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

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Abstract

Introduction: Preeclampsia is a pregnancy-specific syndrome which could affect almost the whole body organs. There are different assumptions concerning reasons behind preeclampsia one of which is concerned with deficiency of vitamin D in pregnancy cases.

Method and Materials: The present study is a randomized controlled clinical trial which aims to determine the effect of vitamin D supplement on reducing probability of recurrent preeclampsia in pregnant women with history of preeclampsia. After satisfaction of inclusion and exclusion, simple randomization and blinding were done concurrently. In this regard, 140 pockets of drug and placebo were randomly (by using table of random numbers) offered and neither physician nor patients know about administration of drug or placebo to patients.

After inclusion in the present study, blood samples of all patients were taken to analyze level of vitamin D. After 12 hours of fasting, level of vitamin D was determined through Liberman-buchard method and in a laboratory. Since date of pregnancy diagnosis, the intervention group received a 50000 IU pearl vitamin D3 once every two weeks. The control group was administered placebo drug up 36^{th} week of pregnancy. Identification of patients with preeclampsia was done through clinical examination and review of laboratory results (e.g. blood pressure of 90/140 mm Hg or higher in sitting position) and proteinuria of higher than +1 were considered as outcome of the present study.

Results: Total number of study participants was 142 individuals who had satisfied inclusion criteria. 72 patients were placed in control group while 70 patients were classified into intervention group. The final outcome of present study was comparing incurrence of preeclampsia in intervention group and control group. The patients in intervention group has significantly lower (p-value=0.036) probability of preeclampsia than patients in control group.

One could state, with confidence interval of 95 percent, risk of preeclampsia for control group was 1.94 times higher than that for intervention group (2.01, 3.71). The intended intervention (i.e. prescription of vitamin D) has a protective effect against recurrent preeclampsia.

Conclusion: Vitamin D deficiency is highly prevalent in all parts of the world. Pregnant women and neonates are highly vulnerable to vitamin D deficiency. Vitamin D supplementation therapy in pregnancy can help in reducing the incidence of gestational hypertension/ preeclampsia.

Keywords: Preeclampsia, Vitamin D Supplement, pregnancy

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

Introduction: Preeclampsia is pregnancy-specific syndrome, characterized by high blood pressure induced and proteinuria after 20 weeks gestation. It complicates 2-8% of all pregnancies, accounts for 25% of all maternal deaths, and perinatal morbidity and mortality. Although preeclampsia is something more than simple gestational hypertension with proteinuria, development of proteinuria is still one of significant and objective diagnostic measures of this disorder. Proteinuria is defined as excretion of more than 300mg of protein in 24-hour urine, protein-creatinine ratio of 0.3 or higher in urine samples or consistent amount of protein (i.e. 30mg per liter) in randomly taken samples of urine (i.e. +1 result on dipstick)(1).

Disorders of calcium metabolism, including hypocalciuria and low vitamin D level, have been consistently described, during clinical disease in pregnancy women who later developed preeclampsia (2-4).

The factors contributing to preeclampsia are diabetes, chronic hypertension before pregnancy, chronic kidney diseases, nulliparity, twin or multiple pregnancy, family history of preeclampsia or eclampsia, obesity, immune disorders and a history of preeclampsia, and eclampsia of the person herself. Of course, incidence of preeclampsia in one pregnancy does not necessarily signify preeclampsia in consequent pregnancies (considering its underlying factors that have not still be determined confidently). However, its initial development will add to its probability in consequent pregnancies.

Vitamin D is especially important during pregnancy as low maternal vitamin D stores may contribute to problems such as low birth weight and small for gestational age babies besides an increased risk of maternal co morbidities(5).

Vitamin D deficiency is a world-wide epidemic, with a prevalence that ranges from 18% to 84% depending upon the country of residence, ethnicity and local clothing customs and dietary intake (6,7). Clinical studies establishing an association between vitamin D levels and adverse pregnancy outcomes such as preeclampsia, gestational diabetes, low birth, preterm labour and caesarean delivery have conflicting results(8).

Previous studies have confirmed that low level of vitamin D disrupts the balance between Th1 and Th2 and contributes to over expression of Th1 cytokines. The latter event affects immunological tolerance of embryo implantation. The studies suggest that deficiency of vitamin D could be associated with higher expression of Th1 which is observed in cases of preeclampsia (9).

There are different assumptions concerning reasons behind preeclampsia one of which is concerned with deficiency of vitamin D in pregnancy cases. In the present study, vitamin D supplement was administered to pregnant women with one record of preeclampsia in previous pregnancies. Considering the fact that one of the reasons behind development of preeclampsia in pregnant women is increased requirement of vitamin D during pregnancy, the increased need is satisfied by prescribing vitamin D supplement so as examine its role in prevention from preeclampsia.

Method and Materials: The present study is a randomized controlled clinical trial which aims to determine the effect of vitamin D supplement on reducing probability of recurrent preeclampsia in pregnant women with history of preeclampsia.

The statistical population included female were referred of obstetrical clinic in Besat Hospital of Sanandaj city who were receiving pre-pregnancy care and had a history of preeclampsia in their previous pregnancies. In the case of willingness to participate in the present study, they were given agreement forms to fill in and their blood levels of vitamin D3 were analyzed by sending a blood sample to laboratory. If a participant's level of 25-hydroxy vitamin D was equal with or higher than 25 ng/ml(i.e. normal range), she would be included in the study (inclusion criteria). Risk of chronic hypertension before pregnancy, concurrent renal, pulmonary and cardiac diseases, immunologic diseases such as Lupus, lack of confidence in patient's cooperation to the end of study, immigration or leaving location of study were regarded as exclusion criteria.

After satisfaction of inclusion and exclusion criteria, simple randomization and blinding were done concurrently. In this regard, 140 pockets of drug and placebo were randomly (by using table of random numbers) offered and neither physician nor patients know about administration of drug or placebo to patients.

After inclusion in the present study, blood samples of all patients were taken to analyze level of vitamin D. After 12 hours of fasting, level of vitamin D was determined through Liberman-buchard method and in a laboratory. Since date of pregnancy diagnosis, the intervention group received a 50000 IU pearl vitamin D3 once every two weeks. The control group was administered placebo drug up 36^{th} week of pregnancy. The drug and placebo were both purchased from Zahravi Pharmaceutical Company.

Identification of patients with preeclampsia was done through clinical examination and review of laboratory results (e.g. blood pressure of 90/140 mm Hg or higher in sitting position) and proteinuria of higher than +1 were considered as outcome of the present study. Blood pressures of patients were measured every two weeks while pearl vitamin D was still being prescribed. If blood pressure was equal with or higher than 90/140 mm Hg in sitting position, urine test was requested. In the case of observing normal blood pressure, the patient was examined again two weeks later. In second and third three months, depending on intervals, treatments were conducted every one week and then every two weeks, Routine tests were done for those mothers who were exposed to high risk of preeclampsia.

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

Total number of study participants was 142 individuals who had satisfied inclusion criteria. The participants were randomly placed into two groups (i.e. intervention group and control group). Consequently, 72 patients were placed in control group while 70 patients were classified into intervention group. The baseline characteristics of both groups are shown in Table 1.

Table 1-Baseline Characteristics of Participants per Group

Baseline Characteristic Variables	**Intervention Group (n=70)**	**Control Group (n=72)**	**Meaningful level (Pvalue)**
Age (Mean± SD)	32.04±5.901	29.77±5.21	0.017
Number of Previous Pregnancies (Mean± SD)	3.04±1.13	2.92±.900	0.463
Weeks of Pregnancy (Mean± SD)	14.39±3.12	14.39±2.69	0.997
Systolic Blood Pressure (mm Hg; Mean± SD)	115.87±14.52	114.51±7.27	0.028
Diastolic Blood Pressure (mm Hg; Mean± SD)	74.28±4.95	74.31±6.40	0.975
Uterine Height✳ cm (Mean± SD)	14.58±3.50	14.28±3.26	0.597
24-h Proteinuria (mg/cc; Mean± SD)	132.22/1844.91±61.447	154.94/1958.53±53.376	0.023
BMI <18.5 kg/m^2 (n(%))	1(1.4%)	1(1.4%)	0.267
BMI,18.5–24.9kg/m^2 (n(%))	23(32.9%)	14(19.4%)	0.267
BMI,25.0–29.9kg/m^2 (n(%))	32(45.7%)	35(49.3%)	0.267
BMI≥30.0kg/m^2 (n(%))	13(18.6%)	21(29.6%)	0.267

✳:Uterine height is measured as the distance between the midpoint of the pubic bone and highest peak of the uterus in cm, while the pregnant woman after voiding, was lying in the supine position.

In intervention group, all patients had singleton pregnancy while two cases of control group (2.8 percent) had twin pregnancy. Two cases (2.9 percent) from intervention group and 4 cases (5.6 percent) of control group had married for second time and the rest of participants had married once.

In regard to residence location, 20 individuals (28.6 percent) of intervention group were living in villages and remaining 50 individuals (71.4 percent) of intervention group were urban residents. In association with control group, one could state that 23 individuals (31.9 percent) were rural residents and the remaining 49 individuals (68.1 percent) were urban residents. Positive previous records of diabetes were found for 4 patients (5.6 percent) of intervention group while there was no such a record for intervention group. No record of previous cardiac diseases, gestational hypertension, high blood pressure, thyroid disease, immunological disorders, lung diseases and renal disorders was found for patients of the two groups. None of the participants had a history of consuming drug and vitamin D supplement. Family history of preeclampsia was negative for all patients. In regard to fetal health, 48 patients (72.7 percent) of intervention group and 62 patients (87.5 percent) of control group were screened.

None of the cases did not mention side effects. Cooperation and compliance of all participants to get the vitamin D supplement, was fine.

The comparison of termination of pregnancy by normal vaginal delivery or caesarean section or abortion is shown in Table 2.

Table. 2-Comparison of Pregnancy Types and End of Pregnancy for Intervention and Control Groups

Group	**Termination of pregnancy**			pvalue
	NVD	C/S	Abortion	
Control group	43(59.7%)	27(37.5%)	2(2.8%)	0.88
Intervention group	33(47.1%)	37(52.9%)	0(0%)	
Total	76(53.5%)	64(45.1%)	2(1.4%)	

P value based on **fisher exact tests**.
P value <0.05 is statistically significant

The final outcome of present study was comparing incurrence of preeclampsia in intervention group and control group. The patients in intervention group has significantly lower (p-value=0.036) probability of preeclampsia than patients in control group. The relevant results are shown in table 3.

Table. 3-Comparison of Preeclampsia Incidence between Intervention Group and Control Group

Group	**termination of pregnancy (non Preeclampsia)**	**Termination of pregnancy (Preeclampsia)**	**Pvalue**
Control group	50(69.4%)	22(30.6%)	0.036
Intervention group	59(84.3%)	11(15.7%)	
Total	109(76.8%)	33(23.2%)	

P-value based on Chi-Square Tests

P-value <0.05 is statistically significant

One could state, with confidence interval of 95 percent, risk of preeclampsia for control group was 1.94 times higher than that for intervention group (1.02, 3.71). The intended intervention (i.e. prescription of vitamin D) has a protective effect against recurrent preeclampsia.

Discussion: The results of present study suggest that prescription of vitamin D supplement in first trimester of pregnancy contributes to preventing from recurrence of preeclampsia (P-value=0.036). In regard to effects of vitamin D on preeclampsia, evidence suggests that vitamin D metabolism is correlated with preeclampsia.

There are many biologically acceptable mechanisms by which the maternal vitamin D status can change the risk of preeclampsia. Preeclampsia is a two-stage disorder (10). In the stage 1 placental perfusion is reduced, usually it could be happened following an abnormal implantation. The poor blood flow of placenta is proposed to produce materials that, in a favorable maternal environment, initiate the ensuing multisystem squeal (stage 2). These pathophysiological

changes are proposed to be subsequently abnormal endothelial function, which is a part of a generalized increase in the inflammatory activation that characterizes natural pregnancy (11). The active form of vitamin D, 1,25-dihydroxyvitamin D_3, has been demonstrated to adjust the transcription and function of genes associated with normal implantation, placental invasion, and angiogenesis (12). Further, abnormal implantation is proposed to be mediated at least in part by an inconvenient immune response between pregnant mother and baby. The immunomodulatory properties of 1,25-dihydroxyvitamin D_3 may be relevant in this consideration (13). Maternal vitamin D deficiency may also prepare to the increased inflammatory reaction (14). Remarkably, vascular function and structure including vascular compliance, elasticity, and intima media thickness are more suitable among pregnant women supplemented with vitamin D (15). Vitamin D deficiency could also elevate blood pressure (16). Finally, the proteinuria of preeclampsia seems to be mediated by renal vascular endothelial growth factor (VEGF). 1,25-Dihydroxyvitamin D_3 has been shown to regulate angiogenic processes through straight effects on VEGF gene transcription (17).

Low level of vitamin D in non-pregnant women was related to increased inflammation. Low levels of vitamin D in blood, as measured by 25-hydroxyvitamin D [25(OH) D], are common in pregnant mothers. Meta-analysis of observational studies has showed positive relations between vitamin D level and adverse pregnancy outcomes such as preeclampsia, gestational diabetes mellitus, preterm birth and small-for-gestational age (18).

Plenty of studies have showed, when 25-hyrdoxyvitamin D levels are low, the risk of preeclampsia is increased (19). It may prevent from preeclampsia during influences on immune modulation and vascular function. The National Institutes of Health has funded many ongoing projects and clinical trials to determine the extent to which vitamin D supplementation during pregnancy may prevent pregnancy complications and adverse outcomes (20).Vitamin D deficiency in pregnant women is associated with a 5-fold increase in the odds of preeclampsia compared with non preeclamptic controls (21).

The prevalence of low vitamin D level status was very high with more than 3 quarters (78%) of all participants having a serum 25(OH)D level<30 ng/ml, in pregnant mothers receiving care at the Dhaka Medical College Hospital with preeclampsia (n=33), eclampsia (n=79), and normal pregnancy (controls, n=76). The mean serum 25(OH)D level was 24.86 ng/ml in controls, 23.96

ng/ml in pre-eclamptic women, and 21.56 ng/ml in eclampsia women. Cosidering to those women who had a serum 25(OH)D level of ≥30 ng/ml, the odds ratio (95% CI) of developing preeclampsia and eclampsia in pregnant women with vitamin D insufficiency were 3.9 (95% CI=1.18-12.87) and 5.14 (95% CI=1.98-13.37), respectively (adjusting for age, BMI and duration of pregnancy) (22).

A recent meta-analysis has demonstrated a strong relation between vitamin D and pre-eclampsia across various study types, suggested that, vitamin D could act as a preventative factor from pre-eclampsia. The studies included in this review show conflicting results about the association of vitamin D levels and the risk of preeclampsia. However, in this review more than half of the studies reported a positive association between Vitamin D deficiency and Preeclampsia. There is a specific need for further trials and other robust studies to identify the effect of Vitamin D on preeclampsia(23).

Two clinical trials show a potential role of vitamin D in the prevention of preeclampsia, although neither of those treated with vitamin D supplements alone. In an uncontrolled trial, supplementation with a multivitamin/mineral supplement and halibut liver oil (containing 900 IU/d vitamin D) provided at 20 wk gestation reduced the odds of preeclampsia by 32% (95% CI, 11–47%) (24). Marya *et al.* (25) randomized 400 women at 20–24 wk gestation to vitamin D (1200 IU/d) and calcium (375 mg/d) supplements or no treatment and found a significant reduction in blood pressure ($P < 0.001$) and a nonsignificant reduction in the incidence of preeclampsia in the treated group compared with the untreated (6 *vs.* 9%). In a cohort study, investigators establish that regular supplementation with vitamin D in the first year of life reduced the risk of preeclampsia by half in the daughter's first pregnancy (26).

There was a extremely significant association between the vitamin D levels and duration of sun exposure ($p < 0.05$). The quantum of UV-B rays (290 to 310 nm) received by a person on exposed body surface distinguishes the amount of vitamin D synthesized by the skin (27). Pregnant women and non pregnant women receive very less amount of sunlight especially in parts of Middle East due traditional norms and customs and governmental rules.

The vitamin D dose recommended to pregnant women is colechalciferol 100 000 UI in the seventh month of pregnancy, or calcifediol supplementation of 400 to 800 UI / day. This could prevent children rickets. It also raise long-term changes in bone growth.

1000 UI daily is recommended to the third trimester also appear acceptable within normal maternal and cord blood and even reduces the risk of neonatal hypocalcaemia, with a frequency 5.1% to 1.9% (28).

A randomized controlled U.S. study compared the daily administration of 400, 2000 or 4000 UI of vitamin D3 in pregnant women between 12 and 16 weeks of pregnancy until child birth. Supplementation with vitamin D to 4,000 UI daily is more effective to maintain plasma levels of 25 (OH) D sufficient (>32 ng/ml), irrespective of ethnicity, and without any toxicity (29).

Women with a previous history of pregnancy complicated by preeclampsia have an increased risk for recurrence in following pregnancies. In women who have a severe preeclampsia history in an initial pregnancy, recurrence rates for any type of preeclampsia are very great, approaching 50% in many studies. Significant maternal and fetal complications are more common in recurrent preeclampsia compared with an initial episode. For women who have a complicated pregnancy history of preeclampsia, a systematic evaluation for underlying risk factors could identify a specific pathway proportionate for a specific intervention(30).

Vitamin D is a promising candidate for preeclampsia prevention, and there is an urgent need for well controlled randomized trials to test its effectiveness and safety.

Conclusion: Vitamin D deficiency is highly prevalent in all parts of the world. Pregnant women and neonates are highly vulnerable to vitamin D deficiency.

Vitamin D supplementation therapy in pregnancy can help in reducing the incidence of gestational hypertension/ preeclampsia.

Registration: This study has been registered in Iranian registry of clinical trials site (IRCT) with ID number: IRCT2017010131695N1 **.**

Conflict of Interest: The authors announce that there was no conflict of interest between different individuals and organizations involved in the study.

Limitations: During the present study, some participating patients were discouraged of participation in the study by non-medical people and even some of clinical colleagues on alleged safety issues. However, a second briefing meeting to address the concerns and encourage the

patients to continue their participation. Because gynecologist might recommend patients to stop taking drugs, a briefing meeting was held with some major gynecologists to address some misinterpretations in regard to prescription of the drug.

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