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Calcidiol Involvement in Hypertension in Pregnancy

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ABSTRACT--- *This study aims to analyse the relationship of vitamin D levels with severe preeclampsia, chronic hypertension in pregnancy and HELLP syndrome. A comparative analytic cross-sectional study on 91 participants. Data and blood samples were taken from all pregnant women with significant months of pregnancy diagnosed with severe preeclampsia, chronic hypertension and HELLP syndrome in educational hospitals. Statistical analysis was performed using Chi Square and one-way ANOVA. From total of 91 participants, there were 18 HELLP syndromes, 11 chronic hypertensions and 62 with severe preeclampsia. Demographic data and Vitamin D levels among groups were compared and association analyzes were performed. There were no statistically significant differences in age, parity, gestational age, pre-pregnancy BMI and weight gain during pregnancy between these groups. The level of SGOT, SGPT, Creatinine, Urea in patients with HELLP syndrome were higher, whereas platelet counts were lower than the 2 other groups (p <0.001). No differences and association were found between vitamin D levels in severe preeclampsia, HELLP syndrome and chronic hypertension in pregnancy. Vitamin D is involved in pathogenesis of hypertension in pregnancy with the finding of lower levels in chronic hypertension compared with levels in severe preeclampsia and HELLP syndrome, however calcidiol is not a factor that directly involved in the pathomechanism of hypertension in pregnancy.*

Keywords--- *Vitamin D levels, severe preeclampsia, HELLP syndrome and chronic hypertension.*

I. INTRODUCTION

Hypertension is responsible for 14% out of all primary maternal death throughout the world, which made it the second most frequent cause of death. It is estimated that around 192 people died due to hypertension. Preeclampsia and eclampsia are hypertension diseases during pregnancy which accounts for the main cause of maternal and fetal death.[1]

Preeclampsia and eclampsia affected 3% to 5% of all pregnancy and caused more than 60,000 maternal and 500,000 fetal deaths annually throughout the world.[2] Meanwhile, the HELLP syndrome occurred in 0.2-0.8% of pregnancy in the world with the varying maternal mortality rate from 1% in the US to 30% in Turkey.[3,4]

In Indonesia, according to the 2013 Indonesian Demographic and Health Survey (*Survei Demografi dan Kesehatan Indonesia*; SDKI), there are three main causes of maternal death, i.e. hemorrhage (30.3%), hypertension

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in pregnancy (27.1%), and infection (7.3%). In Indonesia, the incidence of preeclampsia was 128.273/year or approximately 5.3% and did not show any incidence decrease within the last two decades.[5]

To date, the cause of preeclampsia is not known for certain. Thus, experts coined the term *the disease of theories* for preeclampsia. One of the theories of preeclampsia is fetal growth intolerance due to maladaptation of the mother's immune system. Vitamin D is a potent immunomodulatory agent and several studies stated a correlation between vitamin D status and the risk of preeclampsia. Lack of vitamin D is also correlated to the incidence of hypertension in non-pregnant women. This condition can occur due to the activation of the renin-angiotensin-aldosterone system which can increase blood pressure through direct vasoconstriction effect or through the retention of salt and fluid, which lead to increased blood pressure.[6,7]

Vitamin D has a direct effect on the molecular pathway responsible for the pathogenesis of preeclampsia, such as the invasion of trophoblastic and immunomodulation and blood pressure control, proteinuria, abnormal angiogenesis, and excessive inflammation. The 1.25-dihydroxyvitamin D (calcitriol) receptor has been found in the target tissue that regulates blood pressure. Decreased calcitriol level causes a disruption in calcium absorption in the intestines, which leads to hypocalcemia. To compensate, tubular calcium reabsorption is increased, which caused hypocalciuria seen in preeclampsia patients. The occurring hypocalciuria has been reported to predict preeclampsia long before the presentation of clinical manifestation. Therefore, vitamin D has been hypothesized to affect the risk of preeclampsia. However, the correlation between vitamin D and preeclampsia has not been toroughly investigated.[7,8]

Lack of vitamin D is often found during pregnancy in many regions throughout the world. In respect to high vitamin D deficiency with its possible consequences, the ideal amount of vitamin needed to maintain an adequate level in pregnant women has not been determined with certainty.[7] Vitamin D assessment was conducted by measuring the level of Calcidiol (25(OH)D), which is the primary form of vitamin D in the body.

Information and data regarding the correlation between vitamin D level and HELLP syndrome are not available and should be investigated. Therefore, the author would like to analyze the correlation between vitamin D level and severe preeclampsia, chronic hypertension, and HELLP syndrome during pregnancy.

II. METHODOLOGY

This study is comparative analytics with a cross-sectional approach conducted in the Obstetrics Emergency Installation, and the delivery room of Dr. Wahidin Sudirohusodo General Hospital, Makassar, Labuang Baji Hospital, Makassar, Siti Fatimah Mother & Child Hospital, and Bhayangkara General Hospital, Makassar from 1 October 2018 – 31 October 2019. The samples were all pregnant women who were diagnosed with severe preeclampsia, chronic hypertension during pregnancy, or HELLP syndrome who fulfilled the inclusion criteria. The inclusion criteria were: domiciled in South Sulawesi, Mongoloid Malay race, Bugis, Makassar, Toraja, Java and Mandar tribe, all pregnant women during their 37-42 weeks of pregnancy according to the Neagle formula, diagnosed with severe preeclampsia, chronic hypertension in pregnancy, or HELLP syndrome (Tennessee classification), not smoking, both actively or passively, and willing to participate in the study. The total sample was 91 patients divided into 3 groups, i.e. 62 patients with severe preeclampsia, 18 patients with HELLP syndrome, and 11 patients with chronic hypertension.

The materials and ingredients prepared in each hospital were: Informed consent, questionnaire, BD Vacutainer serum (red-colored tube) without EDTA, and flashback blood collection needle. The obtained data were recorded in a special form, analyzed, and presented in a narration, table, or graph. Consecutively, statistical analysis of Chi-Square was performed to test correlation, and one-way ANOVA to test comparison

III. RESULTS

This study included patients with severe preeclampsia, HELLP syndrome, and chronic hypertension, each with 62, 18, and 11 patients, respectively.

Table 1 showed that most subjects were unemployed. The education level of most subjects was within a basic level. The demographic characteristics based on occupation and education were homogenous.

Table 1 Demographic *characteristics of research Subjects*

characteristics	Group						p*
	Severe Preeclampsia (n = 62)		HELLP Syndrome (n = 18)		Chronic Hypertension (n = 11)		
	n	%	n	%	n	%	
Maternal Occupation							
Un Employed	54	87.1	17	94.4	8	72.7	0.243
Employed	8	12.9	1	5.6	3	27.3	
Maternal Education							
Basic Level (1-12 years)	54	87.1	17	94.4	79	86.8	0.792
Higher Level (12+ years)	8	12.9	1	5.6	12	13.2	

Table 2 showed that the blood pressure in all three groups indicated significant differences with the highest mean value of systole and diastole blood pressure in the severe preeclampsia group compared to the others. Pre-pregnancy Body mass index and body weight increase during pregnancy did not show the difference between the three groups.

Table 2 Distribution of several clinical parameters of research subjects

Variables	Group									p
	Severe Preeclampsia (n=62)			HELLP Syndrome (n=18)			Chronic Hypertension (n=11)			
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
Maternal Age (years)	30	6	29	31	7	31	34	6	32	0.111*
Parity	1	2	1	1	1	1	2	2	1	0.443**

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Pre-Pregnancy BMI (Kgm^{-2})	24	4	23	23	2	22	24	2	24	0.299**
Weight Gain during Pregnancy (Kg)	15	4	15	14	4	15	12	4	1313	0.113**
Systolic BP (mmHg)	179	20	180	169	14	170	166	13	170	0.020**
Diastolic BP (mmHg)	111	8	110	107	11	110	92	28	90	0.010**

Abbreviations : BMI, body mass index; BP, blood pressure

*ANOVA, ** *Kruskal-Wallis*

Table 3 presented an increase of SGOT, SGPT, creatinine, urea, LDH, and platelet in HELLP syndrome. The deterioration of laboratory findings was associated with severe preeclampsia complications. In general, the laboratory parameter in the HELLP syndrome group was significantly different from the others. The increase of liver enzyme level was predominant in the HELLP syndrome group due to liver damage, which was not found in the other two groups. Due to hemolysis, the LDH level in the HELLP syndrome group underwent a significant increase. Other than that, the platelet level was also exceptionally low due to increased platelet use from the activation and attachment to damaged vascular area. Higher urea and creatinine levels were also seen in the HELLP syndrome group, albeit still within normal limits which showed that there was no damage to the kidneys of all three groups. The vitamin D level tends to be higher in severe preeclampsia, followed by HELLP syndrome, and lastly chronic hypertension. This condition may be implicated by the acute nature of hypertension in severe preeclampsia and HELLP syndrome compared to long-term chronic hypertension.

Table 3 Laboratory Variables of research Subjects

Variable	Group									p
	Severe Preeclampsia (n=62)			HELLP Syndrome (n=18)			Chronic Hypertension (n=11)			
	Mean	SD	Median	Mean	SD	Median	Mean	SD	Median	
SGOT (IU/L)	28	11	26	174	120	154	19	6	19	0.000*
SGPT (IU/L)	21	13	17	102	65	95	12	5	10	0.000*
Creatinine (mg/dl)	0.65	0.24	0.65	0.98	0.38	0.88	0.54	0.21	0.48	0.000*

Urea (mg/dl)	23	13	21	42	16	44	13	10	11	0.000**
LDH (IU/L)	294	103	276	1178	1040	867	209	16	213	0.000*
Platelets (cell/micro L)	271335	100012	243500	83067	69943	68850	268273	82434	250000	0.000*
Vitamin D (ng/mL)	42	33	34	38	29	32	31	12	31	0.401**

Abbreviations : SGOT, Serum glutamate oxaloacetate transaminase; SGPT, Serum glutamate Pyruvate transaminase ; LDH lactate dehydrogenase

*ANOVA, ** *Kruskal-Wallis*

IV. DISCUSSION

This study implicated that most subjects were unemployed (housewives). This was in contrast to the finding of the Central Bureau of Statistics (*Badan Pusat Statistik*; BPS) which showed that the working participation rate of females in 2018 was 55.48%. The education level of all three groups was within the basic education level (elementary to high school). This condition was following the data from BPS (2018) which showed that 30.43% female population living in the urban areas have the highest education at the high school level. Meanwhile, only 12.83% of the female population living in rural areas achieved the highest education at the junior high school level. This result may be due to most samples were from the urban areas.

The mean age of subjects was within a healthy reproduction range and it was proven that there was no correlation between age and hypertension during pregnancy. This result was in accordance with a retrospective study in Saudi Arabia, which showed that the mean age of the female population with hypertension during pregnancy was 31.3 ± 6.7 years old.[9] The risk of preeclampsia rises along with age both in nulliparity and multiparity. Individuals aged 35 years and above had 1.2 times more risk, while those aged 40 years and above had 1.5 times more risk.[10] Older individuals had a less adaptive vascular system and more vulnerable to comorbidities. Therefore, during pregnancy, physiological changes became intolerable. The finding above disagrees with the result found in this study, whereas the correlation between age and hypertension during pregnancy could not be proven. This may be due to other factors such as maternal and paternal genetics and race. The maternal genetic factor was thought to have a > 50% role as the cause of vulnerability to preeclampsia. A wide genomic study had identified many genes related to hypertension during pregnancy and these genes were different among various races.[11,12,13]

This study did not find any correlation of parity between the three groups. A study in the US found that nulliparity tends to experience hypertension during pregnancy.[14] A different result was found in a study in Saudi Arabia which revealed that the average parity of female individuals with hypertension during pregnancy was 3 ± 2.[9] The correlation between parity and hypertension during pregnancy still produced an inconsistent result. This may be due to other effects from primiparity hypothesis, the time between pregnancies (> 10 years) and the risk of preeclampsia from previous pregnancy.[10,15]

In this study, the pre-pregnancy BMI in three groups were within normal limits and there was no correlation between BMI and severe preeclampsia, HELLP syndrome, and chronic hypertension. This was caused by other factors such as genetics, race, physical activity, and diet, which affected preeclampsia.[16,17,18]

The average weight gain of preeclampsia patients with ≥ 37 weeks of pregnancy was 15.4 ± 6.6 kg. This was in line with this study. Weight gain is identical to increased hormonally-active adipose tissues which can produce proinflammatory cytokines that disrupt the blood vessels' endothelial function.[19] This study described that weight gain had an insignificant effect on severe preeclampsia, HELLP syndrome, or chronic hypertension. This may be due to the weight gain range in these three groups, i.e. between 12-15 kg, which was normal for women with normal pre-pregnancy BMI (18.5-24.9 kg/m^2). Therefore, other factors may affect severe preeclampsia, HELLP syndrome, or chronic hypertension in these subjects as previously stated.

The laboratory parameters showed that groups with severe preeclampsia and chronic hypertension had normal laboratory mean values compared to HELLP syndrome. The diagnosis establishment of HELLP syndrome required laboratory tests compared to severe preeclampsia and chronic hypertension. The kidney function assessed by urea and creatinine levels showed normal values from all three groups.

HELLP syndrome also produced a more severe organ dysfunction compared to the other two groups. The pathology mechanism of HELLP syndrome is not known for certain. However, the complete activation of the coagulation cascade is thought to be the main underlying problem. Fibrins form network-like connecting tissues in small blood vessels. This caused a microangiopathy hemolytic anemia, whereas the formed network caused damage to red blood cells when they passed through these networks. Hemolysis will cause increased LDH, which was not found in chronic hypertension and severe preeclampsia.[3,20]

This study found normal vitamin D levels in all three study groups. This contradicting result compared to other studies may be caused by the measurement of vitamin D, which was conducted during the third trimester (during full-term pregnancy). The 25(OH)D level did not change during the third trimester unless there was a change in the synthesis and intake pattern.[21] Based on the above theory, it can be concluded that there were no changes in the synthesis and intake pattern of vitamin D during pregnancy. Therefore, information regarding vitamin D levels before pregnancy is important to explain why the vitamin D levels in all three groups were normal. Other than that, this study did not provide information regarding vitamin D supplementation, both before and during pregnancy. Thus, the subjects might already have adequate vitamin D levels before pregnancy or received sufficient intake, both from daily nutrition and multivitamin supplementation during pregnancy. The difference in race, diet, and sun exposure may also influence the normal vitamin D level found in this study.[21,22,23] There is a lack of data regarding diet and sun exposure related to adequate vitamin D intake in the Indonesian population.

This study did not show any correlation between vitamin D level and HELLP syndrome. The same was found in severe preeclampsia. Regardless of the controversy on the cause of HELLP syndrome, this syndrome is thought to be the aggravation of preeclampsia.

The results of this study showed that chronic hypertension during pregnancy was not related to vitamin D. Active vitamin D, i.e. 1.25(OH)D, affected blood pressure increase directly from vascular and through the renin-angiotensin-aldosterone system in the kidney. Therefore, 25(OH)D deficiency will lead to a lack of 1.25(OH)D. In a condition of vitamin D deficiency, calcium absorption in the intestines decreases, which leads to decreased serum calcium. Decreased serum calcium will trigger the calcium sensors in the parathyroid gland to secrete parathyroid hormone. This hormone acts by stimulating the kidney to produce 1.25(OH)D to increase calcium

absorption in the intestines. This mechanism causes patients with vitamin D (25(OH)D) deficiency to have normal 1.25(OH)D level and might even increase. Thus, there will be no activation of the renin-angiotensin-aldosterone system or vascular dysfunction which will lead to hypertension.[22]

V. CONCLUSION

Based on the results of this study concluded that vitamin D is involved in pathogenesis of hypertension in pregnancy with the finding of lower levels in chronic hypertension compared with levels in severe preeclampsia and HELLP syndrome, however calcidiol is not a factor that directly involved in the pathomechanism of hypertension in pregnancy

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