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Preeclampsia: current understanding of the molecular basis of vascular dysfunction

Sowndramalingam Sankaralingam, Ivan A. Arenas, Manoj M. Lalu and Sandra T. Davidge

Preeclampsia is a pregnancy-specific disorder characterised by hypertension and proteinuria occurring after the 20th week of gestation. Delivery of the placenta results in resolution of the condition, implicating the placenta as a central culprit in the pathogenesis of preeclampsia. In preeclampsia, an inadequate placental trophoblast invasion of the maternal uterine spiral arteries results in poor placental perfusion, leading to placental ischaemia. This could result in release of factors into the maternal circulation that cause widespread activation or dysfunction of the maternal endothelium. Factors in the maternal circulation might induce oxidative stress and/or elicit an inflammatory response in the maternal endothelium, resulting in the altered expression of several genes involved in the regulation of vascular tone. This review addresses the potential circulating factors and the molecular mechanisms involved in the alteration of vascular function that occurs in preeclampsia.

Preeclampsia is a pregnancy-specific disorder characterised by hypertension and proteinuria occurring after 20 weeks of gestation and resolving after delivery. It is estimated to affect 5–7% of all pregnancies (Ref. 1) and is one of the leading causes of maternal and fetal morbidity and mortality (Refs 2, 3). Although the causative factor(s) involved in the pathogenesis

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of preeclampsia remain(s) obscure, the two-stage model of preeclampsia (Ref. 4) provides, to a reasonable extent, an explanation for the events occurring in this disorder. According to this model, the first stage is an inadequate trophoblastic invasion of uterine spiral arteries that results in placental ischaemia (Ref. 5), and the second stage is the release of factors that activate or cause dysfunction of the maternal endothelium (Refs 5, 6, 7). Furthermore, the haemochorial placentation facilitates the shedding of a range of trophoblast debris into the maternal circulation, referred to as 'trophoblast deportation', which elicits an inflammatory response in the maternal vasculature, further resulting in alteration of endothelial function (Ref. 8). Hence, preeclampsia has been proposed to be an endothelial cell disorder (Ref. 9). In addition, circulating factors that impair endothelial cell function might originate from sources other than the placenta (Ref. 10), and the maternal response to circulating factors might be altered in preeclampsia (Refs 11, 12).

There is accumulating evidence to support the roles of both oxidative stress and inflammation in preeclampsia, both of which have been documented in preeclampsia (Refs 13, 14). A state of oxidative stress results in the generation of reactive oxygen species (ROS) and reactive nitrogen species, which might alter endothelial cell function directly or through activation of inflammatory pathways in the vasculature. The subsequent sections review the potential mechanisms culminating in oxidative stress and inflammation, and how these processes ultimately result in maternal endothelial cell dysfunction.

Models of investigation

One of the challenges facing research in preeclampsia has been the lack of a suitable laboratory model to study this disorder. Since preeclampsia is a complex disorder specific to humans, no single model has fully replicated this condition. In order to overcome this difficulty, researchers have employed a variety of in vitro and ex vivo techniques on human and animal tissue, as well as several 'preeclamptic-like' animal models.

In vitro methods have been used to assess the mechanisms of endothelial dysfunction. It has been suggested that circulating factors in preeclampsia may be the cause of endothelial dysfunction. In order to elucidate the factors and their possible mechanisms, researchers have examined the effects of plasma or serum from preeclamptic women on various pathways in endothelial cells in culture (Refs 15, 16). The source of endothelial cells used in these experiments has been varied both in terms of vascular bed and animal species. Several studies have used human umbilical vein endothelial cells (HUVECs) for such studies, and, although these are fetal cells, they serve as a tool to test mechanisms and are probably the only source of endothelial cells from the pregnant state. This work regarding the functional effects of circulating factors has been extended to study the effects of plasma on isolated blood vessels obtained from animals (Ref. 11) or pregnant women (Ref. 17). More recently, the behaviour of blood vessels from normal pregnant and from preeclamptic women has been studied ex vivo using various pharmacological agents to compare endothelial function in these groups (Refs 18, 19). Another methodology has been to determine the expression of various enzymes and factors involved in the pathophysiology of preeclampsia using immunohistochemistry on blood vessels obtained from either subcutaneous or omental fat biopsies and in placental tissues (Refs 20, 21, 22). As detailed in subsequent sections of this review, these in vitro and ex vivo studies have provided invaluable insight into the underlying mechanisms of preeclampsia.

Animal models of preeclampsia-like syndrome have also been identified. Unfortunately, no single animal model has been able to replicate the full pathophysiology of this complicated condition. Nonetheless, these models have enabled researchers to study certain aspects of preeclampsia. For instance, renin–AGT transgenic mice (Ref. 23), the BPH/5 mouse strain (Ref. 24) and mice deficient in $p57^{Kip2}$ (Ref. 25) exhibit symptoms such as hypertension and proteinuria, which are the diagnostic criteria for preeclampsia. However, the renal lesions exhibited by these mice models are different from the glomerular endotheliosis observed in preeclampsia. Other models include infusion of low doses of endotoxin (Refs 26, 27) or soluble Fms-like tyrosine kinase 1 (sFlt1) (Ref. 28), which also produce symptoms indicative of preeclampsia. These animal models have proven useful to test specific hypotheses relating to preeclampsia. However, preeclampsia still remains a human-specific syndrome, with many potential factors that may converge to cause endothelial dysfunction.

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Inflammation in preeclampsia

Preeclampsia is characterised by an increased systemic inflammatory response. Several studies have reported higher levels of pro-inflammatory cytokines such as tumour necrosis factor α (TNF-α), interleukin 6 (IL-6) (Refs 29, 30), IL-1 (Ref. 29) and C-reactive protein (CRP) (Ref. 31) in the serum and plasma of preeclamptic women compared with normal pregnancies. It is known that vascular cells undergo functional alterations after cytokine stimulation, resulting in a pro-inflammatory and pro-thrombotic phenotype referred to as 'activation' (Ref. 32). Activated endothelial cells express adhesion molecules and produce chemoattractants that result in leukocyte recruitment and infiltration at vascular sites. In fact, consistent with a state of endothelial activation, levels of adhesion molecules (Refs 33, 34) and chemokines (Ref. 22) are also increased in preeclamptic women. Accordingly, systemic vessels from preeclamptic women also have increased leukocyte infiltration compared with normal pregnant women (Ref. 22). Overall, it has been proposed that circulating cytokines mediate part of the endothelial alterations in preeclampsia (Ref. 35).

One of the mechanisms by which inflammation might cause altered endothelial cell function is by inducing the release of ROS that in turn can act as second messengers and activate pro-inflammatory transcription factors such as NF-κB (Ref. 36), which controls expression of adhesion molecules and other inflammatory factors. Thus, activation of NF-κB by free radicals might further stimulate inflammation. In fact, increased lipid peroxides in plasma from preeclamptic women have been found to activate NF-κB and increase the expression of intercellular cell adhesion molecule 1 (ICAM-1) in isolated endothelial cells (Ref. 37). In addition, ROS generation can occur independently of inflammation. Thus, inflammation and oxidative stress might act synergistically to induce vascular dysfunction in preeclampsia.

Oxidative stress in preeclampsia

Oxidative stress has been implicated in the pathogenesis of endothelial dysfunction in preeclampsia, as previously reviewed (Refs 38, 39, 40, 41). Briefly, oxidative stress is a term used for the imbalance of pro-oxidants and anti-oxidants, such that pro-oxidants predominate. Pro-oxidants include oxygen-derived free radicals such as superoxide anion, which is generated by NAD(P)H oxidase, xanthine oxidase and a variety of other enzymes. Anti-oxidant defences include enzymes such as superoxide dismutase as well as vitamins C and E.

Free radicals have varying downstream effects, including lipid peroxidation of biological membranes and oxidative modification of lipoproteins. In women with preeclampsia, there are increased levels of lipid peroxidation products, such as F2-isoprostanes and malondialdehyde (reviewed in Ref. 42). Moreover, there is an increased malondialdehyde to total anti-oxidant capacity ratio that is also suggestive of enhanced oxidative stress in preeclampsia (Ref. 43). Additional evidence for oxidative stress in preeclamptic women is provided by data showing a decrease in plasma vitamin C levels (Ref. 44). By contrast, Regan et al. compared urinary 8,12-iso-iPF2alpha-VI, a chemically stable isoprostane, between normotensive (i.e with normal blood pressure) and preeclamptic pregnant women and concluded that there is no evidence for oxidative stress in preeclampsia (Ref. 45). However, these results should be interpreted with caution because the authors measured only one biochemical marker of oxidative stress, which has not been widely validated (Ref. 46). A more recent study examined various biomarkers of oxidative stress in preeclampsia and concluded that preeclampsia is a state of mild oxidative stress (Ref. 47). This study found decreased plasma vitamin C levels and significantly elevated lipid hydroperoxides, indicative of oxidative stress, as well as elevated serum levels of soluble vascular cell adhesion molecule 1 (VCAM-1), which is suggestive of endothelial dysfunction (Ref. 47). Furthermore, elevated lipid peroxides in circulating preeclamptic plasma have been shown to activate NF-κB, which subsequently upregulates ICAM-1 in endothelial cells (Fig. 1). This endothelial cell activation could be prevented by pretreatment with the anti-oxidants vitamin E and *N*-acetyl cysteine (Ref. 37).

Ultimately, there is substantial evidence for enhanced oxidative stress in preeclampsia, although whether oxidative stress is a cause or a consequence of the disease remains controversial. However, oxidative stress may provide a feed-forward mechanism in the pathogenesis of preeclampsia, which the ongoing vitamin supplementation trials might address. Moreover, oxidative stress might affect factors including inflammatory mediators that alter endothelial cell function. Below we describe possible mediators

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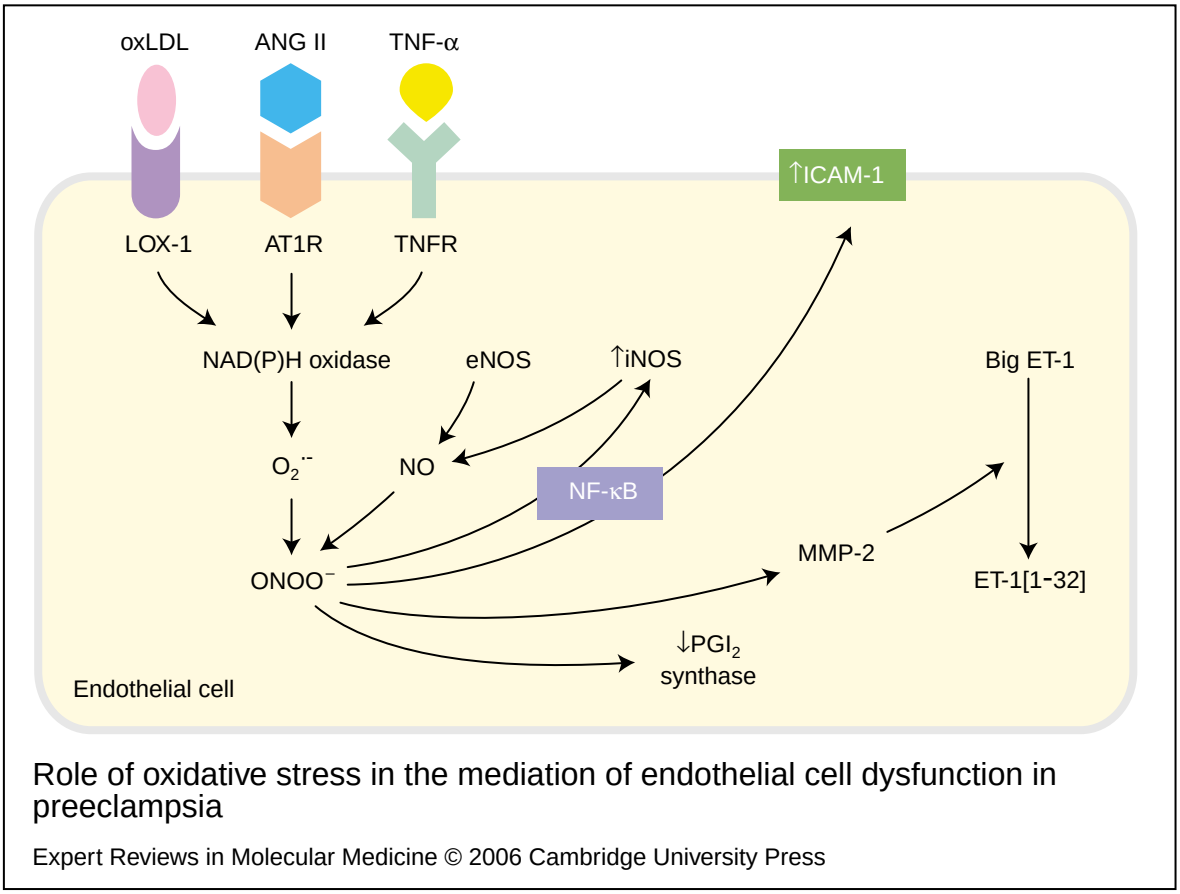


Figure 1. Role of oxidative stress in the mediation of endothelial cell dysfunction in preeclampsia. Oxidised low-density lipoprotein (oxLDL), angiotensin II (ANG II) and tumour necrosis factor α (TNF-α) bind to lectin-like oxidised LDL receptor (LOX-1), ANG II type I receptor (AT1R) and TNF-α receptor (TNFR), respectively, and generate superoxide anions ($O_2^{\cdot-}$) through NAD(P)H oxidase. Superoxide anions scavenge nitric oxide (NO) produced by endothelial nitric oxide synthase (eNOS) to generate peroxynitrite ($ONOO^-$). Peroxynitrite increases inducible NOS (iNOS) and intercellular cell adhesion molecule 1 (ICAM-1) expression, a marker of endothelial dysfunction, by activation of nuclear factor κB (NF-κB) and decreases prostacyclin (PGI_2) synthase, which ultimately results in inflammation and vasoconstriction. Peroxynitrite also activates matrix metalloproteinase 2 (MMP-2), which subsequently cleaves 'big endothelin-1' (Big ET-1) to yield a more potent vasoconstrictor ET-1[1–32].

of endothelial cell dysfunction, such as low-density lipoprotein (LDL), nitric oxide (NO), and angiotensin II (ANG II), and integrate these findings with evidence for vascular dysfunction caused by the inflammatory mediator TNF-α. The last sections include evidence for vascular endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) as other potential mediators of vascular dysfunction in preeclampsia.

Endothelial cell dysfunction: possible mediators

Oxidised low-density lipoprotein

Oxidative modification of low-density lipoprotein (oxLDL) has been implicated in the pathogenesis of endothelial dysfunction in atherosclerosis (Ref. 48) and may therefore be a plausible candidate in the pathogenesis of endothelial dysfunction in women with preeclampsia. Normotensive pregnancies are characterised by progressive increases in serum LDL levels accompanied by increases in serum triglyceride levels (Refs 49, 50), followed by a sharp fall post-partum (Refs 49, 51). Interestingly, an increase in the triglyceride content of LDL results in smaller but denser LDL particles (Refs 50, 52). These smaller, denser LDL particles are more atherogenic (Ref. 53) and are more susceptible to oxidative modification (Refs 48, 53, 54). Sattar et al. first reported that smaller, denser LDL particles are increased in

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preeclamptic plasma when compared with normotensive controls (Ref. 55), and this was subsequently confirmed by Hubel et al. (Ref. 50). By contrast to the above studies, Raijmakers et al. have shown that plasma levels of oxLDL are in fact decreased in preeclampsia compared with age-matched normotensive pregnancies (Ref. 56). The authors suggested that the decreased plasma oxLDL levels in preeclamptic women could be a result of increased levels of autoantibody to oxLDL (Ref. 56). Indeed, several studies have reported increased serum levels of autoantibodies to oxLDL (Refs 57, 58), whereas some studies have found no differences (Refs 59, 60). The differences in these reports could be attributed to differences in gestational age at sampling (Refs 57, 58, 59, 60). Nevertheless, it is important to note that autoantibodies to oxLDL failed to alter the clearance of oxLDL injected into apolipoprotein-E-deficient mice (Ref. 61). Hence, whether increased levels of autoantibodies to oxLDL could be a reasonable explanation for reports of decreased plasma oxLDL levels in preeclampsia is questionable.

Another explanation for decreased plasma oxLDL might be the presence of scavenger receptors that promote uptake of oxLDL. Sawamura and colleagues demonstrated that a novel lectin-like oxidised LDL receptor 1 (LOX-1) exists on bovine aortic endothelial cells (Ref. 62). Following this report, LOX-1 was also identified in vascular smooth muscle cells (Ref. 63) and macrophages (Ref. 64). LOX-1 is a type II membrane protein that can act as a cell-surface endocytosis receptor for oxLDL (Ref. 65). LOX-1 receptor is involved in binding, internalising and degrading oxLDL (Ref. 62) and accounts for 50–70% of oxLDL uptake in endothelial cells (Ref. 66), resulting in the generation of superoxide anion through activation of NAD(P)H oxidase (Ref. 67) (Fig. 1). Whereas basal levels of LOX-1 expression are low in vitro, factors such as TNF-α (Refs 68, 69), transforming growth factor β (Refs 68, 70), oxLDL (Refs 67, 71, 72, 73, 74, 75), ANG II (Refs 76, 77), endothelin 1 (ET-1) (Refs 78, 79), CRP (Ref. 80) and 8-iso-prostane (Ref. 81) have all been shown to upregulate LOX-1 expression. Since all of these factors have been reported to be elevated in the plasma of preeclamptic women (Refs 82, 83, 84), enhanced LOX-1 expression and uptake of oxLDL mediated through LOX-1 could be important in endothelial cell activation and/or dysfunction. This speculation is based on the fact that LOX-1 mRNA expression showed highest expression in human placenta when compared with other human tissues (Ref. 62) and is increased in women with preeclampsia (Ref. 85). Given the increased LOX-1 expression in the placenta of women with preeclampsia, it is tempting to speculate that such increases in LOX-1 expression can also occur in the maternal systemic vasculature of these women. In addition, Halvorsen et al. (Ref. 81) detected LOX-1 receptor in trophoblastic cells and, using a choriocarcinoma cell line, showed that 8-iso-PGF2α, a product of lipid peroxidation and a marker of oxidative stress in vivo, could enhance oxLDL uptake through LOX-1.

Nitric oxide

NO synthase (NOS) catalyses the conversion of L-arginine to L-citrulline and NO (Ref. 86). Since pregnancy is a state of vasodilation mediated in part by NO, a decrease in NO modulation of vascular tone could partly explain the pathogenesis of hypertension in preeclampsia. One mechanism by which oxygen free radicals might alter endothelial cell function is by scavenging NO, thereby impairing bioavailability of this potent vasodilator. Moreover, reduced NO bioavailability could be attributed to increased plasma levels of *S*-nitrosoalbumin in preeclampsia, which results in a decrease in the release of NO (Ref. 87). This decreased release of NO could also be partly due to decreased vitamin C levels, since *S*-nitrosoalbumin-mediated relaxation of resistance-sized vessels is enhanced by ascorbate (Ref. 88).

Another pathway that might result in reduced NO levels involves arginase, an enzyme that catalyses the conversion of L-arginine to L-ornithine and urea (Ref. 89). Since L-arginine is also a substrate for NOS, arginase reciprocally regulates NOS (Ref. 90); thus increased arginase activity could result in decreased NO production. Furthermore, a decrease in the substrate could result in uncoupling of endothelial NOS (eNOS), whereby electron flow from the reductase domain to the oxygenase domain is diverted to molecular oxygen rather than to L-arginine, resulting in the generation of superoxide anion (Refs 91, 92) (Fig. 2). This might result not only in decreased generation of NO but also increased scavenging of NO by superoxide to generate peroxynitrite.

There are two isoforms of arginase (arginase I and II) that are found in the cytosol and

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mitochondria, respectively. Arginase II mRNA expression is increased in the villous tissue of preeclamptic women and this inversely correlates with fetal L-arginine levels, suggesting excess consumption of the substrate (Ref. 93). In preeclamptic women, arginase II expression as assessed by immunohistochemistry was found to be increased in syncytiotrophoblast and endothelial cells of villous vessels in their placenta (Ref. 93). Based on the studies in the placenta, it is tempting to speculate that there may be increased arginase II expression in the maternal vasculature of preeclamptic women.

Although NO bioavailability may be decreased in women with preeclampsia, endothelial cells exposed to preeclamptic plasma showed an increase in NOS activity (Ref. 94), an increase in eNOS protein expression (Ref. 15), and an increase in nitrite / nitrate production (Ref. 94), suggesting that factors in the circulation may promote increased NO production in the vasculature of women with preeclampsia. Unfortunately, an increase in NO production in the face of oxidative stress could be damaging. NO reacts with superoxide anion to generate peroxynitrite (Refs 86, 95, 96), which modifies tyrosine residues in proteins. There is evidence of increased peroxynitrite formation in the placenta (Ref. 20) and the endothelium of maternal vasculature (Ref. 21). It is therefore reasonable to speculate that nitrotyrosine staining, which is an indicator of peroxynitrite formation, observed in preeclamptic tissue might also be due to arginase upregulation. This would result in L-arginine depletion and the generation of superoxide, which quenches NO to form peroxynitrite, providing a potential rationale for L-arginine supplementation. Consistent with this speculation, L-arginine has been shown to reduce blood pressure of pregnant rats with reduced uterine perfusion pressure (Ref. 80).

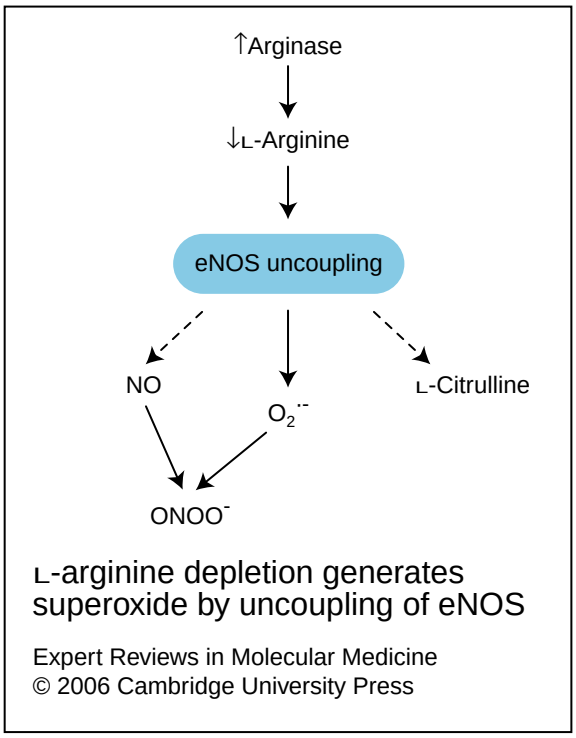


Figure 2. L-arginine depletion generates superoxide by uncoupling of eNOS. Endothelial nitric oxide synthase (eNOS) catalyses the conversion of L-arginine to nitric oxide (NO) and L-citrulline. An upregulation of arginase results in depletion of L-arginine and causes uncoupling of eNOS to generate superoxide anions ($O_2^{\cdot-}$), which subsequently scavenge NO to generate peroxynitrite ($ONOO^-$).

Peroxynitrite is not only an indicator of NO scavenging: it also affects endothelial function. Peroxynitrite increases inducible (i)NOS protein expression in isolated endothelial cells through activation of NF-κB (Ref. 97) (Fig. 1). Thus, a peroxynitrite-induced increase in NO could be deleterious in the face of increased oxidative stress, whereby there is a feed-forward mechanism to generate more peroxynitrite (Ref. 97). Furthermore, peroxynitrite decreases prostacyclin synthase expression (Fig. 1), which could alter the balance towards vasoconstriction.

These studies are indicative of the deleterious effects of enhanced NO production in the face of oxidative stress. The end result is a decrease in NO-mediated relaxation of the vasculature in preeclampsia, ultimately increasing peripheral vasoconstriction and hence increasing blood pressure. Interestingly, it seems that in normal pregnancy there is a compensatory pathway mediated by endothelium-derived hyperpolarising factor(s) [EDHF(s)] that cause relaxation when NO and prostacyclin are inhibited (Ref. 98). This compensatory pathway may be altered in preeclampsia.

EDHF(s) are non-NO, non-prostanoid, endothelium-derived vasodilator(s) (Ref. 99). Epoxyeicosatrienoic acid, cannabinoids, potassium ions, myo-endothelial gap junction and hydrogen peroxide have all been identified as EDHFs in various species and vascular beds (Ref. 99). EDHF is the predominant mediator of vasorelaxation in resistance-sized arteries (Ref. 100). Pascoal et al.

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reported that endothelium-dependent relaxation to acetylcholine and bradykinin in omental vessels from pregnant women was preserved after inhibition of both NO and prostacyclin, suggesting the presence of an intact EDHF pathway during pregnancy (Ref. 18). Kenny et al. reported an absence of EDHF-mediated relaxation in myometrial vessels from preeclamptic women but not normal pregnant women (Ref. 101). Further studies have revealed the role of gap junctions in EDHF-like relaxation during pregnancy (Ref. 102). Recently, Luksha et al. observed that, in subcutaneous resistance-sized arteries from normal pregnant women, bradykinin-induced relaxation is mediated entirely by gap junctions (Ref. 103). By contrast, in preeclampsia, EDHF-mediated relaxation is reduced and is mediated by a combination of gap junctions, hydrogen peroxide and cytochrome P450 metabolites. Such a heterogeneous nature of EDHF may be attributed to the ultrastructural changes occurring in the preeclamptic vessel wall (Ref. 104).

Ultimately, there is reduced endothelium-dependent relaxation in the vasculature of women with preeclampsia. Enhanced generation of superoxide anion could scavenge NO and this, coupled with an absence of compensatory pathway such as EDHF, might lead to the symptoms observed in women with preeclampsia. One primary source for superoxide anion formation is NAD(P)H oxidase. Circulating factors such as ANG II (Ref. 105) and TNF-α (Ref. 14) can activate endothelial NAD(P)H oxidase. The subsequent sections review the involvement of these factors in the pathophysiology of preeclampsia.

Angiotensin II

The renin–angiotensin system (RAS) is involved in the control of blood pressure and normal vascular homeostasis. During the first and second trimester of normal pregnancy, acute inhibition of the angiotensin-converting enzyme (ACE), the endothelial enzyme that generates active ANG II, decreases blood pressure and subsequently causes a compensatory elevation of plasma renin (Ref. 106), indicating that the RAS is important for the maintenance of blood pressure during pregnancy.

Pregnancy is associated with changes in the RAS system. Plasma renin activity increases progressively until 32 weeks of gestation, and then gradually decreases and normalises three weeks after delivery (Ref. 107). Along with renin, angiotensinogen levels also increase during normal pregnancy, probably as a result of increases in levels of estrogen, which stimulate its hepatic synthesis (Ref. 108). The increase in angiotensinogen and renin activity during pregnancy results in higher circulating levels of ANG II during the third trimester of normal pregnancy (Ref. 109). However, pregnant women are less sensitive to the pressor effects of ANG II compared with non-pregnant women.

Gant et al. first reported several decades ago that women who later developed pregnancy-induced hypertension showed increased sensitivity to ANG II compared with normal pregnant women, starting at 12 weeks of gestation (Ref. 12). The authors proposed that pregnancy-induced hypertension was the result of a failure of physiological adaptation of blood vessels to ANG II and that the vasoconstriction and hypertension in preeclampsia were triggered by renin released from the placenta (Ref. 12). However, in women with preeclampsia, plasma renin concentration and angiotensinogen are reduced compared with normotensive pregnant women (Ref. 108). Similarly, ANG II levels in preeclamptic women have been reported to be similar or decreased compared with normal pregnancy (Ref. 110). It has been postulated that the reduction in renin activity and ANG II levels may result from the increased sensitivity to ANG II. However, the mechanisms involved remain unclear.

All of the RAS components have been found in placental tissues, and seem to play an important role in the control of placental perfusion and remodelling of spiral arteries (reviewed by Refs 111, 112). In fact, a mutation (Met235Thr) within the gene encoding angiotensinogen has been associated with a higher risk of developing preeclampsia in some populations. Women who are heterozygous for this mutation show alterations in the remodelling of the spiral arteries (Ref. 113). Thus, placental RAS may be involved in decreased perfusion of the placenta, which could result in the release of factors into the maternal circulation. Moreover, transgenic female mice expressing human angiotensinogen, mated with transgenic male mice expressing human renin, develop placental alterations, high blood pressure and proteinuria during pregnancy (Ref. 23). However, in this model (Ref. 23) circulating ANG II levels were increased as

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compared with the reduced levels of ANG II seen in preeclamptic women.

ANG II has been shown to have multiple effects in the vasculature such as remodelling and inflammation. The effects of ANG II on vascular remodelling are mainly mediated through its type I receptor (AT1R). AT1R activation may increase the generation of ROS through direct activation of endothelial NAD(P)H-oxidase (reviewed by Ref. 114) (Fig. 1). Furthermore, ANG II, via AT1R, can induce the production of pro-inflammatory cytokines such as TNF-α (Ref. 115), which has been linked with pathophysiology of preeclampsia (discussed in next section). It has been reported that women with preeclampsia have increased expression of ANG II receptors (AT1R on platelets), in comparison with normal pregnant women (Ref. 116). Recently, AbdAlla et al. found that increased formation of heterodimers between the bradykinin receptor and AT1R in preeclamptic women resulted in enhanced ANG II signalling through G proteins (Ref. 74). In normal conditions, superoxide anion generated via binding of ANG II to AT1R acts as negative feedback to downregulate AT1R and decrease ANG II signalling. However, the presence of heterodimers make AT1R unresponsive to negative feedback from oxidant stress, thus exposing the vascular cells to the deleterious effects of ANG II (Ref. 74).

Furthermore, agonistic auto-antibodies against the AT1R receptor have been reported in the serum of patients with preeclampsia (Ref. 117). These antibodies can target AT1R on vascular cells and activate tissue factor (Ref. 118), promoting a pro-thrombotic phenotype. In addition, ANG-II-induced MMP-2 and TNF-α release from endothelial cells could result in a pro-thrombotic and pro-inflammatory phenotype in preeclampsia (Ref. 115). However, the role of these pathways in the pathophysiology of preeclampsia remains to be determined.

It is currently believed that the ANG II type 2 receptor (AT2R) modulates the pressor and remodelling effects of ANG II via AT1R. In normal conditions, AT2Rs are more prevalent in fetuses than in adults, but have been found to be up-regulated in processes that occur with vascular inflammation (Ref. 119). McMullen et al. found that down-regulation of AT2R in uterine arteries of ewes led to a state of hyper-reactivity of these arteries similar to that seen in preeclampsia (Ref. 120). Therefore, an imbalance between the actions of ANG II through AT1R and AT2R might be involved in preeclampsia.

Furthermore, Doering et al. (Ref. 121) found that in pregnant rats infused with endotoxin, which have been shown to develop some of the relevant clinical features of human preeclampsia, administration of an AT1R antagonist tended to diminish the rise in arterial pressure and completely prevented proteinuria (Ref. 121). While ANG II blockade is contraindicated in pregnancy because of its adverse effects on fetal development (Ref. 122), one recent retrospective study, evaluating the effects of ACE inhibition in cases of severe and unresponsive hypertension in pregnancy, reported an increase in cardiac output and a reduction in total peripheral resistance in patients who received ACE inhibitors (Ref. 123). Thus, ANG II may be an important factor in the pathophysiology of preeclampsia.

Tumour necrosis factor α

Several inflammatory factors have been postulated to play a role in the pathophysiology of preeclampsia (recently reviewed by Ref. 124). TNF-α is a primary cytokine (regulates the production of other pro- and anti-inflammatory factors) prominently linked to preeclampsia. Indeed, several observational studies have reported that preeclamptic women have higher levels of TNF-α compared with normal pregnant women, which normalises after delivery (Ref. 83). For instance, higher levels of TNF-α have been demonstrated in the first and second trimester of gestation of women that developed preeclampsia, suggesting that TNF-α could be involved in the early events that lead to this disorder (Refs 125, 126). Levels of TNF-α receptors correlate well with the increments in blood pressure and fibronectin levels in preeclamptic women (Ref. 127). Moreover, Anim-Nyame et al. found that the increase in microvascular permeability in preeclamptic women was related to higher levels of TNF-α compared with normal pregnant and non-pregnant women (Ref. 128).

The source of TNF-α in preeclamptic women is unknown. Placentas from preeclamptic women have increased mRNA and protein expression of TNF-α compared with placentas from normal pregnant women (Ref. 6), suggesting that the placenta could be a source of this cytokine. However, Benyo et al. (Ref. 10) found that although peripheral and uterine venous levels of TNF-α were elevated in preeclamptic women

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compared with normal term patients, their peripheral versus uterine levels were not significantly different, suggesting that sources other than the placenta, such as activated leukocytes and endothelium in the maternal system, could be the principal contributors to higher maternal levels of TNF-α in preeclamptic women. Furthermore, adipose tissue might also be an important source of TNF-α (Ref. 129) since it has been shown that the pre-pregnant body mass index positively correlates with the risk of developing preeclampsia (Ref. 130).

Experimental findings support a role of TNF-α in the maternal vascular alterations associated with preeclampsia. TNF-α alters the balance between endothelium-derived vasoconstrictors and vasodilators. TNF-α decreases the availability of the vasodilator NO by decreasing eNOS expression in endothelial cells, resulting in decreased NO formation (Ref. 131) and/or by increasing the production of superoxide anion via activation of NAD(P)H oxidase (Ref. 132), resulting in scavenging of NO (Fig. 1). Moreover, TNF-α might induce the formation of vasoconstrictors such as thromboxane (Ref. 133) and ET-1 (Ref. 134), which are increased in preeclampsia patients (Ref. 135). Furthermore, TNF-α can also induce mitochondrial alterations resulting in enhanced ROS production (Ref. 35).

In addition, TNF-α increases the expression of adhesion molecules by the endothelium such as ICAM-1 (Ref. 136), induces the expression of tissue procoagulant factor (Ref. 137), inhibits the thrombomodulin/protein C anticoagulation pathway (Ref. 138), and blocks fibrin dissolution by stimulation of the type I inhibitor of plasminogen activator (Ref. 139). All of these alterations may lead to a pro-inflammatory and pro-coagulant state similar to that described in preeclampsia women.

A few studies have examined the effects of TNF-α during pregnancy. Alexander et al. found that chronic infusion of TNF-α in rats starting at day 14 of gestation results in hypertension and decreased renal neuronal NOS and iNOS protein expression (Ref. 73). Moreover, TNF-α induces vasoconstriction and impairs endothelium-dependent relaxation in aortic ring preparations from pregnant rats more prominently than from non-pregnant rats (Ref. 140). Furthermore, Vizi et al. reported that intraperitoneal injection of lipopolysaccharide, a potent stimulus for endogenous TNF-α production, induces greater TNF-α plasma levels and higher mortality in pregnant mice compared with non-pregnant animals (Ref. 141). This suggests that pregnancy is associated with a higher susceptibility to the effects of this cytokine, and thus it might be a potential target for therapeutic intervention.

Vascular endothelial growth factor

VEGF, originally termed vascular permeability factor (VPF), belongs to a family of glycoproteins that express their biological effects by binding to VEGF receptor 1 (fetal liver tyrosine-like; Flt-1) (Ref. 142) and VEGF receptor 2 (kinase-domain-related receptor; KDR) (Ref. 143). VEGF promotes angiogenesis (Ref. 144), induces endothelial cell production of vasodilatory NO and prostacyclin (Ref. 17), and may be important in the regulation of vascular tone (Ref. 145). Although VEGF has vasodilatory capacity, recent studies have reported detrimental effects of in vivo administration of VEGF. When administered in this manner, VEGF causes enhanced leukocyte rolling, adhesion, vascular leakage and inflammation (Ref. 88). In addition, VEGF increased expression of ICAM-1 and VCAM-1 in HUVECs in vitro via activation of NF-κB (Ref. 146). It is tempting to speculate that such pro-inflammatory actions of VEGF could be involved in the pathogenesis of endothelial dysfunction in preeclampsia.

Brockelsby et al. have examined the role of VEGF in preeclampsia (Ref. 17) by incubating myometrial resistance vessels obtained from normotensive pregnant women with VEGF, which resulted in a blunted endothelium-dependent relaxation, mimicking the effects of preeclamptic plasma. Furthermore, pre-incubation of preeclamptic plasma with anti-Flt1 receptor antibody but not anti-KDR receptor antibody enhanced endothelium-dependent relaxation. These results suggest that VEGF might act as a mediator of endothelial dysfunction in preeclampsia through the Flt1 receptor.

However, there are conflicting reports regarding the role of VEGF in the pathophysiology of preeclampsia. Although the above study provides evidence for the harmful effects of VEGF, other studies have reported that antagonising the actions of VEGF may lead to preeclampsia. Specifically, a circulating soluble Flt receptor (sFlt) is increased in preeclampsia and has been found to act as a potent antagonist of VEGF and placental growth factor (PlGF) (Ref. 147). sFlt is a splice variant of Flt1 receptor that lacks the

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transmembrane and cytoplasmic domains (Ref. 95), and is produced by several organs including the placenta (Refs 17, 148), lung, liver, kidney and uterus (Ref. 17). Recent reports have shown elevated placental sFlt1 expression (Ref. 149) and sFlt1 levels in the amniotic fluid (Ref. 150) of preeclamptic women. Furthermore, gene expression profiling of placental tissue by Maynard et al. demonstrated upregulated mRNA expression of sFlt1 in preeclampsia and elevated systemic levels of sFlt1 levels in preeclamptic women (Ref. 28); the latter has also been confirmed by other investigators (Refs 151, 152, 153). Moreover, there is a positive correlation between the severity of preeclampsia and serum sFlt1 levels (Ref. 28). sFlt1 levels also vary inversely with serum VEGF and PlGF levels (Refs 28, 153), an effect that can partly be attributed to the binding of sFlt1 to these factors. However, a recent study has shown decreased PlGF levels during the first trimester without an increase in sFlt1 levels (Ref. 153), suggesting that decreased PlGF levels observed in preeclampsia could also arise as a result of inadequate placental production. Moreover, there is a strong association between decreased urinary PlGF and the subsequent development of preeclampsia (Ref. 154). However, sFlt1 and PlGF could together serve as predictors of preeclampsia (Ref. 153). While Baker and colleagues have performed vascular function studies to elucidate the contribution of VEGF to endothelial dysfunction in preeclampsia, Karumanchi and co-workers have examined the circulating levels of VEGF and sFlt1 and suggested that decreased VEGF levels resulting from sFlt1 elevation might be a potential cause in the pathogenesis of preeclampsia. These differences in methodologies could be a plausible explanation for the opposite findings of these researchers. Further studies are needed to confirm the contribution of VEGF in the role of preeclampsia.

Matrix metalloproteinases

A common pathway for altered vascular function by the factors mentioned above might be through MMPs, which are a large family of zinc-dependent endopeptidases expressed ubiquitously throughout the body. In vivo, MMP activity is regulated by the four tissue inhibitors of MMPs (TIMPs 1–4), which bind and inhibit the zinc-catalytic domain of these enzymes (reviewed by Refs 155, 156). An imbalance between MMP activity and TIMP inhibition has long been recognised to lead to degradation of extracellular matrix, and in this manner contribute to remodelling in long-term physiological processes [e.g. embryogenesis (Ref. 157)] and chronic pathological processes [e.g. heart failure, atherosclerosis (Refs 158, 159)]. More recently, however, MMPs have also been shown to cleave non-extracellular-matrix proteins and contribute to acute processes such as vascular reactivity (Ref. 160) and platelet aggregation (Ref. 161). Since such acute processes contribute to the pathology of preeclampsia, the potential role of MMPs in this disease warrants attention.

MMP-2 may be of particular relevance in preeclampsia since its circulating levels have been found to be elevated in preeclamptic women compared with normal pregnant women (Ref. 162). Myers et al. demonstrated that the MMP-2 to TIMP-1 ratio is imbalanced in women that develop preeclampsia (Ref. 163). This imbalance preceded the onset of the condition and continued up to the time of delivery. Kolben et al. also found that circulating TIMP-1 is decreased in preeclampsia (Ref. 164). The circulating levels of other TIMPs in preeclampsia still remain to be determined.

In vitro studies also suggest an imbalance between MMPs and TIMPs in preeclampsia. HUVECs from preeclamptic pregnancies release more MMP-2 than endothelial cells from normal pregnancies (Ref. 165). In this case, the increase in MMP-2 activity occurred with no change in TIMP-1 or -2 protein levels, suggesting a net increase in proteolysis. Since the cells studied in these experiments were of fetal origin, it raises the possibility that alterations also occur in the fetal cardiovascular system during preeclampsia. These changes may contribute to a predisposition to increased blood pressure later in life (Ref. 166). These in vitro experiments also indirectly suggest that the source of increased circulating MMP-2 in preeclampsia may be the dysfunctional endothelium.

In vitro, several studies have demonstrated that many of the circulating factors already discussed in this article increase MMP activity. For instance, VEGF was found to markedly increase MMP-2 release from endothelial cells in a time- and concentration-dependent manner (Ref. 162). Other studies have demonstrated that peroxynitrite, TNF-α, ANG II and oxLDL can also activate MMPs in vitro (Refs 167, 168, 169). Thus, it is possible that multiple molecular mediators

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of preeclampsia might converge to promote MMP production and release in this condition.

The functional significance of elevated MMP-2 might lie in accumulating evidence suggesting that this enzyme promotes vasoconstriction. We have previously demonstrated that MMP-2 can cleave 'big endothelin' [the precursor to ET-1 with 38 amino acids (aa)] to yield the vasoconstrictor ET[1–32 aa] (Fig. 1), a peptide that is more potent than the product of endothelin-converting enzyme (ET[1–21 aa]) (Ref. 160). Since numerous studies have suggested a role for endothelin in preeclampsia (Refs 135, 170), the possibility exists that MMP-2 might contribute to hypertension in preeclampsia through endothelin processing.

In a separate investigation, MMP-2 was also found to cleave and inactivate the vasodilator calcitonin-gene-related peptide (Ref. 149). Similarly, Martinez et al. (Ref. 171) found that MMP-2 vasoconstriction was mediated by cleavage of the vasodilator adrenomedullin to form a novel vasoconstrictor peptide. This peptide product of MMP-2 proteolysis could be found in the urine of normal human volunteers, and infusion of the peptide into normal rats resulted in elevated systemic blood pressure. Interestingly, there is a lack of compensatory elevation of both calcitonin-gene-related peptide and adrenomedullin in preeclampsia (Refs 172, 173). It remains to be resolved whether MMP-2 contributes to these inappropriately low levels by degrading these vasodilators. In addition, since MMP-7 has also been shown to regulate vascular function (Ref. 174), the role of other MMPs in preeclampsia needs to be explored.

Although the studies discussed above support a vasoconstrictor role of MMPs, several investigations have also reported a possible role of MMP-2 as a vasodilator. Interestingly, this vasodilation may in fact be mediated by the formation of endothelin, which then acts on endothelial ET_B receptors that mediate vasodilation (as opposed to ET_A receptors that mediate vasoconstriction). In two independent studies, exogenous MMP-2 induced vasodilation in normal rat aortas (Ref. 175) and in rat mesenteric arteries (Ref. 176). Moreover, in the latter study using mesenteric arteries, thrombin-induced vasorelaxation was found to be mediated through release of MMP-2. Recently, Jeyabalan et al. (Ref. 177) have also shown that relaxin-induced renal vasodilation in pregnant rats is mediated by release of MMP-2. As a part of this investigation, the application of TIMP-2 was actually found to promote vasoconstriction as opposed to the previously described vasodilatory effects of this MMP inhibitor (Ref. 160). Vasorelaxation was probably mediated through ET_B receptors since relaxin could not induce vasorelaxation in ET_B-receptor-deficient rats, despite an increase in gelatinase activity (Ref. 177).

With studies showing both vasoconstrictor and vasodilator abilities of MMP-2, future investigations need to determine the role of MMPs in vascular dysfunction of women with preeclampsia. In a preliminary study we determined the effect of MMP inhibition on mice mesenteric vessels incubated with plasma from either non-pregnant, normotensive pregnant or preeclamptic women (Ref. 11). In these experiments, incubation of mice mesenteric arteries with plasma from either non-pregnant or preeclamptic women enhanced myogenic tone and decreased endothelium-dependent relaxation compared with vessels incubated with plasma from normotensive pregnant women. Myogenic tone was further increased, and vasorelaxation further dampened, when the broad-spectrum MMP inhibitor GM6001 was added to preeclamptic-plasma-treated vessels (but not the other two groups), suggesting that MMP inhibition blocked the modulation of a vasodilator in these vessels (Ref. 11). An interesting finding in this study was the similarity in vascular function between vessels treated with plasma from either non-pregnant or preeclamptic women. This similarity suggests that preeclampsia might be due, in part, to the lack of a necessary adaptation to pregnancy.

Overall, it is likely that the role of MMPs as modulators of vascular tone in preeclampsia will depend on the balance between the pro- and anti-constrictor properties of MMPs. In the pro-inflammatory, pro-vasoconstrictor state of preeclampsia, the in vivo functional significance of the elevated levels of circulating MMP-2 remains to be determined.

Conclusion

Preeclampsia is an endothelial cell disorder mediated by a panoply of circulating factors. Factors such as oxLDL, ANG II and TNF-α result in oxidative stress, inflammation and vasoconstriction, features that have been well documented in preeclampsia. Moreover, these factors may act both individually and in concert to cause alteration of the maternal endothelial

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function. This may result in increased NO scavenging, leading to peroxynitrite formation, which could subsequently activate MMPs to further induce vasoconstriction. The above mechanisms suggest a role for anti-oxidants and/or anti-inflammatory agents in the prevention of preeclampsia, whereas vasodilators or anti-hypertensive agents could possibly play a role in the treatment of preeclampsia. Despite extensive research, the mechanisms by which the levels of such factors are altered, and their subsequent effect on the maternal endothelium, remain to be fully elucidated. Without better understanding of the mechanisms of maternal endothelial dysfunction, prevention and treatment of preeclampsia will remain elusive.

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References

1 August, P. and Lindheimer, M.D. (1995) Pathophysiology of preeclampsia. In Hypertension (2nd edn) (Laragh, J.L. and Brenner, B.M., eds), pp. 2407-2426, Raven Press Ltd

2 Roberts, J.M. (1998) Pregnancy related hypertension. In Maternal Fetal Medicine (Creasy, R.K. and Resnik, R., eds), pp. 833-872, W.B. Saunders

3 Villar, K. et al. (2003) Eclampsia and preeclampsia: a health problem for 2000 years. In Preeclampsia (Critchley, H. et al., eds), pp. 189-207, RCOG Press

4 Roberts, J.M. and Hubel, C.A. (1999) Is oxidative stress the link in the two-stage model of pre-eclampsia? Lancet 354, 788-789, PubMed: 10485715

5 Fisher, S.J. and Roberts, J.M. (1999) Defects in placentation and placental perfusion. In Chelsey's Hypertensive Disorders in Pregnancy (2nd edn) (Lindheimer, M.D., Roberts, J.M. and Cunningham, F.G., eds), pp. 377-394, Appleton and Lange

6 Rinehart, B.K. et al. (1999) Expression of the placental cytokines tumor necrosis factor alpha, interleukin 1beta, and interleukin 10 is increased in preeclampsia. Am J Obstet Gynecol 181, 915-920, PubMed: 10521753

7 Roberts, J.M., Taylor, R.N. and Goldfien, A. (1991) Clinical and biochemical evidence of endothelial cell dysfunction in the pregnancy syndrome preeclampsia. Am J Hypertens 4, 700-708, PubMed: 1930853

8 Sargent, I.L. et al. (2003) Trophoblast deportation and the maternal inflammatory response in pre-eclampsia. J Reprod Immunol 59, 153-160, PubMed: 12896819

9 Roberts, J.M. et al. (1989) Preeclampsia: an endothelial cell disorder. Am J Obstet Gynecol 161, 1200-1204, PubMed: 2589440

10 Benyo, D.F. et al. (2001) Expression of inflammatory cytokines in placentas from women with preeclampsia. J Clin Endocrinol Metab 86, 2505-2512, PubMed: 11397847

11 Merchant, S.J. and Davidge, S.T. (2004) The role of matrix metalloproteinases in vascular function: implications for normal pregnancy and pre-eclampsia. Bjog 111, 931-939, PubMed: 15327607

12 Gant, N.F. et al. (1973) A study of angiotensin II pressor response throughout primigravid pregnancy. J Clin Invest 52, 2682-2689, PubMed: 4355997

13 Raijmakers, M.T., Dechend, R. and Poston, L. (2004) Oxidative stress and preeclampsia: rationale for antioxidant clinical trials. Hypertension 44, 374-380, PubMed: 15326082

14 Redman, C.W. and Sargent, I.L. (2003) Pre-eclampsia, the placenta and the maternal systemic inflammatory response—a review. Placenta 24 Suppl A, S21-27, PubMed: 12842410

15 Davidge, S.T., Baker, P.N. and Roberts, J.M. (1995) NOS expression is increased in endothelial cells exposed to plasma from women with preeclampsia. Am J Physiol 269, H1106-1112, PubMed: 7573508

16 Zhang, Y. et al. (2003) Increased endothelial monolayer permeability is induced by serum from women with preeclampsia but not by serum from women with normal pregnancy or that are not pregnant. Hypertens Pregnancy 22, 99-108, PubMed: 12648447

17 Brockelsby, J. et al. (1999) VEGF via VEGF receptor-1 (Flt-1) mimics preeclamptic plasma in

Accession information: DOI: 10.1017/S1462399406010465; Vol. 8; Issue 3; 27 January 2006
©2006 Cambridge University Press

https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

inhibiting uterine blood vessel relaxation in pregnancy: implications in the pathogenesis of preeclampsia. Lab Invest 79, 1101-1111, PubMed: 10496528
18 Pascoal, I.F. et al. (1998) Preeclampsia selectively impairs endothelium-dependent relaxation and leads to oscillatory activity in small omental arteries. J Clin Invest 101, 464-470, PubMed: 9435319
19 Ashworth, J.R. et al. (1997) Loss of endothelium-dependent relaxation in myometrial resistance arteries in pre-eclampsia. Br J Obstet Gynaecol 104, 1152-1158, PubMed: 9332993
20 Myatt, L. et al. (1996) Nitrotyrosine residues in placenta. Evidence of peroxynitrite formation and action. Hypertension 28, 488-493, PubMed: 8794838
21 Roggensack, A.M., Zhang, Y. and Davidge, S.T. (1999) Evidence for peroxynitrite formation in the vasculature of women with preeclampsia. Hypertension 33, 83-89, PubMed: 9931086
22 Leik, C.E. and Walsh, S.W. (2004) Neutrophils infiltrate resistance-sized vessels of subcutaneous fat in women with preeclampsia. Hypertension 44, 72-77, PubMed: 15148293
23 Takimoto, E. et al. (1996) Hypertension induced in pregnant mice by placental renin and maternal angiotensinogen. Science 274, 995-998, PubMed: 8875944
24 Davisson, R.L. et al. (2002) Discovery of a spontaneous genetic mouse model of preeclampsia. Hypertension 39, 337-342, PubMed: 11882569
25 Kanayama, N. et al. (2002) Deficiency in p57Kip2 expression induces preeclampsia-like symptoms in mice. Mol Hum Reprod 8, 1129-1135, PubMed: 12468647
26 Faas, M.M. et al. (1994) A new animal model for human preeclampsia: ultra-low-dose endotoxin infusion in pregnant rats. Am J Obstet Gynecol 171, 158-164, PubMed: 8030692
27 Sakawi, Y. et al. (2000) Evaluation of low-dose endotoxin administration during pregnancy as a model of preeclampsia. Anesthesiology 93, 1446-1455, PubMed: 11149440
28 Maynard, S.E. et al. (2003) Excess placental soluble fms-like tyrosine kinase 1 (sFlt1) may contribute to endothelial dysfunction, hypertension, and proteinuria in preeclampsia. J Clin Invest 111, 649-658, PubMed: 12618519
29 Greer, I.A. et al. (1994) Increased concentrations of cytokines interleukin-6 and interleukin-1 receptor antagonist in plasma of women with preeclampsia: a mechanism for endothelial dysfunction? Obstet Gynecol 84, 937-940, PubMed: 7526306
30 Conrad, K.P., Miles, T.M. and Benyo, D.F. (1998) Circulating levels of immunoreactive cytokines in women with preeclampsia. Am J Reprod Immunol 40, 102-111, PubMed: 9764352
31 Qiu, C. et al. (2004) A prospective study of maternal serum C-reactive protein concentrations and risk of preeclampsia. Am J Hypertens 17, 154-160, PubMed: 14751658
32 Mantovani, A. et al. (1990) The role of cytokines as communication signals between leukocytes and endothelial cells. Prog Clin Biol Res 349, 343-353, PubMed: 2204933
33 Phocas, I. et al. (2000) A comparative study of serum soluble vascular cell adhesion molecule-1 and soluble intercellular adhesion molecule-1 in preeclampsia. J Perinatol 20, 114-119, PubMed: 10785888
34 Coata, G. et al. (2002) Soluble adhesion molecules: marker of pre-eclampsia and intrauterine growth restriction. J Matern Fetal Neonatal Med 12, 28-34, PubMed: 12422906
35 Stark, J.M. (1993) Pre-eclampsia and cytokine induced oxidative stress. Br J Obstet Gynaecol 100, 105-109, PubMed: 8476799
36 Li, N. and Karin, M. (1999) Is NF-kappaB the sensor of oxidative stress? Faseb J 13, 1137-1143, PubMed: 10385605
37 Takacs, P. et al. (2001) Increased circulating lipid peroxides in severe preeclampsia activate NF-kappaB and upregulate ICAM-1 in vascular endothelial cells. Faseb J 15, 279-281, PubMed: 11156936
38 Davidge, S.T. (1998) Oxidative stress and altered endothelial cell function in preeclampsia. Semin Reprod Endocrinol 16, 65-73, PubMed: 9654609
39 Raijmakers, M.T. et al. (2004) NAD(P)H oxidase associated superoxide production in human placenta from normotensive and pre-eclamptic women. Placenta 25 Suppl A, S85-89, PubMed: 15033313
40 Poston, L. and Chappell, L.C. (2001) Is oxidative stress involved in the aetiology of pre-eclampsia? Acta Paediatr Suppl 90, 3-5, PubMed: 11332954
41 Redman, C.W. and Sargent, I.L. (2000) Placental debris, oxidative stress and pre-eclampsia. Placenta 21, 597-602, PubMed: 10985960
42 Rodrigo, R. et al. (2005) Pathophysiological basis for the prophylaxis of preeclampsia through early supplementation with antioxidant vitamins. Pharmacol Ther 107, 177-197, PubMed:

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https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

15896847
43 Davidge, S.T. et al. (1992) Sera antioxidant activity in uncomplicated and preeclamptic pregnancies. Obstet Gynecol 79, 897-901, PubMed: 1579310
44 Chappell, L.C. et al. (2002) A longitudinal study of biochemical variables in women at risk of preeclampsia. Am J Obstet Gynecol 187, 127-136, PubMed: 12114900
45 Regan, C.L. et al. (2001) No evidence for lipid peroxidation in severe preeclampsia. Am J Obstet Gynecol 185, 572-578, PubMed: 11568780
46 Poston, L. and Mallet, A. (2002) No evidence for lipid peroxidation in severe preeclampsia. Am J Obstet Gynecol 187, 1118; author reply 1119-1120, PubMed: 12389014
47 Llurba, E. et al. (2004) A comprehensive study of oxidative stress and antioxidant status in preeclampsia and normal pregnancy. Free Radic Biol Med 37, 557-570, PubMed: 15256227
48 Wakatsuki, A. et al. (2000) Lipoprotein particles in preeclampsia: susceptibility to oxidative modification. Obstet Gynecol 96, 55-59, PubMed: 10862842
49 Potter, J.M. and Nestel, P.J. (1979) The hyperlipidemia of pregnancy in normal and complicated pregnancies. Am J Obstet Gynecol 133, 165-170, PubMed: 217273
50 Hubel, C.A. et al. (1998) Small low-density lipoproteins and vascular cell adhesion molecule-1 are increased in association with hyperlipidemia in preeclampsia. Metabolism 47, 1281-1288, PubMed: 9781635
51 Hubel, C.A. et al. (1996) Fasting serum triglycerides, free fatty acids, and malondialdehyde are increased in preeclampsia, are positively correlated, and decrease within 48 hours post partum. Am J Obstet Gynecol 174, 975-982, PubMed: 8633679
52 Griffin, B.A. (1995) Low-density lipoprotein heterogeneity. Baillieres Clin Endocrinol Metab 9, 687-703, PubMed: 8593120
53 Witztum, J.L. (1993) Susceptibility of low-density lipoprotein to oxidative modification. Am J Med 94, 347-349, PubMed: 8475927
54 Anber, V. et al. (1996) Influence of plasma lipid and LDL-subfraction profile on the interaction between low density lipoprotein with human arterial wall proteoglycans. Atherosclerosis 124, 261-271, PubMed: 8830938
55 Sattar, N. et al. (1997) Lipoprotein subfraction concentrations in preeclampsia: pathogenic parallels to atherosclerosis. Obstet Gynecol 89, 403-408, PubMed: 9052594
56 Raijmakers, M.T. et al. (2004) Low plasma levels of oxidized low density lipoprotein in preeclampsia. Acta Obstet Gynecol Scand 83, 1173-1177, PubMed: 15548151
57 Branch, D.W. et al. (1994) Pre-eclampsia and serum antibodies to oxidised low-density lipoprotein. Lancet 343, 645-646, PubMed: 7509433
58 Uotila, J. et al. (1998) Antibodies against copper-oxidised and malondialdehyde-modified low density lipoproteins in pre-eclampsia pregnancies. Br J Obstet Gynaecol 105, 1113-1117, PubMed: 9800936
59 Gratacos, E. et al. (2001) Serum antibodies to oxidized low-density lipoprotein in pregnant women with preeclampsia and chronic hypertension: lack of correlation with lipid peroxides. Hypertens Pregnancy 20, 177-183, PubMed: 12044328
60 Armstrong, V.W. et al. (1994) Serum antibodies to oxidised low-density lipoprotein in pre-eclampsia and coronary heart disease. Lancet 343, 1570, PubMed: 7911891
61 Reardon, C.A. et al. (2004) Autoantibodies to OxLDL fail to alter the clearance of injected OxLDL in apolipoprotein E-deficient mice. J Lipid Res 45, 1347-1354, PubMed: 15102879
62 Sawamura, T. et al. (1997) An endothelial receptor for oxidized low-density lipoprotein. Nature 386, 73-77, PubMed: 9052782
63 Draude, G., Hrboticky, N. and Lorenz, R.L. (1999) The expression of the lectin-like oxidized low-density lipoprotein receptor (LOX-1) on human vascular smooth muscle cells and monocytes and its down-regulation by lovastatin. Biochem Pharmacol 57, 383-386, PubMed: 9933026
64 Yoshida, H. et al. (1998) Identification of the lectin-like receptor for oxidized low-density lipoprotein in human macrophages and its potential role as a scavenger receptor. Biochem J 334 (Pt 1), 9-13, PubMed: 9693095
65 Masaki, T. (2003) Endothelial dysfunction and LOX-1: forty years from muscle to endothelium. Circ Res 92, 819-820, PubMed: 12730125
66 Yamada, Y. et al. (1998) Scavenger receptor family proteins: roles for atherosclerosis, host defence and disorders of the central nervous system. Cell Mol Life Sci 54, 628-640, PubMed: 9711230
67 Cominacini, L. et al. (2001) The binding of oxidized low density lipoprotein (ox-LDL) to ox-LDL receptor-1 reduces the intracellular

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©2006 Cambridge University Press

https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

concentration of nitric oxide in endothelial cells through an increased production of superoxide. J Biol Chem 276, 13750-13755, PubMed: 11278710
68 Hofnagel, O. et al. (2004) Proinflammatory cytokines regulate LOX-1 expression in vascular smooth muscle cells. Arterioscler Thromb Vasc Biol 24, 1789-1795, PubMed: 15271788
69 Chiba, Y. et al. (2001) PPARgamma ligands inhibit TNF-alpha-induced LOX-1 expression in cultured endothelial cells. Biochem Biophys Res Commun 286, 541-546, PubMed: 11511093
70 Chen, H. et al. (2001) Transforming growth factor-beta(1) modulates oxidatively modified LDL-induced expression of adhesion molecules: role of LOX-1. Circ Res 89, 1155-1160, PubMed: 11739280
71 Cominacini, L. et al. (2000) Oxidized low density lipoprotein (ox-LDL) binding to ox-LDL receptor-1 in endothelial cells induces the activation of NF-kappaB through an increased production of intracellular reactive oxygen species. J Biol Chem 275, 12633-12638, PubMed: 10777555
72 Mehta, J.L. et al. (2004) Aspirin inhibits ox-LDL-mediated LOX-1 expression and metalloproteinase-1 in human coronary endothelial cells. Cardiovasc Res 64, 243-249, PubMed: 15485683
73 Alexander, B.T. et al. (2002) Tumor necrosis factor-alpha-induced hypertension in pregnant rats results in decreased renal neuronal nitric oxide synthase expression. Am J Hypertens 15, 170-175, PubMed: 11863253
74 AbdAlla, S., Lother, H. and Quitterer, U. (2000) AT1-receptor heterodimers show enhanced G-protein activation and altered receptor sequestration. Nature 407, 94-98, PubMed: 10993080
75 Dechend, R. et al. (2003) AT1 receptor agonistic antibodies from preeclamptic patients stimulate NADPH oxidase. Circulation 107, 1632-1639, PubMed: 12668498
76 Morawietz, H. et al. (1999) Angiotensin II induces LOX-1, the human endothelial receptor for oxidized low-density lipoprotein. Circulation 100, 899-902, PubMed: 10468518
77 Chen, H. et al. (2000) Upregulation of LOX-1 expression in aorta of hypercholesterolemic rabbits: modulation by losartan. Biochem Biophys Res Commun 276, 1100-1104, PubMed: 11027596
78 Morawietz, H. et al. (2002) Augmented endothelial uptake of oxidized low-density lipoprotein in response to endothelin-1. Clin Sci (Lond) 103 Suppl 48, 9S-12S, PubMed: 12193044
79 Morawietz, H. et al. (2001) Induction of the oxLDL receptor LOX-1 by endothelin-1 in human endothelial cells. Biochem Biophys Res Commun 284, 961-965, PubMed: 11409887
80 Alexander, B.T. et al. (2004) L-arginine attenuates hypertension in pregnant rats with reduced uterine perfusion pressure. Hypertension 43, 832-836, PubMed: 14769812
81 Halvorsen, B. et al. (2001) 8-iso-prostaglandin F(2alpha) increases expression of LOX-1 in JAR cells. Hypertension 37, 1184-1190, PubMed: 11304522
82 Hayashi, M. et al. (2005) Tumor necrosis factor-alpha in the placenta is not elevated in pre-eclamptic patients despite its elevation in peripheral blood. Am J Reprod Immunol 53, 113-119, PubMed: 15727564
83 Kupferminc, M.J. et al. (1996) Soluble tumor necrosis factor receptors and interleukin-6 levels in patients with severe preeclampsia. Obstet Gynecol 88, 420-427, PubMed: 8752252
84 Muy-Rivera, M. et al. (2004) Transforming growth factor-beta1 (TGF-beta1) in plasma is associated with preeclampsia risk in Peruvian women with systemic inflammation. Am J Hypertens 17, 334-338, PubMed: 15062887
85 Lee, H. et al. (2005) Expression of lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) in human preeclamptic placenta: possible implications in the process of trophoblast apoptosis. Placenta 26, 226-233, PubMed: 15708124
86 Ignarro, L.J. (1990) Nitric oxide. A novel signal transduction mechanism for transcellular communication. Hypertension 16, 477-483, PubMed: 1977698
87 Tyurin, V.A. et al. (2001) Elevated levels of S-nitrosoalbumin in preeclampsia plasma. Circ Res 88, 1210-1215, PubMed: 11397789
88 Gandley, R.E. et al. (2005) S-nitrosoalbumin-mediated relaxation is enhanced by ascorbate and copper: effects in pregnancy and preeclampsia plasma. Hypertension 45, 21-27, PubMed: 15569857
89 Li, H. et al. (2001) Regulatory role of arginase I and II in nitric oxide, polyamine, and proline syntheses in endothelial cells. Am J Physiol Endocrinol Metab 280, E75-82, PubMed: 11120661
90 Berkowitz, D.E. et al. (2003) Arginase reciprocally regulates nitric oxide synthase activity and contributes to endothelial dysfunction in aging

Accession information: DOI: 10.1017/S1462399406010465; Vol. 8; Issue 3; 27 January 2006
©2006 Cambridge University Press

https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

blood vessels. Circulation 108, 2000-2006, PubMed: 14517171
91 Kuzkaya, N. et al. (2003) Interactions of peroxynitrite, tetrahydrobiopterin, ascorbic acid, and thiols: implications for uncoupling endothelial nitric-oxide synthase. J Biol Chem 278, 22546-22554, PubMed: 12692136
92 Xia, Y. et al. (1996) Nitric oxide synthase generates superoxide and nitric oxide in arginine-depleted cells leading to peroxynitrite-mediated cellular injury. Proc Natl Acad Sci U S A 93, 6770-6774, PubMed: 8692893
93 Noris, M. et al. (2004) L-arginine depletion in preeclampsia orients nitric oxide synthase toward oxidant species. Hypertension 43, 614-622, PubMed: 14744923
94 Baker, P.N., Davidge, S.T. and Roberts, J.M. (1995) Plasma from women with preeclampsia increases endothelial cell nitric oxide production. Hypertension 26, 244-248, PubMed: 7543451
95 Beckman, J.S. and Koppenol, W.H. (1996) Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. Am J Physiol 271, C1424-1437, PubMed: 8944624
96 Huie, R.E. and Padmaja, S. (1993) The reaction of no with superoxide. Free Radic Res Commun 18, 195-199, PubMed: 8396550
97 Cooke, C.L. and Davidge, S.T. (2002) Peroxynitrite increases iNOS through NF-kappaB and decreases prostacyclin synthase in endothelial cells. Am J Physiol Cell Physiol 282, C395-402, PubMed: 11788351
98 Gillham, J.C., Kenny, L.C. and Baker, P.N. (2003) An overview of endothelium-derived hyperpolarising factor (EDHF) in normal and compromised pregnancies. Eur J Obstet Gynecol Reprod Biol 109, 2-7, PubMed: 12818435
99 Busse, R. et al. (2002) EDHF: bringing the concepts together. Trends Pharmacol Sci 23, 374-380, PubMed: 12377579
100 Shimokawa, H. et al. (1996) The importance of the hyperpolarizing mechanism increases as the vessel size decreases in endothelium-dependent relaxations in rat mesenteric circulation. J Cardiovasc Pharmacol 28, 703-711, PubMed: 8945685
101 Kenny, L.C. et al. (2002) Differential mechanisms of endothelium-dependent vasodilator responses in human myometrial small arteries in normal pregnancy and pre-eclampsia. Clin Sci (Lond) 103, 67-73, PubMed: 12095405
102 Kenny, L.C. et al. (2002) The role of gap junctions in mediating endothelium-dependent responses to bradykinin in myometrial small arteries isolated from pregnant women. Br J Pharmacol 136, 1085-1088, PubMed: 12163339
103 Luksha, L., Nisell, H. and Kublickiene, K. (2004) The mechanism of EDHF-mediated responses in subcutaneous small arteries from healthy pregnant women. Am J Physiol Regul Integr Comp Physiol 286, R1102-1109, PubMed: 14751845
104 Luksha, L., Nisell, H. and Kublickiene, K. (2005) Functional and morphological signs of endothelial dysfunction in preeclampsia: role of endothelium-derived hyperpolarizing factor (EDHF). J Soc Gyn Invest 12, 274A (Abstract)
105 Brown, M.A., Wang, J. and Whitworth, J.A. (1997) The renin-angiotensin-aldosterone system in pre-eclampsia. Clin Exp Hypertens 19, 713-726, PubMed: 9247750
106 Baylis, C. et al. (1998) Recent insights into the roles of nitric oxide and renin-angiotensin in the pathophysiology of preeclamptic pregnancy. Semin Nephrol 18, 208-230, PubMed: 9541274
107 Davison, J.M. and Dunlop, W. (1980) Renal hemodynamics and tubular function normal human pregnancy. Kidney Int 18, 152-161, PubMed: 7003196
108 Skinner, S.L., Lumbers, E.R. and Symonds, E.M. (1972) Analysis of changes in the renin-angiotensin system during pregnancy. Clin Sci 42, 479-488, PubMed: 4336430
109 Wier, R.J. et al. (1975) Relationship between plasma renin, renin-substrate, angiotensin II, aldosterone and electrolytes in normal pregnancy. J Clin Endocrinol Metab 40, 108-115, PubMed: 234473
110 Hanssens, M. et al. (1991) Angiotensin II levels in hypertensive and normotensive pregnancies. Br J Obstet Gynaecol 98, 155-161, PubMed: 2004051
111 Nielsen, A.H., Schauser, K.H. and Poulsen, K. (2000) Current topic: the uteroplacental renin-angiotensin system. Placenta 21, 468-477, PubMed: 10940196
112 Shah, D.M. (2005) Role of the renin-angiotensin system in the pathogenesis of preeclampsia. Am J Physiol Renal Physiol 288, F614-625, PubMed: 15753325
113 Morgan, T. et al. (1997) Angiotensinogen T235 expression is elevated in decidual spiral arteries. J Clin Invest 100, 1406-1415, PubMed: 9294106
114 Weiss, D., Sorescu, D. and Taylor, W.R. (2001) Angiotensin II and atherosclerosis. Am J Cardiol 87, 25C-32C, PubMed: 11334765
115 Arenas, I.A. et al. (2004) Angiotensin II-induced

Accession information: DOI: 10.1017/S1462399406010465; Vol. 8; Issue 3; 27 January 2006
©2006 Cambridge University Press

https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

MMP-2 release from endothelial cells is mediated by TNF-alpha. Am J Physiol Cell Physiol 286, C779-784, PubMed: 14644777
116 Pawlak, M.A. and Macdonald, G.J. (1992) Altered number of platelet angiotensin II receptors in relation to plasma agonist concentrations in normal and hypertensive pregnancy. J Hypertens 10, 813-819, PubMed: 1325514
117 Wallukat, G. et al. (1999) Patients with preeclampsia develop agonistic autoantibodies against the angiotensin AT1 receptor. J Clin Invest 103, 945-952, PubMed: 10194466
118 Dechend, R. et al. (2000) AT(1) receptor agonistic antibodies from preeclamptic patients cause vascular cells to express tissue factor. Circulation 101, 2382-2387, PubMed: 10821814
119 Akishita, M. et al. (2000) Inflammation influences vascular remodeling through AT2 receptor expression and signaling. Physiol Genomics 2, 13-20, PubMed: 11015577
120 McMullen, J.R. et al. (1999) Interactions between AT1 and AT2 receptors in uterine arteries from pregnant ewes. Eur J Pharmacol 378, 195-202, PubMed: 10478632
121 Doering, T.P. et al. (1998) The role of AT1 angiotensin receptor activation in the pathogenesis of preeclampsia. Am J Obstet Gynecol 178, 1307-1312, PubMed: 9662316
122 Martinovic, J. et al. (2001) Fetal toxic effects and angiotensin-II-receptor antagonists. Lancet 358, 241-242, PubMed: 11480433
123 Easterling, T.R. et al. (2000) Low-dose, short-acting, angiotensin-converting enzyme inhibitors as rescue therapy in pregnancy. Obstet Gynecol 96, 956-961, PubMed: 11084185
124 Matthiesen, L. et al. (2005) Immunology of preeclampsia. Chem Immunol Allergy 89, 49-61, PubMed: 16129952
125 Hamai, Y. et al. (1997) Evidence for an elevation in serum interleukin-2 and tumor necrosis factor-alpha levels before the clinical manifestations of preeclampsia. Am J Reprod Immunol 38, 89-93, PubMed: 9272206
126 Williams, M.A. et al. (1999) Maternal second trimester serum tumor necrosis factor-alpha-soluble receptor p55 (sTNFp55) and subsequent risk of preeclampsia. Am J Epidemiol 149, 323-329, PubMed: 10025474
127 Madazli, R. et al. (2003) Maternal plasma levels of cytokines in normal and preeclamptic pregnancies and their relationship with diastolic blood pressure and fibronectin levels. Acta Obstet Gynecol Scand 82, 797-802, PubMed: 12911439
128 Anim-Nyame, N. et al. (2003) Microvascular permeability is related to circulating levels of tumour necrosis factor-alpha in pre-eclampsia. Cardiovasc Res 58, 162-169, PubMed: 12667958
129 Kern, P.A. et al. (1995) The expression of tumor necrosis factor in human adipose tissue. Regulation by obesity, weight loss, and relationship to lipoprotein lipase. J Clin Invest 95, 2111-2119, PubMed: 7738178
130 O'Brien, T.E., Ray, J.G. and Chan, W.S. (2003) Maternal body mass index and the risk of preeclampsia: a systematic overview. Epidemiology 14, 368-374, PubMed: 12859040
131 Yoshizumi, M. et al. (1993) Tumor necrosis factor downregulates an endothelial nitric oxide synthase mRNA by shortening its half-life. Circ Res 73, 205-209, PubMed: 7685252
132 Li, J.M. et al. (2002) Essential role of the NADPH oxidase subunit p47(phox) in endothelial cell superoxide production in response to phorbol ester and tumor necrosis factor-alpha. Circ Res 90, 143-150, PubMed: 11834706
133 Perkins, D.J. and Kniss, D.A. (1997) Tumor necrosis factor-alpha promotes sustained cyclooxygenase-2 expression: attenuation by dexamethasone and NSAIDs. Prostaglandins 54, 727-743, PubMed: 9440135
134 Marsden, P.A. and Brenner, B.M. (1992) Transcriptional regulation of the endothelin-1 gene by TNF-alpha. Am J Physiol 262, C854-861, PubMed: 1566813
135 Taylor, R.N. et al. (1990) Women with preeclampsia have higher plasma endothelin levels than women with normal pregnancies. J Clin Endocrinol Metab 71, 1675-1677, PubMed: 2229324
136 Pober, J.S. et al. (1986) Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. J Immunol 137, 1893-1896, PubMed: 3091693
137 Bevilacqua, M.P. et al. (1984) Interleukin 1 (IL-1) induces biosynthesis and cell surface expression of procoagulant activity in human vascular endothelial cells. J Exp Med 160, 618-623, PubMed: 6332168
138 Nawroth, P.P. and Stern, D.M. (1986) Modulation of endothelial cell hemostatic properties by tumor necrosis factor. J Exp Med 163, 740-745, PubMed: 3753996
139 van Hinsbergh, V.W. et al. (1988) Tumor necrosis factor increases the production of plasminogen

Accession information: DOI: 10.1017/S1462399406010465; Vol. 8; Issue 3; 27 January 2006
©2006 Cambridge University Press

https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

activator inhibitor in human endothelial cells in vitro and in rats in vivo. Blood 72, 1467-1473, PubMed: 3140909
140 Giardina, J.B. et al. (2002) TNF-alpha enhances contraction and inhibits endothelial NO-cGMP relaxation in systemic vessels of pregnant rats. Am J Physiol Regul Integr Comp Physiol 283, R130-143, PubMed: 12069938
141 Vizi, E.S. et al. (2001) Enhanced tumor necrosis factor-alpha-specific and decreased interleukin-10-specific immune responses to LPS during the third trimester of pregnancy in mice. J Endocrinol 171, 355-361, PubMed: 11691656
142 Vaisman, N., Gospodarowicz, D. and Neufeld, G. (1990) Characterization of the receptors for vascular endothelial growth factor. J Biol Chem 265, 19461-19466, PubMed: 2246236
143 Terman, B.I. et al. (1992) Identification of the KDR tyrosine kinase as a receptor for vascular endothelial cell growth factor. Biochem Biophys Res Commun 187, 1579-1586, PubMed: 1417831
144 Morbidelli, L. et al. (1996) Nitric oxide mediates mitogenic effect of VEGF on coronary venular endothelium. Am J Physiol 270, H411-415, PubMed: 8769777
145 Ku, D.D. et al. (1993) Vascular endothelial growth factor induces EDRF-dependent relaxation in coronary arteries. Am J Physiol 265, H586-592, PubMed: 8368362
146 Min, J.K. et al. (2005) Hepatocyte growth factor suppresses vascular endothelial growth factor-induced expression of endothelial ICAM-1 and VCAM-1 by inhibiting the nuclear factor-kappaB pathway. Circ Res 96, 300-307, PubMed: 15637298
147 Shibuya, M. (2001) Structure and function of VEGF/VEGF-receptor system involved in angiogenesis. Cell Struct Funct 26, 25-35, PubMed: 11345501
148 Clark, D.E. et al. (1998) A vascular endothelial growth factor antagonist is produced by the human placenta and released into the maternal circulation. Biol Reprod 59, 1540-1548, PubMed: 9828203
149 Zhou, Y. et al. (2002) Vascular endothelial growth factor ligands and receptors that regulate human cytotrophoblast survival are dysregulated in severe preeclampsia and hemolysis, elevated liver enzymes, and low platelets syndrome. Am J Pathol 160, 1405-1423, PubMed: 11943725
150 Vuorela, P. et al. (2000) Amniotic fluid—soluble vascular endothelial growth factor receptor-1 in preeclampsia. Obstet Gynecol 95, 353-357, PubMed: 10711543
151 Koga, K. et al. (2003) Elevated serum soluble vascular endothelial growth factor receptor 1 (sVEGFR-1) levels in women with preeclampsia. J Clin Endocrinol Metab 88, 2348-2351, PubMed: 12727995
152 Tsatsaris, V. et al. (2003) Overexpression of the soluble vascular endothelial growth factor receptor in preeclamptic patients: pathophysiological consequences. J Clin Endocrinol Metab 88, 5555-5563, PubMed: 14602804
153 Levine, R.J. et al. (2004) Circulating angiogenic factors and the risk of preeclampsia. N Engl J Med 350, 672-683, PubMed: 14764923
154 Levine, R.J. et al. (2005) Urinary placental growth factor and risk of preeclampsia. Jama 293, 77-85, PubMed: 15632339
155 Visse, R. and Nagase, H. (2003) Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 92, 827-839, PubMed: 12730128
156 Nagase, H. and Woessner, J.F., Jr. (1999) Matrix metalloproteinases. J Biol Chem 274, 21491-21494, PubMed: 10419448
157 Fernandez-Patron, C. et al. (2000) Vascular matrix metalloproteinase-2-dependent cleavage of calcitonin gene-related peptide promotes vasoconstriction. Circ Res 87, 670-676, PubMed: 11029402
158 Galis, Z.S. and Khatri, J.J. (2002) Matrix metalloproteinases in vascular remodeling and atherogenesis: the good, the bad, and the ugly. Circ Res 90, 251-262, PubMed: 11861412
159 Lindsey, M.L. (2004) MMP induction and inhibition in myocardial infarction. Heart Fail Rev 9, 7-19, PubMed: 14739764
160 Fernandez-Patron, C., Radomski, M.W. and Davidge, S.T. (1999) Vascular matrix metalloproteinase-2 cleaves big endothelin-1 yielding a novel vasoconstrictor. Circ Res 85, 906-911, PubMed: 10559137
161 Sawicki, G. et al. (1997) Release of gelatinase A during platelet activation mediates aggregation. Nature 386, 616-619, PubMed: 9121586
162 Narumiya, H. et al. (2001) Matrix metalloproteinase-2 is elevated in the plasma of women with preeclampsia. Hypertens Pregnancy 20, 185-194, PubMed: 12044329
163 Myers, J.E. et al. (2005) MMP-2 levels are elevated in the plasma of women who subsequently develop preeclampsia. Hypertens Pregnancy 24, 103-115, PubMed: 16036395

Accession information: DOI: 10.1017/S1462399406010465; Vol. 8; Issue 3; 27 January 2006
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https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

164 Kolben, M. et al. (1996) Proteases and their inhibitors are indicative in gestational disease. Eur J Obstet Gynecol Reprod Biol 68, 59-65, PubMed: 8886683
165 Merchant, S.J. et al. (2004) The effects of preeclampsia and oxygen environment on endothelial release of matrix metalloproteinase-2. Hypertens Pregnancy 23, 47-60, PubMed: 15117600
166 Vatten, L.J. et al. (2003) Intrauterine exposure to preeclampsia and adolescent blood pressure, body size, and age at menarche in female offspring. Obstet Gynecol 101, 529-533, PubMed: 12636958
167 Robbesyn, F. et al. (2005) High-density lipoproteins prevent the oxidized low-density lipoprotein-induced endothelial growth factor receptor activation and subsequent matrix metalloproteinase-2 upregulation. Arterioscler Thromb Vasc Biol 25, 1206-1212, PubMed: 15817880
168 Rajagopalan, S. et al. (1996) Reactive oxygen species produced by macrophage-derived foam cells regulate the activity of vascular matrix metalloproteinases in vitro. Implications for atherosclerotic plaque stability. J Clin Invest 98, 2572-2579, PubMed: 8958220
169 Okamoto, T. et al. (2001) Activation of matrix metalloproteinases by peroxynitrite-induced protein S-glutathiolation via disulfide S-oxide formation. J Biol Chem 276, 29596-29602, PubMed: 11395496
170 Sudo, N. et al. (1993) Plasma endothelin-1 and big endothelin-1 levels in women with pre-eclampsia. Acta Endocrinol (Copenh) 129, 114-120, PubMed: 8372594
171 Martinez, A. et al. (2004) Matrix metalloproteinase-2 cleavage of adrenomedullin produces a vasoconstrictor out of a vasodilator. Biochem J 383, 413-418, PubMed: 15307819
172 Schiff, E. et al. (1995) Plasma and placental calcitonin gene-related peptide in pregnancies complicated by severe preeclampsia. Am J Obstet Gynecol 173, 1405-1409, PubMed: 7503177
173 Minegishi, T. et al. (1999) Adrenomedullin and atrial natriuretic peptide concentrations in normal pregnancy and pre-eclampsia. Mol Hum Reprod 5, 767-770, PubMed: 10421805
174 Hao, L. et al. (2004) Agonist-induced activation of matrix metalloproteinase-7 promotes vasoconstriction through the epidermal growth factor-receptor pathway. Circ Res 94, 68-76, PubMed: 14656925
175 Chew, D.K., Conte, M.S. and Khalil, R.A. (2004) Matrix metalloproteinase-specific inhibition of Ca2+ entry mechanisms of vascular contraction. J Vasc Surg 40, 1001-1010, PubMed: 15557917
176 Fernandez-Patron, C., Radomski, M.W. and Davidge, S.T. (2000) Role of matrix metalloproteinase-2 in thrombin-induced vasorelaxation of rat mesenteric arteries. Am J Physiol Heart Circ Physiol 278, H1473-1479, PubMed: 10775124
177 Jeyabalan, A. et al. (2003) Essential role for vascular gelatinase activity in relaxin-induced renal vasodilation, hyperfiltration, and reduced myogenic reactivity of small arteries. Circ Res 93, 1249-1257, PubMed: 14593002

Accession information: DOI: 10.1017/S1462399406010465; Vol. 8; Issue 3; 27 January 2006
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https://doi.org/10.1017/S1462399406010465 Published online by Cambridge University Press

Further reading, resources and contacts

Davidge, S.T. (2000) Antioxidants and vascular function in preeclampsia. In Handbook of Hypertension (Birkenhager, W.H. and Reid, J.L., eds), pp. 91-112, Elsevier

Gillham, J.C., Kenny, L.C. and Baker, P.N. (2003) An overview of endothelium-derived hyperpolarising factor (EDHF) in normal and compromised pregnancies. Eur J Obstet Gynecol Reprod Biol 109, 2-7, PubMed: 12818435

Granger, J.P. et al. (2002) Pathophysiology of preeclampsia: linking placental ischemia/hypoxia with microvascular dysfunction. Microcirculation 9, 147-160, PubMed: 12080413

Horstman, L.L. et al. (2004) Endothelial microparticles as markers of endothelial dysfunction. Front Biosci 9, 1118-1135, PubMed: 14977533

Kashiwagi, M., Zimmermann, R. and Beinder, E. (2003) Pathophysiology of pre-eclampsia: update on the role of nitric oxide. Curr Hypertens Rep 5, 493-497, PubMed: 14594570

Masse, J. et al. (2002) Pathophysiology and maternal biologic markers of preeclampsia. Endocrine 19, 113-125, PubMed: 12583608

Maynard, S.E. et al. (2005) Soluble Fms-like tyrosine kinase 1 and endothelial dysfunction in the pathogenesis of preeclampsia. Pediatr Res 57, 1R-7R, PubMed: 15817508

Poston, L., Raijmakers, M. and Kelly, F. (2004) Vitamin E in preeclampsia. Ann N Y Acad Sci 1031, 242-248, PubMed: 15753150

Roberts, J.M. and Cooper, D.W. (2001) Pathogenesis and genetics of pre-eclampsia. Lancet 357, 53-56, PubMed: 11197372

Roberts, J.M. and Lain, K.Y. (2002) Recent insights into the pathogenesis of pre-eclampsia. Placenta 23, 359-372, PubMed: 12061851

Sargent, I.L. et al. (2003) Trophoblast deportation and the maternal inflammatory response in pre-eclampsia. J Reprod Immunol 59, 153-160, PubMed: 12896819

Features associated with this article

Figures

Figure 1. Role of oxidative stress in the mediation of endothelial cell dysfunction in preeclampsia.
Figure 2. L-arginine depletion generates superoxide by uncoupling of eNOS.

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