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Vitamin D Status During Pregnancy at High Risk of Placenta-Mediated Complications: Angiopred VITAD Study

Camille SARKIS[1], Céline CHAULEUR[1,2], Florence RANCON[2,3], Anne-Sophie PERRON[1], Lise THIBAUDIN[4], Jean-Christophe GRIS[5,6], Nadia ALFAIDY[7]and Tiphaine RAIA-BARJAT[1,2,7*]

[1]Department of Gynecology and Obstetrics, University Hospital, Saint Etienne, France
[2]Jean Monet Saint-Etienne University, INSERM, SAINBIOSE (SAnte, INgénierie, BIOlogie, Saint- Etienne) U1059, Saint-Etienne, France
[3]INSERM, Centre d'Investigation Clinique 1408, Saint-Etienne, France
[4]Biochemistry Laboratory, University Hospital, Saint-Etienne, France
[5]Laboratory of Hematology, University Hospital, Nimes, and University of Montpellier, France
[6]I.M. Sechenov First Moscow State Medical University, Moscow, Russian Federation
[7]Institut National de la Santé et de la Recherche Médicale, Unité 1292, Biosanté, University Grenoble-Alpes; Commissariat à l'Energie Atomique et aux Energies Alternatives (CEA), Biosciences and Biotechnology Institute of Grenoble, Grenoble, France

***Corresponding author:** Tiphaine Raia-Barjat, Department of Gynaecology and Obstetrics Hôpital Nord, University Hospital, Avenue Albert Raimond, 42270 Saint Priest en Jarez France, Tel: +33 - 4 - 77 82 86 09, Fax: +33 - 4 - 77 82 89 54, E-mail: tiphaine.barjat@chu-st-etienne.fr

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Abstract

Background & aims: Vitamin D status during pregnancy in a population at high risk of placenta-mediated complications is available in a unique study. The study aims at describing the vitamin D profile in such a population and to follow its evolution during pregnancy.

Methods: A prospective multicenter cohort study of two hundred pregnant patients was conducted between June 2008 and October 2010 with samples collected at 18, 22, 26, 30 and 34 gestational weeks. Serum 25(OH)D concentrations were quantified using the immunodiagnostic systems (IDS) automated competitive binding chemiluminescence 25-OHD method on the IDS-iSYS analyzer (IDS-iSYS).

Results: We could test 182 patients. The 25(OH)D levels were low from 18 gestational weeks (GW) and remained stable during pregnancy. Only 10.3 % of the patients had concentrations ≥ 30ng / ml at 18 GW and 13.2% at 34 GW. Vitamin D deficiency (≤ 20 ng/mL) was evidenced in 59.4% of the patients at 18 GW, 58.6% at 22 GW, 52.9% at 26

GW, 43% at 30 GW and 42.7% at 34 GW. Concentrations at 34 GW and 18 GW correlated positively (Pearson r= 0.124; p<0.0001). Only a personal history of placenta-mediated complications was associated with vitamin D deficiency at 18 GW.

Conclusions: The prevalence of vitamin D insufficiency and deficiency in a population at high risk of placenta-mediated complications is strikingly high.

Keywords: Vitamin D; Pregnancy; Prevalence; Determinant; Placenta-Mediated Pregnancy Complications

Introduction

Vitamin D plays a role in various organs and not only in the bone compartment, especially in the placenta [1]. Sun exposure is the primary source of vitamin D. Its synthesis depends on multiple parameters, including the term of season, latitude, time of day, skin color, use of sunscreen or clothing [2]. The absorption of vitamin D in populations with very dark skin is significantly reduced [3]. The concentration of 25-hydroxyvitamin D [25(OH)D] in pregnant women is identical to that of the general population, however it increases gradually during pregnancy (50-150%) without hypercalcemia, thanks to renal and placental synthesis. Calcitriol levels and calcitriol/25(OH)D ratio are higher in pregnant women to allow fetal growth development and calcium homeostasis. Importantly, it is well established that fetal serum concentration depends on the maternal 25(OH)D [4,5].

Vitamin D status is assessed using the serum circulating 25(OH)D levels, measured by a reliable assay. According to the Endocrine Society Clinical Practice Guideline, vitamin D insufficiency is defined as a 25(OH)D concentrations of 21–29 ng/ml (525–725 nmol/L) and vitamin D deficiency as a 25(OH)D below 20 ng/mL (50 nmol/L) [6]. Surprisingly, there is no clear definition of vitamin D deficiency in pregnancy. Endocrine society recognize that at least 1500–2000 IU/d of vitamin D may be needed to maintain a blood level of 25(OH)D above 30 ng/ml [6]. Insufficiency and deficiencies in 25(OH)D during pregnancy are frequent and depend on the geographic region and skin pigmentation [7].

In a large French cohort, 46.5% of pregnant women had a 25(OH)D below 20 ng/mL [5]. During pregnancy, maternal vitamin D insufficiency could increase the risk of preeclampsia, preterm birth, small-for-gestational age (SGA) or intrauterine growth retardation (IUGR) and gestational diabetes mellitus [8]. Supplementation during pregnancy was the subject of several Cochrane reviews in 2000 [9], 2012 [10] and 2016 [11], which concluded that there was not enough data in the literature to authorize supplementation of pregnant patients in vitamin D. The last one in 2019 concluded that supplementing pregnant women with vitamin D alone probably reduces the risk of pre-eclampsia, gestational diabetes, low birthweight and may reduce the risk of severe postpartum haemorrhage [8,12]. In France, supplementation has been recommended since 1995 with an ampoule of 100.000 IU at 28 gestational weeks (GW), but this strategy has not been evaluated and this recommendation is scarcely applied [13].

The vitamin D profile of pregnant women has been described in a large French cohort study at the first and third trimesters [5]. Obesity is associated with vitamin D deficiency because the body fat sequesters the fat-soluble vitamin [14]. Overweight before pregnancy (Body Mass Index ≥25 kg/m2) was associated with vitamin D insufficiency in the first trimester but not in the third trimester of pregnancy [5]. Most studies offered only one or two dosages of vitamin D throughout pregnancy and were related on general population at low risk of poor pregnancy outcomes. Few studies have focused on patients at high risk of placenta-mediated complications (PMC), which are in greater need of vitamin D supplementation. In our population, 12% of patients presented a preeclampsia while that affects an estimated 4–5% of pregnancies worldwide [15]. The vitamin D profile is closely linked in this population to the occurrence of a PMC [16,17].

The main objective of this study was to characterize the vitamin D profile in a population at high PMCs risk and to follow its evolution throughout pregnancy.

Materials and Methods

Study population

Our study is based on data from the AngioPred study. The AngioPred study is a prospective multicenter cohort study conducted between June 2008 and October 2010 in the Obstetrics and Gynecology department of Saint Etienne and Nimes University Hospitals and the Laboratory of Hematology in Nimes

University Hospital. The patients included in this study were all affiliated or entitled to social security, had consulted within 18 GW, and were all at high risk for occurrence or recurrence of PMCs. Only patients that have been included in the University Hospital of Saint Etienne benefited from the vitamin D dosage, i.e. 182 patients out of the 200 patients constituting the initial cohort.

The expected incidence of PMC in our population is approximately 12%. A total of 100 patients therefore appears sufficient to demonstrate the predictive value of some biomarkers on the risk of PMC. However, to test different biomarkers in a multivariate model and therefore adjust the model to the already identified prognostic factors in order to see if the biomarkers could be an independent prognostic factor, we therefore chose to increase the size of the cohort; a total of 200 patients were chosen arbitrarily.

Inclusion criteria were: [1] diabetes (in diet or insulin), [2] hypertension (previously treated before pregnancy or hypertension > 140/90 twice before 20 weeks), [3] obesity (Body Mass Index ≥ 30) [4] maternal age younger than 18 years or older than 38 years, [5] chronic kidney disease (proteinuria ≥ 300mg for 24 hours or creatinine ≥ 1.5 mg/dl before 20 weeks), [6] systemic lupus erythematosus, [7] antiphospholipid syndrome, [8] family history of cardiovascular disease or venous thromboembolism (VTE,) [9] biological thrombophilia without any personal history of VTE or of PMC, [10] a history of one or more episodes of PMCs or [11] personal history of VTE. The exclusion criteria were: [1] twin pregnancies; [2] patients with a history of fetal death due to congenital malformations, Rh incompatibility or infectious cause; [3] IUGR whose etiology was of chromosomal origin, gene or infectious abnormality or [4] the presence of a placenta-mediated complication or VTE at inclusion.

The Ethics Committee and Institutional Review Board of the University Hospital of Saint Etienne approved the protocol in March 2008, and all subjects provided written informed consent. The study is registered with the ClinicalTrials.gov (identifier NCT00695942).

All patients were included before 18 GW and gave their written consent. At inclusion, demographic data were collected by interview, physical examination and consultation of obstetrical medical record. Blood samples provided in the protocol were taken in complement to the conventional laboratory tests for the monitoring of pregnancy. Data on vitamin D supplementation during pregnancy were not available.

Blood collection and laboratory methods

Blood samples were collected at the collection center of University Hospital of Saint Etienne and Nimes at 20, 24, 28, 32 and 36 weeks of amenorrhea (WA) corresponding to 18, 22, 26, 30 and 34 gestational weeks (GW), totaling 5 samples per patient. The samples were immediately sent to laboratories for analysis, then centrifuged, aliquoted and stored at -80°C. Each analysis was then performed blind to other analyses. All samples from the same patient were grouped in the same series of assays.

Vitamin D analysis can only be performed on a blood sample taken on dry tubes; this limitation made it mandatory to exclude all patients enrolled at of Nimes center, as their samples have been collected in anticoagulated tubes. The assays were carried out by the biochemistry laboratory of Saint Etienne university hospital. 25(OH)D was quantified with the immunodiagnostic systems (IDS) automated competitive binding chemiluminescence 25-OHD method on the IDS-iSYS analyzer (IDS-iSYS). A value of 7 ng/mL, corresponding to the limit of quantification that we determined in our laboratory was assigned to any undetectable concentration.

We have defined the vitamin D deficiency by a 25(OH) D level < 20 ng/ml and vitamin D insufficiency < 30 ng/ml [6].

Statistical analysis

Statistical analysis was performed using XLSTAT®. Qualitative data were described by absolute and relative frequencies (expressed in %). Quantitative variables were described by mean and standard deviation. Evolution of 25(OH)D during pregnancy were summarized by boxplots. Prevalence of vitamin D insufficiency and deficiency were estimated on the available samples at each time (18, 22, 26, 30 and 34 GW). Pearson's test was used to analyze the correlations between vitamin D at 18 GW and at 34 GW. Associations between characteristics of women and 25(OH)D insufficiency were investigated using chi-2 test (or Fisher's test when it was appropriate) for qualitative parameters.

Whatever the statistical analysis considered, the significance of the result was only accepted for a risk alpha less than 5%.

Results

Description of the study population

One hundred eighty-two patients were included, allowing the analysis of 859 plasma samples. All samples were taken before the onset of preeclampsia or intrauterine growth retardation. Forty-three patients developed a PMCs (23.6%). The demographics and inclusion criteria are summarized in Table 1. Almost two-thirds of our patients had a history of PMCs.

Table 1: Patient characteristics and inclusion criteria

	N Total = 182	**Mean ± Standard deviation or median (Quartile 1– Quartile 3) or n (% of patients)**
Age (years)		
mean ± SD	178	32 ± 5.0
median (Q1–Q3)		32 (28–36)
(%)**Age ≥ 35 years,** n		(30.9) 55
Parity		
0	178	34 (19.1)
1		81 (45.5)
>1		63 (35.4)
BMI before the beginning of pregnancy (kg/m2)	176	
mean ± SD		25.3 ± 6.6
median (Q1–Q3)		23.6 (20.9–28.2)
BMI >25 (kg/m2)		71 (40.3)
Smoking, n (%)	178	22 (12.4)
Diabetes, n (%)	180	6 (3.3)
Kidney disease, n (%)	180	4 (2.2)
Hypertension, n (%)	180	17 (9.4)
Lupus, n (%)	180	12 (6.6)
Antiphospholipid Syndrome, n (%)	179	4 (2.2)
Personal history of VTE, n (%)	181	35 (19.2)
Personal history of PMCs, n (%)	180	119 (65.4)
Familial history of cardiovascular disease or VTE, n (%)	180	38 (21.1)

BMI: body mass index, VTE: venous thromboembolism, PMPCs: Placenta-mediated pregnancy

Vitamin D evolution during pregnancy

The concentrations of 25(OH)D in sera collected from patients at 18 GW were low and remained stable throughout pregnancy (Figure 1 and Table 2).

Only 10.3 % of patients have 25(OHG)D ≥ 30ng / ml at 18 GW and 13.2% at 34 GW. An evidence of vitamin D deficiency (≤ 20 ng/mL) was objectivized in 59.4% of patients at 18 GW, 58.6% at 22 GW, 52.9% at 26 GW, 43% at 30 GW and 42.7% at 34 GW (Table 2). Very low 25(OH)D concentrations (<10 ng/mL) were found in 11.4% of patients at 18 GW, 10.3% at 22 GW, 6.3% at 26 GW, 4.7% at 30 GW and 3.2% at 34 GW. The prevalence of insufficiency, deficiency and very low concentrations of 25(OH) D are illustrated in Figure 2.

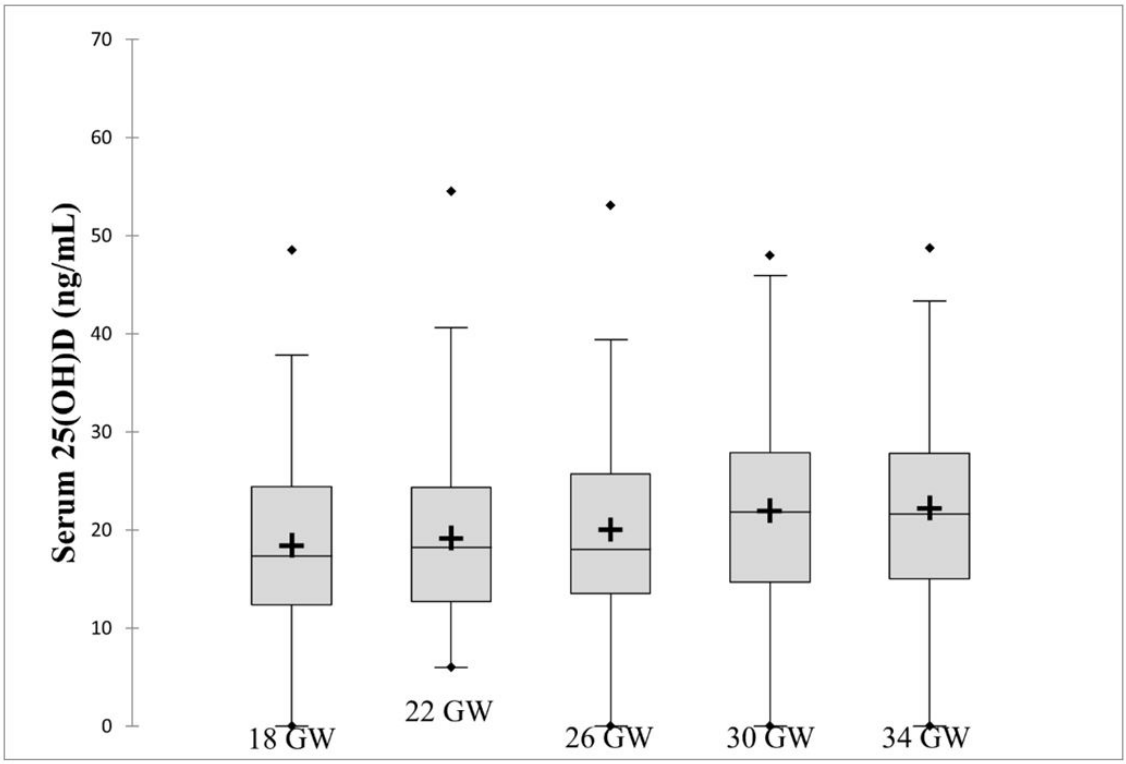

Figure 1: Profile of the 25(OH)D during pregnancy

The crosses are the means. The central horizontal bars are the medians. The lower and upper limits of the boxes are the first and third quartiles. The points are the minimum and maximum for each species. GW: gestational weeks

Table 2: Serum 25(OH)-vitamin D during pregnancy

Gestational age at sampling **Number of patients**	**18 GW** **n= 175**	**22 GW** **n= 174**	**26 GW** **n= 174**	**30 GW** **n= 170**	**34 GW** **n= 157**
Serum 25(OH)D (ng/mL)					
mean ± SD	18.4 ± 8.6	19.1 ± 8.3	20.2 ± 8.5	22.4 ± 9.2	22.2 ± 8.3
median (Q1–Q3)	17.3 (12.4–24.4	18.2 (12.7–24.3)	18.0 (13.5–25.7)	22.2 (14.7–28.3)	21.6 (15.0–27.8)
25(OH)D categories n (%)					
≤20 ng/mL	104 (59.4)	104 (59.8)	94 (54.0)	73 (42.9)	67 (54.0)
21–29 ng/mL	53 (30.3)	52 (29.9)	45 (25.9)	56 (32.9)	59 (25.9)
≥30 ng/mL	18 (10.3)	18 (10.3)	23 (13.2)	30 (17.6)	31 (13.2)

complications, SD: standard deviation, Q1: 1st Quartile, Q3: 3th Quartile, n: number of patients.

GW: gestational weeks

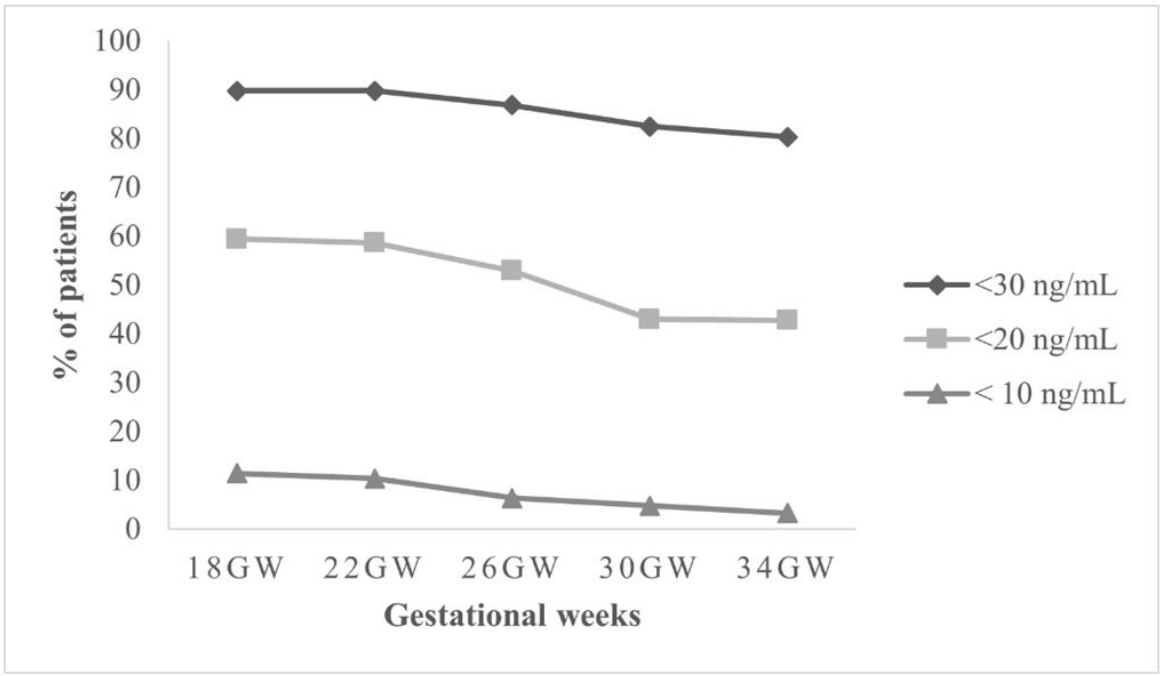

Figure 2: Prevalence of 25(OH)D insufficiency (<30 ng/mL), deficiency (<20 ng/mL) and very low concentrations (<10 ng/mL). GW :gestational weeks

Determinants of vitamin D status during pregnancy

Serum 25(OH)D at 34 GW positively but weakly correlated with concentrations at 18 GW (Pearson r= 0.124; p<0.0001) (Figure 3).

Table 3 shows univariate analysis of determinants of 25(OH)D deficiency (25(OH)D ≤ 20 ng/mL) at 18 and 34 GW. Age, BMI, parity and smoking were not associated with vitamin D deficiency. Only the personal history of PMPCs was associated with vitamin D deficiency at 18 GW.

Figure 3: Correlation between serum 25(OH)-vitamin D (25(OH)D) at 18 GW and at 34 GW

Table 3: Univariate analysis of the determinants of 25(OH)D concentrations during pregnancy

Gestational age at sampling	**18 GW 25(OH)D (ng/mL)**		**P value**	**34 GW 25(OH)D (ng/mL)**		**P value**
	≤20 N= 104	**>20 N= 71**		**≤20 N= 67**	**>20 N= 90**	
Age (years)						
< 35	66 (64.1)	52 (76.5)	0.09	44 (67.7)	62 (71.3)	0.64
≥ 35	37 (35.9)	16 (23.5)		21 (32.3)	25 (28.7)	
BMI (Kg/m²)						
<25	61 (59.8)	40 (58.8)	0.90	38 (57.6)	55 (64,0)	0.42
≥25	41 (40.2)	28 (41.2)		28 (42.4)	31 (36.0)	
Parity [a]						
0	19 (18.5)	14 (20.3)	0.76	10 (15.2)	20 (23.0)	0.23
≥ 1	84 (81.6)	55 (79.7)		56 (84.9)	67 (77.0)	
Smoking [b]						
No	93 (90.3)	58 (84.1)	0.22	59 (89.4)	76 (87.4)	0.70
Yes	10 (9.7)	11 (15.9)		7 (10.6)	11 (12.6)	
Personal history of PMCs						
No	26 (31.1)	32 (46.4)	**0.004**	21 (31.3)	32 (36.4)	0.51
Yes	78 (75.7)	37 (53.6)		46 (68.7)	56 (63.6)	

BMI: body mass index, PMPCs: Placenta-mediated pregnancy complications, GW: gestational weeks

[a] Excluding the ongoing pregnancy

[b] Active at the beginning of the pregnancy

Discussion

Vitamin D concentrations in our group of women remained very stable throughout pregnancy. The prevalence of vitamin D insufficiency and deficiency in the population at high risk of placenta-mediated complications is strikingly high throughout pregnancy. There is a weak correlation between vitamin D concentrations at 18GW and 34GW. Importantly, the personal history of placenta-mediated complications was associated with vitamin D deficiency.

Most studies have described vitamin D profiles in pregnant women in the general population, but not in populations at risk of pregnancy complications, nor at high risk of PMCs.

In non-pregnant patients, a French cohort study demonstrated that 25(OH)D concentrations of <10, <12, <20, and <30 ng/mL were found in respectively 6.3, 9.9, 34.6, and 80.3 % of individuals [18]. The prevalence of insufficiency and deficiency is very similar in different European countries [19]. In pregnant women at low risk of complications, numerous investigators in different countries have been interested in the vitamin D profile. In a systematic review of the literature, Saraf et al. analyzed 95 studies reporting maternal and newborn vitamin D status [20]. The prevalence of 25(OH)D <20 ng/mL in pregnant women was: 64% in America, 57% in Europa, 46% in Eastern Mediterranean, 87% in South-East Asia and 83% in Western Pacific. In France, a large cohort study evaluated vitamin D concentrations during

the first and the third trimesters of pregnancy and in cord blood. In 2,803 low-risk pregnant women, the prevalence of vitamin D deficiency was 46.5% of patients during the first trimester, 14% during the third trimester and 68.5% in cord blood samples [5]. We found only one study focused on vitamin D profiles in women at high risk of pregnancy complications. The prevalence of vitamin D deficiency (<20 ng/mL) was 53% of pregnant women between 10 and 20 weeks of gestation. In our study, the prevalence of vitamin D deficiency during the second trimester was 59.4% and during the third trimester 42.7%. Our results confirmed the assumption of the higher prevalence of vitamin D deficiency in a pregnant population at high risk of PMCs.

Among determinants of vitamin D deficiency, some exhibit positive association with maternal vitamin D concentrations. These include skin color (light), dressing patter (uncovered), maternal vitamin D supplementation, maternal calcium intake and season of gestation (spring/summer). In contrast, some parameters such as, maternal BMI exhibit negative association (obesity) and some other unsure determinants do not affect maternal vitamin D concentrations; these include maternal vitamin D intake, rural evidence, maternal age, parity, weight gain during pregnancy, birth weight, maternal vitamin B12, and maternal PTH concentrations. Importantly, it has been reported that maternal vitamin D concentrations change inversely to gestational age (U-shaped curve) [21]. In our study, only the antecedent of PMCs are associated with lower concentrations of vitamin D. We did not find any other study that investigated this determinant, while this high-risk population could benefit the most from supplementation.

Currently, there is no real consensus regarding vitamin D supplementation during pregnancy. Recently, Curtis et al. described the discrepancies in vitamin D supplementation between multiple countries [22]. In United States and Canada, the Institute of Medicine or the European Food Safety Authority recommend 600 IU supplementation. In England it is recommended to patients daily vitamin supplements containing at least 400 IU of vitamin D. For the Dutch, supplementation depends on sun exposure and varies between 300 IU and 400 IU per day. In the general population, several studies have already raised the question of higher vitamin D supplementation. Dietary restrictions during pregnancy could influence the daily intake of vitamin D [23]. In France, Vitamin D supplementation, 100,000 IU of cholecalciferol, is recommended at the seventh month of pregnancy with. However, these supplementation does not seem to modify vitamin D levels. A French cohort study showed that supplementation during the 3rd trimester of pregnancy led to 0.8% of the patients having vitamin D level <10 ng/ml versus 5.4% in the non-supplemented group. Upon supplementation, 58.2% of patients had their Vitamin D levels > 30 ng/ml vs. 36.1% in the control group. This study suggested that the recommended supplementation in France is insufficient to ensure a serum 25 (OH) D concentration> 30ng / ml during the 3rd trimester of pregnancy [5]. These results are in line with our findings. The most recent meta-analysis on the topic concluded that vitamin D supplementation alone in pregnant women probably reduces the risk of gestational diabetes, preeclampsia, and low infant birthweight. It may make little or no difference in reducing the risk of preterm birth at 37 weeks'gestation or less [8,24].

Our study has some limitations. This is a multicenter study, however concerning the dosage of vitamin D, we were able to use patients from one unique center. Also, the study did not examine all the determinants of vitamin D concentration and there was no assay on the cord blood. We used the immunodiagnostic systems (IDS) automated competitive binding chemiluminescence 25-OHD method on the IDS-iSYS analyzer (IDS-iSYS) which is not the reference method for vitamin D assay [25]. In comparative study, the IDS-iSYS correlated well with both established methods (validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method and an IDS enzyme immunoassay (IDS-EIA) method) [26]. However, the strength of our study is it focus on the study of vitamin D in a high-risk pregnant population. It is a prospective study with repeated dosages throughout pregnancy. To date, our study is the only one that considered the history of PMCs as a determinant of maternal vitamin D.

In conclusion, we demonstrate in France that the prevalence of vitamin D insufficiency and deficiency is strikingly high in a population at high risk of PMCs is and thatA personal history of PMCs was associated with vitamin D deficiency. Because, maternal vitamin D insufficiency during pregnancy, could increase risks of preeclampsia and IUGR, one can speculate that vitamin D supplementation in pregnant women may reduce this risk. The high-risk population is certainly the one that should benefit the most from supplementation.

Statement of authorship

CS and TRB interpreted the data and wrote the manuscript.

TRB and CC analyzed and interpreted the data.

CC, FR and JCG conceived and designed the study.

LT performed 25(OH)D measurements.

ASP and NA reviewed the manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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