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CLINICAL ARTICLE

First-trimester maternal serum 25-hydroxyvitamin D₃ status and pregnancy outcome

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ABSTRACT

Objective: To determine the pregnancy outcome as a function of the first-trimester serum 25-hydroxyvitamin D₃ [25(OH)D] status and to compare the 25(OH)D levels in the first and third trimesters. **Methods:** Pregnant women (n = 466) tested for serum 25(OH)D levels during the first trimester were followed up until the end of pregnancy, and the obstetric and neonatal outcomes were compared in reference to the baseline 25(OH)D status. The third-trimester 25(OH)D levels were additionally measured in a subset of women (n = 148). **Results:** The obstetric and neonatal outcomes did not vary as a function of the first-trimester 25(OH)D status. Neither did the 25(OH)D levels vary as a function of pregnancy outcomes. Overall, the 25(OH)D levels significantly decreased from the first to the third trimester. The first- and third-trimester 25(OH)D levels of samples initially taken during autumn/winter were significantly lower than those that were initially taken during spring/summer. Interestingly, the decrease in 25(OH)D levels during the third trimester was independent of the season of sampling. **Conclusion:** The pregnancy outcome was independent of the first-trimester 25(OH)D status. Overall, the 25(OH)D levels significantly decreased in the third trimester. More research in this area is warranted.

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1. Introduction

Vitamin D is involved in many aspects of human life such as bone metabolism, cell functioning, and reproduction. These aspects have been studied in women from childhood and puberty to old age [1,2]. In addition, vitamin D is involved in implantation and placental development and displays antiproliferative and immunomodulatory actions [3,4]. Low serum 25-hydroxyvitamin D₃ [25(OH)D] levels have been related to adverse obstetric outcomes such as preterm birth, low birth weight, hypertension, and gestational diabetes mellitus (GDM) [3–6]. Cesarean deliveries are 4 times more common among those displaying lower 25(OH)D levels, even after adjustment for confounding factors [7]. Moreover, neonatal respiratory infections and neurologic diseases are more prevalent among infants with lower birth cord-blood 25(OH)D levels [3,4,8].

A previous study [9] has reported risk factors for a low first-trimester 25(OH)D status among Spanish women living on the Mediterranean coast. In that series, 64.1% of pregnant women had deficient

(less than 20 ng/mL) or insufficient (20–29.99 ng/mL) first-trimester serum 25(OH)D levels, with an increased risk of insufficiency related to non-Caucasian ethnicity, a higher body mass index, the first trimester occurring in autumn/winter, and nulliparity. No correlation was found between 25(OH)D, circulating beta-human chorionic gonadotropin, and pregnancy-associated plasma protein A levels [10]. The present study was performed to determine the obstetric and neonatal pregnancy outcomes of the original cohort [9] as a function of the first-trimester serum 25(OH)D status and to compare the 25(OH)D levels in the first and third trimesters.

2. Materials and methods

A cross-sectional study was carried out from May 1, 2009, to April 30, 2010, at the outpatient clinic of the Torrecárdenas Hospital, Almería, Spain, among pregnant women attending their first prenatal visit (11–14 weeks of pregnancy). The women were tested for serum 25(OH)D after having been informed about the research and its objectives, and after having given their consent to participate. Data relating to the first phase of the project, namely factors associated with a low first-trimester 25(OH)D status, have been published previously [9]. In the second phase, the participants were followed up until the end of their pregnancies and the obstetric and neonatal outcomes were analyzed as a function of their first-trimester 25(OH)D status.

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Additionally, a second 25(OH)D determination was performed in the third trimester (36–39 weeks) in a subset of participants.

All participants lived on the Spanish Mediterranean coast near Almería. The climate characteristics of this geographic area have been described previously [9], with further information provided by the Spanish Meteorological Agency [11]. The exclusion criteria included an increased risk for intrauterine fetal growth restriction, specifically hereditary or acquired thrombophilias. No participant was on vitamin D supplementation upon recruitment or follow-up.

The following maternal data were taken: Age, parity, season and duration of pregnancy at blood sampling, body mass index, ethnicity (Caucasian yes/no), smoking status, residency (coast/highland), and nationality. Obstetric data included: Type of labor initiation, route of delivery, and frequency of pregnancy-related complications. Neonatal variables included: Gestational age, weight, and Apgar scores at birth. Preterm birth was defined as birth between 21 weeks and 36 weeks 6 days of pregnancy [12]. Infants with birth weights below the 10th percentile for their gestational age were considered to be small for gestational age (SGA) [13]. Pre-eclampsia was defined as a blood pressure of 140/90 mmHg or higher after 20 weeks of pregnancy in women with previously normal blood pressure, accompanied by proteinuria of 0.3 g or more in a 24-hour urine collection or a urine dipstick result of 1+ or greater [14]. The diagnosis of GDM was performed using a 2-step approach, which involved an initial screening for glycemia levels of 140 mg/dL or more 1 hour after a 50-g oral glucose load, followed on a separate day by a diagnostic oral glucose tolerance test using a 100-g oral glucose load among those who screened positive [15].

The serum 25(OH)D levels were determined on a Roche Modular E 170 analyzer (Roche Diagnostics, Burgess Hill, UK) by means of an electrochemiluminescence immunoassay using a polyclonal antibody against 25(OH)D. The cross-reactivity was lower than 10% for 25-hydroxyvitamin D₂ and 24,25-dihydroxyvitamin D₃, and lower than 1% for cholecalciferol and ergocalciferol. The coefficient of variation for the method was below 5%. The 25(OH)D results are expressed in ng/mL (1 ng/mL is equivalent to 2.496 nmol/L). This methodology is capable of detecting 25(OH)D levels in the range of 4–96 ng/mL [7]. Depending on their 25(OH)D levels, the women were categorized as sufficient (30 ng/mL or more), insufficient (20–29.99 ng/mL), or deficient (less than 20 ng/mL) in vitamin D.

The software package SPSS version 10 (SPSS, Chicago, IL, USA) was used to perform the statistical analysis. The data are presented as medians, interquartile ranges (IQR), and percentages. The Kolmogorov–Smirnov test was used to determine the normality of the data distribution. Continuous nonparametric data were analyzed with the Mann–Whitney *U* test (2 independent samples), the Kruskal–Wallis test (several independent samples), or the Wilcoxon rank test (2 related samples). The χ^2 test was used to compare percentages, with the Yates correction performed where applicable. The Fisher exact test was applied where appropriate. Spearman rho coefficients were calculated to determine the correlations between the 25(OH)D level and several numeric outcome variables: Interval (number of days) from sampling to birth, neonatal gestational age, weight, and Apgar score. Prior to any statistical analysis, the 25(OH)D values were log-transformed. $P < 0.05$ was considered statistically significant.

The study protocol was approved by the Research Ethics Committee of the study hospital.

3. Results

A total of 507 women (11–14 weeks of pregnancy) were recruited during the study period. Forty-one cases were excluded from the analysis for reasons such as unavailable baseline 25(OH)D data ($n = 5$), abortion ($n = 6$), and loss to follow-up ($n = 30$). Hence, 466 women who gave birth at the study institution were initially sampled during spring ($n = 45$), summer ($n = 280$), fall ($n = 110$), or winter ($n = 31$). The serum 25(OH)D levels were sufficient in 166 (35.6%) women, insufficient in 191 (41.0%), and deficient in 109 (23.4%). Other baseline characteristics of the participants were similar to those reported for the original cohort [9], in which lower serum 25(OH)D levels were significantly related to non-Caucasian ethnicity, higher maternal body mass index, tobacco use, and season and gestational age at blood sampling [9].

The frequency of various indicators of obstetric and neonatal outcome did not differ as a function of the first-trimester 25(OH)D status (Table 1). In addition, the 25(OH)D levels did not differ as a function of the various measured outcomes (present or not), as analyzed with the Mann–Whitney or Kruskal–Wallis tests. Finally, no significant correlations were found between the first-trimester 25(OH)D levels and several numeric outcome variables (time interval from sampling

Table 1
Pregnancy outcome in relation to first-trimester vitamin D status ($n = 466$)^a.

Parameters	All ($n = 466$)	25(OH)D < 20 ng/mL ($n = 109$)	25(OH)D 20–29.99 ng/mL ($n = 191$)	25(OH)D \geq 30 ng/mL ($n = 166$)	<i>P</i> value
Labor initiation ^b					
Spontaneous	255 (54.7)	64 (58.7)	104 (54.5)	87 (52.4)	0.58
Induced	167 (35.8)	36 (33.0)	75 (39.3)	56 (33.7)	0.43
Route of delivery					
Cesarean delivery	105 (22.5)	23 (21.1)	41 (21.5)	41 (24.7)	0.65
Emergency cesarean	61 (13.1)	14 (12.8)	29 (15.2)	18 (10.8)	0.47
Elective cesarean	44 (9.4)	9 (8.3)	12 (6.3)	23 (13.9)	0.06
Premature rupture of membranes	63 (13.5)	11 (10.1)	29 (15.2)	23 (13.9)	0.45
Hypertensive states					
Pre-eclampsia	7 (1.5)	2 (1.8)	3 (1.6)	2 (1.2)	0.91
Gestational hypertension	11 (2.4)	3 (2.8)	5 (2.6)	3 (1.8)	0.84
Chronic hypertension	1 (0.2)	1 (0.9)	0 (0.0)	0 (0.0)	0.19
Gestational diabetes	36 (7.7)	12 (11.0)	12 (6.3)	12 (7.2)	0.32
Intrauterine fetal demise	1 (0.2)	0 (0.0)	1 (0.5)	0 (0.0)	0.48
Preterm birth	33 (7.1)	7 (6.4)	15 (7.9)	11 (6.6)	0.86
Neonatal gender masculine	236 (50.6)	50 (45.9)	95 (49.7)	91 (54.8)	0.33
Apgar score					
<7 at 1 minute	14 (3.0)	4 (3.7)	6 (3.1)	4 (2.4)	0.82
<7 at 5 minutes	2 (0.4)	0 (0.0)	2 (1.0)	0 (0.0)	0.90
Small for gestational age	46 (9.9)	9 (8.3)	19 (9.9)	18 (10.8)	0.78
Congenital malformation	7 (1.5)	2 (1.8)	3 (1.6)	2 (1.2)	0.91

Abbreviation: 25(OH)D, 25-hydroxyvitamin D₃.

^a Values are given as number (percentage).

^b Elective cesarean not included.

Table 2
Vitamin D level changes during pregnancy.

Season of blood sampling	Serum 25-hydroxyvitamin D ₃ level, ng/mL ^a		P value ^b
	First trimester	Third trimester	
All (n = 148)	27.6 (9.9)	18.2 (8.8)	0.0001
Baseline: spring/summer (n = 99)	30.1 (7.8)	18.6 (8.9)	0.0001
Baseline: autumn/winter (n = 49)	21.1 (9.2) ^c	17.0 (10.0) ^c	0.0001
Baseline: spring/summer; follow-up: autumn/winter (n = 82)	30.1 (7.6)	18.5 (8.7)	0.0001
Baseline: spring/summer; follow-up: spring/summer (n = 17)	28.7 (8.5)	19.4 (9.9)	0.0001
Baseline: autumn/winter; follow-up: spring/summer (n = 48)	20.7 (9.4)	17.1 (10.3)	0.0001
Baseline: autumn/winter; follow-up: autumn/winter (n = 1)	22.6 (0.0)	16.9 (0.0)	— ^d

^a Values are given as median (interquartile range).

^b Wilcoxon rank test comparing first and third trimester.

^c Significant difference compared with spring/summer (Mann–Whitney *U* test).

^d Calculation not possible owing to 1 observation only.

to birth, neonatal gestational age, birth weight, and Apgar score), as determined by Spearman bivariate analysis.

In a subset of 148 women, the 25(OH)D levels were additionally determined during the third trimester. In these women, the 25(OH)D levels significantly decreased from the first to the third trimester (Table 2). The first- and third-trimester 25(OH)D levels of women whose first trimester occurred during autumn/winter were significantly lower than those of women whose first trimester occurred during spring/summer. Interestingly, independent of the season of baseline and follow-up sampling, the 25(OH)D levels significantly decreased in the third trimester of pregnancy.

4. Discussion

In humans, 25(OH)D circulates bound to the vitamin-D-binding protein, has a 2-week half-life, and is an indicator of the endogenous vitamin D status. It may be further hydroxylated to bioactive 1,25-dihydroxyvitamin D [1,25(OH)₂D]. Depending on the extent of vitamin D acquisition (i.e. sun exposure, diet/food content, and supplement consumption), circulating 25(OH)D levels in pregnancy have been reported to remain unchanged or to decline [3,4]. During pregnancy, the decidual, placental, and maternal renal synthesis of 1,25(OH)₂D increases the maternal serum levels of 1,25(OH)₂D [3,4], thereby enhancing the maternal calcium absorption in order to fulfill fetal needs [16]. The human fetus seems to be protected against excessive maternal 1,25(OH)₂D increases [4].

In a study by Merewood et al. [7], the risk of pre-eclampsia was 5-fold increased among women with 25(OH)D levels below 15 ng/mL at a pregnancy duration of up to 22 weeks. Similarly, Powe et al. [17] reported that first-trimester 25(OH)D levels of less than 15 ng/mL were related to the development of pre-eclampsia. In a case-control study [18], women with early-onset (before 34 weeks) severe pre-eclampsia displayed lower serum 25(OH)D levels (median 18 ng/mL, IQR 13–31 ng/mL) than did healthy controls (median 32, IQR 20–44 ng/mL). By contrast, Shand et al. [19] found no significant difference in the 25(OH)D levels (measured between 10 and 20 weeks of pregnancy) of women who subsequently developed pre-eclampsia and those who did not, a situation that is consistent with the findings of the present study. Indeed, only 7 cases of pre-eclampsia, 11 of gestational hypertension, and 1 of chronic hypertension were reported after follow-up, with no prevalence differences found among women with different first-trimester 25(OH)D levels.

Despite reports evidencing a possible link between a low 25(OH)D status and pre-eclampsia, the precise mechanisms involved are yet to be determined. Conflicting results may arise from methodologic issues such as sample size, study design, season of sampling, ethnic and genetic characteristics of the participants, and/or other biologic factors that may influence the heterogeneity of the results. Hence, more research is warranted in this regard.

The serum 25(OH)D levels seem to correlate with insulin sensitivity and pancreatic cell function [20]. However, studies investigating the correlation between 25(OH)D status and GDM risk have produced conflicting results. One case-control study [6] reported that lower 25(OH)D levels (24.2 ng/mL versus 30.1 ng/mL) at 16 weeks of pregnancy were associated with a higher risk for GDM. Another case-control study [20] determined that women with GDM and impaired glucose tolerance (screened at 24–28 weeks) were 2.7 times more likely to display serum 25(OH)D levels below 20 ng/mL; this analysis was controlled for gestational age, maternal age, and body mass index. By contrast, Baker et al. [21] found no association between maternal serum 25(OH)D levels and the development of GDM among pregnant women with mostly sufficient first-trimester 25(OH)D levels (defined as 20 ng/mL or more). The results by Baker et al. are in agreement with the present series. Indeed, no association was found between the maternal first-trimester 25(OH)D status and the subsequent risk of GDM. Further studies are required to determine the precise role of the maternal first-trimester 25(OH)D status in the development of GDM. Such studies should include women with a very low 25(OH)D status and incorporate the assessment of other biologic co-factors such as the vitamin D receptor status and the vitamin-D-binding protein polymorphism status.

A low maternal vitamin D status has also been implicated in the risk of preterm labor. In comparison with term controls, Japanese women with a high risk of preterm labor displayed significantly lower serum 25(OH)D levels (11.2 ± 3.2 ng/mL versus 15.6 ± 5.1 ng/mL, determined after the 30th week of their pregnancy) [22]. In the present study, 7.1% of the Spanish women had a preterm birth, but this figure was independent of the first-trimester 25(OH)D level. Hollis et al. [23] reported that pregnant women commencing vitamin D supplementation (400, 2000, or 4000 IU/day) at 12–16 weeks presented lower preterm labor/birth rates. Interestingly, this effect was dose-dependent. Further studies are required to determine the role of vitamin D supplementation in the prevention of preterm birth.

Low maternal serum 25(OH)D levels have also been associated with a low birth weight and a shorter infant length [3,4,24]. Bodnar et al. [25] reported that the relationship among Caucasian women between maternal serum 25(OH)D levels before the 22nd week of pregnancy and the risk of an SGA birth is U-shaped. The lowest risk was observed at 25(OH)D levels between 24 and 32 ng/mL. Lefelaar et al. [24] reported data from the Amsterdam Born Children and their Development cohort, which included 3730 women of various ethnicities. Women with first-trimester 25(OH)D levels of 12 ng/mL or less were at higher risk (odds ratio 2.4) of delivering SGA infants with lower birth weights (–114 g) than were women with first-trimester 25(OH)D levels of 20 ng/mL or more. The present series found no correlation between first-trimester 25(OH)D levels and neonatal gestational age or weight.

Higher cesarean delivery rates have been reported for women with serum 25(OH)D levels below 15 ng/mL [7]. In the present study, the cesarean delivery rate did not differ in relation to the first-trimester 25(OH)D status.

The second aim of the present analysis was to assess 25(OH)D changes during pregnancy. As previously described [9], the first-trimester 25(OH)D levels in the original cohort were related to the women's ethnicity and body composition, and the season in which the first trimester of pregnancy occurred. Follow-up of a subset of the original cohort revealed that women whose first trimester occurred during autumn/winter displayed lower first- and third-trimester 25(OH)D levels than did those whose first trimester occurred during spring/summer (Table 2). In fact, independent of the season when the initial and follow-up blood samples were taken, the 25(OH)D levels significantly decreased from the first to the third trimester.

Unfortunately, it was not possible to confirm this trend for the whole cohort or to determine the pregnancy outcome within the subset as a function of overall 25(OH)D decrease or seasonal variation. Nevertheless, given that the outcome for the whole cohort did not differ depending on the baseline 25(OH)D status, it seems reasonable to assume that the outcome will not be worse even with any further decrease in 25(OH)D levels, and hence the importance of vitamin D supplementation in the prevention of pregnancy-related disorders may be challenged. Reports like the present are scarce or still lacking, and although the presented assumptions are interesting, more research is warranted.

It is important to mention that the women in the present study did not receive any vitamin D supplementation, except for the vitamin D provided through the diet, demonstrating that without any specific intervention and regardless of seasonal variation, endogenous 25(OH)D levels will decrease without any negative impact on the pregnancy outcome.

Finally, the limitations of the present study include its cross-sectional design and the limited availability of third-trimester 25(OH)D values. The authors also recognize the fact that the small number of adverse pregnancy outcomes may have limited the present comparisons. Nevertheless, the present series adds to the small number of cross-sectional studies reported in the literature that measure 25(OH)D levels during the first trimester and compare these values with third-trimester levels. It should be noted that these types of report are limited in number and sample size. The findings that the 25(OH)D levels decreased at follow-up despite seasonal variations and that the 25(OH)D status seemed to exert no net effect on the pregnancy outcome are interesting, and may be explained by the fact that Almería has a sunny climate all year round. Studies providing standard or normal 25(OH)D levels during the third trimester are warranted.

In conclusion, the pregnancy outcome did not vary as a function of the first-trimester 25(OH)D status. Overall, the 25(OH)D levels significantly decreased in the third trimester. More research in this area is warranted.

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Conflicts of interest

The authors have no conflicts of interest.

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