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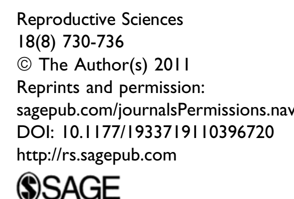

First Trimester Serum 25-Hydroxyvitamin D Status and Factors Related to Lower Levels in Gravids Living in the Spanish Mediterranean Coast

Faustino R. Pérez-López, MD, PhD[1,2], Ana M. Fernández-Alonso, MD, PhD[3], Patricia Ferrando-Marco, MD[3], María D. González-Salmerón, MD[3], Elia C. Dionis-Sánchez, MD[3], Gabriel Fiol-Ruiz, MD, PhD[3], and Peter Chedraui, MD, MSc[4]

Abstract

Objective: To assess first trimester serum 25-hydroxyvitamin D [25(OH)D] status and factors related to deficient levels in pregnant Spanish women. **Methods:** This cross-sectional study was carried out among 502 gravids (11 to 14 weeks) living in the Spanish Mediterranean sea coast (near Almería at latitude 36° N, longitude 2° W) to whom serum 25(OH)D levels were measured by electrochemiluminescence immunoassay. Logistic and multiple linear regression analysis were performed to assess the influence of ethnicity, immigration status, season of the year at blood sampling, body mass index (BMI), parity and smoking habit over 25(OH)D levels. **Results:** The median (interquartile range, IQR) serum 25(OH)D levels for the entire sample was 27.4 ng/mL (IQR = 20.9-32.8). Only 35.9% of participants had adequate serum 25(OH)D levels ($\geq$30 ng/mL) whereas in 41.4% and 22.7% these levels were found to be insufficient (20-29.9 ng/mL) and deficient (<20 ng/mL), respectively. Vitamin D status was found to be significantly lower in Arab women as compared to Caucasian women. 25(OH)D levels were positively correlated with gestational age at sampling and inversely with BMI values (univariate analysis). Logistic regression analysis determined that non-Caucasian ethnicity, season at sampling (autumn/winter), and nulliparity were factors related to deficient 25(OH)D levels. Multiple linear regression found a similar model yet also including maternal weight inversely correlating with 25(OH)D levels. **Conclusion:** Despite living in one of the sunniest, warmest, and driest climates of Europe, gravids displayed a high prevalence of first trimester insufficient/deficient serum 25(OH)D levels related to season at sampling, nulliparity, maternal weight, and non-Caucasian ethnicity.

Keywords

vitamin D, 25 hydroxyvitamin D, pregnancy, ethnicity, risk factors, sunlight, body mass index, maternal weight

Introduction

The vitamin D system includes a group of fat-soluble secosteroids. Metabolism of vitamin D among mammals is largely influenced by species-specific skin characteristics, sun exposure, nutrition, latitude of residency, and individual behavior. In humans, most vitamin D is obtained by keratinocyte cholecalciferol photosynthesis after skin exposure to solar ultraviolet B radiation.[1] The second source of vitamin D is the digestive absorption of food and supplement intake. Vegetable products provide ergocalciferol (vitamin D_2) whereas animal food provides cholecalciferol (vitamin D_3). Both vitamin D_2 and D_3 are transferred to the blood where they bind to a vitamin D binding protein. In the liver, they are then converted to 25-hydroxyvitamin D [25(OH)D], which is the major circulating

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form of vitamin D, and the best indicator of its sufficiency. In the kidney, [25(OH)D] is converted to 1,25-dihydroxycholecalciferol [1,25(OH)$_2$D], the major active form of vitamin D. A 24 hydroxylation reaction in the kidney leads to inactivation of 1,25(OH)$_2$D.

The placenta is an extrarenal source of 1,25(OH)$_2$D during human pregnancy.[2-5] The CYP24A1 gene, which controls 24 hydroxylation, is downregulated in placenta, purified cytotrophoblasts, and chorionic villous tissue.[6] Thus, serum 1,25(OH)$_2$D levels significantly increase during pregnancy, particularly in the second and third trimesters.[7,8] Lower serum 25(OH)D levels have been reported at the early antenatal visit among pregnant women of a non-European ethnic minority population living in South Wales or The Netherlands, to whom subsequent supplementation was recommended.[9,10] Moreover, a high prevalence of low serum 25(OH)D levels has also been reported among Caucasian gravids from central Europe and the United Kingdom.[11,12] Vitamin D synthesis in humans is highly dependent on weather including cloud cover, ozone, air pollution, and sunshine hours.[13-15] The objective of the present investigation was to assess first trimester serum 25(OH)D status and factors related to lower levels in pregnant women living in a sunny Spanish region on the Mediterranean sea coast.

Material and Methods

The present cross-sectional research was approved by the Research Ethics Committee of the Torrecárdenas Hospital, Almería, Spain. Pregnant women attending the outpatient clinic of the Torrecárdenas Hospital from May 2009 to April 2010 for their first antenatal visit (11 to 14 weeks gestation) were informed about the observational nature of the study and requested to participate after giving written consent. Participants with increased risk for intrauterine fetal growth restriction were excluded namely hereditary (factor V Leyden mutation, S protein deficiency, C protein deficiency, factor XII deficiency, methylenetetrahydrofolate reductase mutation) or acquired thrombophilias (antiphospholipid syndrome or systemic lupus erythematosus). Upon recruitment, no participant was on vitamin D supplementation.

All participants lived in the Spanish Mediterranean coast (near Almeria at latitude 36° N, longitude 2° W). This geographical area has one of the sunniest, warmest, and driest climates in Europe. Indeed, it has annually about 3000 hours of sunshine, 320 sunny days, and only 25 to 30 wet days.[16]

Serum 25(OH)D Immunoassay

Serum 25(OH)D levels were measured on a Roche Modular E 170 analyzer (Roche Diagnostics, West Sussex, England) by electrochemiluminescence immunoassay using a polyclonal antibody against 25(OH)D. Results are expressed in ng/mL (equivalence of 1 ng/mL = 2.496 nmol/L). This method has been validated against high-performance liquid chromatography (HPLC) and radioimmunoassay methodology and is capable of detecting 25(OH)D levels in the range of 4 to 96 ng/mL.[17] Women were categorized according to determined 25(OH)D levels as sufficient ($\geq$30 ng/mL), insufficient (20 to 29.9 ng/mL), and deficient (<20 ng/mL).

Statistical Analysis

Statistical analysis was performed using SPSS software package (Version 13.0 for Windows, SPSS Inc, Chicago, Illinois). Data are presented as medians, interquartile ranges (IQR), percentages, odds ratios (OR), and confidence intervals. Kolmogorov Smirnov's test was used to determine the normality of data distribution. According to this, continuous nonparametric data were analyzed with the Mann-Whitney test (2 independent samples) or the Kruskal Wallis test (various independent samples). Chi-square test was used to compare percentages with Yates correction performed when applicable. Logistic regression analysis was used to assess risk factors related to deficient 25(OH)D levels (<20 ng/mL). The regression model was constructed using significant variables provided from univariate analysis. Independent variables considered in the logistic regression model included maternal age, ethnicity, native/immigrant status, altitude of residency (coast or highlands), season of the year and gestational age at blood sampling, weight, height, body mass index (BMI), parity, and smoking habit. Entry of variables into the model was considered by including all those with less than 20% significance level found during univariate analysis. In the final multivariable model, variables obtaining a *P* value >.05 were removed (forward stepwise procedure). Adequacy of the regression model was demonstrated with the Hosmer-Lemeshow goodness-of-fit test. Pearson or Spearman correlation coefficients were used to determine linear relationships between 25(OH)D levels and several continuous variables: maternal age, gestational age at sampling, parity, and BMI values. Additionally, multiple linear regression analysis was performed adjusting for several confounding factors. Prior to any linear regression analysis, numeric data was log transformed. For all calculations, a *p* value of <.05 was considered as statistically significant.

Results

During the study period, a total of 507 gravids (11 to 14 weeks) were recruited. A total of 502 participants providing serum in adequate conditions for 25(OH)D level determinations were recruited in spring (n = 50), summer (n = 300), fall (n = 118), or winter (n = 34). Other basal characteristics of participants and 25(OH)D levels are depicted on Table 1. Of the total, 419 were Spanish and 83 were immigrants (25 Caucasian Slavic, 49 Arabic, 3 Black African, 3 South American, and 3 Asiatic). Median serum 25(OH)D levels for the entire sample was 27.4 ng/mL (IQR = 20.9-32.8). Only 35.9% of participants had adequate serum 25(OH)D levels, whereas in 41.4% and 22.7%, these levels were found to be insufficient and deficient, respectively. Vitamin D status was found to be significantly lower in Arab women as compared to Caucasian women. Pregnant women of Spanish nationality (independent of their ethnic component) had significantly higher median 25(OH)D levels

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Table 1. Basal Characteristics and 25(OH)D Status of the Studied Population (n = 502)[a]

Parameters	25(OH)D Levels (ng/mL), Median (IQR)	25(OH)D Levels, <20 ng/mL n (%)	25(OH)D Levels, 20-29.9 ng/mL n (%)	25(OH)D Levels, ≥30 ng/mL n (%)
All (n = 502)	27.4 (20.9-32.8)	114 (22.7)	208 (41.4)	180 (35.9)
Age				
<20 (n = 28)	28.8 (22.6-34.0)	5 (17.8)	12 (42.9)	11 (39.3)
20-29 (n = 222)	26.3 (19.4-32.5)	60 (26.9)	89 (39.9)	74 (33.2)
≥30 (n = 252)	28.0 (21.8-32.8)	49 (19.5)	107 (42.6)	95 (37.9)
	P = .10	*P* = .13	*P* = .82	*P* = .53
Ethnic				
Caucasian (n = 419)	28.0 (22.8-33.5)	67 (16.0)	185 (44.1)	167 (39.9)
Slavic Caucasian (n = 25)	28.6 (23.9-34.1)	3 (12.0)	12 (48.0)	10 (40.0)
Arabic (n = 49)	14.6 (10.6-18.6)	41 (83.7)	6 (12.2)	2 (4.1)
Other ethnics (n = 9)	28.8 (18.3-26.4)	3 (33.3)	5 (55.6)	1 (11.1)
	***P*= .0001[a]**	***P*= .0001[b]**	***P*= 0.0001[b]**	***P*= .0001[b]**
Nationality				
Spanish (n = 419)	27.8 (21.5-32.8)	91 (21.7)	172 (41.1)	156 (37.2)
Immigrants (n = 83)	23.8 (19.5-32.0)	23 (27.7)	36 (43.4)	24 (28.9)
	***P*= .03[c]**	*P* = .23	*P* = .69	*P* = .14
Body mass index (kg/m^2)				
<25 (n = 307)	28.4 (22.3-33.3)	58 (18.9)	126 (41.0)	123 (40.1)
25-30 (n = 132)	25.6 (19.5-32.0)	35 (26.5)	58 (43.9)	39 (29.6)
≥30 (n = 63)	23.8 (17.8-31.7)	21 (33.3)	24 (38.1)	18 (28.6)
	***P* = .01[a]**	***P* = .02[b]**	*P* = .72	***P* = .04[b]**
Parity				
0 (n = 262)	27.0 (20.3-32.0)	64 (24.4)	110 (42.0)	88 (33.6)
1-2 (n = 228)	28.0 (22.0-33.7)	45 (19.7)	95 (41.7)	88 (38.6)
≥3 (n = 12)	21.5 (12.0-32.9)	5 (41.7)	3 (25.0)	4 (33.0)
	P = .10	*P* = .13	*P* = .50	*P* = .50
Smoking habit				
Yes (n = 89)	30.1 (24.7-35.9)	10 (11.2)	31 (34.8)	48 (53.9)
No (n = 413)	26.8 (19.9-31.8)	104 (25.1)	177 (42.9)	132 (32.0)
	***P*= .001[c]**	***P*= .004[b]**	*P* = .16	***P*= .001[b]**
Altitude of residency				
Coast (<500 mt) (n = 479)	27.4 (20.7-32.9)	110 (23.0)	195 (40.7)	174 (36.3)
Highland (>500 mt; n = 23)	28.0 (23.4-30.3)	4 (17.4)	13 (56.5)	6 (26.1)
	P = .92	*P* = .53	*P* = .13	*P* = .31
Gestational age				
<12 weeks (n = 175)	23.4 (17.7-30.0)	63 (36.0)	67 (38.3)	45 (25.7)
≥ 12 weeks (n = 327)	28.5 (23.2-34.1)	51 (15.6)	141 (43.1)	135 (41.3)
	***P*= .001[c]**	***P*= .0001[b]**	*P* = .29	***P*= .0001[b]**
Season at entry				
Spring (n = 49)	33.2 (25.4-46.7)	4 (8.2)	16 (32.7)	29 (59.1)
Summer (n = 300)	29.1 (24.9-34.1)	33 (11.0)	134 (44.7)	133 (44.3)
Autumn (n = 120)	20.7 (16.5-25.0)	56 (46.7)	47 (39.1)	17 (14.2)
Winter (n = 33)	17.2 (13.7-23.3)	21 (63.7)	11 (33.3)	1 (3.0)
	***P* = .0001[a]**	***P* = .0001[b]**	*P* = .26	***P* = .0001[b]**

Abbreviation: IQR, interquartile range.
Provided *P* values are for intragroup comparisons; significant ones in bold.
[a] *P* value as calculated with the Kruskal Wallis.
[b] *P* value as calculated with the Chi-square.
[c] *P* value as calculated with the Mann Whitney test

than pregnant immigrant women. Significant differences were found in relation to 25(OH)D levels and BMI values, season and gestational age at entry, and smoking habit (Table 1).

Logistic regression analysis determined that non-Caucasian ethnicity, season at sampling (autumn/winter) and nulliparity were factors related to deficient 25(OH)D levels (Table 2). Best model predicting vitamin D levels after multiple linear regression analysis is presented on Table 3. In this model, 25(OH)D levels positively correlated with gestational age at sampling, and inversely with non-Caucasian ethnicity, autumn/winter season, nulliparity, and maternal weight (kg).

Discussion

Casual sunlight exposure provides more than 90% of vitamin D requirements among humans. A minor amount derives from

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Table 2. Factors Related to Deficient 25(OH)D Status (<20 ng/mL): Logistic Regression Analysis[a]

Factors	Odds Ratio[b] (CI 95%)	*P* Value
Race[c]		
Caucasian	1.0 (reference)	
Non-Caucasian	36.29 (15.83-83.18)	.0001
Season at sampling		
Spring/summer	1.0 (reference)	
Autumn/winter	10.93 (6.02-19.84)	.001
Parity		
≥1	1.0 (reference)	
Nulliparity	2.47 (1.40-4.37)	.002
Gestational age		
≥12 weeks	1.0 (reference)	
<12 weeks	2.17 (1.23-3.8)	.007

Abbreviation: CI, confidence interval.
[a] Adequacy of the regression model was demonstrated with the Hosmer-Lemeshow goodness-of-fit test (chi-square = 1.99; $P = .85$).
[b] Odds ratios are adjusted for the other factors in the table.
[c] Caucasian includes Caucasian and Slavic Caucasian; non-Caucasian includes Arabic and other ethnic origin.

food and oily fish.[3,18] Serum 25(OH)D levels therefore reflect endogenous vitamin D synthesis, intake from dietary sources and supplements and sequential biosynthesis in the liver. The human genome has nearly 2800 vitamin D receptor-binding sites. Vitamin D exerts significant effects on the activity of several hundred key genes basically in relation to the intestine and bone with nonclassical actions that include effects on cell physiology and the immune system.[19,20] In nonpregnant women, low vitamin D intake (diet and supplementation), obesity, physical inactivity, low sunlight exposure, and low milk and calcium intake are the most important modifiable predictors of low serum 25(OH)D.[21-23] Nonmodifiable predictors of hypovitaminosis D include genetics, skin characteristics, and environmental factors (weather or season of the year).[4,23-25]

The present study aimed at assessing first trimester serum 25(OH)D levels in pregnant women living in a sunny southern Spanish region (Almería). A 22.7% of sampled women presented levels defined as deficient (<20 ng/mL) and 41.4% as insufficient, with no differences observed for maternal age. Similar rates have been reported in populations living farther from the Equator region, in both, nonpregnant[26-30] and pregnant women.[12,22,23,31,32] Although we did not assess pregestational 25(OH)D status, values found in the present report could be similar to maternal baseline levels and be indicative of low vitamin D intake and low sunlight exposure in this particular Spanish sunny region. A recent study reported that first trimester 25(OH)D levels were similar to those of nonpregnant women.[22]

Younger maternal age among Australian women studied at 23 to 32 weeks gestation related to vitamin D deficiency.[23] Equally, a multicenter American study reported that adolescents, as compared to adults, displayed higher first trimester 25(OH)D deficiency rates.[22] Contrary to this, neither with logistic or multiple regression analysis, the present series found no significant differences in 25(OH)D levels when adolescents were compared to their adult counterparts.

Studies addressing serum 25(OH)D levels in relation to parity have rendered conflicting results, some reporting differences,[33] others not.[34,35] In the present series, nulliparous women were more likely to be vitamin D deficient, similar to the findings of a recent North American report that included first trimester gravids of different ethnics.[32]

Vitamin D status among mammals may vary throughout the year depending on species and in relation to sunlight exposure and type of food intake.[36-38] As evidenced in several studies carried out at different latitudes, lower vitamin D levels during winter may be due to shorter daytime and hence lower skin sunlight exposure.[15,39-41] Maximal skin cholecalciferol synthesis occurs when levels of ultraviolet B radiation are highest, at around midday. During the winter, the ozone layer absorbs more ultraviolet B photons mainly due to a longer light traveling distance. This phenomenon at latitudes beyond 37° reduces some 80% of the photons reaching the earth surface.[13,14] In agreement with the latter, the present series found upon univariate, logistic and multiple linear regression analysis a significant serum 25(OH)D level variation in relation to season. Women sampled during autumn/winter displayed lower vitamin D levels. This result did not vary when each season was analyzed independently.

Vitamin D deficiency is common in dark-skinned individuals. Higher rates of low serum 25(OH)D levels have been reported among non-Western European pregnant women living in the Netherlands[8,9] or Norway.[42] Even when pregnant women are compliant with prenatal vitamins, in Australia and in both Northern and Southern USA, the prevalence of vitamin D insufficiency has been found to be high, particularly among black women. These rates were higher among black women than white ones.[22,23,31,32] Pregnant African-American, Hispanic, and Caucasian women living in southern latitudes of North America reportedly have low first trimester mean serum levels of 25(OH)D. In that study, logistic regression analysis determined that race was the most important factor related to vitamin D deficiency or insufficiency.[32] Immigrants in our study sample, specifically those of non-Caucasian (mainly Arabic) origin, displayed significantly lower 25(OH)D levels. This may be related to a poorer nutritional status, a higher prevalence of dark-skinned individuals, and/or lower sunlight exposure. Skin melanin content absorbs ultraviolet B photons. Hence, individuals with increased pigmentation need longer sunlight exposure in order to produce the same amount of vitamin D.[43]

Previous studies have shown that overweight and obese nonpregnant women are at higher risk of vitamin D deficiency, largely due to excess adiposity rather than inadequate vitamin D intake. In these nonpregnant women, an inverse association begins at a BMI cut-off value of 27.7 kg/m^2.[44] In multivariate regression models, prepregnancy obese women (BMI ≥30), as compared to those with BMI <25, displayed lower 25(OH)D levels and a higher prevalence of values considered as deficient. Moreover, an increase in BMI from 22 to 34 kg/m^2 at mid-gestation has been reported to increase vitamin D

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Table 3. Best Model Predicting Log Transformed Vitamin D Levels: Multiple Linear Regression Analysis

	Beta Coefficient	SE	CI 95%	*t*	*P* Value
Non-Caucasian	−.605	0.046	−0.695 to −0.514	−13.15	.0001
Season at sampling (autumn/winter)	−.343	0.035	−0.412 to −0.274	−9.78	.0001
Nulliparity	−.066	0.029	−0.124 to −0.008	−2.23	.02
Gestational age at sampling	.036	0.016	0.004 to 0.070	2.19	.02
Maternal weight (kg)	−.003	0.001	−0.005 to −0.001	−2.76	.006

Abbreviations: CI, confidence intervals; SE, standard error.
$r^2 = .429$; adjusted $r^2 = .424$, $P < .0001$;

deficiency risk 2-fold.[45] Our series found that women with higher BMI values displayed lower 25(OH)D values (univariate and simple linear regression analysis). This was not found during logistic and multiple linear regression analysis. Interestingly, maternal weight (kg), instead of BMI values, inversely and significantly correlated with 25(OH)D values in the multiple regression model, suggesting weight as a better predictor of vitamin D levels. Body mass index is a function of weight and height; in our series, possibly weight displayed a higher variation than height. Important to mention is the fact that our data represents a sample drawn during the first trimester. Unfortunately, multisampling was not possible for our study in order to assess changes in vitamin D levels in relation to weight and gestational age increase.

Data regarding smoking habit and vitamin D status is lacking in the literature, although newborns of mothers who smoked during pregnancy had significantly lower anthropometric measurements and lower serum 25(OH)D levels.[46] No significant relation was found between smoking habit and vitamin D status in our series, after adjustment for possible confounding factors in the multivariate analysis. In non-pregnant older participants, smoking habit did not predict vitamin D status after adjustment for confounding factors.[47]

Finally, we acknowledge the limitations of the current study. Firstly, it was an observational cross-sectional design, hence temporal relationships between the factors cannot be totally assumed. Secondly, we did not have genetic data so that information regarding vitamin D-related genetic polymorphisms could not be included in the regression analysis. Although no women were taking vitamin D supplementation upon recruitment, not assessing maternal nutritional habits maybe seen as another drawback.

Despite these limitations, our study adds to the few reporting first trimester vitamin D status in gravids living in a sunny Southern Spanish region (latitude 36° N) in which a significant proportion presented low vitamin D levels (deficient-insufficient). This is a relevant issue since growing evidence shows that low vitamin D maternal serum levels relate to adverse neonatal outcomes and postnatal sequelae. Follow-up data of our cohort will provide valuable information in relation to perinatal outcomes. Hypovitaminosis D requires lifestyle changes such as regular mild sunshine exposure (favoring vitamin D precursor skin synthesis), a vitamin D rich diet, and the use of specific supplements. The latter is still an issue despite the fact that some countries have fortified vitamin D in some foods.[26] Our results highlight the fact that vitamin D supplementation should commence at or before the first trimester in order to fulfill the needs of the developing embryo.[2,4-6,48-51]

In conclusion, despite living in one of the sunniest, warmest, and driest climates of Europe, first trimester gravids of this series displayed a high prevalence of insufficient/ deficient serum 25(OH)D levels related to non-Caucasian ethnicity, season at sampling, maternal weight and nulliparity. More research is warranted in this regard and programs aiming at increasing information related to vitamin D and pregnancy should be encouraged among health care professional and patients.

Declaration of Conflicting Interests

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