HYPERTENSIVE DISORDERS OF PREGNANCY

DR HIDAYATUL RADZIAH ISMAWI
DR MAIZURA MOHD ZAINUDIN
DR NURJASMINE AIDA JAMANI

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BY:
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EDITOR:
DR HIDAYATUL RADZIAH ISMAWI

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PREFACE

This e-book was published to embrace the concept of open access of knowledge and sustainability.

A World Health Organization (WHO) review identified hypertension as the main cause of maternal mortality in industrialised countries, accounting for up to 16% of maternal deaths. Hypertensive disorders of pregnancy are annually responsible for about 25,000 maternal deaths in Africa, 22,000 maternal deaths in Asia, 38,000 maternal deaths in Latin America and the Caribbean and 150 maternal deaths in industrialised countries.

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AUTHORS

Asst. Prof. Dr Hidayatul Radziah Ismawi

MBBS, IIUM
PhD (Medical Sciences), IIUM
Lecturer, Kulliyyah of Medicine, IIUM

Asst. Prof. Dr Maizura Mohd Zainudin

MBBS, IIUM
PhD (Medical Sciences), UKM
Lecturer, Kulliyyah of Medicine, IIUM

Assoc. Prof. Dr Nurjasmine Aida Jamani

MD (UKM)
M.Med (Fam Med), UKM
Lecturer, Kulliyyah of Medicine, IIUM

EPIDEMIOLOGY OF HDP

Epidemiology of HDP

A World Health Organization (WHO) review identified hypertension as the main cause of maternal mortality in industrialised countries, accounting for up to 16% of maternal deaths. Other studies state that in Africa and Asia, hypertensive disorders accounted for 9% of maternal deaths, whereas, in Latin America and the Caribbean, the figure was over 25%. Hypertensive disorders of pregnancy are annually responsible for about 25,000 maternal deaths in Africa, 22,000 maternal deaths in Asia, 38,000 maternal deaths in Latin America and the Caribbean and 150 maternal deaths in industrialised countries (Duley, 2009; Hutcheon et al., 2011).

HDP affects about 5-10% of pregnancies with approximately 1% of pregnancies are complicated by pre-existing hypertension, 5–6% by GH without proteinuria, and 1–2% by PE worldwide (Al Khaja et al., 2014; Hutcheon et al., 2011; Yelumalai et al., 2010). The prevalence of HDP in Malaysia is approximately 23.3 per 1000 live births (Yelmizaitun et al., 2010).

In Malaysia, HDP is among the most common causes of maternal death. HDP accounted for 14.2% of maternal deaths reported in Malaysia between 1997-2000. The Maternal Mortality Rate (MMR) was 28.1 per 100 000 live births in 2000 (Jeevaratnam et al., 2010). In the year 2007, HDP including PE contributed to about 18.1% of maternal deaths in Malaysia (Kaur & Singh, 2011; Zuo et al., 2016). In Hospital USM Kubang Kerian, a total of 854 cases of PE occurred between the year 2005 to 2013 (Unit Rekod Perubatan Hospital USM, 2014).

Risk factors of HDP

Risk factors of HDP and more specifically PE include family history, primiparity, pre-existing hypertension or diabetes mellitus, smoking, previous history of PE, older maternal age, obesity and multiple pregnancy (Cunningham et al. 2010, Hutcheon et al., 2011).

Complications of HDP

HDP is associated with maternal and foetal morbidity and mortality. The risks of these unwanted outcomes increases dramatically with the superimposition of PE. Although maternal mortality is the most serious outcome of HDP, the risks of other serious complications such as acute renal failure, pulmonary oedema, placental abruption, thrombocytopaenia, disseminated intravascular coagulation, HELLP syndrome and aspiration pneumonia are increased, in severe pre-eclampsia as much as 10-30 fold (Ananth & Basso, 2010; Ghulmiyyah & Sibai, 2012; Hutcheon et al., 2011).

Studies found that well controlled chronic hypertension in pregnancy causes only minimal increased risk for perinatal or foetal death. However, women with PE have a 35% higher risk of stillbirth (Hutcheon et al., 2011). Neonatal mortality is about two-fold higher among infants of mothers with PE, and this increased risk has not changed during recent decades. The risk of small for gestational age (SGA), a birth weight <10th percentile; higher frequency of induced labour,

babies having low Apgar scores, neonatal respiratory difficulties, febrile seizures, encephalopathy, and neonatal intensive care unit admission (Ananth & Basso, 2010; Hutcheon et al., 2011; Rasmussen & Irgens, 2008; Reem Mustafa et al., 2012).

The risk of recurrent PE in subsequent pregnancies varies with the severity and time of onset of the acute episode. Women with milder PE have a 7–15% chance of developing PE in a subsequent pregnancy, compared with a 1% chance for women with no PE in their first pregnancy. Women with severe, early PE during their first pregnancy will have a high risk of recurrent PE in their subsequent pregnancies (25-65%). The risk of PE in a third pregnancy increases to 30% if a woman's first two pregnancies were complicated by PE, whereas the risk remains at 1% for women with no history of PE. The risk of recurrence is influenced by gestational age at onset and plurality of the index pregnancy (Dssursuldwh et al., 2013; Hutcheon et al., 2011; Reem Mustafa et al., 2012). Incidence and prevalence rates for other types of HDP are scarce.

Long-term Sequelae of HDP

Studies have found a consistent association between PE and long-term risk of maternal cardiovascular and metabolic disease. In fact, the overall increase in mortality risk after PE is largely driven by increased risk of death due to CVD (Hutcheon et al., 2011).

Significantly increased risks were seen for women with new-onset isolated systolic or diastolic hypertension as well as among women with de novo GH even in the absence of traditional risk factors such as smoking, over-weight or obesity, and advanced age, have high risk for future disease, particularly for fatal myocardial infarctions (MI), compared to normotensive women; suggests that hypertension during pregnancy has an independent effect on long-term risk. There is also with increased risk for arterial hypertension and cardiovascular morbidity and mortality, heart failure, ischemic heart disease (IHD) (Ghulmiyyah & Sibai, 2012; Männistö et al., 2013). Additionally, women with PE have a 3-4-fold increased risk of developing CH and an approximately 2-fold increased risk of IHD, stroke

and venous thromboembolism (Ghulmiyyah & Sibai, 2012; Hutcheon et al., 2011; Männistö et al., 2013).

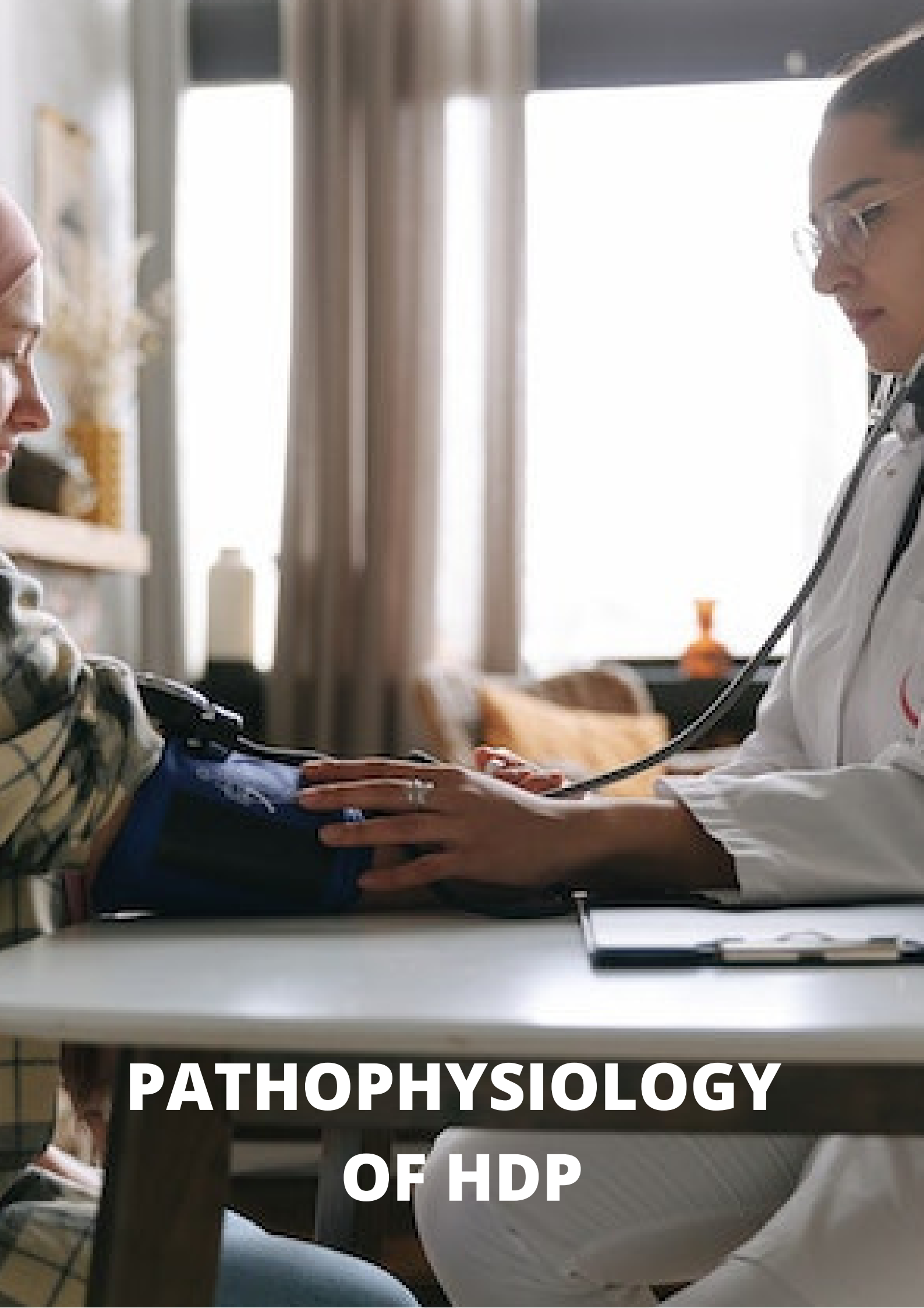
Although the CVD risks are associated with HDP as a whole, most of the previous research has focused on PE. A large population-based cohort study of Asian women from Taiwan examined the association between PE/eclampsia and MACEs including MI, heart failure, percutaneous cardiac intervention, coronary artery bypass grafting, malignant dysrhythmia, cardiac shock, thrombolysis, and implantable cardiac defibrillator. Their findings were consistent with previous reports, where the investigators found that women with PE/eclampsia had a significantly greater risk of MACEs, especially MI and stroke. This elevated risk remained significantly high throughout the early years postpartum (≥36 months) (Lisonkova & Joseph, 2013; Mangos et al., 2012; Männistö et al., 2013; Veerbeek et al., 2015).

Not surprisingly, the same conditions that have been implicated in the pathogenesis of HDP are also strong risk factors for future development of CVD, including insulin resistance, DM, obesity, chronic hypertension, systemic inflammation, and renal disease. Thus, shared risk factors rather than a causative relationship could explain the apparent associations between HDP and later CVD (Magnussen et al., 2007; McDonald et al., 2008; Melchiorre et al., 2011).

Evans et al. (2011) found that women with previous history of PE have higher MAP and DBP, higher TPR, tendency toward higher peripheral (small vessel) vascular stiffness, endothelial dysfunction, and marginal insulin resistance. Other studies show vascular changes that could modify the woman's risk for future CVD with endothelial dysfunction measured at 6–12 months, 1 year, 5–6 years, and even up to 15–25 years.

Although, these findings were not consistent in all the studies (Drost et al., 2010; Valdiviezo et al., 2012). Despite abundant data supporting the long-term CVD risk with PE touted as a marker for future CVD, traditional risk factors and risk-stratification tools generally fail to take sex-specific risk factors for women into consideration. Identification of these higher-risk women would provide the opportunity for closer surveillance and preventive programs to reduce CVD risk (Heida et al., 2015; Lei et al., 2011).

Other than CVD, there have also been studies into possible associations with other types of diseases although the results have not been congruous. There is reportedly both decreased and increased risks of cancer after PE, with a meta-analysis reporting a null effect. Elevated BP during pregnancy have been found to signal higher risk of cerebrovascular, and kidney disorders, as well as DM, later in life (Lin et al., 2011; Männistö et al., 2013).



PATHOPHYSIOLOGY OF HDP

PATHOPHYSIOLOGY OF HDP

The exact pathophysiology of HDP is still not fully understood. However, there are a few common theories. Most researchers focus on PE, due to the more immediate clinical implications. What essentially happens can be divided into two stages which are usually sequential but not necessarily so, namely placental ischaemia and the maternal response. The events are thought to occur to a lesser degree in HDP not involving PE (Roberts & Hubel, 2009). Endothelial dysfunction and maternal autoimmune responses are also implicated in this complex pathophysiology.

Placental ischaemia

A successful outcome of pregnancy is dependent on sufficient placental perfusion and adequate blood flow via utero-placental and feto-placental circulatory systems. Physiologically, blood volume during pregnancy increases by nearly 50%, CO increases by 30–40%, and blood flow to the uterus increases by approximately 8-fold. Therefore, the maternal vascular system must adapt accordingly to ensure adequate oxygenation and nutrient supply to the foetus and placenta, as well as for the pregnancy to proceed successfully (Brennan et al., 2014; Roberts & Hubel, 2009). Consequently, during normal pregnancy, there is a conversion of the high-resistance, small-diameter blood vessels into high-capacitance, low-resistance vessels when foetal derived cytotrophoblasts invade the maternal spiral arteries of the uterus. These will replace the maternal endothelium, and undergo differentiation into an endothelial-like phenotype. This physiological process ensures adequate delivery of maternal blood to the developing utero-placental unit (George & Granger, 2012).

Generally, the utero-placental circulation starts with the maternal blood flow into the intervillous space through uterine spiral arteries. After exchange of oxygen and nutrients in the intervillous space, the in-flowing maternal arterial blood pushes deoxygenated and nutrient-depleted blood into the endometrium and then flows back to the maternal circulation through uterine veins. The feto-placental circulation allows umbilical arteries to carry deoxygenated and nutrient-depleted feotal blood from the foetus to the villous core foetal vessels. After exchange of oxygen and nutrients, the umbilical vein carries fresh oxygenated and nutrient-rich blood back to the foetal circulation. The feto-placental circulation is composed of two umbilical arteries, one vein and a placental vascular tree, which includes chorionic plate (feotal stem villous) arteries and their branches, terminal villi and veins (Burke & Karumanchi, 2013; Lyall et al., 2013; Osol & Moore, 2014).

The placental vascular bed is often regarded as a comparatively low-resistance circulation in which blood flow is determined by the foetal cardiac output, contributing to the circulation, when maternal arterial pressure propels maternal blood flow through the placenta. Therefore, placental vascular tone is essential for maintaining the adequate placental blood flow and volume. Because placental vessels lack automatic innervation (Walker & MacLean, 1971), local vasoconstrictor and vasodilator systems, including prostanoids, endothelins, HA, serotonin (5-HT), catecholamines, RAAS and NO, are of paramount importance for controlling placental vasoactivities and blood flow in the placental circulation.

Maternal Autoimmune Response

As an endocrine organ, the placenta can produce numerous vasoactivators that are released into the circulation, dominating the regulation of placental vascular reactivity (Gao et al., 2017). The balance between vasodilators and vasoconstrictors in placental circulation is crucial for a homeostatic balance. Therefore, the compromised and abnormal constriction and relaxation of the placental vasculature influences blood flow in the placenta, a root cause for placental ischemia, leading to an abnormal course of pregnancy such as HDP and PE. Remodeling of placental arteries, like spiral arteries, was also suggested as a main pathological cause for local ischemia (Burke & Karumanchi, 2013; Gathiram & Moodley, 2016; Lyall et al., 2013). Either placental vessels became narrow or there is a reduction in vascular branches (Furuya et al., 2011; Furuya et al., 2008), which could induce poor blood flow or ischemia in the placenta.

Altered utero-placental blood flow has long been proposed as the main culprit in the pathophysiology of pre-eclampsia and HDP. This is because the only effective resolution of PE is delivery of the placenta, and not simply delivery of the foetus (George & Granger, 2012). Researchers postulate that the key pathophysiological processes are initiated by reduced placental insufficiency resulting from inadequate remodeling of the maternal vasculature and inadequate trophoblastic invasion (Aggarwal et al., 2012).

In patients with HDP and especially PE there is poor trophoblastic invasion of the uterus with incomplete endovascular invasion of the spiral arteries. This failure of the cytotrophoblasts to penetrate deep results in high-resistance vessels and relative reduction in utero-placental blood flow. Subsequently, there is inadequate delivery of blood to the developing utero-placental unit, which creates hypoxia and chronic ischemia within the placenta. Additional pathologic findings include placental infarcts (George & Granger, 2012; Reem Mustafa et al., 2012).

In response to placental insufficiency, there is overproduction of pathogenic factors including anti-angiogenic peptides and inflammatory mediators. These factors enter the maternal bloodstream and manifests as a clinical syndrome characterized by widespread systemic endothelial dysfunction (Aggarwal et al., 2012; George & Granger, 2012). Among the anti-angiogenic peptides produced are soluble sFlt-1, which is a splice variant of fms-like tyrosine kinase-1 and soluble endoglin (sEng), a truncated form of endoglin. These peptides act by binding with their ligands, VEGF and PlGF; and transforming growth factor-b, respectively, in circulation, thereby preventing the binding of these pro-angiogenic molecules to their native endothelial cell-surface receptors. (Aggarwal et al., 2012; Nadarajah et al., 2009). The reduced uterine perfusion pressure (RUPP) animal models of placental ischaemia results in hypertension, proteinuria and renal histological changes including endotheliosis and deposition of fibrin and fibrinoid deposits; as well as reduced platelet count and an increase in circulating sFlt-1 (McCarthy et al., 2011).

Other observations that support utero-placental ischemia as a key factor in HDP and specifically preeclampsia is that the disorder occurs predominantly in primagravidas with immature uterine vasculature. There are also consistent abnormalities of the placentae and utero-placental vascular interface, with an increased risk in multiple pregnancies (multiple placentas). The disease is also noted to often occur late in gestation, with increased incidence in patients with underlying vascular disease such as DM, hypertension and systemic lupus erythematoses (SLE) (Reem Mustafa et al., 2012).

Although there is no systemic inflammation during pregnancy, circulating cytokines are found to be elevated in maternal plasma inflammatory cytokines are thought to link placental ischemia with cardiovascular and renal dysfunction symptoms seen in this disorder. Excessive inflammation is central to the activation of maternal immune response. The autoimmune components of PE can be further divided into, the production of autoantibodies and the innate immune response (Hausvatera et al., 2011; George & Granger, 2012).

Production of agonistic ANG II type 1 receptor autoantibodies (AT1-AAs), which have been found in the circulation of women with preeclampsia. Researchers theorize that this agonistic autoantibody, specifically targeted to the AT1-AA is produced by women with PE. This autoantibody is thought to play an important role in mediating hypertension during pregnancy. Brewer et al. (2013) further hypothesized that the AT1-AA is important in causing enhanced blood pressure sensitivity to ANG II (Brewer et al., 2013; George & Granger, 2012).

The innate inflammatory response is mediated by inflammatory cytokines. Maternal serum levels of IL-6 and TNF-α play a significant role in pathogenesis of PE. TNF-α is produced by monocytes, induces apoptosis, and inhibits proliferation of trophoblast cells in PE. Soluble TNF-α receptors bind with circulating TNF-α leading to a decrease of the ligand's availability (LaMarca, 2012). Even the antibodies appear to be induced by the production of TNF-α. Elevated levels of many cytokines and chemokines have been identified in the maternal circulation at various stages of gestation, including TNF-a, IL-6, IL-2, IL-8, IL-10, IP-10, MCP-1. (Brennan et al., 2014; Vitoratos et al., 2010).

Endothelial dysfunction

There are numerous studies indicating that hypertension causes endothelial dysfunction and vice versa, it can be said that the link between the two is cyclical, like the “chicken and egg dilemma”, rather than sequential. Therefore, whether the former precedes the latter or it occurs as a consequence of essential hypertension still remains unclear. However, association of endothelial dysfunction with essential hypertension is increasingly recognised since a large number of studies have proved their relationship (Bernatova, 2014; Lau et al., 2012; Mordi et al., 2016).

Even though the endothelium has several functions, generally the term endothelial dysfunction refers to an impairment in its vasodilatory capacity. This is characterized by an imbalance between endothelium-dependent vasodilation and vasoconstriction.

This event can occur through several mechanisms, including:

1. reduced NO synthesis
2. reduced NO bioavailability
3. antagonism of NO by endothelium derived contracting factors such as ET-1

One of the causes that can reduce synthesis of NO is decreased endothelial nitric oxide synthase (eNOS) activity caused by competitive inhibition of eNOS by ADMA. Furthermore, ROS can cause reduced bioavailability of NO by converting it to peroxynitite (Hybertson et al., 2011). Figure 2.10 summarises the effect of reduced NO bioavailability on endothelial function.

Therefore, endothelial dysfunction is essentially an imbalance between the production and bioavailability of endothelium-derived relaxing factors (EDRFs) and endothelium-derived contractile factors (EDCFs) (Silva et al., 2012). It may be manifested by the altered synthesis and release of endothelial cell products.

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