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Comparison of Serum Vitamin D Levels in Patients with Severe Preeclampsia and Normal Pregnancy at Dr. Zainoel Abidin Regional General Hospital Banda Aceh

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Abstract

AIM: This study aims to assess differences in the mean maternal Vitamin D levels between severe preeclampsia (SPE) and normal pregnant women at the Dr. Zainoel Abidin Hospital Banda Aceh, Indonesia.

METHODS: This research was a case–control study conducted at the Dr. Zainoel Abidin Regional General Hospital Banda Aceh. Pregnant women with confirmed SPE and normal pregnancies were involved in the study. The level of 25(OH)D3 was assessed by taking serum samples and examined by the enzyme immunoassay method. The Mann–Whitney U test analysis was conducted for bivariate analysis with a 95% confidence level.

RESULTS: A total of 82 participants were involved in this study, with 41 subjects in the case group and 41 patients in the control group. A total of 30 SPE patients (70.3%) showed moderate Vitamin D deficiency. The mean levels of 25(OH)D3 in the SPE and normal pregnancy groups, respectively, were 14.43 ng/mL and 27.94 ng/mL ($p < 0.001$). Based on the 20 ng/mL cutoff point, the difference in 25(OH)D3 levels between the two groups showed an odd ratio (OR) of 15.05.

CONCLUSION: Serum Vitamin D levels in SPE patients were two times lower than in the normal group. Evaluation of serum Vitamin D levels needs to be carried out periodically during pregnancy as a screening and diagnostic effort to prevent the potential development of SPE.

Introduction

Vitamin D deficiency is a worldwide health problem. In pregnancy, low Vitamin D concentrations in blood are also common [1], [2]. The prevalence of low Vitamin D levels varies widely, with the Asian region having the highest prevalence of Vitamin D deficiency in pregnant women, with an average of 79.5% [3]. Recent studies have reported that the prevalence of Vitamin D deficiency in pregnancy ranges from 39.4% to 76.5% [4].

Vitamin D plays a key role in fetal development, whereas levels of 1,25-dihydroxy Vitamin D increase in early pregnancy until delivery [5]. Several studies have reported that maternal Vitamin D status is associated with pregnancy and neonatal development outcomes [6], [7], [8]. Maternal Vitamin D deficiency is associated with an increased risk of preeclampsia (PE), whereas this condition will increase maternal and neonatal mortality and morbidity [9]. A meta-analysis of eight clinical trials reported that 25(OH)D levels less than 50 nmol/L increased the risk of PE [10]. Furthermore, PE and low blood Vitamin D concentrations are directly and indirectly associated with immune system dysfunction, impaired placental implantation, abnormal angiogenesis, excessive inflammatory reaction, and hypertension [3].

Hypovitaminosis D or Vitamin D deficiency has been widely associated with the incidence of PE [11], [12]. Several hypotheses show how the role of Vitamin D may influence the process of developing PE, such as the role of Vitamin D in modulating the pro-inflammatory response and reducing oxidative stress in PE, promoting angiogenesis through *vascular endothelial growth factor*(VEGF) and gene modulation, and lower blood pressure via the renin-angiotensin (RAS) [13], [14], [15], [16]. Increased risk of preeclampsia was associated with Vitamin D deficiency at a cutoff of 20 ng/ml [17]. The odds of severe preeclampsia increased by 3 times in pregnant women with low Vitamin D levels at 23–28 weeks of gestation [18].

There is a paucity of literature discussing the association between Vitamin D levels and preeclampsia in a sun-rich country such as Indonesia.

Preeclampsia contributes to 23.9 % of maternal deaths in Indonesia [19]. Therefore, finding the association between Vitamin D deficiency in pregnancy may lead us to an efficient preventive measure in maternal death caused by preeclampsia. This study aims to assess differences in the mean maternal Vitamin D levels between severe preeclampsia (SPE) and normal pregnant women.

Methods

Ethical approval

This study has been approved by the Health Research Ethics Commission (KEPK) Faculty of Medicine, Syiah Kuala University, and Dr. Zainoel Abidin General Hospital Banda Aceh with no. 247/EA/FK-RSUDZA/2021. Written informed consents were also collected from all participants.

Study design and population

This study was an observational survey with case–control (case-control). Participants were pregnant women who delivered baby in the delivery room and emergency room at Dr. Zainoel Abidin Hospital Banda Aceh, Indonesia, from August to December 2021. The inclusion criteria were women with live singleton pregnancies diagnosed with severe preeclampsia and normal pregnant patients who consented to participate in the study. The total sample was 82 women divided into case group (41 women with severe preeclampsia) and control group (41 normal pregnant women).

Patients with a history of kidney disease, chronic hypertension, cardiovascular disease, liver disease, diabetes, endocrine disease, malignancy, history of smoking, alcohol consumption, and use of drugs that affect blood pressure were excluded from this study.

Severe preeclampsia (SPE) was defined as blood pressure greater than 140/90 mmHg with gestational age above 20 weeks and no prior history of hypertension accompanied by the presence of one or more of the following conditions: proteinuria (≥300 mg/24h) or urinary protein: persistent +1 dipstick and one sign of creatinine ratio 0.3 or evidence of thrombocytopenia (<100,000/μl), renal insufficiency (creatinine >1.1 mg/dl or an increase of 2 times above the normal value), serum transaminase increased 2 times above the normal value, cerebral symptoms (headache, blurred eyes, and seizures), and pulmonary edema.

The measurement of vitamin D level

Vitamin D concentration (25-OH-D) was measured using an enzyme immunoassay and results were reported as ng/ml. The IDS 25-OH-D EIA kit was used to quantify the 25-OH-D level in the serum. The concentration of Vitamin D was defined as follows: Normal (30–60 ng/ml or 75–150 nmol/l), insufficiency (20–30 ng/ml or 50–75 nmol/l), moderate deficiency (10–20 ng/ml or 25–50 nmol/l), and severe deficiency (<10 ng/ml or <25 nmol/l).

Statistical analysis

Univariate analysis was used to present the data in a table distribution. The bivariate analysis (difference test) used in this study was the Mann–Whitney U test with a confidence level of 95%. Furthermore, this study assessed the odds ratio (OR) of pregnancy status based on serum Vitamin D levels. The analyses were performed using SPSS Statistics, Version 24.0 (IBM Corp., NY).

Results

Table 1 showed the characteristic of participants in this study. The average age in the SPE group was 32 years, while the normal pregnancy group was relatively younger, with an average age of 31 years. No significant difference in age was observed between the study groups (SPE and normal with p>0.05). The SPE group showed a higher number of obese patients than those with normal pregnancies, 14.6% (obesity I) and 17.1% (obesity 2). The mean pregnancy status in the SPE group was G1 P0 A0 with a blood pressure of 170/100 mmHg. Proteinuria was observed in SPE group, with proteinuria two in 32/41 people (78%) and positive three in 9/41 people (22%).

Table 1: Characteristics of study subject

Characteristics	SPE (+) (n = 41)	Normal (n = 41)	p-value
Age (years), median (min-max)	32 (21–24)	31 (21–43)	0.741
Body mass index, n (%)			0.019*
Normoweight	26 (63.4)	35 (85.4)	
Overweight	2 (4.9)	1 (2,4)	
Obesity I	6 (14.6)	4 (9.8)	
Obesity II	7 (17.1)	1 (2.4)	
Gestation, median (min-max)	1 (1–4)	2 (1–4)	0.165
Parturition, median (min-max)	0 (0–3)	1 (0–3)	0.051
Abortion, median (min-max)	0 (0–3)	0 (0–1)	0.675
Systolic BP (mmHg), median (min-max)	170 (160–200)	120 (100–130)	<0.001*
Diastolic BP (mmHg), median (min – max)	100 (100–120)	70 (70–90)	<0.001*
Proteinuria, n (%)			
Negative	0 (0)	41 (100)	<0.001*
Positive 2	32 (78)	0	
Positive 3	9 (22)	0	

In PEB patients, none of the patients showed normal Vitamin D levels. Most SPE patients had moderate Vitamin D deficiency (73.2%). Severe Vitamin D deficiency was observed in 9.8% of the SPE group (4/41). More than half of normal pregnant women have Vitamin D insufficiency (53.7%). A normal level of Vitamin D was observed in 22% (9/41) of normal

pregnancies, while moderate Vitamin D deficiency was found in 24.4% (10/41). None of normal pregnant woman has severe Vitamin D deficiency (Table 2).

Table 2: The distribution of serum Vitamin D levels

Serum Vitamin D level	SPE (+) (n = 41)	Normal (n = 41)
Normal	0	9 (22)
Insufficiency	7 (17.1)	22 (53.7)
Moderate deficiency	30 (73.2)	10 (24.4)
Severe deficiency	4 (9.8)	0

Table 3 showed that serum Vitamin D levels in SPE patients were statistically lower than those in the normal pregnancy group ($p < 0.05$). The mean maternal Vitamin D level in SPE group was twice lower than normal pregnant women (14.43 ng/ml compared to 27.94 ng/ml).

Table 3. Analysis of the difference in mean maternal Vitamin D levels in SPE and normal at Dr. Zainoel Abidin Regional General Hospital Banda Aceh

Vitamin D levels	Median	Min–Max	p-value*
SPE (+), n = 41	14.43	8–28.31	<0.001
Normal, n = 41	27.94	14.58–47.62	

*Mann–Whitney U test.

Table 4 showed that 41.5% of SPE patients had serum Vitamin D levels of ≤20 ng/mL, whereas in the normal group, only 12.5% of participants showed serum Vitamin D levels ≤20 ng/mL. Most of the normal group showed serum Vitamin D levels >20 ng/mL with a percentage of 37.8%. Pregnant women with serum Vitamin D levels ≤20 ng/mL had 15.05-fold odds of developing SPE when compared to pregnant women with serum Vitamin D levels >20 ng/mL (95% CI: 5.1–44.4).

Table 4: The odds value analysis of the difference in mean maternal Vitamin D levels in preeclampsia and normal groups at the Dr. Zainoel Abidin Regional General Hospital Banda Aceh

	SPE (+)	Normal	p-value*	OR
≤20 ng/mL	34 (41.5)	10 (12.5)	< 0.001	15.05
>20 ng/mL	7 (8.5)	31 (37.8)		

*Chi-square test, OR: Odd ratio.

Discussion

Vitamin D is a secosterol hormone with the primary role of calcium homeostasis [20]. Physiologic Vitamin D status can be measured by the 25-hydroxyvitamin D (25[OH]D) level [21]. Recent evidence suggests that Vitamin D, especially a deficiency of vitamin D, may be involved in adverse pregnancy outcomes [22]. Most of the studies are from countries situated in different latitudes, generally away from the equator [22], [23], [24]. Despite its sunny climate and proximity to the equator, deficiency of Vitamin D deficiency is prevalent among pregnant women in Indonesia [25], [26], [27], [28].

No significant age difference was observed between the study groups ($p > 0.05$) in this study. This finding was in line with the results of Yakub *et al.*'s study, which concluded that the age of pregnant women was not associated with the incidence of preeclampsia [29]. Ghafarzadeh *et al.* also showed that Vitamin D levels-related preeclampsia did not significantly correlate with maternal age [30]. However, several studies show maternal age as a risk factor for preeclampsia. Tessema *et al.* found that women over 35 years of age had a 4.5 times greater risk of developing preeclampsia than women aged 25–29 years [31]. A similar study in China showed that women aged 35–39 years and 40 years had 3.80 times and 7.46 times higher risk of developing preeclampsia than normal reproductive age, respectively [32]. These differences might be attributed to different study designs and characteristics of the participants included in the studies [33].

This study found that obesity is related to severe preeclampsia ($p < 0.05$). Dumais *et al.* also found a relationship between obesity in pregnancy and preeclampsia [34]. Obesity can increase the risk of preeclampsia about 3 times, and in developed countries is the main risk that can be associated with the disorder. There is a hypothesis that asymmetric dimethyl arginine (ADMA) is one of the convergence points for obesity mechanisms that increase the risk of preeclampsia, including SPE [35].

The mean pregnancy status of the SPE group in this study was G1 P0 A0. It was consistent with the findings of Grum *et al.* where primigravida is a risk factor for preeclampsia and eclampsia in addition to multiple pregnancies, a history of preeclampsia, and alcohol consumption during pregnancy [36]. A study by Vincent *et al.* also showed that the highest cases of preeclampsia and eclampsia occurred in primigravida women [37].

Tables 3 and 4 showed a low level of serum Vitamin D increased the odds of severe preeclampsia by 15 times compared to a normal level of Vitamin D. Vitamin D in SPE group was 2 times lower than the normal group, with an average of 14.43 ng/mL ($p < 0.05$). Seifer *et al.* reported that SPE patients showed high antiangiogenic factors and low serum Vitamin D levels at the delivery time. Furthermore, the study concluded a significant difference between levels of Vitamin D and antiangiogenic factors between SPE patients and the control group [38]. Schulz *et al.* showed that Vitamin D deficiency was associated with severe preeclampsia because hypovitaminosis D increases sFlt-1, which also increased antiangiogenic factors and contributed to vascular complications in pregnancy, such as SPE [39].

Sahu *et al.* explained that Vitamin D deficiency plays a role in the incidence of SPE because of the key role of Vitamin D in placental development. In this case, calcitriol (the active form of Vitamin D) exerts its hormonal action by binding to the nuclear Vitamin D receptors in the nucleus throughout the body, including pregnancy-specific tissues such as the placenta and uterine placental bed (decidua) [40]. During pregnancy,

Vitamin D plays a role in placental implantation and function due to its angiogenic, immunomodulatory, and anti-inflammatory effects. In addition, Vitamin D has a significant role in the synthesis and regulation of effective genes in the early stages of placental development, so this placental abnormality associated with SPE may result from Vitamin D deficiency [41]. Thus, the immunomodulatory properties of Vitamin D play a key role in the development of immunological tolerance in pregnancy. Therefore, sufficient Vitamin D has a role in the management and prevention of SPE [42].

Purswani *et al.* showed evidence of the association between low Vitamin D concentrations and adverse pregnancy-induced hypertension (PIH) outcomes [43]. Sasan *et al.* showed that prenatal Vitamin D supplementation therapy could help reduce the incidence of gestational hypertension/ preeclampsia [32]. Hutabarat *et al.* concluded that Vitamin D deficiency was associated with an increased risk of early-onset preeclampsia [44]. However, other studies showed different results from this study, such as Wibowo *et al.*, which showed that maternal serum Vitamin D_3 levels, umbilical cord blood, and placental tissue Vitamin D levels were similar between patients with and without preeclampsia [45]. Differences in the studies may occur due to different participant's characteristics in the study.

Vitamin D deficiency increases the risk of SPE and adversely affects trophoblast survival capacity in patients with preeclampsia. Hutabarat *et al.* showed that the placenta, as a special pregnancy organ, has adaptive and compensatory mechanisms to fight environmental stress [44]. The damaged placenta in preeclampsia is negatively supported by Vitamin D deficiency which is supposed to act as a major biological buffer of cellular hemodynamics. Vitamin D and its cellular binding component, Vitamin D receptor (VDR), play a role in trophoblasts' survival capacity, especially in preeclampsia [45].

Conclusion

This study showed that pregnant women with severe preeclampsia have significantly lower level of serum Vitamin D levels compared to women with normal pregnancies. A low level of Vitamin D in pregnancy increases the odds of severe preeclampsia by 15-fold.

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