ISSN: 2581-3366

Effects of Vitamin D Deficiency on Pregnancy Outcomes Among Iraqi Women in Baghdad – a Clinical Evaluation

Dr. Ibtisam AbdulKareem Idan
M.B.Ch.B. , DOG, Al-Karama Teaching Hospital, Baghdad, Iraq
Contact: 009647813945301

Abstract

Vitamin D deficiency is a significant health problem worldwide, it is a growing health problem among adults and children . In pregnant women Vitamin D deficiency had an increasing concern in several previous studies due to its possible effect on the maternal and fetal outcomes. This study aimed to assess the prevalence and the effect of VD deficiency on the pregnancy outcomes. Hence a total of 314 Iraqi pregnant women at first trimester were enrolled and followed during their gestation until delivery . Vitamin D level and other clinical and laboratory parameters were assessed at first visit. At subsequent visits and follow up the women were assessed clinically to detect any complication or adverse outcome during pregnancy, after birth neonates were clinically examined and all data reported. Data analysis revealed that vitamin D deficiency and insufficiency was highly prevalent among pregnant Iraqi women and associated with more frequent preeclampsia, small for gestational age, low birth weight and preterm birth and the covered style of dressing are associated with higher prevalence of VD deficiency.

Keywords: 25-hydroxyvitamin D; pregnancy outcome; vitamin D deficiency, prevalence

1. Introduction:

1.1.Vitamin D deficiency

Is a common problem in reproductive aged women in worldwide and its prevalence may be increasing (1). The etiology for this increase is likely multifactorial, but due in part to low dietary intake of vitamin D and limited exposure to sunlight. Certain high risk groups for vitamin D deficiency in pregnancy have been identified, including vegetarians, women with limited sun exposure (e.g., those who live in cold climates, northern latitudes, or wear sun and winter protective clothing), and ethnic minorities, especially those with darker skin . Vitamin D deficiency is also more common among heavier women than leaner individuals. During pregnancy, severe maternal vitamin D deficiency, as defined as serum 25-hydroxyvitamin D (25-OH vitamin D) concentrations less than 5 ng/mL, has been associated with disordered skeletal homeostasis, congenital rickets, and fractures of the new- born. (2)However, the effect of less severe vitamin D deficiency and insufficiency on maternal and fetal outcomes during pregnancy is less clear. Recent observational and randomized control trials have attempted to investigate this issue, but there remains limited guidance on the management of vitamin D deficiency during pregnancy.(2,3)

1.2.Physiology and Changes in vitamin D metabolism in pregnancy

Vol. 2, No. 03; 2018

ISSN: 2581-3366

Pregnancy is accompanied by a variety of physiological changes. From the twelfth week of pregnancy, the reflection is located on calcitriol (1,25-Dydroxycholecalciferol: in pregnancy a significant change takes place in the vitamin D metabolism. Through the changes in the maternal tissues and body systems during the fetal development. The high rate of cell division results in a significant increase in demand for many vitamins and minerals. This is also reflected in the recommended intake , they are up to 100 percent higher than non-pregnant women, while the energy demand increases only slightly by around ten percent. The active form of vitamin D, about three times higher than in non-pregnant women. (4). Pregnancy is characterized by physiological changes in mineral metabolism, to allow calcium accretion in the fetal skeleton (5,6). These changes start in the first trimester, and culminate during the third trimester, a period during which fetal calcium requirements increase exponentially(5,6). Indeed, it is in anticipation of such requirements that maternal calcitriol levels increase during pregnancy. While the total calcitriol levels double in the first trimester, free calcitriol levels do not increase until the third trimester and remain so until lactation (5). Conversely, parathyroid hormone (PTH) levels decrease early on and increase back to mid-normal range by term.2 The total calcium level decreases during pregnancy, due to haemodilution, while the ionized calcium level remains stable(5). Vitamin D binding proteins also increase during pregnancy secondary to high estrogen levels,45 but the 25-hydroxyvitamin D (25(OH)D) level, the single best nutritional indicator of vitamin D status,6 remains stable (7). The changes in calcitriol levels led to the description of pregnancy as a state of ‘absorptive hypercalciuria (8). The above adaptive physiology is key to safety considerations when using vitamin D supplementation during pregnancy, as well as to determining key bio- chemical and hormonal parameters to be monitored (4). Both placental and fetal tissues have vitamin D receptors - a fact which already indicates the signification of vitamin D during pregnancy. In fact, vitamin D influences both the trophoblast invasion, and the formation of new vessels. Both are critical processes for implantation of the fertilized egg. The development of the fetal skeleton and the maturation of the immune system depends on an adequate vitamin D status(9) .

1.3.Maternal vitamin D status during pregnancy

Vitamin D deficiency during pregnancy is prevalent worldwide, especially in developing countries (10). In a systematic review of 18 studies conducted in Western coun- tries during the first trimester, white Caucasian pregnant women were found to have a mean 25(OH)D level between 29 and 73 nmol/L. 9 Mean 25(OH)D levels were lower in non-Caucasian pregnant women, ranging between 15.2 and 43 nmol/L. In addition to ethnicity, higher latitude was a significant predisposing factor for hypovitaminosis D (11). Similarly, in non-Western countries, more than half of the pregnant women who were beyond their first trimester had 25(OH)D levels below 75 nmol/ L; these include countries such as India, Kuwait, Pakistan and Turkey (2). Even lower levels (<25 nmol/L) have been reported at delivery in Saudi Arabia, Iran and the United Arab Emirates.14 Furthermore, immigrant women were at particular risk. An observational study from the Netherlands showed significantly lower 25(OH) D levels during the first trimester in immigrant pregnant women (Turkish, Moroccan and others), compared to western participants. (2,12,13)

1.4.Maternal vitamin D status and maternal adverse outcomes

Vol. 2, No. 03; 2018

ISSN: 2581-3366

Vitamin D insufficiency during pregnancy is associated with adverse maternal outcomes such as increased risk of gestational diabetes mellitus (GDM), preeclampsia, caesarean-section delivery and bacterial vaginosis . A meta-analysis of observational studies, the risk of GDM was found to be increased by 40–84% in pregnant women with low 25(OH)D levels, defined as <50 nmol/L or <75 nmol/L, depending on the studies (14,15) While preeclampsia risk was significantly increased in vitamin D insufficient women(16). cesarean section rates were inconsistently affected by vitamin D status (4,17)

1.5.Maternal vitamin D level and neonatal adverse outcomes

Low maternal 25(OH)D levels were recently linked to fetal programming, and were found to be associated with adverse events in neonates, resulting in small for gestational age (SGA) at birth, and also later on during childhood, leading to reduced muscle and bone mass in offspring at 4 and 9 years (18–20). Furthermore, maternal vitamin D may influence the fetal muscle motor unit size, and consequently muscle mass and strength after birth. It is noteworthy that fetal bone development is one of the predictors of peak bone mass, adult bone mineral content and hip geometry, thus correlating with fracture risk later in life(2).

1.6.Vitamin D replacement during pregnancy

The guidelines regarding vitamin D replacement or supplementation during pregnancy vary substantially. The 2010 Institute Of Medicine (IOM) Report on Dietary Reference Intakes for Calcium and Vitamin D recommended 600 IU to pregnant women as the recommended daily allowance (RDA), the RDA being the dose that is projected to allow at least 97.5% of the pregnant women population to reach the desirable target 25(OH) D level Conversely, the Endocrine Society 2011 guidelines recommended that 1500–2000 IU daily of vitamin D is needed to reach a target 25(OH)D level ≥75 nmol/L. Moreover, the WHO 2012 guidelines on vitamin D replacement during pregnancy did not recommend vitamin D supplementation as part of prenatal care(2,21)

The evaluation of the supply of vitamin D is best done by measuring the concentration of vitamin D metabolites calcidiol. (25-hydroxycholecalciferol) in serum or Plasma. Other metabolites such as the actually active calcitriol (1,25-hydroxycholecalciferol) are - not suitable - due to the short half-life of a few hours, generally accepted definition of vitamin D deficiency vary according to the specific limits in the international literatures, is consensus that a blood levels below 50 nanomoles per liter reflecting an insufficient supply, connected with disorders of muskoskeletalen functions(22).

1.7.Epidemiology

Despite abundant, year-long sunshine in the Middle East, vitamin D deficiency and inadequacy is prevalent due, in large part, to traditional clothing covering most of the body and the lack of foods rich in, or fortified with, vitamin D (23).

When reviewing available data on vitamin D deficiency from Middle Eastern countries, comparisons were difficult due to the diverse cut-off points used to define deficiency and the varied assays used to measure it. Internationally, and according to the map developed by the International Osteoporosis Foundation, a 25-hydroxyvitamin D (25(OH)D) serum level of <25

ISSN: 2581-3366

nmol/L is generally acknowledged as indicating vitamin D "deficiency", a serum level of 25–49 nmol/L as "insufficient", 50–74 nmol/L as "inadequate" and >75 nmol/L as "sufficient". The highest deficiency was reported among Saudi adolescents and women of childbearing age (50%) (23). No clear prevalence rates was reported on vitamin D deficiency among pregnant women in the Middle East; however, high insufficiency levels were found in the KSA (86.4%) and Egypt (40%). In the Middle East, prevalence of vitamin D deficiency and insufficiency is high in women of childbearing age, ranging from 24% to 72%. In the UAE, VD deficiency was 51.8% and 42.8% were insufficient, among residents pregnant women(24).

2. Methods

2.1.Study design , setting and participants:

This was a prospective study conducted during a period of two years from January 2015 to January 2017, in Baghdad, Capital of Iraq, included 342 pregnant Iraqi women at first trimester who were attended the gynecology and obstetrics department for follow up and examination at Al Shaheed Mohammad Baqir AlHakeem Hospital , AlKarama Teaching hospital and the private obstetrics clinic of the researcher, all participant were informed about the nature of the study and verbal consent obtained. However, 28 women were missed to follow up and the remaining 314 participant women followed up during their gestation until delivery.

2.2.Inclusion criteria:

Pregnant Iraqi women at 14 weeks or less of gestation aged 18 years or more.

2.3.Exclusion criteria:

Woman was excluded if she had one or more of the following

1. History of chronic diseases such as diabetes mellitus of any type, neurological disorders, cardiovascular diseases, renal diseases , thyroid disease, asthma, and hypertension and periodontitis.
2. History of psychological or social stress or currently on anticonvulsant .
3. A prior pregnancy that had progressed beyond the first trimester and resulted in a fetal loss or intrauterine fetal demise
4. Polycystic ovarian syndrome,
5. Glycosuria
6. Multiple gestations
7. Underweight
8. Intrauterine infection
9. Abortion

Gestational ages were confirmed clinically in addition to a first or a second trimester ultrasound, verified by chart review at study completion.

2.4.Data collection:

Data of the studied group were collected using a pre-constructed data collection sheet for each participant woman. Through direct interview with the participant woman, full history and complete clinical examination were performed. Demographic data and anthropometric measurements of the studied group were reported.

2.5.Blood samples and Vitamin D measurement:

A sample of venous blood was taken from each participant woman at the first visit under aseptic venipuncture technique. Blood samples send to the laboratory for analysis looking for the levels of 1,25-Dihydroxy-vitamin D using an electro-chemiluminescence immunoassay and commercially available diagnostic kit. Furthermore other biochemical parameters, lipid profile and hormonal assay were performed.

Vitamin D status of the patients categorized into three categories according to the following cutoff points (25)

Deficient: < 20 ng/mL, Insufficient: 20 to < 30 ng/mL, Sufficient: ≥ 30 to 60 ng/mL

2.6.Statistical analysis

Data of the studied group were transformed into computerized database, checked for errors or inconsistency, entered and analyzed using the statistical package for social sciences version 22. Descriptive statistics were expressed as mean, standard deviation (SD), frequencies and simple percentages. Appropriate statistical tests were used accordingly, chi square test was used to assess the significance of association between categorical variables, Fisher's exact test was used as an alternative when chi square was inapplicable. Level of significance was ≤ 0.05 considered as significant. Finally, results and findings were presented in tables and or figures with an explanatory paragraph for each.

3. Results

There were 314 women complete the study and follow u period, enrolled with a mean age of 25.8 ± 6.1 (range: 17 – 36) years. The baseline characteristics of the studied group at the first visit are shown in (Tables 1 and 2). Majority of the women were of urban residence 255 (81.2%), 226 (72%) were covered dressed, and 190 women (60.5%) were sufficiently consumed dairy products (Table 1). The baseline laboratory findings of the studied group revealed that the mean values of all biochemical parameters were within the normal reference ranges, (Table 2).

The mean vitamin D level of the study participants at first visit was 20.7 ± 9.8 (range: 7.2 – 47.9) ng/mL, this mean value slightly above the critical cutoff point of deficiency (< 20) and at the lower border of the insufficiency status (20 - < 30). Furthermore, more than half of the studied group, (52.2%), had vitamin D deficiency , 116 women (36.9%) had insufficient and only 34 women, (10.9%), had sufficient vitamin D levels, (Figure 1). To assess the association between vitamin D levels and the pregnancy outcome of the studied group, multiple logistic regression was performed which revealed that vitamin D deficiency, was significantly associated with higher prevalence of preeclampsia; women with deficient vitamin D were about 1.6 folds more likely to develop preeclampsia than those with sufficient vitamin D level, (OR = 1.58, P< 0.05). Additionally, women with vitamin D deficiency were about 1.7 folds more likely to have small for gestational age fetuses, (OR = 1.72, P<0.05), low birth weight neonates (OR = 1.66, P<0.05), and also more likely to have preterm labor (OR 2.02, P< 0.05). Other outcomes and or

Vol. 2, No. 03; 2018

ISSN: 2581-3366

complication of pregnancy and the gender of the neonates in this study showed no significant association with vitamin D level, (P>0.05), (Table 4).

Table 1. Baseline demographic and clinical characteristics of the studied group

Variable	Value
Age (years)	25.8 ± 6.1
Residence Urban / Rural	255/59
Gestational age (weeks)	11.6 ± 2.8
Parity (median (range)	2 (1 – 4)
BMI (kg/m^2)	26.8 ± 5.9
Dressing style Covered/uncovered	226/88
Consumption of dairy products sufficient/insufficient	190/124
Systolic blood pressure (mmHg)	116.2 ± 14.1
Diastolic blood pressure (mmHg)	70.4 ± 6.7

Table 3. Mean values of the laboratory chemical parameters of the studied group (N=314)

Variable	Value
Blood glucose (mg/dL)	84.6 ± 8.2
Triglycerides (mg/dL)	115.1 ± 28.3
Total cholesterol (mg/dL)	186.2 ± 20.3
HDL-cholesterol (mg/dL)	52.6 ± 13.1
LDL-cholesterol (mg/dL)	121.7 ± 26.5
Calcium (mg/dL)	8.6 ± 1.1
Albumin (g/dL)	3.8 ± 1.4
Creatinine (mg/dL)	0.62 ± 0.23
Vitamin D (1,25-Dihydroxy-vitamin D) ng/ml	20.7 ± 9.8

Table 3. Descriptive statistics of vitamin D levels of the studied group (N = 314)

Statistic	Value
Mean	20.7
Median	19.9
Std. Deviation	9.8
Minimum	7.2
Maximum	47.9

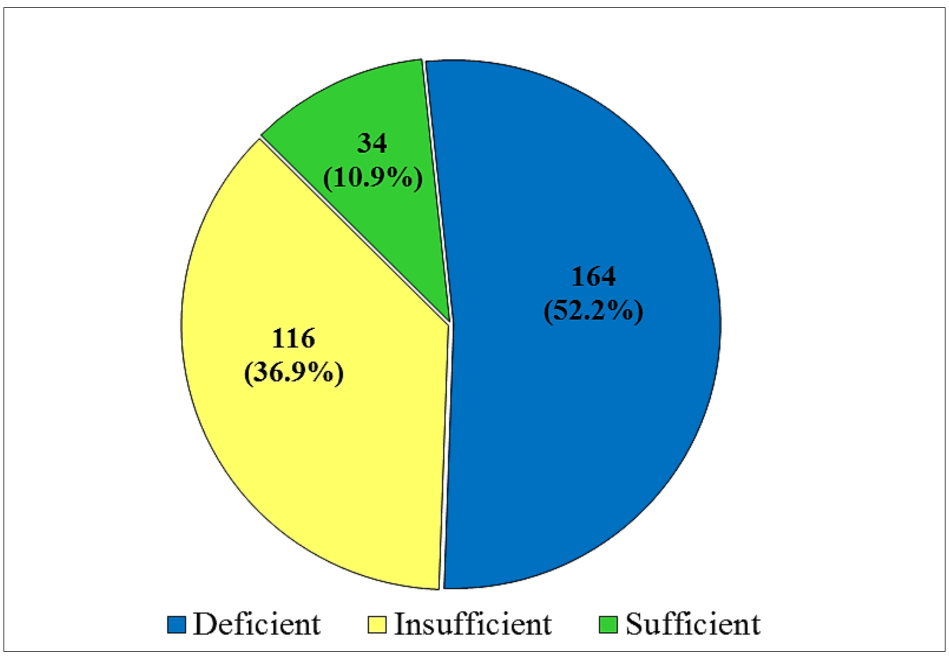

Figure 1. Distribution of the studied group according to the vitamin D levels (N = 314)

ISSN: 2581-3366

Table 4. Results of logistic regression analysis for the correlation of vitamin D level at first visit and pregnancy outcome of the studied group (N = 314)

Pregnancy outcome	OR*	95 CI% OR	P. value
Preeclampsia	1.58	1.21 - 4.25	**0.013**
Gestational hypertension	1.33	0.87 - 3.28	0.42
Gestational diabetes	1.41	0.68 - 2.89	0.36
Small for gestational age	1.72	1.28 - 2.85	**0.004**
Low birth weight	1.66	1.09 - 5.20	**0.008**
Preterm birth	2.02	1.57 - 4.39	**0.002**
Congenital malformation	1.14	0.68 - 1.69	0.82
Infant gender Male	1.02	0.34 - 1.29	0.93

OR: odds ratio, 95% CI: 95% confidence interval of IR

Table 5. ***Results of logistic regression analysis for the predictors of vitamin D level at first visit of the studied group(N = 314)***

Variable	OR*	95 CI% OR	P. value
Age	1.10	0.23 - 1.49	0.62
Residence (Urban)	1.07	0.39 – 2.14	0.56
Gestational age	1.14	0.64 – 2.04	0.71
Parity (median (range)	1.27	0.54 – 1.88	0.43
BMI (kg/m^2)	1.38	0.91 – 2.36	0.09
Dressing style (covered)	2.66	1.28 – 4.76	**0.001**
Insufficient Consumption of dairy products	1.31	0.88 – 3.36	0.11

4. Discussion:

Vitamin D deficiency is a significant health problem worldwide, it is a growing health problem among adults and children . In pregnant women Vitamin D deficiency had an increasing concern in several previous studies due to its possible effect on the maternal and fetal outcomes(26). Some previous clinical trials suggested that vitamin D supplementation during pregnancy could improve the pregnancy outcome and public health (27,28)

The effect of vitamin D deficiency during pregnancy has been studied in many previous studies, reviews and meta analyses. However, heterogeneous findings of previous studies and inconsistency among prvious studies which could be attributed, but not restricted, to the differences in the ethnicity, geographical variation, and using of different cutoff point for the determination of vitamin D deficiency . In Iraq, very few studies concerned with this issue, hence the current study tried to assess the association between level of vitamin D at first trimester and the pregnancy outcome of group of Iraqi women at their first trimester of gestation and to add to growing database in Iraq about the vitamin D deficiency in pregnant women. During a period of two years, the current study enrolled 342 women at their first trimester of gestation. Unfortunately 28 women were missed to follow up for different reasons, and were excluded from the analysis because their outcomes were unknown. Nonetheless, we still have a good sample size of 314 women which was enough to meet the requirement of statistical data analysis. The mean vitamin D level at baseline first visit was 20.7 ng/mL, which was close to the upper cut-off value of the deficient status and at the lower border of insufficiency, furthermore, the vitamin D levels of the studied group ranged from severe deficiency of 7.2 ng/mL to sufficient level of 47.9 ng/mL, the mean VD level reported in our study was higher than that reported in previous Iraqi study was conducted by Issa and Ibraheem in 2007 who reported a mean of 14.56 ng/mL, however, that study included only 31 non-pregnant women and could not be generalized to the total pregnant women population, (29), moreover, the present study found that more than half of the studied group had vitamin D deficiency, (52.2%), these findings agreed that reported in previous studies and literatures about the prevalence of vitamin D deficiency; in the middle east high prevalence of vitamin D (VD) deficiency was reported in some countries, in Saudi Arabia Al-Faris N. (30) found that among 160 Saudi pregnant women 50% had VD deficiency and 43.8% had insufficiency which was close to our findings where the VD deficiency was reported in 52.2% and insufficiency 36.9%. In a study of vitamin D status among 82 women residing in the UAE, Sridhar et al. found that 51.8% were deficient, 42.8% were insufficient, 25.4% were inadequate, and 30.8% had sufficient levels Interestingly, traditional clothing was not found to significantly affect vitamin D status(24). In Lebanon, Gannage-Yared et al. reported vitamin D deficiency in 25% and insufficiency in 50% of women. (31), however, this inconsistency in the prevalence rates could be attributed to the differences in the sample size and the differences in the life styles among Iraqi and Saudi populations. The VD status is often affected by different factors such as latitude, season of the year, air pollution, and other factors that affect the skin and dermal synthesis rate of VD. (30,32,33).

During pregnancy, mobilization of maternal calcium increases to meet the demands of adequate fetal bone mineralization . As a consequence, a number of physiological adaptations take place, including increased maternal serum calcitriol, vitamin D binding protein, placental VD receptors and renal and placental CYP27B1 activity to maintain normal serum levels of 25OHD and calcium (28) Maternal 25OHD crosses the placenta and is the main form of vitamin D for the fetus . Calcitriol rises during pregnancy, almost doubled by the end of third trimester and then returns to normal levels after delivery (28,34)

ISSN: 2581-3366

The present study found that VD deficiency was significantly associated with preeclampsia, Small for gestational age, Low birth weight and preterm birth , the odds ratio ranged from 1.58 for preeclampsia to 2.02, which indicated that pregnant women with VD deficiency are more likely to have these adverse outcomes of pregnancy. The protective role of vitamin D in preeclampsia can be explained by multiple mechanisms. One of them is the immune-modulatory role of calcitriol in regulating immune response (28). Also, vitamin D plays a role in regulating blood pressure and angiogenesis(28). Several observational studies were performed to investigate an association between vitamin D deficiency and preeclampsia but the findings have been inconsistent; In Canada, Achkar et al (2015) concluded that vitamin D deficiency (<30 ng/ml) was associated with increased risk of preeclampsia(35) Similar results were also reported by other studies (28,36,37)

Conversely, , Bomba-Opon et al (2014) enrolled 280 pregnant women and foud no significant association between VD levels and preeclampsia (38). Also Schneuer et al reported no increased risk of preeclampsia in vitamin D deficient pregnant women (39).

Despite VD plays a role in glucose homeostasis by multiple mechanisms , our study found no significant association between the level of VD and incidence of gestational hypertension, or gestational diabetes , (P>0.05), these findings in accordance with previous studies that found no significant role for VD in prevention of gestational DM (2,39). Conversely, Arnold et al (40) in their case control study found an inverse relationship between VD status in early pregnancy and risk of gestational diabetes. In Canada Lacroix et al (2014) (41) documented that an increase in VD level by 5 ng/mL associated with a 14% reduction in the risk of gestational diabetes, also similar effect was reported by Lithy et al (2014) in an observational study on Arab women in Canada (42).

Through its role in the anti-inflammatory pathway, VD can play a role in prevention of infection (one of the most common cause of preterm birth) (43), however, the exact role of vitamin D in the pathogenesis of preterm birth has not yet been clearly defined. In the present study we found a significant inverse correlation between the VD level and incidence of preterm delivery and that women with VD deficiency were more likely to have preterm labour. Bodnar et al (2015) found a preventive protective association between VD sufficiency and preterm birth (44) and Thota et al (2014) reported similar results (45). In contrast other investigators found no similar association and did not supported our findings(39,46).

Consistently with our findings regarding the significant association between the low birth weight and small for gestational age with the low VD levels, Chen et al (2015) documented a positive correlation between maternal VD level and neonatal birth weight. Similarly other investigators supported that of Chen et al (Khalessi et al, 2015; Morgan C et al, 2016; Gernand et al, 2014; Mirzaei et al, 2015; Aydogmus et al, 2016).

Conflicting results were found in the interventional studies for vitamin D supplementation and its impact on offspring birth weight. Mojibian et al (2015) in Iranian pregnant women found no difference on vitamin D supplementation on the fetal outcomes (47). Another RCT carried out by Hossain et al (2014) found improved outcomes with vitamin D supplementation, but the results did not reach statistical significance(48).

Other findings in the present study that among the confounder factors, only dressing style showed a significant correlation with VD level, the covered women were about two-fold more likely to have VD deficiency. These finding was not unexpected according to the nature of Iraqi women customs and norms in this country, however, these conditions are almost similar to that of other countries in the region like Saudi Arabia, Kuwait, Jordan, Syria, UAE , Qatar, and other border countries like Iran and Turkey where covered women are the dominant, and VD deficiency is more prevalent in these women. Prior studies have shown that covered dress style may be an important factor affecting the prevalence of vitamin D deficiency in Muslim populations due to the religious and cultural reasons (24,49–52). In conclusions, VD deficiency and insufficiency was highly prevalent among pregnant Iraqi women, associated with more frequent preeclampsia, small for gestational age, low birth weight and preterm birth and the covered style of dressing are associated with higher prevalence of VD deficiency.

Acknowledgments

Author would like to thank all who supported the study, particularly the staff of the department of gynecology and obstetrics and the laboratory staff in the hospitals. Also I'd like to register my great thanks to all participants of the study hoping to them and their babies good health and life.

Conflict of interest Author declared: None

Source of Funding: Self-funded

Ethical clearance: Data of participants were collected according to the Declaration of Helsinki, Informed verbal consent was obtained from each participant, and all official agreements were obtained from the concerned private healthcare sectors prior to initiation of the study

References

1. Looker AC, Pfeiffer CM, Lacher DA, Schleicher RL, Picciano MF, Yetley EA. Serum 25-hydroxyvitamin D status of the US population: 1988–1994 compared with 2000–2004.AmJ Clin Nutr 2008; 88(6):1519–1527.
2. Flood-Nichols SK, Tinnemore D, Huang RR, Napolitano PG, Ippolito DL. Vitamin D deficiency in early pregnancy. PLoS One. 2015;10(4):1–15.
3. Al-Ajlan A, Al-Musharaf S, Fouda MA, Krishnaswamy S, Wani K, Aljohani NJ, et al. Lower vitamin D levels in Saudi pregnant women are associated with higher risk of developing GDM. BMC Pregnancy Childbirth. 2018;18(1):1–7.
4. Chakhtoura M, Nassar A, Arabi A, Cooper C, Harvey N, Mahfoud Z, et al. Effect of Vitamin D replacement on maternal and neonatal outcomes: A randomised controlled trial in pregnant women with hypovitaminosis D. A protocol. BMJ Open. 2016;6(3).
5. Kovacs CS. Calcium and bone metabolism disorders during pregnancy and lactation. Endocrinol Metab Clin North Am 2011;40:795–826.
6. Parkes I, Schenker JG, Shufaro Y. Parathyroid and calcium metabolism disorders during

ISSN: 2581-3366

pregnancy. Gynecol Endocrinol 2013;29:515–19.

7. Kovacs CS. Maternal vitamin D deficiency: fetal and neonatal implications. Semin Fetal Neonatal Med 2013;18:129–35.
8. Hossain N, Khanani R, Hussain-Kanani F, et al. High prevalence of vitamin D deficiency in Pakistani mothers and their newborns. Int J Gynaecol Obstet 2011;112:229–33.
9. Wei SQ, Qi HP, Luo ZC, Fraser WD. Maternal vitamin D status and adverse preg- nancy outcomes: a systematic review and meta-analysis. J Matern Fetal neo- natal Med 2013; 26:. 889-99.
10. Robinson CJ, Wagner CL, Hollis BW, Baatz JE, Johnson DD. Maternal vitaminD and fetal growth in early-onset severe preeclampsia.AmJ Obstet Gynecol 2011; 204(6):556 e551–554 doi: 10.1016/j. ajog.2011.03.022.
11. Zhang C, Qiu C, Hu FB. Maternal plasma 25-hydroxyvitaminD concentrations and the risk for gesta- tional diabetes mellitus. PLoS One 2008; 3(11):e3753.
12. Management of recurrent pregnancy loss. Practice Bulletin No. 124. American College of Obstetricians and Gynecologists. Int J Gynaecol Obstet 2002; 78(2):179–190.
13. Management of Stillbirth.ACOGPractice Bulletin No. 102. American College of Obstetricians and Gy- necologists. Obstet Gynecol 2009; 113:748–61. doi:
14. Hollis BW, Wagner CL. Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. Calcif Tissue Int. 2013; 92: 128-39.
15. Aghajafari F, Nagulesapillai T, Ronksley PE, et al. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ 2013;346.
16. Tabesh M, Salehi-Abargouei A, Tabesh M, et al. Maternal vitamin D status and risk of pre-eclampsia: a systematic review and meta-analysis. J Clin Endocrinol Metab 2013;98:3165–73.
17. Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatr Perinat Epidemiol 2012;26(Suppl 1):75–90.
18. Sibai BM, Caritis S, Hauth J. What we have learned about preeclampsia. Semin Perinatol 2003; 27(3):239–246.
19. Roberts CL, Ford JB, Algert CS. Population-based trends in pregnancy hypertension and pre- eclampsia: an international comparative study. BMJ Open 2011; 1(1):e000101.
20. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, treatment, and prevention of vitaminD deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011; 96(7):1911–1930.
21. Strohle A, Hahn A. Vitamin D in pregnancy. Raises the sun vitamin and shadow? Med month Pharam. 2016a; 39: 213-215.
22. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: When to test and how to treat. Mayo Clin Proc. 2010;85(8):752–8.
23. Hwalla N, Al Dhaheri AS, Radwan H, Alfawaz HA, Fouda MA, Al-Daghri NM, et al. The prevalence of micronutrient deficiencies and inadequacies in the middle east and approaches to interventions. Nutrients. 2017;9(3):1–28.

24. Sridhar, S.B.; Rao, P.G.; Multani, S.K.; Jain, M. Assessment of prevalence of hypovitaminosis D in multiethnic population of the United Arab Emirates. J. Adv. Pharm. Technol. Res. 2016, 7, 48–53.
25. Talaei A, Rafee M, Moini A, Yadegari N, Rezvanfar M. Prevalence and cut-off point of vitamin D deficiency among secondary students of Arak, Iran in 2010. Indian J Endocrinol Metab [Internet]. 2012;16(5):786. Available from: http://www.ijem.in/text.asp?2012/16/5/786/100676
26. Weinert S, Silveiro P. Maternal – Fetal Impact of Vitamin D Deficiency : A Critical Review. Matern Child Health J. 2015;19(1):94–101.
27. Christesen HT, Falkenberg T, Lamont RF, Christian H. The impact of vitamin D on pregnancy : a systematic review. Acta Obstet Gynecol Scand. 2012;91(12):1357–67.
28. Agarwal S, Kovilam O, Agrawal DK. Vitamin D and its impact on maternal-fetal outcomes in pregnancy: A critical review. Crit Rev Food Sci Nutr. 2018;58(5):755–69.
29. Issa AM, Ibraheem SA. Alterations of Vitamin " D " level in Sera of Iraqi Population. J Kerbala Univ. 2007;5(1):58–64.
30. Al-Faris NA. High prevalence of vitamin D deficiency among pregnant saudi women. Nutrients. 2016;8(2):6–15.
31. Gannage-Yared, M.H.; Helou, E.; Zaraket, V.; Abi Akl, S.; Antonios, L.; Moussalli, M.L.; Wakim, S. Serum 25 hydroxyvitamin D in employees of a Middle Eastern university hospital. J. Endocrinol. Investig. 2014, 37, 541–546.
32. Lehmann B, Meurer M. Vitamin D metabolism. Dermatol Ther. 2010;23(1):2–12.
33. Christakos S, Ajibade D V, Dhawan P, Fechner AJ, Mady LJ. Vitamin D: metabolism. Endocrinol Metab Clin. 2010;39(2):243–53.
34. Marshall I, Mehta R, Petrova A, Marshall I, Mehta R, Petrova A. Vitamin D in the maternal – fetal – neonatal interface : clinical implications and requirements for supplementation and requirements for supplementation. J Matern Fetal Neonatal Med. 2013;26(.
35. Achkar M, Dodds L, Giguère Y, Forest J, Armson BA, Woolcott C, et al. Vitamin D status in early pregnancy and risk of preeclampsia. Am J Obstet Gynecol [Internet]. Elsevier Inc.; 2015 Apr;212(4):511.e1–7.
36. Singla R, Gurung P, Aggarwal N. Relationship between preeclampsia and vitamin D deficiency : a case control study. Arch Gynecol Obstet Internet . Springer Berlin Heidelberg; 2015;291(6):1247–51.
37. Abedi P, Mohaghegh Z, Afshary P, Latifi M. The relationship of serum vitamin D with pre-eclampsia in the Iranian women. Matern Child Nutr. 2014;10 (2): 206– 12.
38. Bomba-Opon DA, Brawura-Biskupski-Samaha R, Kozlowski S, Kosinski P, Bartoszewicz Z, Bednarczuk T, et al. First trimester maternal serum vitamin D and markers of preeclampsia. J Matern Fetal Neonatal Med [Internet]. 2014 Jul;27(10):1078–9.
39. Schneuer FJ, Roberts CL, Guilbert C, Simpson JM, Algert CS, Khambalia AZ, et al. Effects of maternal serum 25-hydroxyvitamin D concentrations in the first trimester on subsequent pregnancy outcomes in an Australian population. Am J Clin Nutr. 2014;99(2):2.
40. Arnold DL, Enquobahrie DA, Qiu C, Huang J. Early Pregnancy Maternal Vitamin D Concentrations and Risk of Gestational Diabetes Mellitus. Paediatr Perinat Epidemiol.

2015;29(3):200–10.
41. Lacroix M, Myriam MB. Lower vitamin D levels at first trimester are associated with higher risk of developing gestational diabetes mellitus. Acta Diabetol. 2014;51(4):609–16.
42. Lithy A El, Abdella RM, El-faissal YM, Sayed AM, Samie RMA. The relationship between low maternal serum vitamin D levels and glycemic control in gestational diabetes assessed by HbA1c levels : an observational cross-sectional study. BMC Pregnancy Childbir.
43. Sangkomkamhang US, Lumbiganon P, Prasertcharoensuk W, Laopaiboon M. Antenatal lower genital tract infection screening and treatment programs for preventing preterm delivery (Review). Cochrane Database Syst Rev. 2015;2:CD006178.
44. Bodnar LM, Platt RW, Simhan HN. Early-Pregnancy Vitamin D Deficiency and Risk of Preterm Birth Subtypes. Obstet Gynecol. 2015;125(2):439–47.
45. Thota C, Menon R, Fortunato SJ, Brou L, Lee J, Al-hendy A. 1 , 25- Dihydroxyvitamin D Deficiency Is Associated With Preterm Birth in African American and Caucasian Women. Reprod Sci. 2014;21(2):244–50.
46. Wetta LA, Biggio JR, Cliver S, Barnes S, Tita ATN, Abramovici A. Is Midtrimester Vitamin D Status Associated with Spontaneous Preterm Birth and Preeclampsia ?. Am J Perinatol. 2014;31(6):541-6.
47. Mojibian M, Soheilykhah S, Moghadam J. The effects of vitamin D supplementation on maternal and neonatal outcome: A randomized clinical trial. Iran J Reprod Med. 2015;13(11):687–96.
48. Hossain N, Kanani FH, Ramzan S, Kausar R. Obstetric and Neonatal Outcomes of Maternal Vitamin D Supplementation : Results of an Open- Label , Randomized Controlled Trial of Antenatal Vitamin D Supplementation in Pakistani Women. J Clin Endocrinol Metab. 2.
49. Leffelaar ER, Vrijkotte TG, van Eijsden M. Mater- nal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Am- sterdam Born Children and their Development cohort. Br J Nutr 2010; 104 (1): 108 -117.
50. Ustuner I, Keskin HL, Tas EE, Neselioglu S, Sen- gul O, Avsar AF. Maternal serum 25(OH)D levels in the third trimester of pregnancy during the winter season. J Matern Fetal Neonatal Med 2011; 24 (12): 1421-1426.
51. Halicioglu O, Aksit S, Koc F, Akman SA, Albudak E, Yaprak I, et al. Vitamin D deficiency in pregnant wom- en and their neonates in spring time in western Turkey. Paediatr Perinat Epidemiol 2012; 26 (1): 53-60.
52. Ates S, Sevket O, Ozcan P, Ozkal F, Kaya MO, Dane B. Vitamin D status in the first-trimester: Effects of vitamin D deficiency on pregnancy outcomes. Afr Health Sci. 2016;16(1):36–43.