

Review

## Vascular function in preeclampsia

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### Abstract

Preeclampsia is a multisystem disorder peculiar to human pregnancy. It occurs in 4–5% of all pregnancies and remains a leading cause of maternal and neonatal mortality and morbidity. The pathophysiology of this syndrome is not fully understood. Two stages of vascular dysfunction seem to be involved. In the early stage suboptimal development of the placenta and a hemodynamic maladaptation to pregnancy exist. At this stage maternal constitutional factors such as genetic and immunological factors and pre-existing vascular diseases may play a role. Due to this defective placentation a factor is released from the placenta, supposedly under the influence of ischemia. This factor then results in the late vascular dysfunction characterised mainly by a generalised endothelial dysfunction, leading to the clinical syndrome of preeclampsia. This review attempts to unravel the mechanisms that may contribute to preeclampsia-associated changes in vascular function and to indicate the research needed to improve our understanding of this disease. © 2000 Elsevier Science B.V. All rights reserved.

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### 1. Introduction

In 4–5% of all human pregnancies preeclampsia (PE) develops. This condition is characterised by an elevated blood pressure and proteinuria, developing after 20 weeks gestational age. PE can result in eclampsia, when convulsions develop, or manifest itself as the HELLP syndrome, in which Hemolysis, Elevated Liver enzymes and Low Platelet count (HELLP) are present. Both conditions are associated with severe complications such as cerebral hemorrhage, lung edema or liver hemorrhage and rupture. Moreover women with PE are two and a half times more likely to die from ischemic heart disease later in life [1]. Intrauterine growth restriction and iatrogenic preterm birth of the fetus are associated with PE, resulting in a high risk of early neonatal death and infant mortality or morbidity, mainly due to respiratory disease and long term neurological morbidity [2].

The mechanisms causing PE are still unclear. Current

treatment consists of symptom relief and ultimately delivery. Unravelling the mechanisms causing PE may provide more and better therapeutic options and ultimately a method for prevention of this disease. The purpose of this review is to give an overview of the vascular mechanisms that could be involved in the development of PE and to indicate the research needed to improve our understanding of this disease.

### 2. Hemodynamic alterations in pregnancy and preeclampsia

Normal pregnancy is associated with extensive anatomical and functional changes of the cardiovascular system to accommodate the demands of pregnancy. There is a rapid expansion of the total circulating blood volume, an increase in heart rate and stroke volume and thus an increase in cardiac output. Blood pressure declines progressively until it reaches its nadir at 20–24 weeks and progressively increases again towards term [3]. Hemo-

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dynamic adaptation is detectable from early in pregnancy. Generalised vasodilatation develops already during the luteal phase after conception [4] and peripheral vascular resistance falls substantially after 5 weeks gestation, until reaching values 34% lower than preconceptional at 20 weeks [5]. As a result of maternal vasodilatation peripheral blood flow increases substantially, primarily in the cutaneous [6], renal [7] and uteroplacental circulation [8]. Alterations in synthesis of or response to vasoactive substances such as nitric oxide (NO), prostaglandins, endothelin and angiotensin may be involved in the decrease of peripheral resistance in these vascular beds [9].

In PE the hemodynamic and vascular adaptation to pregnancy is disturbed. Of the few studies available on early hemodynamic changes in pregnancy one longitudinal study showed that women who subsequently develop PE have an increased cardiac output throughout pregnancy [10]. However after development of PE cardiac output has been reported to be decreased [11], normal [12,13] or increased [14]. These different findings probably reflect the heterogeneity of PE [15]. Late hemodynamic changes in PE are characterised by increased blood pressure, reduced plasma volume, increased peripheral vascular resistance and vasoconstriction [16].

### 3. The etiology of preeclampsia

The etiology of PE is still unclear. Early in pregnancy there is a suboptimal placentation, and an inadequate hemodynamic adaptation to pregnancy. Maternal constitutional factors such as genetic predisposition, immunological maladaptation to pregnancy and pre-existing vascular diseases seem to be involved in this early vascular

dysfunction. The disturbed placentation supposedly leads to hypoperfusion of the placenta and ischemia, resulting in the release of one or more unidentified factors, factor X, from the placenta. Factor X then causes the late vascular dysfunction of PE, consisting mainly of generalised endothelial dysfunction, resulting in vasoconstriction, activation of the coagulation system and redistribution of fluids, the symptoms of PE, and often in fetal growth restriction (see Fig. 1).

## 4. Early vascular dysfunction

### 4.1. Defective placentation

In early pregnancy trophoblast cells invade the placental bed, leading to remodeling of the spiral arteries into maximally dilated low resistance vascular channels, unable to constrict to vasoactive stimuli [17], thereby guaranteeing a high flow volume to the uteroplacental bed. In PE trophoblast invasion is impaired and the spiral arteries keep their endothelial lining and musculature. Therefore the vessels remain narrow and reactive. In PE the invasion is confined to the decidual part of the spiral arteries, while about one third of these arteries completely escapes trophoblast invasion (see Fig. 2) [18,19]. In order to answer the question whether the observed abnormal trophoblastic invasion is a primary or secondary phenomenon to the disease, work on intrinsic defects in trophoblast function (attachment properties, adhesion molecules, enzyme secretions, cytokines and growth factors) has become important. Zhou et al. found that in PE the invading cytotrophoblast expresses different adhesion molecules and

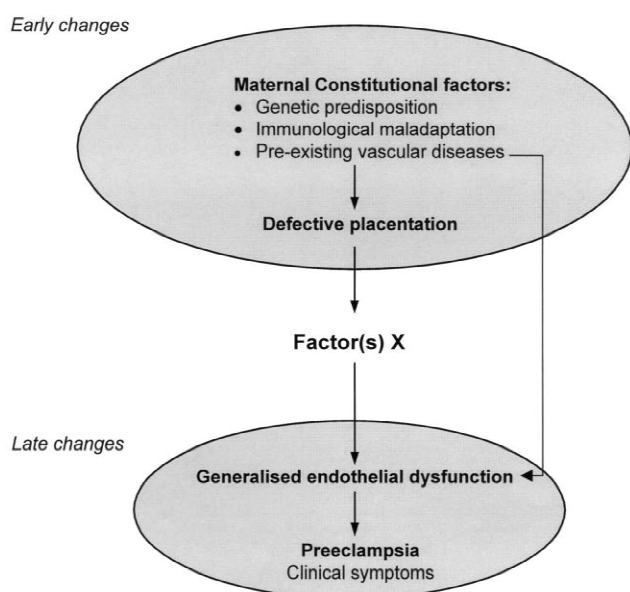


Fig. 1. Schematic representation of the etiology of PE.

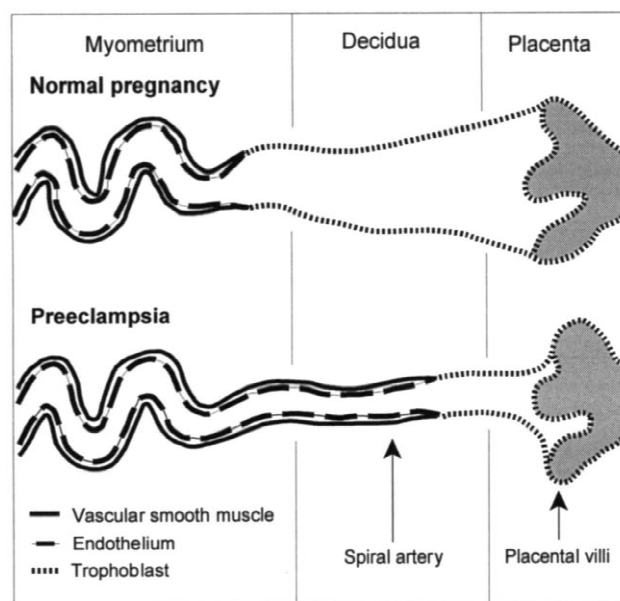


Fig. 2. Trophoblast invasion into the spiral arteries in the placental bed in normal pregnancy and in preeclampsia.

integrins, thereby failing to adapt its adhesion type from one characteristic of trophoblast cells to one characteristic of endothelial cells [20]. It is also possible that the abnormal trophoblast invasion is a consequence of cytokine (TNF- $\alpha$ ) production by activated decidual leukocytes [21] or altered growth factor production, such as vascular endothelial growth factor (VEGF) and placental growth factor [22].

Based on the above described defective placentation, a hypoperfusion of the placenta is presumed. While there is no substantial evidence for placental hypoxia, *in vitro* models show altered cytotrophoblast differentiation at low oxygen tension [23] and the defects in PE placentas resemble those seen in hypoxic trophoblast cultures [24]. The structural abnormalities of acute atherosclerosis and placental thrombi, seen in the uteroplacental bed of PE pregnancies, can also contribute to development of hypoxia. In acute atherosclerosis spiral arteries are occluded by fibrinoid material and surrounded by foam cells. Its presence is not specific for PE, though; it can also be seen in the case of low birthweight babies and in hypertensive mothers. In addition to these structural changes there are also functional changes aggravating tissue ischemia. For example, the decreased ratio of prostacyclin (PGI<sub>2</sub>) to thromboxane (TxA<sub>2</sub>) production [25] may contribute to a state of vasoconstriction and platelet aggregation, leading to a further reduction of the fetal blood supply in PE.

## 4.2. Maternal constitutional factors involved in defective placentation

### 4.2.1. Genetics

Epidemiological data show a genetic component in the development of PE [26]. Early work suggested a single recessive gene inheritance, but this model could not explain all available data [27]. Later both maternal and fetal genotypes were proposed to be responsible for increased susceptibility to PE [28], partly by the association between fetal chromosomal abnormalities and PE [29]. More recently it has been suggested that PE is a polygenic trait, with a strong maternal factor [30]. PE genes probably act as susceptibility loci, lowering the threshold for the disease [31]. Implicated in this process are the angiotensin gene, where the variant Met235→Thr235 correlates with the risk for PE or rather hypertension [32–34], the endothelial nitric oxide synthase gene on chromosome 7, associated with familial pregnancy-induced hypertension [35] and genes involved in TNF $\alpha$ -production [36], thrombophilic disorders, such as the factor V Leiden mutation (1691 G→A) [31] and hyperhomocysteinemia, hypertension and obesity [37]. Thus far most studies investigating the role of genetics in PE have been small scale and a large database of genotypes, present in women with PE and their children, is needed to elucidate to which extent genetics are involved in PE.

### 4.2.2. Immunology

Prior blood transfusion, a prior miscarriage, the practice of oral sex, a longer cohabitation period before conception and immunisation with paternal lymphocytes all reduce the risk for PE. In contrast first pregnancy, change of partner, donor insemination and barrier contraceptives all increase the risk for PE [38,39]. This strongly suggests that a prior immune response to foreign or paternal antigens protects against the development of PE. Lymphocytes of women with PE do not show the cellular hyporesponsiveness to fetal cells that is typical of normal pregnancy [40], the activity of circulating natural killer cells, neutrophils and cytokines, such as TNF- $\alpha$ , IL-6, IL-2 and IL-12 is increased [38,39]. In PE HLA-G, a surrogate auto-antigen known to prevent recognition by natural killer cells [41], is not expressed as general in the placenta as in normal pregnancy [42,43]. The resulting activation of leukocytes in the decidua, can cause release of cytokines, elastase and oxygen free radicals, all of which can interact with endothelial function. Whether the decreased HLA-G expression is caused by aberrant trophoblast differentiation or results from an underlying genetic disorder, is still unknown.

### 4.2.3. Vascular diseases

Patients with pre-existing vascular diseases have an increased risk of developing PE. Chronic hypertension and autoimmune disorders, such as systemic lupus erythematosus and antiphospholipid syndrome increase the risk 10 times, chronic renal insufficiency 20 times and diabetes mellitus 2 times [44]. Furthermore 40–50% of the women with severe PE have thrombophilic disorders, such as protein S deficiency, activated protein C resistance, anticardiolipin antibodies and hyperhomocysteinemia [37,45].

## 5. Factor X

To link the placental abnormalities to the generalised endothelial dysfunction seen in PE, the existence of factor X, released from the placenta into the maternal circulation, was proposed. Indeed, sera of PE patients are toxic to cultured endothelial cells [46,47], with cytotoxicity disappearing *post partum*, consistent with improvement of the clinical condition [46]. The factor seems to modulate endothelial cell function rather than damage the cells. In response to PE serum/plasma, PGI<sub>2</sub> [48] and NO [49] production are altered, triglycerides accumulate intracellularly [50], cellular permeability is increased [51] and endothelium-dependent dilatation in isolated arteries is diminished [52]. Initially factor X was thought to be a single factor, but increasing evidence suggests the presence of several interacting factors, which might also explain the heterogeneity of the PE manifestations.

Among the candidate factors are syncytiotrophoblast

microvillous membrane particles (STBM). Syncytiotrophoblast is the outer layer of the placenta with countless microvilli on its surface, that forms the contact with maternal blood. PE placentas show abnormally shaped microvilli and areas of focal necrosis [53], changes similar to those induced by hypoxia in cultured placental villi [54]. Whole trophoblast cells are shed into the maternal circulation in pregnancy [55]. This deportation is exaggerated in PE [56]. Likewise, the plasma STBM concentration is increased in PE [57]. STBM interfere with growth of cultured endothelial cells, irrespective of whether a PE or normal placenta is used for STBM preparation [58]. Perfusion of isolated subcutaneous arteries with a very high STBM concentration caused abolishment of acetylcholine-mediated vasodilatation [59]. In a recent study, however, we demonstrated that STBM in concentrations found in vivo in PE patients have no effect on bradykinin-mediated dilatation in isolated myometrial arteries (unpublished observations). Therefore the involvement of STBM as factor X in PE remains unclear.

Factor X could also be oxidative stress. Activated decidual large granulocytes produce cytokines, proteases and oxygen free radicals. When oxygen free radicals are not eliminated by antioxidants, lipid peroxide formation is induced [60]. All these substances can cause endothelial damage [61]. Indeed several authors reported increased levels of lipid peroxidation products in PE in blood and decidua basalis [62–64] and PE placentas produce more lipid peroxides than control placentas [60]. Antioxidant levels, such as thiols [65], vitamin E, C and carotenoids [66] are all decreased in PE. Moreover superoxide dismutase was decreased in neutrophils [67] and placentas [68] of women with PE. STBM and oxidative stress could be potentiating each others effects. When cultured endothelial cells are incubated with STBM, a substance is produced that activates peripheral leukocytes and primes monocytes to respond stronger upon activation [69]. Chappell et al. recently showed that treatment of women at increased risk for PE with high dose vitamin C and E from 16 to 22 weeks of gestation onwards decreases their risk to develop PE. Larger trials are needed to confirm this and to choose the right moment to start, the optimum dose and type of antioxidants [70].

Another possibility for factor X relates to the lipid metabolism. In PE lipid levels are increased even more than in normal pregnancy [71]. Incubation of endothelial cells with PE sera increased their triglyceride content and reduced thrombin-stimulated PGI<sub>2</sub> release in one study [50], although this could not be confirmed by others [72]. Endothelial cells incubated with fatty acids show impaired endothelial PGI<sub>2</sub> and NO production [73]. Thus, an altered fat metabolism can cause functional changes of the endothelium. The alterations in the lipid metabolism in PE could be caused by cytokines, like TNF- $\alpha$ , IL-1 and IL-6, that are lipolytic in adipocytes, by promotion of de novo hepatic fatty acid synthesis and impairment of hepatic fatty

acid oxidation and ketogenesis [39]. An interesting finding in this respect is the increased incidence of HELLP (15%) found when the fetus is homozygous or compound heterozygous for Glu474Gln causing long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency (LCHAD), a genetic disorder affecting fatty acid  $\beta$ -oxidation [74]. This could be due either to the obligate heterozygosity of the mother for LCHAD mutations, which can cause decreased fatty acid  $\beta$ -oxidation, and thus to an increase in plasma fatty acids, as has indeed been found in PE [75] or to accumulation of long-chain 3-hydroxyacyl metabolites produced by fetus or placenta. The importance of the latter factor might be minor however, since *ante partum* fatty acid  $\beta$ -oxidation in the fetus is limited and most energy is supplied by glucose transport from the mother [74].

## 6. Late systemic vascular dysfunction

### 6.1.1. The endothelium

The endothelium plays a major role in the vascular changes in pregnancy. The endothelium appears to be upregulated in pregnancy, producing vasodilatation either as a result of an increased release of vasodilators or a decreased vasoconstrictor output [9]. In PE there is overwhelming evidence for endothelial dysfunction [76,77]. Morphological evidence includes glomerular endotheliosis, with swollen endothelial cells in the glomeruli, which could cause hypoperfusion of the kidney and protein leakage [78]. Structural changes of the endothelium have also been found in the uteroplacental vessels [79]. In addition extensive evidence exists for functional disorders of the endothelium. The concentrations of Von Willebrand factor, endothelin, fibronectin and several cell adhesion molecules are increased and there is a change in balance between tissue plasminogen activator and inhibitor and between PGI<sub>2</sub> and TxA<sub>2</sub>, all indicating endothelial cell activation [76]. Vascular tone and thus peripheral resistance are known to be under continuous influence of endothelium derived factors. Consequently the altered state of the endothelium in PE has major consequences for the regulation of tone. The mechanisms for endothelium-dependent vasodilatation and vasoconstriction and the vasoactive substances implicated to be involved in PE will be discussed below. Table 1 gives a summary of vasoactive substances whose altered productions have been implicated in PE.

### 6.1.2. Endothelium-dependent vasodilatation

Investigations in isolated arteries have yielded some direct evidence for vascular endothelial dysfunction in PE and generally agree that endothelium-dependent dilatation is impaired in PE [80–83]. The endothelium-derived vasodilatory substances PGI<sub>2</sub>, NO and endothelium de-

Table 1

Vasoactive substances that have been implicated to play a role in PE, along with their vasoactive effect, the reported concentrations (conc.) in preeclamptic patients as compared to normal pregnancy (Conc.: ↑=increased, ↓=decreased, = =no difference, *M*=metabolites measured) in samples from different sampling sites and the relevant references

| Substance         | Vasoactive Effect | Sample site                     | Conc. | References |
|-------------------|-------------------|---------------------------------|-------|------------|
| PGI <sub>2</sub>  | Vasodilatation    | Peripheral blood/urine <i>M</i> | ↓     | [85–87]    |
|                   |                   | Placental production <i>M</i>   | ↓     | [89,90]    |
| TxA <sub>2</sub>  | Vasoconstriction  | Urine <i>M</i>                  | ↑     | [85]       |
|                   |                   | Placental production <i>M</i>   | ↑     | [89,90]    |
| NO                | Vasodilatation    | Peripheral blood/urine <i>M</i> | ↑     | [96–98]    |
|                   |                   |                                 | ↓     | [92]       |
|                   |                   |                                 | =     | [93–95]    |
| EDHF              | Vasodilatation    |                                 | ?     |            |
| Endothelin        | Vasoconstriction  | Peripheral blood/uterine vein   | ↑     | [109–113]  |
| VEGF              | Vasoconstriction  | Peripheral blood                | ↑     | [122–125]  |
|                   |                   |                                 | ↓     | [126,127]  |
| ANP               | Vasodilatation    | Peripheral blood                | ↑     | [117,145]  |
| Renin,            |                   |                                 |       |            |
| Aldosterone, ATII | Vasoconstriction  | Peripheral blood                | ↓     | [134]      |
| Catecholamines    | Vasoconstriction  | Peripheral blood/urine <i>M</i> | ↓/↑   | [141]      |

rived hyperpolarising factor (EDHF) could all mediate this impairment of dilatation.

The first substance implicated in PE was PGI<sub>2</sub> [84]. PGI<sub>2</sub> metabolites were found to be reduced in urine [85] and plasma of women with PE [86,87]. PGI<sub>2</sub> synthesis was already decreased in the first trimester [85]. Furthermore incubation of endothelial cells with PE serum inhibits PGI<sub>2</sub> release [50]. PGI<sub>2</sub> is usually analysed in relation to TxA<sub>2</sub>, a potent vasoconstrictor and platelet aggregator, produced mainly by platelets and to a lesser degree by endothelium. A reduced PGI<sub>2</sub> production can cause an increased TxA<sub>2</sub> concentration due to platelet aggregation. Indeed, urinary TxA<sub>2</sub> metabolites are increased in PE [85] and correlate with disease severity [88]. A reduced PGI<sub>2</sub>/TxA<sub>2</sub> ratio, found in blood, cytotrophoblast [89] and placental extracts [90] of PE patients, was thus proposed to cause the vasoconstriction in PE. Although most studies have indeed found evidence for an imbalance in the PGI<sub>2</sub>/TxA<sub>2</sub> ratio, restoration of the PGI<sub>2</sub>/TxA<sub>2</sub> ratio with low dose aspirin hardly prevents the development of PE, indicating that the PGI<sub>2</sub>/TxA<sub>2</sub> mechanism is not the only mechanism involved [91].

The vasodilatory responses to endothelium-dependent agonists such as acetylcholine and bradykinin are impaired in isolated arteries from women with PE [80–83]. Although NO plays a dominant role in these responses current evidence related to the involvement of NO in PE remains controversial, with studies favouring [81,82] and challenging [83] it. Not only data concerning vascular responses to bradykinin and acetylcholine are conflicting, also levels of NO metabolites were found lower [92], similar [93–95] or even increased [96–98] in PE, whereas sera from PE pregnancies were found to increase nitric oxide synthase activity in endothelial cell cultures [49]. The concept of NO deficiency in PE therefore remains controversial. The predominant physiological stimulus for endothelial NO synthesis is shear stress [99]. Flow-induced

shear stress is a modulator of vascular tone in isolated arteries from normal pregnant women, mediated by NO, but not prostanoids [100]. In PE shear-mediated NO release is impaired, which could contribute to the vasoconstriction and increased vascular resistance [101,102]. Clinical studies have shown NO donors to strongly suppress hypertension in PE patients [103] and to improve umbilical cord blood flow to the fetus [103,104]. This indicates a role for NO in PE at least in the uteroplacental circulation, although it remains unclear whether this is just symptom relief or there is an etiological role for NO.

Recently the presence of a vasodilatory substance, produced by the endothelium and acting by hyperpolarising vascular smooth muscle cells, EDHF, has been discovered [105]. It has been suggested that EDHF is a cytochrome P450-derived arachidonic acid product [106] or an endogenous cannabinoid [107]. In resistance arteries of normal pregnant and women with PE endothelium-dependent dilation was attenuated despite blockade of prostanoids and NO, suggesting a role for EDHF [108]. Further research is needed to identify EDHF and to elucidate its role in PE.

### 6.1.3. Endothelium-dependent vasoconstriction

Endothelin, a vasoconstrictive substance produced by the endothelium, has been implicated in the pathogenesis of PE. Plasma endothelin concentrations appear to be elevated in PE [109–113], although there is a substantial overlap with normal values. Uterine vein endothelin levels were three times higher in PE, indicating a role for endothelin in the decreased uteroplacental blood flow [110]. Incubation of endothelial cells with PE serum suppresses endothelin production. This may however be caused by a factor in the serum, released in response to the elevated endothelin concentrations [114]. Endothelin-induced constriction was similar in PE and normal pregnant patients in isolated myometrial arteries but enhanced in

omental arteries [90,115,116]. This could be explained by receptor down-regulation in uteroplacental circulation in response to the increased concentrations. The role of endothelin in PE, thus, seems to be restricted to the uteroplacental circulation.

## 6.2. Circulating vasoactive substances

Atrial natriuretic peptide (ANP) is a vasodilatory hormone produced mainly in the atrial myocytes in response to wall stretch and in the placenta. In PE plasma ANP levels have been found to be increased [117]. ANP opposes the vasoconstrictive action of endothelin [118] and angiotensin [119], and induces vasodilatation in the uteroplacental vasculature of women with PE as well as a small reduction in blood pressure [120].

More recently VEGF was proposed to be involved in PE (see [121]). VEGF is not only involved in vascular growth, but also has a vasoactive effect and causes increased vascular permeability. Circulating levels of VEGF were found to be elevated [122–125] and correlated to blood pressure in patients with PE [123], although others found decreased concentrations [126,127]. The observed decreased concentrations could however be due to the use of a detection technique, in which VEGF binding proteins interfere, thereby disabling detection of bound VEGF [128]. VEGF was not detectable before the onset of clinical symptoms [122]. The source of the increased VEGF in PE is unclear. VEGF is expressed in the placenta [129] and trophoblast cells cultured under hypoxic conditions show increased VEGF production [130]. However, VEGF mRNA expression in placental tissue decreases with increasing gestation and is even further decreased in PE [131]. VEGF might also be released by aggregating platelets [132] and vascular smooth muscle cells [133]. Increased VEGF concentrations could contribute to the extravasation of plasma proteins and subsequent development of proteinuria, both characteristic features of PE. Hayman et al. reported that VEGF impairs endothelium-dependent dilatation to levels similar to those obtained in arteries of women with PE. This response was largely reversed by incubation with antibody to VEGF [121]. Confirmation of these findings and further research into the origin of the increased VEGF concentration and its mechanism of action in PE is needed to develop therapeutic strategies directed against this substance.

### 6.2.1. Vascular smooth muscle

The increased vascular resistance in PE is closely related to an increased responsiveness to vasopressors. While angiotensin (AII), as well as the active renin and aldosterone concentrations [134], is decreased in PE, the sensitivity of the vasculature to AII is increased. Women who subsequently develop PE lose their resistance to AII as early as gestational week 23, and become even more sensitive to AII near term than non pregnant women [135].

This increased pressor response may be due to altered numbers of AII receptors or altered affinity of the receptor [136]. Since prostacyclin is one of the factors regulating renin release, the reduced prostacyclin production in PE can be the cause of the reduced AII concentrations, which could result in upregulation of receptors and sensitivity. Therapy with angiotensin converting enzyme inhibitors however is not a possibility in pregnancy since they are toxic to the fetus [138]. However the link of the AII gene to hypertension suggests involvement of the angiotensin system already in the early phase of PE. Agonistic auto-antibodies to the AII receptor have been observed in PE [137]. These auto-antibodies could only be detected shortly before development of clinical symptoms, suggesting them to play a role in the late rather than the early phase of PE. Enhanced pressor responses are not unique to AII, but are also seen in vivo to norepinephrine [139] and in vitro, in isolated arteries, to vasopressin and prostaglandin F<sub>2α</sub> [140].

Furthermore an enhanced pressure-induced myogenic tone was found [82]. This could be due not only to the increased sensitivity to vasopressors and the endothelial dysfunction, but also to an increased activity of the sympathetic nervous system or an altered calcium sensitivity of the contractile apparatus. The sympathetic nervous system can control vascular tone by releasing catecholamines that can induce vascular smooth muscle contraction. Research first focussed on circulating catecholamine concentrations, but results were conflicting, and it is now accepted that this is an insensitive method of measuring sympathetic activity. Schobel et al. measured sympathetic nerve activity of fibers innervating blood vessels in skeletal muscle and found an increased sympathetic activity in PE [141]. The fact that age-matched non pregnant hypertensive women did not show any increase in sympathetic activity, indicates that the changes found in PE are specific to the disease rather than secondary to high blood pressure [141]. The mechanisms underlying this increased sympathetic activity are unclear. The increase is not linked to heart rate or baroreceptor-mediated feedback on central sympathetic outflow. However the role of humoral and paracrine factors, influencing the central nervous system has not yet been investigated [141]. The fact that methyldopa, a centrally acting drug, reducing sympathetic outflow, is the drug of choice for longer term blood pressure control in PE indicates the involvement of this system in PE [141]. However with progression of the disease additional medication is usually required indicating other systems to be involved. An increased calcium sensitivity can be caused by various substances through several pathways [142]. On the other hand, endothelium can reduce calcium sensitivity by NO production. In PE, where the endothelium is dysfunctional and the sensitivity to vasopressors changed, this could result in an increased smooth muscle calcium sensitivity. We have indeed found the increased vascular tone in PE to be associated with an

increased sensitivity of subcutaneous arteries to intracellular calcium (unpublished observations). From this perspective modulators of calcium sensitivity can in the future provide us with a more accurate therapy for PE.

It should be kept in mind that the increased peripheral resistance in PE can be the result of either vasoconstriction, due to an altered production of or sensitivity to vasoactive substances, inward vascular remodeling, or even rarefaction (i.e. the disappearance of arterioles). Concerning remodeling, the observed greater media thickness to lumen diameter ratio in omental arteries of PE patients indeed indicates an altered wall structure [143], although it remains unclear whether this represents an adaptation to the increased pressure or is a cause of increased blood pressure. Recent *in vitro* work showed that arteriolar remodeling can occur within a period of 3 days [144]. This rapid alteration in arteriolar structure allows a role for remodeling in the increased peripheral resistance in PE and in its fast reversal after delivery.

## 7. Conclusions and future perspectives

The multitude of systems involved in the pathophysiology of PE and their complex interactions provide an intriguing challenge. It is essential to clarify the mechanisms involved in early and late vascular dysfunction and to identify the factor(s) connecting them in order to understand, treat and eventually prevent PE. There are however many concerns that complicate research on PE. A major problem in PE research is the lack of a valid animal model that can enable a more thorough investigation of the pathogenesis of this disease and allow for the test of possible interventions. One important confining factor in development of new therapies is the exposure of not only the mother but also the fetus to the treatment. Furthermore the fact that PE only presents itself in the late phase of the disease, necessitating large numbers of patients to enter studies to find only few PE patients, prevents the development of satisfactory screening strategies and the thorough investigation of early pregnancy pathophysiology. Finally for obvious reasons the use of invasive investigations in early pregnancy can only be very limited.

Understanding the mechanisms leading to defective placentation, where the roots of PE seem to be, is required to provide clues for prevention. Growth factors, adhesion molecules, cytokine production and antigen expression of the placenta are of importance in this respect. An extensive database with genotypes of women who developed PE and their children is needed to gain knowledge about the role of genetics in the pathophysiology of PE. Such information may result in new methods for screening or, in the future, even in possibilities of gene therapy.

A large amount of scientific research is required to elucidate the mechanisms of defective placentation. It is therefore not conceivable that a therapy aimed at these

primary events will become available in the near future. Until then treatment should be aimed at reduction or prevention of endothelial damage. Elucidating the mechanisms involved in this damage obviously would improve our chances of finding effective treatment strategies. Based on the evidence that oxidative stress and free radical formation are increased in PE, treatment with antioxidants might prove worthwhile, and indeed such trials are in progress and promising. The possibilities for correction of hyperlipidemia also need to be studied. If indeed a role for STBM can be established, therapies could be developed to remove these particles from the circulation or to prevent their damaging effect. The finding of impaired shear-mediated NO release in isolated arteries in PE suggests that increasing NO in circulation with NO donors or the substrate for NO, L-arginine, may prove to be a successful treatment strategy. Confirmation of the results reported by Hayman et al. on the role of VEGF in PE [121] is required. If VEGF is indeed involved, therapeutic use of heparin should be reconsidered, since heparin is known to strongly bind VEGF. The option of intervention at the level of vascular smooth muscle cells is insufficiently explored. From this perspective calcium sensitivity modulators form a new group of possible therapeutic agents.

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