Vitamin D Supplementation at time of Pregnancy Diagnosis may ameliorate Maternal Pregnancy-associated Complications
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Abstract

Objectives: This placebo-controlled study aimed to evaluate the effect of prophylactic vitamin D supplemental therapy (VD-ST) started at time of pregnancy diagnosis on pregnancy-induced morbidities.

Patients & Methods: 200 newly pregnant women were randomly divided into control group received placebo and study group received VD-ST as a daily oral dose of 1000 IU started at time of pregnancy diagnosis after giving blood sample for estimation of baseline levels of 25-hydroxy VD (25-OHVD). During follow-up visits, all pregnant women were clinically evaluated for development of disturbed pregnancy, or manifestations suggestive of development of pregnancy-induced anemia (PIA), gestational diabetes mellitus (GDM) or Pre-eclampsia (PE). Study outcomes included incidence of pregnancy-associated morbidities and its relation to receiving VD-ST regarding incidence and severity

Results: 17 women had sufficient, 43 women had insufficient and 140 women had deficient 25-OHVD levels. Total number of women had disturbed pregnancy, PIA, PE and GDM was significantly lower among women of study versus control group. Extent of decrease in hemoglobin concentration at 3rd trimester was significantly lower with VD-ST compared to placebo. VD-ST reduced the frequency of PE, severe and early PE by 2.1, 3.5 and 6 folds, respectively and reduced the frequency of GDM by 2.4 folds in comparison to placebo. There was negative significant correlation between receiving VD-ST and incidence of PIA, GDM and PE (p=0.016, 0.023 and 0.032, respectively).

Conclusion: Hypovitaminosis D (HVD) is prevalent among apparently healthy newly pregnant women. HVD is positively related to the majority of pregnancy-associated morbidities. VD-ST appeared to minimize the insult of HVD on pregnant women concerning both the incidence and severity of morbidities. VD-ST started at time of diagnosis of pregnancy and given in a dose of 1000 IU/day is an appropriate safe prophylactic modality for pregnant woman, irrespective of her baseline serum 25-OHVD.

Keywords: Hypovitaminosis D, Prophylactic vitamin D supplemental therapy, Pregnancy-associated morbidities, Pregnancy outcomes

Introduction

Vitamin D (VD) is an important secosteroid hormone produced on exposure of skin to sunlight through UVR or obtained from diet and dietary supplements. After absorption, VD is carried in blood stream bound to specific binding protein to the liver to be hydroxylated into 25-OHVD and then to the kidneys to undergo another hydroxylation reaction catalyzed by CYP27B1 cytochrome into 1,25-(OH)2-VD (calcitriol), which is the hormonal form and most active VD metabolite.Degradation of calcitriol is dependent
on the expression and activity of CYP24A1 cytochrome \(^5\). Expression and activity of CYP27B1 and CYP24A1 cytochromes are regulated in a tissue-specific manner \(^6\).

Calcitriol mediates its biological effects through specific nuclear receptor, Vitamin D receptors (VDR), which is found in many non-skeletal tissues \(^6\), so binding of VD to its receptor can produce number of desired biological effects via different mechanisms and, therefore, contributes to the improvement of human health \(^7\).

Accumulating evidence suggests that VD metabolic pathways may play a key role in the development of gynecological/obstetric diseases \(^8\). During the first gestational weeks calcitriol synthesis is increased by >2-3 folds \(^9\) and VDR and its metabolic enzymes are expressed at placenta and decidua, indicating the potential role of VD in immunomodulation processes at the maternal-fetal interface \(^10\). Breakdown in VD homeostasis may underlie infertility, or development of preeclampsia (PE) and gestational diabetes mellitus (GDM) \(^11\).

Hypovitaminosis D (HVD) is a global health issue that had been associated with a myriad of acute and chronic illnesses \(^12\) and during pregnancy is directly linked with severe maternal, fetal and neonatal complications \(^2\).

Multiple-micronutrient deficiencies often coexist among women of reproductive age and are exacerbated in pregnancy due to the increased demands of the developing fetus, leading to potentially adverse effects on the mother and baby \(^13\). Supplementation with VD alone during pregnancy probably reduces the risk of PE, GDM, and low birthweight and may reduce the risk of severe postpartum hemorrhage \(^14\). However, dosing regimen is still under research, one study found supplementation with 2,000-IU/d was more effective than 1,000 IU/d in increasing circulating VD levels, ameliorating pro-inflammatory markers and improving neonatal outcomes \(^15\), while another reported that supplementation with doses higher than the recommended may make little or no difference to the risk of PE, preterm birth (PTB) and low birthweight \(^16\).

**Hypothesis**

Prophylactic vitamin D supplemental therapy (VD-ST), irrespective of serum 25-OHVD, for pregnant women at time of pregnancy diagnosis may improve pregnancy outcome

**Objectives**

The current placebo-controlled study aimed to evaluate the effect of prophylactic VD-ST on pregnancy-induced morbidities.
Design
Prospective comparative interventional study

Setting
University Hospital & Multiple Private Hospitals, Benha, Egypt

Patients & Methods

This study was started since March 2015 after approval of the study protocol by the Local Ethical Committee and only women who signed written consent to attend follow-up visits and to donate blood sample for assigned investigations were included in the study. All women who attended the Antenatal Outpatient Clinic (OPC) for assurance of being pregnant were eligible for study inclusion. Exclusion criteria included manifest diabetes mellitus, essential hypertension, renal or hepatic diseases, endocrinopathy and obesity defined as body mass index (BMI) ≥ 35 kg/m². Also, women attended the clinic for first time outside the time range for case collection which extended between March and June of each year, were also excluded from the study.

At time of diagnosis of pregnancy (Booking time), women's demographic and anthropometric data and previous clinical and obstetric data were collected. BMI was calculated using the formula: weight (kg)/ height (m²) and patients were classified according to BMI using the World Health Organization ranges as underweight: BMI <18.5 kg/m², normal weight: BMI=18.5-24.9 kg/m², overweight: BMI=25-29.9 kg/m² and obese: BMI ≥30 kg/m² (17). Baseline systolic and diastolic blood pressures (SBP & DBP) were recorded and midstream urine sample was obtained to be check for proteinuria.

At meantime, a random blood samples were obtained under complete aseptic conditions from the antecubital vein and divided into two parts:

A) The first part was put in a tube containing sodium fluoride (2 mg sodium fluoride/ ml blood) to prevent glycolysis. Plasma was separated by centrifugation and used for estimation of fasting blood glucose (FBG) by glucose oxidase method (18) to assure absence of manifest DM.

B) The second part was put in a plane container and left to clot at room temperature for 30 minutes before centrifugation for 20 minutes at 1,000g. Freshly prepared serum was stored at -20°C till estimation of fasting serum 25-OHD levels using an ELISA kit (Cayman Chemical, Ann Arbor, MI, USA) (19). Vitamin D sufficiency status was defined according to 25-OHD concentration as follows: ≥75 nmol/L sufficient level, 50-75 nmol/L insufficient level and <50 nmol/L deficient level. Vitamin D deficiency was categorized as mild, moderate and severe if 25-OHD concentration was 25-50 nmol/L, 12.5-25 nmol/L and <12.5 nmol/L, respectively (20).
All pregnant women were asked to attend the OPC at the start of the 12th, 24th, and 36th GW for follow-up including clinical evaluation, recording of SBP and DBP, fasting and postprandial blood glucose (FBG & PPBG). Also, they were asked to attend the OPC at any time if there are any complaints or manifestations of early pregnancy loss (EPL), premature labor (PML), premature preterm rupture of membrane (PPTRM), or manifestations suggestive of development of GDM or Pre-eclampsia (PE)

**Study grouping**

After fulfilling the inclusion and exclusion criteria, enrolled women were randomly divided using sealed envelopes, prepared by an assistant blinded about the study plan, target for grouping and results of laboratory investigation, and chosen by pregnant women herself into two equal groups:

- Study group included pregnant women who received vitamin D3 supplemental therapy as a daily oral dose of 1000 IU softgels with mail (Sunvite High Potency Vitamin D3 1000 IU; Puritan's Pride, Inc., Oakdale, NY, USA) after giving blood samples, at time of 1st attendance to OPC, till delivery.

- Control group included pregnant women who received placebo and completed their pregnancy without VD-ST.

**Evaluated parameter during follow-up**

1. Gestational hypertension was defined as development of hypertension after the 20th GW in women who were normotensive at time of 1st antenatal visit. PE was diagnosed if SBP was ≥140 mmHg and DBP was ≥90 mmHg with proteinuria (>0.3g/in a 24-h period). PE was considered severe if SBP was >160 mmHg, DBP>110 mmHg, and proteinuria >5 g/in a 24-h period or the development of oliguria, thrombocytopenia, microangiopathic hemolysis, HELLP syndrome and/or neurologic symptoms.

2. GDM was diagnosed according to the criteria of the International Association of Diabetes and Pregnancy Groups for abnormal 75g Oral Glucose Tolerance Test (75-OGTT), as follows: FBG ≥92 mg/dl, 1-h BG ≥180 mg/dl and 2-h BG ≥153 mg/dl.

3. EPL defined as pregnancy loss before the 12th gestational week.

4. Cervical insufficiency (CI) was defined as development of cervical softening, shortening and dilatation between 18 and 22 GW and PTL was defined as any birth before completed 37 GW.

5. PPTRM defined as ruptured membranes before the onset of labor at < 32 weeks of gestation (Early PPTRM) or between 34 weeks and 36 weeks (Late PPTRM).
Study outcomes
1. The incidence of pregnancy-associated morbidities in women of both groups
2. The relation between these frequencies and receiving VD-ST
3. The effect of VD-ST on the frequency and severity of these morbidities

Statistical analysis

Obtained data were presented as mean±SD, numbers and percentages. Results were analyzed using One-way ANOVA Test, Chi-square test (X² test). Possible relationships were investigated using Spearman's linear regression analysis. Statistical analysis was conducted using the IBM SPSS (Version 23, 2015; IBM, South Wacker Drive, Chicago, USA) for Windows statistical package. P value <0.05 was considered statistically significant.

Results

Throughout duration of study 237 women were eligible for evaluation; 37 were excluded and 200 women were randomly divided into two groups. All women continued follow-up and those escaped, missed or had EPL were replaced by another to maintain fixed number per group (Fig. 1).

There were non-significant (p>0.05) differences between women of both groups regarding enrolment data. Only 17 women (8.5%) had sufficient serum 25-OHVD levels, 43 women (21.5%) had insufficient and 140 women (70%) had deficient levels with non-significant differences between women of both groups regarding frequency and levels (Table 1)
Table (1): Enrolment data of women of both groups determined at time of pregnancy diagnosis (Booking time)

<table>
<thead>
<tr>
<th>Group Data</th>
<th>Control (Placebo; n=100)</th>
<th>Study (VD-ST; n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>27.6±2.7</td>
<td>28±2.5</td>
<td>0.278</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73.8±6.9</td>
<td>73.6±6.8</td>
<td>0.837</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.2±3.2</td>
<td>169.6±3.1</td>
<td>0.372</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>&lt;25 4 (4%) 25-30 27 (27%) &gt;30 69 (69%)</td>
<td>3 (3%) 36 (36%) 61 (61%)</td>
<td>0.382</td>
</tr>
<tr>
<td>Mean</td>
<td>25.6±2.5</td>
<td>25.8±2.4</td>
<td>0.456</td>
</tr>
<tr>
<td>Obstetric data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gravida</td>
<td>2.2±0.8</td>
<td>2.1±0.8</td>
<td>0.371</td>
</tr>
<tr>
<td>Para</td>
<td>1.2±0.8</td>
<td>1.1±0.8</td>
<td>0.378</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>114.7±3.2</td>
<td>113.9±9.3</td>
<td>0.399</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>72.3±3.3</td>
<td>71.9±4.5</td>
<td>0.508</td>
</tr>
<tr>
<td>Lab findings</td>
<td>Hb. conc. (gm/dl)</td>
<td>11.41±0.44</td>
<td>11.38±0.71</td>
</tr>
<tr>
<td>Fasting blood glucose (mg/dl)</td>
<td>96.5±3.8</td>
<td>97.8±6.9</td>
<td>0.111</td>
</tr>
<tr>
<td>Serum 25-OHVD (nmol/L)</td>
<td>Sufficient</td>
<td>Number</td>
<td>6 (6%)</td>
</tr>
<tr>
<td></td>
<td>Level</td>
<td>77.8±1.52</td>
<td>76.5±1.12</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Number</td>
<td>26 (26%)</td>
<td>17 (17%)</td>
</tr>
<tr>
<td></td>
<td>Level</td>
<td>61.8±8.3</td>
<td>60.9±6.5</td>
</tr>
<tr>
<td>Deficient</td>
<td>Number</td>
<td>68 (68%)</td>
<td>72 (72%)</td>
</tr>
<tr>
<td></td>
<td>Level</td>
<td>27.4±8</td>
<td>25.7±7.3</td>
</tr>
<tr>
<td>Total</td>
<td>Level</td>
<td>37.3±20.2</td>
<td>39.3±19.5</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD; numbers & percentages; VD-ST: Vitamin D supplemental therapy, BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; Hb. Conc.: Hemoglobin concentration; 25-OHVD: 25-hydroxy vitamin D; P indicates significance of intergroup difference; P>0.05 indicates non-significant difference.

Three women had early pregnancy loss and were substituted by other pregnant women. Nineteen women (9.5%) had disturbed pregnancy; 9 women, 7 control and 2 study, had premature preterm rupture of membrane with non-significantly (p=0.088) lower incidence among women of study group. Ten women had PTB; 8 in control and 2 in study groups with significantly (p=0.03) lower incidence among women of study group. Total number of women had disturbed pregnancy was significantly (p=0.008) lower among women of study versus control group (Table 2).

At booking time, 102 women had Hb conc. <11 gm/dl; 56 in control and 46 in study groups with non-significant difference between both groups regarding the estimated Hb conc. and the frequency of anemic women. On the other hand, at the 3rd trimester, 151 women had Hb conc. <11 gm/dl with significantly (p=0.0001) higher incidence of anemia at 3rd trimester compared to at booking time. Moreover, at the 3rd trimester, 82 control and 69 study women had anemia with significantly lower (p=0.033) frequency of anemic women among those received VD-ST. Despite of the non-significant difference between Hb conc estimated at the 3rd trimester among women had Hb conc. >11 gm/dl in both groups, the difference among women had Hb conc.
<11gm/dl was significant (p=0.002) in favor of VD-ST compared to placebo. Moreover, the extent of decrease in Hb conc was significantly (p=0.0078) lower with VD-ST compared to placebo (Table 2).

Thirty-one pregnant women (15.5%) developed PE; 21 controls and 10 of study women with significantly (p=0.032) lower frequency of PE among women of study group. Seven women had early and 9 women had severe PE with non-significant differences between both groups. However, VD-ST reduced the frequency of PE, severe and early PE by 2.1, 3.5 and 6 folds, respectively. Twenty-seven (13.5%) women developed GDM; 19 control and 8 study women with significantly (p=0.023) reduced the frequency of GDM among women who received VD-ST by 2.4 folds (Table 2).

There was negative significant correlation between receiving VD-ST and incidence of PE (Rho=-0.152, p=0.032), GDM (Rho=-0.161, p=0.023) and pregnancy-associated anemia (Rho=-0.170, p=0.016).

Table (2): Pregnancy outcomes of women enrolled in both groups

<table>
<thead>
<tr>
<th>Data</th>
<th>Group</th>
<th>Control (Placebo; n=100)</th>
<th>Study group (VD-ST; n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disturbed pregnancy</td>
<td>EPL*</td>
<td>2 (2%)</td>
<td>1 (1%)</td>
<td>0.561</td>
</tr>
<tr>
<td></td>
<td>PPTRM</td>
<td>7 (7%)</td>
<td>2 (2%)</td>
<td>0.088</td>
</tr>
<tr>
<td></td>
<td>PTB</td>
<td>8 (8%)</td>
<td>2 (2%)</td>
<td>0.030</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>15 (15%)</td>
<td>4 (4%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Pregnancy associated anemia</td>
<td>Booking time</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>&lt;11 gm/dl</td>
<td>56 (56%)</td>
<td>46 (40%)</td>
</tr>
<tr>
<td></td>
<td>&gt;11 gm/dl</td>
<td>44 (44%)</td>
<td>54 (60%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level</td>
<td>&lt;11 gm/dl</td>
<td>10.76±0.15</td>
<td>10.67±0.19</td>
</tr>
<tr>
<td></td>
<td>&gt;11 gm/dl</td>
<td>11.64±0.22</td>
<td>11.87±0.48</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>11.41±0.44</td>
<td>11.38±0.71</td>
<td>0.848</td>
</tr>
<tr>
<td></td>
<td>3rd trimester</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>&lt;11 gm/dl</td>
<td>82 (82%)</td>
<td>69 (69%)</td>
</tr>
<tr>
<td></td>
<td>&gt;11 gm/dl</td>
<td>18 (18%)</td>
<td>31 (31%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Level</td>
<td>&lt;11 gm/dl</td>
<td>10.26±0.34</td>
<td>10.57±0.33</td>
</tr>
<tr>
<td></td>
<td>&gt;11 gm/dl</td>
<td>11.37±0.2</td>
<td>11.44±0.36</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>10.7±0.42</td>
<td>10.78±0.69</td>
<td>0.105</td>
</tr>
<tr>
<td></td>
<td>% of decrease</td>
<td>5.35±1.8</td>
<td>6.18±2.55</td>
<td>0.0078</td>
</tr>
<tr>
<td></td>
<td>PE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Frequency</td>
<td>Early PE</td>
<td>6 (82%)</td>
<td>1 (69%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Late PE</td>
<td>15 (82%)</td>
<td>9 (69%)</td>
</tr>
<tr>
<td></td>
<td>According to severity</td>
<td>Mild PE</td>
<td>14 (14%)</td>
<td>8 (8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe PE</td>
<td>7 (7%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>21 (21%)</td>
<td>10 (10%)</td>
<td>0.032</td>
</tr>
<tr>
<td></td>
<td>GDM</td>
<td>19 (19%)</td>
<td>8 (8%)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Data are presented as mean±SD; numbers & percentages; VD-ST: Vitamin D supplemental therapy, EPL: Early pregnancy loss [*excluded]; PPTRM: Premature preterm rupture of membranes; PE: Preeclampsia; GDM: Gestational diabetes mellitus; P indicates significance of intergroup difference; P>0.05 indicates non-significant difference; P<0.05 indicates significant difference.

Discussion

This study targets to evaluate the effect of prophylactic VD-ST initiated at time of pregnancy diagnosis (Booking time) on maternal outcome. Such
rational for institution of VD-ST early in pregnancy coincided with Rostami et al. (31) who found prenatal VD screening and treatment program is effective for detection of VD-deficient women, improving VD levels, and decreasing pregnancy adverse outcomes and with Wheeler et al. (32) who recommended 1st trimester maternal VD screening and supplementation for women at risk of hypovitaminosis D (HVD). Also, Aji et al. (33) found low VD levels were common among pregnant women and stressed that supplemental VD intake is important to meet the recommended dietary level for pregnant women.

The incidence of disturbed pregnancy and PTB among women received VD-ST was significantly lower than among control women who received placebo. These findings are in accordance with Pérez-López et al. (34) who documented that VD-ST during pregnancy was associated with increased circulating 25-OHVD levels, birth weight and length and with Miliku et al. (35) who found low maternal 25-OHVD concentrations are associated with proportional fetal growth restriction and increased risk of PTB. Also, Eremkina et al. (36) out of literature review reported that HVD during pregnancy is associated with higher incidence of spontaneous abortions and PTB and adequate VD supply during pregnancy improves these outcomes. These data may be explained by the findings that altered cord serum VD mediated signaling that may trigger modulation of placental inflammatory responses and eliciting premature activation of spontaneous PTB as evidenced by the downregulated VD signaling markers and the upregulated inflammatory markers in placental tissue of PT born babies (37).

At booking time, 102 women (51%) were anemic with Hb conc <11 gm/dl, such figure for the frequency of anemia among newly pregnant women coincided with the previously reported that the worldwide prevalence of anemia ranged between 20-80% (38), and was 57.7% among Sudanese pregnant women (39), 65-80% of European women of reproductive age (40) and 75% among pregnant Singaporean women (41).

Pregnancy deleteriously affected Hb conc. as evidenced by the significantly higher incidence of anemia and lower Hb conc. at end versus start of pregnancy. However, VD-ST ameliorated this effect where the frequency of anemic women, and the extent of decreased Hb conc were significantly lower in women received VD-ST compared to control women who did not receive ST. Moreover, statistical analyses showed a negative correlation between Hb conc and serum 25-OHVD and between receiving VD-ST and extent of decrease of Hb conc at the 3rd trimester. Similarly, Judistiani et al. (42) found women with insufficient VD had the highest proportion of anemia, while women with normal VD level had the highest proportion of low ferritin level. The effect of VD-ST on women's Hb estimates may be attributed to the effect of administered VD on erythropoietin metabolism (43) or to decreasing hepcidin level with subsequent release of iron from its stores (44) or to the suppression of neonatal IFN-γ production with its hazardous maternal, fetal and neonatal effects (45).
VD-ST reduced the frequency of PE, severe and early PE types by 2.1, 3.5 and 6 folds, respectively with a negative significant correlation between incidence of PE and VD-ST. In line with these findings, Arora et al. (46) reported significant VD deficiency and insufficiency among women developed PE in comparison to normotensive pregnant women and concluded that HVD was associated with PE. In support of the ameliorating effect of VD-ST on frequency and severity of gestational hypertension; Nassar & Badae (47) experimentally found VD-ST decreased systolic blood pressure and proteinuria in deoxycorticosterone rat model of PE. Clinically, Ali et al. (48) reported decreased incidence of PE among screened women for HVD and the received VD-ST decreased incidence of PE down to 1.2% versus 8.6% among women who received no VD-ST. Also, Chrisostomo et al. (49) detected higher prevalence of HVD among PE women and found this association was independent of BMI, maternal age, and pregnancy duration.

These findings could be attributed the previously reported significant association between maternal VD status and placental expression of soluble FMS-like tyrosine kinase 1 (sFlt-1) and vascular endothelial growth factor (VEGF) at mRNA level (50) (Kim et al., 2017). Schulz et al. (51) found maternal circulating 25(OH)D ≥100nmole/L potentially decreases sFlt-1 and VEGF through an impact of maternal VD-ST on its placental gene transcription. Also, Ma et al. (52) found VD-ST downregulates placental sFlt-1 which induced reduced uterine perfusion pressure and alleviates PE through reducing sFlt-1 induced endothelial dysfunction.

Moreover, in vitro studies found physiologic concentrations of VD attenuated and/or reversed the effects of PE fetal serum on endothelial functional properties (53) that reduces the ability of fetal endothelial progenitor cells to incorporate into fetal endothelial cell networks (54); these data appear consistent with lines of evidence that VD has anti-preeclampsia effects (53).

VD-ST also reduced the frequency of GDM significantly in comparison to control women. This result indicated the protective effect of VD-ST against the glucogenic impact of pregnancy. In support of this finding, multiple recent studies assured the relation between HVD and both type-1 (55) and type-2 (56) diabetes mellitus, and documented the protective effect of VD-ST. Concerning GDM, Al-Ajlan et al. (57) detected significantly higher risk of GDM among pregnant women having deficient VD status and Walsh et al. (58) found avoiding maternal HVD since early pregnancy is associated with lower blood glucose in early pregnancy and throughout pregnancy. Also, Yin et al. (59) reported that GDM risk was significantly reduced only in pregnant women with VD level of >50 nmol/L and pregnant women taking VD in a daily dose of 400-600 IU with mean VD concentrations of 50 nmol/L had a lower risk of GDM.

Conclusion

Hypovitaminosis D is prevalent among apparently healthy newly pregnant women. HVD is positively related to the majority of pregnancy-
associated morbidities. VD-ST appeared to minimize the insult of HVD on
pregnant women concerning both the incidence and severity of morbidities.
VD-ST started at time of diagnosis of pregnancy and given in a dose of 1000
IU/day is an appropriate safe prophylactic modality for pregnant woman,
irrespective of her baseline serum 25-OHVD. However, wider scale studies are
mandatory for establishment of such prophylactic therapy regarding timing of
start, dose-adjustment and outcome.

Acknowledgment
I would like to acknowledge Dr Ebrahim Rageh(clinical pathology Banha University)
for doing the laboratory work of this study.

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