SSRG International Journal of Medical Science
ISSN: 2393–9117 / https://doi.org/10.14445/23939117/IJMS-V11I4P105

Volume 11 Issue 4, 29-36, Jul-Aug 2024

Original Article

Administration of Vitamin D Supplements in the Prevention of Preeclampsia in High-Risk Pregnant Women

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Received: 17 June 2024 Revised: 31 July 2024 Accepted: 20 August 2024 Published: 31 August 2024

Abstract *- Preeclampsia is still one of the most important obstetric complications during pregnancy and still constitutes a substantial proportion of maternal morbidity in the triad responsible for this morbidity, along with sepsis and hemorrhage. Vitamin D has gained great importance in biochemical medicine because it is connected with the pathology of many pregnancy complications, and preeclampsia is one of the most important of these complications. Objective: To determine a relationship between the administration of vitamin D supplements and neutralizing preeclampsia in pregnant women at high risk for developing the syndrome. Materials and methods: Our study is a prospective comparative study that included 300 pregnant women at Tishreen University Hospital between March 2023 and March 2024. In our study, we divided the sample into two groups: the control group, which consisted of 150 pregnant women who were not given the supportive dose of vitamin D studied in our research and the exposure group, which consisted of 150 pregnant women who were given 50000 IU of vitamin D every two weeks from the first trimester of pregnancy until delivery. Pregnant women in both groups were followed throughout the pregnancy, and the fetal growth was assessed by ultrasound while screening for signs of preeclampsia. Results: The sample was controlled for parental age, material status and body mass index BMI. The statistical differences favored the exposure group significantly with regard to the development of proteinuria, high blood pressure and the development of fetal measurements of Abdominal Circumference (AC) and the estimated Fetal Weight (FW) when performing an ultrasound examination. Conclusion: Our study unveiled that the administration of vitamin D supplements prevented pregnant women at high risk of preeclampsia from developing the syndrome, and it is connected with good birth outcomes. The differences were also significant with regard to birth weights and also in favor of the exposure group.*

Keywords *- Vitamin D, Preeclampsia, Proteinuria, Arterial pressure, Intrauterine growth restriction, Birth weight.*

1. Introduction

Preeclampsia is still one of the most important obstetric complications during pregnancy. Still, it constitutes a significant proportion of maternal morbidity in the triad responsible for this morbidity, along with sepsis and hemorrhage.

Vitamin D has been given great importance in biochemical medicine because it is linked to the pathology of many pregnancy complications, and preeclampsia is one of the most important of these complications. This is consistent with our goal in this research, hoping to reduce maternal and fetal morbidity caused by this syndrome that threatens the lives of both the mother and her fetus.

Therefore, over the past decades, especially the past few years, obstetricians have given great attention to vitamin D through many clinical trials and research.

Preeclampsia is the third leading cause of maternal morbidity in the United States, and most cases are due to central nervous system hemorrhage. Rates of hypertensive disorders during pregnancy vary according to the studied population and criteria used in the study. However, we can say that the prevalence rates range from 12-22%, while preeclampsia is observed in approximately 5-8% of all patients. (1)

Preeclampsia is defined as a distinctive pregnancy syndrome that manifests in the second half with elevated blood pressure and proteinuria. (2) The following criteria are essential for diagnosing the syndrome: (3)

- Hypertension: Systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after 20 weeks of gestation in a woman with previously normal blood pressure.

- Hyperproteinuria: Defined as the presence of more than 300 mg of protein in a 24-hour urine collection, usually corresponding to a result of +1 or more on urine dipstick testing.

1.1. The Relationship between Vitamin D and Preeclampsia

Vitamin D deficiency causes immune system suppression and affects placental development, thus interfering with the pathogenesis of preeclampsia.

Additionally, vitamin D deficiency in the syndrome is associated with its interaction with the renin-angiotensin system. However, there is currently no conclusive evidence of this association, making it difficult to provide specific therapeutic recommendations.

In this study, our goal was to determine a relationship between giving vitamin D supplements and protecting pregnant women at high risk for preeclampsia from developing the syndrome.

Two meta-analyses of 31 studies, as well as many studies, found that vitamin D deficiency is associated with the development of preeclampsia. (4,6,7,8,16,17,18,20,21) Also, many studies linked vitamin D supplementation to a significant reduction in the risk of preeclampsia development (especially in high-risk pregnant women). They concluded that vitamin D is a promising candidate for preventing preeclampsia. (5,9,10,11,12,19,22)

It is worth mentioning that according to numerous studies, no relationship was found between vitamin D status and the development of preeclampsia. (13,14,15)

Also, according to many studies, levels of vitamin D during pregnancy are positively associated with the percentile of birth weight. (7,22,23,24). However, results are generally contradicting among studies, with some reporting a positive correlation and others finding no relationship (16).

The World Health Organization guideline (WHO) in 2012 did not recommend vitamin D supplementation during pregnancy to prevent the development of preeclampsia and its complications.

2. Materials and Methods

2.1. Study Inclusion Criteria

- Primigravidas.
- Multiparous women (having more than 4 deliveries).
- Family or personal history of preeclampsia.
- Multiple pregnancies.
- Pregnant women with pre-existing diagnosed internal diseases: diabetes mellitus, hypertension, renal diseases, thyroid disorders, autoimmune diseases.
- Obstetric history in previous pregnancies: delivery of low-birth-weight infants, hypertensive disorders of pregnancy, placental abruption, fetal demise.
- Pregnant women aged 35 years or older.
- Pregnant women with a Body Mass Index (BMI) greater than 25.

2.2. Exclusion Criteria from the Study

- Pregnant women without internal diseases with a singleton pregnancy and without obstetric complications in their history.
- Miscarriage.
- Premature birth for reasons other than preeclampsia.
- Termination of pregnancy for urgent medical reasons not caused by the studied obstetric complications in our research.
- Maternal malnutrition.

2.3. Study Sample

The study covered 300 pregnant women referred to Tishreen University Hospital in Latakia during the study period. Investigators acted in accordance with the inclusion criteria for the study. The sample was divided into two groups: the control group, which consisted of 150 pregnant women who were not given vitamin D except the recommended dose for all pregnant women available in calcium supplements, and the exposure group, which included 150 pregnant women who were given 50,000 IU of vitamin D every two weeks starting from the first trimester and continued throughout the pregnancy until delivery.

The study and procedures were explained to the pregnant women, and then informed consent was obtained and signed in writing by the research participants or their families.

An interrogation was conducted to:

- Take a detailed medical history
- Clinical examination
- Laboratory evaluation

We follow up on the pregnant women with the necessary examinations and analysis at the optimal time for diagnosis throughout the pregnancy.

The values measured in the gestational period between 24 and 28 weeks were adopted when running statistical analysis regarding the detection of the development of intrauterine growth restriction IUGR.

Diastolic arterial pressure values were higher than normal for all the pregnant women who developed hypertension. We can explain this since diastolic pressure expresses increased vascular resistance, and therefore, the diastolic pressure value was used when running the statistical analysis.

2.1. Ethical Consideration

All patients were provided complete and clear informed consent after discussing the study. This study was performed in accordance with the Declaration of Helsinki.

2.4. Statistical Study

Statistical analysis was conducted, and statistical parameters were calculated using the Statistical Package for the Social Sciences (SPSS) software (version 20). A significance level of less than 0.05 (P value < 0.05) will be considered statistically significant.

Descriptive Statistics:
Qualitative variables were analyzed using frequencies and percentages.
Quantitative variables were analyzed using measures of central tendency and measures of dispersion.

Inferential Statistics:
Use paired T-tests and X^2test to study the relationship between two related samples.

3. Results

Our study sample was well-adjusted in terms of maternal age, gestational status, and body mass index.

As shown in Table 1, both groups were approximately similar in terms of maternal age, as the mean age in group (A) was 28.31 years versus 28.01 in group (B) and no substantial difference was found between the two groups; also there was not a significant difference between the two groups regarding the following variables (group A versus group B): Obstetric condition (first pregnancy 58.0% vs 52.7%) and BMI (overweight 58.7% vs. 59.3%).

Table 1. Comparison of maternal characteristics between the two groups

Maternal characteristics	Group		P-value
	(A) Control n=150	(B) Exposure n=150	
Age	28.31	28.01	> 0,05
Primigravidas	58.0%	52.7%	> 0,05
BMI (overweight)	58.7%	59.3%	> 0,05

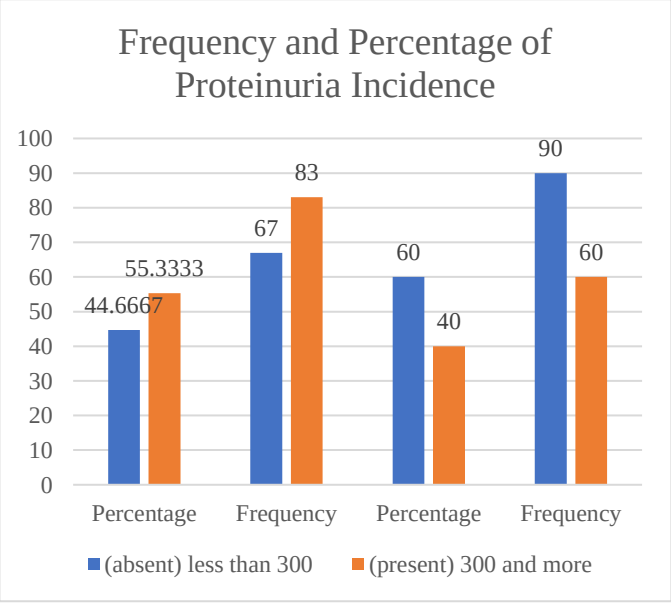
3.1. Results of the Survey on Proteinuria

As shown in Table (2), the presence of clinically significant proteinuria was more frequent in group (A) and statistically significant (60% in group A vs. 44.6% in group B, p= 0.008). The following conclusions were reached:

Table 2. Frequencies and percentage distribution of proteinuria incidence in the exposure and control groups

Proteinuria	Group			
	Control Group (A)		Exposure Group (B)	
	Frequency	Percentage	Frequency	Percentage
Clinically insignificant proteinuria (absent)	60	40	83	55.3333
Clinically significant proteinuria present)	90	60	67	44.6667

The following figure illustrates this:



To determine the significance of the differences between the control and exposure samples, we apply the Chi-square test to compare the frequencies between the two samples. The findings are as follows:

Table 3. Chi-square test for variance in differences between frequencies

Pearson Chi-Square Tests		
proteinuria	**Chi-square**	7.069
	df	1
	Sig.	.008*

Table 3 is evident that the Chi-square statistic is 7.069. Given that the p-value is 0.008, which is much smaller than the significance level adopted in the study (a = 0.05), this confirms that the differences between the exposure and control groups are statistically significant.

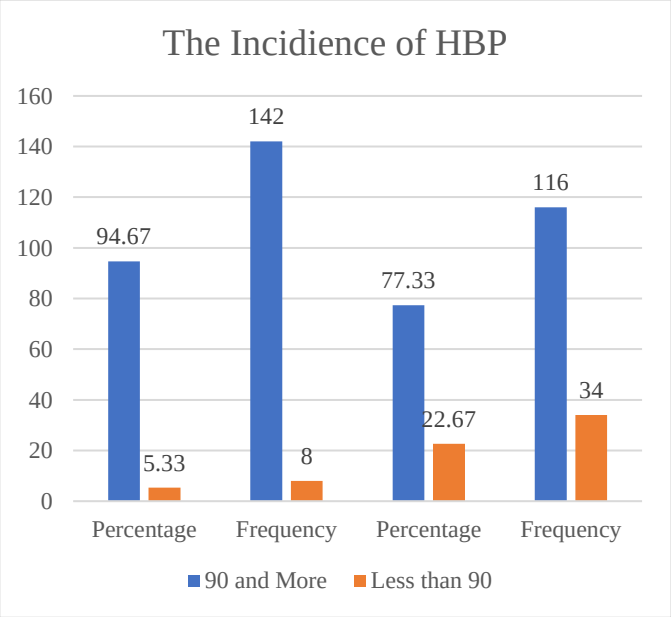
3.2. Survey Results on Arterial Blood Pressure Values

Hypertension (diastolic arterial blood pressure) was more frequent in group (A) and statistically significant (22.6% in group A vs. 5.33% in group B, p= 0.000).

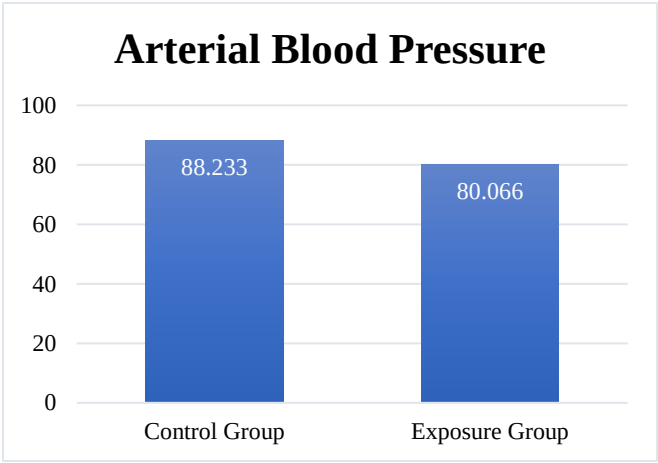
Table 4. Frequency of occurrence of hypertension between the control and exposure groups

Diastolic Blood Pressure	Group			
	Control Group (A)		Exposure Group (B)	
	Occurrence	Percentage	Occurrence	Percentage
90 mmHg or higher	34	22.67	8	5.33
Less than 90 mmHg	116	77.33	142	94.67

The following figure illustrates this:



The following figure illustrates clear differences in diastolic arterial blood pressure values among pregnant women in both the control and exposure groups. According to our results, the average diastolic blood pressure for pregnant women in the control group (A) was 88.23, while the average diastolic blood pressure for pregnant women in the exposure group (B) was (80.06).



The data were subjected to a T-Student test to determine if these differences are statistically significant, and the results are as follows.

Table 5. T- Student test for the significance of differences between the mean arterial blood pressure values in the control and exposure groups

Independent Samples Test							
T-test for the significance of differences between the averages							
Variable	Group	Average	Standard Deviation	T-Test	Degree of Freedom	Probabilities (p-values)	Decision
Arterial Pressure	Exposure	80.0667	7.46326	9.267	298	0.0000	D
	Control	88.2333	7.79642				

These results confirm the significance of the differences between the exposure and control groups.

3.3. Results of the Survey on the Development of Intrauterine Growth Restriction in Embryos IUGR

Also, there were significant differences between the two groups regarding the following variables (group A versus group B): Abdomen Circumference (lower than the estimated age of pregnancy according to LMP) (10% vs 0%, p= 0.000), Estimated Weight (lower than the estimated age of pregnancy according to LMP) (8.67% vs 0%, p= 0.000) and Birth Weight (BW) (2634.67 grams vs 2717.17 grams, p= 0.032).

Table 6 shows that there were /15/ cases in which the abdomen circumference at the time of the examination was lower than the estimated age of pregnancy according to LMP, which constituted 10% of the control group (A), while there was no deficiency in the abdomen circumference of the exposure group embryos, and the improvement rate was 10%.

Table 6. Repetition and percentages of correspondence in control and exposure groups

Group	Fetal measurements, when tested							
	Femur Length		Head Circumference		Abdomen Circumference		Estimated Weight	
	Compatible with the gestational age estimated by the LMP	Less than the gestational age estimated by LMP	Compatible with the gestational age estimated by the LMP	Less than the gestational age estimated by LMP	Compatible with the gestational age estimated by the LMP	Less than the gestational age estimated by LMP	Compatible with the gestational age estimated by the LMP	Less than the gestational age estimated by LMP
Control Group (A)	150	0	150	0	135	15	137	13
Percentage	100%	0%	100%	0%	90%	10%	91.33%	8.67%
Exposure Group(B)	150	0	150	0	150	0	150	0
Percentage	100%	0%	100%	0%	10%	0%	100%	0%

Table 7. Regression variance analysis (explanatory power of the model)

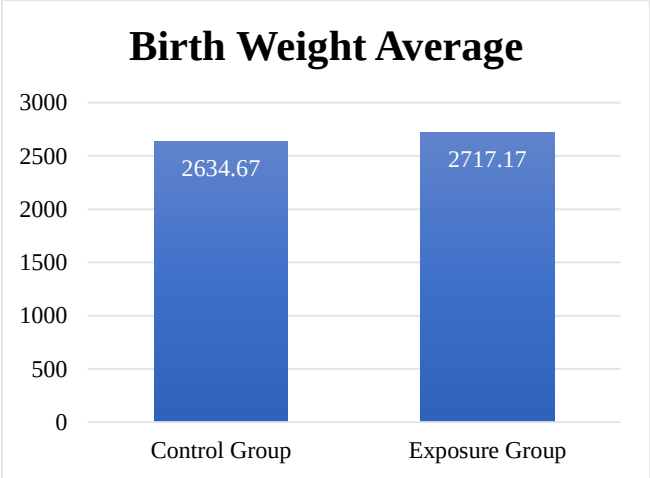
ANOVA[a]						
Model		**Sum of squares**	**Degree of Freedom**	**Squares average**	**F**	**Probabilities value**
1	**regression**	258.757	3	86.252	146.534	.000
	residuals	174.230	296	.589		
	Total	432.987	299			
a. Dependent Variable: Estimated weight b. Predictors: (Constant): Abdomen Circumference, head Circumference, Femur Length						

It also shows that /13/cases in which the estimated weight at ultrasound examination was lower than the age of the pregnancy, which is 8.67% of the control group (A), while no estimated weight deficiency was recorded at the examination from the embryos of the exposure group (B), and an estimated weight increase of 8.67%.

3.4. Regression Variance Analysis to Determine the Explanatory Power of the Model (Model Significance)

Table (7) represents the regression variance analysis table, which allows for the assessment of the overall explanatory power of the model using the F statistic. As evident from the variance analysis table, the high significance of the F test (p-value less than 0.05) confirms the explanatory power of the multiple linear regression model from a statistical perspective. The p-value of the model (F statistic) being smaller than the significance level of 0.05 indicates the model's statistical significance.

The following figure illustrates apparent differences in birth weights between the fetuses in the control and exposure groups. According to Table (6), the results favor the fetuses in the exposure group, with an average birth weight of 2717.17 grams compared to 2634.67 grams for the control group (A), showing a difference of approximately 80 grams.



To determine if these differences are statistically significant, the data were subjected to a T-Student's test to test the significance of these differences. The results are as follows:

Table 8. T-Student's test for the significance of differences between the average birth weights in the control and exposure groups

Independent Samples Test							
T-Student's test for the significance of differences between the averages							
Variable	**Group**	**Average**	**Standard Deviation**	**T-Test**	**Degree of Freedom**	**Probabilities (p-values)**	**Decision**
Birth Weight	**Exposure (B)**	2717.17	353.69	2.153	298	0.032	D
	Control (A)	2634.67	308.39				

This confirms that the differences between the exposure and control groups are statistically significant**.**

Table 9. Comparison of maternal, fetal and neonatal characteristics between the two groups

Maternal characteristics	**Group**		**P-value**
	(A) Control n=150	**(B) Exposure n=150**	
Proteinuria	90 (60%)	67 (44.6%)	0.008
Hypertension (diastolic arterial blood pressure)	34 (22.6%)	8 (5.33%)	0.000
Abdomen Circumference (lower than the estimated age of pregnancy according to LMP)	15 (10%)	0 (0%)	0.000
Estimated Weight (lower than the estimated age of pregnancy according to LMP)	13 (8.67%)	0 (0%)	0.000
Birth Weight (BW)	2634.67 gram	2717.17 gram	0.032

4. Discussion

This study was conducted on 300 pregnant women with risk factors for developing preeclampsia, followed up at Tishreen University Hospital in Latakia. Despite the absence of similar local studies, numerous comparable studies were found in the global medical literature.

Our study sample was well-adjusted in terms of maternal age, gestational status, and body mass index. During the study period, these pregnant women were followed up from the first trimester until delivery. The study sample was divided into two groups: 150 pregnant women receiving 50,000 IU of vitamin D every two weeks and 150 pregnant women who did not receive the studied vitamin D supplementation in our research. The statistical analysis results indicated the following:

- Pregnant women receiving a dose of 50,000 IU of vitamin D showed improvement in proteinuria values and a decrease in the likelihood of developing significant proteinuria during pregnancy, thereby contributing to the reduction of preeclampsia development.
- The administration of 50,000 IU of vitamin D to pregnant women contributed to the improvement of their blood pressure values and the maintenance of stability within normal limits, thus reducing the risk of preeclampsia development.
- Vitamin D played a significant role in the fetal development parameters (femur length, head circumference, abdominal circumference, estimated weight) as assessed by ultrasound examination in the exposure group. Vitamin D supplementation led to improved fetal growth during pregnancy and reduced the risk of intrauterine growth restriction, with statistically significant differences observed between the control and exposure groups.
- Ultrasound examinations showed that both head circumference (BPD) and Femur Length (FL) measurements were consistent with gestational age estimated by the Last Menstrual Period (LMP) in both study groups.

Additionally, during ultrasound examinations, fetal abdominal circumference growth among pregnant women receiving

vitamin D supplementation matched the gestational age estimated by the Last Menstrual Period (LMP) in all women. There was an improvement in these values compared to those in the control group, with an increase of 10%. Moreover, the estimated weight was within the normal range for gestational age in all pregnant women in the exposure group, indicating an improvement in weight compared to the control group by 8.67%.

There were differences between the exposure and control groups regarding fetal growth, specifically birth weight. These differences were statistically significant in favor of the exposure group, indicating that vitamin D supplementation contributed to increased fetal growth in terms of birth weight.

Our results approximated the results of other researchers (5,9,10,11,12,19,22); our study agreed with previous studies regarding the presence of a proven positive effect of supporting high-risk preeclampsia with vitamin D, with variation in improvement of the percentage of hyperproteinuria – high arterial pressure – development of fetal measurements, the most important of which are abdominal circumference and estimated weight during the fetal ultrasound examination. The statistical differences for the variables studied were significant in most of these studies.

5. Conclusion

We recommend administering a supplemental dose of 50,000 IU of vitamin D every two weeks to all high-risk pregnant women for the development of preeclampsia, starting from the first trimester until the completion of pregnancy and delivery.

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