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RESEARCH

The Role Of Vitamin D And Calcium In Pre-Eclampsia And The Association With Neonatal Outcomes

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Abstract

Introduction: *Pre-eclampsia is one of the main causes of maternal and neonatal death in developing countries. A low vitamin D level can increase the risk of neonatal abnormalities. Clinical studies reported various complications of low vitamin D levels, such as pre-eclampsia, gestational diabetes, low birthweight, and caesarean section. This study aimed to investigate the role of vitamin D in pregnancy with pre-eclampsia and its association with neonatal outcomes.*

Methods: *This is an observational analytical study uses a cross-sectional approach to investigate vitamin D levels and pre-eclampsia, conducted in General Hospital Dr. M. Djamil Padang from Mei 2021 – April 2022. A total of 5 mL blood was withdrawn to analyzed vitamin D. This study has been approved by Health Research Ethics Committee Andalas University (Approved number: 339/KEPK/2021).*

Results: *There was a significant difference in the levels of 1,25 dihydroxy vitamin D3 between normal pregnancy and pre-eclampsia patients (99,18 vs 72,53 pg/ml; p = 0,033). In the pre-eclampsia patients' first APGAR score, there was a significant difference in the levels of 1,25 dihydroxy vitamin D3 between normal, moderate, and severe asphyxia groups (114,19 vs 66,75 vs 74,78 pg/ml; p = 0,025).*

Conclusion: *Measuring early maternal 1,25 dihydroxy vitamin D3 can lower the pre-eclampsia risks and the impact the perinatal outcomes, particularly in determining first Apgar scores.*

Keywords: *1,25 dihydroxy vitamin D3, Calcium, Pre-eclampsia, Neonatal*

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INTRODUCTION

According to the intercensal population survey, Indonesia has a high maternal mortality rate among the ASEAN countries, with 305 per 100.000 deaths recorded in 2019. The mortality rate was associated with diseases and related pregnancy complications. Post-partum hemorrhage, infection, pre-eclampsia or eclampsia, prolonged or delayed parturition, and unsafe abortion contributed to 75% of maternal death, with most of the causes being preventable and can be rescued.[1, 2]

Pre-eclampsia (PE) is one of the main causes of maternal and neonatal death in developing countries. It is a specific pregnancy syndrome and contributes to the higher morbidity and mortality rate of maternal and neonatal due to asphyxia and prematurity. Early PE occurs before 34 weeks' gestation and is associated with fetal growth restriction, premature birth, and poor neonatal development. The characteristics of PE include elevated blood pressure (systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) with proteinuria (>300 mg/24 hours) after 20 weeks' gestation (usually manifested in the third trimester) and accompanied by maternal organ dysfunctions.[3-5]

The metabolism abnormality of Vitamin D and calcium during pregnancy are associated with the risks of PE. It was reported that vitamin D supplements in the first trimester would prevent PE by regulating the metabolism process of vitamin D. Additionally, various conditions, such as diabetes, pre-pregnancy chronic hypertension, chronic renal failure, nulliparity, single or twin pregnancy, family history of PE or eclampsia, obesity, immune system abnormality, and previous history of PE and eclampsia are the associated factors that contributed in PE.[3, 4]

Vitamin D plays an essential role during pregnancy. Vitamin D deficiency is a global pandemic with 18 – 84% prevalence. A low vitamin D level can increase the risk of maternal morbidities and neonatal abnormalities. Clinical studies reported various complications of low vitamin D levels, including gestational diabetes, low birth weight, and caesarean section. A previous study confirmed that low vitamin D caused the imbalance of Th1 and Th2 regulation and overexpressed Th1 cytokine. Furthermore, the mechanisms will influence immunological tolerance derived from embryo implantation. Additionally, the association between vitamin D deficiency and high expression of Th1 was also reported in PE cases.[3]

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The levels of vitamin D and zinc serum in severe PE and normal pregnancy patients were reported lower in the patients with severe PE.[6] Additionally, a previous study investigated the differences between serum 1,25(OH)D and calcium in the pregnancy with PE and normal pregnancy, and found a significantly lower 1,25(OH)D in the early onset of PE.[7]

A deficiency of vitamin D can lead to hypoperfusion from spasium intervilosum, placenta hypoxia and oxidative stress due to vascular remodelling abnormality of the uterus and eventually will induce maternal syncytiotrophoblast and endothelial dysfunction. The substances released by the placenta into the maternal circulation, such as free radicals, oxidized lipids, cytokines, sVEGFR-1, and EG-VEGF, were found to be the associated mechanisms related to vitamin D deficiency and PE manifestation.[4] This study aimed to investigate the role of vitamin D in pregnancy with PE and its association with neonatal outcomes.

METHODS

Study design

This observational analytical study uses a cross-sectional approach to investigate vitamin D levels and PE. This study was conducted in General Hospital Dr. M. Djamil Padang, Obstetrics and Gynecology Department from Mei 2021 – April 2022. This study has been approved by the Health Research Ethics Committee of Andalas University (Approved number: 339/KEPK/2021). The patients signed informed consent.

Patients and sample collection

The normal pregnant, PE, and severe PE patients admitted to the General Hospital Dr. M. Djamil Padang were selected using a consecutive sampling method. Patients with normal pregnancy, diagnosed with PE, and willing to sign the informed consent were included in this study. The exclusion criteria: were malabsorption, superimposed PE, thyroid, renal, and liver abnormality; ineligible serum due to damage; and dropped-out patients. A total of 5 mL of blood was withdrawn to analyse vitamin D using ELISA Kit (R&D system).

Statistical analysis

Univariate analysis was performed to evaluate frequency distributions and proportions in categorical data; mean and standard deviations in numerical data for age, gestational age, parity, BMI before pregnancy, and perinatal outcome variables (birth weight, first and second

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APGAR scores). Bivariate analysis was performed to analyse the differences of 1,25 dihydroxy vitamin D3 between normal pregnancy and PE. Data normality was assessed based on the Shapiro-Wilk test. All p values < 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Eighty pregnant patients were observed in this study. The total of normal pregnancy and pre-eclampsia patients was 40 in both groups.

Patient characteristics

The characteristics of the patients are shown in Table 1.

Table 1. Patient Characteristics

Characteristics	Normal Pregnancy (n = 40)	Pre-eclampsia (n = 40)
Age (years), mean±SD	33,13 ± 4,99	30,48± 6,82
BMI (kg/m^2), mean±SD	22,75 ± 3,24	26,73 ± 5,30
Parity, n (%)		
Primipara	6 (15,0)	16 (40,0)
Multipara	34 (85,0)	24 (60,0)
SBP (mmHg), mean±SD	117,40 ± 7,21	164,63± 18,93
DBP (mmHg), mean±SD	76,00 ± 5,06	101,30± 7,67
MAP (mmHg), mean±SD	89,60 ± 4,54	122,03 ± 10,15
GA (weeks), mean±SD	37,50 ± 1,22	32,58± 5,10
Birthweight (kg), mean±SD	3.024,13± 420,03	1.924,25 ± 998,39
1st Apgar score, mean±SD	7,33 ± 0,80	5,53 ± 2,47
2nd Apgar score, mean±SD	8,53 ± 0,60	6,95 ± 2,80
Vitamin D (pg/ml), mean±SD	111,11 ± 52,49	88,73 ± 42,22
Calcium (mg/dL), mean±SD	9,55 ± 0,93	8,67 ± 0,49

Table 1 shows the mean age of patients with normal pregnancy was older than the PE (33,13 ± 4,99 vs 30,48 ± 6,82 years old). Our study showed that PE patients were younger than the normal pregnancy. A similar study by Muarrofah, et al., showed that the pregnant women with age of 12 – 35 years old were at higher risk of severe PE.[8] The age of < 20 and > 35 years old women is in the initial and last reproduction period, respectively. Within the period, the

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pregnant women are prone to PE.[9] The age-risk based might also determine the preparedness of the pregnant women in physical, emotional, psychological, social, and economy.[8]

Patients with PE had a higher BMI than the normal pregnancy (26,73 ± 5,30 Kg/m^2 vs 22,75 ± 3,24 Kg/m^2). Our study showed that the BMI of normal pregnant was lower than the PE patients. Additionally, in the PE patients' BMI, there was no significant difference in the levels of 1,25 dihydroxy vitamin D3 between normal weight, overweight, and obesity groups (67,97 vs 87,56 vs 71,37 pg/ml; p = 0,586), as seen in Table 2. Similar finding of BMI and its association to the PE was also reported by Andriani et al.[10] The BMI indicates nutritional status of the individual to determine normal, underweight, overweight, or obesity. In Asia-Pacific, BMI ≥ 25 kg/m^2 is categorized as obesity. Obesity is one of the risk factors for PE. A study was conducted to the women population showed that PE was increased three times in the pregnancy women with obesity.[10]

Table 2. Profile of 1,25 Dihydroxy Vitamin D3 in BMI of Pre-eclampsia Patients

	Normal weight (n = 16)	**Overweight (n = 16)**	**Obesity (n = 8)**	***p* Value**
1,25 dihydroxy vitamin D3 (pg/ml), median (min – max)	67,97 (41,73-168,80)	87,56 (25,86-215,23)	71,37 (52,40-133,92)	0,586

Table 1 shows the multiparities were higher in patients with normal pregnancy (85,0%) and PE (60,0%). A study by Diah et al., also showed that majority of the severe PE patients were characterized with primiparous. Hypertension in pregnancy is commonly occur in primigravida due to implantation process and causes placental ischemia followed by inflammatory syndrome. The parity factor plays important role in hypertension or PE since 20% of the nulliparous pregnancy were affected compared to multiparous. In the first pregnancy, formation of blocking antibodies towards placenta antigen were not completed, therefore, it might cause unfavorable effects in placental tissue formation.[9]

Table 1 shows the gestational age for normal pregnancy was higher than PE patients (37,50 ± 1,22 vs 32,58 ± 5,10 weeks). A previous study by Lisonkova et al., reported that PE commonly occur in the late onset (GA ≥34 weeks) than the early onset (GA <34 weeks).[11] Additionally, in the PE patients' GA, there was a significant difference in the levels of 1,25 dihydroxy

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vitamin D3 between early and late-onset groups (67,43 vs 86,38 pg/ml; p = 0,026), as seen in Table 3. This contrasts with our study that showed PE were commonly present in the early onset (32 weeks) than in the late onset (38 weeks. A study by Aksornphusitaphong et al., stated that maternal with chronic hypertension history were at higher risk for early onset PE, additionally, maternal with family history of chronic hypertension were 18 times higher for late onset PE.[12] We did not report the association of PE in the pregnancy with GA of 32 weeks, and further study is required in the future.

Table 3. Profile of 1,25 Dihydroxy Vitamin D3 in GA of Pre-eclampsia Patients

	Early onset (n = 19)	**Late onset (n = 21)**	***p* Value**
1,25 dihydroxy vitamin D3 (pg/ml), median (min – max)	67,43 (25,86-168,80)	86,38 (52,40-215,23)	0,026

Table 1 shows the mean birthweight of normal pregnancy was higher than PE patients (3.024,13 ± 420,03 vs 1.924,25 ± 998,39 grams). The pregnancy women with PE had lower birthweight in this study. A similar study by Reza et al found that the prevalence of low birthweight in mother with PE were higher. It has been reported that pregnant mother with PE had 3,48 times of higher risk having low birthweight compared to the one without PE.[13] A study by Imdad et al., reported that calcium supplement has reduced low birthweight prevalence by 15%.[14] Pre-eclampsia will cause placenta abnormalities, vasospasm, and endothelial injury.[15] In PE, the levels of prostacyclin are lower in vascular endothelial cells of umbilical cord and reducing placental perfusion and umbilical cord circulation.[16] The unsuccessful trophoblast invasion due to PE in spiralis artery will impact the remodelling and lower blood circulation and further causing hypoxia and placental ischemia, and ultimately manifest with fetal growth restriction.[15]

Table 1 shows that the first and second Apgar scores were higher in the normal pregnancy compared to the PE patients (7,33 ± 0,80 and 8,53 ± 0,60 vs 5,53 ± 2,47 and 6,95 ± 2,80). Additionally, in the PE patients' first APGAR score, there was a significant difference in the levels of 1,25 dihydroxy vitamin D3 between normal, moderate, and severe asphyxia groups (114,19 vs 66,75 vs 74,78 pg/ml; p = 0,025), as seen in Table 4. Furthermore, in the PE patients' second APGAR score, there was no significant difference in the levels of 1,25 dihydroxy

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vitamin D3 between normal, moderate, and severe asphyxia groups (70,29 vs 108,86 vs 74,78 pg/ml; p = 0,710), as seen in Table 5.

Table 4. Profile of 1,25 Dihydroxy Vitamin D3 in *1st Apgar Score* of Pre-eclampsia Patients

	Normal (n = 17)	Moderate asphyxia (n = 16)	Severe asphyxia (n = 7)	*p* Value
1,25 dihydroxy vitamin D3 (pg/ml), median (min – max)	114,19 (58,61-215,23)	66,75 (24,86-168,80)	74,78 (33,63-150,29)	0,025

Table 5. Profile of 1,25 Dihydroxy Vitamin D3 in *2nd Apgar Score* of Pre-eclampsia Patients

	Normal (n = 33)	Moderate asphyxia (n = 2)	Severe asphyxia (n = 5)	*p* Value
1,25 dihydroxy vitamin D3 (pg/ml), median (min – max)	70,29 (25,86-215,23)	108,86 (67,43-150,29)	74,78 (33,63-127,40)	0,710

Our study reports lower Apgar score in the pregnancy with PE. A similar study by Mihu et al also showed the same finding. Additionally, Mihu et al., also reported that the number of underweight neonates were significantly higher in pregnancy with severe PE.[17] Lower Apgar scores were mainly caused by uteroplacental insufficiency due to incomplete placentation and placental ischemia which might be manifested by PE and can lead to high perinatal morbidity and mortality.[18, 19] A newborn baby with lower Apgar score (<7) is commonly present with premature birth. The low Apgar score is associated with larger placenta in which required larger amount of oxygen and nutrition. This condition may cause the demand of supply to the fetus. Therefore, the fetus with low Apgar score might having less optimum growth and development after birth.[20]

The Association between 1,25 dihydroxy vitamin D3 and calcium in pre-eclampsia

Table 1 shows that the levels of 1,25 dihydroxy vitamin D3 in normal pregnancy were higher than in PE patients (111,11 ± 52,49 vs 88,73 ± 42,22 pg/ml). The calcium levels in normal pregnancy were higher than in PE patients (9,55 ± 0,93 vs 8,67 ± 0,49 mg/dL). Additionally, there was a significant difference in the levels of 1,25 dihydroxy vitamin D3 between normal

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pregnancy and PE patients (99,18 vs 72,53 pg/ml; $p = 0,033$). There was a significant difference in calcium levels between normal pregnant and PE patients (9,55 vs 8,67 mg/dL; $p = <0,0001$), as seen in Table 6.

Table 6. Profile of 1,25 Dihydroxy Vitamin D3 and Calcium

Variables	Normal Pregnancy (n = 40)	Pre-eclampsia (n = 40)	*p* Value
1,25 dihydroxy vitamin D3 (pg/ml), median (min – max)	99,18 (34,38-263,62)	72,53 (25,86-215,23)	0,033
Calcium (mg/dL), median (min – max)	9,55 (7,70-11,80)	8,67 (7,60-10,30)	<0,0001

The levels of 1,25 dihydroxy vitamin D3 were higher in the normal pregnancy. The previous study also found the similar result in which the vitamin D showed a gradual increased three times from early pregnancy to the third trimester.[10] The increased of vitamin D levels is vital for bone growth, produce anti-inflammatory and pro-inflammatory cytokines, blood pressure regression, and insulin secretion regulation.[21, 22] In pregnancy, low levels of vitamin D is associated with low bone mineralization, glucose balance impairment, and softening of the bone due to growth impairment within the uterus as a consequence of low vitamin D. Additionally, low levels of vitamin D also caused preterm birth. In the last decades, the prevalence vitamin D deficiency in pregnancy had increased and contributed to the global health problem with the impact to both mother and fetal.[23] Vitamin D is associated with PE by affecting blood pressure regulation and immune modulator.[23] A meta-analysis reported that there were abnormality biomarkers in the pregnancy and associated with PE progression during first trimester.

This study shows a higher levels of calcium in the normal pregnancy compared to the PE patients. A study by Dhungana et al., and Kumar et al., reported the similar finding to this study.[24, 25] Kumar et al., reported a significant association between calcium levels in both normal pregnancy and PE, in which the levels of calcium in pregnancy with PE were lower.[25] Calcium is one of the most abundant substances in our body to support various body functions, such as for the normal growth and development, neuronal excitability process, neurotransmitter releasing, muscle contraction, membrane integrity, and blood clotting.[26, 27] During pregnancy, several physiological changes occur to maintain maternal homeostasis, while also maintain and support the growth and development for the baby. Low albumin levels, increased extracellular

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volume, elevation of renal function, and placental calcium transfer are some of the alterations occurred due to the influence of calcium metabolism. Calcium homeostasis is a complex mechanisms involves calcitropic hormones (parathyroid, calcitonin, and 1,25 dihydroxy vitamin D3).[28]

Low levels of calcium contributed to the progression of PE or hypertension during pregnancy. Decreased of calcium levels will elevate parathyroid and renin hormone released, and eventually increased blood intracellular calcium. High intracellular calcium in the vascular smooth muscle will increase vascular resistance and vasoconstriction, further causing high blood pressure. During pregnancy, hemodilution, increased urinary excretion and calcium mineral transfer from maternal to fetal will reduce calcium concentration progressively.[27, 29] In the second and third trimesters, metabolism and absorption of the calcium is high, and the sufficient calcium will reduce uterus smooth muscle contraction and prevent delivery complications and premature birth.[26, 28] A study conducted in North India to the 524 primigravida pregnancies by giving calcium supplement 2 gr/day reported that the risk of PE were lower to 66,7%. Additionally, the study also showed that daily calcium intake reduced premature birth events significantly.[25, 30] Similarly, a randomized trials study by Imdad et al., also found that premature birth events had 24% lower during pregnancy after given calcium supplement (0,5 – 2 gr/day).[14]

A linear regression statistical method (Table 7) shows the levels of 1,25 dihydroxy vitamin D3 of PE patients were 0,899 mg/dL, and in each supplement of 1 mg/dL calcium will elevate the levels of 1,25 dihydroxy vitamin D3 as much of 0,02 pg/mL. There was a weak and positive correlation (r = 0,167) between calcium levels and the elevation of 1,25 dihydroxy vitamin D3 in PE patients; additionally, there was no significant association between levels of 1,25 dihydroxy vitamin D3 and calcium in PE patients (p > 0,05), as seen in Table 7.

Table 7. Correlation of 1,25 Dihydroxy Vitamin D3 and Calcium in Pre-eclampsia

	Similarity	**R**	**R^2**	***p* Value**
Calcium (mg/dL)	1,25 dihydroxy vitamin D3 = 0,899 + 0,020 (Calcium)	0,167	0,028	0,302

The association of 1,25 dihydroxy vitamin D3 with perinatal outcomes of pre-eclampsia patients

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Our study reports a mother with low birthweight had a lower 1,25 dihydroxy vitamin D3. Vitamin D deficiency can lower the serum calcium and causing uterine atony and postpartum hemorrhage.[31] Vitamin D deficiency is associated with the fetal growth via calcium metabolism, bone growth, and placental function alteration.[32] During pregnancy, synthesis of $1,25(OH)_2D$ in mother decidua, placenta, and kidney will enhance the serum $1,25(OH)_2D$ levels to increase the calcium absorption for the fetal.[33] A study by Merewood et al., reported the risk of PE were 5 times in the women with 25(OH)D < 15 ng/mL with gestational age of 22 weeks.[34] Additionally, powe et al., also reported that 25(OH)D levels < 15 ng/mL in the first trimester was associated with PE development. The women with severe PE (gestational age < 34 weeks) showed a lower levels of 25(OH)D.[35, 36]

Previous studies reported no correlation between serum vitamin D with small for gestational age or low birthweight, while other studies found that low levels of vitamin D will tend to have low birthweight baby. Vitamin D deficiency might be an independent risk factor for abnormal fetal growth, and it was reported that a deficient of 1 ng/ml 25(OH)D was associated with 19% risk of small for gestational age. Vitamin D deficiency will directly affect fetal bone growth. Some of the steroid hormone, such as thyroid interacts with vitamin D to support fetal growth. Therefore, nutritional metabolism in the pregnancy is modulated by vitamin D to promote fetal development.

A study by Robinson et al., found a significant association between maternal vitamin D and fetal growth. There was a positive correlation between vitamin D and baby's birtweight.[32, 33] In placental trophoblast model, vitamin D played a role in signaling genetic regulation expression in the early placental development. Placenta has the molecular components to transform 25(OH)D into active vitamin D form $1,25\text{-}(OH)_2D3$ for local utilization or paracrine. The $1,25\text{-}(OH)_2D3$ has been shown to improve endothelial function in hemodylisis patients through paracrine action. In endothelial cells, $1,25\text{-}(OH)_2D3$ improved vascular endothelial growth factor, and strong proangiogenic proteins (which are lowered in PE) via vitamin D receptor binding and colocalization with responsive vitamin D in promoting vascular endothelial growth factor. Therefore, insufficient vitamin D levels can affect PE and fetal growth via modification of vascular endothelial growth factor activity.[33]

In this study, there was a significant association of the first Apgar score (normal vs moderate vs severe asphyxia), while the second Apgar score showed no significant association in the PE

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patients. A study by Zhou et al., reported that not every study showes a similar result in which a low statistic power could be a contributing factor.[31] Born with asphyxia can result in a serious impication for the children, including higher mortality and abnornal neurological conditions.[37]

A cohort prospective study was conducted by Augustine et al., in Sweden reported that vitamin D deficency could be a contributing factor for birth asphyxia. The study found that the women with vitamin D deficiency had twice risk factors having birth asphyxia and low Apgar score.[37] A study by Lu T el al., reported that low Apgar score of one and five minutes premature baby in the bronchopulmonary dysplasia (BPD) group were lower compared to the non-BPD. The results showed that neonatal pneumonia and asphyxia were higher in BPD group compared to the non-BPD.[38]

Zhang et al., stated that vitamin D is an inflammatory T-cells regulator to inhibit Th17 cells activation. The IL-27 is an anti-inflammatory cytokine induced by Th17 was also reported having correlation with 25(OH)D in normothermic hypoxic ischemic encepalopathy (HIE). This result showed that a baby with low vitamin D levels had limited ability to reduce inflammatory reaction post-HIE Th17.[39]

CONCLUSION

There is a difference serum 1,25 dihydroxy vitamin D3 levels between normal pregnancy and pre-eclampsia patients. There was no association between calcium and perinatal outcomes between normal pregnancy and pre-eclampsia patients. In the first Apgar scores, there was a significant difference in the levels of 1,25 dihydroxy vitamin D3 between normal, moderate, and severe asphyxia groups. Measuring early maternal 1,25 dihydroxy vitamin D3 can lower the pre-eclampsia risks and the impact the perinatal outcomes, particularly in determining Apgar scores.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interests in preparing this article

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