Full length article

Preeclampsia and coronary plaque erosion: Manifestations of endothelial dysfunction resulting in cardiovascular events in women

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ABSTRACT

Atherosclerosis is the major underlying pathology of cardiovascular disease (CVD). The risk for CVD is increased in women with a history of preeclampsia. Multiple studies have indicated that accelerated atherosclerosis underlies this increased CVD risk. Furthermore, it has been suggested that endothelial dysfunction and inflammation play an important role in the increased CVD risk of women with preeclampsia. Rupture or erosion of atherosclerotic plaques can induce the formation of thrombi that underlie the onset of acute clinical CVD such as myocardial infarction and stroke. In relatively young women, cardiovascular events are mainly due to plaque erosions. Eroded plaques have a distinct morphology compared to ruptured plaques, but have been understudied as a substrate for CVD. The currently available evidence points towards lesions with features of stability such as high collagen content and smooth muscle cells and with distinct mechanisms that further promote the pro-thrombotic environment such as Toll Like Receptor (TLR) signaling and endothelial apoptosis. These suggested mechanisms, that point to endothelial dysfunction and intimal thickening, may also play a role in preeclampsia. Pregnancy is considered a stress test for the cardiovascular system with preeclampsia as an additional pathological substrate for earlier manifestation of vascular disease. This review provides a summary of the possible common mechanisms involved in preeclampsia and accelerated atherosclerosis in young females and highlights plaque erosion as a likely substrate for CVD events in women with a history of preeclampsia.

1. Plaque erosion as a substrate for CVD in young women

Cardiovascular disease (CVD) often manifests through an occluding thrombus as a consequence of a ruptured atherosclerotic plaque, or due to arterial plaque erosion. Interestingly, the current hypothesis is that the pathogenic mechanisms leading to either an atherosclerotic plaque rupture or erosion are different. Most of our knowledge on the pathology of plaque erosion is based on studies by the group of Virmani and colleagues that has elegantly described plaque erosion as a mechanism of sudden death in autopsy studies from the 1980s onwards (Farb et al., 1996; Kolodgie et al., 2001). Of all thrombi, approximately 31% is caused by plaque erosion (Jia et al., 2013; White et al., 2016). Plaque erosion is especially common in young women (Farb et al., 1996; Yahagi et al., 2015), and accounts for approximately 80% of all

thrombi in women under the age of 50 years (Campbell et al., 2014). Plaque histology is different for plaque rupture and plaque erosion. Ruptured plaques have a thin cap, macrophage infiltration, and lipid core that exposes to the blood upon plaque rupture. Eroded plaques are often characterized by a thick, intact cap and minor or no lipid core. In addition, eroded plaques have an altered subendothelial matrix that contains increased proteoglycans, hyaluronan, and smooth muscle cells. Exposure of this matrix to platelets and blood coagulation factors can cause thrombus formation (White et al., 2016). In the carotid artery, histological analysis of atherosclerotic plaques consistently showed that women display plaques with more stable features and less inflammation, suggestive of plaque erosion as a more prevalent substrate for CVD as compared to men (Hellings et al., 2007; Vrijenhoek et al., 2014, 2013). Interestingly, the finding that symptomatic women reveal more

stable plaques is independent of cardiovascular risk profile and clinical presentation.

Eroded plaques, more common in women, show much less markers of inflammation compared to unstable and ruptured plaques (Campbell et al., 2014). Yet, inflammation may stimulate plaque erosion by negatively affecting the function and integrity of the endothelial lining of the atherosclerotic plaque. Proteases capable of degrading the basement membrane are produced in response to inflammation (White et al., 2016). Different cytokines might have a role in the pathogenesis of plaque erosion, potentially via the induction of endothelial dysfunction. Although plaque erosion has been understudied as compared to plaque rupture, the potential mechanisms involved in the erosion of the plaque have been extensively reviewed. These generally consist of four components: (1) *endothelial dysfunction and endothelial apoptosis*, (2) *Toll Like Receptor signaling, (3) extracellular matrix changes and (4) changes in platelet adhesion*. With atherosclerotic plaque erosion being a more common substrate for acute CVD in younger women, and preeclampsia being a risk factor for CVD in women, we hypothesize that preeclampsia may predispose to plaque erosion via shared pathophysiological mechanisms.

2. Preeclampsia and CVD risk, the link with atherosclerosis

Preeclampsia is a hypertensive pregnancy disorder complicating around 1–5% of pregnancies and is characterized by *de novo* hypertension and proteinuria, maternal organ dysfunction or uteroplacental dysfunction manifesting in the second half of pregnancy (Baumwell and Karumanchi, 2007; Hernandez-Diaz et al., 2009). Preeclampsia is a major cause of maternal and fetal morbidity and mortality and may affect the health of the mother in the years directly following preeclampsia. Observational studies have consistently shown that women with former preeclampsia have a 2-fold increased risk to develop CVD later in life. In particular, there is cumulating evidence that preeclampsia predisposes to ischemic heart disease that occurs at younger age than in women who have uncomplicated pregnancies. In a study of 3658 women with preeclampsia, $\approx$ 50% developed future hypertension with a 3.70 times higher risk compared to women with a normotensive pregnancy (Bellamy et al., 2007). In addition, women with a history of preeclampsia have a 2.2 times higher risk of developing ischemic heart disease. The risk of fatal ischemic heart disease was increased in women with preeclampsia, and early onset preeclampsia (before week 37) significantly added to this risk, resulting in a relative risk of 7.71 (Bellamy et al., 2007). Similar, the risk of future stroke was 1.81 times higher in women with preeclampsia compared to normotensive pregnancy (Bellamy et al., 2007). Finally, the risk of future thromboembolism is increased 1.79-fold for women with a preeclamptic pregnancy, although absolute risk remains low (0.1% at 4.7 years after delivery) (Bellamy et al., 2007). Also, but to a lesser extent, there is a relationship between the severity of preeclampsia when presenting in pregnancy, and the long-term risk of CVD later in life. Whereas for patients with mild preeclampsia a relative risk of CVD of 2.00 was found, this was 2.99 for patients with moderate preeclampsia and 5.36 for patients with severe preeclampsia (McDonald et al., 2008). The exact mechanisms by which preeclampsia increases future cardiovascular risk are unknown although multiple similarities between the mechanisms responsible for CVD and preeclampsia are reported. For example, risk factors for both CVD and preeclampsia in young women include hypertension, obesity, insulin resistance, and hyperlipidemia (Leslie and Briggs, 2016). However, these similarities do not fully explain the increased CVD risk in women with former preeclampsia as adjustment for CVD risk factors shows that preeclampsia is an independent is risk factor for CVD (Berks et al., 2013; McDonald et al., 2008). It has been hypothesized that women who experience preeclampsia already have an increased vascular risk prior to developing CVD. The exposed vascular stress during pregnancy causes the body to reach the threshold for development of endothelial dysfunction,

vascular inflammation and hampered vascular remodeling with insufficient placental oxygen supply, which have all been reported in the presence of preeclampsia (Sattar and Greer, 2002). Later in life, vascular risk factors rise for both the healthy population and women with a history of preeclampsia, but women with a history of preeclampsia are more likely to develop vascular disease earlier compared to the healthy female population pointing to a lower threshold for stressors to elicit vascular occlusive disease. (Powe et al., 2011; Sattar and Greer, 2002). Several studies have revealed that *endothelial dysfunction* and *angiogenic imbalance* are the first indicators of vascular damage in preeclampsia patients. This in combination with the *chronic inflammatory state* in preeclampsia patients may lead to acceleration of atherosclerosis after preeclampsia.

3. Vascular dysfunction in preeclampsia

While atherosclerosis is a slowly developing progressive condition that finds its origin in adolescence and progresses throughout life with atherosclerotic plaques as a final stage, vascular changes such as acute atherosis, occur relatively instantly in the placental blood vessels during preeclampsia. Atherosis in the spiral arteries is characterized by subendothelial lipid filled foam cells, fibrinoid necrosis of the arterial wall, perivascular lymphocytic infiltration, and it is histologically similar to early-stage atherosclerosis (Kim and Kim, 2015). In the spiral artery remodeling study (SPAR) study, systematic screens of vascular pathology in placental bed biopsy samples were related to CVD risk factors in women with preeclampsia or normal pregnancy (Veerbeek et al., 2016). They showed that in women with preeclampsia fewer of the spiral arteries showed complete remodeling and the placenta contained not as much infiltrated CD3$^{\pm}$ T cells compared to health pregnancy. The authors speculate the latter may specifically relate to fewer infiltrating regulatory T cells, which have the ability to control for excessive inflammation. Besides it was suggested that the presence of acute atherosis in the placental bed associated to an unfavorable lipoprotein profile postpartum. Although this study provided valuable insight into the link between placental bed disorders and cardiovascular health, these findings remain to be established in the complete SPAR study cohort (Veerbeek et al., 2016).

Carotid intima media thickness (cIMT) is a surrogate marker for atherosclerosis burden that is assessed non-invasively and associated with the presence of CVD. A recent meta-analysis showed that women who experienced preeclampsia had significantly increased carotid intima-media thickness compared to women without preeclampsia, both at the time of diagnosis and in the first decade postpartum (Grand'Maison et al., 2016; Milic et al., 2017). In addition, impaired coronary flow reserve during preeclampsia has been documented. These measures of vascular dysfunction have been correlated with circulating levels of inflammatory biomarkers such as high sensitive C-reactive protein (hs-CRP) as well (Ciftci et al., 2014). The time course of this vascular dysfunction after preeclampsia has not been established up to now. cIMT was increased the first year after severe preeclampsia, but was no longer elevated approximately 5 years postpartum (Blaauw et al., 2014). This suggests that, despite evident vascular dysfunction during preeclampsia, vascular homeostasis may be restored after preeclampsia (Blaauw et al., 2014). Despite the evident decrease in cIMT after 5 years it remains to be confirmed that vascular homeostasis is fully recovered. It may very well be that the endothelial integrity is not fully restored or that the vasculature may remain more sensitized to stress. As such the former preeclamptic vasculature may have an augmented response to stress-related or inflammatory stimuli as seen in atherosclerosis.

4. Hypoxia, oxidative stress and angiogenesis in preeclampsia

Endothelial dysfunction is caused by a combination of oxidative stress, angiogenic and vasoresponsive imbalance, and inflammation

Table 1

Overview of mechanisms of endothelial dysfunction and inflammation involved in atherosclerosis and preeclampsia.

	Atherosclerosis			Preeclampsia		
Endothelial dysfunction	↑			↑		
Oxidative stress	↑	Plaque		↑	Placenta	Sikkema et al., 2001
Reactive Oxygen Species	↑	Plaque	Harrison et al., 2003; Li et al., 2014b	↑	Placenta	Lazdam et al., 2012; Steegers et al., 2010
NO imbalance	↑	Plaque	Dimmeler et al., 2002	↑	Placenta	Matsubara et al., 2015
Superoxide				↑	Placenta	Lazdam et al., 2012
NF-κB	↑	Plaque	Li et al., 2014b	↑	Placenta	Goulopoulou and David, 2015
Angiogenic imbalance						
Pro-angiogenic	↑			↓		Lazdam et al., 2012
VEGF	↑	Plaque	Roncal et al., 2010	↓	Systemic	Sezer et al., 2013
PlGF	↑	Systemic, Plaque	Roncal et al., 2010; Khurana et al., 2005	↓	Systemic	Levine et al., 2004
HIF-1α	↑	Plaque	Aarup et al., 2016; Akhtar et al., 2015	↑	Placenta	Tal, 2012; Rajakumar et al., 2004
sFlt-1	↑	Plaque	Roncal et al., 2010	↑	Systemic	Levine et al., 2004
sEng	↑	Systemic, Plaque	Nachtigal, 2012	↑	Systemic	Levine et al., 2006; Venkatesha et al., 2006
Vascular compliance						
Vasodilation	↓	Systemic	Knock and Poston, 1996; Noori et al., 2010	↓ and ↑[a]	Systemic	Agatisa et al., 2004; Murphy et al., 2014; Yinon et al., 2010
Arterial stiffness	↑	Systemic	Robb et al., 2009	↑	Systemic	Robb et al., 2009
Microvascular density	↑	Plaque	Depre et al.,1996; Zhang et al., 1993	↓	Placenta	Hasan et al., 2002; Nama et al., 2012; Uras et al., 2012
EndMT						
Myofibroblasts	↑	Plaque	Bostrom et al., 2016; Chen et al., 2015; Evrard et al., 2016	?		
TGF-β	↑	Systemic, Plaque	Goumans et al., 2017; Goumans and Ten Dijke, 2017	?		
Inflammation	↑	Systemic, Plaque	Hansson, 2009	↑	Systemic, Placenta	Harmon et al., 2016
TLR	↑	Systemic, PBMC	Bjorkbacka, 2006; Roshan et al., 2016 Elsenberg et al., 2013	↑	Placenta PBMC	Li et al., 2016 Van Rijn et al., 2016
IL-6	↑	Systemic	Ridker, 2016	↓ and ↑	Systemic	Stubert et al., 2016; Pinheiro et al., 2015
TNFα	↑	Systemic	Zhang et al., 2009	↓ and ↑	Systemic	Ferguson et al., 2017; Udenze et al., 2015; Moreno-Eutimio et al., 2014; Mudin et al., 2016; Taylor et al., 2016
					Placental	Weel et al., 2016; Li et al., 2016; Azizieh and Raghupathy, 2015

[a] Decreased in macrovasculature and increased in microvasculature.

(Table 1) (Lazdam et al., 2012). As a result, women with endothelial dysfunction reveal decreased vasodilation (Knock and Poston, 1996; Noori et al., 2010), increased arterial stiffness (Robb et al., 2009) and atherosclerosis (Anastasakis et al., 2008) in the larger vessels. Skin microvascular density (Hasan et al., 2002; Nama et al., 2012) and placenta microvascular density (Uras et al., 2012) were found to be decreased in women with preeclampsia, while others have shown that vascular growth was not significantly affected in preeclampsia (Li et al., 2015). A negative correlation in vasodilator response between the macro and microcirculation has been suggested and this negative correlation was also observed in women with preeclampsia (Agatisa et al., 2004; Murphy et al., 2014; Yinon et al., 2010). Incomplete remodeling of the uterine spiral arteries causes placental ischemia-reperfusion episodes. During these episodes, reactive oxygen species are formed, (Lazdam et al., 2012; Steegers et al., 2010). This leads to oxidative stress (Sikkema et al., 2001), shown by increased levels of marker lipid peroxide (Shaker and Sadik, 2013). Reactive Oxygen Species decrease the bioavailability of pro-angiogenic nitric oxide (NO) via the suppression of NO synthase (NOS). In addition, peroxynitrite is formed when Reactive Oxygen Species and NO react. Peroxynitrate can in turn oxidize DNA, proteins, and lipids. As a consequence, NO balance is disturbed, which can result in impaired vasodilation and angiogenesis (Matsubara et al., 2015). Other molecules that are upregulated by oxidative stress are NF-κB and superoxides, resulting in further activation of anti-angiogenic (Lazdam et al., 2012) and pro-inflammatory pathways (Goulopoulou and Davidge, 2015).

Another result from placental ischemia is an angiogenic imbalance towards a more anti-angiogenic and vasoconstrictory state (Table 1) (Lazdam et al., 2012). Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are important pro-angiogenic and vasodilatory molecules (Powe et al., 2011). Serum levels of PlGF (Levine et al., 2004) and VEGF (Sezer et al., 2013) are decreased in women who develop preeclampsia. Both VEGF and PlGF bind to VEGF-receptor 1, also known as Flt-1 (Powe et al., 2011). In a healthy pregnancy, VEGF and PlGF bind to Flt-1 on the endothelial cell surface, resulting in activation of anticoagulant, vasodilatory, and proangiogenic pathways. The soluble form of the Flt-1 receptor, sFlt-1, that is a natural antagonist for VEGF and PlGF, is increased in women with preeclampsia (Levine et al., 2004). sFlt-1 binds VEGF and PlGF, thereby preventing binding to endothelial cell-surface Flt-1 receptors. As a result of decreased binding to the Flt-1 receptor, the anticoagulant, vasodilatory, and proangiogenic pathways are inhibited and endothelial cells become dysfunctional (Hod et al., 2015; Karumanchi et al., 2005). In addition to increased levels of sFlt-1, serum levels of soluble endoglin (sEng) were also found to be increased in patients with preeclampsia (Levine et al., 2006; Venkatesha et al., 2006). Endoglin is a TGF-β co-receptor highly expressed on the membranes of activated endothelial cells (Goumans et al., 2017). Membrane bound endoglin can either stimulate or inhibit cellular responses downstream of TGF-β and of its family members, the Bone Morphogenetic Protein (BMP) ligands. In endothelial cells endoglin stimulates angiogenesis (Lebrin et al., 2004). sEng has different affinity for TGF-β and BMP. sEng interferes with TGF-β signaling by trapping circulating TGF-β1. TGF-β signaling stimulates vasodilation via the activation of NO (Venkatesha et al., 2006), stimulates vascular

homeostasis and can either stimulate or inhibit angiogenesis depending on the context (Powe et al., 2011). As a result of increased sENG, NO induced vasodilation, (Venkatesha et al., 2006) angiogenesis and vascular homeostasis are diminished (Powe et al., 2011) in patients with preeclampsia. TGF-β binds with very low affinity to sEng and likely only does bind in the presence of a soluble TGFβ type II receptor while sEng binds with high affinity to BMP9 and inhibits BMP9 induced signaling (Gregory et al., 2014). Scavenging of BMP9 by sEng reduces the BMP9 induced ET-1 vascular stability and hypertension (Park et al., 2012) It has been suggested that hypoxia-inducible factor 1 subunit α (HIF-1α) is responsible for the increased amounts of sEng and sFlt-1 in preeclampsia (Tal, 2012). The hypoxic environment of the preeclamptic placenta triggers the expression of HIF-1α, which indeed was increased in the placenta of preeclamptic women (Rajakumar et al., 2004). In pregnant mice, overexpression of HIF-1α increased the serum levels of sFlt-1 and sEng and resulted in hypertension and proteinuria, both hallmarks of preeclampsia. These human and animal data suggest that HIF-1α plays an important role in the pathogenesis of preeclampsia via the activation of antiangiogenic pathways (Tal, 2012; Tal et al., 2010). This appears ambiguous, since HIF-1α normally activates the transcription of VEGF (Forsythe et al., 1996), PlGF (Kelly et al., 2003), and other hypoxia- and angiogenesis-associated proteins (Oka et al., 2014) as a response to hypoxia. However, this increase is often brief. Long-term upregulation of HIF-1α has been described in the pathology of multiple diseases, including preeclampsia (Iriyama et al., 2015).

5. Hypoxia, oxidative stress and angiogenesis in atherosclerosis and plaque erosion

Angiogenic imbalance is less well described in atherosclerosis than in preeclampsia. General consensus is that plaque neovessels primarily derive from the preexisting dense vessel network of the adventitial vaso vasorum, rather than the arterial luminal (Depre et al., 1996; Zhang et al., 1993) and increased neovascularization enhances atherosclerotic plaque progression via increasing macrophage infiltration and vessel wall thickening (Chistiakov et al., 2015; Moreno et al., 2012). In addition, the newly formed vessels can rupture, causing intraplaque hemorrhage contributing in lipid rich necrotic core expansion and oxidative stress (Moreno et al., 2012). Although VEGF levels are sequentially increased with progressing atherosclerotic disease burden, the exact role of VEGF in atherosclerosis remains unclear, both in humans and in animal models (Heinonen et al., 2013; Yla-Herttuala et al., 2007). In atherosclerosis, PlGF expression has been shown to be increased, especially in the shoulder region of the atherosclerotic plaque. In early stages of the disease, treatment with anti-PlGF antibodies was able to inhibit the inflammatory process and plaque progression. In later stages of the disease, anti-PlGF antibody treatment had no effect on the plaque development. This suggests that PlGF is primarily involved in plaque development by inducing an inflammatory response (Roncal et al., 2010; Sainz and Sata, 2010). Indeed, PlGF has been shown to increase atherosclerotic development via the stimulation of intimal thickening and macrophage accumulation (Khurana et al., 2005). In addition to VEGF and PlGF, levels of Flt-1 are also increased in the shoulder regions of the atherosclerotic plaque (Roncal et al., 2010). The antagonist of VEGF and PlGF, sFlt-1 has been shown to inhibit plaque formation, possibly via the inhibition of intraplaque angiogenesis (Wang et al., 2011). These processes are opposite to those witnessed in preeclampsia, where VEGF and PlGF levels are decreased and sFlt-1 levels are increased, causing an anti-angiogenic environment (Table 1). In plaque erosion, endothelial cell apoptosis is an important part of the pathologic process. Deprivation of growth factors such as VEGF contributes to this process (White et al., 2016). In addition, decreased levels of VEGF increase oxidative stress and apoptosis (Dimmeler et al., 2002; Hulsmans and Holvoet, 2010). Although the involvement of PlGF in plaque erosion has not yet been described, its involvement is likely similar to that of VEGF. The role of sFlt-1 in

plaque erosion has also not been described yet. Given the function of sFlt-1, increased levels of sFlt-1 would decrease VEGF and PlGF signaling, thereby stimulating endothelial cell apoptosis and plaque erosion. Another important protein in preeclampsia pathophysiology, endoglin, is also expressed by endothelial cells and smooth muscle cells in atherosclerotic vessels. Endoglin expression is associated with plaque neoangiogenesis, collagen deposition and thereby stabilizes the plaque (Bot et al., 2009). Increased levels of sEng are proatherogenic via inhibition of endoglin function and inhibition of TGF-β signaling (Nachtigal et al., 2012). HIF-1α is expressed by various cell types in the atherosclerotic lesion and promotes the development and progression of atherosclerosis (Aarup et al., 2016; Akhtar et al., 2015). Inhibition of HIF-1α has been shown to decrease plaque size (Christoph et al., 2014), reduce vascular inflammation (Akhtar et al., 2015; Liu et al., 2016) and overall inhibit the development of atherosclerosis (Aarup et al., 2016; Christoph et al., 2014; Liu et al., 2016). Although no studies reported a role of sEng in plaque erosion, Matrix metalloproteinase 14 (MMP14) polymorphism was found to be related to a lower risk of vulnerable carotid plaque formation (Li et al., 2014a). Furthermore, sEng induced Il-6 and NF-κB in endothelial cells, generating a pro-inflammatory state of the cells (Varejckova et al., 2017). Finally, KLF6 was found to induce MMP14 in endothelial cells, resulting in increased levels of sEng, and reducing membrane bound Endoglin (Gallardo-Vara et al., 2016). Reduced endoglin levels on the endothelial cell surface renders them more sensitive to endothelial to mesenchymal transition (EndMT).

6. Reactive oxygen species in atherosclerosis and preeclampsia

As well as in preeclampsia, endothelial dysfunction is a pivotal process in the development of atherosclerosis. In preeclampsia, endothelial dysfunction is characterized by oxidative stress, angiogenic imbalance, and vasodilatory imbalance. Endothelial dysfunction has also been described in plaque erosion. This endothelial dysfunction is suggested to be paired with endoplasmic reticulum stress and endothelial cell apoptosis causing detachment of the endothelial cell layer, exposing the sub endothelial matrix and activating thrombus formation (Hansson et al., 2015). Reactive Oxygen Species production is increased by the common risk factors of preeclampsia and CVD, for example hypertension, hypercholesterolemia, diabetes, cigarette smoking, aging (Harrison et al., 2003; Li et al., 2014b). In preeclampsia, this is further driven by excessive Reactive Oxygen Species production in the placenta, and inadequate action of protective placental scavenging enzymes e.g. superoxide dismutase (SOD) (Sikkema et al., 2001). This sustained elevation of Reactive Oxygen Species levels leads to oxidative stress, with endothelial dysfunction as a consequence (Sitia et al., 2010). In addition, Reactive Oxygen Species stimulate inflammation via the activation NF-κB pathway and activation of the macrophages in the plaque (Li et al., 2014b). In plaque erosion, Reactive Oxygen Species cause the production of oxidized lipoproteins. These lipoproteins induce apoptosis of endothelial cells, resulting in plaque erosion (Dimmeler et al., 2002; Hulsmans and Holvoet, 2010). In addition, Reactive Oxygen Species induced endothelial dysfunction might induce the production and activation of proteases and matrix metalloproteinases (MMP), which in turn can degrade the basement membrane. Basement membrane degradation has been described as a process involved in plaque erosion (White et al., 2016). Also, oxidative stress causes a decrease in NO, thereby decreasing its anti-apoptotic effect (Dimmeler et al., 2002).

7. Novel manifestations of endothelial dysfunction in atherosclerosis

Another process that may add to the endothelial dysfunction seen in both atherosclerosis and preeclampsia is endothelial to mesenchymal transition (EndMT). Endothelial to mesenchymal transition (EndMT) is a complex, dynamic and reversible biological process that can change

endothelial cell integrity and can contribute to the pathogenesis of many diseases including hypertensive disorder (Arciniegas et al., 2007). EndMT can be stimulated by differences in several metabolic and inflammatory factors, which are all important in the pathogenesis of atherosclerosis. EndMT is a common phenomenon in atherosclerotic lesions, contributes to plaque progression and lesion calcification (Bostrom et al., 2016; Chen et al., 2015), and is more common in advanced vulnerable plaques (Evrard et al., 2016). As such it has been suggested that the presence of endMT may associate with clinical events (Evrard et al., 2016) and that the process of endMT may be a promising therapeutic target for atherosclerosis (Jackson et al., 2017).

8. Endothelial to mesenchymal transition (EndMT)

When endothelial cells undergo EndMT, they loosen cell-cell contact and change from a cobblestone-like well-structured monolayer into a more chaotic mesenchymal elongated phenotype. Endothelial cells undergoing EndMT down-regulate their endothelial specific markers like Pecam-1, VE-cadherin, and FLK-1, and start to express protein characteristics for a mesenchymal gene signature cells such as α smooth muscle actin (α-SMA), fibroblast specific protein-1 (FSP-1) and type I collagen (Goumans and Ten Dijke, 2017). The EndMT derived mesenchymal cells are often called myofibroblasts as they express both smooth muscle cell and fibroblast specific genes. EndMT is initiated by activation of the endothelium by e.g. inflammatory cytokines which loosens the cell-cell contacts. One of the key regulators of the mesenchymal transition is TGF-β in a variety of endothelial cells. TGF-β can directly influence EndMT by the expression of the transcription factors Snail and Slug, or indirectly by inducing EndMT regulating microRNAs like microRNA-21 (Kumarswamy et al., 2012). Disturbed flow, can induce a morphological switch in endothelial cells. Endothelial cells in high shear areas lose their primary cilia making them more sensitive to TGF-β induced EndMT (Egorova et al., 2011; Hierck et al., 2008; Sanchez-Duffhues et al., 2015). Also in the context of atherosclerosis it has been shown that EndMT can be induced by shear stress modifications (Mahmoud et al., 2017; Moonen et al., 2015) and plaque foam cells can initiate EndMT trough the release of the chemokine CCL4/Macrophage Inflammatory Protein 1β (Yang et al., 2017). As mentioned, these cells are prominent in atherosclerosis, due to disturbed flow at the boundaries of the plaque (Sanchez-Duffhues et al., 2015) with key functions including regulation of inflammation, matrix and collagen production, and plaque structural integrity (Table 1). 'Transitioning' cells are readily detected in human atherosclerotic plaques co-expressing endothelial and fibroblast/mesenchymal proteins, indicative of EndMT (Evrard et al., 2016).

9. Inflammation as common pathway for preeclampsia and atherosclerotic plaque erosion

Besides endothelial dysfunction, inflammation is a major contributor to the onset of preeclampsia and atherosclerosis (Hansson, 2009; Harmon et al., 2016). Endothelial dysfunction causes increased adhesiveness and permeability of the endothelial layer allowing for leukocytes and platelets to adhere and transmigrate through this damaged endothelium. In addition, the dysfunctional endothelium produces cytokines, vasoactive molecules, and growth factors. The inflammatory response initiated in preeclampsia shows many similarities to the inflammatory response of atherosclerosis (Table 1). Atherosclerotic lesion formation is characterized by massive macrophage accumulation in the intimal area, but, as the lesion progresses, can actually contain almost all inflammatory cell types. The placentas of preeclamptic women contain higher numbers of macrophages and the infiltration of macrophages has been associated with impaired trophoblast infiltration (Ning et al., 2016). Similar to that observed in atherosclerosis, these macrophages are predominantly of the pro-inflammatory M1 like phenotype (Huang et al., 2008). The persisting

inflammatory response results in activation of macrophages and lymphocytes in the affected area where they release hydrolytic enzymes, chemokines, cytokines, and growth factors. Although many cytokines and chemokines have been implicated in the development of atherosclerosis and preeclampsia, here we review those most studied in both pathologies.

9.1. Toll like receptors

Toll-like receptors (TLRs) are highly conserved receptors of the innate immune arm that are instrumental in atherosclerotic plaque inflammation by recognizing pathogen- and damage-associated molecular patterns that can be upregulated on, for example, tissue damage or cell stress (Goulopoulou et al., 2016; Roshan et al., 2016; Seneviratne and Monaco, 2015; Vink et al., 2004, 2002). In atherosclerosis, TLR function is traditionally linked to its effect on plaque macrophages and foam cells, but nowadays it is also recognized that certain TLRs can modify endothelial cell function (Salvador et al., 2016). TLR2 and TLR4 are predominantly expressed in endothelial cells of the vascular wall and have been associated to atherosclerotic lesion development in different murine models (Bjorkbacka, 2006; Roshan et al., 2016). Genetic variation in the TLR2 and TLR4 gene have been associated to early onset preeclampsia (van Rijn et al., 2008; Xie et al., 2010), while the association of TLR2 and TLR4 SNPs to cardiovascular risk is debated on. Genetic variations in the TLR4 gene, Asp299Gly and Thr399Ile have been associated to increased risk for cardiovascular events (Boekholdt et al., 2003; Edfeldt et al., 2004), that may be the consequence of modified efficacy of statin treatment in the Asp299Gly carriers. (Boekholdt et al., 2003). On the other hand, it has also been reported that the TLR4 Asp299Gly variant associates to decreased CRP levels and increased carotid artery compliance, suggesting that this variant may also reduce cardiovascular risk (Hernesniemi et al., 2008; Kolek et al., 2004). In an elegant study of Li and colleagues, first trimester primary cytotrophoblast and first trimester decidual macrophages were isolated during normal pregnancy and subsequently stimulated with LPS. Trophoblast are placental epithelial cells that are important for proper implantation of the fertilized eggs. Cytotrophoblasts can differentiate into syncytiotrophoblast which are important in transport of nutrients to the fetal system, or into extravillous trophoblast which are important in uterine vasculature remodeling to ensure proper blood supply. Decidual macrophages are placenta specific macrophages that accumulate in close proximity to the implantation site of spiral arteries with the maternal uterine lining (decidua). Decidual macrophages play an important role in play important roles in spiral artery remodeling and angiogenesis but also in extravillous trophoblast invasion and in modulation of the inflammatory response (Lash et al., 2016). LPS dose-dependently induced cytokine release, including TNFα, IL-6 and IL-1β, from trophoblasts. In addition, LPS stimulation inhibited trophoblast invasion while it increased macrophage accumulation in a TLR4 dependent manner (Li et al., 2016). In line with these findings it was shown that the inflammatory response to the TLR ligands is stronger in women with a history of preeclampsia and remain stronger over time when compared to women without preeclampsia (van Rijn et al., 2016). Similar effects were observed in patient with stable coronary artery disease compared to healthy controls (Elsenberg et al., 2013).

9.2. Interleukin-6 (IL-6)

IL-6 predicts cardiovascular events and has been associated with endothelial dysfunction and arterial stiffness (Ridker, 2016). IL-6 is involved in the causal pathway of atherosclerotic disease progression. The biological function of IL-6 is pleiotropic and includes increased platelet production, differentiation, migration and proliferation of T cells, migration and proliferation of smooth muscle cells, recruitment of neutrophils and the production of matrix metalloproteinases (MMPs), which are all processes driving the inflammatory process in
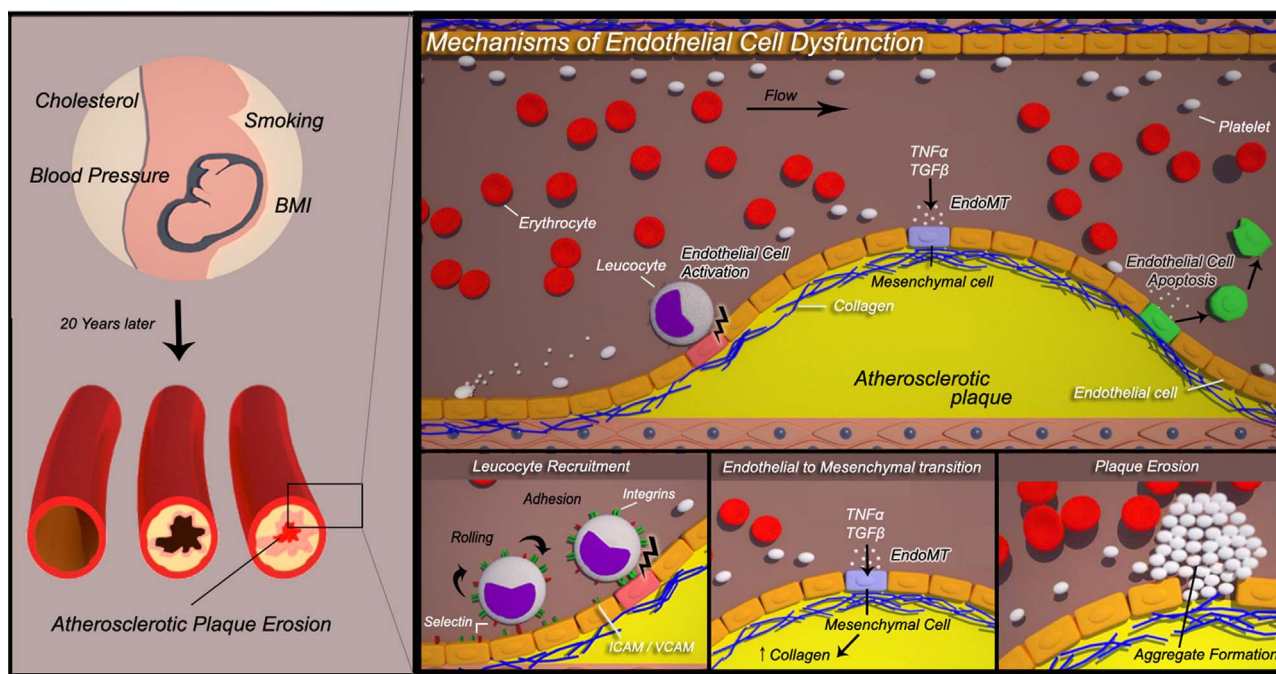
Fig. 1. Mechanisms involving endothelial dysfunction and inflammation in the pathology of preeclampsia that may expedite cardiovascular disease development later in life.

atherosclerosis and preeclampsia. Experimental atherosclerosis studies have shown that in absence of IL-6 atherosclerotic lesion development in ApoE$^{-/-}$ mice is accelerated, which rather appeared to be a consequence of increased plasma lipid levels and not of inflammation, as the latter was decreased in IL-6 deficient animals (Schieffer et al., 2004). Genetic variation in the IL6 gene is associated with reduced CVD risk as shown in a large mendelian randomization study and a meta-analysis (Collaboration et al., 2012; Interleukin-6 Receptor Mendelian Randomisation Analysis et al., 2012). It has been suggested that genetic variation in the promotor region of IL6 also is a genetic regulator of early onset preeclampsia (Sowmya et al., 2015), while there is no association to the IL6 SNPs described to be associated to cardiovascular risk (Fan et al., 2017). In addition, although circulating IL-6 levels did not predict for the onset of preeclampsia (Stubert et al., 2016), IL-6 levels were shown to be significantly increased in severe preeclampsia as compared to normotensive pregnant women (Pinheiro et al., 2015). Thus, IL-6 is a major player in several shared pathologic mechanisms of both preeclampsia and atherosclerotic disease.

9.3. Tumor necrosis factor-α (TNFα)

TNFα is a classical inflammatory cytokine that is increased in patients with atherosclerosis (Zhang et al., 2009). It attributes to the development of atherosclerosis by inducing endothelial dysfunction as a consequence of decreased NOS expression and endothelial cell apoptosis (Grainger, 2007). In addition, TNFα increases oxidative stress, inflammation and vascular remodeling. Data regarding circulating TNFα levels in preeclampsia yielded conflicting results. Some studies showed increased TNFα levels during all trimesters (Ferguson et al., 2017; Udenze et al., 2015), or the last trimester only (Moreno-Eutimio et al., 2014), while others have found TNFα levels to be unchanged or even decreased in 2nd trimester preeclamptic pregnancy (Mundim et al., 2016; Taylor et al., 2016). One prospective study even found that TNFα levels, in combination with mean uterine artery doppler, could have additional value in predicting women at risk for preeclampsia (Gomaa et al., 2015). TNFα is expressed in trophoblasts and its expression is increased in the preeclamptic placenta, predominantly in early preeclampsia (Weel et al., 2016). Exposure of Human primary trophoblast to LPS increased TNFα production in these cells (Li et al.,

2016). In addition, mononuclear cells of women with preeclampsia were more sensitive to stimulation with a mitogen or antigen and consequently produced more TNFα (Azizieh and Raghupathy, 2015). TNFα (G-308A) polymorphism is enriched in preeclampsia patients (Tavakkol Afshari et al., 2016; Zhou et al., 2016) and presence of this polymorphism increased disease risk (Zubor et al., 2014), again suggestive of a genetic component in the inflammatory arm of preeclampsia.

Despite the fact that the exact mechanisms involved in plaque erosion are largely unknown, it is generally accepted that plaque erosion mainly occurs in relatively stable plaques. These plaques are typically characterized by a low amount of plaque inflammation. As such, it has been postulated that plaque inflammation may not be so important for plaque erosion. Systemic inflammatory responses however may affect the process of plaque erosion directly, as a consequence of promoting thrombus formation, or indirectly through induction of endothelial dysfunction or apoptosis.

10. Future perspectives

In summary, many of the determinants that are involved in atherosclerotic plaque erosion are also observed in preeclampsia related vascular disease (Fig. 1). The mechanisms that underlie the predisposition of atherosclerotic CVD early in life in women with a history of preeclampsia is poorly understood. The concept of a pre-existent lowered threshold to withstand vascular stressors is intriguing and positions pregnancy as a clinically relevant vascular stress test. Research on the mechanisms leading to preeclampsia may also unravel the mechanisms that result in early manifestations of cardiovascular disease with plaque erosion as the pathological substrate. If common mechanisms are unraveled it may well become reality that prevention of arterial thrombosis in young females may be directed towards stabilization of endothelial function and subsequent prevention of plaque erosion.

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