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Vitamin D insufficiency in pregnant women from Lebanon: prevalence and key predictors

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Abstract

Background Suboptimal 25-hydroxyvitamin D (25OHD) during pregnancy can have adverse maternal and neonatal outcomes.

Aim This study aimed to estimate the prevalence of vitamin D deficiency in pregnant females in Lebanon and to identify its risk factors.

Methods This is a cross-sectional study involving pregnant females identified during their first-early second trimester visit to obstetricians in two centers in Beirut. We collected blood samples, anthropometric measurements and lifestyle data. We measured maternal serum 25OHD and used the data to explore possible determinants of deficiency.

Results We tested 25OHD levels of 548 females; 270 from American University of Beirut Medical Center and 278 from Bahman hospital. Mean age was 29 ± 5 years and 41.5% were nulliparous. Mean serum 25OHD was 15.4ng/ml and 72.3% had levels < 20 ng/ml. Levels were significantly lower at Bahman hospital, 12.9ng/ml versus 18.1ng/ml at American University of Beirut Medical Center, *p*-value 0.001. The risk of having 25OHD < 20ng/ml was significantly higher in females from Bahman hospital, those who were veiled, those who smoked and had higher pre-pregnancy body mass index, with a trend for significance for early pregnancy body mass index. This risk decreased for older females, those with higher education, employed females, and those screened during summer/fall. Multivariable logistic regression showed that veiling and younger age were significant risk factors for 25OHD < 20 ng/ml.

Conclusion Vitamin D deficiency is prevalent in pregnant females from two centers in Beirut. Our findings emphasize the importance of proper screening and supplementation of vitamin D to ensure adequacy throughout pregnancy.

Keywords Vitamin D, Pregnancy, Middle East, Prevalence, Predictors, Lebanon

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Introduction

Vitamin D deficiency is a global health concern, even in countries with low latitude, where ample ultraviolet B (UVB) radiation was presumed sufficient; and in industrialized countries, where vitamin D food fortification has long been implemented [1]. It has been extensively investigated over the past years, because of increased evidence for potential association with non-classical effects extending beyond calcium and mineral homeostasis and bone health [2, 3]. The prevalence of vitamin D deficiency greatly varies worldwide. It is higher in developing countries [4] and in the Middle East and North Africa (MENA) region, despite plentiful sunshine [5–7]. Hypovitaminosis D, defined as 25-hydroxyvitamin D (25OHD) < 20ng/ml, ranged between 54–96% in pregnant and lactating females in the MENA region; and up to 94% of neonates in Jordan [8].

Pregnant women may be at an increased risk of depleted levels since vitamin D homeostasis is altered to provide the optimal environment for the growing fetus [9, 10]. However, the specific mechanisms underlying these adaptations are not fully understood and pregnancy does not seem to affect serum 25OHD levels [11, 12]. Considering the dependance of the growing fetus on maternal supplies of vitamin D and calcium for proper bone development, inadequate intakes may pose greater concern [13, 14]. Additionally, routine screening and vitamin D supplementation, in case of deficiency, for pregnant females are not a standard practice in many countries leading to unrecognized and unadjusted deficiency [15]. Hypovitaminosis D during pregnancy is of particular interest due to its wide range of potential adverse maternal and neonatal outcomes [16]. Several studies reported associations between low vitamin D status during pregnancy and maternal bone loss, increased risk of recurrent miscarriages, preeclampsia, gestational diabetes, and preterm birth [17–19]. Other studies have concluded that low maternal 25OHD might be related to neonatal wheezing, small for gestational age, language impairment, and induction of specific genomic pathways relevant to autoimmune diseases in childhood [4, 20–22].

Vitamin D deficiency during pregnancy is multi-factorial, as is the case in the general population [17]. Main influencing factors are inadequate sun exposure and insufficient dietary and supplemental intake of vitamin D [23]. Lifestyle factors such as low education, lower socio-economic status (SES), high adiposity levels and clothing style can also affect serum 25OHD levels [5–7, 24]. Supplementation may be indicated in certain high-risk sub-groups of pregnant females [25]. Vitamin D supplementation guidelines in pregnancy vary widely and evidence for global recommendation remain insufficient. Currently, the World Health Organization (WHO) recommends that pregnant females should be encouraged to receive adequate nutrition and only those with suspected deficiency; e.g. those with limited sunlight exposure, may be supplemented with 200 IU/day [26]. The Institute of Medicine (IOM) advises maintaining a circulating 25OHD level of 20 ng/ml, recommending a daily intake of 400–600 IU vitamin D which can be met through diet alone without supplementation [27]. In contrast, the Endocrine Society recommends empiric vitamin D supplementation during pregnancy given its potential to lower the risk of adverse outcomes such as preeclampsia, intrauterine mortality, preterm birth, and neonatal mortality [28]. Despite these facts, population representative data from pregnant females, a most vulnerable sub-group, in the Middle East and especially in Lebanon, remain limited [29–32]. Local data would be instrumental to the development of guidelines on adequate intake and thus supplementation, i.e. doses specific for our populations [27, 28]. We conducted a randomized controlled trial to explore the effect of varying doses of vitamin D among pregnant females in greater Beirut area. The objective of the current study is to examine the prevalence and identify predictors of hypovitaminosis D using the baseline information from pregnant female subjects enrolled in the randomized controlled trial.

Methods

Study design

This study represents baseline cross-sectional data of participants screened for a phase III double blind randomized controlled trial of vitamin D supplementation (NCT 02434380) [33]. Study participants were pregnant females in their first and early second trimesters recruited from two centers: American University of Beirut Medical Center (AUBMC), a tertiary referral center, and Bahman (BH) affiliated Obstetric Clinics. The study spanned over three years from screening until completion of randomization (June 30, 2015, till June 5, 2018). The protocol was approved by the Institutional review board (IRB) at the American University of Beirut (AUB).

Eligibility criteria

We included pregnant females (> 18 years and of gestational age < 17.5 weeks) from middle eastern origins (96% were Lebanese, the remaining 4% were Syrian, Palestinian, and Jordanian), not taking any vitamin D supplementation exceeding 200 IU daily. For those taking vitamin D supplementation > 200 IU daily, they were advised to adjust prenatal multivitamin doses so that total vitamin D supplementation does not exceed 1400 IU per week (inclusive of trial vitamin D), in consultation with their primary obstetrician.

We excluded subjects taking supplementation exceeding 600 IU/day. Females taking medications that might interfere with vitamin D metabolism were excluded. Additional exclusion criteria included having diseases associated with abnormal bone and mineral metabolism, renal stones, thyroid dysfunction, recent cancer diagnosis, diabetes or previous gestational diabetes and presence of fetal congenital malformations.

Data collection

Upon enrollment and after signing an informed written consent, we collected blood samples during the screening visit and participants completed an interviewer-led questionnaire. The questionnaire collected information on participants' age, parity, gravidity, education level, employment status, area of residency, intake of concomitant medications and supplements, calcium and vitamin D supplementation (either as pure Vitamin D or part of multivitamins), smoking and alcohol habits, clothing style and medical history. We categorized the seasons of blood collection as: Spring (April- June), Summer (July–September), Autumn (October-December) and Winter (January -March).

We evaluated dietary calcium and vitamin D intake using an interviewer-administered, semi-quantitative food frequency questionnaire, previously validated in adolescents within our population [34]. It consisted of 38 items classified into six food groups, focusing on foods rich in calcium and vitamin D. Participants reported their typical food consumption in serving sizes. Cumulative calcium and vitamin D intake from diets were then calculated. Additionally, we gathered data on exercise habits including type, activity level (strenuous, moderate and gentle intensity), frequency (number of times if weekly) and duration (min/day). The physical activity questionnaire was adapted from the International Physical Activity Questionnaire (2002) Short version "Short last 7 days self-administered format", designed for use in young and middle-aged adults (15–69 years) [35]. We also measured anthropometrics and vital signs and collected data on pre-pregnancy weight (as self-reported by participants).

Sampling and biochemical parameters

We conducted the following laboratory tests during the screening visit (11-17.5 weeks) : serum 25OHD, calcium, phosphate, magnesium, creatinine, thyroid stimulating hormone (TSH), and total protein. Serum 25OHD measurement was centralized at AUBMC Clinical Chemistry laboratory using the electro-chemiluminescence immunoassay (ECLIA) Roche Cobas 6000 analyzer.

The Roche Elecsys COBAS® is a vitamin D protein binding assay that specifically detects D2 and D3, quantifying 25OHD levels in both serum and plasma. It has an analytical range of 3.0–70.0 ng/ml, with a cross reactivity of 92% to 25OHD2 and 100% to 25OHD3. At AUBMC clinical chemistry laboratory, the intra-assay CV was 4.8–7.4%, and inter-assay CV was 2.4–3.2% for values between 19.6–36.7 ng/ml. The Clinical Chemistry laboratory partakes in the quality assurance, evaluation, and accreditation from the College of American Pathologists (www.cap.org) and DEQAS (www.Deqas.org) and has consistently performed against target values.

Definitions of vitamin D deficiency

We defined vitamin D deficiency, insufficiency, and sufficiency as serum 25OHD of < 30 nmol/L (< 12 ng/mL), 30–50 nmol/L (12–20 ng/mL), and ≥ 50 nmol/L (≥ 20 ng/mL), respectively [27].

Statistical analysis

Based on the central limit theorem, we applied parametric tests considering our large sample size. Baseline demographic characteristics were summarized using frequencies and percentages for categorical variables and mean ± SD for continuous variables. We tabulated descriptive baseline characteristics (clinical, anthropometric, and biochemical) of the overall population and performed independent t-test and ANOVA for continuous variables and chi-square test for categorical variables.

We categorized body mass index (BMI) for the descriptive analysis as: underweight (< 18·5 kg/m^2), normal weight (18·5–24·9 kg/m^2), overweight (25·0–29·9 kg/m^2) or obese (≥ 30·0 kg/m^2). However, in the regression analysis, we utilized a dichotomous variable as proposed by the WHO classifying normal BMI as < 25 kg/m^2 and overweight/obese as BMI ≥ 25 kg/m^2 [36]. In addition, we grouped seasons of blood draw into two groups: winter with spring and summer with fall for the logistic regression analyses. To evaluate the adequacy of dietary calcium and vitamin D intake, we categorized the estimated values based on the IOM recommended dietary intake (RDI) as inadequate (< 1000 mg/day and < 600 IU/day) and adequate (≥ 1000 mg/day and ≥ 600 IU/day) for calcium and vitamin D respectively [27]. We also re-classified levels of education as below college versus college education in the regression models. We used analysis of variance to compare multiple group means; for example, in inspecting seasonal variation of vitamin D levels.

To identify predictors of vitamin D inadequacy, defined as 25OHD < 20ng/ml, vs 25OHD ≥ 20 ng/ml, we performed univariable logistic regression in the overall group. The predictors included center, age, gestational age, season, parity, gravidity, pre-pregnancy & early pregnancy BMI, education, occupation, smoking, exercise, veiling, vitamin D supplementation and dietary vitamin D intake. We further examined potential

determinants of vitamin D deficiency in multivariable logistic regression model by including the significant variables (p-value <0.05) identified in the univariable analysis, those at p-value of 0.2 and those that were consistently associated with our outcome, as identified in the literature (such as age, BMI, season, clothing style, vitamin D supplement intake, parity, and exercise). Additionally, we carried out subgroup analyses examining the correlation of these predictors with 25OHD <20ng/ml in each center. A p-value of <0.05 was considered statistically significant, and it was not corrected for multiplicity of testing. All values were rounded to the nearest whole number in Tables 1 and 2 (if suitable) and in text (except for p-values). Statistical analysis was performed using SPSS V.23 (IBM, Armonk, NY).

Results

General characteristics of the study population

Between July 2015 and June 2018, we prescreened 1600 pregnant females and enrolled a total of 552 participants of whom 548 had serum 25OHD levels measured, 270 from AUBMC and 278 from BH (Appendix Fig. 1). Table 1 details baseline clinical, anthropometric and biochemical characteristics of the participants overall and by center. The rate of missing data ranged from 5% for parity to 24% for pre-pregnancy BMI. Missing data were particularly high for exercise (58%) and dietary vitamin D

Table 1 Baseline Demographic Characteristics of participants- overall and by center

		AUBMC[a] (270) N (%)	BH[b] (278) N (%)	Total (548) N (%)
Residency[c] (AUBMC: 228 BH: 252)	Beirut	116 (51)	221 (88)	337 (70)
	Mount Lebanon	83 (36)	10 (4)	93 (19)
	South Lebanon	13 (6)	16 (6)	29 (6)
	North Lebanon	8 (4)	0 (0)	8 (2)
	Akkar	1 (0.4)	0 (0)	1 (0.2)
	Baalbek	3 (1.3)	5 (2)	8 (2)
	Nabatieh	4 (2)	0 (0)	4 (0.8)
Season	Winter: January-March	69 (26)	78 (29)	147 (27)
	Autumn: October-December	63 (23)	70 (25)	133 (24)
	Spring: April-June	75 (28)	83 (30)	158 (29)
	Summer: July- September	63 (23)	47 (17)	110 (20)
Employment [c] (AUBMC: 242, BH: 254)		155 (64)	77 (30)	232 (47)
Education [c] (AUBMC: 246 BH: 254)	Below High School	10 (4)	46 (18)	56 (11)
	High School	30 (12)	47 (19)	77 (15)
	College	206 (84)	161 (63)	367 (73)
Smoking [c] (AUBMC: 261, BH: 247)		13 (5)	50 (20)	63 (12)
Smoking before pregnancy [c] (AUBMC: 208, BH: 251)		63 (30)	124 (49)	187 (41)
Alcohol consumption [c] (AUBMC: 82, BH: 139)		3 (4)	0 (0)	3 (1.4)
Exercise (AUBMC: 75, BH: 150)		8 (11)	12 (8)	20 (9)
Veiling [c] (AUBMC: 206, BH: 253)		56 (27)	224 (89)	280 (61)
Parity [c] (AUBMC: 262, BH: 254)	Nulliparous	136 (52)	78 (31)	214 (42)
	Primiparous	87 (33)	79 (31)	166 (32)
	Multiparous	39 (15)	97 (38)	136 (26)

Exact total of each variable is included in parentheses as there were missing data

[a] American University of Beirut Medical center

[b] Bahman Hospital

[c] variables significantly different between the two centers at p-value <0.05 using chi-square & independent t-test

Table 2 Anthropometric & Biochemical characteristics of participants- overall and by center

		AUBMC[a] (270) Mean ± SD	BH (278) [b] Mean ± SD	Total (548) Mean ± SD
25(OH)D (ng/ml)[e]		18 ± 9	13 ± 8	15 ± 9
Vit D category (IOM[c]) N(%) [e]	**Deficient**	81 (30)	155 (56)	236 (43)
	Insufficient	83 (31)	77 (28)	160 (29)
	Sufficient	106 (39)	46 (17)	152 (28)
Age [e]		30 ± 5	29 ± 5	29 ± 5
Gestational age [e]		12 ± 1	13 ± 2	13 ± 1
BMI[d] at screening [e]		24 ± 4	25 ± 5	25 ± 4
BMI before pregnancy [e]		23 ± 4	24 ± 5	24 ± 4
Total Supplemental Calcium/day		260 ± 219	242 ± 136	247 ± 159
Total Supplemental Vitamin D/day [e]		534 ± 606	167 ± 149	419 ± 536
Total dietary Calcium/day		581 ± 250	586 ± 253	585 ± 251
Total dietary Vitamin D/day		87 ± 41	100 ± 67	98 ± 65
Calcium(mg/dL) [e]		9 ± 0.4	9 ± 0.5	9 ± 0.4
Creatinine (mg/dL) [e]		0.5 ± 0.1	0.6 ± 0.1	0.5 ± 0.1

[a] American University of Beirut Medical Center

[b] Bahman Hospital

[c] Institute of Medicine

[d] Body mass index

[e] variables significantly different between the two centers at *p*-value < 0.05 using chi-square & independent t-test

intake (79%). The majority (70%) of participants resided in Beirut. Mean population age was 29 ± 5 years (range 18–46) and the mean gestational age at screening was 13 weeks. Approximately 41% of participants were nulliparous and 32% were primiparous (Table 1). The average BMI of our cohort was 25 ± 4 kg/m^2; with almost half of the studied population having normal BMI (57%), while 20% were overweight and 8% were obese. In addition, only 9% reported exercising during pregnancy. A notably high proportion of participants did not smoke during pregnancy (88%); although 28% of those reported halting smoking only upon pregnancy. The mean serum 25OHD concentration in the overall sample was 15 ± 9 ng/ml with 72% of participating females classified as vitamin D insufficient/deficient. All participants had normal levels of serum calcium, creatinine, phosphate, magnesium, total protein, albumin, globulins and TSH.

Bi-center variability

The comparison of maternal baseline characteristics between the two centers is presented in Tables 1 and 2. Participants recruited from AUBMC were more likely to be residing in Beirut, and the North region, and had higher level of education compared to those from BH (84% vs 63% college graduates). Mean serum 25OHD level was 18 ± 9 ng/ml at AUBMC, 5 ng/ml higher than that of BH group ($p < 0.001$) (Table 2). Compared to those at AUBMC, participants from BH were more likely to be unemployed, smoked before and during pregnancy, reported no alcohol consumption and included a higher proportion of multiparous females (Table 1). More participants from BH were veiled ($p < 0.001$) compared to AUBMC and were taking lower doses of vitamin D supplements ($p < 0.001$). In addition, they were slightly younger ($p < 0.001$), had a higher self-reported pre-pregnancy BMI ($p = 0.01$) as well as during their first-early second trimester ($p = 0.03$). Mean dietary calcium at study entry were comparable between the two groups with total calcium/day of 581 ± 250 mg in AUBMC group and 586 ± 253 mg/day in BH group. Similarly, dietary vitamin D was 87 ± 41 IU/day at AUBMC versus 100 ± 67 IU/day at BH. However, supplemental intake of vitamin D was significantly higher in participants from AUBMC ($p < 0.001$) (Table 2).

Seasonal variations of vitamin D levels

Blood collection was evenly distributed across seasons in the overall group (ranging from 20 to 27% per season), and by center. In the overall group, we observed a seasonal trend with levels reaching their peak in the summer 18 ± 10 ng/ml and a nadir in winter 14 ± 9 ng/ml ($p = 0.019$). Subgroup analyses revealed a parallel seasonal trend for participants from AUBMC and a flatter pattern for BH; although variation within each center was not significant between seasons (Fig. 1). On average, mean serum 25OHD levels were below 20 ng/ml in the overall

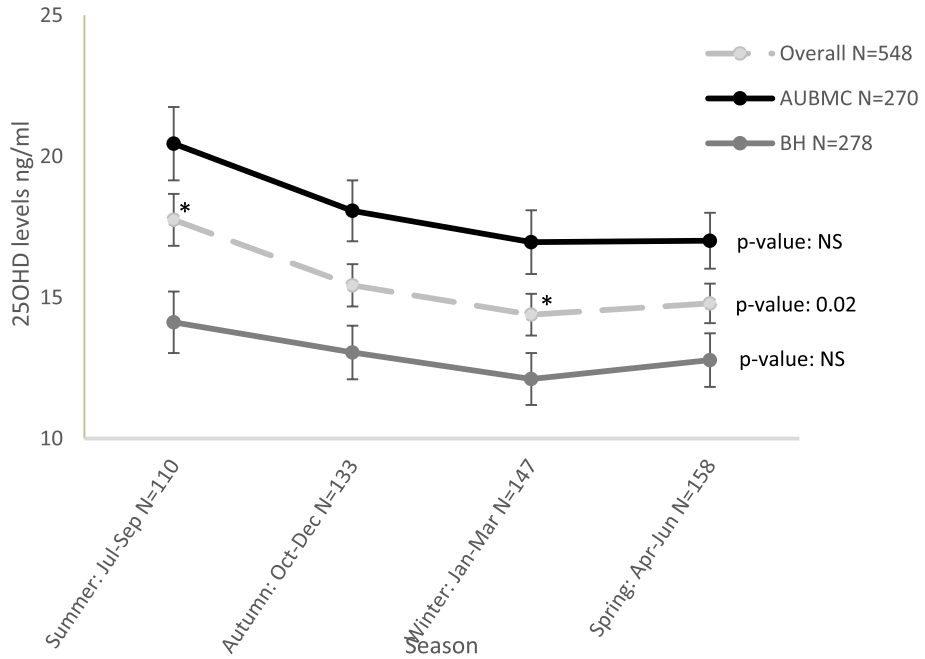

Fig. 1 Change in 25OH D levels across seasons-overall and by center. *Significant difference in 25OHD levels, between Summer and Winter seasons in the overall group. *p*-value < 0.05. NS not significant

group, and by center, in the fall, winter, and spring seasons. Only females at AUBMC reached a mean level of 20 ± 11 ng/ml during the summer (Fig. 1).

Predictors of hypovitaminosis D

Univariable analysis of the association between potential risk factors and 25OHD < 20ng/ml during early pregnancy identified several significant predictors. Key risk factors included pre-pregnancy overweight/obesity (OR 1.9, CI: [1.2–3.2]), and a borderline significance for the first-early second trimester BMI (OR 1.5, CI [0.9–2.3]). Veiling (OR 3.8, CI [2.5–5.8]), smoking during pregnancy (OR 2.08, CI [1.1–4.4]) in addition to being recruited from BH (OR 3.3, CI [2.2–4.9]) were also significantly associated with higher risk of having 25OHD < 20ng/ml.

Conversely, protective factors included attaining higher education (OR 0.3, CI [0.2–0.6]), older age (OR 0.9, CI [0.89–0.96]) and being employed (OR 0.6, CI [0.4–0.9]). Moreover, participants screened during summer/fall had lower risk of being deficient-insufficient compared to those screened in winter/spring season (OR 0.6, CI [0.4–0.9]). Surprisingly, vitamin D supplementation at study entry did not incur a protective effect against deficiency. Other socio-demographic and lifestyle factors did not show significant association with having 25OHD < 20ng/ml.

We further examined potential determinants of vitamin D deficiency in a multivariable logistic model shown in Table 3. Compared to the univariable regression results, only age and veiling remained significant predictors of vitamin D deficiency. Veiled participants had approximately 5 times the odds of having deficiency-insufficiency than non-veiled, and older females had 12% lower odds of being deficient-insufficient. Other variables such as seasonality and BMI lost their significance upon the inclusion of age and veiling into the model (Table 3).

After applying the same multivariable model within each center, clothing style was the only significant predictor in the model at AUBMC while older age was significantly correlated with lower odds of deficiency-insufficiency at BH (Appendix Tables 1a & 1b).

Discussion

Principal findings

We evaluated serum vitamin D status of 548 healthy pregnant females in their first-early second trimester and examined its association with several lifestyle and demographic factors. The mean concentration of 25OHD was 15 ± 9 ng/ml (median 13.5 and interquartile range 13). Although the study cohort was drawn from two heterogeneous centers, representing different SES, vitamin D deficiency was common to both with 72% having levels < 20 ng/ml. Factors significantly associated with hypovitaminosis D in our population at a univariable level included study center, pre-pregnancy BMI (with a trend to significance for first-early second trimester BMI), age,

Table 3 Predictors of vitamin D inadequacy, defined as 25OHD < 20 ng/ml in the multivariable analyses

		Multivariate Model	
Predictor	**β**	**OR**	**[95% CI]**
Age	−0.13	0.88	[0.79–0.97]
Gestational Age	0.15	1.16	[0.85–1.58]
Center: Bahman vs AUBMC (ref)	0.55	1.74	[0.51–5.73]
Season: Summer/Autumn vs winter/spring (ref)	0.27	1.31	[0.55–3.09]
Parity: Multiparous vs nulliparous (ref)	−0.14	0.87	[0.35–2.27]
First trimester BMI: Overweight/Obese vs normal (ref)	0.61	1.85	[0.77–4.43]
Education: College vs below college (ref)	−0.61	0.55	[0.18–1.59]
Working status: Working vs Not working (ref)	−0.39	0.68	[0.26–1.72]
Smoking: Smoker vs non-smoker (ref)	0.36	1.43	[0.38–5.29]
Physical activity: Exercise vs no exercise (ref)	−0.72	0.49	[0.14–1.69]
Veiling: Veiled vs not veiled (ref)	1.55	4.72	[1.58–13.65]
Vitamin D supplement: Taking vs not taking (ref)	0.19	1.21	[0.43–2.99]

Ref: reference group for categorical variables

season of screening, education, employment, smoking and clothing style. However, only age and veiling were significant variables in the multivariable model.

Results in the context of what is known

The observed prevalence of vitamin D deficiency is consistent with the range detected in various epidemiological studies from the Mediterranean and Arab region [8, 31, 37]. However, it exceeds global rates of deficiency in pregnant females (54% with 25OHD < 50 nmol/L) [38]. It also exceeds rates we reported in our general population, where 37% of females and 44% of men were deficient [39]. Prevalence of hypovitaminosis D in regional multicenter studies on pregnant females with sample sizes greater than 300, revealed that 70–90% had serum 25OHD < 50 nmol/L (20 ng/ml), (Appendix Table 2) [29–32].

Rates of deficiency in our study varied between the two centers; yet center did not emerge as a significant predictor in the multivariable analysis. This variability could be attributed to several notable differences in risk factors between AUBMC and BH; mainly veiling, age, vitamin D supplement intake and BMI; however, only age and veiling remained significant in the adjusted model.

Although seasonal variation in 25OHD levels varied across seasons in our study, with peak levels during summer (Fig. 1), season of screening did not maintain its significance in the multivariable model. Seasonal effect is linked to variation in sunlight exposure [40, 41], but this may have been hindered by the concealed clothing style in the MENA region [42]. Indeed, this was evident in our study as veiling, a known risk factor for hypovitaminosis D [7, 43] emerged as the significant and dominant predictor ($p = 0.004$) of deficiency in both univariable and multivariable analyses. In a large study of 578 females from KSA, whole body coverage, age, indoor nature of work, multiparity, physical activity, sun exposure, and educational status were significant predictors of vitamin D deficiency in multivariable analyses [29].

Age was another predictive protective factor in our study in the univariable and multivariable models with older females showing lower risk of deficiency. This association has been reported in a study of pregnant females in the United States but was only significant in univariable analyses [44]. Conversely, other studies conducted in pregnant females have reported an association between aging and increased risk of deficiency, in univariable analyses [45, 46]. The association between age and increased 25OHD deficiency could be explained by the aging of the epigenome, loss of telomeres, or antioxidative effects of vitamin D metabolites [47].

High BMI has been previously linked to vitamin D deficiency in different populations [48, 49], but few studies investigated this link during pregnancy, probably due to the challenges of applying BMI cutoffs during pregnancy [50–52]. Josefson et al. reported a 0.4ng/ml decrease in maternal 25OHD for every 1 kg/m^2 increase in BMI in a model adjusted for maternal age and field center [50]. In our population, an association between BMI and deficiency risk was observed at the univariable level; with a trend to significance (p-value 0.052). However, BMI lost its significance in the multivariable model possibly due to the introduction of veiling; since veiled females also had significantly higher mean BMI (25.4 kg/m^2) compared to non-veiled females (23.4 kg/m^2). Additionally, the observed lower 25OHD levels were associated with pre-pregnancy BMI, ascertaining the effect of body fat on vitamin D availability [53].

Other lifestyle factors identified in our study as significant at the univariable level were smoking, education and employment. A Belgian cross-sectional study and the Generation R study revealed that smoking was linked to higher risk of deficiency in pregnancy [51, 54]. Moreover, education and SES may have significant influence on deficiency rates as females with higher education or SES may be more likely to use vitamin D supplements [29, 52, 55]. Paradoxically, use of vitamin D supplementation at study entry in our population did not significantly protect against deficiency, as would have been expected [56]. This lack of effect could be because only 19% of participants were taking supplements. It is noteworthy that our population did not reach the IOM recommended daily intakes of calcium and vitamin D neither from supplements nor from diet (total Ca 832 mg/day, total vitamin D 517 IU/day).

Clinical and research implications

The evidence for a beneficial effect on maternal-offspring outcomes is scarce, resulting in a lack of cohesive preventive public health strategies, regionally and globally. Indeed, current recommendations are quite variable. The IOM has set the recommended dietary allowance during pregnancy at 600IU/day; while the Endocrine Society suggests empiric supplementation for pregnant females [27, 28]. The American College of Obstetricians and Gynecologists (ACOG) suggests that 1,000–2,000 IU/day is deemed safe for pregnant females with vitamin D deficiency [57] while the WHO recommends a lower supplemental intake of 200IU/day for pregnant females with suspected deficiency [26]. In 2019 the position statement of the European Calcified Tissue Society (ECTS) has recommended a 400–600 IU/day of vitamin D supplementation for all pregnant females [7].

Strengths and limitations

We acknowledge that the current study has some limitations. An important caveat is that not all variables were assessed consistently across all participants; this could have mitigated the possible effects of some risk factors. In addition, our study participants were recruited from only two centers in Beirut area. Other potential determinants such as level of sun exposure, skin color, and body composition were not investigated. The food frequency questionnaire, although validated in adolescents, was not specifically validated in pregnant population [34], and the activity questionnaire was adapted from one used in young and middle-aged adults (15–69 years) [35].

Despite these limitations, our study has several important strengths. It rigorously investigates prevalence of hypovitaminosis D and systematically assesses its predictors in a relatively large, and importantly representative, sample of females, from two centers in Lebanon, adjusting for several significant predictors. Vitamin D levels were assayed in the same laboratory with established quality assurance protocols. Our findings are particularly relevant to females from the region because of similarities in culture and lifestyle, notoriously in clothing style, a dominant predictor of hypovitaminosis D. In addition, our post-hoc sample size calculations revealed that we would need a sample size of 62 participants to detect a significant difference between the observed 72% prevalence of hypovitaminosis D in our study group and the anticipated prevalence of approximately 50%, as published in the literature [38].

Conclusion

Hypovitaminosis D is prevalent among pregnant females in Lebanon, findings explained by veiling and young age on multivariable analyses. Early detection and preventive supplementation may help mitigate the potential adverse outcomes of hypovitaminosis D on maternal and neonatal health.

Abbreviations

AUB	American University of Beirut
AUBMC	American University of Beirut Medical Center
BH	Bahman Hospital
BMI	Body mass index
CV	Coefficient of variation
ECLIA	Electro-chemiluminescence immunoassay
ECTS	European Calcified Tissue Society
25OHD	25-Hydroxyvitamin D
IOM	Institute of Medicine
IRB	Institutional review board
KSA	Kingdom of Saudi Arabia
LMIC	Low- and middle-income countries
MENA	Middle East and North Africa
NCDs	Non-communicable diseases
RDI	Recommended dietary intake
SES	Socioeconomic status
SD	Standard deviation
TSH	Thyroid stimulating hormone
UVB	Ultraviolet B
WHO	World Health Organization

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12978-025-02028-8.

Supplementary Material file 1.

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Authors' contributions
GEHF and MC conceived the idea of the trial; MC, GEHF and AN designed the study protocol. CC and NH provided advice on the trial design and conduct, and piloting of sample size calculation. AN, NT, RT and TD were PIs who contributed to subject recruitment. SA, MR and MA executed the trial, recruited subjects and entered the data. SA conducted the analyses and wrote the manuscript. All authors have read and approved the manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Institutional Review Board at the American University of Beirut.

Competing interests
C.C. reports personal fees, consultancy, lecture fees and honoraria from ABBH, Amgen, Eli Lilly, GSK, Medtronic, Merck, Novartis, Pfizer, Roche, Servier, Takeda and Theramex, outside the submitted work. N.C.H. reports personal fees, consultancy, lecture fees and honoraria from Alliance for Better Bone Health, AMGEN, MSD, Eli Lilly, UCB, Kyowa Kirin, Servier, Shire, Consilient Healthcare, Theramex and Internis Pharma, outside the submitted work. All other authors report no conflict of interest.
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References

1. Palacios C, Gonzalez L. Is vitamin D deficiency a major global public health problem? J Steroid Biochem Mol Biol. 2014;144:138–45.
2. Perampalam S, Ganda K, Chow KA, Opie N, Hickman PE, Shadbolt B, et al. Vitamin D status and its predictive factors in pregnancy in 2 Australian populations. Aust N Z J Obstet Gynaecol. 2011;51(4):353–9.
3. Bouillon R, Marcocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and Extraskeletal Actions of Vitamin D: Current Evidence and Outstanding Questions. Endocr Rev. 2019;40(4):1109–51.
4. Amrein K, Scherkl M, Hoffmann M, Neuwersch-Sommeregger S, Köstenberger M, Tmava Berisha A, et al. Vitamin D deficiency 2.0: an update on the current status worldwide. Eur J Clin Nutr. 2020;74(11):1498–513.
5. Bassil D, Rahme M, Hoteit M, Fuleihan GH. Hypovitaminosis D in the Middle East and North Africa: Prevalence, risk factors and impact on outcomes. Dermato-endocrinology. 2013;5(2):274–98.
6. Karras S, Paschou SA, Kandaraki E, Anagnostis P, Annweiler C, Tarlatzis BC, et al. Hypovitaminosis D in pregnancy in the Mediterranean region: a systematic review. Eur J Clin Nutr. 2016;70(9):979–86.
7. Lips P, Cashman KD, Lamberg-Allardt C, Bischoff-Ferrari HA, Obermayer-Pietsch B, Bianchi ML, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endocrinol. 2019;180(4):P23-p54.
8. Chakhtoura M, Rahme M, Chamoun N, El-Hajj FG. Vitamin D in the Middle East and North Africa. Bone reports. 2018;8:135–46.
9. Karras SN, Wagner CL, Castracane VD. Understanding vitamin D metabolism in pregnancy: From physiology to pathophysiology and clinical outcomes. Metabol Clin Exp. 2018;86:112–23.
10. Kovacs CS. Maternal Mineral and Bone Metabolism During Pregnancy, Lactation, and Post-Weaning Recovery. Physiol Rev. 2016;96(2):449–547.
11. Brannon PM, Picciano MF. Vitamin D in Pregnancy and Lactation in Humans. Annu Rev Nutr. 2011;31(1):89–115.
12. Dawodu A, Akinbi H. Vitamin D nutrition in pregnancy: current opinion. Int J Women's Health. 2013;5:333–43.
13. Mohammad-Alizadeh-Charandabi S, Mirghafourvand M, Mansouri A, Najafi M, Khodabande F. The Effect of Vitamin D and Calcium plus Vitamin D during Pregnancy on Pregnancy and Birth Outcomes: a Randomized Controlled Trial. J Caring Sci. 2015;4(1):35–44.
14. Young BE, McNanley TJ, Cooper EM, McIntyre AW, Witter F, Harris ZL, et al. Maternal vitamin D status and calcium intake interact to affect fetal skeletal growth in utero in pregnant adolescents. Am J Clin Nutr. 2012;95(5):1103–12.
15. Lee SB, Jung SH, Lee H, Lee SM, Jung JE, Kim N, et al. Maternal vitamin D deficiency in early pregnancy and perinatal and long-term outcomes. Heliyon. 2023;9(9):e19367.
16. Gowtham T, Venkatesh S, Palanisamy S, Rathod S. Impact of maternal hypovitaminosis D on birth and neonatal outcome - a prospective cohort study. J Mater Fetal Neonatal Med. 2022;35(25):9940–7.
17. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017;18(2):153–65.
18. Hollis BW, Wagner CL. Vitamin D and pregnancy: skeletal effects, nonskeletal effects, and birth outcomes. Calcif Tissue Int. 2013;92(2):128–39.
19. Tamblyn JA, Pilarski NSP, Markland AD, Marson EJ, Devall A, Hewison M, et al. Vitamin D and miscarriage: a systematic review and meta-analysis. Fertil Steril. 2022;118(1):111–22.
20. Holick MF. A Call to Action: Pregnant Women In-Deed Require Vitamin D Supplementation for Better Health Outcomes. J Clin Endocrinol Metab. 2018;104(1):13–5.
21. Whitehouse AJ, Holt BJ, Serralha M, Holt PG, Kusel MM, Hart PH. Maternal serum vitamin D levels during pregnancy and offspring neurocognitive development. Pediatrics. 2012;129(3):485–93.
22. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ. 2013;346:f1169.
23. Thorne-Lyman A, Fawzi WW. Vitamin D during pregnancy and maternal, neonatal and infant health outcomes: a systematic review and meta-analysis. Paediatr Perinatal Epidemiol. 2012;26 Suppl 1(0 1):75–90.
24. Salman S, Khouzami M, Harb M, Saleh B, Boushnak MO, Moussa MK, et al. Prevalence and Predictors of Vitamin D Inadequacy: A Sample of 2,547 Patients in a Mediterranean Country. Cureus. 2021;13(5):e14881.
25. Palacios C, Kostiuk LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019;7(7):Cd008873.
26. WHO Guidelines Approved by the Guidelines Review Committee. WHO antenatal care recommendations for a positive pregnancy experience: Nutritional interventions update: Vitamin D supplements during pregnancy. Geneva: World Health Organization © World Health Organization 2020. 2020.
27. IOM. Institute of Medicine Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press; 2011.
28. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, Lazaretti-Castro M, et al. Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2024;109(8):1907–47.
29. Al-Musharaf S, Fouda MA, Turkestani IZ, Al-Ajlan A, Sabico S, Alnaami AM, et al. Vitamin D Deficiency Prevalence and Predictors in Early Pregnancy among Arab Women. Nutrients. 2018;10(4):489.
30. Al-Ajlan A, Krishnaswamy S, Alokail MS, Aljohani NJ, Al-Serehi A, Sheshah E, et al. Vitamin D deficiency and dyslipidemia in early pregnancy. BMC Pregnancy Childbirth. 2015;15:314.
31. Fouda MA, Turkestani IZ, Almusharraf S, Al-Ajlan A, Angkaya-Bagayawa FF, Sabico S, et al. Extremely High Prevalence of Maternal and Neonatal Vitamin D Deficiency in the Arab Population. Neonatology. 2017;112(3):225–30.

32. Izzeldin H, Taha Z, Ihab T, Elbadawi S, Hisham S, Rodrigues Amorim Adegboye A, et al. Risk Factors for Maternal Vitamin D Deficiency within the United Arab Emirates. J Pregnancy Child Health. 2016;3.
33. 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):e010818.
34. Kizirian AS, American University of Beirut. Faculty of Food Sciences. Department of Food T, Nutrition. Evaluation of the intake of calcium and vitamin D by adolescents in Beirut. 2000.
35. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International Physical Activity Questionnaire: 12-Country Reliability and Validity. Med Sci Sports Exerc. 2003;35(8):1381–95.
36. WHO. A healthy lifestyle - WHO recommendations. 2010.
37. Hajizadeh S, Rankin Shary J, Gayle Reed S, Lynn WC. The prevalence of hypovitaminosis D and its risk factors in pregnant women and their newborns in the Middle East: A systematic review. Int J Reprod Biomed. 2019;17(10):685–708.
38. Saraf R, Morton SM, Camargo CA Jr, Grant CC. Global summary of maternal and newborn vitamin D status - a systematic review. Matern Child Nutr. 2016;12(4):647–68.
39. Saad RK, Akiki VC, Rahme M, Ajjour S, Assaad M, El-Hajj Fuleihan GA. Time trends and predictors of hypovitaminosis D across the life course: 2009–2016. Metabolism. 2020;105:154138.
40. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab. 1988;67(2):373–8.
41. Holick MF, Chen TC, Lu Z, Sauter E. Vitamin D and skin physiology: a D-lightful story. J Bone Mineral Res. 2007;22(Suppl 2):V28-33.
42. Alagöl F, Shihadeh Y, Boztepe H, Tanakol R, Yarman S, Azizlerli H, et al. Sunlight exposure and vitamin D deficiency in Turkish women. J Endocrinol Invest. 2000;23(3):173–7.
43. Gannagé-Yared MH, Chemali R, Yaacoub N, Halaby G. Hypovitaminosis D in a sunny country: relation to lifestyle and bone markers. J Bone Miner Res. 2000;15(9):1856–62.
44. Ginde AA, Sullivan AF, Mansbach JM, Camargo CA Jr. Vitamin D insufficiency in pregnant and nonpregnant women of childbearing age in the United States. Am J Obstet Gynecol. 2010;202(5):436.e1-.e4368.
45. Shen Y, Pu L, Si S, Xin X, Mo M, Shao B, et al. Vitamin D nutrient status during pregnancy and its influencing factors. Clin Nutr. 2020;39(5):1432–9.
46. Chen G-d, Pang T-t, Li P-s, Zhou Z-x, Lin D-x, Fan D-z, et al. Early pregnancy vitamin D and the risk of adverse maternal and infant outcomes: a retrospective cohort study. BMC Pregnancy Childbirth. 2020;20(1):465.
47. Schöttker B, Hagen L, Zhang Y, Gào X, Holleczek B, Gao X, et al. Serum 25-Hydroxyvitamin D Levels as an Aging Marker: Strong Associations With Age and All-Cause Mortality Independent From Telomere Length, Epigenetic Age Acceleration, and 8-Isoprostane Levels. J Gerontol Series A. 2018;74(1):121–8.
48. Arabi A, Chamoun N, Nasrallah M, Tamim H. Vitamin D Deficiency in Lebanese Adults: Prevalence and Predictors from a Cross-Sectional Community-Based Study. Int J Endocrinol. 2021;2021:1–9.
49. Cheng S, Massaro JM, Fox CS, Larson MG, Keyes MJ, McCabe EL, et al. Adiposity, cardiometabolic risk, and vitamin D status: the Framingham Heart Study. Diabetes. 2010;59(1):242–8.
50. Josefson JL, Reisetter A, Scholtens DM, Price HE, Metzger BE, Langman CB. Maternal BMI Associations with Maternal and Cord Blood Vitamin D Levels in a North American Subset of Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study Participants. PLoS ONE. 2016;11(3):e0150221.
51. Vinkhuyzen AAE, Eyles DW, Burne TH, Blanken LME, Kruithof CJ, Verhulst F, et al. Prevalence and predictors of vitamin D deficiency based on maternal mid-gestation and neonatal cord bloods: The Generation R Study. J Steroid Biochem Mol Biol. 2016;164:161–7.
52. Woolcott CG, Giguère Y, Weiler HA, Spencer A, Forest JC, Armson BA, et al. Determinants of vitamin D status in pregnant women and neonates. Can J Public Health Revue canadienne de sante publique. 2016;107(4–5):e410–6.
53. Bodnar LM, Catov JM, Roberts JM, Simhan HN. Prepregnancy Obesity Predicts Poor Vitamin D Status in Mothers and Their Neonates. J Nutr. 2007;137(11):2437–42.
54. Vandevijvere S, Amsalkhir S, Van Oyen H, Moreno-Reyes R. High Prevalence of Vitamin D Deficiency in Pregnant Women: A National Cross-Sectional Survey. PLoS ONE. 2012;7(8):e43868.
55. Sotunde OF, Laliberte A, Weiler HA. Maternal risk factors and newborn infant vitamin D status: a scoping literature review. Nutr Res. 2019;63:1–20.
56. Pérez-López FR, Pasupuleti V, Mezones-Holguin E, Benites-Zapata VA, Thota P, Deshpande A, et al. Effect of vitamin D supplementation during pregnancy on maternal and neonatal outcomes: a systematic review and meta-analysis of randomized controlled trials. Fertil Steril. 2015;103(5):1278-88.e4.
57. ACOG. American College of Obstetricians and Gynecologists Committee Opinion No 495: Vitamin D: Screening and supplementation during pregnancy. Obstetr Gynecol. 2011;118(1):197–8.

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