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Original article

Relationship between vitamin D status in the first trimester of pregnancy and gestational diabetes mellitus - A nested case–control study

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SUMMARY

Background & aims: Gestational diabetes mellitus (GDM) is one of the most frequent medical complications during pregnancy. It has been associated with many adverse pregnancy, fetal and neonatal outcomes, as well as with an increased risk for mothers and children in the long term. There is a growing interest in vitamin D and its potential role in the development of metabolic disorders. However, the medical literature is not consensual. The aim of this study was to assess the risk of GDM according to vitamin D status during the first trimester.

Methods: This study is a nested case–control study performed from a multicenter prospective observational cohort of pregnant women assessed for 25-hydroxyvitamin D levels (25OHD). Three hundred ninety-three patients were included in the initial cohort. After applying exclusion criteria, a total of 1191 pregnant women were included. Two hundred fifty women with GDM (cases) were matched to 941 women without GDM (controls) for parity, age, body mass index before pregnancy, the season of conception, and phototype. This study was funded by a grant from the "Programme Hospitalier de Recherche Publique 2010".

Results: The GDM risk was significantly greater for patients with 25OHD levels <20 ng/mL (OR = 1·42, 95% CI 1·06–1·91; p = 0·021). However, there was no significant relationship with other thresholds. The study of 25OHD levels with the more precise cutting of 5 units intervals showed a variable

Abbreviations: GDM, Gestational diabetes mellitus; PGDM, Diabetes prior to pregnancy; SGA, Small for gestational age; BMI, Body mass index; WA, Weeks of amenorrhea; 25OHD, 25-hydroxyvitamin D 1,25(OH)2D: 1,25-dihydroxyvitamin D; OGTT, Oral glucose tolerance test.

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relationship with GDM risk, as the risk was low for very low 25OHD levels, increased for moderated levels, decreased for normal levels, and finally increased for higher levels.
Conclusion: According to our study, there seems to be no linear relationship between GDM and 25OHD levels in the first trimester of pregnancy since GDM risk does not continuously decrease as 25OHD concentrations increase. Our results most probably highlight the absence of an association between 25OHD levels and GDM risk.

1. Introduction

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance of variable severity with onset or first recognition during pregnancy [1]. The most common risk factors for GDM are maternal age, a history of GDM or a family history of type 2 diabetes, obesity or overweight, previous fetal death or delivery of a macrosomic infant, and ethnicity [1,2]. GDM is the most common complication during pregnancy in Europe [3], affecting 1–14% of pregnancies [4], and its incidence is rising. GDM has been associated with adverse pregnancy outcomes, fetal and neonatal complications, as well as with an increased risk of obesity, metabolic syndrome, type 2 diabetes and cardiovascular disease in the long term for both mother and child [5,6]. Hence, the challenge is to identify the mechanisms leading to GDM in order to improve its prevention and treatment. The causes of GDM are actively investigated, with a growing interest in poor vitamin D status as a potential cause.

Vitamin D is a steroid with a hormone-like activity that regulates the expression of a wide range of genes. Vitamin D status is evaluated by measuring serum concentration of 25-hydroxyvitamin D (25OHD). Vitamin D deficiency, i.e., 25OHD levels ≤50 nmol/L or 20 ng/mL [7], is widely prevalent worldwide [8]. Pregnant women present a greater risk of vitamin D deficiency; it has been estimated that 18% of pregnant women in England, 25% in the United Arab Emirates, 80% in Iran, 42% in Northern India, and 60–84% of non-western women in the Netherlands, have 25OHD concentrations below 25 nmol/L [9–13]. A recent large cohort study of pregnant women living in France showed that vitamin D insufficiency was highly prevalent at the beginning of pregnancy, with 50% of women with 25OHD below 20 ng/mL [14]. One possible explanation for high rates of vitamin D deficiency during pregnancy may be the increase of vitamin D needs during pregnancy without increasing the intakes. Furthermore, the reduced outdoor activity and sun exposure combined with an increase in fat mass at the end of pregnancy could also explain this association. Vitamin D's function in maintaining phosphocalcic homeostasis and promoting bone mineralization is now well established. There is an increasing interest in a wide range of mechanisms involving vitamin D, particularly during pregnancy, and in its effects on placental function, glucose homeostasis, and inflammatory response.

Low vitamin D status has been associated with adverse pregnancy outcomes such as preeclampsia, preterm labor, small for gestational age (SGA), and neonatal hypocalcemia [15–17]. Furthermore, several epidemiological studies have suggested an association between low serum concentration of 25OHD and impaired glucose metabolism or metabolic syndrome [18–21] as well as GDM. However, the evidence is inconsistent [22,23]. While some studies indicate an increased risk of GDM when maternal blood 25OHD is low during the first trimester [15,24–32], others fail to show such an association [33–35]. Most studies on the topic are cross-sectional, with few participants, different cut-offs and methods of quantifying 25OHD, and lack of adjustments for possible confounding factors, which makes it difficult to draw reliable conclusions.

Regarding interventional studies, a recent randomized controlled trial conducted in Iran, in women at risk for developing GDM, suggested that vitamin D supplementation during pregnancy reduces the incidence of GDM [36]. Another meta-analysis of 87 observational studies and 25 randomized controlled trials showed that vitamin D supplementation during pregnancy could influence not only 25OHD levels but also other biomarkers related to GDM [25]. However, the literature is conflicting [37,38]. The aim of the present study was to assess the risk of GDM according to vitamin D status during the first trimester of women with a singleton pregnancy in five centers of the middle-north of France and one Belgian center.

2. Material and methods

2.1. Study design

This nested case–control study was a secondary analysis of a prospective observational cohort (FEPED cohort) study, conducted from April 2012 through July 2014, which included pregnant women from six centers: one in Belgium (latitude 50·83°N) and five in France. Four of the French centers were in Paris, or its suburbs (Béclère, Bicêtre, Cochin and Trousseau university hospitals, latitude 48·86°N) and the fifth was in Nantes (latitude 47·22°N). The first aim of this study was to assess the association between maternal 25OHD levels during pregnancy and the risk of pre-eclampsia [39].

Eligible women were included in the cohort in the first trimester (i.e., from 10 to <15 weeks of amenorrhea, (WA)) of a singleton pregnancy. The enrolment took place at the first prenatal visit in one of the maternity units participating in the study. Exclusion criteria were: 1) any condition interfering with 25OHD levels such as a history of hypercalcemia (>2·65 mmol/L) or any other phosphocalcic disorder, bone disease, lithium therapy, bowel malabsorption or kidney stone disease; 2) any condition susceptible to interfere with the diagnosis of pre-eclampsia including uncontrolled hypertension (>140/90 mmHg since first trimester) and renal insufficiency (creatinine >120 μmol/L). Furthermore, patients were excluded from case selection if diabetes prior to pregnancy (PGDM) had been diagnosed, if we could not insure whether GDM or PGDM had previously occurred, if the pregnancy was interrupted (abortion, intrauterine fetal death), if missing data on delivery and/or pre-eclampsia. Eligible controls were pregnant women without GDM who had delivered after at least 37 WA, whose newborn was alive in the delivery room and presented no intrauterine growth restriction (<5th percentile) at birth, with first trimester 25OHD measurement available and with no missing data on any matching factor.

Written informed consent was obtained from each patient prior to inclusion in the study. The protocol was conducted in accordance with the Declaration of Helsinki and was approved by the National Data Protection Authority (CNIL no. 911432), and the committee for

the protection of people participating in biomedical research (2011/13NICB).

According to current French recommendations, patients at the 7th month of pregnancy were prescribed a bolus vitamin D dose (100 000 IU of cholecalciferol) [40]. Patients were specifically asked, during follow up, whether recommended vitamin D supplementation was correctly administrated as well as when it took place.

After delivery, sociodemographic and clinical data were abstracted from medical records by personnel trained for the study. Sociodemographic maternal characteristics included parity, maternal age, height, pre-pregnancy weight, ethnicity and smoking status before, and during pregnancy. Information was also collected on medical and obstetrical history (diabetes, chronic hypertension, auto-immune diseases, obstetrical history of SGA infant, stillbirth and other pregnancy complications), ultrasound, complications of the current pregnancy (pre-eclampsia, HELLP syndrome, gestational diabetes), the delivery, and the infant's health status at birth. The phototype of each subject was determined according to the Fitzpatrick skin type classification [41]. Pre-pregnancy body mass index (BMI), calculated from height and pre-pregnancy weight, was classified using the WHO cut-off for overweight (<25 or ≥25 kg/m^2) [42].

The primary objective of our nested case–control study was to assess the risk of GDM according to vitamin D status during the first trimester, before 15 WA.

2.2. Selection of cases and controls

For each case, four controls were matched for parity (primipara or more), age (<35 or ≥35 years), BMI before pregnancy (<25 kg/m^2 or ≥25 kg/m^2), season of conception (autumn/winter or spring/summer) and phototype (<V or ≥V Fitzpatrick scale). In addition, cases were planned to be matched to controls with the closest age whenever possible. Phototype was preferred over ethnicity, because its use seemed more reliable. The matching criteria were chosen according to the main potential confounding factors influencing both 25OHD levels and GDM risk.

2.3. Assessment of vitamin D status

The measurement of 25OHD level was performed on maternal blood samples collected during the first trimester of pregnancy (11 to <15 WA). All blood samples were centrifuged and stored locally at −20 °C and then transferred for centralized 25OHD serum measurement to the Department of Physiology of Necker University Hospital (Paris, France), which has excellent results in the DEQAS proficiency program. 25OHD was measured with the DiaSorin RIA. The limit of detection was arbitrarily set to a value of 4 ng/mL, and any undetectable quantity was assigned a concentration of 4 ng/mL. Vitamin D deficiency, insufficiency, inadequacy and sufficiency were defined as a serum 25OHD level below 10 ng/mL, 20 ng/mL, 30 ng/mL and ≥30 ng/mL, respectively.

2.4. Assessment of gestational diabetes mellitus

GDM was diagnosed according to World Health Organization guidelines [43]. A fasting oral glucose tolerance test (OGTT) was performed after ingestion of 75 g glucose between 24 and 28 WA. GDM was diagnosed if one or more of the following criteria were met: fasting plasma glucose 5·1–6·9 mmol/L (92–125 mg/dL), 1-hour plasma glucose ≥ 10.0 mmol/L (180 mg/dL) and/or 2-hour plasma glucose 8·5–11·0 mmol/L (153–199 mg/dL) following a 75 g oral glucose load. Patients with fasting plasma glucose ≥7 mmol/L (126 mg/mL) or 2-hour plasma glucose ≥ 11·1 mmol/L (200 mg/dL) were considered to have a type 2 diabetes prior to pregnancy. Seventy-eight-point four percent of patients were screened for GDM. Among them, 90·3% had an OGTT and 9·7% had another type of screening. Were qualified as diabetes prior to pregnancy (PGDM), both patients with type 2 diabetes prior to pregnancy as well patients who were diagnosed with GDM with early onset (before 22 WA).

2.5. Statistical analysis

Statistical analysis was performed with R 3.3.1 software. Statistical tests were two-sided, and p values less than 0·05 were considered statistically significant. The baseline characteristics of each group were described as mean ± standard deviation for quantitative variables and frequencies (%) for qualitative variables. Conditional logistic regression models were used to compare cases and controls and to test the association between 25OHD levels and GDM (through likelihood ratio tests). Analyses were not adjusted for multiple comparisons. Post-hoc power analysis was not performed because no a priori hypothesis were made on the true OR.

3. Results

3.1. Demographic and clinical characteristics of cases and controls

The selection of cases and controls is summarized in Fig. 1. In the original cohort, 3129 women were included; however, 36 women were excluded because they had one exclusion criterion or no blood test to measure 25OHD levels. Thus, 3093 pregnant women were included from April 2012 to July 2014 with the last delivery in February 2015. Among the 258 cases of GDM (8·3%), eight were excluded due to missing data on 25OHD assay in the first trimester or missing data on matching criteria (n = 7) and neonatal death at delivery (n = 1). Finally, 250 cases of GDM were matched among the 1852 eligible controls. For 43 cases with the least common profiles, we could not match the four controls required. Overall, the 250 cases were matched to four controls (n = 207), three controls (n = 27) or two controls (n = 16), leading to a total number of 941 controls.

The characteristics of the 250 cases of GDM and the 941 matched controls are summarized in Table 1. As expected, cases and controls were similar in matching characteristics (age, BMI before pregnancy, conception season, phototype, and parity).

3.2. Routine vitamin D supplementation

In agreement with French national guidelines, 83·2% of women received vitamin D after inclusion. The time at first vitamin D supplementation did not differ between cases and controls (p = 0·76). In both groups, some women received a vitamin D supplementation in the month before inclusion (2·8% in the control group and 2·7% among cases, p = 0·89) (Table 2).

3.3. Levels of 25OHD during pregnancy and association with gestational diabetes

In our cohort, mean 25OHD levels in the first trimester were 21·1 ng/mL among cases and 22·7 ng/mL in the control group (p = 0·028). The risk of GDM in inadequate vitamin D patients (25OHD level <30 ng/mL) in the first trimester of pregnancy did not differ significantly from that of sufficient vitamin D patients (OR 1·34, 95% CI 0·94–1·90, p = 0·1). The GDM risk was significantly greater for patients with vitamin D insufficiency (25OHD level < 20 ng/mL): OR = 1·42 (95% CI 1·06–1·91; p = 0·021). With

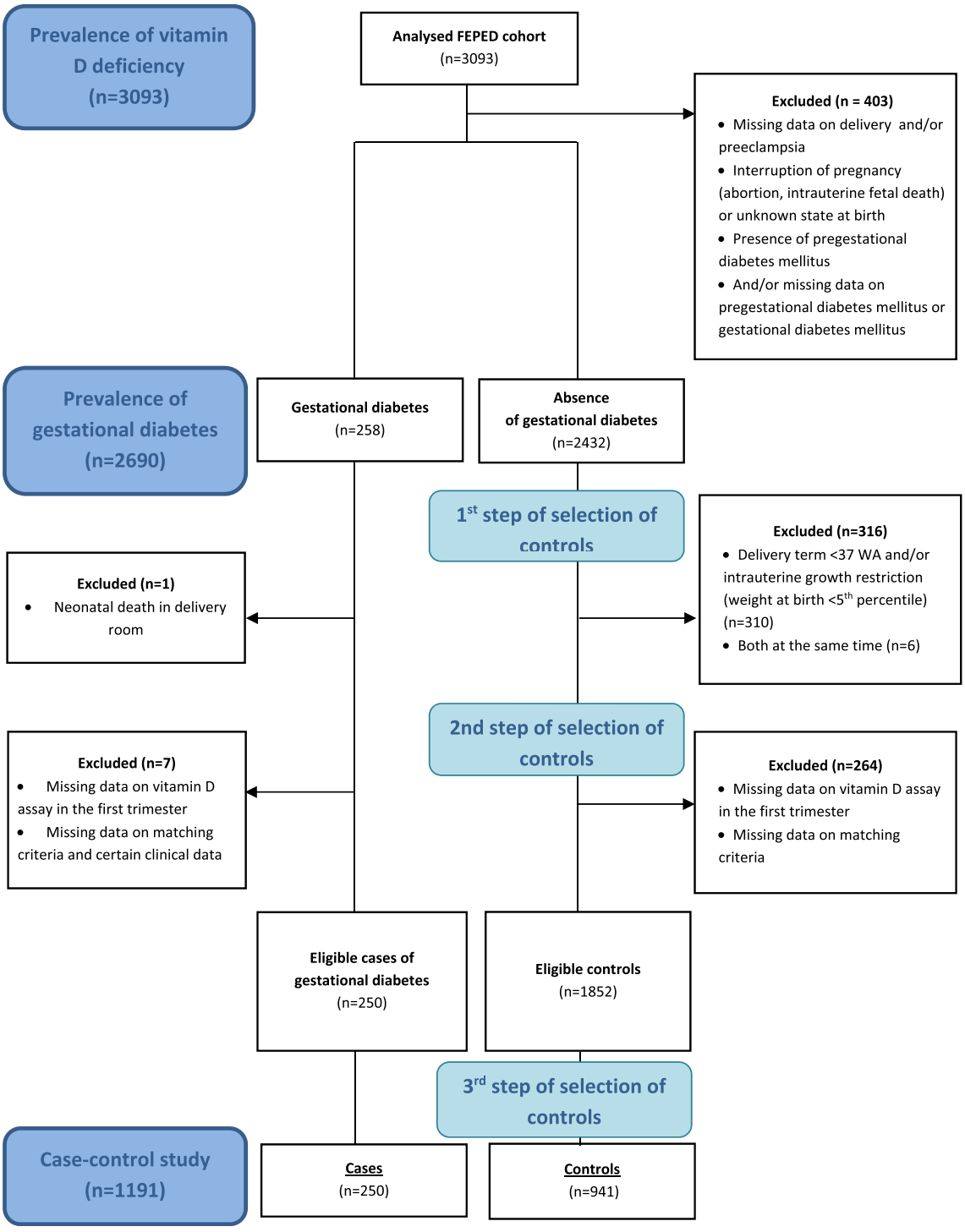

Fig. 1. Flow chart.

other thresholds of 25OHD, such as 10 ng/mL, the difference in risk was not significant anymore (Table 2). To explore this discrepancy, the GDM risk was further tested on 5 units intervals of 25OHD level (Fig. 2). This revealed that GDM risk was not constant over increasing 25OHD levels, highlighting that relationship between the first trimester 25OHD level and the risk of GDM is not linear. The GDM risk was low for very low 25OHD levels (<10 ng/mL), increased for moderate levels (10–25 ng/mL), decreased for normal levels (25–40 ng/mL) and finally increased for higher levels (>40 ng/mL).

4. Discussion

Low vitamin D status in the first trimester may increase GDM risk, but the evidence in the literature is insufficient to draw reliable conclusions. This study was designed to assess the risk of GDM according to vitamin D status during the first trimester of pregnancy.

While the criteria set for the different subcategories of vitamin D are not consensual, it is commonly admitted that a blood level

Table 1
Clinical and demographic characteristics at inclusion of women with gestational diabetes (cases) and matched women without gestational diabetes (controls)[a].

Characteristics at inclusion	Cases (N = 250)	Controls[b] (N = 941)	P-value[c]
Center of inclusion			0·011
Béclère Hospital, Paris	108 (43·2%)	420 (44·6%)	
Bicêtre Hospital, Paris	47 (18·8%)	109 (11·6%)	
Cochin Hospital, Paris	50 (20·0%)	234 (28·9%)	
Trousseau Hospital, Paris	25 (10·0%)	65 (6·9%)	
Nantes University Hospital, Nantes	7 (2·8%)	36 (3·8%)	
CHU Brugmann, Brussels	13 (5·2%)	77 (8·2%)	
Pregnancy term at inclusion (weeks of amenorrhea)	12·9 ± 0·8	12·7 ± 0·9	0·002
Age at inclusion (years)	32·8 ± 5·3	32·3 ± 5·0	0·12
Body mass index before pregnancy (kg/m^2)	25·8 ± 5·5	24·7 ± 4·6	0·001
Parity (previous deliveries)			0·46
0	113 (45·2%)	424 (45·1%)	
1	96 (38·4%)	333 (35·4%)	
>1	41 (16·4%)	184 (19·6%)	
Season of conception			0·70
Spring/Summer	130 (52%)	502 (53·4%)	
Autumn/Winter	120 (48%)	439 (46·6%)	
Skin color (Fitzpatrick scale)			0·96
Skin color 1-4	192 (76·8%)	724 (76·9%)	
Skin color ≥5	58 (23·2%)	217 (23·1)	
Origin			0·10
Sub-Saharan Africa	22 (8·8%)	99 (10·6%)	
North Africa	59 (23·6%)	147 (15·6%)	
Asia	12 (4·8%)	28 (3%)	
French overseas departments/territories	11 (4·4%)	41 (4·4%)	
North Europe	7 (2·8%)	35 (3·7%)	
South Europe	13 (5·2%)	53 (5·7%)	
France	115 (46%)	501 (53·4%)	
Other	11 (4·4%)	34 (3·6%)	

[a] Data are presented as number (%) or mean ± SD.
[b] Parity (primipara or more), age (<35 or ≥35 years), body mass index before pregnancy (<25 kg/m2 or ≥25 kg/m2), season of conception (autumn/winter or spring/summer) and phototype (<V or ≥V Fitzpatrick scale) were matching factors.
[c] Logistic regression model.

Table 2
Association between vitamin D during the first trimester and gestational diabetes mellitus[a].

	Cases N = 250	Controls N = 941	OR [95% CI] P-value
Time of assay (WA)	12·9 ± 0·8	12·7 ± 0·9	0·003
Vitamin D supplementation in the month before inclusion	6 (2·7%)	25 (2·8%)	1·07 [0·42–2·72] p = 0·89
Vitamin D supplementation after inclusion	192 (80·3%)	798 (86%)	0·64 [0·43–0·94] p = 0·022
Time at first vitamin D supplementation (WA)	27·8 ± 3·4	27·8 ± 3·6	0·76
Vitamin D level in first trimester (ng/mL)	21·1 ± 10	22·7 ± 10	p = 0·028
Vitamin D level classes			
<10 ng/mL	22 (8·8%)	82 (8·7%)	1·24 [0·69–2·24], p = 0·47
10–30 ng/mL	176 (70·4%)	615 (65·4%)	1·35 [0·95–1·92], p = 0·1
≥30 ng/mL	52 (20·8%)	244 (25·9%)	Ref
Vitamin D deficiency			
<10 ng/mL	22 (8·8%)	82 (8·7%)	0·98 [0·58–1·63], p = 0·93
≥10 ng/mL	228 (91·2%)	859 (91·3%)	Ref
Vitamin D insufficiency			
<20 ng/mL	125 (50%)	394 (41·9%)	1·42 [1·06–1·91], p = 0·021
≥20 ng/mL	125 (50%)	547 (58·1%)	Ref
Vitamin D inadequacy			
<30 ng/mL	198 (79·2%)	697 (74·1%)	1·34 [0·94–1·90], p = 0·1
≥30 ng/mL	52 (20·8%)	244 (25·9%)	Ref

[a] Data are presented as number (%) or mean ± SD.

below 30 ng/mL is inadequate [44]. The recommended daily intake for vitamin D is 200 IU for children over three years old and adults younger than 65 years and 400–600 IU for those over 65 years old [45].

Vitamin D is well known for its role in maintaining phospho-calcic homeostasis and stimulating bone mineralization. However, interest in other potential roles has grown in recent years, notably a possible association between low vitamin D in early pregnancy and increased risk of adverse pregnancy outcomes such as preeclampsia, preterm births, SGA, and neonatal hypocalcemia [15–17]. Regarding the association between vitamin D deficiency and the risk of GDM, controversy remains as the findings have been inconsistent: disparate populations and conflicting data have been reported. Most studies in the medical literature are inconclusive because of their cross-sectional design, a limited number of participants, or absence of adjustments for major confounding factors. Moreover, vitamin D deficiency is variably defined between studies and is sometimes only analyzed in late

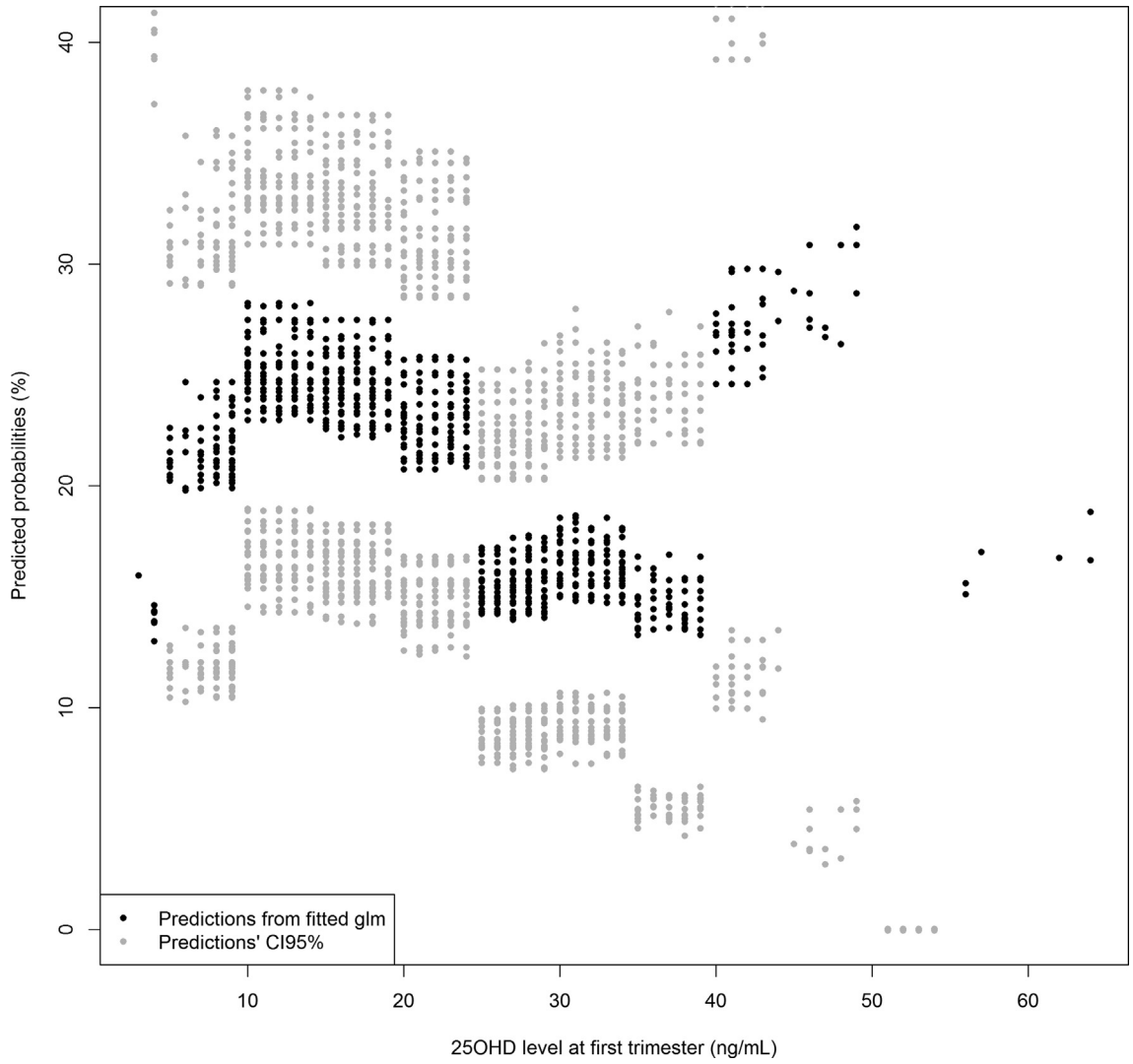

Fig. 2. Association between 5 units intervals of maternal serum 25OHD in the first trimester of gestation and the predicted probability of gestational diabetes mellitus. Predicted probabilities of gestational diabetes mellitus (●) and 95% confidence interval (●) were calculated with a logistic model adjusted for matching factors (parity, maternal age, pregnancy BMI, season of conception, phototype) and are represented between 0 and 0·4. Serum 25OHD was divided into 5 units intervals (ng/mL).

pregnancy, plus the diagnostic criteria for GDM are heterogeneous across studies, all of which complicate comparisons. A 2016 meta-analysis of 20 observational studies showed a 45% increase in the risk of GDM in the case of vitamin D deficiency during pregnancy [31]. Three previous meta-analyses of 7, 12 and 22 observational studies, yielded similar results and concluded that there is a statistically significant association between maternal vitamin D deficiency during pregnancy and an increased risk of GDM [15,28,29]. Additionally, a 2017 systematic review and meta-analysis of 38 studies, by Zhang et al., included more studies and parameters than previous analyses, in an attempt to draw a definitive conclusion regarding the relationship between vitamin D and GDM. The results were consistent with the previous meta-analyses: patients with vitamin D deficiency or insufficiency have a higher risk of GDM (OR 1·85, 95% CI 1·471–2·328) and 25OHD levels are significantly lower in patients with GDM ($p < 0·001$) [25]. Lastly, a 2018 meta-analysis by Hu et al. indicates a significant association between vitamin D insufficiency and increased risk of GDM [46].

However, many authors in the medical literature did not demonstrate a significant correlation between vitamin D deficiency and GDM. Farrant et al. found no significant association between vitamin D insufficiency and GDM in a prospective observational cohort of 559 Indian mothers [47]. Likewise, in their nested case–control study of 1100 patients, Savvidou et al. found no significant difference in maternal 25OHD levels during the first trimester between pregnant women with GDM and control patients [48]. Magkoba et al., in a nested case–control study of 90 patients with GDM and 158 healthy controls, also concluded that the increase in the risk of GDM in the case of vitamin D deficiency during first trimester of pregnancy was not significant [49]. Baker et al. reported similar results in a case–control study of 60 cases of GDM and 120 controls in a North Carolina Hospital [50]. In a large prospective cohort of 1953 patients in Guangzhou Hospital in south China, Zhou et al. observed a higher prevalence of GDM in the vitamin D sufficient group than in the low and medium vitamin D group. Thus they concluded that the risk of GDM decreased with vitamin D deficiency [33]. Two recent cross-sectional studies showed no significant difference in 25OHD levels between women with and women without GDM, even after adjustment for confounding factors [34,35]. In an attempt to reach a reliable conclusion, two recent reports summarized several meta-analyses, but

failed to give a clear answer regarding the relationship between vitamin D and the risk of GDM [22,23].

The question of 25OHD levels during early pregnancy and GDM risk therefore remains unresolved. Our study did not show that vitamin D insufficiency during the first trimester increases the risk of GDM. Indeed, this risk seems to oscillate with 25OHD level. These results question the consistency of the association between GDM and vitamin D deficiency previously suggested by many authors, as only usual cut-offs were tested, without studying more precisely various 25OHD levels.

The strength of our study relies on its prospective design, the large sample size, as well as the choice of potential confounding factors as matching profile criteria for cases and controls. However, our study does have some limitations. First, the stated amount of vitamin D taken during pregnancy might not be perfectly accurate as intake may have been increased by the use of additional nutritional supplements and/or because of dietary habits, in addition to the 7th month's national recommended intake. Nevertheless, as GDM is diagnosed late in pregnancy, the latter might not be an issue. Furthermore, there is no information on the extent of solar exposure, which depends on clothing and outdoor activities. Finally, other potential confounding factors such as physical activity, smoking, alcohol intake, socioeconomic status and a family history of diabetes were not taken into consideration in the design of this study.

Several mechanisms can explain the potential physiopathological association between vitamin D insufficiency and the risk of developing GDM. Vitamin D enhances pancreatic insulin secretion, via a beta cell vitamin D receptor, thus lowering circulating glucose levels [19,51]. Furthermore, vitamin D, via its receptor, stimulates the expression of insulin receptors, which stimulates insulin sensitivity and thus increases glucose transport inside the cells [52]. Finally, it plays a major role in the balance of the extracellular and intracellular calcium pools which are essential to intracellular insulin-mediated mechanisms of insulin-sensitive tissues, also resulting in glucose transportation [53]. Vitamin D deficiency may worsen pre-existing insulin resistance with impaired compensation due to pregnancy, leading to GDM. Furthermore, it is possible that the association between vitamin D deficiency and GDM is indirectly regulated via other common risk factors, such as obesity. Our data do not enable us to evaluate the amount of vitamin D at the onset of GDM as only first-trimester and late third-trimester samples are available.

Recommended vitamin D supplementation varies from one country to another, and there is still no standard recommendation. The French National College of Gynecologists and Obstetricians recommends a single 100 000 IU dose of vitamin D administered at the beginning of the 7th month of pregnancy [40]. The World Health Organization recommends a vitamin D intake of 200 IU per day for pregnant women [54].

Considering there might be a link between vitamin D and GDM, vitamin D supplementation during pregnancy could represent a simple and safe intervention to reduce the incidence of GDM. Several randomized clinical trials on the effect of vitamin D supplementation on pregnancy outcomes have been conducted. Some demonstrate a reduced incidence of GDM, as well as correction of vitamin D deficiency, with sufficient vitamin D supplementation. Shahgheibi et al., in a double-blind placebo-controlled randomized study including 90 Iranian pregnant women at high risk of GDM, found a significantly higher incidence of GDM in the placebo group than in the group receiving 5 000 IU per week of vitamin D until the 26th WA [36]. In their meta-analysis, Zang et al. found that vitamin D supplementation during pregnancy seemed to reduce the incidence of GDM, but the results were not statistically significant (RR 0·718, 95% CI 0·392–1·314). Their results also showed that vitamin D supplementation influenced other biomarkers of GDM. It elevated blood 25OHD significantly ($p < 0·001$), glutathione ($p = 0·003$) and HDL cholesterol concentrations ($p = 0·04$) as well as reduced fasting insulin levels ($p = 0·001$), fasting plasma glucose ($p < 0·001$), insulin resistance index ($p < 0·001$), blood CRP levels ($p = 0·02$), blood total cholesterol concentration ($p = 0·003$) and blood LDL cholesterol concentrations ($p = 0·003$) [25]. Other authors, such as Sablok et al. and Tehrani et al., have failed to prove such an effect [37,38]. Regarding our results, it seems most unlikely that achieving a vitamin D sufficient status during early pregnancy is an effective way to reduce the incidence of GDM.

5. Conclusion

The literature on the potential link between vitamin D deficiency and GDM is inconsistent. The use of different thresholds for vitamin D (<30, <20, <10 ng/mL) suggests that the strength and consistency of the association between vitamin D status in early pregnancy and a greater risk of GDM should be questioned. Indeed, the GDM risk does not continuously decrease as 25OHD concentrations increase. Thus, our results do not enable us to establish a relationship between vitamin D and GDM risk. We suggest that among existing publications, authors retrospectively access their data and analyze the vitamin D level per subgroup. Furthermore, large studies are necessary in order to confirm our results and further support the exclusion of vitamin D insufficiency as a potential GDM risk factor in early pregnancy.

Statement of authorship

ES interpreted the data and wrote the manuscript.
TR and CE analyzed and interpreted the data.
AB, CE and JCS conceived and designed the study.
JCS performed 25OHD measurements.
JT, VT, JG, MVS, HH, JJ, DB, EM, MCH, NW, DM, and MC included patients.

All 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 Diagnosis, Abbott, Amgen, Shire, MSD, Lilly, and Rottapharm/Meda.

The other authors declare no conflicts of interest.

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