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RESEARCH ARTICLE

PAPP-A Levels and IGF-1 Levels in Early-Onset Preeclampsia and Late-Onset Preeclampsia

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Abstract

Introduction: The pathophysiology of preeclampsy is not yet fully understood, but failure of tropoblast invasion and placentation, which is influenced by factors such as pregnancy-associated plasma protein A (PAPP-A) and insulin-like growth factor 1 (IGF-1), is thought to play a role.

Aims: This study aimed to explore the difference in PAPP-A and IGF-1 levels between Early Onset Preeclampsia (PEAD) and Late Onset Preeclampsia (PEAL) assuming that the role of PAPP-A and IGF-1 is more significant in the pathogenesis of PEAD than PEAL.

Methods: This is an analytical observational study with a cross-partition comparative study design. Clinical data were obtained at Dr. M. Djamil Padang Hospital, while PAPP-A and IGF-1 levels were measured at the Biomedical Laboratory of the Faculty of Medicine, Andalas University. Samples are tested according to reagent procedures and analyzed by experts.

Results: Average PAPP-A levels were 2.45+0.35 pg/mL in the early onset preeclampsy group and 2.85+0.50 pg/mL in the late onset preeclampsy group. These two levels differed statistically significantly (p=0.006). That means that low levels of PAPP-A are associated with and play a role in the pathogenesis of early onset preeclampsy. Average IGF-1 levels were 4.66+0.91 pg/mL in the early onset preeclampsy group and 5.39+0.74 pg/mL in the late-onset preeclampsy group. These two levels differed statistically significantly (p=0.010). That means that low levels of IGF-1 are associated with and play a role in the pathogenesis of early onset preeclampsy. PAPP-A levels were significantly positively correlated with IGF-1 levels (p=0.000).

Conclusion: PAPP-A levels are lower in PEAD than PEAL, as are IGF-1 levels. These findings confirm the role of PAPP-A and IGF-1 in preeclampsia. Both of these hormones have potential as indicators and markers for the prediction and management of preeclampsy in early and late onset periods.

Keywords: *Physiology, pregnancy, pathogenesis, signs*

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INTRODUCTION

According to Christopher et al. (2010) and Yang et al. (2021), preeclampsia continues to be the leading cause of maternal and perinatal morbidity and mortality worldwide.[1,2] It also has a significant impact on neonatal outcomes, longer hospital stays, and cesarean sections.[3] Prevalence of preeclampsia has been recorded in Sweden (2.8%) and China (2.2%), with 2/3 of cases in Sweden being mild preeclampsia and 2/3 of cases in China being severe preeclampsia.[2] Preeclampsia has been found to be ubiquitous around the world with varied rates. Preeclampsia cases were reported in a hospital in Ethiopia at 12.4%. 2019.[4]

Many theories have been put forward by experts about preeclampsia. However, the underlying mechanisms that are the pathophysiology of preeclampsia are still not known with certainty, so causal structuring and primary prevention of preeclampsia are still impossible. Although there are many theories about preeclampsia, they all boil down to the statement that the pathogenesis of preeclampsia begins with failure of trophoblast invasion and placentation. Trophoblast invasion and placentation are influenced by three factors, namely trophoblast cells, endometrium, and harmonious crosstalk between trophoblasts and endometrium.[5] Pregnancy-associated plasma protein A (PAPP-A) produced by syncytiotroblast cells plays an important role in the process of trophoblast invasion, stimulation of mitosis and differentiation of trophoblast cells, as well as in placental growth. Several clinical studies have been carried out to see the relationship between low PAPP-A levels and invasion disorders (placentation disorders). These studies found that low PAPP-A concentrations in the blood were correlated with placental dysfunction,[6,7] and the incidence of preeclampsia.[8] Low PAPP-A levels predict early onset preeclampsia,[9] but there is no data on the association of PAPP-A with late onset preeclampsia.

Insulin-like growth factor 1 (IGF-1) is a polypeptide hormone whose structure is the same as insulin.[10] IGF-1 plays an important role in trophoblast function, in placenta formation, and in broad regulation of fetal growth. It is suspected that IGF-1 is involved in the pathogenesis of preeclampsia, but the mechanism of IGF-1-mediated preeclampsia progression is still not known with certainty.[11] Based on its appearance according to gestational age, preeclampsia can be divided into Early Onset Preeclampsia/EOP (early onset preeclampsia/PEAD) and Late Onset Preeclampsia/LOPE (late onset preeclampsia/PEAL). Preeclampsia that appears before 34 weeks is called PEAD and preeclampsia that appears after 34 weeks is called PEAL.[3,12-14]

PEAL and PEAD differ in pathogenesis. PEAD shows clear placental abnormalities (placental factor)[15-16]; while PEAL does not clearly show placental abnormalities (maternal factors are more prominent).[13,17] Because PEAL is not based on placental abnormalities (not based on failure of trophoblast invasion), it can be assumed that there is no role for PAPP-A and IGF-1 in the pathogenesis of PEAL, but on the other hand they play an important role in the pathogenesis of PEAD. This assumption can be proven if there are significant differences in PAPP-A levels and IGF-1 levels between PEAD and PEAL. Therefore, the author wants to conduct research on "PAPP-A Levels and IGF-1 Levels in Early-Onset Preeclampsia and Late-Onset Preeclampsia". Proving the assumptions behind this research can certainly contribute to diagnosing, determining the level of severity and prognosis of preeclampsia cases.

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METHODS

The type of research is analytical observational. The research design chosen was a cross-sectional comparative study, with PAPPA-A levels and IGF-1 levels as independent variables and preeclampsia onset (early onset preeclampsia and late onset preeclampsia) as the dependent variable. The research was conducted at the Inpatient Installation (IRNA) A of Dr. Hospital. M. Djamil Padang for clinical data collection and at the Biomedical Laboratory of the Faculty of Medicine, Andalas University for examining PAPP-A levels and IGF-1 levels. The study population was pregnant women who experienced severe preeclampsia who received treatment at Dr. Hospital. M. Djamil Padang. Preeclampsia is when a pregnant woman with a gestational age of > 20 weeks and no history of hypertension is found on physical examination to have a systolic blood pressure > 140 mmHg and/or a diastolic blood pressure > 90 mmHg accompanied by proteinuria.

RESULTS

The mean PAPP-A level was 2.45 + 0.35 pg/mL in the early-onset preeclampsia group and 2.85 + 0.50 pg/mL in the late-onset preeclampsia group. These two levels are statistically significantly different (p = 0.006). This means that low levels of PAPP-A are associated and play a role in the pathogenesis of early-onset preeclampsia. The mean IGF-1 level was 4.66 + 0.91 pg/mL in the early-onset preeclampsia group and 5.39 + 0.74 pg/mL in the late-onset preeclampsia group. These two levels are statistically significantly different (p = 0.010). This means that low IGF-1 levels are associated and play a role in the pathogenesis of early-onset preeclampsia. PAPP-A levels have a significant and strong positive correlation with IGF-1 levels (p=0.000).

DISCUSSION

The mean age of research subjects in the two research groups was (32.5 + 5.90) years and (31.5 + 6.74) years. These two means are not significantly different (p=0.530). This shows that the two research groups are equivalent in terms of age. The distribution of research subjects according to parity in the two research groups was 86.7 and 73.3% multiparous. These two proportions are not significantly different (p=0.433). This shows that the two research groups are equivalent in terms of parity.

The mean gestational age of research subjects in both research groups was (30.32 + 2.93) weeks in the early-onset preeclampsia group and (36.42 + 1.64) weeks in the late-onset preeclampsia group. These two means are statistically significantly different (p=0.000). This shows that the two study groups were at different gestational ages, and were far from the borderline age range between early-onset preeclampsia and late-onset preeclampsia. Thus, it can be believed that the two research groups are clinically different, namely early onset preeclampsia and late onset preeclampsia.

The mean PAPP-A level was 2.45 + 0.35 pg/mL in the early-onset preeclampsia group and 2.85 + 0.50 pg/mL in the late-onset preeclampsia group. These two levels are statistically significantly different (p

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= 0.006). This means that low levels of PAPP-A are associated and play a role in the pathogenesis of early-onset preeclampsia. Several clinical studies have shown that low PAPP-A levels interfere with invasion, placentation, the emergence of preeclampsia and preeclampsia outcome. Low levels of PAPP-A in maternal blood in the first trimester correlate with the onset of preeclampsia with poor outcomes.[6] The expression of circPAPP-A (RNA PAPP-A) was downregulated in the placenta and plasma of preeclamptic patients. Low expression of circPAPP-A disrupts trophoblast proliferation and invasion. Low expression of circPAPP-A causes overexpression of miR-384, which has the potential to inhibit trophoblast proliferation and invasion.[7]

Low levels of PAPP-A in the first trimester of pregnancy are associated with a short fetus and the emergence of diabetes in the mother.[8] Low PAPP-A levels at 12-14 weeks of gestation can be a predictor of preeclampsia at 26-28 weeks of gestation (early onset preeclampsia.[9] The average IGF-1 level is 4.66 + 0.91 pg/mL in the early onset preeclampsia group and 5.39 + 0.74 pg/mL in the late onset preeclampsia group. These two levels were statistically significantly different (p = 0.010). This means that low levels of IGF-1 are associated and play a role in pathogenesis of early-onset preeclampsia.

The main pathological characteristics of preeclampsia are failure of trophoblast cell invasion and dysfunction of spiral artery remodeling. Behaviors of cells (proliferation, invasion), placenta formation, and fetal growth are widely regulated by insulin-like growth factor 1 (IGF-1).[11] PAPP-A levels had a significant and strong positive correlation with IGF-1 levels (p=0.000). This means that IGF-1 production is associated with PAPP-A production.

Binding of PAPP-A to proteoglycans on the cell surface causes proteolytic cleavage of IGFBP-4 near the IGF receptor, increasing the opportunity for IGF release to receptor signaling. Binding to the surface is mediated by the PAPP-A modules SCR3 and SCR4.[17] By breaking down insulin-like growth factor binding proteins (IGFBPs), PAPP-A functions in tissues as a growth promoting enzyme, which releases bioactive IGF near its receptor. The PAPP-A-IGFBP-4-IGF axis is the main axis, which plays regulatory roles at various levels such as transcriptional control, competing reactions potentially sequestering IGF from IGFBP-4, antagonizing PAPP-A mediated IGF activation, and proteolytic inhibition of PAPP-A.[17] This means that low levels of PAPP-A cause low levels of IFG-1, which means that binding of PAPP-A to proteoglycan elements on the cell surface causes proteolytic cleavage of IGFBP-4 near the IGF receptor, increasing the opportunity for IGF to be released to receptor signaling. Binding to the surface is mediated by the PAPP-A modules SCR3 and SCR4.[17] By breaking down insulin-like growth factor binding proteins (IGFBPs), PAPP-A functions in tissues as a growth promoting enzyme, which releases bioactive IGF near its receptor. The PAPP-A-IGFBP-4-IGF axis is the main axis, which plays regulatory roles at various levels such as transcriptional control, competing reactions potentially sequestering IGF from IGFBP-4, antagonizing PAPP-A mediated IGF activation, and proteolytic inhibition of PAPP-A.[17] This means that low levels of PAPP-A cause low levels of IFG-1, which is significant.

CONCLUSION

PAPP-A levels were lower in PEAD than PEAL, as were IGF-1 levels. These findings confirm the role of PAPP-A and IGF-1 in preeclampsia. These two hormones have the potential as indicators and markers for the prediction and management of preeclampsia during early and late onset.

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