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Original Article

Pregnancy Associated Plasma Protein-A (PAPP-A) as a Marker to Distinguish Normotensive with Early 2nd Trimester and Late 3rd Trimester Onset of Preeclampsia

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Abstract

Background : Preeclampsia is a hypertensive condition that occurs after 20 weeks of gestation accompanied by target organ damage. Complications of preeclampsia can cause intrauterine fetal growth retardation, and placental hypoperfusion, even in the most serious situations, namely termination of pregnancy and death of the fetus and/or mother. Pregnancy-associated plasma protein-A (PAPP-A) is a high molecular weight glycoprotein that is produced in the placenta and secreted into the maternal bloodstream. However, based on several studies that have been conducted, there is uncertainty in the results of assessing PAPP-A levels obtained in pregnant women in the second and third trimesters. The aims of this study was to proving differences in PAPP-A levels in the second and third trimesters in the incidence of early-onset preeclampsia and normotensive pregnancy.

Methods : An analytic observational study with a cross-sectional approach was carried out in the delivery room of RSUP Dr. Kariadi Semarang, Halmahera Health Center, Ngesrep Health Center, Bulu Health Center, and private midwife practice in Semarang City. The subjects of the study were six 2nd-trimester preeclampsia patients, fourteen 3rd-trimester preeclampsia patients, and twenty normotensive pregnancy patients who met the inclusion and exclusion criteria. Data were analyzed using Mann Whitney with a significance of $p<0.05$

Results : There was a significant difference in PAPP-A levels ($p<0.001$) between the preeclampsia and normotensive pregnancy groups, whereas PAPP-A levels were higher in the preeclampsia group. There were significant differences in PAPP-A levels ($p<0.001$) between the 2nd-trimester preeclampsia, 3rd-trimester preeclampsia, and normotensive pregnancies, where the highest PAPP-A levels were found in the 2nd-trimester preeclampsia group.

Conclusion : There was a significant difference in PAPP-A levels between the second and third trimesters of early-onset preeclampsia compared to normotensive pregnancies, where PAPP-A levels were higher in the second and third trimesters of early-onset preeclampsia. Elevated PAPP-A levels in the second and third trimesters are associated with an increased risk of early-onset preeclampsia.

Keywords : PAPP-A, Early Onset Preeclampsia, Normotensive Pregnancy, Second Trimester, Third Trimester

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INTRODUCTION

Preeclampsia is a multi-systemic syndrome involving genetic and environmental factors in its pathogenesis. Preeclampsia is divided into two types based on the time of occurrence, early-onset and late-onset preeclampsia.[2] According to the American College of Obstetrics and Gynecology (ACOG), preeclampsia is a condition of hypertension and proteinuria that occurs after 20 weeks of gestation in patients who were previously normotensive. As the understanding of preeclampsia as a heterogeneous hypertensive disorder of pregnancy develops, ACOG's Hypertension 2013 revised the definition of preeclampsia to include worsening of symptoms with or without proteinuria and to exclude the degree of proteinuria as a criterion of worsening symptoms.[2]

Preeclampsia is divided into two types based on the time of occurrence, early onset, and late-onset preeclampsia. The main pathology of early-onset preeclampsia is incomplete spiral artery transformation, resulting in placental hypoperfusion and reduced nutritional supply to the fetus causing signs of fetal growth restriction (FGR). Complications arising from preeclampsia can cause intrauterine fetal growth retardation, and placental hypoperfusion, even in the most serious situations, namely termination of pregnancy and death of the fetus and/or mother.[1,2]

Pregnancy-associated plasma protein-A (PAPP-A) is a high molecular weight glycoprotein that is produced in the placenta and secreted into the maternal bloodstream. Placental pathology is believed to reduce PAPP-A levels. The etiology of preeclampsia is unknown, but several potential etiologies include abnormal trophoblastic invasion of the uterine vessels and immunological intolerance between fetoplacental and maternal tissues. At 11–14 weeks of gestation, PAPP-A levels decrease which then develops into preeclampsia. Pathological processes leading to low maternal serum levels include decreased trophoblast mass and function, and abnormal placental circulation. Maternal serum concentrations of PAPP-A increase soon after the appearance of preeclampsia and increase slightly at 22+0 24+6 weeks of gestation. In women with preeclampsia in the third trimester, levels increase. Elevated serum PAPP-A was reported soon after the onset of preeclampsia with leakage from damaged villous cells and injury to chorionic villus cells. During gestation, most of PAPP-A is synthesized in the placental syncytiotrophoblast, and serum concentrations increase from pregnancy to term.[3]

However, based on several studies that have been conducted, there is uncertainty in the results of assessing PAPP-A levels obtained in pregnant women in the second and third trimesters. The results of the study found that PAPP-A levels tended to be higher in the second and third trimesters.[4] It has been mentioned that there is an increase in PAPP-A levels of up to 20% in the second and third trimesters.[5] However, other studies stated different things, that PAPP-A levels decreased during the first trimester and the value did not differ significantly in the second trimester.[6] At the beginning of the second trimester, PAPP-A levels of women who will experience preeclampsia decrease to 1/3 lower than women who do not experience preeclampsia.[7]

This study aims to prove the difference in PAPP-A levels in the second and third trimesters in the incidence of early-onset preeclampsia and normotensive pregnancy.

METHODS

The research has received ethical permission from KEPK with No. 1453/EC/KEPK-RSDK/2023. An analytic observational study with a cross-sectional approach that was carried out in the delivery room of RSUP Dr. Kariadi Semarang, Halmahera Health Center, Ngesrep Health Center, Bulu Health Center, and private midwife practice in Semarang City. The subjects of the study were 20 early onset preeclampsia patients and 20 normotensive pregnancy patients who met the inclusion and exclusion criteria. The inclusion criteria were: 1) Willing to become research subjects, 2) Pregnant women aged 20–35 years, 3) Primigravida and multigravidas, 4) Preeclampsia with early onset of gestational age <34 weeks, 5) Pregnancy with an intrauterine single fetus. Exclusion criteria were: 1) Unclear first day of last menstrual period (HPHT), 2) History of preeclampsia, 3) Pregnant women with chronic diseases, including diabetes mellitus, cerebrovascular disease, chronic hypertension, chronic kidney failure, and chronic infection. Data were analyzed using SPSS statistics application with a significance of $p<0.05$.

RESULTS

Age, in the preeclampsia group, was found to be an average of 29.9 years with a standard deviation of 6.43 years. In the normotensive group, the mean was 29.35 years with a standard deviation of 4.51 years. There was no significant difference in the age distribution ($p=0.756$) between the preeclampsia and normotensive groups.

Body mass index, in the preeclampsia group, obtained a median value was 28.85 kg/m^2 with the smallest value being 24.8 kg/m^2 and the largest value being 29.7 kg/m^2. In the normotensive group, the median value was 25.7 kg/m^2 with the smallest value being 19 kg/m^2 and the largest value being 29.7 kg/m^2. There was a significant difference in the distribution of body mass index ($p=0.005$) between the preeclampsia and normotensive groups, where a higher body mass index was found in the preeclampsia group (Table 1).

TABLE 1
Characteristics of respondents

Variable	Preeclampsia (n=20)	Normotensive (n=20)	*p*
Age (years)	29.90 ± 6.43	29.35 ± 4.51	0.756†
Body mass index	28.85 (24.8–29.7)	25.7 (19–29.7)	0.005‡

†Independent T-test; ‡Mann Whitney U; *significant *p*<0.05

TABLE 2
PAPP-A levels in cases of preeclampsia

Variable	Preeclampsia Mean ± SD; Median (min–max)	Normotensive Mean ± SD; Median (min–max)	*p*
PAPP-A Level	3.17 (0.63–43.72)	0.67 (0.24–3.01)	<0.001

Mann Whitney U; *significance *p*<0.05

TABLE 3
PAPP-A levels in cases of 2nd-trimester preeclampsia, 3rd-trimester preeclampsia and normotensive pregnancy

Variable	Preeclampsia TM2 Mean ± SD; Median (min–max)	Preeclampsia TM3 Mean ± SD; Median (min–max)	Normotensive Mean ± SD; Median (min–max)	*p*
PAPP-A Level	3.75 (2.38–15.18)	2.3 (0.63–43.72)	0.67 (0.24–3.01)	<0.001

Kruskal Wallis; significant *p*<0.05

TABLE 4
The risk of preeclampsia based on PAPP-A levels

Variable		Preeclampsia		*p*	PR (95% CI)
		Preeclampsia	Normotensive		
Rate PAPP-A	≥1.61 ng/mL	16	5	0.001	3.61 (1.46–8.92)
	<1.61 ng/mL	4	15		

Chi-Square; significant *p*<0.05

PAPP-A levels, in the preeclampsia group, obtained a median value was 3.17 ng/mL with the smallest value being 0.63 ng/mL and the largest value being 43.72 ng /mL. In the normotensive group, the median value was 0.67 ng/mL with the smallest value being 0.24 ng/mL and the largest value being 3.01 ng/mL. There was a significant difference in PAPP-A levels (p<0.001) between the preeclampsia and normotensive groups, where PAPP-A levels were higher in the preeclampsia group (Table 2).

PAPP-A levels, in the 2nd-trimester preeclampsia group, obtained a median value was 3.75 ng/mL with the smallest value being 2.38 ng/mL and the largest value being 15, 18ng/mL. In the 3rd-trimester preeclampsia group, the median value was 2.3 ng/mL with the smallest value being 0.63 ng/mL, and the largest value was 43.72 ng/mL. In the normotensive group, the median value was 0.67 ng/mL with the smallest value being 0.24 ng/mL and the largest value being 3.01 ng/mL. There were significant differences in PAPP-A levels (p<0.001) between the 2nd-trimester preeclampsia, 3rd-trimester preeclampsia, and normotensive pregnancies, where the highest PAPP-A levels were found in the 2nd-trimester preeclampsia group (Table 3).

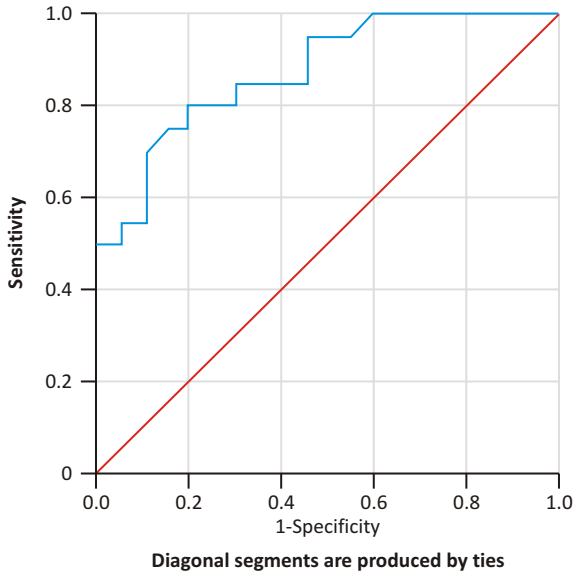

Figure 1. TROC curve of PAPP-A levels on the incidence of preeclampsia.

Based on ROC analysis and AUC curve, it was found that PAPP-A levels (p<0.001; AUC=0.878) were related to the incidence of preeclampsia. PAPP-A levels with a cut off 1.61 ng/mL have a sensitivity of 80% and specificity of 80% (Figure 1).

In subjects with PAPP-A levels >1.61 ng/mL, 16 subjects had preeclampsia and 5 subjects without preeclampsia. In subjects with PAPP-A levels <1.61 ng/mL, there were 4 subjects with preeclampsia and 15 subjects without preeclampsia (Table 4).

There is a relationship between PAPP-A levels and the incidence of preeclampsia (p=0.001). Individuals with PAPP-A levels > 1.61 ng/mL have a 3.61x (PR 3.61; 95% CI 1.46–8.92) greater risk of experiencing preeclampsia than individuals with PAPP-A levels < 1.61 ng/mL.

DISCUSSION

The research subjects were dominated by women aged 29–30 years. In the preeclampsia group, the body weight and body mass index status were significantly higher than in the normotensive group.

Janani F, *et al* who researched cases of preeclampsia found that the average age of patients with preeclampsia was 28.6 years.[8] Tabassum S, *et al* who assessed maternal and perinatal clinical outcomes in patients with preeclampsia also reported that the mean age of patients with preeclampsia was 32.27 years with a body mass index of 33.19 kg/m^2.[9] Arwan B, *et al* in his research stated that patients who tend to preeclampsia are patients with overweight and obese BMI status with a high-risk age range.[10] Excessive weight gain during pregnancy will increase the risk three times greater for preeclampsia.[11] This study shows that there is a relationship between BMI and the incidence of preeclampsia. Motedayen M, *et al* in a systematic research review and meta-analysis regarding the relationship between body mass index and the incidence of preeclampsia reported that there was a significant relationship between BMI and the risk of preeclampsia.[12] In pregnant women who are overweight, preeclampsia can occur through the mechanism of hyperleptinemia, metabolic syndrome, inflammatory reactions and increased oxidative stress which lead to endothelial damage and dysfunction.[13]

In this study, there was a significant difference in PAPP-A levels between the preeclampsia and normotensive groups, where PAPP-A levels were higher in the preeclampsia group. There is a correlation between PAPP-A levels and the incidence of preeclampsia, where increased PAPP-A levels are associated with an increased incidence of early-onset preeclampsia with a moderate positive correlation level. Individuals with PAPP-A levels >1.61 ng/mL have a 3.61x greater risk of experiencing preeclampsia than individuals with PAPP-A levels <1.61 ng/mL.

PAPP-A is a marker used to show perfusion function and vascular resistance. During pregnancy, PAPP-A protein is synthesized primarily by syncytiotrophoblast cells and septal X cells derived from trophoblasts in placental tissue. At concentrations 100–1000 fold lower than those obtained during the first trimester of pregnancy, PAPP-A protein is also expressed in other reproductive tissues (ovaries, uterine tubes, endometrium and myometrium, and prostate in males), in female and non-reproductive tissues. male (kidney,

colon, bone marrow cells, and breast), and in pathophysiologically modified tissues (eg breast and prostate cancers). [14]

Preeclampsia is associated with increased PAPP-A; the highest values are recorded before the obvious manifestations of preeclampsia. Elevated PAPP-A levels occur up to 1.5-fold compared with healthy pregnancies and are observed in both mild and severe preeclampsia, with no difference between mild and severe cases.[15] In addition, PAPP-A is correlated with mean arterial blood pressure. In a recent study, PAPP-A was measured at 30–33 weeks' gestation as a screening method for preeclampsia that developed after 34 weeks and did not differ significantly from controls. Some studies have shown that PAPP-A levels are increased in preeclampsia.[16] A study by Wright and colleagues showed that PAPP-A serum levels increased in pregnant women with above average body weight, in pregnant women from the Afro-Caribbean, South Asian and East Asian races against pregnant women. Caucasian race. Meanwhile, PAPP-A serum levels decreased in pregnant women with above average height, pregnant women who were smokers, and multiparous pregnant women with or without a previous history of preeclampsia compared to nulliparous pregnant women.[5] These factors are thought to have caused a significant increase in PAPP-A levels in this study and led to differences in PAPP-A results with previous studies.

In this study, the highest PAPP-A levels were significantly found in 2nd-trimester preeclamptic subjects, while the lowest PAPP-A levels were found in normotensive subjects.

Research conducted by Spencer K, *et al* found that there was an increase in PAPP-A levels in pregnant women with preeclampsia at 22–24 weeks gestation.[17] Uriel M, *et al* in his research found that PAPP-A levels in first-trimester preeclampsia subjects had a greater value than normal pregnancy subjects.[18]

Multivariate analysis showed that together, there was a relationship between body weight and PAPP-A levels on the incidence of preeclampsia. PAPP-A levels have a stronger relationship to the incidence of preeclampsia than body weight.

Various studies have confirmed that obesity in mothers increases the risk of preeclampsia by 3–4x higher when compared to mothers with normal weight.[19] A cohort study conducted in Lanzou, China supports the hypothesis that weight gain during pregnancy increases the risk of obesity and that pre-pregnancy obesity and gestational weight gain increase the risk of pre-eclampsia, both independently and together, as a combined effect of maternal and maternal obesity. gestational weight gain further increases the risk of pre-eclampsia.[20]

The advantage of this study is that it can show dynamic changes in PAPP-A levels along the trimesters of pregnancy in patients with preeclampsia which is able to show a decrease in values as gestational age increases. The limitation of this study is that the incidence of preeclampsia is not only influenced by PAPP-A levels but also by the body mass index of the study subjects. Future research should control the subject's body mass index to eliminate confounding variables.

CONCLUSION

There was a significant difference in PAPP-A levels between the second and third trimesters of early-onset preeclampsia compared to normotensive pregnancies, where PAPP-A levels were higher in the second and third trimesters of early-onset preeclampsia. Elevated PAPP-A levels in the second and third trimesters are associated with an increased risk of early-onset preeclampsia. Individuals with PAPP-A levels in the second and third trimesters >1.61 ng/mL have a 3.61x (PR 3.61; 95% CI 1.46–8.92) greater risk of experiencing preeclampsia than individuals with PAPP-A levels trimester II and III <1.61 ng/mL

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Conflict of Interest

The authors certify that they have no competing financial interests or personal relationships that could influence the work reported in this paper

Research Ethics

The research was approved by the Health Research Ethics Committee, Faculty of Medicine, Diponegoro University Dr. Kariadi and carried out following the principles of the Declaration of Helsinki.

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