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Predictors for 25-hydroxyvitamin D concentration in early pregnancy

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ABSTRACT

Introduction: There are very few studies of vitamin D deficiency in Indonesia. Since vitamin D deficiency is indicated by the level of 25-hydroxyvitamin D (25(OH) D) in blood, the present study aimed to analyse the predictive factors of 25(OH) D concentration in early pregnancy. **Methods:** The present study was a cross-sectional observational study. The sample consisted of 67 pregnant women in their 1st trimester of pregnancy. Parameters assessed included levels of 25(OH)D, glucose, and haemoglobin in the blood. Demographic information such as parity, family history of diabetes mellitus (DM), exposure to cigarette smoke, physical activity level, dietary intake, and anthropometric measurements were recorded. Linear regression analysis was employed. **Results:** Mean concentration of 25(OH)D was 16.5 (6.6-34.1) ng/ml. Majority of the participants (77.6%) were deficient in vitamin D (25(OH)D <20ng/mL); only 1.5% had normal vitamin D levels (25(OH)D >30 ng/mL). Bivariate analysis performed revealed that vitamin D intake (p=0.002) and family history of DM (p=0.043) played a significant role in determining 25(OH)D concentration. Additionally, dietary vitamin D intake, blood glucose level, exposure to cigarette smoke, and parental DM history served as predictors of 25(OH)D concentration in 54.5% of cases. **Conclusion:** The findings indicate that vitamin D deficiency was high in the target population. Thus, it is critical to ensure that for pregnant women to take vitamin D supplements, since nearly 80% of pregnant mothers are vit D deficient. Vitamin D supplementation can be included in national pregnancy programmes

Keywords: cigarette, diabetes mellitus, pregnant women, vitamin D concentration, vitamin D intake.

INTRODUCTION

While vitamin D deficiency affects people in developed countries (Pérez-López, Pilz & Chedraui, 2020), it remains a significant public health issue in the developing world as well. Vitamin D is a vital micronutrient that enhances glucose and insulin metabolism, and plays an important role in preventing fat accumulation (Cândido & Bressan, 2014; Li *et al.*, 2020; Mathieu, 2015). Vitamin D deficiency can lead to an array of problems, most notably rickets in children and osteoporosis in

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adults. Numerous studies have found a strong association between vitamin D deficiency and chronic diseases such as obesity, diabetes mellitus, and renal failure. Moreover, the large amount of observational data currently available indicate pathophysiological associations between vitamin D and energy homeostasis, as well as regulation of the immune and endocrine systems (Amrein *et al.*, 2020; Kulie *et al.*, 2009).

Recent epidemiological data indicated that vitamin D deficiency is widespread and pregnant women are at greater risk of developing vitamin D deficiency. The data suggest that pregnant women with vitamin D deficiencies are more likely to experience pre-eclampsia (Aghajafari *et al.*, 2013; Pena *et al.*, 2015), gestational diabetes mellitus (Aghajafari *et al.*, 2013; Arnold *et al.*, 2015; Bennett *et al.*, 2013; Chen *et al.*, 2015; Larqué *et al.*, 2018; Skowrońska-Jóźwiak *et al.*, 2014), spontaneous abortion, and to have small-for-gestational age and low birth weight infants (Aghajafari *et al.*, 2013; Chen, Chen & Xu, 2021). However, there is presently very little scientific evidence about the risk factors involved in vitamin D deficiency, for example, sun exposure, vitamin D supplementation, body weight, ethnicity, and age (AlFaris *et al.*, 2019; Ekwaru *et al.*, 2014; Li *et al.*, 2020; Yun *et al.*, 2017). The extent to which other factors, such as food intake, impact vitamin D deficiency is largely unknown.

A study has shown that although the frequency of vitamin D deficiency is higher in pregnant women who are obese, vitamin D level in blood is not significantly influenced by the incidence of obesity (Pena *et al.*, 2015). Some studies indicated that exposure to the sun and cold climates can impact vitamin D deficiency during pregnancy, but findings from different studies have been mixed. As the city of Luwuk on the island of Sulawesi, Indonesia is located on the Equator, it receives more sunlight than other places, thus facilitating the measurement of vitamin D status and its associated factors, other than exposure to sunlight, in pregnant women.

MATERIALS AND METHODS

The present study was a cross-sectional observational study, which served as a baseline study investigating the impact of vitamin D concentrations on blood glucose levels in pregnant women during the first trimester. Characteristics and vitamin D levels were measured at week 11 or 12 of pregnancy. This research was approved by the Research and Community Engagement Ethical Committee Faculty of Public Health, University of Indonesia, as indicated by letter No. 699/UN2.F10.D11/PPM.00.02/2019.

Research time and location

This study was conducted in the city of Luwuk, Central Sulawesi Province, Indonesia. Luwuk is the capital city of the Banggai Regency. The Biak, Kampung Baru, Nambo, and Simpong public health centres in Luwuk City were used as research bases. The main reason for choosing Luwuk was the access to laboratories for analysing vitamin D levels. Data were collected over an eight-month period, from January to August 2020.

Research subject

A total of 67 pregnant women participated in this study. They were recruited from the lists of pregnant women provided by the Biak, Kampung Baru, Nambo, and Simpong public health centres. Inclusion criteria were: age 18-40 years, gestational age <12 weeks, maximum two parities, and willingness to follow research procedures. Exclusion criteria were:

multiple pregnancies, severe anaemia, hyperglycaemia (DM) (as determined by a blood glucose examination > 200 mg/dl), kidney failure, hypertension, high cholesterol level, heart disease, and tuberculosis.

Research variables

The variables in the present study included: 25(OH)D concentration during the first trimester of pregnancy, age, education background, physical activity level, occupation, history of GDM, family history of diabetes, exposure to cigarette smoke, dietary intake, and anthropometric measurements (i.e., body weight, height, mid-upper arm circumference (MUAC), and waist circumference).

Research instruments

25(OH)D levels in blood samples were measured in the Prodia Laboratory using Chemiluminescent Microparticle Immunoassay (CMIA) Method. Research assistants with training in nutritional sciences conducted a semi-quantitative FFQ (food frequency questionnaire) to evaluate and measure the participants' food intakes. The FFQ was developed independently by the research team, based on a preliminary survey of the diets of local pregnant women. Physical activity levels were measured using the Global Physical Activity Questionnaire (GPAQ) (Global Physical Activity Questionnaire (GPAQ) WHO STEPwise Approach to NCD Risk Factor Surveillance, 2016). Anthropometric measurements (height, weight, waist circumference, and mid-upper arm circumference) were taken by assistants trained to use tools such as MUAC tape, digital scale, Microtoise Stature Meter, and waist ruler.

Data analysis

Vitamin D concentration was considered to be deficient when <20ng/mL, insufficient at 20-30 ng/mL, and sufficient at > 30 ng/mL (Holick *et al.*, 2011); by quartiles: Q1 at <13.9 ng/mL; Q2 in the range > 13.9 ng/mL - <15.6 ng/mL; Q3 > 15.6 ng/mL - < 19.7 ng/mL; and Q4 ng/mL > 19.7 ng/mL.

Before the analysis was carried out, a normality distribution test was performed on all continuous variables. The findings of this test indicated that the data distributions for age and waist circumference were abnormal, although the other variables were all found to be normally distributed. Median value (range) was used to describe age and waist circumference values. Mean (standard deviation, *SD*) was taken for all other continuous variables. When performing a descriptive analysis, mean (*SD*) and number of participants in each group (*n* %) were used.

In order to evaluate the relationships between 25(OH)D concentration and different variables, bivariate analysis was performed. Independent *t*-test and one-way analysis of variance (ANOVA) test were carried out to identify differences in vitamin D levels between groups. Pearson's and Spearman's correlation tests were also carried out using continuous data. Meanwhile, linear regression was performed at the multivariate stage, while statistical analysis results and general theory were used to evaluate the interactions among variables (p<0.05). Non-significant variables (i.e., those with p>0.05) were excluded one at a time. To determine confounding variable(s), the difference in coefficient B was calculated before and after removal of a variable from the regression model (i.e., if the coefficient difference was >10%, then it was considered a confounding variable). IBM SPSS Statistics for Windows, version 28.0 (IBM Corp., Armonk, New York, USA) was used to carry out all statistical analyses.

Table 1. Levels and categories of early 25(OH)D concentration in pregnant women

Level and categories of vitamin D	*Mean (min-max) or n (%)*
Vitamin D levels 25 (OH) D (ng/mL)†	16.4 (6.6-34.1)‡
Vitamin D deficiency	52 (77.6)
Vitamin D insufficiency	14 (20.9)
Vitamin D sufficiency	1 (1.5)
Q-1st	16 (23.9)
Q-2nd	18 (26.9)
Q-3rd	17 (25.4)
Q-4th	16 (23.9)

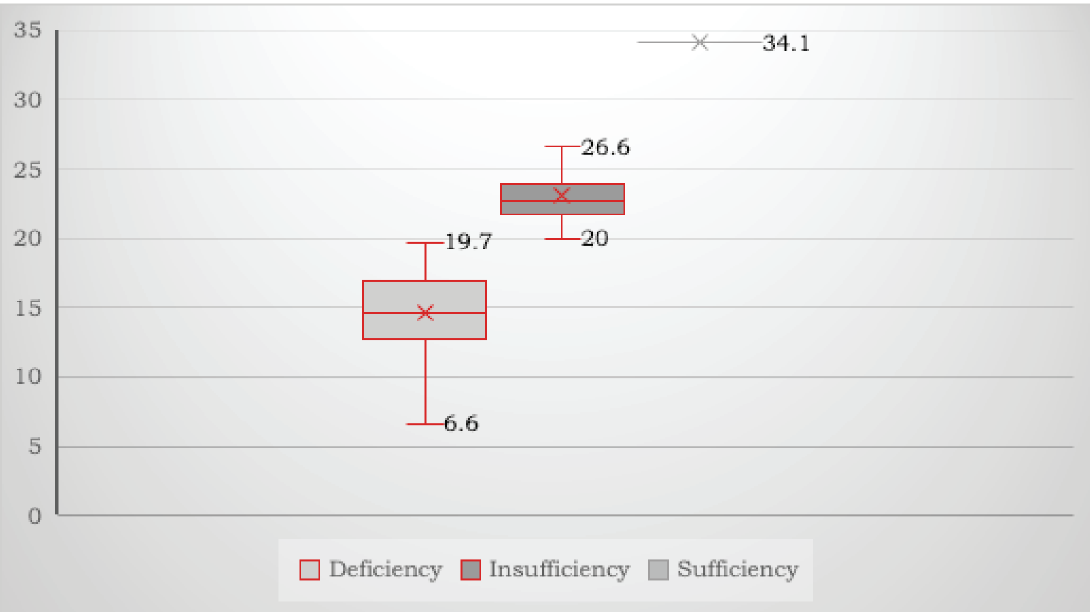
Q-1st until Q-4th are the quartile of 25(OH)D concentration: Q-1st at <13.9 ng/mL; Q-2nd in the range >13.9 ng/mL - <15.6 ng/mL; Q-3rd >15.6 ng/mL - <19.7 ng/mL; and Q-4th ng/mL >19.7 ng/mL)

†Normal distribution; $p>0.05$

‡Minimum and maximum

RESULTS

In Table 1, the average 25(OH)D level in pregnant women (67 respondents) was low, namely 16.4 ng/mL, with a minimum level of 6.6 ng/mL and a maximum level of 34.1 ng/mL. Vitamin D deficiency was a common issue for a majority of pregnant women (77.6%) in the study. In Figure 1, it can be seen that participants in the deficient group had 25(OH)D concentrations that neared the upper limit (maximum value), but vitamin D levels in the insufficient group were closer to the lower limit (minimum value), of their respective groups. There



Number of respondents (mean): Deficiency = 52(14.3); Insufficiency = 14(23.0); Sufficiency =1 (34.1)

Figure 1. Minimum and maximum 25(OH)D concentrations in pregnant women according to different categories

was only one participant in the sufficient category.

Findings from the bivariate analysis presented in Tables 2 and 3 showed that vitamin D intake and family history of diabetes mellitus had statistically significant relationships with 25(OH) D concentration. Thus, these variables

Table 2. Characteristics of pregnant women and their level of vitamin D at recruitment

Characteristics	*Categories of vitamin D, n (%)*		*Mean±SD*	$p^{\dagger}$
	Deficiency	*Insufficiency*		
Mother's occupation[1]				
Government officer	7 (13.5)	2 (14.3)	15.9±5.7	0.251
Private company	7 (15.)	1 (7.1)	15.6±3.4	
Entrepreneur/Freelancer	3 (5.7)	3 (21.4)	20.5±2.5	
Housewives	35 (66.0)	8 (57.1)	15.8±4.8	
Education[1]				
No school	1 (1.9)	0 (0.0)	18.5	0.903
Primary school	3 (5.8)	1 (7.1)	17.7±2.8	
Junior high school	3 (5.8)	1 (7.1)	15.8±5.3	
Senior high school	20 (38.4)	6 (42.9)	16.5±5.3	
Diploma/Bachelor/Undergraduate	25 (48.1)	6 (42.9)	15.8±4.6	
Family history of diabetes mellitus[2]				
Yes	16 (30.2)	1 (7.1)	14.8±3.7	0.043*
No	37 (69.8)	13 (92.9)	17.0±5.5	
Cigarette smoke exposure[2]				
Yes	29 (54.7)	8 (57.1)	16.7±4.2	0.151
No	24 (45.3)	6 (42.9)	15.3±5.4	
Physical activity[2]				
Low (MET≤ 3000)	28 (53.8)	6 (42.9)	15.4±5.0	0.069
High (MET>3000)	24 (46.2)	8 (57.1)	17.1±4.4	
Vitamin D supplement consumption[2]				
No	36 (69.2)	9 (64.3)	16.1±4.6	0.360
Yes	16 (30.8)	5 (35.7)	16.6±5.1	
Parity				
Multiparous	13 (25.0)	6 (42.9)	15.9±6.0	0.940
Primiparous	11 (21.2)	3 (21.4)	16.1±3.7	
Nulliparous	28 (53.8)	5 (35.7)	16.4±4.4	
Categories of body mass index (BMI)				
Obese	13 (25.0)	2 (14.3)	15.9±4.3	0.762
Normal	39 (75.0)	12 (85.7)	16.3±4.9	
Categories of waist circumference				
Central obesity	38 (71.7)	11 (78.6)	16.2±5.0	0.961
Normal	15 (28.3)	3 (21.4)	16.3±4.0	

The number of respondents for each variable varied: occupation= 66, education= 66, parental history of diabetes mellitus= 66, cigarette smoke exposure= 66, physical activity= 66, Vitamin D supplement consumption= 66, parity= 66, BMI= 66, categories of BMI=66, categories of waist circumference= 66

†results of one-way ANOVA test[1] or *t*-test[2]

*p<0.05

Table 3. Correlation between continuous variables and early 25(OH)D concentration

Characteristics	*Mean±SD of each vitamin D categories*		*Total groups*	
	Deficiency	*Insufficiency*	*Mean±SD*	*p*[†]
Age (years)[1]	29.0±5.3	29.0±5.7	29.0±19.0	0.892
Dietary vitamin D intake[1]	16.2±11.5	38.6±25.5	18.1±4.8	0.002*
Body mass index (kg/m^2)[1]	24.7±4.1	24.3±2.6	24.0±17.0	0.305
Waist circumference (cm)[2]	88.5±8.6	86.5±8.1	85.0±10.4	0.668
Mid-upper arm circumference (cm)[1]	27.7±3.5	26.9±3.0	27.3±3.2	0.314
Haemoglobin concentration (mg%)[1]	11.5±1.3	11.7±1.9	12.1±1.5	0.268
Glucose level 1st trimester (mg/dl)[1]	82.0±22.6	76.5±8.0	89.0±11.2	0.264

The number of respondents for each variable varied: age=66, waist circumference=66, mid-upper arm circumference=66, haemoglobin concentration=66, glucose level 1st trimester=66
[†]Correlation: [1]Pearson's; [2]Spearman's
*p<0.01

were used in the multivariate analysis to evaluate their impact on 25(OH)D concentration. In addition, exposure to cigarette smoke and physical activity levels showed a significance value of <0.25, which also met the requirements for incorporation into the multivariate analysis. Finally, considering the significance of body mass index (BMI) and blood glucose levels, these variables were also included in the multivariate analysis.

Interaction tests were performed between vitamin D intake and a number of covariates before confounding factors were evaluated. The analysis findings showed that there were no significant relationships between vitamin D intake, covariates, and blood vitamin D levels (no interactions). Since physical activity and BMI were not found to be statistically significant confounders (change in coefficient B <10%), they were not included in the regression model. Meanwhile, parental history of diabetes and exposure to cigarette smoke were found to be significant confounding factors (change in B coefficient >10%), so they were both included in the regression model.

In Table 4, the parsimony linear regression model used to predict blood

Table 4. Predictor model of early vitamin D concentration in pregnant women

First Model				*Final Model*			
Variable	*Coeff. B*	*p*	*R square*	*Variable*	*Coeff. B*	*p*	*Adjusted R square*
Constant	22.529	0.003	0.498	Constant	24.102	<0.001	0.545
Vitamin D intake	0.259	<0.001		Vitamin D intake	0.260	<0.001	
Parental history of DM	-2.256	0.187		Blood glucose	-0.155	0.004	
Exposure of Smoke	2.298	0.153		Parental history of DM	-2.325	0.147	
Blood glucose	-0.153	0.007		Exposure of Smoke	2.388	0.122	
Physical activity	0.178	0.916					
BMI	0.054	0.778					

DM: diabetes mellitus
*Using multivariate linear regression

25(OH)D concentrations is presented. The final model included the following factors: vitamin D consumption, blood glucose, family history of DM, and smoking exposure, all of which served as predictors of 25(OH)D concentration during the 11th and 12th weeks of pregnancy in 54.5% of participants (*p*=0.001). This was a significant increase from the initial model, of which the percentage was 49.8%.

DISCUSSION

It is important to note that vitamin D can be both produced endogenously and consumed as a micronutrient in food. Key food sources of vitamin D include fish oil (salmon, sardines, mackerel), milk, juice, and egg yolks (AlFaris *et al*., 2019). The World Health Organization (WHO) and the Food and Agricultural Organization (FAO) recommend three strategies to increase micronutrient intake: (1) increase the diversity of foods consumed, (2) food fortification, and (3) supplementation. Each of these strategies, together with sensible sunlight exposure (when and if available), can reduce the widespread prevalence of inadequate vitamin D intake. Dietary supply (including supplementation) is particularly important for those of whom sunlight exposure is limited (Allen *et al*., 2006).

In the present study, 77.6% of the participants experienced vitamin D deficiency, with 20.9% clinically insufficient in vitamin D and just 1.5% sufficient. These findings are consistent with those of other studies that indicated very few pregnant women have sufficient levels of vitamin D (Yun *et al.,* 2017). A study reported that 90% of pregnant Chinese women were found to be vitamin D deficient at 23-28 weeks of gestation (<20 ng/ml) (Zhao *et al.,* 2017), while another research revealed that 31.8% of women were severely deficient in vitamin D, 40.7% were deficient, 25.1% were insufficient, and just 2.4% had normal vitamin D levels (Yang *et al.,* 2021). Thus, it is critical that vitamin D deficiency is detected at an early stage during pregnancy because it has significant impact on the progression of pregnancy and childbirth.

The present study revealed that several factors had significant relationships with vitamin D levels, including dietary intake of vitamin D and family history of diabetes mellitus. The findings showed that pregnant women with vitamin D deficiency consumed less vitamin D than those in the insufficient group. AlFaris *et. al* (2019) showed that women who did not take vitamin D supplements had more than three times (3.14) risk of experiencing vitamin D deficiency than those who took vitamin D supplements. 25(OH)D concentrations also seemed to fluctuate depending on whether or not there is a parental history of diabetes. The results indicated that 25(OH)D concentrations in pregnant women with diabetes were lower than those who did not have diabetes, which is in line with the findings from other studies (AlFaris *et al*., 2019; Al-Timimi & Ali, 2013; Iqbal *et al*., 2016).

Other studies have revealed that vitamin D levels are impacted by factors such as exposure to cigarette smoke. Pregnant women who have been exposed to cigarette smoke are more likely to be vitamin D deficient or have insufficient levels of vitamin D than those who have not been exposed to cigarette smoke (Yun *et al*., 2017). Although this study did not find significant differences in Vitamin D levels between parity groups, Yang *et al.* (2021) found that multiparous women had lower mean 25(OH)D concentrations and were more likely to be obese or centrally obese, as well as low in physical activity levels (Yang *et al*., 2021). Thus, it is critical that multiparous women are provided more care and attention during pregnancy.

The findings in this study showed that there was no statistically significant difference in 25(OH)D concentrations between participants who took oral vitamin D supplements and those who did not. However, it appeared that pregnant women who took vitamin D supplements orally had higher average 25(OH)D concentrations than women who did not take vitamin D supplements. Of the participants who did not consume vitamin D supplements, there was a higher percentage of vitamin D deficiency than vitamin D insufficiency. Conversely, in the group of women who consumed vitamin D supplements, there were more women who were vitamin D insufficient compared to vitamin D deficient. The statistically insignificant results may be due to the higher number of participants who took vitamin D supplements than those who did not. Yosephin *et al.*'s study (2015) showed that vitamin D levels increased after participants took vitamin D supplements (Yosephin *et al.*, 2015). This difference, which was not statistically significant, could have been caused by the small number of participants in the study.

Prior studies have also revealed that overweight or obese individuals should consume 1.5 to 2-3 times more vitamin D per day than those of normal weight (Bouillon, 2017; Ekwaru *et al.,* 2014). Despite these findings, vitamin D supplementation is not yet a regular part of any nationwide maternal health programmes in Indonesia. Thus, it is important that vitamin D supplementation be incorporated in national pregnancy programmes and that the vitamin D levels of pregnant women are carefully monitored.

The parsimony model developed during the multivariate analysis process predicted 54.4% of vitamin D levels in the blood. This model is applicable to the participants in the present study. In terms of other variables, dietary vitamin D intake was found to be positively related to 25(OH)D concentration. To be more precise, the findings indicated that concentration of vitamin D in the blood increased when more vitamin D was consumed.

However, this study found that variables with a negative relationship with 25(OH)D concentration in the blood included parental history of diabetes and blood glucose levels. This is consistent with the findings of other studies, which revealed low serum vitamin D levels in those with poorly controlled type 2 diabetes mellitus (Al-Timimi & Ali, 2013; Iqbal *et al.*, 2016; Zoppini *et al.*, 2013); while statistically significant, we question its clinical relevance. The current research solely establishes statistical proof of this correlation, lacking clinical investigation. Existing studies focus on the link between parental diabetes history and offspring diabetes incidence, suggesting a potential mechanism for the observed correlation. Further research must provide clinical validation of this mechanism.

All variables included in the multivariate model had a simultaneous influence on the dependent variable. Nonetheless, the impact of each variable in this multivariate model differed from those in the bivariate model.

This study had several limitations. Firstly, as a cross-sectional design was used for data collection, it was impossible to determine causality between vitamin D levels and the parameters measured in the research subjects. Secondly, there may be information bias in this study, given the lack of existing data pertaining to vitamin D intake from food sources. Moreover, the sample size was not calculated in relation to the research objective. This is because the study is the first part of a cohort study involving a number of dependent variables, which may impact the statistical significance of the data. These limitations should be carefully considered by researchers examining this topic in the future.

It is evident from this study that more efforts should be made to prevent vitamin D deficiency in women during pregnancy. For example, if a family history of diabetes mellitus is present, appropriate measures should be taken from the start of the pregnancy. The effectiveness of health services for pregnant women such as nutritional management or counselling will increase if they are based on knowledge about health conditions before pregnancy. Moreover, vitamin D and blood glucose levels, as well as other parameters indicative of a syndrome or disease, should be monitored carefully to prevent problems during pregnancy. Pregnant women should be advised on how to manage their food intake and avoid risky behaviours. Maternal health programmes should recommend vitamin D supplementation during the preconception period. Currently, existing antenatal care policies in most regions do not pay attention to medical history or health conditions before pregnancy (preconception period), which impacts antenatal services, especially for pregnant women with poor health histories.

CONCLUSION

The prevalence of vitamin D deficiency in the pregnant women studied was high (77.6%). The average 25(OH)D concentration was only 16.4 (6.6-34.1) ng/ml. Blood glucose level, vitamin D dietary intake, parental history of diabetes, and exposure to smoke were strong predictors of vitamin D deficiency in 54.5% of the cases (adjusted *R* square). Thus, it is critical to ensure that for pregnant women to take vitamin D supplements, since nearly 80% of pregnant mothers are vitamin D deficient. Vitamin D supplementation and monitoring can be included in national pregnancy programmes. However, further investigations are needed regarding the impact of vitamin D intake from food sources and exposure to sunlight on vitamin D levels in the blood.

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Authors' contributions

Lalusu EY, carried out this research; Hatma RD, involved in the implementation of research starting from the initial planning of research and various scientific considerations in conducting research; Sudaryo MK, participated in article review and provided various suggestions for improvement during the preparation of the article, contributed greatly to data processing and analysis; Ocviyanti D, participated in article review and provided various suggestions for improvement during the preparation of the article, contributed more to the discussion of the findings of this study; Rimbawan R, participated in article review and provided various suggestions for improvement during the preparation of the article, contributed more to the discussion of the findings of this study. All authors listed above contributed to preparing, drafting, and revising the manuscript, giving final approval of the published version, and agreeing to be responsible for all aspects of the work.

Conflict of interest

The authors declare that they have no conflict of interest. This article has received approval from all relevant parties to be published.

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