CHAPTER 1

INTRODUCTION

Hypertension is one of the leading pregnancy complications, which leads to significant maternal mortality and morbidity. This complication is found in about 5-10% pregnancy [1,2] and related to 16% maternal mortality in industrialized countries, according to World Health Organization (WHO) report [3]. In another report, hypertension in pregnancy causes 14% of all maternal death worldwide, approximately 42.000 every year [4]. In developing countries, maternal death caused by hypertension in pregnancy was even higher, ranged from 9% in Africa & Asia region until over 25% in Latin America and Caribbean. Most of the maternal death occurs in low social, economic countries (99%), with maternal death in high-income countries being very rare [5].

Hypertension in pregnancy is responsible for maternal death per year around the world for about 22.000 (Asia), 25.000 (Africa), and 3.800 (Latin America and Caribbean's) [3]. Even in developed countries, hypertension in pregnancy still creates significant problems. In the United States, hypertension complicates 1 in 10 gestations and 240.000 women annually [6]. In the United Kingdom (UK), one-third of severe maternal morbidity was caused by hypertension in pregnancy. Furthermore, 5% of pregnant women with preeclampsia or eclampsia need intensive management in the Intensive Care Unit (ICU) [7].

Indonesia, as the 4th most populous country in the world, is still facing a national problem of high maternal mortality rate. Indonesia's maternal mortality rate is the 3rd highest in South Asia and Southeast Asia regions. According to the data from our national health data surveillance (*Survei Demografi dan Kesehatan Indonesia*

[SKDI]), Indonesia's maternal mortality rate in 2012 reached about 359 per 100.000 live-birth deliveries [8]. Hypertension in pregnancy is one of the leading causes of maternal death in Indonesia. Data from the Indonesia multicenter trial performed in 11 tertiary care hospitals show the average incidence of hypertension in pregnancy to be around 22,1% (3219 cases from 17.771 total deliveries). Maternal death caused by hypertension in pregnancy in this study found in 2% of cases, while the perinatal death rate was about 12% [9]. The proportion of hypertension in pregnancy was very high because the study was performed in tertiary care hospitals, which only manage challenging and complicated cases.

Nevertheless, the percentage of maternal and perinatal death from this disease is still very high, contributing to the high number of our national maternal and perinatal mortality rates. In another large population study in 33 provinces in Indonesia, involving 9024 pregnant women sampling from national health data, the prevalence of hypertension in pregnancy is 6,18%, with the highest incidence found in West Java province (10,57%) [10].

Based on the newest ISSHP (International Society for The Study of Hypertension in Pregnancy) criteria [11], hypertensive disorders of pregnancy can be classified into two types based on the onset of the disease. The first is hypertension known before pregnancy or < 20 weeks gestation, consisting of chronic hypertension, white coat hypertension, and masked hypertension. The other is hypertension de novo at or after 20 weeks gestational age: preeclampsia, gestational hypertension, and preeclampsia superimposed on chronic hypertension. Hypertension is defined as a systolic blood pressure > 140 mmHg or diastolic blood pressure > 90 mmHg, with repeated measurement to confirm the diagnosis. Chronic hypertension defined as high blood pressure diagnosed before pregnancy or before 20 weeks gestation. Gestational

hypertension is de novo hypertension develops after 20 weeks of gestation without any sign or features of preeclampsia. Preeclampsia is gestational hypertension that arises after 20 weeks gestational, with one of the following features: proteinuria, maternal organ dysfunction (acute kidney injury (AKI), liver involvement, neurological complications, hematological complications) and uteroplacental insufficiency (fetal growth restriction, stillbirth) [11].

Chronic hypertension complicates 3-5% of pregnancies, and the prevalence is increasing rapidly worldwide [12]. Chronic hypertension is less commonly found in pregnancy compared to preeclampsia. Based on the WHO international survey from hospital data, the prevalence of chronic hypertension in low-middle income countries (LMICs) is 0.29% (total) ranging between 0.21% in the African region and 0.32% in Western Pacific region [13]. While in the high-income countries (HICs), more reliable data are available to be analyzed. In Canada, the prevalence of chronic hypertension is 0.4% based on the national cohort of all hospital deliveries. In United States (US), from the American National Inpatient Sample data set, the prevalence of chronic hypertension was 1.5% from all birth (2007-2008) and 0.83-0.85% of birth in New York State (1995-2004). A similar rate of 1.3% was reported in the UK (1996-2010) [14]. Obesity and advanced maternal age are the two main factors that are contributing to this increase.

Although the majority of chronic hypertension in pregnancy patients have a good outcome, the risk of complication and adverse outcomes is significantly increased compared with normal pregnant women. Chronic hypertension in pregnancy has a risk of developing superimposed preeclampsia, placental abruption, fetal growth restriction, preterm delivery, and risk of cesarean section [15]. This statement is confirmed by extensive meta-analysis data from 55 studies, involving 795.221 pregnancies compared

to US population data [16]. This systematic review shows that pregnant women with chronic hypertension have a higher risk of superimposed preeclampsia (Relative Risk [RR] 7.7, 95% CI 5.7 to 10.1), cesarean delivery (RR: 1.3, 95% CI 1.1 to 1.5), preterm delivery (RR 2.7, 95% CI 1.9 to 3.6), baby birthweight < 2500 g (RR 2.7, 95% CI 1.9 to 3.8), Neonatal Intensive Care Unit (NICU) admission (RR 3.2, 95% CI 2.2 to 4.4), and perinatal death (RR 4.2, 95% CI 2.7 to 6.5) [16]. Until now, there is no publication about the outcomes of chronic hypertension in pregnancy in Indonesia. We performed a study in Dr. Soetomo General Hospital (2013-2017), to evaluate the effect of severity of chronic hypertension in pregnancy on maternal and perinatal outcomes in our population (Chapter 2).

Preeclampsia is the second most maternal mortality and morbidity cause (14%) worldwide after hemorrhagic postpartum. Preeclampsia leads to maternal death about 70.000-80.000 every year and leads to an additional 500.000 perinatal death/year globally [17]. Preeclampsia and eclampsia occur in around 2-8% of total pregnancies. In the US, the prevalence of preeclampsia is increasing as high as 25% in the last two decades. It is consistent with the increasing number of obese women before pregnancy in the countries, reach about 40% [18]. Eclampsia is one of the most severe complications of preeclampsia, which is manifest as a temporary seizure in severe hypertensive pregnant women [11,14]. Based on the WHO extensive database of a survey on maternal and newborn health, which involved a total 313.030 women, the prevalence of chronic hypertension, preeclampsia, and eclampsia were as followed: 914 (0.29%), 6753 (2.16%), and 875 (0,28%) [13]. The risk of maternal death was four times higher in preeclampsia women compared to normal pregnant women, and for eclampsia, this risk increased exponentially (OR= 42,38, 95% CI= 25,14-71,44). Moreover, the risk of being a survivor of a life-threatening condition (maternal near-

miss case) was 8 and 60 times higher in women with preeclampsia and eclampsia [13]. In another report stated that the Case Fatality Rate (CFR) of eclampsia in LMICs almost eight times higher compared to HICs (14% vs 1.8%) [19].

In our province of East Java, preeclampsia and eclampsia were the most common cause of maternal death (30.9%) contribute to a maternal mortality rate of 91/100.000 deliveries (2016)., based on the data from East Java Government Health Agency (*Dinas Kesehatan Provinsi Jawa Timur*). In Dr. Soetomo General Academic Hospital, between 2016-2017, there were 703 cases of severe preeclampsia and 75 eclampsia. From this total of 778 cases, maternal death occurred in 15 (1.9%) eclampsia cases and 11 (1.56%) severe preeclampsia cases (unpublished).

Preeclampsia is currently divided into two types based on the onset of the disease: early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE). Both types have different clinical characteristics, maternal-neonatal outcomes, and possibly different pathogenesis [20]. The cut off of these groups is 34 weeks gestational age. EO-PE is preeclampsia, which occurs before 34 weeks gestation, while the LO-PE appears > 34 weeks. EO-PE is less common (12% from total preeclampsia), but it has a worst clinical appearance, complications, and maternal-neonatal outcomes. EO-PE is commonly associated with fetal growth restriction, abnormal uterine artery Doppler, and adverse outcomes. In contrast, LO-PE is mostly associated with normal uterine artery Doppler examination, less fetal problems, and better perinatal outcomes [21]. EO-PE is more related to placental factors, with the abnormal placental vascular structure and function. LO-PE is less related to the placenta factors and associated with maternal factors such as obesity and metabolic syndrome [22].

These two-groups also has a different hemodynamic status in early state preceding the onset of preeclampsia, as confirmed by Valensise's study [20]. EO-PE

has a higher total vascular resistance and lowers cardiac output compared to LO-PE. LO-PE had a higher proportion of high Body Mass Index (BMI) women, while EO-PE had more bilateral notching finding in the uterine artery Doppler examination. These findings support the hypothesis of different origins and characteristics of these two groups [20]. Another study by Wikstrom et al. supports the hypothesis of poor placentation in EO-PE, but not in the LO-PE [23]. In this study, angiogenic factors (Placental Growth Factor [PlGF], Vascular Endothelial Growth Factor-A [VEGF-A]) & anti-angiogenic factors (soluble FMS like tyrosine kinase 1 [sFlt-1]) were measured in the EO-PE, LO-PE, and compared with the normal control group matched by gestational age range. Both preeclampsia groups are associated with higher anti-angiogenic factors (sFlt-1) and lower angiogenic factor (PlGF). However, the alteration in EO-PE is more pronounced compared to LO-PE [23]. Another study measured the placental perfusion based on MRI (Magnetic Resonance Imaging) in EO-PE, LO-PE, and healthy pregnancy. Women with EO-PE had a smaller placental perfusion fraction. In contrast, LO-PE had more significant placental perfusion fraction compared to normal pregnant women at the appropriate gestational age [24]. These findings are suggesting the hypothesis of different origins between both groups - related to placental function.

Until now, the etiology of preeclampsia is still unclear and become an area of debate. Nevertheless, many scientists agree on this following pathogenesis in early-onset preeclampsia: abnormal spiral artery remodeling leads to high velocity pulsatile flow damaging the vulnerable syncytiotrophoblast, oxidative stress, and excessive inflammation response [25–27]. In the last decade, many studies have shown that the imbalance between angiogenic (VEGF and PLGF) and - anti-angiogenic (sFlt-1, s-Eng) factors play a pivotal role in the pathogenesis of this disease [28]. This angiogenesis

impairment arises because there is less activity of the angiogenic factor (VEGF) caused by the increasing level of sFlt-1, which is works as the antagonist receptor of VEGF [28–33]. This event will result in the endpoint of vascular endothelial dysfunction, which will be a center of the clinical pathogenesis change of preeclampsia [33].

Ahmed A et al., propose a new concept of preeclampsia pathogenesis. Preeclampsia can be caused by two factors, which is in the opposite: first, (which is the main view of many scientists) caused by the excessive accelerating factors, and the second because of a lack of protective factors in the system [34]. Many researchers only focus on the finding of accelerating factors (such as oxidative stress, inflammatory response, angiogenesis imbalance), without concerning about the protective factors. There are two main protective factors in the balance system HO/CO (*Heme Oxygenase* and *Carbon Monoxide*) and CSE (*Cystathione-γ-liase*) pathway [34]. HO is an enzyme that has a role in heme degradation in reticulum endoplasmic, producing biliverdin, iron (Fe), and CO [34,35]. HO and CO already proven from many studies have an essential role in maintaining a pregnancy [36] and modulating uteroplacental circulation [37]. Placental HO enzyme is also protective of placental damage [37]. CO has an active vasodilator property, anti-apoptosis factor. CO also has a vital role in maintaining a healthy pregnancy by modulating the uNK cells (uterine natural killer) on the implantation process, which produces a normal remodeling artery [38]. The deficiency of HO and CO may be involved in the pathogenesis of preeclampsia. HO and CO can reduce the production and release of the sFlt-1 and soluble endoglin (sEng) (the two most essential markers in preeclampsia pathogenesis) from endothelial cells [39]. One study confirmed that the level of chorionic villi HO1 mRNA decrease in 11 weeks gestation in the pregnancy, which develops into preeclampsia, compared to normal [40]. Based on these findings, we test the hypothesis of the possibility of different

pathogenesis, serum markers (sFlt-1 and HO-1), and consequently the clinical outcomes of these two types of preeclampsia (Figure 1). We performed a study to evaluate the difference between EO-PE and LO-PE by measuring the level of protective factors (HO-1), antiangiogenic marker (sFlt-1), and its related maternal-neonatal outcomes (Chapter 3).

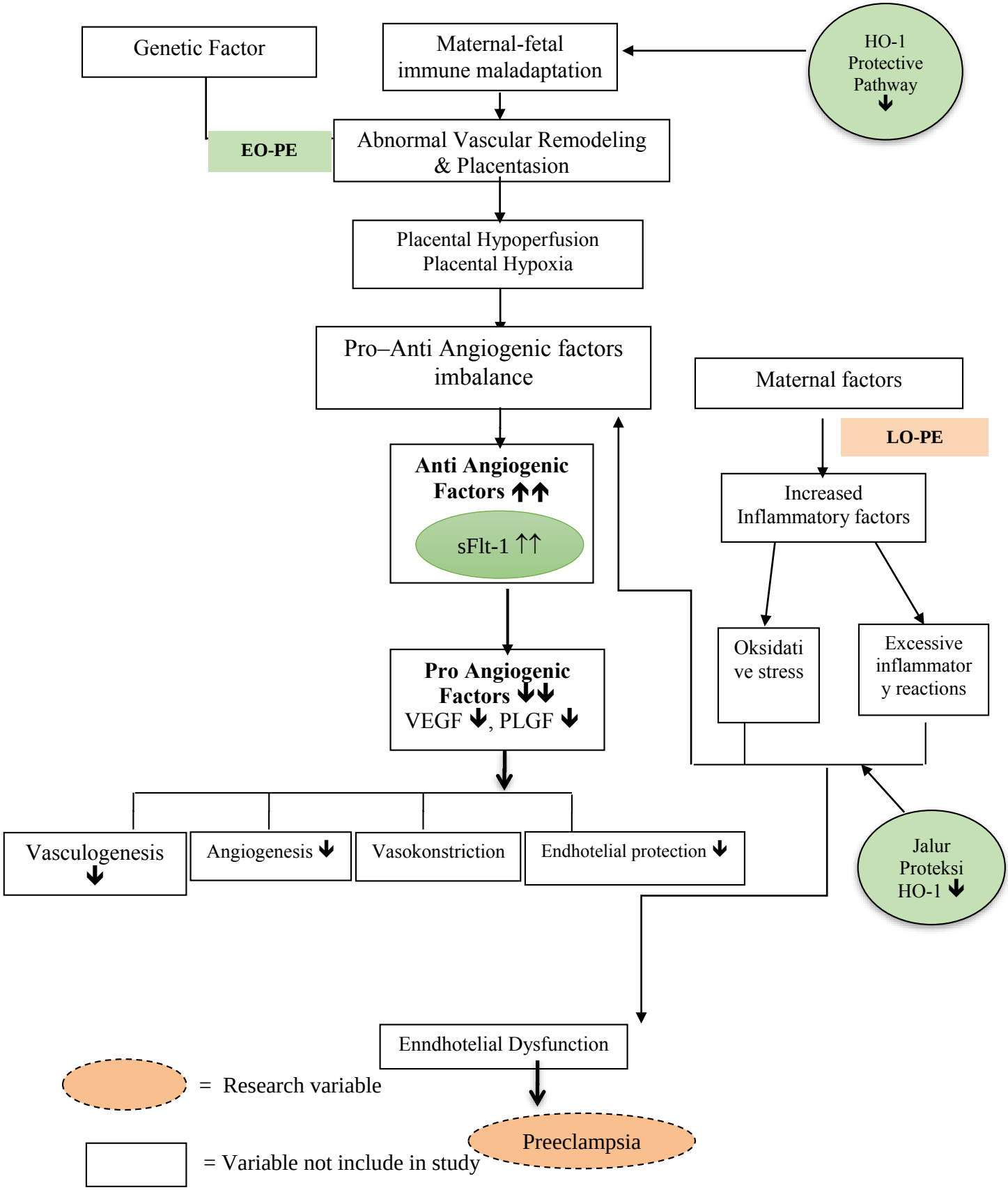

Figure 1. Conceptual framework: the role of sFlt-1 and HO-1 in the pathogenesis of EO-PE and LO-PE.

Classification, diagnosis criteria, management has been a subject of debate worldwide for years. There are many disagreements about any aspect of this disease. However, some major guidelines have agreed upon the diagnostic criteria of preeclampsia. Preeclampsia is gestational hypertension accompanied by one or more of the following conditions after 20 weeks gestation: proteinuria, maternal organ dysfunction, or uteroplacental dysfunction [41–44]. Preeclampsia can be manifest in multiple organs, and impairment in liver function can develop into the unique complication of HELLP syndrome. HELLP is a syndrome consisting of hemolysis, elevated liver enzyme, and low platelets. It is a complication of preeclampsia and occurs in 10-20% of severe preeclampsia women [45]. Unfortunately, several microangiopathic disorders that occur during pregnancy could mimic the sign and symptoms of preeclampsia or its complication (HELLP syndrome), thus provide a diagnostic challenge [46]. Besides that, preeclampsia may be superimposed by this disease, further confounding a difficult differential diagnosis. One of the diseases that imitate the preeclampsia and HELLP syndrome is Acute Fatty Liver of Pregnancy (AFLP) [46,47]. The understanding of the disease that imitates preeclampsia is also crucial in order to make a correct diagnosis and management.

AFLP is a rare complication during pregnancy, which usually occurs in the late trimester and could be disastrous. AFLP has the potential to cause maternal and perinatal death in the 3rd trimester. The incidence range from 1 in 10000 to 1 in 15000 deliveries. This disease is more commonly found in nulliparous woman and multiple pregnancies. The typical characteristics of AFLP include rapid liver failure and coagulopathy, which appears to be triggered by microvesicular fatty infiltration in the hepatocytes [48]. The onset of the symptoms usually starts in the third trimester, with an average of 36 weeks. The symptoms usually start with malaise, anorexia, nausea,

vomiting, epigastric, or right upper quadrant pain, headache, or jaundice [46]. These signs and symptoms can resemble the clinical sign of HELLP syndrome and preeclampsia. Since AFLP is a rare disease and the incorrect diagnoses of this disease can lead to incorrect management, we performed a study of our AFLP cases in Dr. Soetomo General Hospital (2011-2015). All of the clinical characteristics, diagnosis, management, and maternal-fetal outcomes were analyzed in order to have a better understanding of this disease (Chapter 4).

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