The Use of Vitamin D Supplement in Prevention of Preterm Labor

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Abstract

In modern obstetrics, preterm labor remain a major problem. Infection during pregnancy is the commonest cause. Since that vitamin D has been shown to act as an anti-inflammatory& immune modulator in the placenta so it could be used for preterm labor prevention. In pregnant ladies, higher levels of vitamin D were considerably associated with a lower risk of infection, preterm labor & preterm birth.

Vitamin D supplementation during pregnancy has long been a matter of concern, but updated researches showed that even a high dose supplementation in healthy pregnant ladies was safe & effective.

The aim of the study
1. Determine the relationship between maternal 25-hydroxyvitamin D & the risk of spontaneous preterm birth before 37 completed weeks.
2. Determine whether 4000 IU/day of vitamin D supplement prevent preterm birth in those with threatened preterm labor (premature uterine contraction) & those with early preterm labor (in the latent phase). The study was carried:
1. at Babylon Teaching hospital for Maternity & pediatric in the obstetrical word.
2. out patient clinic.

A randomized clinical trial was done on (109) patients from 1st of June 2014 to 1st of Jan 2015. Their gestational age was of (24-<37 completed weeks). Blood samples were taken from all of them for measurement of vitamin D level. Those patients then divided into 2 groups: 1. study group consist of 69 pregnant women who were presented with either threatened preterm labor or early preterm labor (at the latent phase) were given a supplement of vitamin D (4000 IU) daily till term & follow them for their progress of labor. 2. Control group of 40 pregnant women at the same gestational age of the study group but without preterm labor. (just assess vitamin D level).

There was a significant association between low vitamin D level & preterm labor as preterm labor was inversely associated with pre delivery serum level. The study found that (61.1%) of patients with threatened preterm labor & (75.8%) of patients with early preterm labor are presented with low vitamin D level, while (62.5%) of control group presented with sufficient vitamin D level. There was (36.4%) reduction in proportion of early preterm labor as well as (83.3%) reduction in proportion of threatened preterm labor (premature uterine contraction) after vitamin D supplementation.

Conclusion:
Vitamin D supplement has a role in prevention of preterm labor especially in those with low pre delivery serum level & those with threatened preterm labor.

Key words: vitamin D, preterm labor, pregnancy.

الخلاصة


تضمنت الدراسة 109 امرأة حامل ما بين (24-37 أسبوع) حيث تم قياس نسبة فيتامين D من خلال اخذ عينة دم من كل امرأة ثم تقسيمهم الى مجموعتين: المجموعة الأولى (اوضاع حامل واللوائي )تبين تقلصات رحميةFlash و ونسبة فيتامين D ونسبة بالجموعة الثانية وهى مجموعة السيطرة التي تم توصيفها (40 امرأة حامل بدون تقلصات رحمية ومن ثم تم إعطاء 4000 وحدة من فيتامين D (حبة يومية) لكل امرأة لديها تقلصات رحمية أو ولادة مبكرة (المجموعة الأولى) ومن ثم متابعة المرضى لدراي تمام الإدراك فيما إذا توقفت التقلصات أو ولادة المبكرة ام لا.

نتائج الدراسة:
البيانات المتاحة لكل المجموعتين تتضمن العمر عدد الولادات الكلي لدى المريضة، العمر (فترة) الحمل، نسبة فيتامين D في الجسم، معدل وزن المريضة، حالة التدخين، المستوى المهني.

نتائج الدراسة: اثبتت النتائج اغلبية النساء كان معدل الولادات معدل اعمارهن يتراوح ما بين 16-41 سنة (الحمل والانجاب) كما انهن ذات حمل مترتب وجنين حي ولم يكن من المتختر. 

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Introduction

Preterm delivery is the most common problem in recent obstetrics (Hyagriv, 2007). The second leading cause of death among children under the age of 5 years is the preterm labor of less than 37 weeks gestational age; as during the 2010, there were more than 1 million infants who were born preterm had died worldwide. Also the preterm delivery is a cause of neonatal mortality worldwide & has been associated with long term health care problems.

Preterm infants who live are at greater risk of chronic lung disease, deafness, blindness, learning & cognitive disability, and other visual impairment. (March of Diamas, 2012)

Identification of likely targets for preterm birth prevention is a public health urgency (Washington, 2006)

Intrauterine bacterial infection during pregnancy is a highest risk factor for early preterm delivery (Klebanoff, 2005)

The most common cause of preterm birth is premature rupture of membrane due to urinary or vaginal infection (25.9%), other commonest causes of preterm birth are antepartum hemorrhage (10.8%), multiple gestation (4.1%), polyhydramnia (3.4%), malpresentation (14.4%), maternal disease (22%), extreme of age (13.5%) (Singh Uma, 2007)

Deficiency of maternal vitamin D has been linked recently to pregnancy complications like pre eclampsia, fetal growth restriction & preterm birth (Aghajafari, 2013)

Also in the pathogenesis of preterm birth; established physiological pathway including inflammation, immunomodulation & transcription of genes involved in placental function were affected by vitamin D (Lin N, 2009)

During pregnancy, vitamin D supplement is not safe for mother and baby only, but also can prevent infections and preterm delivery according to results of a randomized controlled study which is presented at the Pediatric Academic Societies (PAS). annual meeting in Vancouver, British Columbia& Canada.

Vitamin 25(OH) D is a steroid vitamin from a group of fat soluble pro-hormones which is either taken orally or formed in the skin photo-chemically, the most important component are D2&D3 (Christopher, 2011)
In the liver, cholecalciferol (vitamin D3) is transformed to calcidiol & ergocalciferol (vitamin D2) is converted to 25-hydroxyergocalciferol. These two particular vitamin D metabolites are measured in serum to determine a person's vitamin D status. (Hollis, 1996).

Vitamin D has been long known to be involved in bone metabolism, but recently, it has been concerned in physiologic processes such as vascular health, metabolism, immune function, and placental function. (Urrutia, 2012)

At present vitamin D deficiency or insufficiency is an international pandemic affecting about one billion of all ages and ethnic groups. Developing nations (such as Bangladesh, India, Iran, Pakistan) as well as developed one (such as Australia, Finland, Japan and USA) report a great prevalence of vitamin D deficiency during pregnancy. Maternal vitamin D deficiency in early pregnancy has been related to elevated risk of preterm labor, preterm birth, increased risk of Gestational D.M, low birth weight & also cesarean sections. (Mazhar, 2012)

During pregnancy, the mother needs to make sure that she gets the recommended quantity of vitamin D for her own wellbeing & the baby healthy development. (Chrstopher, 011)

The normal range of 25-hydroxyl vitamin D (an easily measured metabolite) is 50-80 nmol/l for a healthy adult. (Maren, 2015)

The recommended dose range is between 200-400 INU/day, this intake of vitamin D is enough to achieve peak blood concentration of 80nmol/l or 32ng/ml. (Mohamed, 1999)

While Boyles showed in his study that no evidence of harm in women who took 4000 IU of the vitamin daily in their second and third trimesters, but they had half the rate of pregnancy-related complications as women who took 400 IU of vitamin D every day. (Salynn, 2010)

Vitamin D biology is necessary for a healthy host native immune response. vitamin D deficiency weaken toll-like receptor induction of the antimicrobial peptide cathelicidin from systemic macrophage, and Since that the Toll -like receptors are main initiators of host innate system immune defense against microbial pathogens, so vitamin D deficiency enhances susceptibility to infection (Liu, 2006)

Vitamin D is necessary for own personal health as vitamin D act as a natural antibiotic so it induces bacterial fighting protein in the placenta. Recently an extensive research is supporting it's role in healthy cell division, immune function& bone health as it is necessary for absorption & metabolism of calcium & phosphorus. Many factors affect the ability to make & absorb vitamin D like age, sun exposure, season , skin pigmentation, obesity, race& having a healthy intestine with optimal absorption capacity in addition to adequate intake of vitamin D in food like egg yolk, salamon & cod liver oil. (Christopher, 2011)

Preterm delivery is a specific problem for African-American mothers compared to Caucasian mothers, they are twofold as likely to deliver early because people with darker skin filter more sunlight that is required for the conversion of the inactive pro-vitamin to the active form of the vitamin; therefore, adding vitamin D in the diet of African mothers may be helpful (Mortin, 2015)

Moreover, as the vitamin D in blood increases among the nonwhite mothers, the incidence of spontaneous preterm delivery decrease as much as 30%. (Bodner, 2013)
Aim of the study

1. Determine the association between maternal 25-hydroxyvitamin D & the risk of spontaneous preterm delivery before 37 completed weeks.

2. Determine whether 4000 IU/ day of vitamin D supplement prevent preterm birth in those with threatened preterm labor (premature uterine contraction) or early preterm labor.

Patients & Method

Study design & setting

A randomized clinical trial was conducted at Babylon Teaching Hospital for maternity & pediatric & out-patient clinic throughout the period of 1st of June 2014-1st of Jan 2015. The study involves (109) pregnant women, blood sample was taken from all patients for vitamin D level assessment & then divided into 2 groups: 1. study group include 69 pregnant women present with either threatened preterm labor or early preterm labor at gestational age of 24-<37 completed weeks & received vitamin D supplement either as a one capsule of 4000 IU once /day or 2000 IU twice daily & most of them followed after 1 week of the treatment up to 2 months as some patients get benefit as their contraction subsided while other need re-admission to the hospital as they are not responding to treatment & pass in to preterm labor. also those patient in the study group received the usual treatment of tocolytics, dexamethasone & antibiotics. 2. control group consist of 40 pregnant women at the same gestational age but without preterm labor. (assess vitamin D level but not receive any treatment)

Inclusion criteria

1. gestational age 24-<37 weeks
2. singleton pregnancy
3. live born baby.

Exclusion criteria

- Term pregnancy
- previous scar
- twin pregnancy
- intrauterine death
- placenta previa
- premature rupture of membrane
- any medical disorder as hypertension or diabetes.
- induced labor

A verbal informed consent was obtained at enrollment. Data on maternal characteristic, medical & obstetric history was recorded, gestational age, maternal age, parity, smoking, occupation & BMI kg/m² was also obtained.

Gestational age was based on the mother report of the last menstrual period or 1st trimester US, as threatened preterm labor means women who experience symptoms of preterm labor but no cervical changes & more than 70% of them do not progress to active labor (E. Tsol, 2003) while preterm labor means delivery after viability but before 37 weeks gestational age as well as latent phase means that the cervix is thick & 3 cm dilatation or less (Stuart, 2000).

Collection of samples

By using disposable syringes, blood samples (8-10ml) were collected from those patients.

Blood samples were collected in tubes lacking anticoagulants & were left at room temperatures for 15 minutes to clot after that, the blood samples were centrifuged at 3000xg for 15 minutes.
Then by using eppendorf tubes, the serum is isolated and divided into aliquots and kept at (- 20°c) until time of use.

**Quantification of 25-hydroxyvitamin D concentration:**
Assessment of non-fasting serum level of 25(OH)D was done by Enzyme Immunoassay competition method with final fluorescent detection (ELFA) by using VIDASTM 25-Hydroxy Vitamin D total (VITD) kit from biomerieux SA France. (Holick, 2009).

**Range of values:** <20ng/ml: deficient, 20-29ng/ml : insufficient & 30-100ng/ml : sufficient (Holick,2011)

**Data Analysis:** Statistical analysis was carried out using SPSS version 17. Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). ANOVA test was used to compare means among three groups or more. Pearson’s chi square (X²) and Fisher-exact test were used to find the association between categorical variables. A p-value of ≤ 0.05 was considered as significant.

**Results**

1. **Demographic characteristic of both groups(n:109)**

   **Table 1:** shows mean differences of age (years) and BMI (kg/m²) including (threatened preterm delivery, early preterm labor and control group). There were no significant differences between means of age and BMI in both groups.

   **Table 1: The mean differences of age and BMI by study group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study group</th>
<th>No</th>
<th>Mean ± SD</th>
<th>F-test</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Early preterm delivery</td>
<td>33</td>
<td>25.75 ± 5.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Threatened preterm labor</td>
<td>36</td>
<td>24.36 ± 6.02</td>
<td>1.83</td>
<td>0.165</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>40</td>
<td>27.10 ± 6.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Early preterm delivery</td>
<td>33</td>
<td>25.65 ± 5.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Threatened preterm labor</td>
<td>36</td>
<td>25.70 ± 4.77</td>
<td>0.017</td>
<td>0.984</td>
</tr>
<tr>
<td></td>
<td>Control group</td>
<td>40</td>
<td>25.49 ± 5.48</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **The Association between Study Group and Study Variables**

   **Table 2:** shows the association between study group including (early preterm labor, threatened preterm labor and control group) and study variables including (smoking habit, occupation, parity). There was no significant association between study group and all study variables.
Table 2: Association between study group and study variables

<table>
<thead>
<tr>
<th>Study variables</th>
<th>Early preterm labour (%)</th>
<th>Threatened preterm labor (%)</th>
<th>Control (%)</th>
<th>$\chi^2$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking habit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>1 (3.0)</td>
<td>2 (5.6)</td>
<td>2 (5.0)</td>
<td>1.000 a</td>
<td></td>
</tr>
<tr>
<td>Non smoker</td>
<td>32 (97.0)</td>
<td>34 (94.4)</td>
<td>38 (95.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td>0.638</td>
<td>0.72</td>
</tr>
<tr>
<td>House wife</td>
<td>19 (57.6)</td>
<td>24 (66.7)</td>
<td>24 (60.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>14 (42.4)</td>
<td>12 (33.3)</td>
<td>16 (40.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primigravida</td>
<td>12 (36.4)</td>
<td>13 (36.1)</td>
<td>12 (30.0)</td>
<td>0.96 a</td>
<td></td>
</tr>
<tr>
<td>Multipara</td>
<td>19 (57.5)</td>
<td>20 (55.6)</td>
<td>24 (60.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grand multipara</td>
<td>2 (6.1)</td>
<td>3 (8.3)</td>
<td>4 (10.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a : Fisher – exact test.

3. The Distribution of Patients with Threatened Preterm Labour and Those with early preterm labour According to Vitamin D level

The study found that (19.4%) of patients with threatened preterm labor & (27.3%) of patients with early preterm labor were presented with vitamin D deficiency as shown by figure -1-.

![Figure 1: Distribution of patients with threatened preterm labor and early preterm labor according to vitamin D level](image)

4. The Association between Study Group and Vitamin D level:  
Table 3: shows the association between study group including (early preterm delivery, threatened preterm labor and control group) and vitamin D level. There was significant association between study group and vitamin D level. The study found that (75.8%) of patients with early preterm labor were presented with either deficiency or
insufficient vitamin D level (low vitamin D level) as well as (61.1%) of patients with threatened preterm labor were presented with either deficiency or insufficient vitamin D level, while (62.5%) of control group were presented with sufficient vitamin D level.

**Table 3:** Association between study group and study variables

<table>
<thead>
<tr>
<th>Vitamin D level</th>
<th>Study Group</th>
<th></th>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early preterm labour</td>
<td>Threatened preterm labor</td>
<td>Control</td>
<td>(\chi^2)</td>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficiency</td>
<td>9 (27.3)</td>
<td>7 (19.4)</td>
<td>8 (20.0)</td>
<td>12.65</td>
<td>0.013*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insufficient</td>
<td>16 (48.5)</td>
<td>15 (41.7)</td>
<td>7 (17.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sufficient</td>
<td>8 (24.2)</td>
<td>14 (38.9)</td>
<td>25 (62.5)</td>
<td></td>
<td></td>
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</tbody>
</table>

*p value \(\leq 0.05\) was significant

5. The Effect of Vitamin D Supplementation on early Preterm Labor (PTL) (n=33):

There was (36.4%) reduction in proportion of early preterm labor after vitamin D supplementation as shown by figure-2-.

![Figure 2: Effect of vitamin D supplementation in early preterm labor](image)

Total no. of early preterm labor 33(100%) before supplement & % of PTL prevented after supplement is 36.4%
6. The Effect of Vitamin D Supplementation on threatened preterm labor (n=36)

There was (83.3%) reduction in proportion of threatened preterm labor after vitamin D supplementation as shown in figure -3-.

![Figure 3: Effect of vitamin D supplementation on threatened preterm labor](image)

Total no. of threatened preterm labor 36(100%) before supplement & % of TPTL prevented after supplement is 83.3%

Discussion

Since It is doubtful that prenatal vitamins provide sufficient vitamin D, so numerous health organizations recommended vitamin D therapy during conception& lactation as it improves vitamin D status of the mother throughout pregnancy & can prevent many adverse maternal outcomes (Carol, 2015)

Our study shows that taking supplement of 4000 IU of vitamin D daily was associated with reduction in early preterm labor & threatened preterm labor by 36.4% & 83.3% respectively as shown in figure 2&3.

This result agrees with Boyles who showed in his study that no evidence of harm in women who took 4000 IU of the vitamin D/day in their second and third trimesters, but they had declined the rate of pregnancy-related complications by half than those women who took 400 IU of vitamin D every day. (Sallynn,2010)

Researches on maternal vitamin D status and hazard of preterm labour are limited. However in the only randomized controlled trial of vitamin D therapy that evaluated preterm birth, there was no influence of daily doses of 2000 IU or 4000 IU of vitamin D3 on the rate of preterm delivery before 37 weeks. (Hollis, 2013) Which disagree with our results.

While in the reviewing thousands of pregnancies over a 10 years' time, it was found that vitamin D deficiency enhances the risk of preterm birth by 1.5 times. (Kathleen,2015)

In this study , we compare the level of vitamin D in those with preterm labor & those without preterm labor & we found that those with preterm labor (whether...
thwarted or early) had low level of vitamin D (75.85% & (61.1%) respectively compared to 37.5% in control group (those without preterm labor) as shown in table -3.

Also in this study, the percentage of low vitamin D level (<30ng/ml) in early preterm labor or threatened preterm labor were (75.85%) & (61.1%) respectively as shown in figure -2.

This is concomitant with a study which shows that preterm delivery without pre eclampsia was more public among ladies with concentration of 25 (OH) D level of < 80 nmol/l compared with concentration of 80 nmol/l or more at the end of gestation (17.2 vs 10.6 : p=0.07) (Holiss, 2011)

There is no universally accepted definition of vitamin D deficit, so we studied 25(OH)D continuously & by using various cut point. These differences in serum level values of vitamin D might be due to laboratory or racial or social factors as in our study, the values were <20ng/ml considered deficient, 20-29ng/ml : insufficient, 30-100ng/ml: sufficient (Holick. 2011)

Another study shows that women with serum vitamin D of <50nmol/l, the incidence of preterm labor of <37 weeks was 11.3% compared to an incidence of 7.3% in women with serum level of >75nmol/l (P<0.05 for all) after controlling of known confounders, including maternal race, BMI, season & smoking status, the incidence of preterm birth decreases as vitamin D level increases to 90nmol/l, & these results agree with our study. (Lisa, 2014)

A remarkable risk factor for early preterm delivery is resulting from intrauterine microbial infection particularly the initial ones that have the highest risk to the newborn. (Klebanoff, 2005)

As the infections are difficult to identify and treat, most pregnant ladies will experience no symptoms until they pass into early labor. Hewison, M. investigate whether vitamin D can encourage the immune system to fight off infections and aid to stop premature labor & his data suggest that vitamin D fulfills a unique role in pregnancy by both increasing bacterial killing and suppressing associated inflammation. Uterine inflammation, which frequently results from infection, seems to play a significant role in prompting preterm delivery. If the results of his study are proved, his ultimate goal is to develop cheap and actual vitamin D therapeutic regimens that could help prevent infection-related preterm births (Mortin, 2015)

Vitamin D biology is necessary for a healthy- host native immune response. vitamin D insufficiency weaken toll-like receptor induction of the antimicrobial peptide cathelicidin from systemic macrophage, and Since that the Toll -like receptors are important initiators of host innate system immune defense against microbial pathogens, so vitamin D insufficiency increases susceptibility to infection. (Lisa, 2006)

In addition, vitamin D attenuate myometrial contractile associated protein expression in response to labor provocation in human myometrial model system. As vitamin D elicits anti-inflammatory response, that inhibit contractile associated protein & modulate Toll-like receptor in human myometrial cell. (Thotac, 2013)

Bodnar stated that vitamin D deficiency in the mother throughout pregnancy is associated with an enhanced hazard of bacterial vaginosis. In one, a statistically significant inverse relationship between serum 25-hydroxyvitamin D [25(OH)D] and bacterial vaginosis was found for black ladies but not white ones. (Bodnar, 2009)

In this study we found that there was a reduction in proportion of early preterm labor by (36.4%) after vitamin D supplementation as shown by figure -2.

Beside, we found that there is 83.3% reduction in threatened preterm labor after vitamin D supplement & this is statistically significant as shown in figure-3.
This reduction might be due to the role of vitamin D as antimicrobial, anti-inflammatory, inhibitor of contractile associated protein & immune modulator (Liu, 2006) & this is concomitant with Bodner M. who stated in his study that: among nonwhite mothers, serum 25(OH)D levels of 30-50, 50-75 & >75nmol/l were associated with drops of 1.0-1.6 cases of preterm labor per 100 live births & 20-30% declines in the risk of spontaneous preterm labor in comparison with 25(OH)D levels less than 30mmol/l after adjustment for pre-pregnancy body mass index, season, & other cofounders (Bodner, 2013)

Conclusion
Vitamin D supplementation could be an easy way in reducing the high rates of preterm birth.

Recommendation
1. Further study is recommended to ascertain the relationship between vitamin D deficiency & inflammatory placental changes caused by vitamin D deficiency.
2. Further research to confirm the association between vitamin D level & preterm labor through studying the level of 25(OH)D in preterm & term cord blood to see such association with prematurity.
3. Optimum 25-hydroxy vitamin D levels during conception is needed to be identified & requested as routine investigation during antenatal care visit.
4. Information on the most effective and safe dosage, the timing of initiation of vitamin D therapy, the most therapeutic regimen (daily, intermittent or single doses), and the outcome of vitamin D when combined with other vitamins and minerals are also needed for policy-making.

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