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Placental ischemia and cardiovascular dysfunction in preeclampsia and beyond: making the connections

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Abstract

Hypertensive disorders of pregnancy continue to be a significant source of maternal and fetal morbidity and mortality, and recent evidence suggests that the incidence of preeclampsia (PE) is increasing. Recent epidemiological studies indicate that the effects of PE may persist long after pregnancy, in both the mother and the offspring, as increased incidence of cardiovascular disease. The last decade has produced new insights into the pathogenesis of PE. The initiating event in PE appears to be impaired placental perfusion and subsequent placental ischemia, which results in the elaboration of numerous factors. Factors such as soluble fms-like tyrosine kinase-1, soluble endoglin and the angiotensin II type-1 receptor autoantibodies contribute to maternal endothelial and cardiovascular dysfunction, marked by increased reactive oxygen species and decreased bioavailable VEGF, nitric oxide and prostacyclin. However, the importance of the various endothelial and humoral factors that mediate these changes during PE remain to be elucidated.

Keywords

cardiac; cytokines; pregnancy; VEGF

Clinical significance of the hypertensive disorders of pregnancy

Preeclampsia (PE) is a pregnancy-specific syndrome characterized by new-onset hypertension and proteinuria manifesting after 20 weeks of gestation, which may progress and cause injury to the blood vessels of major organs, such as the liver and the brain. The hepatic and neuro logical complications of PE make it a potentially deadly disease, especially when tertiary obstetrical care is lacking. Consequently, PE remains a considerable obstetric problem and a significant source of maternal and neonatal morbidity and mortality [1].

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While PE and related hypertensive disorders of pregnancy continue to affect approximately 8% of all pregnancies, the incidence of PE has seen a 40% increase in recent years [2]. Despite numerous studies that have characterized the preeclamptic syndrome and a suite of known contributing factors [1], the mechanisms underlying the pathophysiology of this troubling condition remain nebulous. Moreover, the only known cure is delivery of the placenta, after which symptoms typically resolve within 48-72 h.

Recently, it has been recognized that women who suffer PE are at a greater risk for cardiovascular and end-stage renal disease (ESRD) than nonpreeclamptic women and the men who fathered those preeclamptic pregnancies [3,4]. Moreover, accumulating data suggest that higher concentrations of circulating factors may contribute to the pathophysiology of the preeclamptic syndrome, and these factors may also predispose the maternal cardiovascular system to subsequent endothelial dysfunction in later life [4-8]. Hence, identifying the mechanisms that underlie the cardiovascular abnormalities during PE is an important endeavor towards realizing potential therapeutic regimens for women with hypertensive disorders of pregnancy. Although numerous other factors, including genetic, immunological, behavioral and environmental influences, have been implicated in the pathogenesis of PE [1], the main focus of this review is to describe the connections between placental ischemia and the cardiovascular dysfunction that is widely recognized as a part of the PE syndrome.

Clinical characteristics of the hypertensive disorders of pregnancy

Normal pregnancy is a chronic state of volume expansion and mild glucose intolerance that is characterized by marked cardiovascular and metabolic adaptations, which are required to support proper fetal growth and development, ultimately culminating in a successful pregnancy [9]. These adaptations, which have been reported in both humans and rats, include increased plasma volume, stroke volume (SV), left ventricular (LV) hypertrophy, decreased total peripheral resistance (TPR) and moderate insulin resistance [9-11]. By contrast, pregnancies affected by PE are often characterized by increased uterine vascular resistance (and reduced uteroplacental blood flow), increased TPR and mean arterial pressure (MAP), diastolic dysfunction indicated by a decreased early-to-late transmitral flow velocity ratio (E/A ratio), a blunting of the normal plasma volume expansion and decreased SV [12-14].

Some clinical studies in preeclamptic patients have reported increased LV mass [15] with signs of diastolic dysfunction, characterized by a decreased E/A ratio, a clinical indicator of the condition [16], when compared with normotensive pregnant women [15,17]. Although these observations are not without controversy, nonetheless they raise interesting questions. While the underlying cause of diastolic dysfunction in PE is unclear, diastolic dysfunction in hypertensive men and nonpregnant women appears to be related to increased ventricular fibrosis [18]. Considering the reported pathological hypertrophy associated with PE [15], alterations in the myocardium remain a possibility.

Figure 1 illustrates an intriguing hypothesis raised by these observations, whereby the aforementioned alterations in cardiovascular physiology could have a deleterious impact on the maternal cardiovascular system in later life, as recent studies have shown that an increased risk of cardiovascular disease is a sequelae of PE [7,8]. Clearly, further studies are needed to evaluate the possible links between PE and the increased risk for subsequent cardiovascular disease in women.

Long-term consequences of preeclampsia

Since the 1960s, it has been observed that formerly preeclamptic women are at increased risk for hypertension and cardiovascular disease in later life [19]. While there have been dissenting reports in the literature, the weight of evidence appears to be in favor of a link between PE and

subsequent cardiovascular disease in the mother and growth-restricted offspring [4-8,19-22]. There are largely two interpretations regarding these observations. The first is that PE is the result of a failed stress test (i.e., pregnancy) for an individual with predisposing factors to cardiovascular disease, and manifestation of disease in later life is related more to the predisposing risk factors than a direct effect of PE. Alternatively, PE may induce changes in the maternal vasculature that in turn predispose to negative cardiovascular consequences in later life.

Increasing evidence supports the idea that women who have had a preeclamptic pregnancy are more likely to have elevations in markers of inflammation, such as C-reactive protein and dyslipoproteinemia, and are at increased risk for ESRD and cardiovascular disease [4-8]. Recent work also suggests that alterations in circulating factors and inflammatory markers (e.g., soluble fms-like tyrosine kinase-1 [sFlt-1], soluble endoglin [sEng] and cytokines) are not only likely to play a significant role in the preeclamptic syndrome, but may also contribute to the predisposition of the maternal cardiovascular system to subsequent endothelial dysfunction [4-8,20-22]. It also appears that these long-term risks are greater than gestational hypertension for women who had PE.

The time of onset of PE may be an important factor in the long-term health risks associated with this syndrome. Using data obtained from the Medical Birth Registry of Norway and the Norwegian Renal Registry, Viske *et al.* have recently shown that women who have had PE are at increased risk of developing ESRD. Furthermore, the authors reported that having a low-birthweight baby also increased the risk of the mother having subsequent ESRD. Late-term PE is less commonly associated with reduced fetal growth and may even result in excessive fetal growth. This suggests that preterm PE (typically associated with reduced fetal growth) may be more strongly linked to long-term health issues in the mother than late-term PE. Finally, preterm birth, independent of PE, is also associated with a subsequently increased maternal risk of cardiovascular disease. These observations raise the possibility that perhaps a common vascular pathology results in an increased rise for preterm PE, preterm birth and subsequent cardiovascular disease.

Experimental studies are relatively few in this area and, given the large number of experimental models (genetic and otherwise) that have been developed for cardiovascular disease, it seems surprising that there remains very few spontaneously arising animal models of PE. While there appears to be a dearth of experimental data on the maternal sequelae of PE, there are numerous studies on the offspring of hypertensive pregnancies [23-27]. Using a model of placental ischemia-induced hypertension during pregnancy, Alexander *et al.* have shown that the offspring of hypertensive rat dams have elevated blood pressure [23] and preliminary studies indicate that those rat dams have persistent deficits in endothelial function [Gilbert JS; Unpublished Data]. Alternatively, using a hypertensive rat model, Gilbert *et al.* have shown that moderate exercise during hypertensive pregnancy in the spontaneously hypertensive rat attenuates hypertension in the offspring, whereas excessive exercise exacerbates hypertension in the offspring [27]. Hence, it is possible that environmental factors, such as exercise, can counteract or exacerbate the effects of hypertension during pregnancy on the offspring.

Placental ischemia/hypoxia & the etiology of preeclampsia

Although the pathophysiology of PE remains unclear, placental ischemia/hypoxia is widely regarded as a key factor [28,29]. Perhaps the foremost hypothesis regarding the initiating event in PE is that reduced placental perfusion leads to widespread dysfunction of the maternal vascular endothelium. Inadequate trophoblast invasion, leading to incomplete remodeling of the uterine spiral arteries, is considered to be a primary cause of the placental ischemia [29]. Thus, the poorly perfused and hypoxic placenta is thought to synthesize and release elevated

amounts of factors, such as sFlt-1 and sEng [30-33]. Figure 2 illustrates a model in which the ischemic placenta may elaborate a combination of factors that are thought to induce widespread activation and/or dysfunction of the maternal endothelium in vessels of the kidney and other organs, which ultimately results in hypertension. Moreover, since the hypertension and greater levels of circulating factors associated with PE remit after delivery, the placenta probably plays a major role in the pathogenesis of this disease.

Placental hypoxia & secretion of cardiovascular disruptors

Several lines of evidence support the hypothesis that the ischemic placenta contributes to endothelial cell dysfunction in the maternal vasculature by inducing an alteration in the balance of circulating levels of angiogenic/antiangiogenic factors, such as VEGF and PlGF, sFlt-1 and sEng [31,32,34-41]. Although recent data suggest circulating sFlt-1 concentrations may presage the clinical onset of preeclamptic symptoms [38,40,42,43], several studies indicate that placental hypoxia and poor placental perfusion may initiate this imbalance of angiogenic factors [31,32,44]. Nevertheless, it remains unclear whether impaired placental perfusion initiates preeclamptic symptoms, such as hypertension, endothelial dysfunction and elevated sFlt-1, or if pathologic overexpression of sFlt-1 occurs initially and is followed by impaired placental blood flow [45].

Recent progress in animal models to study preeclampsia

The physiological mechanisms that mediate the alterations in cardiovascular and renal function that are requisite for a successful pregnancy have been studied in great detail. Nonetheless, experimental data investigating the pathogenesis of PE are limited because of the difficulties inherent to performing mechanistic studies in pregnant women. While several animal models have been developed to study PE, none completely represent the protean characteristics of the syndrome in humans. Furthermore, information on the mechanisms mediating the long-term increase in vascular resistance and arterial pressure associated with placental ischemia is lacking.

Several promising animal models of hypertension in pregnancy have been developed and characterized in recent years [30-33,46-53]. These include adenovirus delivery of sFlt-1 [30], sEng [33], and infusion of sFlt-1 [52,53] and IgG fractions purified from preeclamptic women and containing angiotensin II type I receptor (AT_1) autoantibodies (AA) [51], genetic and/or transgenic models [47-49,54], disruption of fluid balance [46] and placental ischemia [31,32, 50,55]. In addition to the physiological manifestations (e.g., hypertension and proteinuria), many of these models only have, at best, a single factor in common with the preeclamptic endocrine milieu. While these models, no doubt, have their utility, the limitation of studying the contribution of only a single factor to the preeclamptic syndrome must always be recognized.

Several genetic models that mimic the preeclamptic syndrome have been recently described. In their article, Davisson and colleagues discuss the BPH/5 murine model of hypertension during pregnancy [48]. The BPH/5 is an inbred subline generated from brother-sister matings of fully inbred BPH/2 mice over many generations, resulting in mild blood pressure elevation throughout adult life [56]. The etiology of blood pressure elevation in these mice, as in humans, remains incompletely defined [56]. In addition to developing late gestational hypertension and proteinuria, BPH/5 mice also exhibit impaired placental development prior to the manifestation of maternal symptoms, supporting a causative role for the placenta in this model. Moreover, recent work in their laboratory suggests that oxidative stress may play a significant role in this model, as treatment with Tempol reduces reactive oxygen species (ROS) levels and decreased blood pressure and proteinuria in those mice [57].

Another recently described murine model of PE uses mice that have a reduced expression of catechol-*O*-methyltransferase (COMT), an enzyme requisite for the production of 2-methoxyestradiol (2-ME), an estrogen metabolite that is reportedly decreased in preeclamptic women [58]. The authors report that the pregnant $COMT^{-/-}$ mice show a moderate rise in blood pressure and mild proteinuria. Furthermore, the authors suggest that decreased COMT and 2-ME, possibly due to variation in the *Comt* genotype, could favor elevated levels of hypoxia inducible factor-1α, which in turn would increase sFlt-1, leading to angiogenic dysfunction and placental insufficiency. Although the precise role of placental and/or decidual COMT needs further investigation, the initial results from Kanasaki *et al.* provide a basis for future studies.

The experimental induction of chronic uteroplacental ischemia is a promising animal model to study potential mechanisms of PE, since reductions in uteroplacental blood flow in a variety of animals leads to a hypertensive state that has many of the manifestations present in women with preterm PE [11,31,32,50,59,60]. It appears that this model of placental ischemia more closely represents early- rather than late-onset PE. The former is characterized by fetal growth restriction, hypertension and proteinuria, while the latter is not thought to be closely associated with placental ischemia or growth-restricted fetuses. Hence, a considerable strength of the placental ischemia model is that it allows mechanistic investigation of the preterm ischemic placenta, the factors it elaborates and the contribution of these factors to the associated renal and cardiovascular dysfunction.

Cardiovascular dysfunction in models of preeclampsia

The relationship between reduced uteroplacental perfusion pressure (RUPP) and hypertension during pregnancy has been demonstrated in a variety of animals, with the vast majority of the work performed on the rat [11,32,50,55,59,60]. During late gestation, RUPP rats display increased MAP, decreased glomerular filtration rate, decreased renal pressure natriuresis, decreased renal plasma flow and proteinuria, and endothelial dysfunction [11,32,50,55,59, 60]. Sholook *et al.* reported recently that pregnant RUPP rats have increased total peripheral resistance, decreased cardiac index and decreased uteroplacental blood flow [60]. In addition, previous work by Gutkowska *et al.* has shown increased collagen deposition in the left ventricle of the RUPP rat in late gestation [61]. Viewed in concert, the RUPP model displays an array of cardiovascular dysfunction similar to what is observed in preeclamptic women [12,60,62, 63].

Mediators of cardiovascular dysfunction in preeclampsia

The maternal vascular endothelium appears to be an important target of factors that are triggered by placental ischemia/hypoxia in PE. The endothelium is a single-cell lining that covers the luminal side of blood vessels. This strategic location permits it to respond to alterations in hemodynamics and humoral factors by synthesizing and releasing vasoactive substances. Thus, a critical balance exists between endothelium-derived relaxing and contracting factors that maintains vascular homeostasis. When this delicate balance is disrupted, the vasculature is predisposed to vasoconstriction, leukocyte adhesion, mitogenesis, pro-oxidation and vascular inflammation [64,65]. Furthermore, markers of endothelial dysfunction may serve as predictors of the syndrome in women that develop PE, since many are often elevated weeks prior to observance of clinical manifestations. Since mechanistic studies in pregnant women are limited, the role of a variety of substances that are, in the large part, secreted by the ischemic placenta and mediate the cardiovascular dysfunction observed experimentally by chronic RUPP will be the primary focus of the remainder of this review.

Angiogenic factors

Perhaps the most prominent molecule recently proposed to play a key role in the pathogenesis of PE is sFlt-1. Although VEGF is widely recognized for its potent angiogenic and mitogenic effects, it has also been recognized as an important contributor to cell homeostasis; in particular with respect to the balance of oxidative stress [66,67]. The soluble and endogenously produced sFlt-1 largely originates from the placenta due to alternative splicing, and may disrupt VEGF signaling, either by binding VEGF and PlGF or by forming heterodimers that may block access to the other VEGF receptor, the kinase insert domain receptor [68]. While sFlt-1 is not a vasoconstrictor, it does significantly inhibit the dilatory actions of both VEGF and PlGF *in vitro*, and chronic elevations in circulating concentrations result in increased blood pressure [26,30]. Considerable clinical evidence has accumulated, indicating that PE is strongly linked to an imbalance between proangiogenic (VEGF and PlGF) and antiangiogenic (sFlt-1) factors in the maternal circulation [30,34-40]. Both plasma and amniotic fluid concentrations of sFlt-1 are elevated in preeclamptic patients, as well as placental sFlt-1 mRNA expression [26,30, 40,45,69-71]. In addition, higher levels of sFlt-1 are associated with a drop in circulating levels of free PlGF and VEGF in women with PE [38]. Recently, studies have reported that elevated sFlt-1 may have a predictive value in diagnosing PE, as concentrations seem to increase before manifestation of overt symptoms (e.g., hypertension and protein uria) [38,40]. Alternatively, it has been proposed that the ratio of sFlt-1 to PlGF may be the most accurate predictor of PE [39].

Recent experimental studies suggest that elevation of sFlt-1 may result in reductions in circulating PlGF and VEGF. Maynard *et al.* have shown that exogenous administration of sFlt-1 into pregnant rats via adenovirus-mediated gene transfer results in increased arterial pressure and proteinuria, and decreased plasma free VEGF and PlGF concentrations, similar to that observed in the preeclamptic patients [30]. The authors also showed that sFlt-1 impaired VEGF- and PlGF-induced vasorelaxation [30]. Subsequently, similar observations using adenovirus transfection have been reported in the mouse [26]. Recently, Bridges *et al.* have reported a model of increased circulating sFlt-1 in pregnant rats, using recombinant sFlt-1 delivered via osmotic mini-pump placed intraperitoneally, and found that the dams are hypertensive, have smaller placentae and fetuses, are proteinuric and show evidence of impaired vascular function on day 18 of gestation [53]. While these studies have established the importance of sFlt-1 as a preeclamptic factor, further studies are needed to elucidate mechanisms governing the expression and actions of this protein.

Li and coworkers have shown that VEGF infusion attenuates the increased blood pressure and renal damage observed in pregnant rats overexpressing sFlt-1 [72]. Thus, from this study, it can be gleaned that sFlt-1 plays a role in hypertension and renal dysfunction in PE; however, these observations did not shed any light on the matter of pathologic sFlt-1 overexpression. To this end, Gilbert *et al.* have recently demonstrated that utero placental ischemia increased plasma and placental sFlt-1, and this was associated with decreased VEGF and PlGF in the late gestation pregnant rat [32]. Similarly, Makris *et al.* have recently shown that uteroplacental ischemia in the baboon results in hypertension, proteinuria and increased circulating sFlt-1 [31]. Thus, placental ischemia models of PE have many of the features common in preeclamptic women and provide valuable insights regarding mechanisms of hypertension development during pregnancy.

Another antiangiogenic factor, sEng, has also been implicated as a factor in the pathogenesis of PE [33,73]. Endoglin is a component of the TGF-β receptor complex and is a hypoxia-inducible protein associated with cellular proliferation and nitric oxide (NO) signaling [74, 75]. sEng has also been shown to be anti angiogenic, as it is thought to impair TGF-β_1 binding to cell surface receptors [33,74]. Recent work investigating sEng has furthered progression with respect to the role of anti-angiogenic factors in PE. Venkatesha *et al.* have shown that

sEng inhibits *in vitro* endo thelial cell-tube formation to a similar extent as sFlt-1. They have also shown that increasing circulating sEng in pregnant rats, by way of adenovirus transfection, results in many features of the preeclamptic syndrome [33]. Moreover, a synergistic effect was observed when sEng was coexpressed with sFlt-1 in pregnant rats such that, in concert, sFlt-1 and sEng exacerbated the effects of either factor alone and resulted in fetal growth restriction, severe hypertension and nephritic range proteinuria [33]. Recent clinical evidence also suggests that sEng may also presage the onset of PE [39]. Preliminary data from the RUPP model suggests that placental ischemia is a stimulus for sEng production in the placenta [Gilbert JS; Unpublished Observation]. It is also interesting to note that *in vitro* simvastatin appears to reduce expression of sFlt-1 and sEng in endothelial cells through a heme oxygenase-related mechansism [76]. Thus, there is compelling experimental evidence that complements clinical observations suggesting that sEng could be an important factor in the pathogenesis of PE.

Reactive oxygen species & oxidative stress

During states of elevated oxidative stress, an imbalance of pro-and antioxidant factors results in endothelial dysfunction, either by direct actions on the vasculature or through reductions in the bioavailability of vasorelaxing agents [77]. During PE, oxidative stress may result from interactions between the maternal component, which may include pre-existing conditions, such as obesity, diabetes and hyperlipidemia, and the placental component, which may involve production of lipid peroxides [78].

Reduced superoxide dismutase (SOD) levels and decreased SOD activity have been reported in the neutrophils and placentas of women with PE [77]. Clearly significant is the observation that diminished SOD occurs within both the maternal and placental components. As a result, there appears to be a decreased total anti-oxidant protective capacity in women with PE. Several important antioxidants are reportedly decreased in women with PE. Levels of vitamin C, vitamin A, vitamin E, β-carotene and glutathione, as well as iron-binding capacity, are lower in the maternal circulation of women with PE than women with a normal pregnancy [79]. Interestingly, supplementation of these nutrients has not been shown to ameliorate the incidence of PE in multicenter clinical trials and was associated with an increased risk of antenatal maternal hypertension [80,81].

Experimental data reveals that there is an intimate relationship between ROS, NO activity and blood pressure in rats [82]. Thus, it is not surprising that there is increased oxidative stress in the hypertensive pregnant RUPP rat [50]. While antioxidant treatment with vitamins C and E does not decrease blood pressure, the SOD mimetic tempol does attenuate RUPP hypertension [50,83]. Similarly, apocynin, an NADP(H) oxidase inhibitor, attenuates, but does not normalize, the increased blood pressure observed in RUPP hypertension, suggesting that there may be other pathways generating ROS in this model. While oxidative stress is implicated in the pathogenesis of PE, it remains unclear if it is a primary or secondary mediator of increased blood pressure and deranged renal function.

Renin-angiotensin system

The renin-angiotensin (Ang) system (RAS) plays an important role in the long-term regulation of renal function and arterial pressure during a variety of physiological and pathophysiological conditions, and pregnancy and PE are no exception [11]. Although levels of renin, Ang and aldosterone increase in normal pregnancy, blood pressure does not increase due to decreased sensitivity to Ang II. Conversely, in preeclamptic women, renin and aldosterone levels are often decreased, yet sensitivity to Ang II is increased [84]. Recent studies in preeclamptic women have revealed several exciting findings regarding the RAS. Abdalla and colleagues have shown that the AT_1 receptor forms heterodimers with the bradykinin B_2 receptor, resulting in enhanced Ang II sensitivity [85,86]. Furthermore, these authors have shown the AT_1-B_2

heterodimers are present in greater abundance in preeclamptic women, suggesting that this heterodimerization may play a part in the long-observed increased Ang II sensitivity in PE [85,86].

Another intriguing observation regarding the involvement of the RAS in the pathophysiology of PE is the demonstration of elevated circulating concentrations of an agonistic AA to the AT_1 receptor in preeclamptic women [87,88]. Interestingly, the AT_1-AA appears to be responsible for a variety of effects in several different tissues, ranging from increased intracellular Ca^{2+} mobilization to monocyte activation and stimulation of IL-6 production from mesangial cells [89-92]. Another effect that has recently been attributed to the AT_1 receptor is stimulation via calcineurin signaling of sFlt-1 expression from trophoblast cells but not endothelial cells [93]. Viewed in concert, these findings implicate AT_1 as a central mediator of several pathways in PE.

The specific mechanisms that lead to excess production, and the mechanisms whereby AT1-AA increases blood pressure during pregnancy, are currently under investigation. Recently, Linas *et al.* reported that placental ischemia in the rat is associated with increased circulating levels of AT_1-AA, suggesting, yet again, an important link with the ischemic placenta [94]. Zhou *et al.* have recently shown that infusion of either total IgG or affinity-purified AT_1-AA from women with PE into pregnant mice results in a condition that closely resembles PE [51]. They reported that the injected mice presented with most of the key features of the preeclamptic syndrome, including hypertension, proteinuria and glomerular endotheliosis (a classical renal lesion of PE), as well as placental abnormalities and growth-restricted fetuses. Moreover, these features were prevented by coinjection with losartan, an AT_1 receptor antagonist, or an antibody neutralizing seven-amino-acid epitope peptide [51]. While these initial findings are promising, further studies are needed to elucidate the exact mechanisms by which AT_1-AA contributes to the pathophysiology of PE.

Metabolic factors

Other comorbid conditions have been proposed as potential contributors to endothelial dysfunction in PE [95]. Recent studies have indicated a relationship between elements of the metabolic syndrome, such as elevated serum triglycerides and free fatty acids [95-97], insulin resistance [98-102] and glucose intolerance [103,104], and the occurrence of PE. In fact, several authors have suggested insulin resistance may presage the manifestation of PE [101, 103] while Thadhani *et al.* have proposed that insulin resistance during pregnancy may collude with other conditions, such as impaired angiogenesis, to generate a preeclamptic phenotype [105].

Fatty acids may contribute to endothelial dysfunction by serving as substrates to generate lipid peroxides, which are significantly increased in plasma from women with PE [106]. Therefore, the generation of free radicals, lipid peroxides and ROS may be an important mechanism contributing to endothelial dysfunction in PE [65]. Although plasma levels of lipids are elevated during normal pregnancy, plasma concentrations of both triglyceride-rich lipoproteins and nonesterified fatty acids are significantly increased in women who develop PE, relative to normal pregnant women [97,107]. This significantly elevated level of plasma triglycerides in preeclamptic women correlates with increased plasma concentrations of LDLs [108]. Recently, Magnussen and colleagues prospectively examined the association between standardized measurements of blood pressure and lipid concentrations before pregnancy and risk of PE [95]. The authors concluded that the cardiovascular risk factors present years before pregnancy were associated with elevated risk of PE and duly noted that their findings could not rule out the possibility that the preeclamptic process in itself may also contribute to cardiovascular risk [95]. Nevertheless, the nature of this correlative data has made it difficult to determine a causal effect for abnormal lipid metabolism in the pathogenesis of PE.

Gilbert *et al.* recently evaluated whether or not metabolic derangements were contributors or sequelae to placental ischemia in the RUPP rat. Data obtained from the RUPP model suggest that metabolic derangements similar to the metabolic syndrome X are not a direct consequence of placental ischemia [55]. In fact, it appears that factors associated with metabolic abnormalities may contribute to cardiovascular dysfunction in PE rather than resulting from poor placental perfusion [55]. Further studies are underway to determine what influence obesity may exert during experimental placental ischemia.

Expert commentary

Despite being one of the leading causes of maternal death and a major contributor to maternal and perinatal morbidity, the mechanisms responsible for the pathogenesis of PE remain enigmatic. Although it is largely held that the initiating event in PE involves impairment of placental perfusion, which in turn leads to placental ischemia and widespread maternal endothelial dysfunction, there are a wide variety of risk factors, such as nulliparity, extremes of maternal age, obesity and pre-existing diabetes or hypertension. The manner in which these risk factors interact with the gestational environment to result in PE continues to be a matter of debate.

Many investigators have also recently revisited the notion that occurrence of PE may be related to increased incidence of cardiovascular disease in later life. Figure 1 outlines possible pathways by which PE may be linked to increased risk of cardiovascular disease in later life. Whether or not there is a causal link between PE and subsequent disease, continued studies in this area will provide useful data regarding the underlying mechanisms during and after a preeclamptic pregnancy.

Recent years have seen the development and characterization of several innovative models for investigating hypertension associated with PE, as well as the initiation of collaborative efforts, such as the Genetics of Preeclampsia consortium in the UK, which aims to identify genetic factors that contribute to PE. Experimental studies suggest that the mediators of cardiovascular dysfunction during PE operate via increased oxidative stress and decreased bioavailability of vasodilators such as NO. These endothelial stressors, in turn, cause hypertension by impairing renal-pressure natriuresis and increasing total peri pheral resistance (Figure 2).

A primary concern regarding the treatment of PE is that there is currently no highly effective treatment other than the delivery of the fetus and placenta. Some effective treatments for hypertension, such as RAS inhibitors, are contraindicated during pregnancy, having known deleterious effects on fetal development. Hence, much of the intense interest in this area is to establish therapies that may attenuate the maternal symptoms (and prevent progression from PE to ecclampsia) and allow for further fetal growth and development. Future therapies may be directed at restoring normal plasma levels of angiogenic factors, oxidant capacity and circulating lipids. Treatments that suppress production or inhibit action of the AT_1-AA complex may also prove useful. Of course, complicating any therapeutic approach during pregnancy is the unpredictable nature of untoward effects on fetal outcome. capacity and circulating lipids. Treatments that suppress production or inhibit action of the AT_1-AA complex may also prove useful. Of course, complicating any therapeutic approach during pregnancy is the unpredictable nature of untoward effects on fetal outcome.

Five-year view

Uncertainties regarding the mechanisms of PE are, at least in part, attributable to difficulties either faced in performing mechanistic studies in pregnant women or in developing suitable animal models for hypothesis-driven research of this condition. With recent studies supporting a role for antiangiogenic factors, AT_1-AA, ROS and other factors as mediators of endothelial

dysfunction, determining the exact mechanisms by which endothelial dysfunction is produced is essential to interrupting the pathological process. In addition, pinpointing the initiating agent in placental ischemia is paramount to the development of successful therapies and, particularly, preventative measures. Microarray and proteome analysis of the ischemic/hypoxic placenta of women with PE, and in animal models of PE, continue to provide useful insights into novel factors and pathways that may yield fruitful therapeutic strategies. Elucidation of the pathways that result in increased production of deleterious mediators could also direct the development of therapies. Newly developed blocking agents or chemical modulators may be able to restore the balance of vasoactive chemical mediators. PE animal models, including transgenic models, knockout models, infusion models and RUPP, should be more thoroughly characterized in an effort to mimic the human condition as closely as possible.

Treatments, such as statins, which have long been recognized to have pleiotropic effects beneficial to cardiovascular patients, have recently received interest from basic scientists investigating mechanisms of PE. Although statins are considered to be contraindicated for use in pregnancy, recent studies may raise questions that may necessitate a cautious reinvestigation of the current stance. Cudmore *et al.* have shown that simvastatin inhibits sFlt-1 and sEng production *in vitro*,[76] while Elahi and colleagues have shown reductions in blood pressure and cholesterol in a murine model of obesity during pregnancy without any obvious detrimental effects on the fetus or the offspring [109]. The idea that statins may prove beneficial to the mother and fetus during PE may merit further research in the recently developed animal models of PE. With the considerable progress seen in recent years, it appears certain that more effective strategies for the prevention of PE will be forthcoming as the mysteries underlying the pathophysiological mechanisms of PE continue to be unraveled.

Key issues

- Preeclampsia (PE) is a syndrome clinically defined by new-onset hypertension with proteinuria that presents after 20 weeks of pregnancy.
- The manifestations of PE remit soon after delivery of the placenta, suggesting the placenta plays a central role.
- Cardiovascular dysfunction, such as decreased cardiac output and increased vascular resistance, occur in PE.
- Formerly preeclamptic women have increased risk of cardiovascular and renal diseases in later life.
- Offspring of preeclamptic women may be at increased risk for cardiovascular disease in adulthood.
- Suboptimal placental development and poor placental perfusion are regarded as key features in the pathogenesis of PE.
- Imbalances in angiogenic factors, including increased levels of the antiangiogenic factors Flt-1 and endoglin, and reductions in VEGF and PIGF, appear to modulate some of the endothelial dysfunction.
- In PE women, a reduction in superoxide dismutase occurs in both maternal and fetal tissue, along with lowered maternal levels of several antioxidants (e.g., vitamins A, C and E). These changes result in an increase in oxidative stress; however, antioxidant supplementation has not been an effective treatment.
- The increased sensitivity of the vasculature of PE women to angiotensin II appears to be due to both the formation of a heterodimer between the angiotensin type 1

receptor and the bradykinin B2 receptor, and an increase in plasma levels of an agonistic autoantibody to the angiotensin type I receptor.

- Recent animal models include adenovirus transfection of soluble fms-like tyrosine kinase-1, soluble endoglin RNA, infusion of soluble FMS-like tyrosine kinase-1 and IgG fractions from preeclamptic women containing angiotensin type 1 receptors autoantibodies, genetic and/or transgenic models and experimental reduction of uteroplacental perfusion pressure.
- Other conditions may contribute to PE pathology, such as elevations in triglycerides and fatty acids, insulin resistance and glucose intolerance.

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110. Papers of special note have been highlighted as:

111. of interest

112. of considerable interest

113. Excellent review of chronic diseases during and after pregnancy.

114. Experimental study linking hypertensive pregnancy with hypertension in the offspring.

115. First clinical and experimental studies linking soluble fms-like tyrosine kinase 1 (sFlt1) and VEGF/PlGF to preeclamptic pregnancies.

116. First experimental study linking placental ischemia and increased sFlt-1.

117. First experimental study to link placental ischemia and hypertension to increased sFlt-1 and decreased VEGF/PlGF.

118. First clinical and experimental studies linking soluble endoglin to preeclamptic pregnancies.

119. Evidence for antiangiogenic proteins as an early detection biomarker for preeclampsia.

120. Evidence linking hypoxia-inducible factor 1 to sFlt-1 in human placenta.

121. First experimental study demonstrating angiotensin II type I receptor autoantibodies increase blood pressure during pregnancy in the mouse.

122. *In vitro* study linking heme oxygenase-1, and possibly statin therapy, to sFlt-1 and soluble endoglin.

123. Initial study linking angiotensin II type 1 receptor autoantibodies to preeclampsia.

124. Experimental study demonstrating beneficial effects of statin therapy during hypercholestermic pregnancy on the offspring.

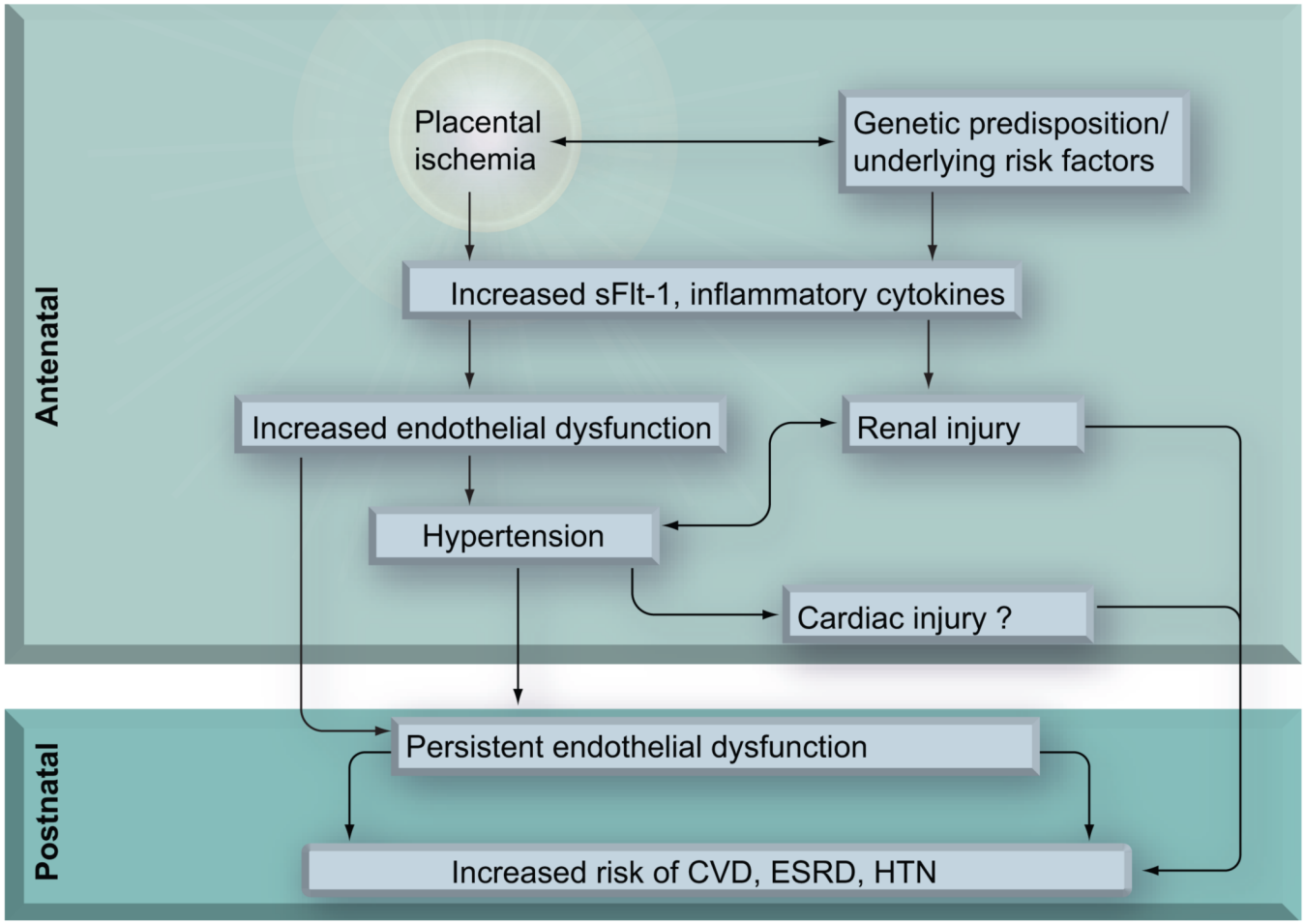

Figure 1. Pathways by which placental ischemia may lead to endothelial and cardiovascular dysfunction during and after pregnancy

Placental ischemia results in increased synthesis of factors such as soluble fms-like tyrosine kinase-1 and various inflammatory cytokines, which in turn result in endothelial dysfunction and ultimately hypertension. Once hypertension is established, it results in ventricular hypertrophy, renal injury and additional endothelial dysfunction, all of which could contribute to in an increased risk of CVD and/or ESRD in later life.

CVD: Cardiovascular disease; ESRD: End-stage renal disease; HTN: Hypertension.

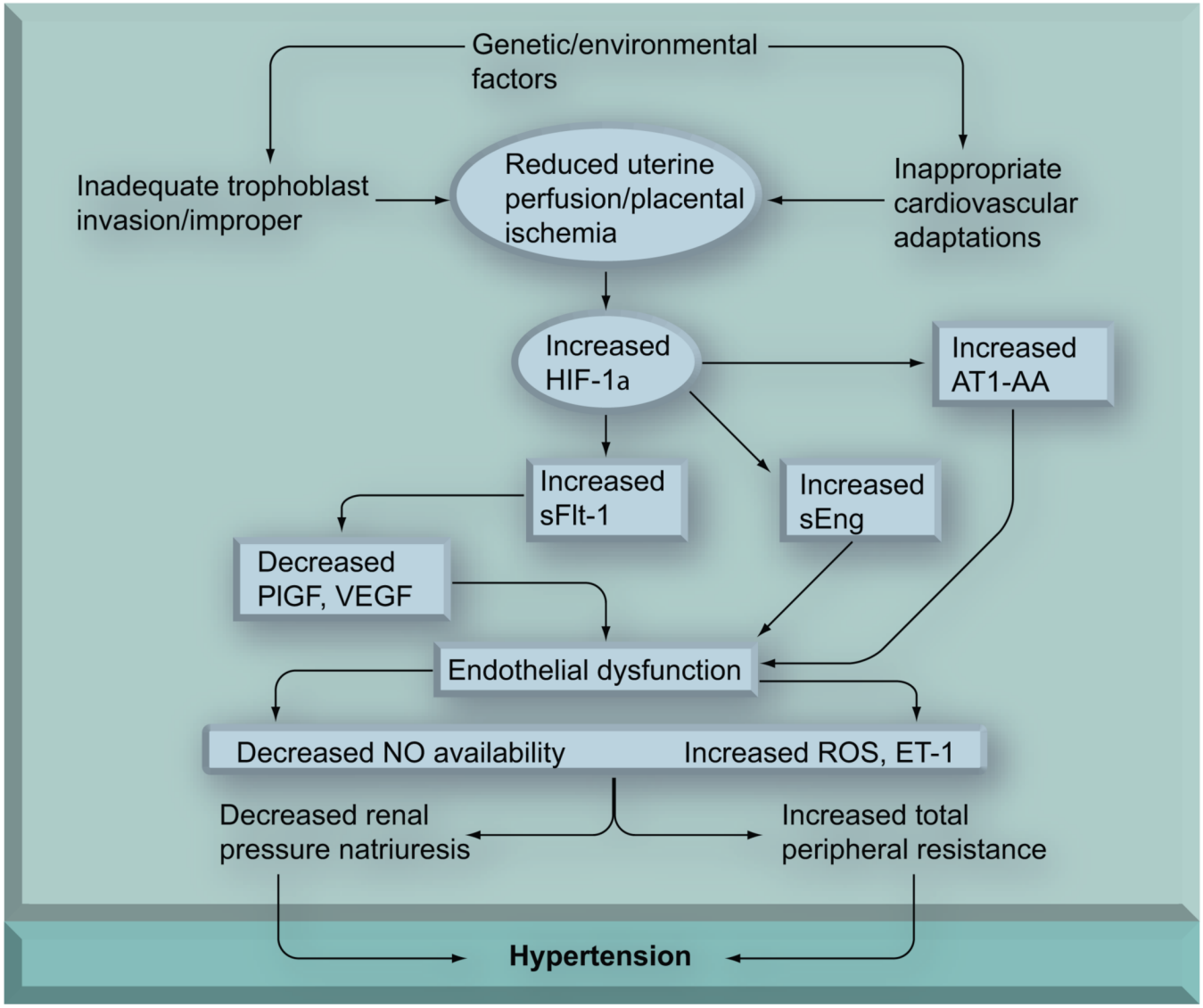

Figure 2. Pathways by which reduced uterine perfusion pressure and placental ischemia may lead to endothelial and cardiovascular dysfunction during pregnancy

Genetic and/or environmental factors may interact with insufficient placentation or inappropriate cardiovascular adaptations to result in reduced uterine perfusion and placental ischemia. Placental ischemia results in increased synthesis of HIF-1α, which increases soluble fms-like tyrosine kinase-1 and soluble endoglin. Placental ischemia also results in production of AT_1-AA. Elevations in these factors are proposed to result in endothelial dysfunction, by decreases in bioavailable nitric oxide, and increased ROS and ET-1, which in turn results in altered renal function, increased total peripheral resistance and, ultimately, hypertension. AT_1-AA: Angiotensin II type-1 receptor autoantibodies; ET: Endothelin; HIF: Hypoxia-inducible factor; ROS: Reactive oxygen species.