# Decidual Killer Immunoglobulin-Like Receptor (KIR)2DL1 Expression and the Onset of Preeclampsia, Birth Weight and Placental Weight in Early and Late Onset Preeclampsia

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Abstract: A successful spiral artery remodelling ensures adequate uteroplacental perfusion and sufficient nutrient supply to fetus. HLA-C interaction with maternal KIR determines the outcome of spiral artery remodelling. Strong KIR2DL1 inhibitory lowers cytokine expression and angiogenic factors that affect uteroplacental perfusion and nutrient supply. We analysed the decidual expression of KIR2DL1 in early-onset preeclampsia (EO-PE) and late-onset preeclampsia (LO-PE) groups. We found a significant difference between KIR2DL1 expression and EO-PE and LO-PE groups ($p < 0.001$), with a strong negative correlation between decidual expression of KIR2DL1 and EO-PE ($p < 0.001$, $r = -0.723$), birth weight ($p < 0.001$, $r = -0,.70$) and placental weight ($p < 0.001$, $r = -0.770$).

## 1 INTRODUCTION

Preeclampsia is a complication of pregnancy characterised by high blood pressure, with or without proteinuria. Preeclampsia is the third cause of maternal mortality after postpartum haemorrhage and infection. Preeclampsia has a prevalence of 5-8%. (Say *et al.*, 2014)

In 2004, the main cause of maternal mortality is preeclampsia (29.9%) and postpartum haemorrhage (26.12%). These two have become the main causes of maternal mortality for a long time. In 2014, there were 567 maternal deaths in East Java, and most cases occurred in Surabaya. (Dachlan *et al.*, 2016)

The early pathology of preeclampsia is the failure of spiral artery remodelling. This causes abnormal placentation and triggers the release of pro-inflammatory mediators. Spiral artery remodelling begins with the invasion of vascular smooth muscle cells and replacement of endothelium by trophoblasts. (Moffett and Colucci, 2014) The process leads to activation of endothelial system, causes high blood pressure and increases protein level in urine. (Kopcow, 2007)

Spiral artery remodelling is related to immune system of the mother and the fetus. This process is mediated by extravillous trophoblast (EVT) that expresses HLA-C molecule. The process will be recognized by Killer Immunoglobulin-like Receptor (KIR) of the uterine natural killer (uNK) cells that produces cytokines and angiogenic factors for placentation and spiral artery remodelling. (Alicia, 2014)

In preeclampsia, KIR-AA inhibitory receptors (one of them is KIR2DL1) from uNK cells will recognize HLA-C molecules from EVT. This lowers cytokine expression and angiogenic factors and increases anti-angiogenic factors, such as *soluble endoglin* (sENG) dan *soluble fms-like tyrosine kinase-1* (sFLT1) (Alicia, 2014)

In addition to NK cells, CD4, CD8 and γδ T cells express Killer Immunoglobulin-like receptors (KIR). Inhibitory KIR on CD8 T cells may modulate the function of the cell and lessen CD8 respons. During the activation process, KIR enhances CD8 function. There is limited information available on how HLA class I molecules affect T cells as they do on NK cells (Björkström *et al.*, 2012). KIR expression on T cells has advantages that T cell may differentiate self-maternal cells from allogeneic fetal cells and modulate decidual immune response during pregnancy. (Tamara *et al.*, 2009)



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This paper analysed decidual expression of inhibitory KIR2DL1 expression and its effect on the onset of preeclampsia, birth weight and placental weight.

# 2 MATERIALS AND METHODS

## 2.1 Study design

This study was designed to analyse the distribution and trend of placental KIR2DL1 expression in early and late preeclampsia group, as well as its effect on pregnancy outcome, which is the onset of preeclampsia, birth weight and placental weight.

## 2.2 Subjects

We examined 35 patients aged 18-40 years old with preeclampsia, in which 14 patients were diagnosed with early preeclampsia (onset <34 weeks) and 21 patients with late preeclampsia (onset ≥34 weeks). Immediately after delivery, placental biopsy with the measurement of 2x2 cm was performed after written informed consent, and samples were preserved in Normal Buffer Formalin. Within 48 hours, paraffin block was made. Baby's birth weight was immediately measured using a standard medical scale.

Ethical approval was obtained from Ethical Committee of Dr Soetomo Hospital (371/Panke.KKE/V/2017) and Dr Soewandhie Hospital (070/16284/436.8.6/2017), Surabaya, Indonesia.

## 2.3 Immunohistochemistry of KIR2DL1

Immunohistochemistry was performed based on IHC protocol supplied from LifeSpan BioSciences, Inc. This study used Primary polyclonal Anti-KIR2DL1/CD 158a LS-C192811 antibody and immunohistochemistry kit from ScyTek laboratories.

For interpretation of immunohistochemistry, manual counting was performed in 10 field of views. We obtain a mean of positive cells in one field view.

## 2.4 Statistical Analysis

The obtained data were analysed using unpaired (two samples) t-test and Pearson and Spearman correlation test. p-value of ≤0.05 was considered statistically significant.

# 3 RESULTS

Placental KIR2DL1 expressions were found in both early and late preeclampsia groups. KIR2DL1 expression was higher in early preeclampsia group (4.42 ± 0.84 positive cells/field view) compared to late preeclampsia group (1.24 ± 0.23 positive cells/field view). We found that KIR2DL1 expressions were not only found on uterine NK cells, but also on T cells in decidual. High expression of KIR2DL1 was not only contributed by NK cells, but also T cells.

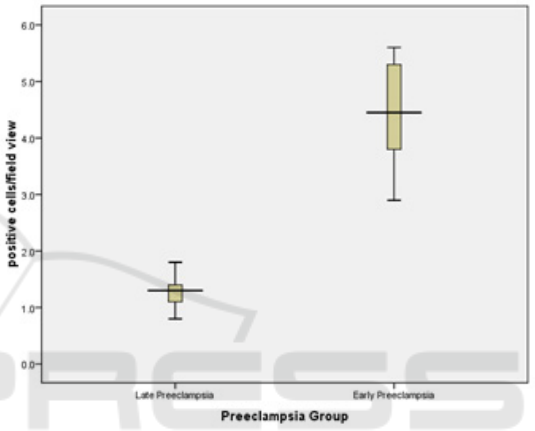


Figure 1: Placental expression of KIR2DL1 in EO-PE and LO-PE group. A significantly higher expression of KIR2DL1 was found in early preeclampsia group (p <0.001)

For the onset of preeclampsia, the mean value for the onset in EO-PE group was 28 ± 3.84 weeks, and 33.37 ± 5.19 weeks for LO-PE group. Spearman test showed a significant strong negative correlation between KIR2DL1 expression and onset of preeclampsia (p <0.001, r=-0.723).

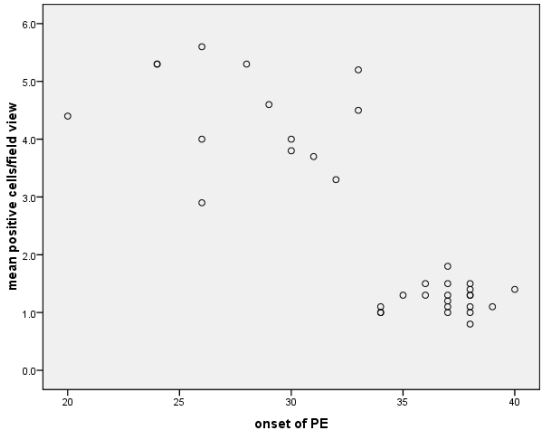


Figure 2: Strong negative correlation between KIR2DL1 expression and the onset of PE ($p < 0.001$, $r = -0.723$).

A higher birth weight was obtained by LO-PE with (2726.90 ± 542.45 gram) compared to EO-PE (1553.57 ± 701.23 gram). There was a strong negative correlation between KIR2DL1 expression and birth weight ($p < 0.001$, $r = -0.770$)

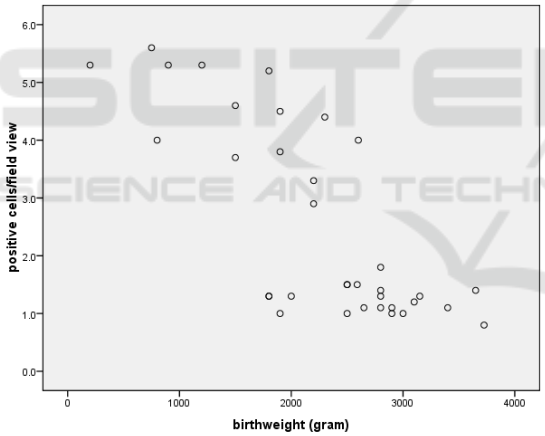


Figure 3: Birth weight is inversely related to KIR2DL1 expression in preeclampsia.

The mean value of placental weight for the whole 35 samples was 427.14 ± 94.11 gram. A higher placental weight was found in LO-PE group. There was a strong negative correlation between KIR2DL1 expression and placental weight ($p < 0.001$, $r = -0.628$)

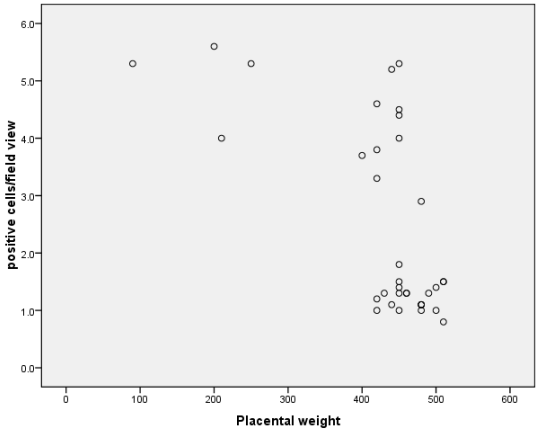


Figure 4: Strong negative correlation between KIR2DL expression and placental weight ($p < 0.001$, $r = -0.628$).

# 4 DISCUSSION

The main pathological features of EO-PE are incomplete transformation of spiral artery, which impairs placental perfusion that results in inadequate nutrition supply to the fetus. While in LO-PE, there is a minimal or no failure in spiral artery remodelling. (Gathiram and Moodley, 2016) Difference in the main pathology is the cause of different expression of KIR2DL1 in both early and late preeclampsia group. KIR2DL1 expression is also found in T cells, and this might contribute to high expression of KIR2DL1.

During day 6-7 after fertilization, embryo will be implanted at the wall of uterus. There are three steps of implantation, which are apposition, adhesion and invasion. Invasion of cytotrophoblast into the vascular system is an important step in spiral artery remodelling. Failure of spiral artery remodelling is not a 'yes' or 'no' phenomenon. Severe failure leads to preeclampsia with an earlier onset. If moderate or minimal remodelling happens, the pregnancy will continue until term, and it is manifested as late preeclampsia. (Redman, Sargent and Staff, 2014)

Spiral artery remodelling involves invasion of spiral artery endothelium and smooth muscle by fetal trophoblast cells. (Whitley and Cartwright, 2010) Uterine NK Cells produces cytokines and angiogenic factors that facilitate trophoblast invasion. Secretion of these factors are lowered in the presence of inhibitory AA haplotype KIR such as KIR2DL1 (Redman, Sargent and Staff, 2014). We found that inhibitory KIR2DL1 will lower the birth weight.

Spiral artery provides nutrition and oxygenation that is essential for fetal growth. Failure in spiral artery remodelling damages uteroplacental perfusion and thus effecting fetal growth.

One of the angiogenic factors secreted by uNK cells are the Placental Growth Factor (PlGF), which is a member of Vascular Endothelial Growth Factor (VEGF). The function of PlGF is to aggravate the growth and maturation of placental vascular system, and also increase trophoblast proloferation. But in the condition where inhibition signal is dominant, PlGF production will be low and this will affect placental growth. (Chau, Hennessy and Makris, 2017)

## 5 CONCLUSION

Higher expression of decidual KIR2DL1, earlier onset of preeclampsia, low birth weight and low placental weight found in EO-PE is consistent with current concept of different pathophysiologic pathway, leading to these different PE phenotypes.

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