Research Article

Vitamin D Levels and Risk Factors in Early Onset Preeclampsia, Late Onset Preeclampsia and Normal Pregnancy

Vaulinne Basyir[1], Aldina Ayunda Insani[2]*, Feni Andriani[2], Afifah Suhaila[2]

[1]Department of Obstetrics and Gynecology
[2]Midwifery Education
Faculty of Medicine Universitas Andalas
Dr. M. Djamil General Hospital
Padang

Abstract

Objective: To determine the frequency distribution and the relation of risk factors to vitamin D levels in women with early onset (EOSPE), late-onset severe preeclampsia (LOSPE), and normal pregnancy.

Methods: This study was cross-sectional with pregnant women diagnosed with EOSPE LOSPE at RSUP DR M Djamil Padang and normal pregnancy at the Pengambiran Health Center. The serum samples of the research subjects were examined for blood levels of Vitamin D using the ELISA kit.

Results: Frequency distribution of risk factors for EOSPE respondents aged 20-35 years 50%, mothers not working 85%, single pregnancy 95%, normal blood sugar 80%, and an increase in the number of leukocytes 90%. Frequency distribution of LOSPE respondents, maternal age 20-35 years 60%, mothers not working 95%, single pregnancy 95%, normal blood sugar 65%, and increasing leukocytes 75%. Based on the data analysis test EOSPE respondents with risk factors for preeclampsia history and body mass index had a significant relation with vitamin D levels with *P Value* 0.00 (P < 0.05). LOSPE mothers with gravid risk factors, history of preeclampsia, history of hypertension, and history of Diabetes Mellitus had a significant relation with Vitamin D levels *P Value* 0.00 (P < 0.05).

Conclusion: The results of statistical tests for LOSPE mothers had a significant relation with Vitamin D levels compared to the risk factors for EOSPE mothers. The incidence of preeclampsia is influenced by complex etiopathogenesis, one of which is influenced by vitamin D levels.

Keywords: EOSPE, LOSPE, Elisa-kit, Vitamin D, Etiopathogenesis**.**

Correspondence author. Aldina A Insani. Midwifery Education. Faculty of Medicine Universitas Andalas. Dr. M. Djamil General Hospital. Padang.
Email; aldinaayundinsani@med.unand.ac.id

INTRODUCTION

According to the World Health Organization (WHO), the Maternal Mortality Rate (MMR) is still very high, around 810 women die from complications related to pregnancy or childbirth every day, and 295,000 women die during and after pregnancy and childbirth.[1] MMR in Indonesia in 2017 and 2019 did not change, 305 per 100,000 live births. The leading cause of maternal death is hypertension in pregnancy 27.2%.[2] According to WHO, incidence of preeclampsia ranges from 0.51% - 38.4%, while the incidence in Indonesia is around 3.4% - 8.5%.[3]

There are many theories about the causes of preeclampsia, including theories of placental vascular abnormalities, placental ischemia, nutritional deficiencies, and inflammation. increased VitD levels may improve the human extravillous trophoblast invasion, which is required for normal placentation.[4]

Vitamin D is produced through food or endogenous synthesis as ergocalciferol (vitamin D2) is obtained from plants while cholecalciferol (vitamin D3) is obtained from animals. The majority is produced endogenously in the skin from ultraviolet radiation.[5] About 50% of the pregnancies are classified as vitamin D deficient.

This deficiency is likely the result of increased melanin content that prevents adequate exposure to ultraviolet B radiation for conversion of 7-dehydrocholesterol to vitamin D. With an increased incidence of vitamin D deficiency, there is increased awareness of the potential impact on pregnancy outcome.[6]

In the antenatal population in London, vitamin D levels were less than 25 nmol/L, found 47% Asian Indian, 64% Middle Eastern, 58% Black and 13% Caucasian. United States, 33% deficient levels of vitamin D, 24% in Canada, 45% in Belgium, 44% in the Netherlands, 20% in Spain, and 77% in Germany. In Asia, the incidence of vitamin D deficiency is 90%, Turkey 67%, Iran 96%, and India 69%.[7]

Recent epidemiologic data has linked Vitamin D deficiency to adverse perinatal outcomes. More recently, data support associations between Vitamin D deficiency, preterm birth, decreased birth weight, and hypertensive disease in pregnancy.[8]

Preeclampsia is classified based on gestational age. Early onset preeclampsia (EOSPE) occurs before 34 weeks of gestation and is closely associated with impaired trophoblast invasion and failure of spiral artery remodelling. Late-onset preeclampsia (LOSPE) occurs at or after 34 weeks of gestation. It is caused by an increased susceptibility of the maternal vasculature to an inflammatory state to normal pregnancy or placental atherosis that initially develops normally.[9-10]

Preeclampsia is the second leading cause of maternal mortality in Indonesia, accounting for 27.1% of maternal deaths, and was the second largest cause of maternal mortality (12%) in West Sumatra in 2015. In 2016, it ranked as the leading cause of maternal death (25%) in Padang. Data from the medical records at Dr. RSUP M. Djamil Padang reported preeclampsia cases at 32.5% in 2016, 38.8% in 2017, and 15.7% in 2018. Given the issues and data presented, the researchers aimed to investigate the relationship between risk factors and vitamin D levels in pregnant women diagnosed with early-onset preeclampsia (EOSPE), late-onset preeclampsia (LOSPE), and those with normal pregnancies in Padang City in 2021.

METHODS

This study used a cross-sectional method, which linked risk factors to vitamin D levels in pregnancies diagnosed with EOSPE, LOSPE, and normal pregnancy at Padang in 2021. Data collection involved the use of a questionnaire, with the respondent's venous serum and a human vitamin D kit serving as the primary materials. The research instrument was an observation sheet that recorded the results of the vitamin D level assessments. Blood samples were collected from the maternity ward and the obstetrics polyclinic at RSUP Dr. M. Djamil, Padang City. The data gathered will be analyzed using both univariate and bivariate analyses, employing the Statistical Program for Social Science (SPSS). The ethical approval from the Faculty of Medicine Ethic Committee, Andalas University No 456/UN.16.2/KEP-FK/2021.

RESULT

Subject Characteristics

Table 1. Frequency distribution of early-onset preeclampsia (EOSPE) and late-onset preeclampsia (LOSPE)

Characteristics		EOSPE		LOSPE	
		Frequency (F)	%	Frequency (F)	%
Age	< 20 years	1	5	-	-
	20 -35 years old	10	50	12	60
	35 years old	9	45	8	40
	Amount	20	100	20	100
Mom's job	Housewife	17	85	19	95
	working mom	3	15	1	5
	Amount	20	100	20	100
Pregnancy	SinglePregnancy	19	95	19	95
	Gameli	1	5	1	5
	Amount	20	100	20	100
Blood pressure	140 - < 160 mmHg	1	5	8	40
	≥ 160 mmHg	19	95	12	60
	Amount	20	100	20	100
blood sugar	Hypoglycemia	1	5	3	15
	Normalblood sugar	16	80	13	65

	Hyperglycemia	3	15	4	20
	Amount	20	100	20	100
Leukocytes	Normal	2	10	5	25
	Leukocytosis	18	90	15	75
	Amount	20	100	20	100

From Table 1 with EOSPE respondents, 50% of mothers 20-35 years, 85% a housewife, 95% of singleton pregnancies, mothers with blood pressure of 160 mmHg 95%, EOSPE mothers with normal blood sugar 80%, and increasing of leukocytes 90%. Mothers diagnosed with LOSPE found 60% aged 20-35 years, a housewife 95%, singleton pregnancies 95%, mothers with blood pressure 160 mmHg was 60%, normal blood sugar 65%, and had an increasing of leukocytes 75%.

Table 2. Distribution of the frequency of normal pregnancies

Normal Pregnancy		Frequency (F)	%
Age	< 20 years	1	3.1
	20 -35 years old	30	93.8
	35 years old	1	3.1
	Amount	32	100
Mom's job	A House Wife	26	81.2
	working mom	6	18.8
	Amount	32	100
Pregnancy	Single Pregnancy	32	100
	Gameli	-	-
	Amount	32	100
Blood pressure	Hypotension	3	9.4
	Normal	28	87.5
	Hypertension	1	3.1
	Amount	32	100

Table 2 shows that 93.8% of normal pregnant women were aged 20–35 years, 81.2% were housewives, 100% had singleton pregnancies, and 87.5% had normal blood pressure.

Table 3. Relation between risk factors for EOSPE and vitamin D levels

Risk Factors	Vitamin D Level				Amount		P-Value
	Deficiency		Severe Deficiency				
	F	%	F	%	F	%	
Age							
< 20 years	0	0	1	5	1	5	0.922 **
20 -35 years old	3	15	7	35	10	50	
35 years old	2	10	7	35	9	45	
Amount	5	25	15	75	20	100	
Gravida							
Primigravida	3	15	4	20	7	35	
Multigravida	2	10	11	55	13	65	0.290***
Amount	5	25	15	75	20	100	
PE history							
Never	4	20	14	70	18	90	0.000*
Ever	1	5	1	5	2	10	
Amount	5	25	15	75	20	100	
History of Hypertension							
Never	4	20	15	75	19	95	
Ever	1	5	0	0	1	5	0.250***
Amount	5	25	15	75	20	100	
History of Kidney Disease							
Never	5	25	15	75	20	100	Constant variables
Ever	0	0	0	0	0	0	
Amount	5	25	15	75	20	100	

DM history							
Never	5	25	15	75	20	100	Constant variables
Ever	0	0	0	0	0	0	
Amount	5	25	15	75	20	100	
IMT							
Underweight	0	0	0	0	0	0	
Normal	3	15	9	45	12	60	0.000*
Overweight	2	10	6	30	8	40	
Obesity	0	0	0	0	0	0	
Jumlah	5	25	15	75	20	100	
Hb level							
Normal	5	25	10	50	15	75	
Mild Anemia	0	0	3	15	3	15	0.150**
Moderate Anemia	0	0	2	10	2	10	
Severe Anemia	0	0	0	0	0	0	
Amount	5	25	15	75	20	100	

Note : *chi-square Test
    **Mann Whitney Test
    ***Fisher's Test

Based on Table 3, 35% of women with early-onset preeclampsia (EOSPE) were aged between 20–35 years and over 35 years, while 55% were multigravida. Additionally, 70% of women with EOSPE had no history of preeclampsia, 75% had no history of hypertension, 75% had no history of kidney disease, and 75% had no history of diabetes mellitus. Among women with EOSPE, 45% had a normal BMI, and 50% had normal hemoglobin levels, with severe vitamin D deficiency observed.

Bivariate analysis revealed a significant relationship between risk factors and vitamin D levels in pregnant women with EOSPE, specifically for a history of preeclampsia (P-value = 0.000) and maternal Body Mass Index (BMI) (P-value = 0.000), both with P-values < 0.005. However, other risk factors such as maternal age (P = 0.922), gravidity (P = 0.290), history of hypertension (P = 0.250), and hemoglobin levels (P = 0.150) did not show a significant association with vitamin D levels, as their P-values exceeded 0.05. Maternal factors such as a history of kidney disease and diabetes mellitus could not be statistically tested against vitamin D levels due to constant variable data.

Table 4. Relation between late onset preeclampsia risk factors (LOSPE) and vitamin D levels

Risk Factors	Vitamin D Level				Amount		P-Value
	Deficiency		Severe Deficiency				
	F	%	F	%	F	%	
Age							
< 20 years	0	0	0	0	0	0	0.075**
20 -35 years old	0	0	12	60	12	60	
35 years old	2	10	6	30	8	40	
Amount	2	10	18	90	20	100	
Gravida							
Primigravida	0	0	4	20	4	20	0.000*
Multigravida	2	10	14	70	16	80	
Amount	2	10	18	90	20	100	
History of PE							
Never	2	10	17	85	19	95	0.000*
Ever	0	0	1	5	1	5	
Amount	2	10	18	90	20	100	
History of Hypertension							
Never	2	10	17	85	19	95	0.000*
Ever	0	0	1	5	1	5	
Amount	2	10	18	90	20	100	
History of Kidney Disease							
Never	2	10	18	90	20	100	Constant variables
Ever	0	0	0	0	0	0	
Amount	2	10	18	90	20	100	

	f	%	f	%	f	%	P-Value
History of DM							
Never	2	10	16	80	18	90	0.000*
Ever	0	0	2	10	2	10	
Amount	2	10	18	90	20	100	
BMI							
Underweight	0	0	0	0	0	0	
Normal	0	0	8	40	8	40	0.131**
Overweight	1	5	8	40	9	45	
Obesity	1	5	2	10	3	15	
Amount	2	10	18	90	20	100	
Hb level							
Normal	1	5	16	80	17	85	
Mild Anemia	1	5	2	10	3	15	0.154**
Moderate Anemia	0	0	0	0	0	0	
Severe Anemia	0	0	0	0	0	0	
Amount	2	10	18	90	20	100	

Note: *chi-square Test
    **Mann Whitney Test
    ***Fisher's Test

Based on Table 4, 60% of women with LOSPE are aged 20-35 years, 70% multigravida, 85% have no history of preeclampsia, 85% have no history of hypertension, 90% have no history of kidney disease, 80% have no history of Diabetes Mellitus, 40% have normal and overweight BMI, and 80% have normal hemoglobin levels and have severe deficiency of Vitamin D levels.

The results of bivariate analysis between gravid (P = 0.000), history of preeclampsia (P = 0.000), history of hypertension (P = 0.000), and history of Diabetes Mellitus (P = 0.000) LOSPE had a significant relationship with vitamin D levels, P Value < 0.005.

Relation between LOSPE such as maternal age (P = 0.075), maternal body mass index (P = 0.131), maternal hemoglobin level (P = 0.154) with vitamin D levels didn't have a significant relationship because P Value > 0.05. Risk factors for a history of kidney disease cannot be statistically tested with vitamin D levels because the variable data are constant.

Table 5. Relation Between Normal Pregnancies and vitamin D levels in Pengambiran Health Center in 2021

Risk Factors	Vitamin D Level				Amount		P-Value
	Deficiency		Severe Deficiency				
	f	%	F	%	f	%	
Age							
< 20 years			1	3.1			
20 -35 years old			30	93.8			
35 years old			1	3.1			
Amount			32	100			
Gravida							
Primigravida			20	62.5			
Multigravida			12	37.5			
Amount			32	100			
History of PE							
Never			32	100			
Ever			0	0			
Amount			32	100			
History of Hypertension							
Never			31	96.9			
Ever			1	3.1			
Amount			32	100			
History of Kidney Disease							
Never			32	100			
Ever			0	0			
Amount			32	100			
History of DM							
Never			32	100			
Ever			0	0			
Amount			32	100			

BMI		
Underweight	2	6.3
Normal	17	53.1
Overweight	11	34.3
Obesity	2	6.3
Amount	32	100

For data on normal pregnancies, it was not possible to statistically test the relationships between maternal age, gravidity, history of preeclampsia, hypertension, kidney disease, diabetes mellitus, or body mass index with vitamin D levels, as the vitamin D levels in all normal pregnant women were constant, showing 100% severe deficiency.

DISCUSSION

Analysis Between Risk Factors for Early Onset Preeclampsia (EOSPE) and Vitamin D Levels

The results showed a significant relationship between maternal age and vitamin D levels as risk factors for early-onset preeclampsia (EOSPE). This finding aligns with research conducted at the Majalengka Health Center, which reported that 70% of preeclampsia cases occurred in women aged 20–35 years. This is consistent with the theory that, as the gestational period progresses, the body's organs must work harder to accommodate the demands of pregnancy, thereby increasing the risk of complications such as preeclampsia.[12]

Additionally, the low levels of vitamin D observed in women with EOSPE in this study are consistent with findings from case-control studies. Specifically, serum 25(OH)D levels below 37.5 nmol/L during early pregnancy (around 22 weeks) are associated with a fivefold increase in the incidence of preeclampsia, with the risk doubling for every 50 nmol/L decrease in serum 25(OH)D levels during pregnancy.[13]

Several studies explaining the age characteristics obtained p> 0.05 which stated that there was no difference between the two age groups of normal pregnancy and preeclampsia with vitamin D levels.[14]

There is no significant relationship between Gravid EOSPE and levels of Vitamin D. Research conducted by Leony in 2020 also obtained the same which stated there was no difference between gravid normal pregnancy and preeclampsia with vitamin D levels.[14]

Risk factors for the history of preeclampsia with EOSPE concluded a significant relationship between the history of preeclampsia in EOSPE and Vitamin D levels. This study was conducted by Robinson et al., regarding EOSPE, 25(OH)D levels were significantly lower than the control. In this study, logistic regression analysis was performed to assess the effect of maternal serum 25(OH)D levels and it was found that every 10 ng/mL increase in serum decreased EOSPE by 63%.[15]

Vitamin D levels assessed in early pregnancy were found to be lower among women who subsequently experienced preeclampsia. The study noted a two-fold increased risk for preeclampsia associated with a decrease of 20 ng/mL in serum vitamin D levels after adjusting for confounding factors.[16]

There is a significant relation between BMI of EOSPE and Vitamin D levels. The results are in accordance with the theory that low levels of vitamin D are one of the causes of being overweight, this is due to a decrease in the bioavailability of vitamin D from the skin and the presence of deposition in fat which causes vitamin D to be trapped in fat and cannot be easily excreted.[17]

Research conducted by the Division of Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, and Department of Pediatrics at the Medical University of South Carolina found that early-onset preeclampsia (EOSPE) was associated with an 8% increase in the odds of EOSPE when comparing the risk factors related to Body Mass Index (BMI) between the EOSPE group and a control group.[18]

50% of EOSPE with normal hemoglobin levels and vitamin D deficiencies. *P value* was 0.150 (p > 0.05), there is no significant relation between EOSPE maternal hemoglobin levels and vitamin D levels.[19]

Conclusion: Risk factors for history of preeclampsia and body mass index are significantly related to vitamin D levels for EOSPE with *P Value* <0.05.

Analysis Between Risk Factors for Late-Onset Preeclampsia (LOSPE) and Vitamin D Levels

The study results indicated that 60% of mothers with late-onset preeclampsia (LOSPE) aged

20–35 years experienced vitamin D deficiency, with a *p-value* of 0.075 (p > 0.05). This suggests that there is no significant relationship between LOSPE, age, and vitamin D levels. Vitamin D deficiency in LOSPE may be attributed to the normal physiological increase in vitamin D levels during pregnancy, which typically begins early in gestation and continues to rise, potentially doubling in the third trimester. Elevated vitamin D levels are essential for various functions, including bone metabolism, immunomodulation, blood pressure regulation, and the maintenance of insulin secretion by pancreatic beta cells. The increase in vitamin D levels during the third trimester may also have implications for LOSPE.[20]

Seventy percent of multigravida women with late-onset preeclampsia (LOSPE) experienced vitamin D deficiencies, with a *p-value* of 0.000 (p < 0.05), indicating a significant relationship between the gravid factor of LOSPE and vitamin D levels. Analysis by Septiasih demonstrated that gravida status was significantly related to the incidence of preeclampsia, as indicated by a *p-value* < 0.05. This suggests that vitamin D deficiencies are associated with preeclampsia, thereby establishing a significant relationship between gravida status and vitamin D levels.[21]

Eighty-five percent of women with late-onset preeclampsia (LOSPE) who had no prior history of preeclampsia experienced vitamin D deficiency. The *P-value* of 0.000 (p < 0.05) indicates a significant relationship between the history of preeclampsia and vitamin D levels in LOSPE. This study aligns with previous research, which found a significant difference in vitamin D status between women with and without preeclampsia (< 50 nmol/L versus ≥ 50 nmol/L, p = 0.002). Among pregnant women with vitamin D deficiency (< 50 nmol/L), 1.4% developed severe preeclampsia, whereas only 0.6% of those with sufficient vitamin D levels (≥ 50 nmol/L) experienced severe preeclampsia.[22]

Eighty-five percent of LOSPE did not have a history of hypertension having severe deficiency of vitamin D levels, *p-value* 0.000 (p < 0.05) there is a significant relationship between a history of hypertension in LOSPE and levels of Vitamin D. This study is in line with research about the relation between vitamin D levels and blood pressure in pregnancies which explains that vitamin D intake is significantly related to blood pressure (p = 0.028).20 The lower vitamin D intake, the systolic blood pressure will increase. The risk of hypertension in pregnancy increases when serum vitamin D levels are low. Vitamin D levels (1,25 dihydroxyvitamin D) can prevent hypertension in pregnancy by its effects on immune modulation and vascular function.[23]

In PE, circulating serum angiotensin I, angiotensin II, and aldosterone are lower compared to normotensive women, while plasma active rennin levels and autoantibodies to the Angiotensin II type I receptor, which stimulate receptor signaling to increase systemic blood pressure, are higher.[24]

Eighty percent of LOSPE have no history of Diabetes Mellitus having severe deficiency. The *p-value* was 0.000 (p < 0.05), so there is a significant relationship between the history of Diabetes Mellitus in LOSPE and the levels of Vitamin D. This study is in line with the theory that pregnant women with a history of gestational diabetes had significantly lower levels of 25-OHD than the comparison group. Gestational diabetes results from pregnancy-induced insulin resistance and impaired compensatory insulin secretion. Evidence suggests that vitamin D improves insulin sensitivity by enhancing the insulin response to glucose transport. In addition, vitamin D plays a role in early placental development through gene regulation and expression, which may influence the development of preeclampsia.[25]

Forty percent of LOSPE with normal BMI and 40% overweight have severe deficiency of Vitamin D levels. *P value* 0.131 (p > 0.05) shows no significant relationship between LOSPE maternal body mass index and vitamin D levels. Tested the relation between 2 groups of normal pregnancies and preeclampsia with BMI, it was found that 61.9% of obese women experienced preeclampsia during pregnancy, this was associated with vitamin D levels where the BMI factor was not significantly associated with vitamin D levels with *p value* 0.200.16 In normal BMI, increased levels of adiponectin can suppress the expression of adhesion molecules on vascular endothelial cells and cytokines. Production of macrophages to minimize the inflammatory process associated with preeclampsia.[26]

Eighty percent of LOSPEs with normal hemoglobin have severe deficiency of vitamin D levels. The *p-value* of 0.154 (p > 0.05) shows no significant relation between LOSPE maternal hemoglobin levels and Vitamin D levels. This study is not in line with the results of studies showing that mothers with vitamin D deficiency have the highest proportion of anemia, which may indicate that anemia has a stronger relation

with vitamin D levels than other factors.[27]

Thus, that gravid, history of preeclampsia, history of hypertension, and history of Diabetes Mellitus, had a significant relation with Vitamin D levels with late-onset preeclampsia (LOSPE).

Analysis Between Normal Pregnancies and vitamin D levels in Pengambiran Health Center

For data of normal pregnancies, it is not possible to do statistical tests between age, gravid, history of preeclampsia, history of hypertension, history of kidney disease, history of diabetes mellitus, maternal body mass index with vitamin D levels because the data is constant (100% Weight Deficiency).

In 2012, Wei et al. retrospectively analyzed vitamin D status for PE risk in 697 nulliparous women with singleton pregnancies in a randomized, placebo-controlled trial of Vitamin C and E supplementation to prevent PE. After controlling smoking habits, the results showed that in first trimester pregnant women (average 11 weeks), vitamin D deficiency was not associated with an increased risk of PE (P = 0.58).[28]

Observational studies evaluating the association between vitamin D and PE have shown inconsistent results and must be interpreted cautiously. This may result from study design and methodology issues, including a lack of adjustment of key confounding variables and methods of measuring vitamin D levels. [29]

Need for further research on populations with very low vitamin D levels to understand this observation and identify factors that predispose high-risk groups to PE and its more threatening clinical subtypes.[30]

CONCLUSIONS

Mothers with early-onset preeclampsia (EOSPE), a history of preeclampsia, and maternal body mass index showed a significant relationship with vitamin D levels. In mothers with late-onset preeclampsia (LOSPE), risk factors such as gravidity, a history of preeclampsia, a history of hypertension, and a history of diabetes mellitus were significantly related to vitamin D levels. Statistical analysis indicated that the risk factors associated with LOSPE (gravidity, history of preeclampsia, history of hypertension, and history of diabetes mellitus) had a more significant relationship with vitamin D levels compared to the risk factors for EOSPE respondents (history

of preeclampsia and body mass index). The incidence of preeclampsia remains influenced by a complex etiopathogenesis.

CONFLICT of INTEREST

There are no conflicts of interest in this report.

ACKNOWLEDGMENT

REFERENCES

1. WHO.2020. *Maternal Mortality The Sustainable Development Goals and the Global Strategy for Women's, Children's and Adolescent's Health.*Diakses tanggal 2 Juni 2022 pukul 11.50 melalui https://www.who.int/en/newsroom/fact-sheets/detail/maternal-mortality

2. Profil Kesehatan Indonesia.2019. Kementrian Kesehatan Indonesia

3. Legawati, Nang Randu Utama. 2017. Analisis Faktor Risiko Kejadian Preeklampsia Berat di RSUD Rujukan Kabupaten dan Provinsi Kalteng. Jurnal Surya Medika. Vol 3(1)

4. Hu, K.-L.; Zhang, C.-X.; Chen, P.; Zhang, D.; Hunt, S. Vitamin D Levels in Early and Middle Pregnancy and Preeclampsia, a Systematic Review and Meta-Analysis. Nutrients 2022, 14, 999. https://doi.org/10.3390/nu14050999

5. Dror DK, King JC, Fung EB, Van Loan MD, Gertz ER, Allen LH. Evidence of associations between feto-maternal vitamin D status, cord parathyroid hormone and bone-specific alkaline phosphatase, and newborn whole body bone mineral content. Nutrients. 2012 Feb;4(2):68-77. doi: 10.3390/nu4020068. Epub 2012 Feb 6. PMID: 22413062; PMCID: PMC3296991.

6. Christopher J.Robinson, MD, MSCR et al. 2010. Plasma 25-Hydroxyvitamin D Levels In Early-Onset Severe Preeclampsia. American Journal Obstetric & Gynecology.

7. De-Regil LM, Palacios C, Lombardo LK, Peña-Rosas JP.2016.*Vitamin D supplementation for women during pregnancy. Cochrane Database of Systematic Reviews,* Issue 1. Art. No.: CD008873. DOI: 10.1002/14651858. CD008873.pub3

8. Haugen M, et al. 2009. Vitamin D Supplementation and reduced risk of preeclampsia in Nulliparous Women. Epidemiology; 20: 720-6

9. Raymond, D. and Peterson, E. 2011. *A Critical Review of Early-Onset and Late-Onset Preeclampsia. Obstetrical & Gynecological Survey,* 66, 497-506

10. Costa t al. 2011. *Early Screening for Preeclampsia.* Ginecol Obstet. 33(11)

11. Profil Kesehatan Kota Padang. 2019. Dinas Kesehatan Kota Padang

12. Manuaba. 2012. Ilmu Kebidanan, Penyakit Kandungan dan Keluarga Berencana, Jakarta:EGC

13. Bodnar.LM, et al.2010. *Maternal Serum 25-Hidroxy Vitamin D Concentrations Are Associated With Small Gestational Age Birth in White Women.* J Nutr. 140(5): 999-1006

14. Leony Lim et al. 2022. Kadar 25(OH)D dan Rasio HDL-LDL, Serum Yang Rendah Sebagai Faktor, Risiko Terjadinya Preeklampsia dengan Gambaran Berat. Intisari Sains Medis. 13(1): 35-40

15. Robinson Cj, Alanis MC, Wagner CL, Hollis BW, Jhonson DD. 2010. *Plasma 25-hydroxyvitamin D Levels in Early-Onset Severe Preeclampsia. Am J Obstet Gynecol.* 203(4): 366

16. Bodnar LM et al. 2007. Maternal Vitamin D Deficiency Increases the risk of preeclampsia. J Clin Endocrinol Metab; 92: 3517-22

17. Radjmuda, Nelawati dan Montolalu, Agnes. 2014. Faktor-Faktor Resiko yang Berhubungan dengan Kejadian Hipertensi pada Ibu Hamil di Poli Klinik Obs-Gin RDSJ Prof. Dr.V.L. Ratumbusyang kota Manado. Jurnal Ilmiah Bidan. 2(1) : 1-17

18. Juhi M. Purswani et al. 2017. The Role of Vitamin D in Pre-Eclampsia: A Systematic Review. BMC Pregnancy and Childbirth. 17:231

19. Ekadewi Retnosari et al. 2015. Korelasi Antara Kadar Vitamin D dengan Kejadian Preeklampsia. IJEMC. 2(5): 53-60

20. Ajabshir Sahat AA, Nayer Ali. 2014. *The Effect of Vitamin D on The Renin Angiotensin System.* Journal of Nephropathology. 3: 41

21. Septiasih. 2017. Faktor Risiko Kejadian Preeklampsia Pada Ibu Bersalin di RSUD Wonosari Kabupaten Gunung Kidul Tahun 2017. Poltekes Kemenkes Yogayakarta

22. Zhao, et al. 2017. *Maternal Vitamin D Status in the Late Second Trimester and the Risk of Severe Preeclampsia in Southeastern China.* Nutrients 9(138)

23. Anugrah Novianti, Anindya Billa Mustika, Erry Yudhya Mulyani. 2021. Pengetahuan Gizi Asupan Natrium, Kalium, Vitamin D Berhubungan Dengan Tekanan Darah Ibu Hamil. Darussalam Nutrition Journal. 5(2): 90-100

24. Faulkner JL et al. 2017. Vitamin D supplementation reduces some AT1-AA-induced downstream targets implicated in preeclampsia including hypertension. Am J Physiol Regul Integr Comp Physiol.;312(1): R125–31.

25. Linda Yusanti. 2015. Efek Vitamin D Selama Kehamilan. Proceeding Book, Simposium Dan Workshop Nasional Pengembangan Pendidikan dan Pelayanan Kebidanan Indonesia. 2 (2): 13-17

26. Yuniarti, Fitri, Wahyu Wijayanti, Dintya Ivantarina. 2018. Analisis Perilaku Kesehatan Dan Faktor Resiko Kejadian Preeklampsia Pada Ibu Hamil di Poliklinik Obstetri Gynekologi RSUD Kabupaten Kediri. Journal of Issues in Midwifery.1 (13):1-17

27. Judistiani RTD et al. 2019. Asosiasi Antara Vitamin D Maternal Pada Trimester pertama, Ferritin, dan Kadar Haemoglobin dengan Biometri Trimester ketiga: Hasil Penelitian Kohort Mengenai Status Vitamin D dan Dampaknya Saat Kehamilan dan Masa Kecil di Indonesia. BMC Pregnancy and Childbirth

28. Wei SQ et al. 2012. Longitudinal Vitamin D status in pregnancy and the risk of preeclampsia. BJOG. 119(7):832-9

29. Redman CW. 2013. Immunological aspects of pre-eclampsia. Baillieres Clin Obstet Gynaecol. 6 (3): 601-15

30. Wetta LA et al.2014. Is Midtrimester Vitamin D Status Associated with Spontaneous Preterm Birth And Preeclampsia?. Am J Perinatol. 31(6):541-6