patients</td>
<td>88.5</td>
<td>88.5</td>
</tr>
<tr>
<td>Kusanovic et al. (2009) [41]*</td>
<td>62 (1560)</td>
<td>All patients</td>
<td>40.3</td>
<td>78.5</td>
</tr>
<tr>
<td></td>
<td>9 (1613)</td>
<td>Early-onset PE</td>
<td>100</td>
<td>89.1</td>
</tr>
<tr>
<td><strong>During PE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verlohren et al. (2010) [44]</td>
<td>37 (268)</td>
<td>Early-onset PE</td>
<td>89</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>34 (268)</td>
<td>Late-onset PE</td>
<td>74</td>
<td>89</td>
</tr>
<tr>
<td></td>
<td>71 (268)</td>
<td>All patients</td>
<td>82</td>
<td>95</td>
</tr>
<tr>
<td>Ohkuchi et al. (2010) [158]</td>
<td>15 (144)</td>
<td>Early-onset PE</td>
<td>100</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>19 (144)</td>
<td>Late-onset PE</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>34 (144)</td>
<td>All patients</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Sunderji et al. (2010) [45]</td>
<td>39 (388)</td>
<td>All patients</td>
<td>96</td>
<td>97</td>
</tr>
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</table>

*PlGF/sFlt-1 ratio.
REFERENCES


CONCLUSIONS AND PERSPECTIVES

A host of new information has accrued on this major public health problem. Nevertheless, major challenges remain in elucidating mechanisms, developing novel early diagnostic predictors and preventative strategies. Determination of sFlt-1, sEng, PI GF and ADMA are promising, but not ready for general application in the prediction of pre-eclampsia. Uterine Doppler studies remain in elucidating mechanisms, developing novel early diagnostic predictors and preventative strategies. Determination of sFlt-1, sEng, PI GF and ADMA are promising, but not ready for general application in the prediction of pre-eclampsia.


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