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The role of oxidative stress, endothelial dysfunction and cardiometabolic risk in the pathophysiology of preeclampsia in women: review of the literature

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ABSTRACT

Background

Preeclampsia (PE) complicates up to 10% of pregnancies worldwide (Nirupama et al., 2021). Foetal and maternal deaths associated with preeclampsia are highest in women who are of Hispanic and African descent (Karrar and Hong., 2022). Women with PE are at an increased risk of developing cardiovascular diseases and complications later in life (de Havenon et al., 2021; Hod et al., 2015).This study sought to review the existing literature that combined the highlighted gap in the pathophysiology of preeclampsia with a focus on maternal cardiovascular health.

Objectives

*To investigate the discrepancy between normal placentation and placentation in preeclampsia destined pregnancies.
*To investigate the precursors of maternal endothelial dysfunction in preeclamptic pregnancies.
*To investigate cardiometabolic risk and its impact on maternal vascular health.

Methods

Meticulous identification of relevant studies via a predefined search strategy applied to electronic databases like Medline/PubMed, Excerpta Medica Database (Embase), Web of Science, Scopus, Cochrane Library, and African Journals Online. Additionally, a manual search was conducted.

Conclusion

Endothelial dysfunction is a hallmark of preeclampsia. Retinal arterial narrowing is strongly associated with hypertension. This association is observed even in cases of preeclampsia. Retinal imaging allows for a non-invasive measurement of the development of cardiovascular disorders (Giarratano et al., 2024). There are a few studies that look into the microvascular status in pregnant women and even fewer studies that have done so in relation to cardiometabolic risk in South Africa

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INTRODUCTION

Preeclampsia (PE) is a pregnancy-specific hypertensive disorder that is diagnosed as the onset of hypertension (Blood pressure ≥140/90 mmHg) with proteinuria at or after 20 weeks of gestation (Bergman et al., 2023). The risk factors reported to precede the development of PE include hypertension, obesity, kidney disease, oxidative stress and diabetes (Perišić et al., 2022). Preeclampsia complicates up to 10% of pregnancies worldwide (Nirupama et al., 2021). It is responsible for more than 500,000 foetal deaths and 50,000 maternal deaths worldwide, with 26% of the reported cases being patients of African and Hispanic descent, outlining these ethnic groups as the most at risk for developing PE (Karrar and Hong., 2022). In South Africa, hypertensive disorders of pregnancy (HDP) account for 18% of all maternal deaths and are the most prevalent direct cause of maternal mortality (Moodley et al., 2019). According to a one-year prospective study in the Western Cape Province of South Africa, 17.7% of women with PE gave birth to stillborn babies (Nathan et al., 2018). A triennial report of the National Committee for Confidential Enquiry into Maternal Deaths (NCCEMD) in South Africa, noted that PE was linked to the maternal deaths of over 50% of hypertensive pregnancies (Moodley and Ngene, 2016). It is reported that women with complications associated with hypertension during pregnancy are at a greater risk of developing cardiovascular diseases (CVDs) after pregnancy (Melchiorre et al., 2020, Tooher et al., 2017). Although, there are differing studies that attempt to outline the pathophysiology of PE, there is a consensus that the placenta plays a critical role. Special cells known as cytotrophoblasts, produced by the developing placenta, invade the uterine wall to widen the spiral arteries in order to increase perfusion to the placenta (Spradley et al., 2015). However, in PE these cytotrophoblasts fail to adequately invade the uterine walls or fail to modify the spiral arteries, leading to a hypoxic placental environment and ultimately an ischemic placenta. The ischemic placenta releases anti-angiogenic factors, inflammatory factors and factors leading to reduced expression of proangiogenic factors into the maternal circulation (Brennan et al., 2014). These factors cause endothelial dysfunction leading to hypertension in the mother (Spradley et al., 2015). Endothelial dysfunction is a hallmark feature of preeclampsia and is characterized by impaired vascular relaxation, increased vascular tone, and decreased vasodilatory capacity (Boeldt and Bird, 2017). This dysfunction is thought to arise from various factors, including oxidative stress, inflammation, and placental ischemia, all of which can lead to reduced production of nitric oxide (NO) (Possomato-Vieira and Khalil., 2016). In preeclampsia, the reduced bioavailability of NO leads to vasoconstriction and increased peripheral resistance, contributing to the development of hypertension and other complications of the disease (Tashie et al., 2020; Bueno-Pereira et al., 2022). Additionally, the reduced NO production and increased levels of reactive oxygen species (ROS) can lead to endothelial damage and dysfunction, further exacerbating the disease (Bueno-Pereira et al., 2022). Oxidative stress is defined as an imbalance between reactive oxygen species (ROS) production and antioxidant defence mechanisms (Toboła-Wróbel et al., 2020). Reactive oxygen species (ROS) are highly reactive molecules that are produced naturally during normal metabolic processes within cells. ROS include free radicals such as superoxide anion (O_2^-) (Fisher et al., 2020). Under normal physiological conditions, ROS are produced in low to moderate quantities and facilitate normal endothelial cell signalling and vascular function (Redza-Dutordoir and Averill-Bates., 2016). However, excessive production of ROS, as in cases of oxidative stress, can lead to endothelial dysfunction by the impairment of nitric oxide (NO) signalling and promoting vascular inflammation and cell apoptosis. This can lead to reduced vasodilation, increased vascular tone, and increased permeability of blood vessels, ultimately contributing to the development of hypertension and other cardiovascular related complications such as PE (Shaito et al., 2022). The ischaemic placenta, found in cases of PE, induces maternal oxidative stress by producing excessive ROS, which in turn leads to endothelial dysfunction and ultimately, PE (Sánchez-Aranguren et al., 2014). Malondialdehyde (MDA) is a byproduct of lipid peroxidation and is a reliable marker for oxidative

stress (Bassu et al., 2020). Research suggests that MDA may not only serve as a marker of oxidative stress but also contribute to the pathogenesis of PE. MDA can induce apoptosis and inflammation in endothelial cells, disrupt nitric oxide signaling, and impair vascular function, all of which are key features of PE (Asiltas et al., 2018; D'Souza et al., 2016). Studies have outlined MDA levels to have been significantly increased in women with PE (Khadir et al., 2022; Tenório et al., 2019). According to a study conducted in southern Spain involving 4711 cases, obesity showed a strong association with the development of PE and other hypertensive disorders of pregnancy. Additionally, dyslipidaemia in the form of high levels of triglycerides, high levels of low density lipoprotein and low levels of high density lipoprotein have been associated with PE (Fernández et al., 2018, Mousa et al., 2018).

Under physiological conditions, the micro-vascular environment is protected from high blood pressures by the macro-vasculature. However, in pathological conditions, such as hypertension, the microvasculature is exposed to high pressured blood (Climie et al., 2019a). This leads to vascular damage in the form of arterial stiffening and overall increase in peripheral vascular resistance which leads to an increase in systemic blood pressure (Climie et al., 2019b). Studies have shown that in pregnancy, pathological changes in microvasculature are strongly associated with endothelial dysfunction and other cardiovascular disorders (Garcia-Ortiz et al., 2011, Giarratano et al., 2024).

Understanding the mechanisms underlying endothelial dysfunction and its contribution to the pathophysiology of PE is crucial given the adverse maternal and foetal outcomes associated with the disease. Involving the study of microvasculature may also assist in determining the severity of endothelial dysfunction, aiding in understating the progression of preeclampsia. Studies in this vein may be a step towards developing effective preventive and therapeutic strategies for this devastating disorder. The pathophysiology of preeclampsia, as well as the factors that predispose women to the disorder, are still under critical investigation. This review is an expansion on what is currently known and what remains to be understood about the development of preeclampsia and the influence of various factors on its progression.

Methods

We meticulously identified relevant studies via a predefined search strategy applied to electronic databases like Medline/PubMed, Excerpta Medica Database (Embase), Web of Science, Scopus, Cochrane Library, and African Journals Online. Additionally, a manual search was also conducted to collect the relevant literature.

Epidemiology of Pre-eclampsia

Preeclampsia (PE), a complication during pregnancy, is a leading cause of illness and death among both mothers and their offspring worldwide (Boldeanu et al., 2023). Clinically, PE is diagnosed as the presence of hypertension (BP> 140/90) coupled with proteinuria and end-organ damage such as kidney and liver failure that begins to manifest at or after 20 weeks of gestation (AlSubai et al., 2023). It occurs in 2 to 8% of pregnancies globally (Boldeanu et al., 2023). The occurrence of PE differs across Africa, with incidence ranging from 1.8% to 16.7%. In Sub-Saharan Africa, the incidence of preeclampsia has been reported to be 13%. (Jikamo et al., 2023). In South Africa, the prevalence of PE is reported to occur in 5 to 8% of pregnancies. Ethnicity has been outlined as a risk factor for PE, and women of African ethnicity have been seen to be at higher risk of developing PE (Karrar and Hong, 2022). Debates on the exact cause of PE are ever-growing; however, a pathological change in the normal placentation process has been universally accepted as one of the key events leading to the incidence of PE (Chatzakis et al., 2023; Gibbs et al., 2023; MO et al., 2023).

Normal placentation

The placenta is an organ formed during the first three months of pregnancy. It is an essential part of pregnancy that ensures the baby's proper development (Turco and Moffett., 2019). Major and crucial placental development occurs during the first 12 weeks, known as the first trimester of pregnancy (Burton and Jauniaux., 2018). The placenta's development stems from the blastocyst's external layer, termed the trophoectoderm (TE). The TE fuses, resulting in the formation of a syncytium. After implantation, the syncytium rapidly invades the endometrium, now termed the decidua (Turco

and Moffett., 2019). Part of this invasion includes the erosion of the glands in the decidua, which causes the decidual secretions to bathe the syncytium. These secretions promote cytotrophoblast proliferation into the syncytiotrophoblast (Herrick and Bordoni., 2020). Continued proliferation results in the formation of villous trees. The cytotrophoblast breaks through, forming a cytotrophoblast shell (CS) that lies between the blastocyst and the decidua. Singular cytotrophoblast cells, termed extravillous trophoblast (EVT), begin to depart the CS and invade the decidua, forming the structural plan for the placenta. The EVT invasion is via two methods: invasion as interstitial EVT (iEVT) and invasion as endovascular EVT (eEVT) (Turco and Moffett, 2019). The eEVT travel within the spiral arteries that supply the uterus, forming plugs that effectively reduce maternal blood flow to the placenta. This allows for the uninterrupted invasion of the eEVT into the endothelial cell layer of the spiral arteries (Bulmer et al., 2020). At this level, the eEVT replaces the smooth muscle cells, ultimately modifying the structures of the vessels. The iEVT travel through the uterine stroma adjacent to the spiral arteries. The iEVT erodes the actin filaments of the arteries' smooth muscles, replacing them with other materials that impede vasoactivity while modulating immune interactions (Zhang et al., 2023). The combined action of the iEVTs and the eEVTs leads to spiral artery remodelling to serve as a low-pressure, high-volume conducting vessel for the foetus (Turco and Moffett, 2019). As pregnancy progresses, the plugs formed by the eEVT dissipate and the spiral arteries can now transport the increased maternal blood, via the placental membrane, to the foetus, providing it with nutrients and oxygen (Herrick and Bordoni., 2020).

Blood volume and pressure regulation in normal pregnancy

Blood pressure can be described as the force the circulating blood exerts on the arterial walls. It is divided into systolic and diastolic pressure, which describe the pressure while the heart is contracting and when it is relaxing, respectively (Das, 2019). During pregnancy, the mother undergoes physiological and anatomical changes that allow her to accommodate and care for the foetus forming in the uterus (Soma-Pillay et al., 2016). There are significant hemodynamic and cardiovascular changes that occur, namely, an increase in blood volume of up to 45%, an increase in cardiac output up to 50%, and a decrease in blood pressure during the first and second trimesters (Soma-Pillay et al., 2016). Other adaptations include the formation of new blood vessels to support the additional cardiac output. Vasodilation is the hallmark of these changes and is mediated mainly by the potent vasodilator, NO (Soma-Pillay et al., 2016).

Pathophysiology of Preeclampsia

The pathophysiology of preeclampsia is characterised by abnormal placentation, abnormal spiral artery remodelling, placental insufficiency, and endothelial dysfunction (Nirupama et al., 2021). Abnormal placentation has been highlighted as a key instigator in the pathophysiology of preeclampsia. Abnormal placentation occurs when the cytotrophoblast cells of the placenta fail to adequately remodel the maternal spiral arteries (Rana et al., 2019). Abnormal spiral artery remodelling leads to reduced perfusion to the placenta (placental ischemia). Persistent placental ischemia causes the placenta to enter a state of hypoxia (Viana-Mattioli et al., 2023). The ischemic placenta contributes to the development of preeclampsia by releasing three kinds of factors, namely, antiangiogenic factors, inflammatory cytokines, and oxidative stress markers, into the maternal circulation (Hariharan et al., 2017). These factors produced by the placenta in response to ischemia cause endothelial dysfunction in the maternal circulation, which is linked to hypertension and proteinuria, both of which are clinical signs of preeclampsia (Apicella et al., 2019).

Antiangiogenic factors and endothelial dysfunction

As the placenta develops, it produces factors and hormones that promote changes in blood volume and pressure during normal pregnancy. Vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) are proteins produced by the placenta that stimulate angiogenesis and modify the maternal systemic vasculature (Brennan et al., 2014). This is achieved by binding these proteins to the VEGF receptor 2 (VEGFR 2) located on the maternal endothelial cells, transducing a signalling

pathway via mediators such as phosphatidylinositol-3 kinase (Pl3k). This results in the formation of new blood vessels, lowering the blood pressure by decreasing systemic vascular resistance (SVR) (Padley et al., 2018). However, in preeclampsia, the hypoxic placenta releases antiangiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt-1) into maternal circulation (Flint et al., 2019). The sFlt-1 binds to circulating VEGF and PlGF, inhibiting their interaction with their receptors, causing a reduction in VEGF and PlGF signalling (Kara et al.,2021; Akasaki, 2024) (Figure 1a). This effectively disrupts VEGFR and PlGF signalling, leading to endothelial activation, cell injury and ultimately endothelial dysfunction (Sani et al., 2019) (Figure 1b).

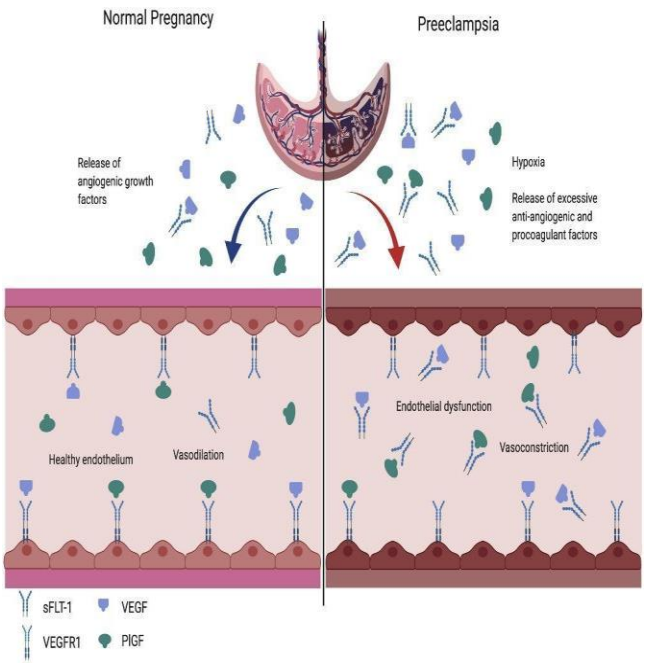


Figure 1.1a

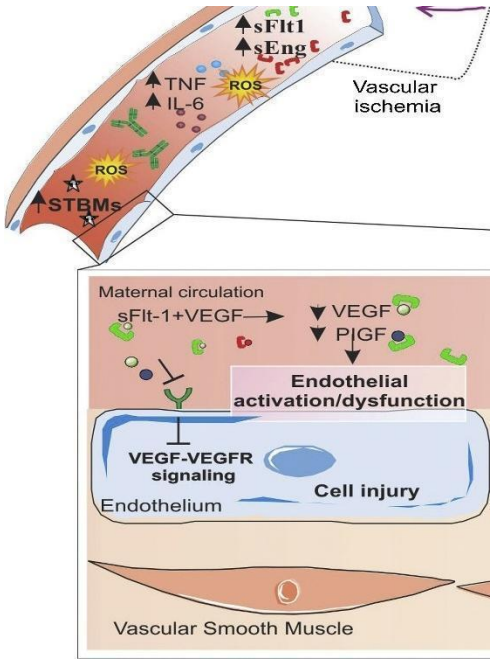


Figure 1.1b

Figure 1.1a (left): A contrast of the pro-angiogenic and anti-angiogenic factors imbalance in normal and preeclamptic pregnancies. Emphasising the decreased bioavailability of VEGF due to circulating sFLT-1. **Figure 1.1b (right):** Endothelial cell injury due to decreased VEGF-VEGFR signalling. VEGF: Vascular Endothelial Growth Factor. PlGF: Placental Growth Factor. sFLT-1: Soluble fms-like tyrosine kinase 1. VEGFR1: Vascular Endothelial Growth Factor Receptor 1 (Rana et al.,2022; Sani et al., 2019).

Oxidative stress and Preeclampsia

During normal pregnancy, there is a steady rise in the presence of circulating reactive oxygen species (ROS), such as superoxide and hydrogen peroxide. These are products of physiological processes within cells, and in pregnancy, ROS are mainly regulated by the developing placenta (Chiarello et al., 2020). However, as evident in cases of preeclampsia, the production of ROS goes unchecked and increases to levels that the mother's body cannot overcome with antioxidants, resulting in oxidative stress (Guerby et al., 2021). Lipid peroxidation occurs due to interactions between ROS and the lipid bilayer of cell membranes (Juan et al.,2021). The oxidative stress observed in preeclampsia leads to increased lipid peroxidation, resulting in local tissue damage. Endothelial nitric oxide synthase (eNOS) is an enzyme that, in conjunction with its cofactor, tetrahydrobiopterin (BH_4), produces nitric oxide (NO) in the maternal endothelium and placenta (Perez de la Lastra et al., 2022). Nitric oxide is a regulator of endothelial health, maintaining the endothelium's anatomical and physiological state (Vanhoutte., 2018). The presence of ROS results in

endothelial dysfunction mainly via two pathways. The first pathway involves the uncoupling of the eNOS by inhibiting BH_4, through the binding of superoxide to BH_4, causing the eNOS to produce superoxide instead of NO (Vanhoutte, 2018). Secondly, superoxide readily binds to available NO to form peroxynitrate, which also falls under the family of ROS, further inducing oxidative stress (Wang et al., 2021). The decreased bioavailability and bio-production of NO leads to endothelial dysfunction, and in pregnancy may lead to preeclampsia (Meister and Feresin, 2023) (Figure 2). The base guanine in DNA is the most susceptible to being oxidised, and as a result, formations of 8-oxo-7,8-dihydroguanine (8-oxodG) and 8-hydroxyguanine (8-OHdG) are abundant in cases of oxidative stress. Due to this reason, 8-OHdG is a marker of oxidative stress (Halczuk et al., 2020).

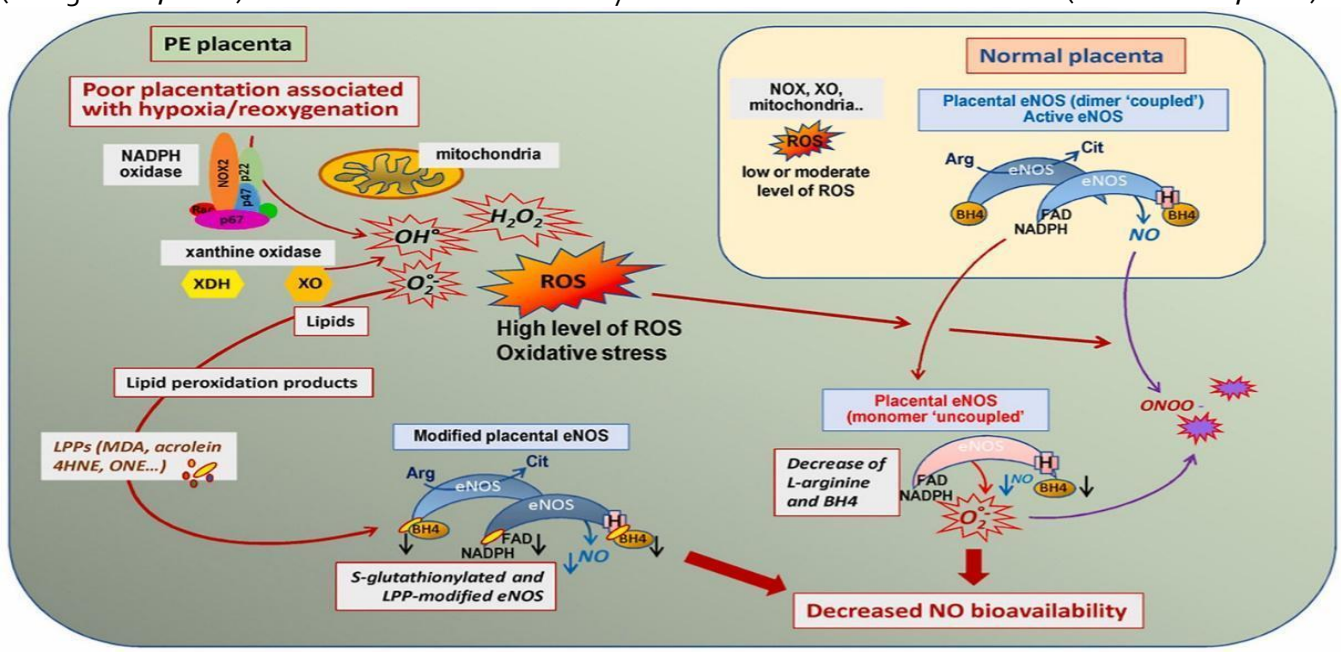


Figure 2.2: Role of oxidative stress and lipid peroxidation in decreased Nitric Oxide production in Preeclampsia (Guerby et al.,2016).

Macro-vascular Function and Cardiovascular Health

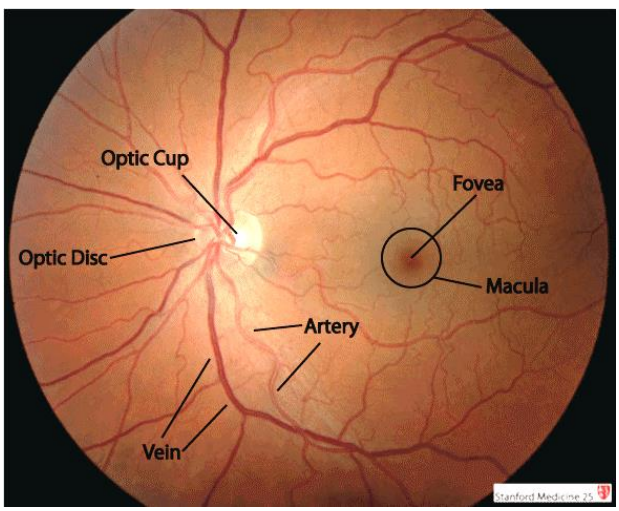
Arterial stiffness describes the anatomical characteristic of arterial walls and their functional ability to distend and contract as a response to changes in blood pressure. Arterial stiffness, therefore, has an observable impact on blood pressure and general haemodynamics and is a cardiovascular disease risk factor (Townsend et al., 2015; Hofmann et al., 2014). Pulse Wave Velocity (PWV) quantifies the speed at which arterial pulses move through the arterial network, with a greater PWV signifying increased arterial stiffness (Wu et al., 2019). Carotid femoral Pulse wave velocity (cfPWV) is accepted as the gold standard for assessing central arterial stiffness (Phan et al.,2021). The clinical cutoff point for normal cfPWV is 10 m/s. Readings above this value indicate increased arterial stiffness and cardiovascular disease risk (Ceponiene et al., 2014; Van Bortel et al., 2012). Flow-mediated slowing (FMS) is a method used to measure the minimum PWV during reactive hyperaemia (Basgaran et al., 2016). Flow-mediated slowing is used to assess endothelial function, with increased measurement indicating increased endothelial function (Stoner et al., 2020). The clinical cut-off point for a normal FMS reading is 11.3%. An FMS reading of less than 11.3% has been associated with poor endothelial function and preeclampsia (Shechter et al., 2014; Lößner et al., 2023). Peripheral artery disease is associated with increased cardiovascular risk. Ankle Brachial Index (ABI) is a non-invasive screening tool for peripheral artery disease (Aboyans, 2012). ABI is calculated by dividing the ankle level systolic pressure by the brachial systolic pressure (Aerden et al., 2011). Cut-off points for normal ABI are 0.9-1.4, with values lower than 0.9 indicating the presence of peripheral

disease (Marius et al., 2014).

Asymmetric dimethylarginine (ADMA) is a naturally occurring metabolite in the human body. ADMA competes with the nitric oxide synthase (NOS) substrate, L-arginine, binding to the enzyme, NOS, effectively inhibiting the biosynthesis of NO (Guo et al.,2023). A pathological increase in serum levels of ADMA leads to a greater inhibition of NOS (Selanno et al.,2020). ADMA has been observed as a marker of endothelial dysfunction and a strong indicator of cardiovascular disease dysfunction (Doğan et al.,2018; Espinoza et al.,2019).

Retinal Microvasculature and Cardiovascular Health

Microvasculature, which constitutes small arteries (lumen<300µm in diameter) and arterioles (lumen<100µm in diameter), make up 45%-50% of total peripheral resistance in systemic vascular circulation (Laurent et al.,2019). The inversely proportional relationship between arteriolar lumen diameter (four times) and vascular resistance means that a slight alteration in arteriolar diameters significantly changes vascular resistance (Rizzoni et al.,2023). Pregnancy results in physiological stress that affects every organ system, including the visual system (Kalogeropoulos et al., 2019). Retinal microcirculation refers to blood flow through the network of blood vessels within the retina. Retinal vasculature offers the only non-invasive method for observing microcirculation in the human body. (Naegele et al., 2018). Pathological changes within the retinal microvasculature may manifest as a result of newly developed disorders in pregnancy, such as preeclampsia (Qin, 2020). Retinal vessel calibres have been used to assess cardiovascular risk, with narrower arterioles, wider venules and a decreased arteriolar-venular ratio being associated with increased incidents of stroke and coronary heart disease (von Hanno et al., 2014; Chandra et al.,2019). Changes in retinal vessel diameters have been shown to predict cardiovascular disease risk (Drobnjak et al.,2016). Modifications of the retinal microvasculature in Preeclampsia - provoked retinopathy are similar to those observed in hypertensive retinopathy (Ciloglu et al., 2019). Reported changes include the narrowing of retinal arteries as well as abnormal vessel crossing (Modi and Arsiwalla, 2023). Optical coherence tomography angiology (OCTA) is an imaging technique that offers a non-invasive method to evaluate changes within the retinal microvasculature, such as vessel nicking or abnormal vessel crossing (Kızıltunç et al., 2020) (Figure 3b).



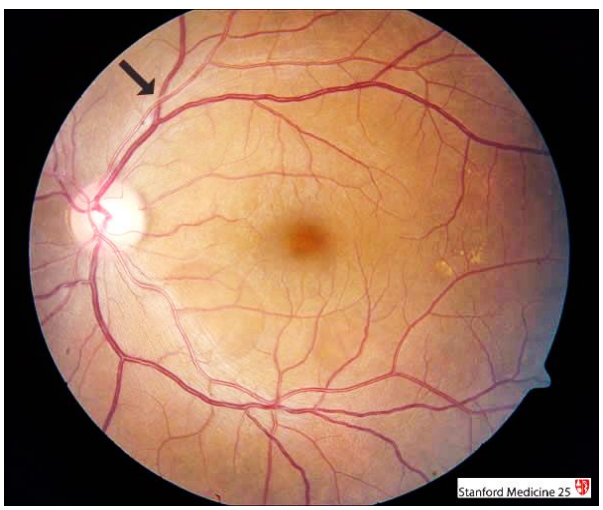


Figure 1.3a: Fundus picture of a left eye, demonstrating normal vasculature (Arteries and veins) (left image). **Figure 1.3b shows an abnormal vessel crossing (black arrow) observed in patients** with systemic hypertension (right image). Images captured using OCTA (Stanford Medicine, 2019).

Cardiometabolic Risk and Vascular Health

Women with preeclampsia are at an increased risk of developing cardiovascular diseases postpartum (Thilaganathan and Kalafat, 2019). Cardiometabolic risk is described by a collection of factors that increase an individual's risk for experiencing cardiovascular diseases (Mezhal et al., 2023). These factors include: elevated blood pressure, triglycerides, total cholesterol, blood glucose, glycated haemoglobin, lowered high-density lipoprotein (HDL-C) and obesity (Despres et al.,2008; Lancellotti, 2023). Hyperlipidaemia is a physiological occurrence during normal pregnancy. It is attributed to the growing baby's increasing demands for nutrients; however, in normal pregnancies, the lipid changes are under hormonal control. This is not the case in preeclamptic pregnancies, as changes in lipid circulation have been observed to be exaggerated (Mousa et al.,2018; Khoury et al., 2009). The increased lipid circulation leads to a build-up of lipid deposits on the arterial walls, triggering an immune response which leads to a build-up of oxidative stress and ultimately endothelial dysfunction (Hadden and McLaughlin, 2009). Therefore, studying the cardiometabolic health status of this high-risk population may be paramount and will assist in understanding the factors that contribute to the adverse cardiovascular events associated with preeclampsia.

Conclusion

Preeclampsia remains a complex and multifactorial disorder with profound implications for maternal and foetal health. The current literature reviewed underscored the central role of abnormal placentation and placental ischemia in initiating a cascade of pathological events — including angiogenic imbalance, oxidative stress and endothelial dysfunction, that all together make up the clinical manifestations of preeclampsia. Elevated levels of antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1), coupled with reduced bioavailability of nitric oxide and increased reactive oxygen species, contribute to vascular injury and impaired hemodynamic regulation. Furthermore, the interplay between microvascular and macrovascular dysfunction, as well as emerging evidence on retinal microvasculature and cardiometabolic risk, highlights the systemic nature of the disease and its long-term cardiovascular consequences. Given the disproportionate burden of preeclampsia among women of African descent and the growing recognition of its intergenerational impact, future research must prioritize precision-based interventions and early diagnostic strategies that integrate molecular, vascular, and metabolic biomarkers. Advancing our understanding of these mechanisms is essential for developing targeted therapies and improving outcomes for high-risk populations.

Abbreviations
8-OHdG- 8-hydroxyguanine
8-oxodG- 8-oxo-7,8-dihydroguanine
ABI- Ankle Brachial Index
ADMA- Asymmetric dimethylarginine
BH_4- Tetrahydrobiopterin
cfPWV- Carotid femoral Pulse wave velocity
CS- cytotrophoblast shell
CVD- Cardiovascular disease
eEVT endovascular extravillous trophoblast
eNOS- Endothelial nitric oxide synthase
EVT- extravillous trophoblast
FMS- Flow-mediated slowing
HDL-C- high-density lipoprotein
HDP-hypertensive disorders of pregnancy

iEVT- interstitial extravillous trophoblast
NCCEMD- National Committee for Confidential Enquiry into Maternal Deaths
NO-Nitric oxide
NOS- Nitric oxide synthase
OCTA- Optical coherence tomography angiology
PE- Preeclampsia
Pl3k- phosphatidylinositol-3 kinase
PlGF- Placental Growth Factor
PWV- Pulse Wave Velocity
ROS- Reactive oxygen species
sFLT-1- Soluble fms-like tyrosine kinase 1.
SVR- Systemic vascular resistance
TE- trophectoderm
VEGF- Vascular Endothelial Growth Factor
VEGFR1- Vascular Endothelial Growth Factor Receptor 1
VEGFR2- Vascular Endothelial Growth Factor Receptor 2

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