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Original article

Vitamin D status during pregnancy and in cord blood in a large prospective French cohort

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SUMMARY

Background & aims: Vitamin D status during pregnancy and in newborns has never been studied in France. This study aims at determining the vitamin D status during the first and third trimesters of pregnancy (T1, T3) and in cord blood (CB) in the middle-north of France.

Methods: We conducted a prospective cohort study in five French centers (latitude 47.22 to 48.86°N). Serum 25(OH)-vitamin D (25(OH)D) concentrations were measured using a radioimmunoassay during T1, T3 and in CB. According to the French guidelines, pregnant women received cholecalciferol, 100,000 IU, in the seventh month.

Results: Between April 2012 and July 2014, 2832 women were included, of whom 2803 were analyzed (mean ± SD age: 31.5 ± 5.0 years; phototypes 5–6: 21.8%). Three and 88.6% of participants received supplementation during the month before inclusion and in the seventh month, respectively. At T1, T3, and CB, mean 25(OH)D concentrations were 21.9 ± 10.4, 31.8 ± 11.5, and 17.0 ± 7.2 ng/mL, respectively, and 25(OH)D was <20 ng/mL in 46.5%, 14.0%, and 68.5%, respectively. At T1, body mass index ≥25 kg/m^2, dark phototypes, sampling outside summer, and no supplementation before inclusion were independently associated with vitamin D insufficiency (25(OH)D < 20 ng/mL). Women who received cholecalciferol supplementation in month 7 had higher 25(OH)D at T3 than non-supplemented women (32.5 ± 11.4 *versus* 25.8 ± 11.4 ng/mL, p = <0.001) and marginally higher 25(OH)D in CB (17.2 ± 7.2 *versus* 15.5 ± 7.1 ng/mL, p = 0.004).

Conclusions: Despite the recommended supplementation, vitamin D insufficiency is frequent during pregnancy and in newborns in France.

1. Introduction

Vitamin D is a prohormone with effects beyond the prevention of rickets/osteomalacia. In addition to its protective effect against bone demineralization, vitamin D sufficiency is associated with a

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reduced risk of many chronic diseases including type 2 diabetes mellitus, cardiovascular diseases, cancers, and auto-immune and infectious diseases [1]. During pregnancy, poor vitamin D status is associated with pregnancy complications such as pre-eclampsia [2,3], gestational diabetes mellitus [4], and increased risk of caesarean section [5] and of preterm birth [6,7]. It is also associated with an increased risk of wheezing and asthma [8,9], of respiratory tract infections [10] and of low bone mass [11,12] in newborns and children.

The assessment of vitamin D status is based on the measurement of the serum concentration of 25(OH)-vitamin D (25(OH)D). During pregnancy, free 25(OH)D might reflect better the vitamin D status than total 25(OH)D due to the rise of vitamin D protein levels [13]. Although there is a consensus to define vitamin D deficiency as serum 25(OH)D below 10 ng/mL (25 nmol/L), the definition of vitamin D insufficiency is less consensual. Whereas the US Institute of Medicine (IOM) defines vitamin D insufficiency as serum 25(OH)D concentrations below 20 ng/mL (50 nmol/L) in the general population [14], the Endocrine Society considers 25(OH)D levels below 30 ng/mL (75 nmol/L) to be inadequate in chronically ill patients [15].

With low contemporary sun exposure and/or use of sunscreens, the relative contribution of the solar source to total basal input of vitamin D seems to be at best of 25%, the remaining coming from food sources [16]. Regardless of the threshold for vitamin D insufficiency or inadequacy, prevalence of low serum 25(OH)D concentrations is high in most countries, including France, in all age groups [17].

Vitamin D status during pregnancy or in cord blood has been evaluated in studies conducted in North America [18,19] and in many European countries, mainly northern Europe, although few studies have measured 25(OH)D throughout the pregnancy or in cord blood in large cohorts [20–22]. Considering i) the high prevalence of vitamin D deficiency or insufficiency during pregnancy reported in most of these studies, ii) the potential deleterious consequences of low 25(OH)D circulating levels on health of both mother and child, and iii) the absence of uniform guidelines for vitamin D supplementation in pregnant women, there is an urgent need to assess vitamin D status in large populations of pregnant women and newborns and, for each country, to systematically evaluate recommendations for vitamin D supplementation during pregnancy. To our best knowledge, such a study has never been conducted in France. That's why we felt important to gather national data given the particularity of the French recommendation for vitamin D supplementation during pregnancy [23] and the lack of food fortification in France.

The aims of the present study were to determine the vitamin D status and its evolution in a large cohort of pregnant women living in France by analysis in the first and third trimesters and in cord blood. We sought to assess the determinants of vitamin D status at each time point and to study the impact of the French recommendations regarding vitamin D supplementation during pregnancy. To answer these questions, we used the prospective observational FEPED cohort study including pregnant women first seen during the first trimester in five centers of the middle-north of France.

2. Patients and methods

2.1. Study protocol

The FEPED study was initially designed to investigate the association of vitamin D status during pregnancy with pre-eclampsia in six centers (five French and one Belgian). Written informed consent was obtained from each patient before inclusion in the study. The protocol was conducted in accordance with the Declaration of Helsinki and was approved by a local independent Ethics Committee (2011/13NICB). It is registered with the ClinicalTrials.gov (identifier NCT01648842). Samples were stored in the Perinat Collection (ANR-10-EQPX-0010).

For the purpose of the present epidemiological study, which aimed to determine the 25(OH)D status of pregnant women living in France and in their newborns (in cord blood), we did not include women recruited in Bruxelles (Belgium). The patients included in this study were recruited between April 2012 and July 2014 in five French maternity departments ensuring the obstetrical follow-up from the first trimester of pregnancy until delivery. Four of these departments are located in Paris area (Béclère, Bicêtre, Cochin, and Trousseau University hospitals, latitude 48.86°N) and one is located in Nantes in the mid-western part of France (latitude 47.22°N). Patients were told about the study by the obstetrician or the midwife during the first consultation for pregnancy follow-up if the following inclusion and exclusion criteria were fulfilled. Inclusion criteria were: age $\geq$18 years, single pregnancy, gestational age from 10 to <15 weeks of amenorrhea (WA), corresponding to 8 to <13 gestational weeks (GW), at inclusion, and healthcare coverage. Exclusion criteria were conditions for which vitamin D level could have been modified or vitamin D supplementation during the third trimester could have been contra-indicated or inefficient, including serum calcium levels >2.65 mmol/L or other known pathologies of mineral metabolism, constitutive bone disease, history of urinary stones, lithium treatment, or intestinal malabsorption, and conditions susceptible to interfere with the diagnosis of pre-eclampsia, including uncontrolled hypertension (>140/90 mm Hg from the beginning of pregnancy) and renal insufficiency (serum creatinine >120 μmol/L). For all included patients, a blood sample was collected for 25(OH)D measurement between 11 and 14 WA, or between 9 and 12 GW, (the first trimester, T1, sample), during the third trimester (between 28 WA, or 26 GW, and delivery, the T3 sample) and from cord blood (CB) within the framework of the research protocol. The patients were not required to fast before blood sample collection. Vitamin D (100,000 IU of cholecalciferol) was prescribed to all women in the seventh month of pregnancy as a routine procedure in agreement with the French guidelines [23]. At obstetrics clinic from 28 GW the patient was asked whether and when she took the vitamin D supplementation and the date was recorded in the patient file. Follow-up outcomes were recorded such as outcome at birth (live birth, per partum demise, termination of pregnancy), gestational age at delivery, birth weight, vitamin D status in the first, third trimester and cord blood.

We defined vitamin D deficiency, insufficiency, inadequacy, and sufficiency as serum 25(OH)D concentrations of <10 ng/mL, <20 ng/mL, <30 ng/mL, and $\geq$30 ng/mL, respectively. The phototype of each subject was determined according to the Fitzpatrick skin type classification [24]. Pre-pregnancy body mass index (BMI) calculated from height and pre-pregnancy weight was classified using the WHO cut-off for overweight (<25 or $\geq$25 kg/m^2) [25].

2.2. Biological analysis

All blood samples were centrifuged and stored locally at −20 °C and were subsequently transferred monthly to the Department of Physiology of Necker University Hospital (Paris, France) for centralized 25(OH)D measurement from serum. 25(OH)D was measured with the DiaSorin radioimmunoassay (RIA). The Necker Hospital Physiology Laboratory participates in the DEQAS proficiency control with excellent results. A value of 4 ng/mL, corresponding to the limit of quantification that we determined in our laboratory, was assigned to any undetectable concentration.

2.3. Statistical analyses

All statistical analyses were undertaken using R 2.11.1 software. Statistical tests were two-sided and p values less than 0.05 were considered statistically significant. Baseline characteristics of women were described as means ± standard deviations for quantitative variables and frequencies (%) for qualitative variables.

Prevalence of vitamin D insufficiency and inadequacy (serum 25(OH)D concentrations <20 ng/mL and <30 ng/mL respectively) were estimated on the available samples at each time (T1, T3, and CB) along with their corresponding 95% Wald CI.

Associations between characteristics of women and 25(OH)D insufficiency were investigated using chi-squared test (or Fisher's test when it was appropriate) for qualitative factors and Student's t test for quantitative parameters. Pearson's r and p value of its test were computed to examine correlations between continuous variables. Multiple logistic regression models were performed to assess determinants of 25(OH)D insufficiency at T1 and T3 and in CB. Initial models included all significant factors identified by univariate analysis ($p < 0.05$). A backward selection procedure based on likelihood ratio tests was used. Odds ratios, 95% CI, and p values of determinants in the final models were computed.

3. Results

3.1. Description of the study and of the study population

The flow chart of the study protocol is shown in Fig. 1. None of the patients were included twice during the study. Among the 2658 women with available data regarding pregnancy outcomes, pregnancies were terminated as follows: 2621 (98.6%) live births, six (0.2%) newborn deaths during labor, 10 (0.4%) in utero deaths, and 21 (0.8%) medical abortions. The mean delivery term was 37.5 ± 1.8 GW.

Characteristics of the cohort are shown in Table 1. Among the 2779 women with available data regarding ethnical origin, 1550 (55.8%) patients originated from Continental France, 63 (2.3%) from northern Europe, 122 (4.4%) from southern Europe, 420 (15.1%) from northern Africa, 292 (10.5%) from Sub-Saharan Africa, 116 (4.2%) from French West Indies, 105 (3.8%) from Asia, and 111 (4%) from other countries. Of note, most women received vitamin D after inclusion in agreement with the French national guidelines.

3.2. Evolution of vitamin D status during pregnancy and in cord blood

Mean serum 25(OH)D concentrations for all women with available samples at each time point are presented in Table 2. Vitamin D deficiency (25(OH)D < 10 ng/mL) was present in more than 10% of cases during the first trimester and a cord blood but was nearly absent during the third trimester. As shown in Fig. 2, around half of the women had vitamin D insufficiency (25(OH)D < 20 ng/mL) during the first trimester but only 14% had vitamin D insufficiency during the third trimester. Vitamin D inadequacy (25(OH)D < 30 ng/mL) was found in three-quarters of women during the first trimester and was present in nearly half of women during the third trimester. Of note, vitamin D insufficiency or inadequacy was highly prevalent in newborns based on our cord blood analyses.

Serum 25(OH)D significantly increased between the first and the third trimesters among the 2289 women with serum 25(OH)D measurements available at these two visits (22.2 ± 10.5 ng/mL *versus* 31.8 ± 11.5 ng/mL, respectively, with a mean difference of 9.5 ± 12.8 ng/mL, $p < 0.001$). Serum 25(OH)D significantly decreased between the third trimester and cord blood among the 1606 women

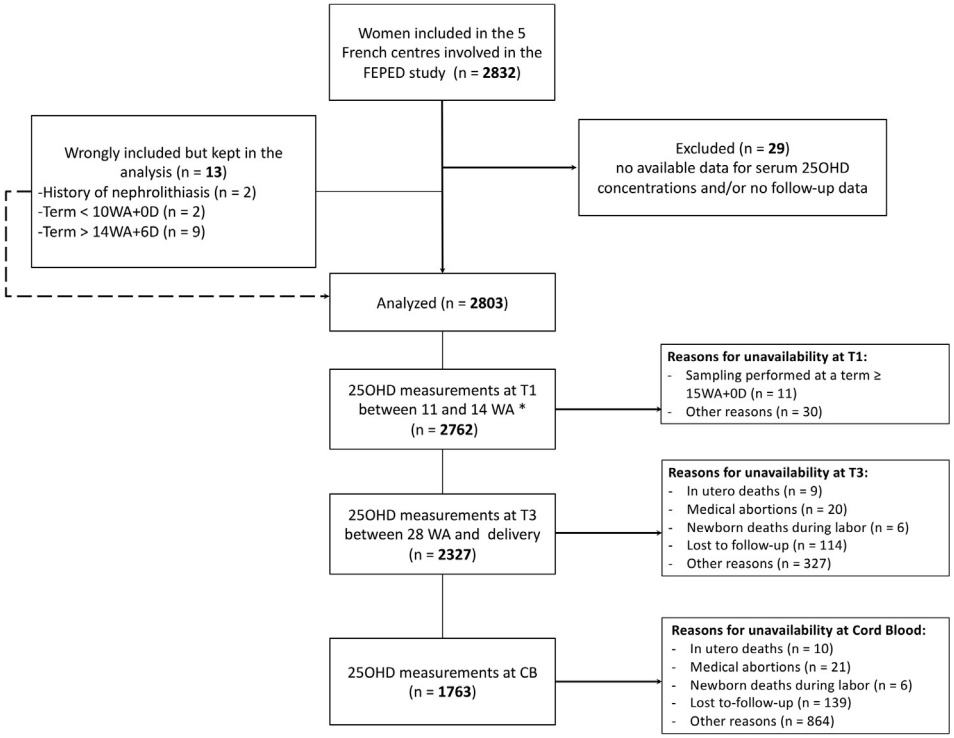

Fig. 1. Flow chart of the study protocol. 25(OH)D: 25(OH)-vitamin D, D: day, T1: first trimester, T3: third trimester, CB: cord blood, GW: gestational weeks. *25(OH)D measurements performed for women at a term ≥13 GW+0D at the time of T1 sampling were excluded from the analysis.

Table 1
Characteristics of the population.

	n	Mean ± SD or n (% of patients)
Age at inclusion (years)	2803	31.5 ± 5.0
Age ≥35 (years)		734 (26.2%)
Gestational age at inclusion (GW)	2803	10.8 ± 0.8
BMI before the beginning of pregnancy (kg/m^2)	2773	23.5 ± 4.6
BMI ≥25 (kg/m^2)		861 (31.1%)
Pre gestational diabetes mellitus	2778	103 (3.7%)
Season of conception	2803	
Summer		712 (25.4%)
Fall		692 (24.7%)
Winter		704 (25.1%)
Spring		695 (24.8%)
Phototype[a]	2803	
Types 1 to 4		2191 (78.2%)
Types 5 and 6		612 (21.8%)
Parity[b]	2781	
0		1349 (48.5%)
1		966 (34.7%)
>1		466 (16.8%)
Smoking		
Before the ongoing pregnancy	2760	569 (20.6%)
Active at the beginning of pregnancy	2743	317 (11.6%)
Active at inclusion	2727	225 (8.2%)
Vitamin D supplementation during the month before inclusion	2452	74 (3.0%)
Vitamin D supplementation in 7th month[c]	2592	2296 (88.6%)

BMI: body mass index, GW: gestational weeks, n: number of patients with available data, SD: standard deviation.
[a] According to the Fitzpatrick phototyping scale.
[b] Excluding the ongoing pregnancy.
[c] Vitamin D supplementation in 7th month of pregnancy consists of 100,000 IU cholecalciferol, according to the French guidelines.

with serum 25(OH)D measurements available at these two visits (31.7 ± 11.5 ng/mL *versus* 17.1 ± 7.3 ng/mL respectively, with a mean difference of −14.7 ± 8.9 ng/mL, p < 0.001). Figure 3a shows that serum 25(OH)D during the third trimester positively correlates with serum 25(OH)D during the first trimester. Figure 3b shows that the positive correlation between serum 25(OH)D during the third trimester and in cord blood is even stronger.

3.3. Determinants of vitamin D status during pregnancy and in newborns

Univariate analysis of determinants of vitamin D insufficiency (25(OH)D < 20 ng/mL) during pregnancy and in cord blood is summarized in Table 3. Table 4 shows 25(OH)D concentrations and categories among women who received or did not receive the recommended supplementation during the seventh month of pregnancy. Vitamin D supplementation during the seventh month did not significantly influence the presence of vitamin D insufficiency in cord blood (Table 3). However, serum 25(OH)D was slightly but significantly higher in cord blood in case of vitamin D supplementation during the seventh month of pregnancy (Table 4). Moreover, there was less vitamin D deficiency (25(OH)D < 10 ng/mL) in cord blood in supplemented women (Table 4).

Supplementation had a significant impact on serum 25(OH)D concentration during the third trimester since there was virtually no vitamin D deficiency during the third trimester in supplemented women (Table 4). Of note, 11.6% and 41.8% of the supplemented women had vitamin D below 20 or 30 ng/mL, respectively, during the third trimester.

Weight gain during pregnancy was not associated with vitamin D insufficiency during the third trimester (+8.7 ± 5.0 kg in the 308 women with serum 25(OH)D < 20 ng/mL *versus* +8.5 ± 4.3 kg in the 1908 women with serum 25(OH)D ≥ 20 ng/mL, p = 0.54).

Table 5 shows variables independently associated with serum 25(OH)D concentration <20 ng/mL during pregnancy and in cord blood. In multivariate analysis, overweight before pregnancy, dark phototype, sampling during fall, winter, or spring, and absence of vitamin D supplementation at the very beginning of pregnancy were independently associated with vitamin D insufficiency in the first trimester. In the third trimester, age below 35 years, parity ≥1, dark phototype, sampling during fall, winter, or spring, absence of vitamin D supplementation during pregnancy, and presence of vitamin D insufficiency or deficiency in the first trimester were independently associated with vitamin D insufficiency. Vitamin D insufficiency in newborns was independently associated with overweight before pregnancy, sampling during fall, winter, or spring, and presence of vitamin D insufficiency or deficiency in the third trimester.

4. Discussion

We report the first large scale population cohort study describing serum 25(OH)D status during pregnancy and in cord blood in French women. Given the disparities in results from vitamin D studies conducted during pregnancy world-wide, we will compare our results to those from other European studies.

As highlighted in Table 6, during early or mid-pregnancy in countries of northern Europe, serum 25(OH)D levels are relatively low with a mean or median value around 20–22 ng/mL, as in our study [20,21,26–28]. In the two studies with serum 25(OH)D values above 30 ng/mL despite the high latitudes (Finland and northwest of England) [29,30], a large proportion of women received vitamin D supplementation (95% in the Finland study and 73% in England study). Moreover, there are vitamin D food fortification policies in Finland [31]; thus, in the Finnish study the mean vitamin D intake was 15.7 μg/day [29]. Mean vitamin D intake for the French general population is 2.3 μg/day [32], a value that can be extrapolated to French pregnant women before

Table 2
Serum 25(OH)-vitamin D during pregnancy and at cord blood.

	n	1st trimester	3rd trimester	Cord blood
		2762	2327	1763
Gestational age (GW)	Mean ± SD [Min-Max]	10.8 ± 0.8 [6.6–12.9]	33.4 ± 2.4 [23.9–39.9]	37.6 ± 1.5 [25.4–40.7]
Serum 25(OH)D (ng/mL)	Mean ± SD [Min-Max]	21.9 ± 10.4 [3.0–78.0]	31.8 ± 11.5 [1.0–99.0]	17.0 ± 7.2 [3.0–54.0]
25(OH)D categories n (%)	<10 ng/mL	286 (10.4%)	29 (1.2%)	231 (13.1%)
	10–20 ng/mL	998 (36.1%)	297 (12.8%)	977 (55.4%)
	20–30 ng/mL	829 (30.0%)	703 (30.2%)	439 (24.9%)
	≥30 ng/mL	649 (23.5%)	1298 (55.8%)	116 (6.6%)

n: number of patients, SD: standard deviation, Min: minimum, Max: maximum, 25(OH)D: 25(OH)-vitamin D, GW: gestational weeks.

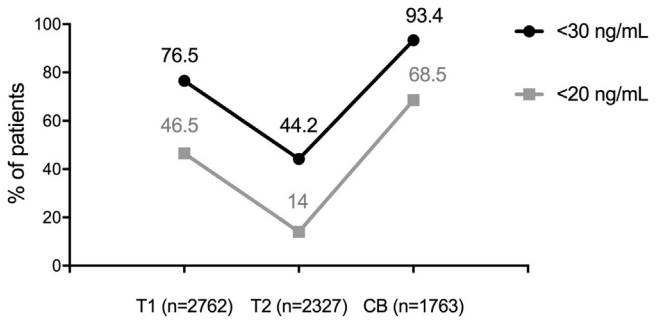

Fig. 2. Prevalence of 25(OH)-vitamin D (25(OH)D) insufficiency (serum 25(OH)D < 20 ng/mL, grey line) and inadequacy (serum 25(OH)D < 30 ng/mL, black line) at the first and third trimesters (T1 and T3) and in cord blood (CB) (with 95% confidence interval). N = number of patients for whom serum 25(OH)D measurements were performed at T1, T2 and T3.

the third trimester in the absence of vitamin D supplementation and of food fortification policies in France. Low vitamin D levels are also frequently found in pregnant women in countries from southern Europe despite theoretically higher and more efficient UVB radiation [33]. The close values between northern and southern European countries may be explained by high consumption of fatty fish in northern European countries and by vitamin D food fortification policies in some countries [31,33], but also by less voluntary sun exposure and by darker phototype in southern Europe.

We observed a clear increase in serum 25(OH)D concentrations between the first and third trimester. Our results must be interpreted taking into account the vitamin D supplementation currently recommended in France (100,000 IU of cholecalciferol during the seventh month) [23]. Consequently, 25(OH)D levels were overall higher in our study during the third trimester than levels reported in most European studies (Table 6) [26,27,33,34].

We observed a dramatic decrease in 25(OH)D levels between the third trimester and sampling of cord blood. As observed in previous studies, 25(OH)D levels were approximately two-fold lower in cord blood than in mother's serum during pregnancy [20–22,30,35]. In our study, as in these previous studies, sampling in the mother was performed several weeks before delivery. By contrast, in two studies with maternal sampling performed at delivery, exactly at the same time as cord blood sampling, 25(OH)D concentrations in mothers were similar to the ones found in newborns [34,36]. This finding suggests that the decrease in serum 25(OH)D observed between the second or third trimesters and cord blood may be due to a rapid decrease in serum 25(OH)D concentrations between sampling and delivery. Possible explanations for this rapid decrease in 25(OH)D levels during the last 4 weeks of pregnancy (mean delay between the third trimester and cord blood samplings in our study) in the absence of further supplementation could be reduced outdoor activity and sun exposure combined with an increase in fat mass at the end of pregnancy. Another explanation could be the rapid decrease in serum 25(OH)D concentrations after the single administration of 100,000 IU of vitamin D_3, as recently described [37]. Another hypothesis to explain the discrepancy between 25(OH)D levels in mothers during the second or third trimesters and in newborns could be that 3-epi-25(OH)D_3, an isoform not detected by the current immunoassays, may be present at high concentrations in cord blood. However, this theory was ruled out by a study showing that the proportion of 25(OH)D as 3-epi-25(OH)D_3 was only 11.2% in cord blood [22] and by another study reporting similar levels of 3-epi-25(OH)D_3 in mothers at delivery and in newborns [36]. We would like to emphasize that our study demonstrates that this

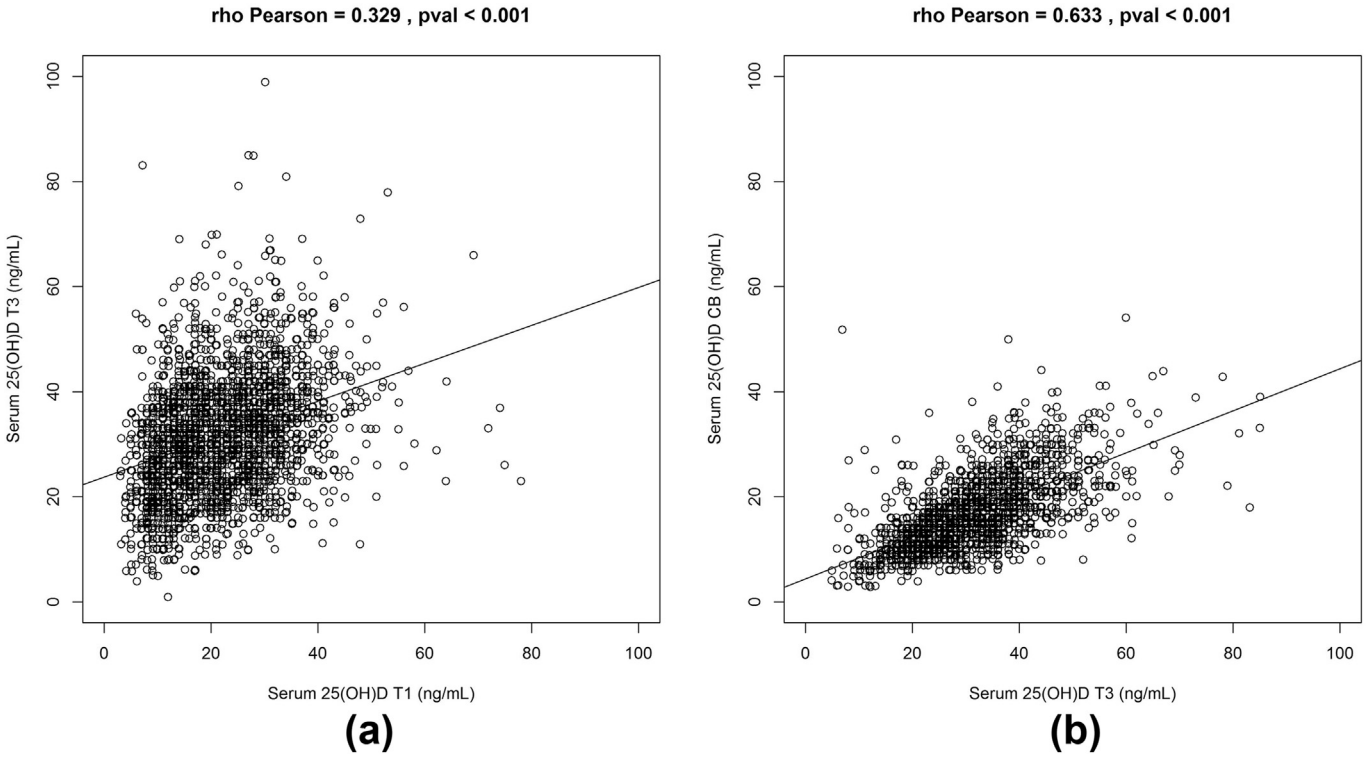

Fig. 3. a: Correlation between serum 25(OH)-vitamin D (25(OH)D) at the first trimester (T1) and at the third trimesters (T3) for the 2289 women with serum 25(OH)D measurements at T1 and at T3. **b**: Correlation between serum 25(OH)D at T3 and in cord blood (CB) for the 1606 women with serum 25(OH)D measurements at T3 and at CB.

Table 3
Univariate analysis of the determinants of severe vitamin D insufficiency (defined as serum 25(OH)-vitamin D < 20 ng/mL) during pregnancy and in cord blood.

	1st trimester			3rd trimester			Cord blood		
	25(OH)D (ng/mL)		P value	25(OH)D (ng/mL)		P value	25(OH)D (ng/mL)		P value
	<20 n = 1284	≥20 n = 1478		<20 n = 326	≥20 n = 2001		<20 n = 1208	≥20 n = 555	
Age (years)			0.029			0.017			0.18
<35	973 (75.8)	1066 (72.1)		256 (78.5)	1445 (72.2)		913 (75.6)	403 (72.6)	
≥35	311 (24.2)	412 (27.9)		70 (21.5)	556 (27.8)		295 (24.4)	152 (27.4)	
BMI (kg/m^2)			<0.001			0.012			<0.001
<25	827 (65.3)	1056 (72.0)		205 (63.3)	1401 (70.2)		797 (66.4)	420 (75.8)	
≥25	439 (34.7)	411 (28.0)		119 (36.7)	594 (29.8)		403 (33.6)	134 (24.2)	
Phototype[a]			<0.001			<0.001			<0.001
1 to 4	901 (70.2)	1259 (85.2)		209 (64.1)	1657 (82.8)		931 (77.1)	483 (87.0)	
5 and 6	383 (29.8)	219 (14.8)		117 (35.9)	344 (17.2)		277 (22.9)	72 (13.0)	
Parity[b]			0.026			0.002			0.062
0	587 (46.2)	741 (50.4)		135 (41.5)	1015 (50.7)		573 (47.5)	290 (52.2)	
≥1	684 (53.8)	728 (49.6)		190 (58.5)	985 (9.3)		634 (52.5)	265 (47.8)	
Smoking[c]			0.41			0.64			1
no	1112 (89.0)	1277 (87.9)		287 (89.4)	1750 (88.5)		1050 (88.2)	484 (88.2)	
yes	138 (11.0)	175 (12.1)		34 (10.6)	227 (11.5)		141 (11.8)	65 (11.8)	
Season[d]			<0.001			0.014			<0.001
Summer	160 (12.5)	455 (30.8)		59 (18.2)	529 (26.5)		245 (20.3)	207 (37.3)	
Fall	305 (23.7)	416 (28.2)		103 (31.7)	595 (29.7)		326 (27.0)	154 (27.7)	
Winter	394 (30.7)	274 (18.5)		70 (21.5)	366 (18.3)		284 (23.5)	82 (14.8)	
Spring	425 (31.1)	333 (22.5)		93 (28.6)	510 (25.5)		353 (29.2)	112 (20.2)	
Vitamin D before inclusion[e]			<0.001						
no	1101 (99.1)	1245 (95.2)		NA	NA		NA	NA	
yes	10 (0.9)	63 (4.8)		NA	NA		NA	NA	
Vitamin D in 7th month[f]						<0.001			0.20
no				74 (23.8)	148 (7.6)		119 (10.2)	44 (8.2)	
yes				237 (76.2)	1802 (92.4)		1052 (89.8)	493 (91.8)	
Previous 25(OH)D[g]						<0.001			<0.001
≥30 ng/mL				28 (8.7)	530 (26.9)		436 (39.7)	450 (88.7)	
20–30 ng/mL				77 (24.1)	624 (31.7)		456 (41.5)	43 (8.5)	
10–20 ng/mL				136 (42.5)	664 (33.7)		190 (17.3)	12 (2.4)	
<10 ng/mL				79 (24.7)	151 (7.7)		17 (1.5)	2 (0.4)	

BMI: body mass index, 25(OH)D: serum 25(OH)-vitamin D concentration, NA: non-applicable.
[a] According to the Fitzpatrick phototyping scale.
[b] Excluding the ongoing pregnancy.
[c] Active at the beginning of pregnancy.
[d] Season of sampling.
[e] Vitamin D supplementation during the month before inclusion.
[f] Vitamin D supplementation in 7th month of pregnancy (cholecalciferol, 100,000 IU).
[g] Serum 25(OH)D concentrations at the previous visit (for the third trimester, the previous visit took place in the first trimester; for cord blood, the previous visit took place in the third trimester. Results are shown as n (%).

high dose of cholecalciferol given once, 100,000 IU theoretically corresponding to 1100 IU daily during 3 months [23], is clearly insufficient to obtain serum 25(OH)D levels above 20 ng/mL in most newborns and is also insufficient to completely prevent vitamin D deficiency.

Finally, we analyzed the determinants of vitamin D insufficiency (25(OH)D < 20 ng/mL) at each time point. Most studies found, as we did, that season of sampling was strongly associated with 25(OH)D status during pregnancy, with maximal concentrations reached during summer [20,26–28,30,33,38]. As in our study, dark phototype was also reported to be independently associated with maternal vitamin D status [26,27,30,33,39]. As in other European studies [20,26–28,30,33], we found that vitamin D supplementation during pregnancy was a strong independent determinant of vitamin D status. Whereas some studies found no association between BMI and vitamin D status in pregnant

Table 4
Serum 25(OH)-vitamin D at the third trimester and in cord blood for subjects who were and who were not supplemented as recommended by the French guidelines in the 7th month of pregnancy (cholecalciferol, 100,000 IU)*.

	Supplementation*	3rd trimester			Cord blood		
	n	No	Yes	P value	No	Yes	p value
		222	2039		163	1545	
Serum 25(OH)D (ng/mL)	Mean ± SD	25.8 ± 11.1	32.5 ± 11.4	<0.001	15.5 ± 7.1	17.2 ± 7.22	0.004
25(OH)D categories n (%)	<10 ng/mL	12 (5.4%)	16 (0.8%)	<0.001	33 (20.2%)	191 (12.4%)	0.03
	10–20 ng/mL	62 (27.9%)	221 (10.8%)		86 (52.8%)	861 (55.7%)	
	20–30 ng/mL	68 (30.6%)	616 (30.2%)		37 (22.7%)	388 (25.1%)	
	≥30 ng/mL	80 (36.1%)	1186 (58.2%)		7 (4.3%)	105 (6.8%)	

n: number of subjects, SD: standard deviation, 25(OH)D: 25(OH)-vitamin D.
The asterisk refers to the recommended vitamin D supplementation during pregnancy.

Table 5
Multivariate analysis of the determinants of severe vitamin D insufficiency (defined as serum 25(OH)-vitamin D < 20 ng/mL) during pregnancy and in cord blood.

	1st trimester		3rd trimester		Cord blood	
	OR [95% CI]	p value	OR [95% CI]	p value	OR [95% CI]	p value
Age (years)						
<35			1.00			
≥35			0.66 [0.48–0.91]	0.01		
BMI (kg/m^2)						
<25	1.00				1.00	
≥25	1.33 [1.10–1.61]	0.003			1.32 [1.00–1.73]	0.049
Phototype[a]						
1-4	1.00		1.00			
5-6	2.70 [2.17–3.36]	<0.001	1.80 [1.34–2.40]	<0.001		
Parity[b]						
0			1			
≥1			1.47 [1.12–1.92]	0.005		
Season[c]						
Summer	1.00		1.00		1.00	
Fall	2.03 [1.57–2.63]	<0.001	1.86 [1.27–2.72]	0.002	2.18 [1.59–2.99]	<0.001
Winter	4.43 [3.41–5.76]	<0.001	4.04 [2.62–6.23]	<0.001	3.15 [2.19–4.51]	<0.001
Spring	4.16 [3.22–5.38]	<0.001	2.24 [1.51–3.31]	<0.001	1.96 [1.39–2.75]	<0.001
Vitamin D before inclusion[d]			NA	NA	NA	NA
no	1.00		NA	NA	NA	NA
yes	0.16 [0.08–0.31]	<0.001	NA	NA	NA	NA
Vitamin D in 7th month[e]	NA	NA				
no			1.00			
yes			0.21 [0.15–0.29]	<0.001		
Previous 25(OH)D[f]	NA	NA				
≥30	NA	NA	1.00		1.00	
20-30	NA	NA	2.83 [1.77–4.53]	<0.001	10.59 [7.49–14.98]	<0.001
10-20	NA	NA	4.71 [2.98–7.47]	<0.001	16.26 [8.89–29.74]	<0.001
<10	NA	NA	13.84 [8.18–23.43]	<0.001	7.66 [1.73–33.90][g]	0.007

BMI: body mass index, 25(OH)D: serum 25(OH)-vitamin D concentration, NA: non-applicable.
[a] According to the Fitzpatrick phototyping scale.
[b] Excluding the ongoing pregnancy.
[c] Season at the time of sampling.
[d] Vitamin D supplementation during the month before inclusion.
[e] Vitamin D supplementation in 7th month of pregnancy (cholecalciferol, 100,000 IU).
[f] Serum 25(OH)D concentrations at the previous visit (for the third trimester, the previous visit took place at the first trimester; for cord blood, the previous visit took place at the third trimester).
[g] Among women with 25(OH)D below 10 ng/mL at the third trimester, only two had 25(OH)D above 20 ng/mL in cord blood.

women [27,34], others found, like us, a negative association [40,41].

Few European studies have described the determinants of vitamin status in cord blood. A study from Scotland [20] and a study from Ireland [22], found, like us, that seasonal variation and maternal 25(OH)D status were independently associated with 25(OH)D levels in cord blood. Whereas the study from Scotland [20] found, as we did, that vitamin D supplementation during pregnancy did not influence vitamin D insufficiency in cord blood, two studies [22,29], reported a positive association between antenatal vitamin D supplements and vitamin D concentrations in cord blood. Finally, unlike us, others did not find that maternal BMI was an independent determinant of 25(OH)D levels in cord blood [20,22,29].

We must acknowledge that our study has some limitations. First, although the DiaSorin RIA used to measure 25(OH)D concentration in our study is a "historic" 25(OH)D assay that has been used in many studies, it does not allow a strict comparison with the previously published data on vitamin D status in pregnant women due to a certain degree of inter-method variability. Such a comparison is, however, important to develop evidence-based international guidelines for vitamin D supplementation during pregnancy. A way to achieve this goal would have been to collaborate with a laboratory that uses a CDC-certified chromatography tandem-mass spectrometry (LC-MS/MS) method in order to apply the VDSP protocols for standardizing existing 25(OH)D data from national surveys around the world [42]. However, when the present study was designed (in 2009), the new international and the standard LC-MS/MS reference method for measuring 25(OH)D were not published so such a collaboration was not possible. Moreover, we did not assess the concentration of the biologically active free 25(OH)D. Of note, Patients were recruited only in centers from the middle-north of France, so we cannot extrapolate our results to the whole French territory. Finally, some data susceptible to modify serum 25(OH)D concentration including dietary habits, sun exposure, use of sunscreen and outdoor activity were not recorded in the present study.

Our study also has several strengths. To our best knowledge, it is the first study to evaluate the vitamin D status of a French cohort during pregnancy and in cord blood and this study is the largest European study regarding this issue. We also evaluated the effects of the supplementation recommended by current French guidelines [23], which is of high importance to improve the care of pregnant women and newborns.

In conclusion, vitamin D insufficiency is highly prevalent at the beginning of pregnancy and in cord blood in the middle-north of France. The supplementation with cholecalciferol 100,000 IU during the seventh month of pregnancy is insufficient to prevent vitamin D insufficiency and deficiency in newborns and should therefore be reevaluated.

Table 6
Vitamin D status during pregnancy and in cord blood reported in studies from northern Europe (countries with latitudes equal or higher than the one reported in the present study: 47–49°N). Studies are presented according to the latitude of the country (higher to lower latitudes). Results from the countries of southern Europe are not mentioned in this table since it was the purpose of a review by Karras et al published in 2016 [33].

Country	Latitude	n	Pregnancy		Cord Blood	Method for 25(OH)D measurement
			Timing of sampling	25(OH)D concentrations (ng/mL), and by category when available (%)	25(OH)D concentrations (ng/mL), and by category when available (%)	
Finland [29]	60°N	584	T1 GW 6–13	Mean ± SD 35.5 ± 7.6 −1%<20 ng/mL	Mean ± SD 35.3 ± 8.8 −1%<20 ng/mL	CLIA
south-western Sweden GraviD study [27]	57–58°N	1985	T1 before GW 17	Mean ± SD 25.8 ± 9.8 - 25% < 20 ng/L - 10% < 12 ng/mL	NO	LC-MS/MS
		1836	T3 after GW 31	Mean ± SD 29.8 ± 13.8		
Scotland [20]	57°N	1205 (T1 and cord blood)	T2 GW 19	Mean (95%CI) 16.0 (15.4–16.7) - 21·5% < 10 ng/mL	Mean (95%CI) 8.7 (8.2–9.4) - 50% < 10 ng/mL	LC-MS/MS
Denmark [28]	54-57°N	1494	T2 GW 25	Mean ± SD 22.7 ± 9.8 - 76.9% < 0.30 ng/mL - 42.3% < 20 ng/mL - 10.1% < 10 ng/mL	NO	LC-MS/MS
North West of England [30]	53°N	- Mother: 608 - CB: 345	T2/T3 26.9 GW (range 26.0–28.7)	Median (IQR) 30.6 (19.2–38.1) −27% < 20 ng/mL −7% <10 ng/mL	Median (IQR) - 15.4 (9.8–22.4) - 65% < 20 ng/mL - 26% < 10 ng/mL	LC-MS/MS
Ireland SCOPE study [21]	52°N	1768	T2 GW 15 (range, 14–16)	Mean ± SD 22.7 ± 10.4 - 75% < 30 ng/mL - 44% < 20 ng/mL - 11% < 10 ng/mL	NO	LC–MS/MS
Ireland SCOPE study [22]	52°N	1050			Mean ± SD 14.0 ± 7.2 - 80% < 20 ng/mL - 35% (50% during winter) <10 ng/mL	LC–MS/MS
Belgium [26]	49-51°N	640	T1	Median 20.4	NO	RIA
		666	T3	Median 22.7		
		1311	T1+ T3 (+5 patients at T2)	- 74.1% < 30 ng/mL - 44.6% < 20 ng/mL - 12.1% < 10 ng/mL		
Germany [34]	47- 54°N	- Mother: 261 - CB: 328	delivery or within 72 h post-partum	Median (IQR) 10.0 (5.0–18.2) −77% < 20 ng/mL	Median (IQR) 13.6 (7·1–23.4) - 69% < 20 ng/mL	CLIA
Germany [38]	47- 54°N	429	between the 2nd and 41st GW (mean ± SD: 23.8 ± 11.5)	Mean ± SD 14.2 ± 8	NO	CLIA
Switzerland [39]	47°N	204 n = 75 Vit ≥20 ng/mL n = 129 Vit <20 ng/mL	7 GW 7 GW 7 GW	63% < 20 ng/mL Mean (95%CI) 26.1 (24.8–27.4) Mean (95%CI) 10.5 (9.7–11.5)	NO	CLIA

CLIA: chemiluminescence immunoassay, LC-MS/MS: chromatography tandem-mass spectrometry, RIA: Radioimmunoassay, GW: gestational weeks, T1: first trimester, T2: second trimester, T3: third trimester, CB: cord blood, SD: standard deviation, IQR: interquartile range, CI: confidence interval, 25(OH)D: serum 25(OH)-vitamin D concentration, n: number of patients.

Statement of authorship

MC interpreted the data and wrote the manuscript.
ABa and CE analyzed and interpreted the data.
ABe, CE and JCS conceived and designed the study.
JCS performed 25(OH)D measurements.
JT, VT, JG, MVS, HH, JJ, MG, JMJ, MCH, NW, and DM included patients.

All the authors contributed substantially to the acquisition of data and to drafting the article or revising it critically for important intellectual content and to final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Conflict of interest

JC. Souberbielle reports lecture fees and/or travel/hotel expenses from DiaSorin, Roche Diagnostics, Abbott, Amgen, Shire, MSD, Lilly, and Rottapharm/Meda. The other authors declare no conflicts of interest.

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