Long-term Developmental Outcome in Preterm Infants born with Preeclampsia

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Increasing evidence has demonstrated that preeclampsia as the one of pregnancy-induced hypertensive disorders is correlated with an increased risk for developmental outcomes such as language development, and also behavior development such as ADHD or ASD. Fetal exposure to maternal preeclampsia appear to increased risk for altering anatomy and vascular of the brain during development. This can be used to explain the findings of various specific developmental disorders such as cognitive and behavioral in preterm-born children to preeclampsia mothers. Characterization of a preterm-born infant to preeclampsia "brain imaging signature" could help identify children who may need enhanced educational or medical support (Dang, 2016). And, given the potential for preeclampsia to disrupt mechanisms regulating fetal growth and development, a better understanding of the pathophysiology of the disorder may allow us to develop strategies to prevent morbidities from fetal through adult life (Backes et al., 2011). This review explores the impact of maternal preeclampsia upon the offspring's long-term developmental outcomes include the development of behavior and cognitive.

Preeclampsia has been examined as a risk factor long-term developmental disorders, such as autism spectrum disorder (ASD), attention deficit hyperactive disorders (ADHD), and many forms of developmental delay (DD) in many investigations with varied conclusions. Preeclampsia may trigger various developmental disorders through maternal (vascular damage, enhanced systemic inflammation and insulin resistance), fetal (growth restriction and progressive hypoxemia), and placental (oxygen and nutrient transfer restriction and oxidative stress) mechanisms (Walker et al., 2015).

Preeclampsia is a heterogeneous disorder, therefore the long-term developmental outcomes of exposed infants are varied. One study showed that preeclampsia is associated with a decreased risk of cerebral palsy. These authors found a protective effect of maternal preeclampsia on cerebral palsy regardless of exposure to magnesium sulfate (Gray, 1998). Several studies concluded that magnesium sulfate, a commonly used medication for seizure prophylaxis in maternal preeclampsia, has been shown to have a neuroprotective effect on the preterm infant, such as it is associated with a decreased incidence of cerebral palsy among survivors exposed to the medication between 24 and 31 weeks gestation (Rouse et al., 2008). And also, a meta-analysis showed that antenatal magnesium sulfate given to women at risk for preterm birth decreased the incidence of cerebral palsy (RR 0.68, 95% CI 0.54–0.87) and gross motor dysfunction (RR 0.61, 95% CI 0.44–0.85) (Doyle, 2009).

Meanwhile, another study showed a result that infants born to mothers with preeclampsia have lower mental development index (MDI) scores at 24 months of age compared to infants without maternal preeclampsia (P = 0.04) (Cheng, 2004). However, in fact, the correlation between maternal preeclampsia and long-term worse developmental outcomes has been challenged with a study by Silviera et al., 2011, that suggesting infants exposed to preeclampsia have a higher scores on developmental score at 18 months corrected age (Silviera *et al*., 2011).

A study of Whitehouse AJ et al, 2012, showed that hypertensive diseases of pregnancy (gestational hypertension and pre-eclampsia) are related with neurocognitive outcomes in middle childhood which is verbal ability was assessed with the Peabody Picture Vocabulary Test – Revised (PPVT-R) at age 10 years. This study showed that offspring of pregnancies complicated by maternal hypertension (gestational hypertension or pre-eclampsia) had a mean PPVT-R score that was 1.83 ([95% confidence interval (CI) −3.48, −0.17], P = 0.03) points lower than children from normotensive pregnancies (Figure 1). Maternal hypertensive diseases of pregnancy are a risk factor for a small reduction in offspring verbal ability (Whitehouse et al., 2012).

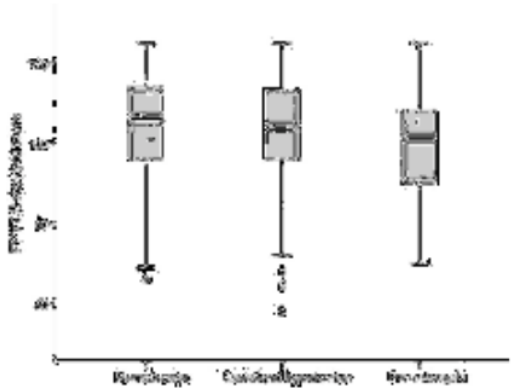

Figure 1. The score of the Peabody Picture Vocabulary Test – Revised (PPVT-R) at age 10 years of offspring form normotensive pregnancies and form pregnancies complicated by maternal gestational hypertension or pre-eclampsia (Whitehouse AJ, 2012)

Several key findings related to the offspring of preeclampsia pregnancies brain and cognition was summarized by Dang, 2016, such as lower IQ scores, smaller head circumferences at birth, higher rates of depression, reduced verbal ability, lower mean verbal IQ (VIQ) and lower full scale IQ (FSIQ), enlarged brain regional volumes in five regions (cerebellum, temporal lobe, brainstem and right and left amygdala), and deficits in working memory and visuospatial processing (Dang, 2016).

A study also revealed that newborns born growth restricted after pregnancies complicated by preeclampsia compared to growth-restricted babies without preeclampsia was no significant difference in the neurological exam score between groups after adjustment for gestational age. However, they have a lower IQ at the age of 3 years (85.5 in the preeclamptic group and 96.9 in the non-preeclamptic group, $p<0.03$). (Many et al., 2003)

Experience at Soetomo Hospital Surabaya in 2012 showed that the assessment of general movements (GMs) quality may improve the sensitivity of head-USG examination to predict developmental disorders of preterm-infant who born from mother with severe preeclampsia (SN 0.80; SP 0.50; PPV 0.67; NPV 0.67; LLR 1.60) compared to head-USG only (SN 0.20; SP 1.0; PPV 1.0; NPV 0.5; LLR 5.0) (Rochmah, 2012).

In the one of meta-analysis, over 50 prenatal factors have been examined to study the association with autism risk, revealed that factors with the strongest evidence against a role in autism risk included previous fetal loss and maternal hypertension, proteinuria, preeclampsia, and swelling (Gardener, 2009).

Children with ASD were more than twice as likely to have been exposed in utero to preeclampsia as controls with typical development (aOR: 2.36; 95% CI, 1.18-4.68); risk increased with greater preeclampsia severity (test for trend p=0.02). Placental insufficiency appeared responsible for the increase in risk for developmental disorders associated with severe preeclampsia (aOR: 5.49; 95% CI, 2.06-14.64) (Walker, 2015).

Synthesizing from the many published literature in a systematic review and meta-analysis was conducted by Maher et al, 2018, revealed that exposure to hypertensive disorders of pregnancy may be associated with an increase in the risk of ASD with a pooled aOR 1.35 (95% CI, 1.11-1.64) and ADHD with a pooled aOR of 1.29 (95% CI, 1.22-1.36) in offspring (Maher *et al*., 2018).

Those differences of several evidences above highlight the fact that preeclampsia represents a common endpoint for a number of adverse maternal conditions and that efforts to better characterize subtypes of preeclampsia may allow for a clearer understanding of the impact of preeclampsia on short and long-term neonatal outcomes. (Backes et al., 2011). These findings highlight the need for greater pediatric surveillance of infants exposed to preeclampsia to allow early intervention that may improve developmental outcomes.

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