Al-Azhar International Medical Journal

Volume 4 | Issue 4 Article 8

2023

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How to Cite This Article

Garhy, Ismael Talat El; Saeed, Ahmed Mohammed; Elghaffar, Medhat Ali Salah Abd; and Ali, Metwally Awad Farag (2023) "Role of Vitamin D in Preeclampsia," *Al-Azhar International Medical Journal*: Vol. 4: Iss. 4, Article 8.
DOI: https://doi.org/10.58675/2682-339X.1749

ORIGINAL ARTICLE

Role of Vitamin D in Pre-Eclampsia

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Abstract

Background: **Pre-eclampsia is a multisystem illness that affects pregnant women. Its cause is unclear. The condition affects between 2 and 8% of pregnancies and is a main reason of maternal and fetus sickness and death. One of the most recent developments in this sector is the interest in vitamin D, since several recent research have shown that pre-eclampsia and vitamin D have a link.**

Aim of the study: **The goal of this research was to see whether there was a link between vitamin D and preeclampsia.**

Patients and methods: **This research was conducted on one hundred pregnant female, between the age of (20−35) years. And excluded from this study: cases who were taking vitamin D or any other medications during the previous 6 months and cases that suffer from chronic diseases, as well as cases of obesity.**

Results: **Vitamin D levels in the blood were substantially larger in the case group as compared to the control group. When compared to the control group, the incidence of caesarean section was substantially larger in the case group. Level of hemoglobin, pregnancy ultrasound, amniotic fluid coefficient and placental differentiation, there were no substantial variations between the two study groups. regarding vitamin D, there were no substantial variations compared to the different criteria of the study, such as pregnant age, weight, pregnancy and birth rate, blood pressure, hemoglobin percentage, fetal weight, and amniotic fluid rate.**

Conclusion: **According to our research outcomes that vitamin D deficiency has a weak significant relation to pre-eclampsia.**

Keywords: Preeclampsia, Pregnancy women, Vitamin D

1. Introduction

Pre-eclampsia (PE), a pregnancy-related condition that impacts 3−7% of all pregnancies, is a leading etiology of maternal and fetus illness and death, as well as an elevated potential danger of cardiovascular occurrences later in life. High blood pressure, proteinuria, and multiorgan damage are caused by endothelial impairment.[1]

PE is a pregnancy-related condition that affects around 10% of all pregnancies globally.[2]

Recently a survey of expert suggested that from early infancy through adolescence, mother PE was linked to greater offspring SBP. Greater cord blood 25(OH) D values in a dose-response way decreased these correlations.[3]

PE is hypothesized to develop as a result of aberrant angiogenesis and immune response at implantation and trophoblast invasion early in pregnancy. Vitamin D seems to alter the transcription and activity of genes involved in trophoblast invasion, implantation-critical angiogenesis, and fetus allograft immunologic tolerance.[4]

Dietary substances may either stimulate or prevent the stimulation of immune cells like macrophages, which leads to the generation of cytokines. Mono-unsaturated fatty acids, antioxidants, and calcium have a negative relationship with cytokine generation, but saturated fatty acids and insufficient vitamin D have a positive relationship, which may lead to low-grade inflammation. Vitamin D has been reported as having an anti-inflammatory impact in this regard.[5]

Accepted 16 October 2022.
Available online 27 June 2023

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https://doi.org/10.58675/2682-339X.1749

Prediction, prevention, detection, and treatment have all improved recently. Risk modeling has been used to detect women at the greatest risk of developing PE, as well as to predict maternal unfavorable results in women who have been diagnosed with the illness.[6]

PE has been linked to a variety of biological activities in the last decade, involving immunological malfunction, placental implantation, aberrant angiogenesis, excess inflammation, and hypertension, all of which may be influenced directly or indirectly by vitamin D. Vitamin D has been linked to an elevated risk of PE.[7]

The aim of this research was to evaluate the impact of vitamin D insufficiencyto PE incidence by estimation of vitamin D level after the 20th week of gestation.

2. Subjects and methods

This case-control prospective research carried out in Al-Azhar University Hospitals at Cairo in the outpatient clinic for antenatal care and inpatient ward, started at August 2020 and for eight months.

The study was carried according to sample size estimation equation on 100 patients attending or referred to the outpatient clinic or emergency of Obstetrics and Gynecology and meeting the following inclusion and exclusion criteria.[8]

2.1. Inclusion criteria

Singleton pregnancy, maternal age ranging from 20 to 35years, 50 normotensive pregnant as control, and 50 confirmed preeclamptic patients diagnosed as per NICE criteria:(SBP$\geq$ 140 mmHg/DBP $\geq$90 mmHg with proteinuria (greater than 300 mg/l in 24 h urine) on two or more times at least 6 h apart after 20 weeks of gestations.

2.2. Exclusion criteria

Fetal malformations, patients with systemic disease (chronic hypertension, diabetes mellitus, renal disease), patients with BMI >30 kg/mm^2, and TB drug intake (aspirin, omeprazole, steroids, multivitamins).

Before enrolling in the study, the researcher got written informed permission from each study population.

These cases were divided into two equal groups: First group (Cases): consisted of fifty pregnant women suffering from PE, and the Second group (Control): consists of fifty pregnant women who do not suffer from any diseases related to pregnancy.

Women eligible to the study underwent the following: (1) Name, age, employment, housing, social standing, particular habits, parity, and chronic sickness are all part of a complete personal biography. (2) Medical issues, includes prior and family medical histories. (3) Antenatal care was given to pregnant women according to the following schedule to both groups.[8]

As shown in the previous table the routine antenatal care schedule was applied to all study members weather control or at risk.

Ultrasound was done serially to both groups using the convex abdominal probe with center frequency 3.5 MHz.

Venous blood samples were analyzed for vitamin D level and results were collected after 20 weeks gestational age for both groups.

Planning and follow-up for each group:

The above-mentioned ANC protocol were introduced and applied to both groups.

Vitamin D was estimated after 20 weeks gestational age for both case and control groups.

Routine measurement of blood pressure as a part of the above-mentioned NICE antenatal care and antihypertensive medications was prescriped for the group who are at risk.

Close monitoring for the appearance of symptoms and/or signs and even complications of PE.

Follow up of both groups until labor.

Relation of vitamin D levels and occurrence of PE.

2.3. Statistical analysis

IBM SPSS statistics (Statistical Package for Social Sciences) software version 22.0, IBM Corp., Chicago, USA, was used to code, tabulate, and assess the obtained data. For quantitative normally distributed data, descriptive statistics included the lowest and maximum of the range, as well as mean $\pm$ SD (standard deviation), whereas qualitative data included number and proportion. For quantitative variables, inferential analyses were conducted using the Shapiro-Wilk test for normality testing and an independent *t*-test in the case of two unrelated groups with normally distributed data. Inferential studies for unrelated variables in qualitative data were performed using the Chi-square test for proportional variances and Fisher's exact test for variables with small anticipated numbers. For numerical regularly distributed data, Pearson correlation was used for correlations. The performance of several tests to predict FGR was evaluated using the ROC curve. To determine independent determinants impacting fetal weight, a linear regression model was utilized. *P* value < 0.050 was used as

Table 1. General characteristics of the investigated groups.

			Cases (n = 50)	Controls (n = 50)	P value
Age (years)	Mean ± SD		25 ± 4	25 ± 3	0.551
Body mass index (BMI)	Mean ± SD		26.4 ± 1.6	26.5 ± 1.6	0.774
Level of education	No to low	n (%)	14 (28.0)	26 (52.0)	0.014[a]
	Medium to high	n (%)	36 (72.0)	24 (48.0)	
Gravidity	Mean (range)		3 (0–7)	2 (0–5)	0.012[a]
Parity	Mean (range)		1 (0–3)	1 (0–4)	0.24
Mode of delivery	Vaginal delivery	n (%)	8 (16.0)	36 (72.0)	<0.001[a]
	Cesarean section	n (%)	42 (84.0)	14 (28.0)	

[a] Significant.

the threshold for relevance; otherwise, it was considered as non.

3. Results

Medium to high education was substantially greater in cases (72.0%) compared to controls (48%). P value was 0.014. Also, median gravidity was substantially greater in cases (3) compared to controls (2) (P value = 0.002). In addition, Cesarean section was substantially greater in cases (84%) than controls (28.0%) (P value < 0.001). No substantial variations were noted at both groups according to age, BMI, and parity (Table 1).

Systolic blood pressure was substantially greater in cases (158) than controls (120). (P value < 0.001). Also, diastolic blood pressure was substantially greater in cases (97) than in controls (70). P value was <0.001. About two-thirds of cases (60%) showed grade 2 proteinuria, and 40% showed grade 3 proteinuria. Ultrasound was normal in both cases and controls (Table 2).

EFW was significantly higher in controls (3257) than cases (2989). P value was <0.001. S/D ratio at 36 weeks was significantly higher in controls (2.67) than in cases (2.55). P value was 0.033. No substantial variances were noted between both groups according to placental grade, hemoglobin, and AFI (Table 3).

The normal level of vitamin D ranges between 25 and 40 ng ⧹ ml (nanogram per milliliter). Vitamin D level was substantially greater in cases (26) than in controls (23). P value was 0.027 (Table 4).

Vitamin D level showed no substantial correlations with different study parameters., including age, BMI, gravidity, parity, SBP, DBP, EFW, Hb AFI, and S/D ratio (Table 5).

ROC analysis was done for vitamin D in predicting PE. It showed an unsatisfactory AUC of 0.654 with a 95% CI ranged from 0.547 to 0.761. The best cut-off point was >25, at which vitamin D showed low sensitivity, specificity, PPV, and NPV of 72%, 52%, 60%, and 65%, respectively (Table 6) (Fig. 1).

Multivariate logistic regression analysis revealed that the only predictors for PE were level of education (OR = 2.714, 95% CI = 1.085–6.788, P value = 0.033) and gravidity (OR = 3.657, 95% CI = 1.361–9.826, P value = 0.01) (Table 7). So, vitamin D has a low significance in the prediction of PE.

4. Discussion

Fifty verified preeclamptic pregnant women served as the study group, whereas 50 normotensive pregnant women served as the control group in the present research.

Serum vitamin D level is estimated in both study and control groups and was correlated to the occurrence of PE.

Vitamin D levels were substantially greater in the case group (26) than in the control group in the present investigation (23). The connection between vitamin D insufficiency and PE was faintly substantial, with a P-value of 0.027.

In the current study, regarding Systolic blood pressure was substantially greater in cases (around

Table 2. The study groups' clinical features.

		Cases (n = 50)	Controls (n = 50)	P value
Systolic blood pressure	Mean ± SD	158 ± 10	120 ± 7	<0.001[a]
Diastolic blood pressure	Mean ± SD	97 ± 9	70 ± 9	<0.001[a]
Proteinuria	+2 n (%)	30 (60.0)	–	–
	+3 n (%)	20 (40.0)	–	
Ultrasound	Normal n (%)	50 (100.0)	50 (100.0)	–

[a] Significant.

Table 3. EFW, placental grade, HB, AFI, and S/D ratio at 36 weeks in both groups.

		Cases ($n = 50$)	Controls ($n = 50$)	*P*-value
Expected fetal weight (EFW) (gm)	Mean ± SD	2989 ± 401	3257 ± 287	<0.001[a]
Placental grade at 36 weeks	Grade II n (%)	12 (24.0)	6 (12.0)	0.118
	Grade III n (%)	38 (76.0)	44 (88.0)	
HB at 36 weeks	Mean ± SD	10.9 ± 0.6	11 ± 0.7	0.245
AFI at 36 weeks	Mean ± SD	20 ± 5	21 ± 3	0.126
S/D ratio at 36 weeks	Mean ± SD	2.55 ± 0.4	2.67 ± 0.02	0.033[a]

[a] Significant.

158) than controls (around 120) with *P* value < 0.001, also diastolic blood pressure was substantially greater in cases (97) than in controls (70). *P* value was <0.001.

About two-thirds of cases (60%) showed grade 2 proteinuria, and 40% showed grade 3 proteinuria.

In current study, regarding ultrasound was normal in both cases and controls with no significant differences.

In current study, regarding EFW was substantially greater in controls (3257) than cases (2989). *P* value was <0.001.

In current study, regarding placental grade, hemoglobin, and AFI no significant differences was detected.

In our study, analysis was done for vitamin D in predicting PE. It showed an unsatisfactory AUC of 0.654 with a 95% CI ranged from 0.547 to 0.761. The best cut-off point was >25, at which vitamin D showed low sensitivity, specificity, PPV, and NPV of 72%, 52%, 60%, and 65%, respectively.

On the other hand another study done by Fogacci et al.[9] done on 257 women found that Even though vitamin D supplementation may be useful in preventing PE, there are some restrictions to that analysis, the most substantial of which is connected to the various administration timing and medicinal forms of vitamin D supplemented to pregnant women at a large dose. Because vitamin D accumulates in body fat, even a single doses of vitamin D may be sufficient to avoid PE.

Another study done at Delhi by Khari et al.[4] showed that Vitamin D supplementation has an important role in the prevention of PE in pregnant women. The supplemented group had a lower rate of PE. The research comprised 200 pregnant women between 16 and 20 weeks of pregnancy. They were divided into two groups at random: the research group and the control group. The research included 100 pregnant women between 16 and 20 weeks of pregnancy who received vitamin D supplementation (regardless of vitamin D level) in the form of oral cholecalciferol sachets 60, 000IU weekly for 10 weeks, as well as regular iron, folic acid, and calcium supplementation.A control group of 100 pregnant women between the ages of 16 and 20 weeks got just regular iron, folic acid, and calcium supplements (irrespective of vitamin D level). A full history was gathered at the initial prenatal appointment, and all individuals were thoroughly examined and regular antenatal investigations were performed. Vitamin D supplementation has a long-term function in preventing PE. The effects of vitamin D supplementation on maternal outcomes such as PE, GDM, preterm labor, mode of delivery, and fetusoutcomes such as LBW, NICU hospitalization, and tetany were compared between the two groups. If the results of the research do not match those of ours, it might be due to differences in sample size, demographic or dietary habits, or other variables that should be investigated in bigger investigations.

Another study done Bodnar et al.[7] and it was found that Vitamin D insufficiency in the mother might be a separate risk factor for PE. PE cases were more likely than non-preeclamptic controls to be older, non-Hispanic white, married, better educated, nonsmokers, and overweight at the outset of gestation, according to the research, which included 1198 women from the primary 2211. In

Table 4. Vitamin D level in both groups.

	Cases (n = 50)	Controls (n = 50)	*P*-value
Vit D level Mean ± SD	26 ± 6	23 ± 6	0.027[a]

[a] Significant.

Table 5. Correlation between vitamin D level and other parameters.

	Vit D level	
	r (Correlation coefficient)	*P* value
Age (years)	−0.165	0.253
BMI	−0.003	0.982
Gravidity	−0.109	0.452
Parity	−0.247	0.084
Systolic blood pressure	0.104	0.47
Diastolic blood pressure	−0.066	0.647
EFW	0.114	0.432
HB at 36wks	0.054	0.719
AFI at 36wks	−0.039	0.787
S/D ratio at 36wks	−0.073	0.612

Table 6. ROC analysis of vitamin D in the prediction of pre-eclampsia.

ROC characteristics	
AUC (95% CI)	0.654 (0.547–0.761)
Cutoff point	>25
Sensitivity	72%
Specificity	52%
PPV	60%
NPV	65%
P-value	0.008[a]

95% CI, 95% confidence interval; AUC, Area Under Curve; NPV, Negative predictive value; PPV, Positive predictive value.
[a] Significant.

both cases and controls, serum samples were obtained at comparable gestational ages. The research suggests that maternal vitamin D deficiency in early gestation is an independent risk factor for PE, with adjusted blood 25(OH) D levels 15% lower in women who later had PE compared to controls.

Another study done by Singla et al.[10] It was a case-control study on 174 pregnant women to see whether there was a link between PE and vitamin D insufficiency. Cases had systolic and diastolic blood pressures of 156 ± 19.5 and 104 ± 10.5 mmHg, respectively, whereas the control group had 117 ± 4.7 and 75 ± 5.2 mmHg.The research found that women with PE had considerably reduced vitamin D levels than normal women (9.7 ± 4.95 ng/ml vs. 14.8 ± 6.68 ng/ml); $P = 0.0001$.

Matching with our study it was found in Singla et al.[10] that the PE (case) group had a mean age of 25.22 ± 3.08 years, whereas the control group had a mean age of 25.11 ± 3.12 years; the variation was not substantial ($P = 0.6$). The average systolic and diastolic blood pressures of the patients were 156 ± 19.5 and 104 ± 10.5 mmHg, respectively, whereas the control groups were 117 4.7 and 75 ± 5.2 mmHg, respectively. The patients' mean blood vitamin D level was substantially lower (9.7 ± 4.95 ng/ml) than the controls' (14.8 ± 6.68 ng/ml); $P = 0.0001$. In comparison to the controls, a substantially bigger percentage of the patients (93.2%) were vitamin D insufficient.

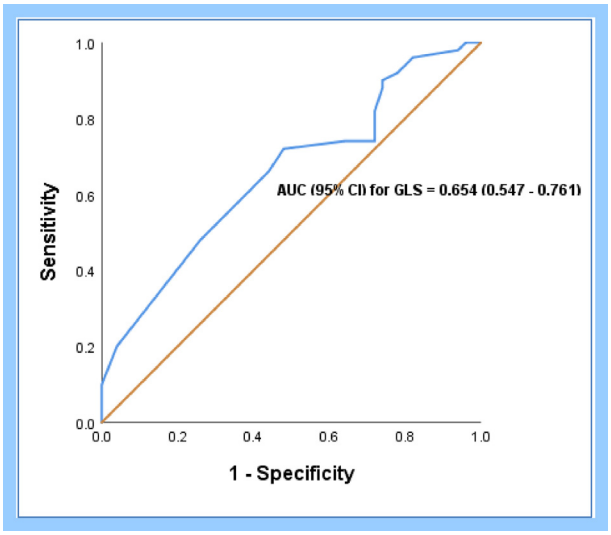

Fig. 1. ROC analysis of vitamin D in the prediction of PE.

Both systolic (r = −0.370; $P = 0.001$) and diastolic blood pressure (r = −0.387; $P = 0.001$) were negatively correlated with vitamin D concentration.

17 (23%) of the 74 patients had mild PE, whereas 57 (77%) had severe PE. Women with moderate PE and those with severe illness had comparable vitamin D levels ($P = 0.811$). (Table 8). Eclampsia was impending in sixteen of the participants. Though the existence or lack of impending eclampsia had no effect on mean vitamin D concentration ($P = 0.310$), none of the participants with a vitamin D level of [20 ng/ml experienced this problem (Table 1). Also, although the average value was equal in women with and without eclampsia, all seven women with eclampsia were vitamin D deficient (20 ng/ml), suggesting that vitamin D levels are unrelated to the severity of PE.

Matching with our study it was found that Patients who needed a cesarean delivery had substantially lower vitamin D levels than those who had a normal vaginal birth ($P = 0.022$). Fetal discomfort (in 20 women) and Abruptio placentae were the most common reasons for cesarean section (in 5 women). Vitamin D levels in cesarean birth women were likewise substantially lower than in vaginal delivery women (10.71 ± 6.32 vs. 13.45 ± 6.45 ng/ml; $P = 0.013$) in the overall research sample of 174 participants.

Another study done by de Souza and Pisani[11] to detect Inflammation in pregnancy is a prevalent issue, according to the link between vitamin D, TLR4 pathway, and PE. High levels of pro-inflammatory cytokine production, on the other hand, may lead to

Table 7. Analysis of multivariate logistic regression for predicting pre-eclampsia.

	OR (95% CI)	*P* value
Age (years)	0.952 (0.814–1.113)	0.535
BMI	1.001 (0.757–1.324)	0.995
Level of education	2.714 (1.085–6.788)	0.033[a]
Gravidity	3.657 (1.361–9.826)	0.01[a]
Parity	0.281 (0.068–1.162)	0.08
Vit D level	1.083 (1–1.174)	0.05

BMI, Body mass index; CI, 95%. Confidence interval; OR, Odds ratio95%.
[a] Significant.

Table 8. The routine antenatal care schedule to all study groups.

Item	Primigravida	Multigravida	G.A.
1st visit	Weight, BMI, pregnancy dating, complete history taking and examination, including US, BLP.	Weight, BMI, pregnancy dating, complete history, including past obstetric history taking and examination.	10 wks
2nd visit	US, BMI, BLP measurement, complete assessment.	US, BMI, BLP measurement, complete assessment.	12wks
3rd visit	US, BMI, BLP measurement, complete assessment.	US, BMI, BLP measurement, complete assessment.	16wks
4th visit	US with screening for fetal anomilies, BMI, BLP measurement, complete assessment, venous blood sample.	US with screening for fetal anomilies, BMI, BLP measurement, complete assessment, venous blood sample.	20wks
5th visit	US, BMI, BLP measurement, complete assessment.	US, BMI, BLP measurement, complete assessment.	22wks
6th visit	US, BMI, BLP measurement, complete assessment.		25wks
7th visit	US, BMI, BLP measurement	US, BMI, BLP measurement	28wks
8th visit	US, BMI, BLP measurement	US, BMI, BLP measurement	32wks
9th visit	US, BMI, BLP measurement, venous blood sample	US, BMI, BLP measurement, venous blood sample	36wks
10th visit	US and detection of position, BMI, BLP measurement	US and detection of position, BMI, BLP measurement	40wks

poor pregnancy outcomes. Vitamin D is vital in this condition because it both stimulates and suppresses the immunological response. More research is required to evaluate the link between maternal vitamin D value and the risk of PE, but the study found that vitamin D plays a significant role in this setting, both boosting and dampening the immunological response. More research is required to evaluate the link between maternal vitamin D value and the risk of PE. To enhance prenatal care and minimize unfavorable pregnancy outcomes, future study might look at designing vitamin D supplementation guidelines for various trimesters of pregnancy.

In our study, we found Medium to high education was substantially greater in cases (72.0%) compared to controls (48%). *P* value was 0.014 which means that educational level may has role regarding diet and nutrition and care of pregnancy which may has role in avoidance of PE.

In our study we found that Cesarean section was substantially greater in cases (84%) than controls (28.0%) (*P* value < 0.001), which looks logic and coinciding with safe termination of pregnancy in preeclamptic women in order to avoid a multisystemic complications.

In our study, it was found that no substantial variations were noted between both groups regarding age.

In our research Vitamin D level revealed no substantial correlations with different study parameters. Including age, BMI, gravidity, parity, and SBP, DBP, EFW, HB. , AFI, and S/D ratio.

In our study ROC analysis was done for vitamin D in predicting PE. It showed an unsatisfactory AUC of 0.654 with a 95% CI ranged from 0.547 to 0.761. The best cut-off point was >25, at which vitamin D showed low sensitivity, specificity, PPV, and NPV of 72%, 52%, 60%, and 65%, respectively.

In our study we found that Multivariate logistic regression analysis revealed that the only predictors for PE were level of education (OR = 2.714, 95% CI = 1.085–6.788, *P*value = 0.033) and gravidity (OR = 3.657, 95% CI = 1.361–9.826, *P* value = 0.01).

4.1. Conclusion

We conclude according to our research findings that vitamin D insufficiency has a weak significant relation to PE.

4.2. Recommendations

The current study recommends multicenter study with larger sample size taking in consideration demographic and nutritional habits that have direct effect on vitamin D.

Conflicts of interest

Authors declare that there is no conflict of interest, no financial issues to be declared.

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