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THE CONTINUUM OF CARE IN PRE ECLAMPSIA MOTHER INFANT CHILD

Penulis:
Agus Harianto, dr., SpA(K)
Divisi Neonatologi
Dr. Risa Etika, dr., SpA(K)
Divisi Neonatologi
Dr. Ahmad Suryawan, dr., SpA(K)
Divisi Tumbuh Kembang Pediatri Sosial
Prof. Dr. Erry Gumilar, dr., SpOG(K)
Divisi Fetomaternal
Dr. Ernawati Darmawan, dr., SpOG(K)
Divisi Fetomaternal
Muhammad Aldika Akbar, dr., SpOG(K)
Divisi Fetomaternal
Dr. S.M. Mei Wulan, dr., SpKFR(K)
Divisi Pediatri

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Penerbit
CV Saga Jawadwipa
PUSTAKA SAGA
Jl. Kedinding Lor,Gg.Delima,no 4A. Kenjeran, Surabaya
Email: saga.penerbit@gmail.com, HP: +62 856 5539 6657

DAFTAR ISI

Neonatal Respiratory Outcome in Pregnancy-Induced Hypertension

Agus Harianto, Risa Etika, Martono Tri Utomo, Dina Angelika, Kartika D Handayani, Mahendra Tri Arif Sampurna.

Division of Neonatology, Department of Child Health, Faculty of Medicine, Universitas Airlangga, Surabaya.

Abstract

Pregnancy-induced hypertension (PIH) is the most common medical complications in pregnancy globally and becomes one main cause of maternal morbidity and mortality. The classification of PIH are gestational hypertension, chronic hypertension, preeclampsia (PE), and pre-eclampsia superimposed on chronic hypertension. Based on literature, gestational hypertension and pre-eclampsia are the leading causes of maternal and perinatal mortality and morbidity. However, all types of PIH has less favorable outcome compared to newborns with normotensive mothers.

All newborns from mothers with PIH has higher prematurity rates, lower birthweight and longer hospital stay. Since PIH, especially preeclampsia, is a progressive disorder, delivery of fetus and placenta is the treatment of choice, especially when the gestational age greater than 34

weeks to terminate the progression. Even though, some studies showed contradictory results regarding respiratory outcome of newborns from hypertensive mothers less than 34 weeks of gestational age. Obstetricians should make sure that the benefits of terminating the pregnancy outweighs the risks including the maturity of newborns' respiratory system. On the other hand, it is important for neonatologists to understand the neonatal outcome of mothers with PIH especially the respiratory outcome. Since PE has high incidence and has less favorable outcome especially respiratory disorders, this article will focus in PE and neonatal respiratory outcomes.

The most recent cohort study showed that having pre-eclampsia mother is independently associated with higher risk for severe respiratory distress syndrome (RDS) and Bronchopulmonary Dysplasia (BPD). A theory states preeclampsia may cause acceleration in fetal lung maturation and will reduce the risk of RDS, but in the other hand, some studies suggested that PE may not accelerate lung maturity. Several studies examined the relationship between intrauterine exposure to maternal PE and the risk of the infant developing BPD. Some of these report that PE is protective and reduces the incidence of BPD. Others report that PE is associated with an increased incidence of BPD. Still others have found no change.

Pregnancy induce hypertension especially PE has less favorable outcomes mainly respiratory problems in neonates such as RDS and BPD. Proper resuscitation and intervention should be prepared in this matters. Multidisciplinary and collaborative approach between the field of maternal-fetal medicine and neonatology is necessary to optimize maternal and neonatal management of mothers who have PE.

Keywords : Pregnancy-Induced Hypertension, Preeclampsia , Respiratory Distress Syndrome, Bronchopulmonary Dysplasia

Introduction

Pregnancy-induced hypertension (PIH) which currently complicates around 10% pregnancy globally[1] is the most common medical complications in pregnancy[2]. In Indonesia, the prevalence of PIH is around 12.7% and becomes one main causes of maternal morbidity and mortality [3]. Furthermore, in a higher income country such as United States, it affects between 6-8 % of all pregnancies [4].

The classification of PIH based on National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (2000) are gestational hypertension, chronic hypertension, preeclampsia (PE), and PE superimposed on chronic hypertension. Each type of PIH has different fetal and

neonatal outcome.[5] Based on literature, gestational hypertension and PE are the leading causes of maternal and perinatal mortality and morbidity. Majority of maternal and perinatal deaths occurred in Low and Middle Income Countries (LMICs), while High Income Countries (HICs) have relatively low maternal and perinatal mortality ratio.[2]

A study conducted by Tachiwenyika et al, stated that PIH increased the risk of perinatal mortality [6]. Another study also supported this finding by stating that women with hypertensive disorders of pregnancy have higher perinatal mortality ratio [7]. In that study also revealed that risk factors of higher perinatal mortality are gestational age, parity, type and onset of hypertension, birth weight, mode of delivery, and maternal outcome.

According to our perspective, there are theories stated the definitive cure of PE is to end the pregnancy and deliver the baby. However, there is no clear guideline addressing the optimal timing for delivery. Furthermore, its significant effects on pregnancy outcome have become obstetricians' consideration in terminating pregnancy. Obstetricians should make sure that the benefits of terminating the pregnancy outweigh the risks including the maturity of newborns' respiratory system. On the other hand, it is important for neonatologists to understand the respiratory outcome of newborns from mothers with PIH. At this

point, neonatologists have important roles to prevent perinatal morbidity and mortality by providing early life treatment based on known PIH risk factor. There is also the need for multidisciplinary and collaborative approach between the field of maternal-fetal medicine and neonatology to optimize maternal and neonatal management of mothers who have PE. Therefore, this paper aims to discuss the Neonatal Respiratory Outcome in Pregnancy-Induced Hypertension.

Classification of Hypertensive Disorders of Pregnancy

It is important to understand types of PIH because each type has different pathogenesis and possibly management. Each type of PIH also has its own diagnostic criteria.

Table 1. Classification of Pregnancy-Induced Hypertension [8]

Category	Diagnostic Criteria
Chronic hypertension	Hypertension manifested before pregnancy, before 20 weeks of gestation, or persisting more than 12 weeks postpartum.
Gestational hypertension	Hypertension manifested after 20 weeks of gestation.
Preeclampsia	Development of hypertension after 20 weeks of gestation, associated with proteinuria (≥0.3 g in a 24-hour urine specimen or ≥1+ on dipstick in two urine samples) in previously normotensive women.
Preeclampsia superimposed on chronic hypertension	Preeclampsia diagnosed in previously hypertensive women.

From National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy 2000

The gestational week of the first manifestation of hypertension is crucial in diagnosing PIH.

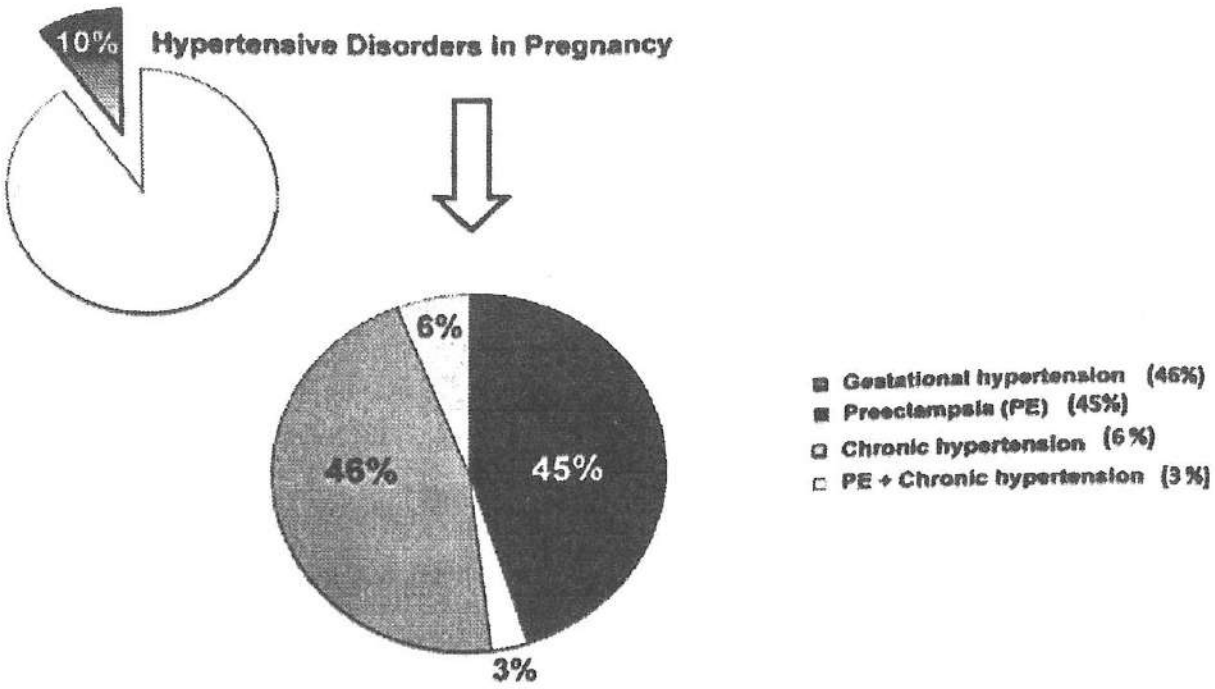


Figure 1. Incidence and classification of hypertensive disorders in pregnancy.

Roberts CL et al. Hypertensive disorders in pregnancy: a population based study. *MJA*. 2005;182:332–335

Currently, PIH accounts for almost 10% of all pregnancies worldwide. PIH itself are divided by several classifications. Gestational hypertension is the leading type of PIH. Followed by with PE which only have 1% incidence difference compared to gestational hypertension. Due to its substantial

percentage and complex pathogenesis, the later part of this paper will focus on PE.

PE is a great challenge for obstetricians due to its unknown cause, its pathophysiology is complex and incompletely understood, its diagnosis may be difficult to determine, there's still no effective treatments, and antenatal care involves a difficult balance between the risks for women to continue pregnancy and those for the baby's early birth.

Patophysiology of Preeclampsia

Definite cause of PE still remains unknown, but immune and vascular matters have been involved in its pathogenesis. PE considerably have two-stage disease (figure 2), the placental effects and systemic effects. The combination of imbalance of angiogenic factors and oxidative stress plays role in this pathophysiology. [10]

In a mouse model study, it showed that less favorable outcome was found among fetuses and infants from mothers with early PE, it is because PE is a placental disease and late PE is a maternal systemic disease [11]

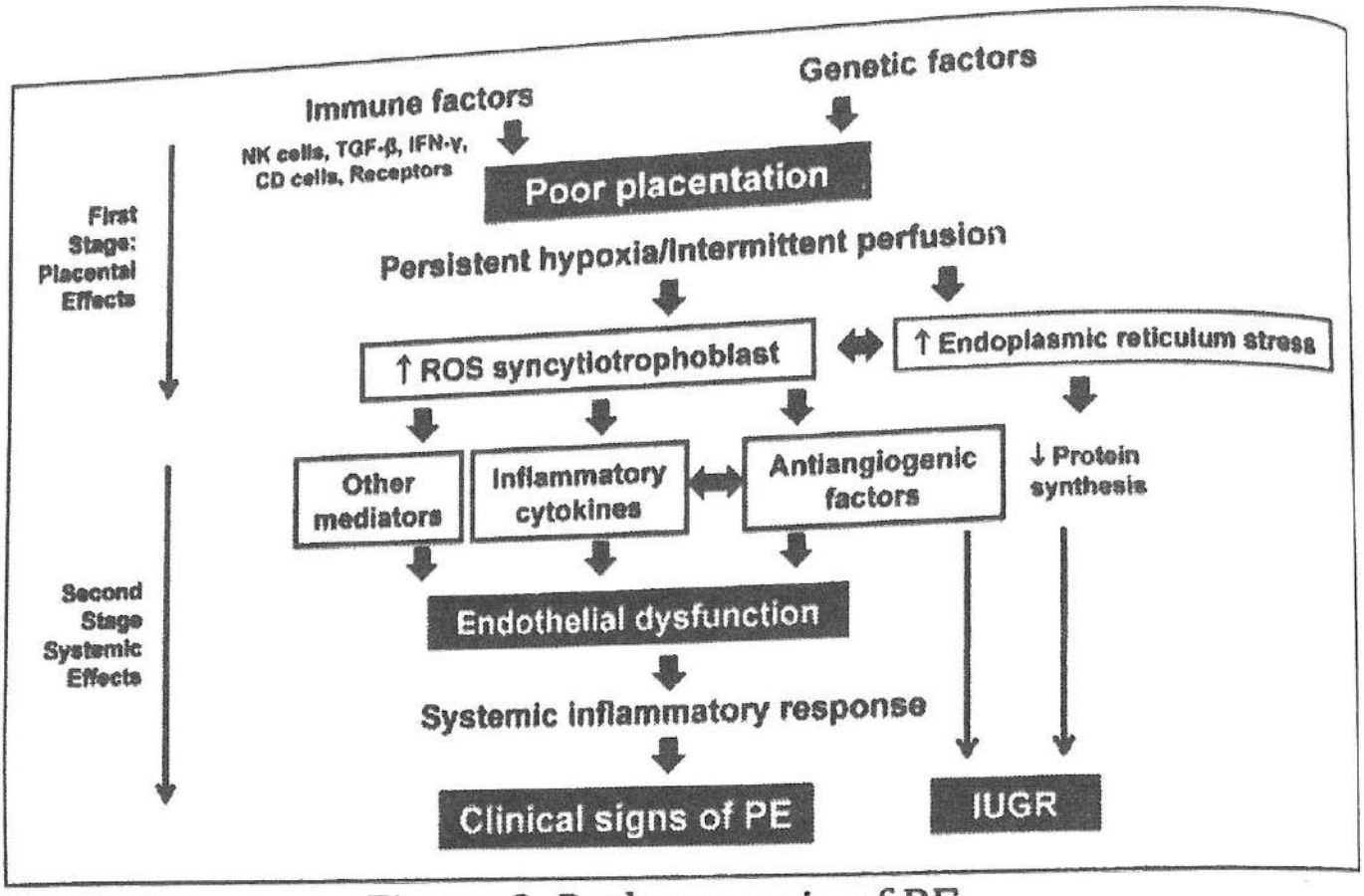


Figure 2. Pathogenesis of PE.

de Souza Rugolo L et. al. PE: Effect on the Fetus and Newborn. *Neoreviews*. 2011;12(4):e198-e206.

In addition, placental oxidative stress is considered as an intermediate event in PE pathogenesis. Some studies showed that oxidative stress plays role in endothelial dysfunction and lead to PE.[12,13,14]

Evidence suggests that angiogenic factors also play role in PE pathophysiology. Imbalance of angiogenic-antiangiogenic factors might affect pregnancy outcome such as observed in PE and Intra Uterine Growth Restriction (IUGR) condition. Placental angiogenesis is regulated by many growth

factors, however vascular endothelial growth factor (VEGF) is involved in this critical step. A subtype of VEGF, placental growth factor (PIGF), enhances the VEGF response itself.[15] Antiangiogenic factors which consist of soluble form of endoglin (sEng) and tyrosine kinase (sFlt1) are increased in PE and have role in PE complications. However, the mechanisms by which angiogenic factors play role in PE remains unclear.[15,16]

Recently, epigenetic factors have been considered to play role in PE pathogenesis, although it still remains unclear.[17,18] Recent experimental studies have been conducted to discover new insights into PE pathophysiology. It was found that disturbed regulation in genes expression considerably plays role in pathogenesis of placental insufficiency.[18] Those complex mechanisms of PE are not fully understood and still remain unclear.

Outcome

Regardless of types of PIH, it has less favorable outcome compared to newborns with normotensive mothers. All newborns from mothers with PIH has higher prematurity rates, lower birthweight and longer hospital stay [19].

One of types of PIH, PE is a progressive disorder and delivery of fetus and placenta is the treatment of choice especially when the gestational

age greater than 34 weeks to terminate the progression [20,21,22]. However, premature delivery has adverse effects on neonatal outcomes [22].

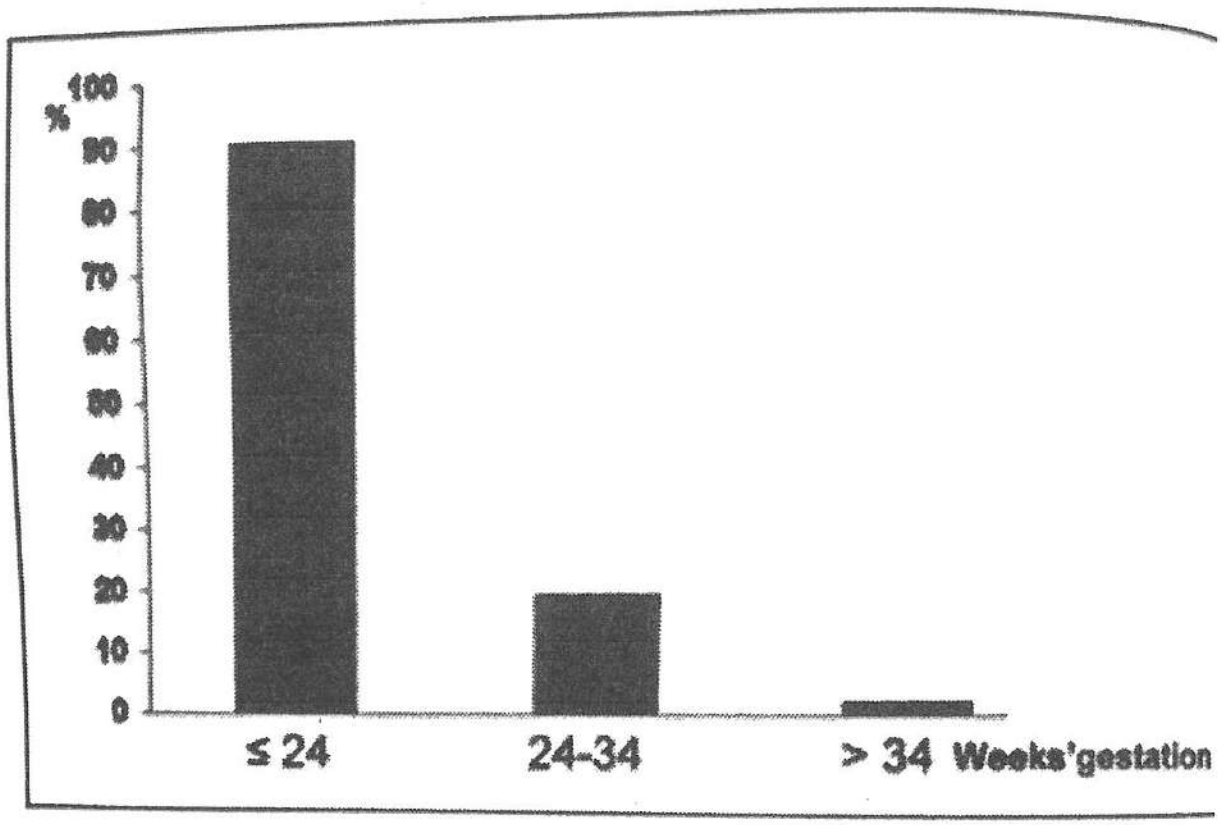


Figure 3. Perinatal Mortality in PE according to Gestational Age

Haddad B et al. Expectant management in pregnancies with severe pre´-eclampsia. *Semin Perinatol.* 2009;33:143–151

Several studies showed the rates of all preterm and late preterm deliveries in healthy nulliparous women with mild PE. Hauth et al found only 1,9% infants born before 34 weeks of gestation, 10,6% infants born between 34 weeks until 37 weeks, and in total there was 12,5% infants born prior to 37 weeks. In addition, there was study that

showed similar results. Hnat et al found only 2,3% infants born before 34 weeks of gestation, 11,7% infants born between 34 weeks until 37 weeks, and in total there was 14% infants born prior to 37 weeks. Those results implied that the rates of preterm and late preterm infants were very low in healthy nulliparous women with mild PE.[24,25]

Table 2. Neonatal Complication in Pregnancies involving PE

Problem	Comments
Respiratory Distress Syndrome	No difference in incidence; lung maturity is not accelerated in PE.
Thrombocytopenia	Associated with low birthweight and prematurity; early manifestation and transient course
Neutropenia	High incidence in the first 72 hours after birth and may be associated with increased risk of infection
Necrotizing Enterocolitis	Increased risk, primarily newborns who have intrauterine growth restriction.
Intraventricular Hemorrhage/Periventricular Leukomalacia	Increased neonatal encephalopathy in term neonates. No difference or decreased incidence of IVH and PVL in preterm infants Neuroprotective effect of Magnesium Sulfate

de Souza Rugolo L et. al. PE: Effect on the Fetus and Newborn. *Neoreviews*. 2011;12(4):e198-e206.

From the table above it is showed that the effects of PE on neonatal outcome also includes respiratory system which is respiratory distress syndrome. Furthermore, late preterm infants have greater risk for various complications, mainly respiratory problems. Several studies showed that late-preterm infants have greater risk for respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), persistent pulmonary hypertension (PPHN), and respiratory failure compared to term infants [22,26]. The most recent cohort study showed that having pre-eclampsic mother is independently associated with higher risk for severe RDS and Bronchopulmonary Dysplasia (BPD) [27].

Respiratory Distress Syndrome

Respiratory Distress Syndrome or Hyalin Membran Disease is one of the leading causes of death among premature newborns [28]. It affects 1% of all newborn infants and about 10% of preterm babies in the United States each year. The syndrome is mainly due to immaturity of lungs in producing surfactant which affects lungs' ability to support respiration [28].

In the context of PE, there's a theory that PE may cause acceleration in fetal lung maturity because it may escalate cortisol production via chronic stress condition caused by PE. In this logic, the increasing production of cortisol should reduce the risk of

experiencing RDS [10], the data regarding this matter have been contradictory so far.

RDS incidence was found lower among preterm infants less than 34 weeks from hypertensive mothers compared to the control [29]. The same results were also found in late preterm infants according to a large population study in the Netherlands [30].

Nevertheless, other studies showed different results. Large cohort studies revealed that preterm infants from mothers with PE especially with gestational age less than 32 weeks have higher risk of RDS [28]. Another study which monitored lung maturity of late preterm infants by measuring lecithin – sphingomyelin ratios which later underwent elective deliveries, those infants were still at risk of RDS because almost 10% of them developed RDS. Those studies suggested that PE may not accelerate lung maturity [31].

Despite of conflicting results of those studies, neonatologists should be prepared to provide respiratory support to newborns with hypertensive mothers. Early termination of pregnancy due to PE will lead to smaller gestational age. Smaller gestational age is likely to have any respiratory distress, significant physiologic derangement, or experiencing assisted ventilation. Babies born at 37 weeks were twice as likely to be ventilated, whereas

babies born at 36 weeks were five times as likely, and babies born at 35 weeks, nine times as likely compared with babies with gestational ages of 38 to 40 weeks [32]. In addition, Wang ML et al found that late-preterm infants have a nine times greater incidence of respiratory distress syndrome than term infants (28.9% versus 4.2%, P < .001).[33]

Bronchopulmonary Dysplasia

One of chronic lung disease in infancy is bronchopulmonary dysplasia (BPD) that usually occurs in infants born prematurely [34]. This also often seen among newborns from mothers with preeclampsia. Several studies examined the relationship between intrauterine exposure to maternal PE and the risk of the infant developing BPD. Some of these report that PE is protective and reduces the incidence of BPD [35, 36, 37]. Others report that PE is associated with an increased incidence of BPD [38, 39]. Still others have found no change [40,41]. A study reported that infants born from PE mothers were more likely to develop BPD compared to infants born from mothers with other causes of preterm delivery. They found that PE increased the likelihood of developing BPD with almost 3-fold (Bivariate OR= 2.96 95% CI = 1.17 to 7.51; P = .01). Since BPD has several other risk factors, in this study, the logistic model of other BPD risk factors showed that PE had highest OR (OR: 18.7 CI: 2.44-144.76 P .005) [38]. However, another study showed contradictory result

that BPD was not associated to PE exposure either before and after adjustment for relevant variables (OR 0.73; 95% CI 0.05, 1.06 and OR 1.14; 95% CI 0.71, 1.81). They concluded that PE exposure had insignificant effect on the risk of developing BPD [42].

BPD itself is due to impaired lung growth following early lung injury. It shows the effects of persistent distal lung structure abnormalities including a decrease in alveolarization and pulmonary vascular bed malformations [34,43]. In normal lung development, angiogenesis is important process for alveolarization and disruption of pulmonary circulation development plays role in lung hypoplasia [44]. However, angiogenic and antiangiogenic factors imbalance was considered to be a cause of normal placental angiogenesis disruption in PE and also a cause of abnormal fetal angiogenesis which included vasculature of the fetal lung [39].

Intrauterine vascular growth plays role in pulmonary alveolarization. Greater levels of a Vascular Endothelial Growth Factor (VEGF) antagonist that is soluble VEGF receptor-1 (soluble VEGFR1, also known as soluble fms-like tyrosine kinase 1, sFlt- 1) had been found in pregnant women with PE. There might be an antiangiogenic state in PE that gave a suggestion that newborn from PE mothers had greater risk of developing BPD due to impaired fetal angiogenesis, included impaired lung

development [38,45]. A study found that preterm infants with BPD have lower concentration of VEGF in tracheal aspirates [46] and higher concentration of anti angiogenic growth factors, endostatin, in cord blood compared those who do not develop BPD [47].

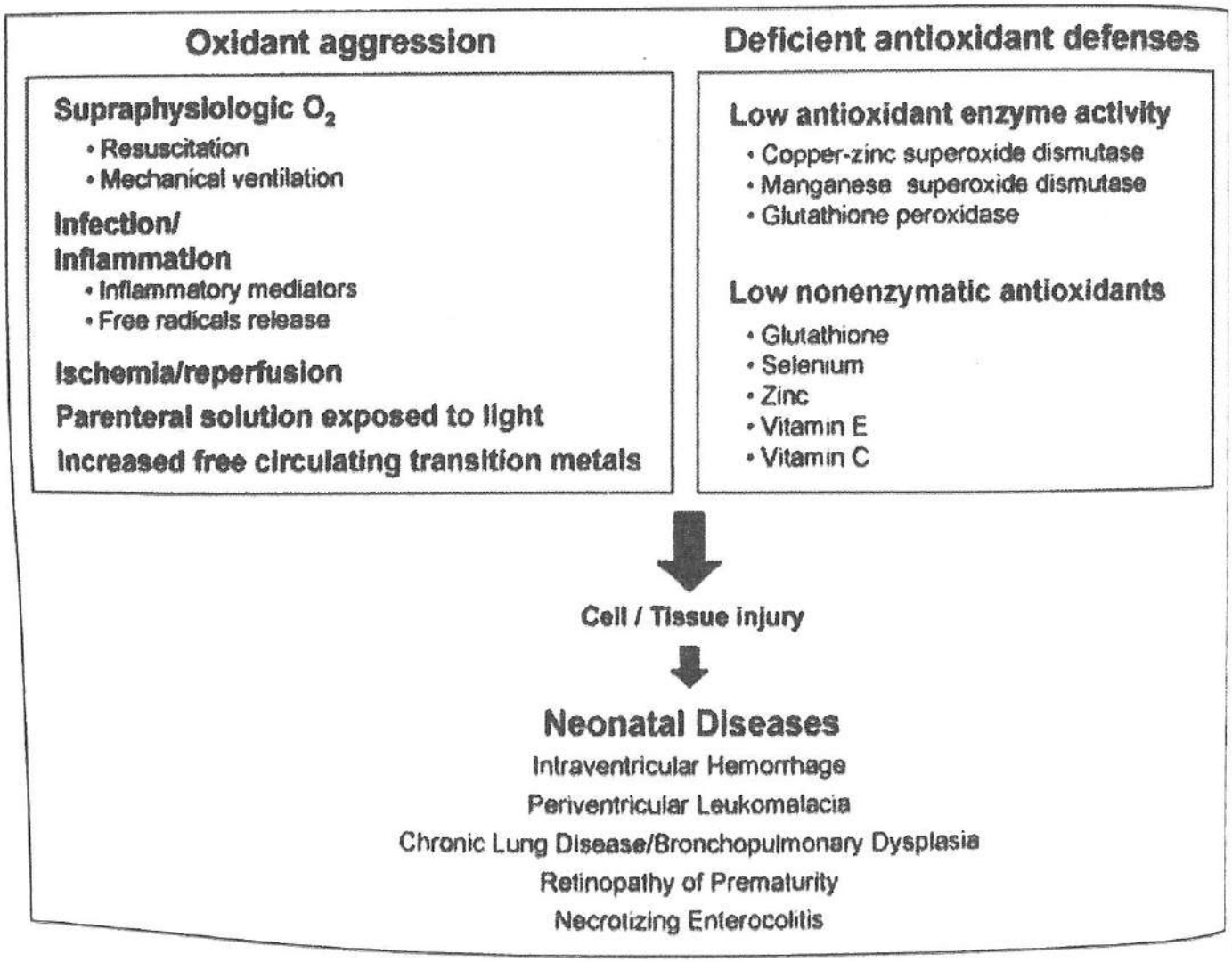
Impairment of VEGF signaling in utero can cause disruption of lung development and in addition can increase the risk of BPD. An experimental study conducted in rats revealed this mechanism. After intra-amniotic infusion of sFlt-1, there were a decrease in both pulmonary alveoli and vessel number and an increase in fetal pulmonary endothelial and mesenchymal cells apoptosis. So, there was a suggestion that fetal exposure to greater levels of intra-amniotic sFlt-1 can cause increased risk for BPD and vascular dysfunction in infants from PE mothers [45].

PE, BPD, and Oxidative Stress

Newborns from mothers with PE are prone to be exposed with oxidative stress. PE is associated with the release of free radicals produced by placenta. This could be the result of persistent hypoxia or intermittent perfusion due to poor placentation. Immune and genetic factors are responsible for poor placentation.[10]

Oxidative stress is one of the causes of BPD from mothers who have PE. Oxidative stress could be

also originated from resuscitation and mechanical ventilation. Newborns with asphyxia are prone to have high exposure of oxygen which may lead to oxidative stress[48]. A systematic review study which compared ambient air with 100% oxygen given to depressed preterm and term infants showed significant decrease in neonatal mortality and faster recovery among those who were resuscitated with ambient air [49].



The deficiency of enzymatic and non-enzymatic antioxidant could also become the factor of cell/tissue injury caused by oxidative stress. However, studies regarding supplementation of antioxidant agents to prevent oxidative stress haven't resulted encouraging outcome [48].

Figure 4. Factors that increase susceptibility of preterm infants to free radical-mediated diseases

Trindade C et al. Free Radicals and Neonatal Diseases. *Neoreviews*. 2007;8(12):e522-e532.

Conclusion

Neonatal Respiratory Outcome in Pregnancy-Induced Hypertension especially in PE has less favorable outcome although there are evidences oppose this view. However, although the pathophysiology still unclear until today, attention should always be given to newborns from mothers with PE. The theory that states mother with PE have lower risk to have newborns with RDS is still a controversy. The newest research regarding BPD also have contradictory results. Newborns from mothers with PE still at risk of suffering poor respiratory outcome such as RDS and BPD. Proper resuscitation and intervention should be prepared in this matter. Oxygen therapy should be given wisely to prevent the adverse effects of free radicals. Multidisciplinary

cooperation is important to provide quality care to newborns from mothers with PE.

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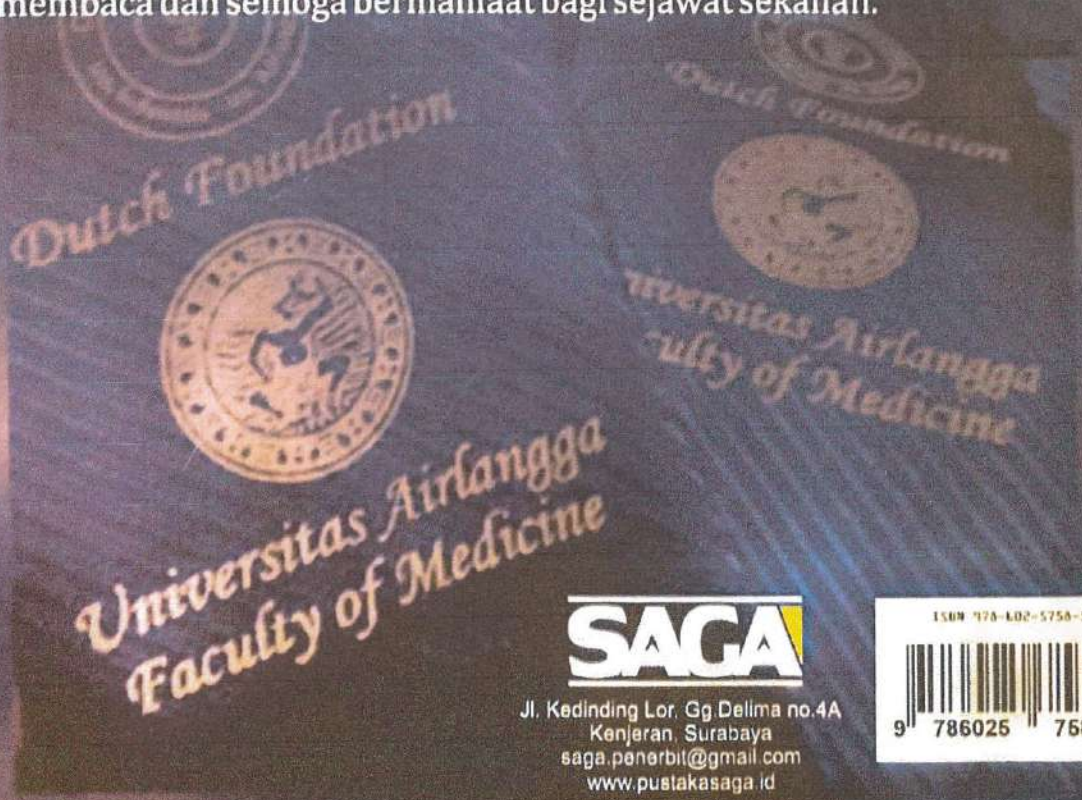
Di Indonesia, berdasarkan hasil evaluasi MDGs, tingkat kasus kematian ibu (AKI) dan bayi baru lahir (AKB) masih tergolong tinggi. Padahal target yang dicanangkan PBB dalam era SDGs saat ini yaitu 70/100.000 (AKI) dan 23/1.000 (AKB) kelahiran hidup.

Salah satu penyebab masih tingginya AKI-AKB adalah karena belum maksimalnya kualitas pelayanan kesehatan maternal-neonatal di berbagai tatanan fasilitas kesehatan terutama dalam penanganan kasus ibu hamil dengan pre-eklampsia serta dampak pada bayi yang dilahirkannya. Sehingga kita memerlukan rangkaian upaya strategi khususnya dalam usaha peningkatan kualitas pelayanan perinatal dengan memfasilitasi para profesional medis di bidang kesehatan ibu hamil serta bayi baru lahir, terutama para dokter spesialis kandungan, spesialis anak, dokter umum serta bidan dan perawat, untuk senantiasa meningkatkan kapabilitas profesionalitasnya dalam menurunkan angka kematian ibu-bayi dengan tanpa melupakan agar tetap menjaga kualitas luaran dari generasi bangsa dalam perspektif ilmu tumbuh kembang dan rehabilitasi medik.

Buku ini diterbitkan sebagai bahan referensi dalam proses pembelajaran demi majunya pelayanan kesehatan perinatal di tempat sejawat masing-masing bekerja, buku ini berisikan materi-materi topik yang disajikan dalam temu ilmiah yang telah berlangsung. Selamat membaca dan semoga bermanfaat bagi sejawat sekalian.



SAGA
Jl. Kedinding Lor, Gg.Delima no.4A
Kenjeran, Surabaya
saga.penerbit@gmail.com
www.pustakasaga.id

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