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The Effects of Vitamin D Supplement on Prevention of Recurrence of Preeclampsia in Pregnant Women with a History of Preeclampsia

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ABSTRACT

Background: Many studies hypothesized a strong relation between vitamin D level during pregnancy and the frequency of recurrent preeclampsia (PE).

Objectives: The aim of the current study was to determine the effect of vitamin D supplement on reducing the probability of recurrent preeclampsia in pregnant women with history of preeclampsia.

Patients and Methods: The study population included 50 women having a history of preeclampsia in previous pregnancies. They were referred to the obstetrical clinic in Diarb Negm Centeral Hospital in Diarb Negm City, for prenatal care. Women were classified into two groups, the first one (I) received 25-hydroxy vitamin D supplements and the other (II) received placebo. **Results:** Eight patients had pre-eclampsia in group II (34.8%) while in group I only 4 patients had preeclampsia (16%) (p=0.133). There were no significant statistical differences between the two groups according to pre-eclampsia incidence. The mean vitamin D level was 25.72 ± 7.69 and 28.33 ± 7.40 among patients without and with preeclampsia respectively. (p=0.309) there were no significant relation between the preeclampsia incidence and vitamin D level.

Conclusion: vitamin D supplement may not have a role in prevention of preeclampsia recurrence.

Keywords: Preeclampsia, Vitamin D, Eclampsia.

INTRODUCTION

Hypertensive disorders of pregnancy are among the major complications that account for approximately 14% of maternal mortality [(1,2)] and these include gestational hypertension, preeclampsia (PE), and eclampsia. Blood pressure greater than 140/90 mmHg on two consecutive occasions ≥ 6 h apart occurring after 20 weeks of pregnancy is defined as pregnancy induced hypertension with an incidence of approximately 10% of all pregnancies worldwide [(2)]. Hypertension and proteinuria (protein in urine ≥ 0.3 g/24 h (1+ dipstick) on two occasions ≥ 6 h apart) or edema is considered to be Pre-eclampsia (PE) [(3,4)]. It is a significant contributor for morbidity and mortality and complicates 2% to 8% of pregnancies [(5)]. If the disorder is diagnosed between 20 to 34 weeks gestation it is named early onset severe PE (EOSPE) which is usually associated with a 20-fold increased risk for maternal mortality compared to PE after 34 weeks gestation [(6)] called late onset severe PE (LOSPE). Eclampsia, which is the occurrence of unexplained seizures [(7)] can affect pregnant women who show signs of pregnancy induced hypertension or PE. Vitamin D deficiency has been associated with PE [(8)]. The mechanism by which vitamin D deficiency affect preeclampsia is not clearly understood, nevertheless, some theories have been developed. Pro-inflammatory responses modulation and decreasing oxidative stress in PE, promoting angiogenesis through VEGF and gene modulation, and decreasing blood pressure through the renin-angiotensin system (RAS) are among these theories [(9,10)].

The aim of the current study was to determine the effect of vitamin D supplement on reducing the probability of recurrent preeclampsia in pregnant women with history of preeclampsia.

PATIENTS AND METHODS

This randomized controlled clinical trial study included a total of 50 women having a history of preeclampsia in previous pregnancies. They were referred to the obstetrical clinic in Diarb Negm Centeral Hospital in Diarb Negm City, for prenatal care. **Approval of the ethical committee of Al-Azhar University and a written informed consent from all the subjects were obtained.** This study was conducted between January 2018, and January 2019.

25-hydroxy vitamin D plasma level was measured and the concentration equal or higher than 25 ng/ml (i.e., normal range) was the inclusion criterion. The exclusion criteria were chronic hypertension before pregnancy, immunologic diseases such as lupus, concurrent renal, pulmonary and cardiac diseases, immigration or leaving location of study, and lack of confidence in patient's cooperation to complete study.

The pockets of placebo and drug were assigned randomly and neither physician nor patients knew about administration of drug or placebo.

Blood samples of all patients were taken after 12 hours of fasting to analyze level of vitamin D according to Liebermann–Burchard method.

The patients in the intervention group received a 50000 IU pearl vitamin D3 once every two weeks while subjects in the control group was administered placebo.

Statistics

Through SPSS software (version 16), independent t-test of normal quantitative variables was conducted for both independent groups. In addition, chi-square

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test was conducted for comparison of nominal variables of the two groups. Controlling other factors, logistic regression was done to compare development of preeclampsia in both groups.

RESULTS

The demographic data of the two studied groups is illustrated in table (1). The mean age (years) was 29.52 years ± 3.75 years and 30.72 years ± 3.48 years for group I and II respectively; (p=0.247) while the mean gestational age (weeks) was 12.64 ± 2.12 and 12.48 ± 1.92 respectively; (p=0.781) and the mean BMI (kg/m2) was 28.65 ± 2.14 and 28.57 ± 1.88 respectively; (p=0.889). There were no significant statistical differences between the two studied groups as regards to demographic data.

Table (2) portrays the differences between the two groups as regards to gravidity and abortion. Most of patients in group I were gravid 3 (44.0%) and most of patients in group II were gravid 4 and 2 (24.0%) while the least number of patients were gravid 4 in group I (8.0%%) and gravid 3 in group II (20.0%). With respect to abortion, only 2 patients had abortion, and both were in group II. There were no significant statistical differences between the two groups according to gravidity or abortion.

The mean systolic blood pressure was 118.0 mmHg ± 5.92 mmHg and 119.7 mmHg ± 5.68 mmHg for group I and II respectively (p=0.300) while the mean diastolic pressure was 80.96 mmHg ± 3.76 and 80.16 mmHg ± 3.93 respectively (p=0.446). There were no significant statistical differences between the two studied groups according to BP. The mean 25-hydroxy vitamin D plasma concentration was 26.72 ng/ml ± 7.31 and 26.40 ng/ml ± 7.88 for group I and II respectively (p=0.882). There were no significant statistical differences between the two groups as regards to vitamin D level.

Eight patients had pre-eclampsia in group II (34.8%) while in group I only 4 patients had pre eclampsia (16%) (p=0.133). There were no significant statistical differences between the two groups according to preeclampsia incidence. The mean GA at delivery was 38.48 ± 0.96 and 38.17 ± 1.03 for group I and group II respectively (p=0.268). Number of NVD was 9 in group I and 11 in group II, nevertheless, the number CS was higher namely 16 in group I and 12 in group II; (p=0.406). There were no significant statistical differences between the two groups according to GA at delivery or mode of delivery.

Table (7) illustrates the relation between the preeclampsia incidence and demographic data. There were no significant relations between the incidence of preeclampsia and age; (p=0.964), Gestational age; (p=0968) or BMI; (p=0.818).

The highest incidence of preeclampsia was among patients who were gravid 3 followed by patients gravid 2 and the least was patients who gravid 5. No significant relation was found also between preclampsa incidence and gravidity; (p=0.186)

The mean systolic blood pressure was 118.58 ± 4.66 among patients who had preeclampsia and 118.72 ± 6.14 in patients with no preeclampsia (p=0.943) while the mean diastolic BP was 80.53 ± 3.87 and 81.25 ± 3.84 in patients without and with preeclampsia respectively; (p=0.578). There were no significant relation between preeclampsia incidence and blood pressure. Table (10) illustrates the relation between preeclampsia incidence and vitamin D level. The mean vitamin D level was 25.72 ± 7.69 and 28.33 ± 7.40 among patients without and with preeclampsia respectively; (p=0.309). There were no significant relation between the preeclampsia incidence and vitamin D level. There was a border line significance between the incidence of preeclampsia and mode of delivery as patients with preeclampsia were more likely to have NVD (66.7%), however, no significant relation between incidence of preeclampsia and GA at delivery was found; (p=0.172).

Table (1): Comparison between the two studied groups according to demographic data

	Group I (n = 25)	Group II (n = 25)	T	p
Age (years)				
Min. – Max.	24.0 – 35.0	25.0 – 35.0		
Mean ± SD.	29.52 ± 3.75	30.72 ± 3.48	1.172	0.247
Median	31.0	32.0		
Gestational age (weeks)				
Min. – Max.	10.0 – 16.0	10.0 – 16.0		
Mean ± SD.	12.64 ± 2.12	12.48 ± 1.92	0.280	0.781
Median	12.0	13.0		
BMI (kg/m2)				
Min. – Max.	25.60 – 32.0	25.60 – 31.50		
Mean ± SD.	28.65 ± 2.14	28.57 ± 1.88	0.140	0.889
Median	28.90	28.20		

t: Student t-test, p: p value for comparing between the two studied groups

Table (2): Comparison between the two studied groups according to obstetric data

	Group I (n = 25)		Group II (n = 25)		Test of Sig.	p
	No.	%	No.	%		
Gravidity	3.0(2.0 – 5.0)		4.0(2.0 – 5.0)		U=247.50	0.191
2	7	28.0	6	24.0		
3	11	44.0	5	20.0	χ^2=	^{MC}p=
4	2	8.0	6	24.0	4.872	0.186
5	5	20.0	8	32.0		
Abortion						
No	25	100.0	23	92.0	χ^2=2.083	^{FE}p=
	0	0.0	2	8.0		0.490

χ^2: **Chi square test** MC: **Monte Carlo** **FE: Fisher Exact**
U: Mann Whitney test
p: p value for comparing between the two studied groups

Table (3): Comparison between the two studied groups according to blood pressure

Blood pressure on admission (mmHg)	Group I (n = 25)	Group II (n = 25)	t	p
Systolic				
Min. – Max.	110.0 – 130.0	110.0 – 130.0		
Mean ± SD.	118.0 ± 5.92	119.7 ± 5.68	1.049	0.300
Median	119.0	119.0		
Diastolic				
Min. – Max.	75.0 – 87.0	75.0 – 88.0		
Mean ± SD.	80.96 ± 3.76	80.16 ± 3.93	0.735	0.466
Median	80.0	79.0		

t: Student t-test
p: p value for comparing between the two studied groups

Table (4): Comparison between the two studied groups according to 25-hydroxy vitamin D

	Group I (n = 25)	Group II (n = 25)	t	p
25-hydroxy vitamin D (μg/dl)				
Min. – Max.	15.0 – 40.0	14.0 – 40.0		
Mean ± SD.	26.72 ± 7.31	26.40 ± 7.88	0.149	0.882
Median	25.0	25.0		

t: Student t-test
p: p value for comparing between the two studied groups

Table (5): Comparison between the two studied groups according to preeclampsia

	Group I (n = 25)		Group II (n = 25)		χ^2	p
	No.	%	No.	%		
Pre eclampsia						
No	21	84.0	15	65.2	2.254	0.133
Yes	4	16.0	8	34.8		

χ^2: **Chi square test**
p: p value for comparing between the two studied groups

Table (6): Comparison between the two studied groups according to GA at delivery and mode of delivery

	Group I (n = 25)		Group II (n = 25)		Test of Sig.	p
	No.	%	No.	%		
GA at delivery						
Min. – Max.	37.0 – 40.0		37.0 – 40.0		U= 236.00	0.268
Mean ± SD.	38.48 ± 0.96		38.17 ± 1.03			
Median	38.0		38.0			
Mode of delivery						
NVD	9	36.0	11	47.8	χ^2= 0.689	0.406
	16	64.0	12	52.2		

χ^2: **Chi square test** **U: Mann Whitney test**
p: p value for comparing between the two studied groups

Table (7): Relation between preeclampsia with demographic data

	Preeclampsia		t	p
	No (n = 36)	Yes (n = 12)		
Age				
Min. – Max.	24.0 – 35.0	24.0 – 34.0		
Mean ± SD.	29.97 ± 3.67	29.92 ± 3.63	0.046	0.964
Median	31.0	31.50		
Gestational age				
Min. – Max.	10.0 – 16.0	10.0 – 15.0		
Mean ± SD.	12.61 ± 2.07	12.58 ± 1.98	0.041	0.968
Median	12.50	12.50		
BMI				
Min. – Max.	25.60 – 32.0	25.60 – 31.30		
Mean ± SD.	28.71 ± 2.08	28.56 ± 1.82	0.231	0.818
Median	28.85	28.0		

t: Student t-test
p: p value for comparing between the two studied groups

Table (8): Relation between preeclampsia with obstetric data

	Preeclampsia				Test of Sig.	p
	No (n = 36)		Yes (n = 12)			
	No.	%	No.	%		
Gravidity	3.0(2.0 – 5.0)		3.0(2.0 – 5.0)		U=162.5	0.186
2	9	25.0	4	33.3		
3	10	27.8	5	41.7		
4	6	16.7	2	16.7	χ^2= 2.683	^{MC}p= 0.465
5	11	30.6	1	8.3		
Abortion						
Yes	0	0.0	0	0.0	-	-
No	36	100.0	12	100.0		

χ^2: **Chi square test** MC: **Monte Carlo**
U: Mann Whitney test
p: p value for comparing between the two studied groups

Table (9): Relation between pre eclampsia with blood pressure

Blood pressure on admission (mmHg)	Pre eclampsia		t	p
	No (n = 36)	Yes (n = 12)		
Systolic				
Min. – Max.	110.0 – 130.0	110.0 – 127.0		
Mean ± SD.	118.72 ± 6.14	118.58 ± 4.66	0.072	0.943
Median	119.0	119.50		
Diastolic				
Min. – Max.	75.0 – 87.0	76.0 – 88.0		
Mean ± SD.	80.53 ± 3.87	81.25 ± 3.84	0.561	0.578
Median	80.0	82.0		

t: Student t-test

p: p value for comparing between the two studied groups

Table (10): Relation between pre eclampsia with blood pressure hydroxy vitamin D

	Pre eclampsia		t	p
	No (n = 36)	Yes (n = 12)		
Hydroxy Vitamin D				
Min. – Max.	14.0 – 40.0	16.0 – 39.0		
Mean ± SD.	25.72 ± 7.69	28.33 ± 7.40	1.028	0.309
Median	25.0	26.0		

t: Student t-test

p: p value for comparing between the two studied groups

Table (11): Relation between pre eclampsia with GA at delivery and mode of delivery

	Pre eclampsia				Test of Sig.	p
	No (n = 36)		Yes (n = 12)			
	No.	%	No.	%		
Mode of delivery						
NVD	12	33.3	8	66.7	χ^2= 4.114*	0.043*
C.S	24	66.7	4	33.3		
GA at delivery						
Min – Max	37.0 – 40.0		37.0 – 40.0		U= 161.0	0.172
Mean ± SD	38.44 ± 1.0		38.0 ± 0.95			
Median	38.0		38.0			

χ^2: **Chi square test** **U: Mann Whitney test**

p: p value for comparing between the two studied groups

DISCUSSION

Diabetes, chronic hypertension before pregnancy, chronic kidney diseases, nulliparity, twin or multiple pregnancy are factors contributing to preeclampsia. Preeclampsia in one pregnancy does not usually predict the occurrence of preeclampsia in subsequent pregnancies[11]. Low birth weight and small for gestational age infants, as well an increased risk of maternal comorbidities can be contributed low levels of Vit D [12] Many clinical studies tried to establish an association between vitamin D levels and adverse pregnancy outcomes such as preeclampsia, gestational diabetes, and low birth weight, preterm labor, and caesarean delivery have conflicting results. In the current study we aimed to test this hypothesis and provide some evidence for further studying [13].

The biggest finding of the current study is that there was no significant relation between the vitamin D level and preeclampsia incidence. Furthermore, patients without vitamin D supplements had a higher incidence of preeclampsia, however this difference was not statistically significant.

This finding was in complete accordance with the previous meta analysis which was published in 2017 [14]. They conducted a literature search using MEDLINE electronic databases (via PubMed) to identify published studies until February 2015. A total of 33 studies were extracted for further review. The reviewed studies included 3 cross-sectional studies, 20 case control studies, 2 retrospective cohort studies, 6 prospective cohort studies and 2 randomized controlled trials. They concluded that included clinical trials did not show an independent effect of vitamin D supplementation in preventing PE; however, issues with dose, timing, and duration of supplementation have not been completely addressed.

This was also in agreement with the study of ***Wei et al.*** [15] that aimed to examine the associations of maternal plasma levels of 25-hydroxyvitamin D [25(OH)D] with angiogenesis and endothelial dysfunction indicators: soluble fms-like tyrosine kinase-1 (sFlt-1), placental growth factor (PlGF), intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), and risk of preeclampsia. They found a similar results to our study which was that patients without vitamin D supplementation were more likely to have preeclampsia but the prevalence was not statistically significant.

Shand and his colleagues[16] also agreed to our results. It was conducted on women attending a specialist antenatal clinic because of clinical or biochemical risk factors for pre-eclampsia to determine in a group of pregnant women if vitamin D status, based on serum 25-hydroxyvitamin D (25OHD) concentration, was associated with a subsequent risk of pre-eclampsia or adverse pregnancy outcomes. They found that 78% were vitamin D insufficient (25OHD <75 nmol/l) and 53% were vitamin D deficient (25OHD <50 nmol/l). There was no difference in the rates of pre-eclampsia, gestational hypertension, preterm birth or composite adverse pregnancy outcomes by 25OHD concentration. So, they concluded that Vitamin D deficiency and insufficiency were common in a group of women at high risk of pre-eclampsia; however, it was not associated with subsequent risk of an adverse pregnancy outcome.

Another study that completely agreed to our results was ***Powe et al.*** [17] that was a case control study that aimed to identify the relation between vitamin D and the risk of preeclampsia. They suggested that suggest that first trimester total and free 25-hydroxyvitamin D levels are not independently associated with first trimester blood pressure or subsequent preeclampsia.

Burris and his colleagues [18] examined associations of 25(OH)D levels obtained at 16.4 –36.9 weeks of gestation with hypertensive disorders of pregnancy, including preeclampsia and gestational hypertension. Agreeing to our results, they did not found any association between the vitamin D level and hypertensive co-morbidities related to pregnancy.

Halhali et al. [19] aimed to determine the longitudinal changes of serum 1,25-dihydroxyvitamin D and insulin like growth factor I (IGF-I) levels at 20.7, 27.6, and 35.5 week periods of gestation in 40 pregnant women who remained normotensive and in 10 women who developed preeclampsia. They found that IGF levels but not Vitamin D levels were altered in patients who developed preeclampsia and this was consistent with our findings.

Wetta et al.[20] also was consistent with our results as they found that after adjusting for potential cofounders, neither vitamin D insufficiency nor deficiency was significantly associated with preeclampsia. Likewise, spontaneous preterm birth was not significantly associated with either vitamin D insufficiency or deficiency.

Nevertheless, some studies did disagree with our results. ***Behjat et a.l***[21] was one of the most recent studies that aimed to test the hypotheses concerning the etiology of preeclampsia and its relation to vitamin D deficiency during pregnancy. It was a randomized controlled clinical trial which enrolled 72 patients placed in control group while 70 patients were randomized to the intervention group. The intervention group received a 50000 IU pearl vitamin D3 once every two weeks. The control group was administered placebo. Vitamin D or placebo was given until the 36th week of pregnancy. They found that patients in intervention group have significantly lower (P value = 0.036) probability of preeclampsia than patients in the control group. The risk of preeclampsia for the control group was 1.94 times higher than that for the intervention group which was in consistent with our results.

A case-cohort study of women from 12 different United States (US) sites whose vitamin D levels were measured at ≤26 weeks of gestation showed that 25(OH)D levels greater than 50 nmol/L were associated with a 40% reduction in risk for severe PE (0.65 [95% CI 0.43 to 0.98]), although there was no reduction in absolute and relative risk for the milder clinical subtypes of PE when 25(OH)D levels were greater than 50 nmol/L[22]. In a nested case control study of 274 nulliparous pregnant women conducted previously by the same investigator, there was an OR of 5.0 for PE in early pregnancy (<22 weeks) when maternal 25(OH)D was less than 37.5 nmol/l after controlling for education in addition to the common confounders (95% CI: 1.7–14.1). Interestingly, it was reported that newborns of pre-eclamptic mothers were more than twice as likely to have 25(OH)D levels less than 37.5 nmol/L (aOR = 2.2, 95% CI: 1.2–4.1) than newborns of healthy controls [23]. Another nested case control study of 225 women with singleton pregnancies reported an OR of 5.41 for severe PE among women with mid-gestation vitamin D

deficiency after controlling for multi-parity (95% CI: 2.02–14.52) compared to women with vitamin D levels of at least 75 nmol/L[24]. A larger Canadian case control study reported a more than twice as likely odds for PE in women with 25(OH)D less than 30 nmol/L compared to women with at least 50 nmol/L (95% CI: 1.29–3.83). There was a dose response relationship between maternal 25(OH)D and risk of PE with a threshold of effect at 50 nmol/L [25].

Observational studies which measured vitamin D status after the onset of PE near delivery [26] or at delivery [27] suggest an inverse association with PE. A US case control study reported a trend toward increased risk of PE with 25(OH)D levels less than 15.0 nmol/L (OR = 2.5 [95% CI: 0.89-6.9]) when compared to the controls (chosen randomly from among women who remained normotensive throughout pregnancy, and did not have gestational diabetes mellitus or gave birth to SGA infants). However, this trend was not significant after adjusting for BMI and other covariates. The investigators observed a trend towards increased risk of PE at very low levels of 25(OH)D, suggesting that there may be an association at the low extreme [28]. A recent North Indian case control study of nulliparous women with PE and singleton pregnancies reported serum vitamin D to be significantly lower among PE cases vs. controls at the time of delivery (24.2 +/− 12.4 nmol/L, 36.9 +/− 16.7 nmol/L, respectively; p = 0.0001). Similar vitamin D levels were found in women with mild and severe PE[29]. Two cross-sectional studies report 25(OH)D and 1,25(OH)2D levels to be lower in women with PE in the third trimester. Although these studies find an inverse association between vitamin D levels and PE, this association may be confounded by the gestational age at serum collection. These studies are also limited in that odds ratios are not reported [30].

The lack of an association between 25(OH)D level and preeclampsia may be because we obtained samples later in pregnancy than other studies[25] or because we did not focus on severe preeclampsia which has been more consistently linked to vitamin D status[27,28].

Another side finding of the present study is that preeclampsia was not associated with BMI, age or blood pressure. This was in consistent with previous studies, who found that first trimester blood pressures were higher in women who went on to develop preeclampsia than in women who remained normotensive[28], this also mismatched the previous results which found positive relation between adiposity and preeclampsia as well as an inverse relation between adopisity and vitamin D levels[20,21].

Strengths and limitations

Our study had several strengths including a prospective cohort design, with randomized inclusion of women with history of preeclampsia. Another strength point is that the outcome data were based on vital signs not a clinical diagnosis like some reviewed studies, and finally we had gathered detailed information on multiple potential confounding variables.

The main and may be the only limitation was the relatively small size of studied material which may interfere with the level of the evidence we provide in addition to limited variability in the vitamin d levels and categories of preeclampsia

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