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Plasma Aldosterone and Angiotensin 1-7 Levels with Early Preeclampsia Without Comorbidities at the Obstetrics and Gynecology Polyclinic of Universitas Airlangga Hospital

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ABSTRACT

Dysfunction of the Renin-Angiotensin-Aldosterone System (RAAS) is thought to play an important role in the pathogenesis of preeclampsia. Further research is needed to improve understanding of the underlying mechanisms of this disease and to investigate safer and more effective diagnostic and therapeutic options for pregnant women. Objective: to determine the correlation between plasma aldosterone and angiotensin 1-7 levels with the incidence of preeclampsia, especially early preeclampsia. Methods: A cross-sectional study using a total sampling of pregnant patients with a gestational age of more than 20 weeks and a single live baby who underwent antenatal examination at the RSUA Polyclinic from May to June 2023. Exclusion criteria included pregnant patients with multiple comorbidities. The immunoassay method took venous blood samples (5 cc) for aldosterone and angiotensin (1-7) measurements. Statistical analysis was performed using SPSS 26.1 software with the ANOVA statistical method and Tukey's post hoc test. Further statistical approaches included subgroup analysis of early preeclampsia and subgroup analysis of late preeclampsia. Results: 114 patients were included in this study, consisting of 21 preeclamptic patients and 93 non-preeclamptic patients. Statistical analysis showed that both angiotensin (1-7) and aldosterone levels did not significantly correlate with the incidence of preeclampsia ($p = 0.852$; $p = 0.419$, respectively). However, in the subgroup analysis of early preeclampsia ($n = 11$), aldosterone levels were significantly higher than in non-preeclamptic cases ($p = 0.024$). Conclusion: The correlation of aldosterone levels with early preeclampsia cases indicates a specific role of aldosterone. Increased aldosterone levels protect the placental angiogenesis-branching system, with the mechanism of volume retention and sodium levels in early preeclampsia.

Keywords: *Preeclampsia, Angiotensin (1-7), Aldosterone, Renin-Angiotensin-Aldosterone System (RAAS)*

1. INTRODUCTION

Preeclampsia is one of the leading causes of maternal and fetal death worldwide, with incidence rates varying between 0.5% and 38.4% [1]. Globally, the prevalence of early preeclampsia is estimated to reach 0.2-0.38% of all preeclampsia cases [2]. In developing countries, the prevalence of preeclampsia tends to be higher, ranging from 1.8% to 16.7% [3]. As a developing country, Indonesia has a relatively high prevalence of preeclampsia, which is around 25% [4], which contributes significantly to the high Maternal Mortality Rate (MMR) recorded at 4,627 people in 2020, with East Java in second place with 565 incidents [5][6].

Although there has been extensive research on preeclampsia, its pathogenesis is still not fully understood. One of the factors identified in the development of preeclampsia is dysfunction of the Renin-Angiotensin-Aldosterone system (RAAS), which regulates blood pressure and intravascular volume. Decreased regulation of RAAS due to hypoxia or placental ischemia is believed to disrupt maternal hemodynamics. Previous studies on Aldosterone and Angiotensin II (Ang II) levels in

preeclampsia have shown inconsistent results. Several studies found no significant difference in Aldosterone, Ang (1-7) levels between normal and preeclamptic pregnancies. In contrast, other studies in Australia, India, Myanmar, and Malaysia showed that preeclamptic patients had lower levels of these biomarkers [7][8]. The discrepancy in these findings is thought to be due to methodological difficulties, differences in the characteristics of the populations studied, and variations in the sample sizes used [9].

One of the essential components of RAAS that plays a role in the pathogenesis of preeclampsia is Angiotensin-Converting Enzyme 2 (ACE2), which is abundantly found in vascular endothelial cells [10]. ACE2 converts Aldosterone to Angiotensin (1-7), which can regulate two significant pathways in the RAAS system. Studies measuring Ang II, Aldosterone, and Angiotensin (1-7) levels in preeclampsia are still limited, but the Meryl-Brosnihan study in 2019 revealed a significant decrease in Ang (1-7) levels in patients with preeclampsia. Increased Ang II followed by increased Aldosterone levels contribute to intravascular volume overload, which further causes hypertension and is one of the main features of preeclampsia [11][12][13].

Preeclampsia can cause various serious complications, both for the mother and the fetus. Maternal complications include HELLP syndrome, disseminated intravascular coagulation, and acute renal failure [14]. Meanwhile, for the fetus, preeclampsia can cause IUGR (Intrauterine Growth Restriction), fetal hypoxia, and fetal distress, which can lead to neonatal morbidity and mortality [15]. In addition, women who have experienced preeclampsia are at higher risk of developing cardiovascular disease later in life. Research shows that women who have experienced preeclampsia have a 4-fold greater risk of developing heart failure, as well as a 2-fold greater risk of coronary heart disease (CHD), stroke, and other cardiovascular diseases [16].

Although it is known that Angiotensin II (Ang II) plays a vital role in the pathogenesis of preeclampsia, treatments targeting this system in pregnant women are limited. Drugs such as ACE inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) cannot be given to pregnant women due to potential teratogenic side effects on the fetus and renal impairment in the second and third trimesters of pregnancy [17]. Therefore, it is essential to develop safer therapeutic alternatives for pregnant women, especially by utilizing more specific pathways in the RAAS system.

This study aims to investigate the relationship between Angiotensin (1-7) levels and preeclampsia and to identify new biomarkers that can be used for early detection of preeclampsia. It is expected to contribute to developing safer and more effective therapies without causing risk to the fetus. In addition, these findings can be the basis for finding new solutions to prevent and treat preeclampsia and reduce maternal and fetal mortality in Indonesia.

2. METHODS

This study is an observational analytical study with a cross-sectional research design. The study was conducted at the Pregnant Polyclinic of Airlangga University Hospital, Surabaya, from May to June 2023. The sample of this study used pregnant women who were being controlled at the pregnant polyclinic with a total sampling method based on inclusion and exclusion criteria. The inclusion criteria in this study were all pregnant women with a gestational age of 20 weeks or more, with a single live baby without comorbidities. The exclusion criteria for the study were pregnant women with comorbidities (heart failure, kidney failure, severe infection, stroke, malignancy, and blood or immunity disorders).

Data obtained from primary data, namely blood sampling of patients, was then subjected to Immunoassay examination. Pregnant women with a gestational age of over 20 weeks who were undergoing control at the RSUA maternity clinic. A venous blood sample of 5 cc was taken and then stored in a five cc EDTA vacutainer tube. Serum creatinine levels were measured first to minimize exclusion criteria; if they met the requirements, aldosterone and angiotensin 1-7 measurements were continued in the venous blood of pregnant women. The venous blood was taken 5 cc, stored in a vacutainer tube, to be then checked with Aldosterone and Ang 1-7 reagents in the RSKI RSUA Surabaya laboratory. Pregnant women patients with a gestational age of at least 20 weeks who were treated at the Universitas Airlangga Hospital maternity clinic, then 5 cc of venous blood was taken, which was stored in a vacutainer tube. The blood will be checked with Aldosterone and Ang 1-7 reagents to determine the levels of Aldosterone and Ang 1-7 in the patient.

The data obtained will be analyzed univariately and bivariately. Univariate analysis is conducted to explore the characteristics of each variable with descriptive presentation through a frequency distribution table accompanied by:

a. mean, median, and mode to determine the distribution of data

b. range, standard deviation, variance, and coefficient of variance to determine the variability in the data

Bivariate analysis was conducted to determine the relationship between aldosterone levels and preeclampsia, and Ang (1-7) levels with the incidence of preeclampsia. The T2 Free Sample comparison test will be conducted to determine the correlation between Aldosterone levels and angiotensin 1-7 levels with the incidence of preeclampsia if the data distribution is normal. Meanwhile, the Mann-Whitney test is used when the data distribution is abnormal. The multi-sampling ANOVA test with post hoc Turkey to analyze which pathway is stronger in influencing the incidence of preeclampsia between Aldosterone and Ang (1-7) levels.

The research was conducted at the maternity clinic of Airlangga University Hospital after obtaining an ethical feasibility statement from the Research Ethics Committee of Airlangga University Hospital, Surabaya, with Number 071/KEP/2024 until the data was processed and presented.

3. RESULT

This three-month study was conducted at the Pregnant Polyclinic of Airlangga University Hospital, Surabaya. One hundred fourteen patients met the inclusion criteria and were included as research samples.

Table 1 shows that the average age of patients in this study was 29.30 (±5.85) years. Patients who worked had a higher percentage of preeclampsia (28.63%) than non-preeclamptic patients who also had jobs (28.00%). The average education of patients in this study was high school/vocational school for 67 patients (58.77%).

Table 1. Distribution of characteristics of the respondent

Variable	Preeclampsia (N=21)	Non-Preeclamsia (N=93)	p-value
Age [Mean (± SD)]	29,52 (± 6,74)	29,25 (± 5,44)	0,428[a]
Status of Employment			
Working	6 (28,63%)	26 (28.00%)	0,955[b]
No working	15 (71,45%)	67 (72.00%)	
Education			
No School	0	1 (1,11%)	
Elementary School	2 (9,54%)	4 (4,32%)	0,619[b]
Junior High School	0	14 (15,11%)	
Senior High School	17 (81,00%)	50 (53,84%)	
Diploma/bachelor	2 (9,54%)	24 (25,83%)	
Family comorbidities			
Hipertensi	10 (47,66%)	31 (33,33%)	0,218[c]
Diabetes mellitus	4 (19,00%)	24 (25,83%)	0,516[c]
Jantung	0	3 (3,32%)	1,000[c]
Gestational age			
<34 Minggu	11 (52,46%)	43 (46,21%)	0,611[c]
≥34 Minggu	10 (47,66%)	50 (53,84%)	
Gravida			
1	6 (28,63%)	25 (26,94%)	
2	7 (33,33%)	28 (30,12%)	0,460[d]
3	7 (33,33%)	22 (23,71%)	
>3	1 (4.84%)	18 (19.41%)	
Abortus			
No	14 (66,66%)	71 (76,32%)	0.358[c]
Yes	7 (33,33%)	22 (23,72%)	

Signifikan a: *Paired T-Test* ; b: *Spearman* ; c: *Chi-Square* ; c: *Mann*

17 patients (15% of the total patients and 81% of the total patients with preeclampsia) had a high school and vocational high school education level. The group of patients with gestational age <34 weeks was called early preeclampsia, and the group of patients with gestational age ≥34 weeks was called late preeclampsia. Based on this grouping, there were 60 patients (52.6%) with gestational age ≥34 weeks, while 54 patients (47.4%) had gestational age <34 weeks. The number of patients with preeclampsia in this study was slightly higher in the early preeclampsia group (52.46% of preeclampsia and 9.6% of all samples) compared to late preeclampsia (48.66% of preeclampsia and 8.8% of all samples).

In this study, the number of gravida varied, from gravida 1 (first pregnancy) to gravida 5 (fifth pregnancy), with the highest. This study found Gravida 2 was the most common gravida found in 35 patients (30.7%). Gravida 2 and 3 were the most gravida with preeclampsia, each with 7 patients (33.33% preeclampsia and 6.1% of the total sample). A total of 7 patients (33.33% of preeclampsia and 6.14% of the total sample) experienced preeclampsia, while 22 patients with a history of other abortions did not experience preeclampsia.

The results of the analysis of the basic characteristics of the research subjects showed that there was no relationship between employment status, education level, family history of disease, history of hypertension, gestational age, number of gravida, incidence of abortion, compared to the incidence of preeclampsia (p>0.05).

Table 2. Characteristics of angiotensin 1-7 and aldosterone in pregnant women

	Mean (± SD)	Median (min-max)
Angiotensin 1-7 (pg/ml)	61,46 (±27,203).	67,75 (4,11-118,53)
Aldosteron (pg/ml)	195,16 (±74,14)	180,04 (69,07-636,662)

Table 2 shows that the average angiotensin 1-7 is 61.46 (±27.203) pg/ml, while the average aldosterone is 28.06 (±1.01) pg/ml. The next sub-chapter will discuss the relationship between the two independent variables and each of the main variables.

Table 3. Angiotensin 1-7 and Aldosterone in normal pregnancy compared with the incidence of preeclampsia

	Preeklamsia (n=21)	Non-Preeklamsia (n=93)	p-value
Angiotensin 1-7 (pg/ml)	67,91 (13,38-107,37)	67,60 (4,11-118,49)	0,852*
Aldosteron (pg/ml)	199,77 (111,65-301,55)	177,66 (69,07-636,66)	0,419*

**Mann-Whitney*

Based on the table above, the results show that Angiotensin 1-7 and Aldosterone levels are not significantly related to the incidence of preeclampsia (p>0.05). The relationship analysis was then focused on the preeclampsia group (n=21), which was divided based on the patient's gestational age. The group of patients with a gestational age of <34 weeks is called early preeclampsia, and the group of patients with a gestational age of ≥34 weeks is called late preeclampsia. The two group divisions were then compared with the two independent variables: Angiotensin 1-7 and Aldosterone. Based on the Kolmogorov-Smirnov normality test, angiotensin 1-7 and aldosterone were customarily distributed (p-value Kolmogorov-Smirnov>0.05). The data will be presented as a mean (Standard Deviation) if it is usually distributed. The data will be presented as a median (minimum value-maximum value) if it is not normally distributed.

Table 4. Angiotensin 1-7 compared with the incidence of preeclampsia based on gestational age and non-preeclampsia

	Angiotensin 1-7 (pg/ml)	Anova p-value	Post Hoc Test (Turkey)		
Non-Preeklamsia (n=93)	61,06 (±21,23)	0,880	Ref	0,871	1,000
Early Preeklamsia (Gestational Age <34 weeks) (n=11)	65,41 (±29,69)		0,871	Ref	0,922

Late Preeklamsia (Gestational Age ≥34 weeks) (n=10)	60,84 (±33,76)		1,000	0,922	Ref

Table 4 shows the relationship between each level of the two independent variables and the incidence of preeclampsia based on gestational age group.

Table 5. Aldosterone compared with the incidence of preeclampsia based on gestational age and non-preeclampsia

	Aldosteron (pg/ml)	Anova p-value	Post Hoc Test (Turkey)		
Non-Preeclamsia (n=93)	118,61 (±61,49)		Ref	0,024	0,956
Early Preeclamsia (Gestational Age <34 weeks) (n=11)	250,22 (±146,51)	0,032	0,024	Ref	0,199
Late Preeclamsia (Gestational Age ≥34 weeks) (n=10)	195,47 (±48,58)		0,956	0,199	Ref

Based on Table 5, the results show that Aldosterone levels are significantly related to the incidence of preeclampsia ($p < 0.05$). Post-hoc test using the Turkey HSD test showed that the significance was in comparing the mean of the non-preeclampsia group with early preeclampsia, where the mean aldosterone levels of the early preeclampsia group were higher than those of the non-preeclampsia group. Angiotensin levels 1-7 did not have a significant relationship.

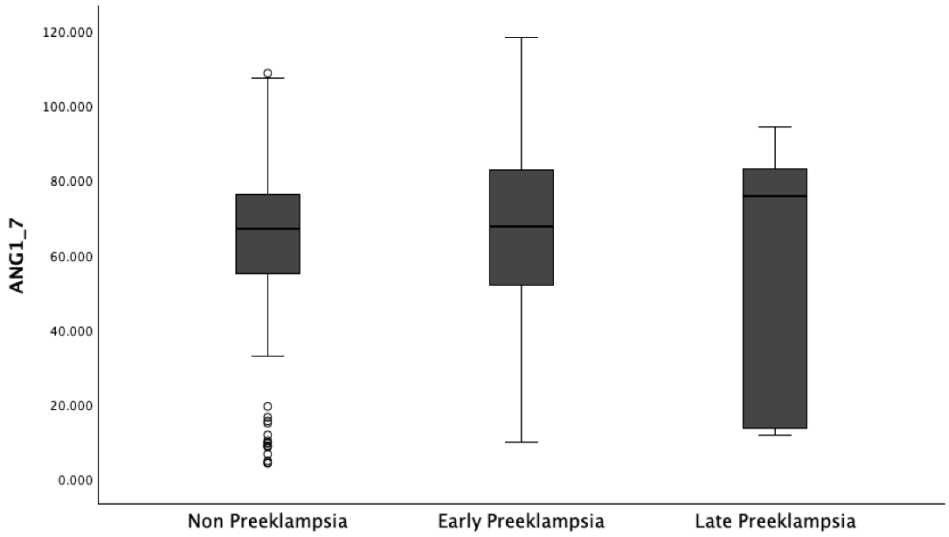

Figure 1. Graph of angiotensin 1-7 against the incidence of preeclampsia based on gestational age.

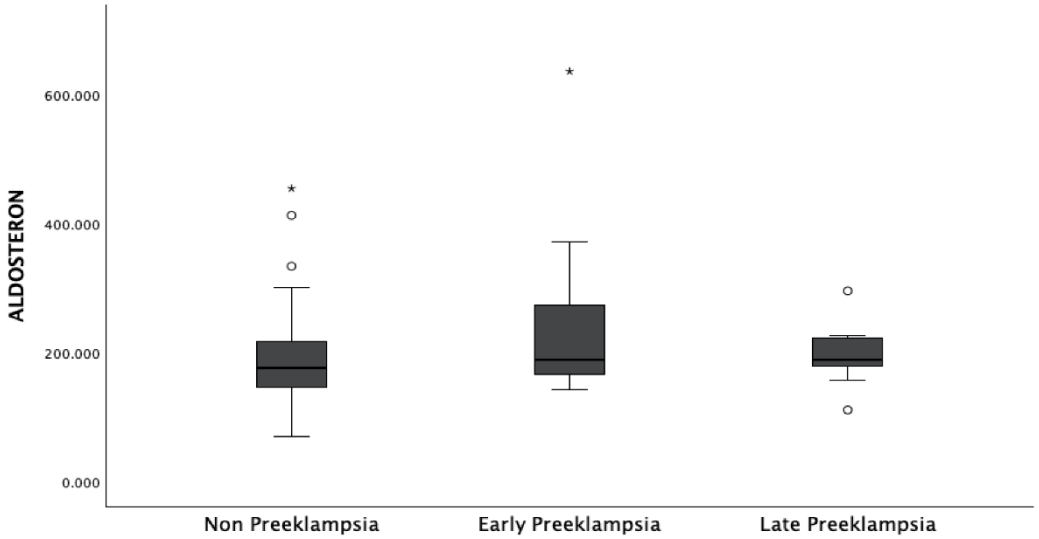

Figure 2. Graph of aldosterone against the incidence of preeclampsia based on gestational age.

Table 6. Angiotensin 1-7 and Aldosterone compared with the incidence of preeclampsia based on gestational age

	Early Preeclamsia (Gestational Age) <34 weeks (n=11)	*Late* Preeclamsia (Gestational Age) ≥34 weeks (n=10)	p-value
Angiotensin 1-7 (pg/ml)	73,39 (±21,81)	47,56 (±30,14)	0,099**
Aldosteron (pg/ml)	185.12 (±33,70)	221,82 (±63,48)	0,081**

Based on the table above, the results show that Angiotensin 1-7 and Aldosterone levels are not significantly related to the incidence of preeclampsia (p>0.05). The image in this outbreak shows a candlestick graph of angiotensin 1-7 against the incidence of preeclampsia based on age groups.

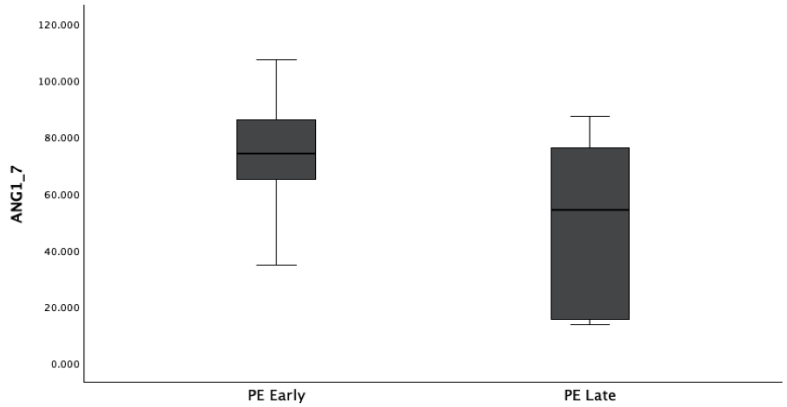

Figure 3. Graph of angiotensin 1-7 against the incidence of preeclampsia based on gestational age.

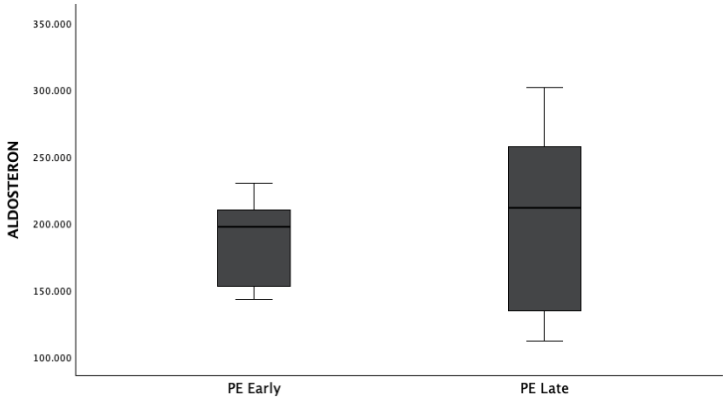

Figure 4. Graph of aldosterone against the incidence of preeclampsia based on gestational age.

4. DISCUSSIONS

Preeclampsia is also called the "disease of theory" because many factors influence the occurrence of preeclampsia, and the underlying pathogenesis is still unclear. Risk factors for preeclampsia have been widely studied. The main risk factors include a history of preeclampsia, chronic hypertension, pregestational diabetes mellitus, and obesity. Other risk factors include advanced maternal age, nulliparity, and a history of chronic kidney disease.[18]

This study is similar to the study conducted by Menard et al in 1986, with a total sample of 67 patients, showing no difference in Ang 1-7 levels between the preeclampsia and non-preeclampsia populations. However, different research results were obtained by Meril 2002 with the results that there was a decrease in Ang II and Ang 1-7 levels. Still, aldosterone levels tended to remain the same in PE pregnant patients compared to normotensive pregnant women. [19] This also has the same results as the study by Borsnihan in 2020, with a sample size of 86 patients, which showed that Ang II and Ang 1-7 decreased in patients with preeclampsia. [20]

In recent years, many studies have emerged that support the body's compensation stage in the development of preeclampsia. Research conducted by Julia J. (2012) at the University of New South Wales, Australia, has shown that the body's vascular compensation mechanism occurs at 16 weeks of gestation until decompensation occurs (which underlies the onset of proteinuria). However, the time of onset of the disease is still difficult to predict, this is based initially on new findings about the new RAAS pathway, namely through ACE-2 and AT2R which are upregulated during pregnancy so that the levels of Angiotensin 1-7 (which has its own MAS receptor) which functions to balance the traditional renin-angiotensin system (Ang II-AT1R) The main effects of ACE-2, Ang 1-7 are vasodilation, anti-angiogenesis, anti-inflammation and anti-proliferation. In addition, angiotensin 1-7 can contribute to plasma volume regulation because it may function as an aquaretic that increases diuresis if there is hypervolemia in pathological pregnancy. Recent studies have shown that in normal pregnancy, not only is the traditional vasoconstrictor side at work, but the vasodilator side of the RAS is also activated to achieve homeostasis. In pre-eclampsia, the vasodilator renin-angiotensin system is down-regulated. The relatively low levels of Ang (1-7) may represent the presence of AT1-AA (an antibody that arises from placental hypoxia and ischemia), and the increased sensitivity of AT1 receptors may result in a shift of hormones to the stronger vasoconstrictor side. In normal pregnancy, both Ang 1-7 and angiotensin II contribute to regulating and invading trophoblasts and placental angiogenesis. In pre-eclampsia, excessive activation of AT1 receptors in the uteroplacental unit (local) by AT1-AA or angiotensin II (systemic) may lead to the release of pathogenic substances, leading to impaired placentation and reduced placental blood flow.[21][22]

This study is different from the studies conducted by Merril (2002) and Genevieve Escher (2007) in that there was a decrease in Aldosterone levels in PE pregnant patients compared to normotensive pregnant women, and research by Borsnihan in 2020 with indirect analysis, which concluded that Aldosterone decreased in patients with preeclampsia. [13][20]

The increase in Aldosterone levels in this study is in line with the basic science theory that Aldosterone is involved in the retention of blood volume and sodium levels, which are indirectly thought to have a protective effect on the placental angiogenesis-branching system by the mechanism of increasing and maintaining blood flow to the placental capillary system temporarily. This is evidenced by a study by Kim et al. in Yonsei (replicated study in experimental animals-rabbit by Eun Jung et al, 2021), South Korea in 2008, where plasma aldosterone levels increased significantly with increasing gestational age. Compared with preeclamptic pregnancies, a twofold increase was seen in the ARR (Aldosterone-Renin Ratio) in the first 16 weeks of pregnancy. In addition, it has recently been reported that plasma ARR may play an important role in aortic systolic pressure, and a relative increase in aldosterone levels increases cardiovascular risk, which ultimately results in end-organ damage. The conclusion of Kim's study shows that women with preeclampsia have decreased plasma renin activity but relatively greater aldosterone stimulation compared to normal pregnancies. This study also suggests that excessively high ARR may hurt uterine arterial perfusion.[23][24]

Research conducted by Bosnihan et al. in 2020 on humans to examine the levels of the renin-angiotensin-aldosterone system stated that in preeclampsia, MasR and ACE2 proteins decreased significantly. So that there is a decrease in the production and sensitivity of Ang (1-7) which impacts increasing blood pressure. Another theory put forward by Genevie`ve Escher in 2007 that in pregnant women with preeclampsia, there was a decrease in Aldosterone levels and activity compared to women with normal pregnancies, it is believed that the decrease in levels is related to the presence of competitive receptors (progesterone and cortisol) in preeclampsia patients which increases and the presence of AT-1 receptor antibodies which reduce the sensitivity of mineralocorticoids compared to other receptors. However, this theory is still a postulate. [22][25]

5. CONCLUSIONS

Plasma Angiotensin (1-7) levels were not significantly different in early preeclamptic patients compared to non-preeclamptic and late preeclamptic patients. Aldosterone levels increased significantly in early preeclamptic patients compared to non-preeclamptic patients, but were not significantly different compared to late preeclamptic patients.

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